

# PDGFRB and JAK1 are promising druggable targets for treating Colorectal Neoplasms that control activity of NR3C1, MAFK and PAX8 transcription factor on promoters of genes carrying sequence variations

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Genome Enhancer release 3.8 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2026.1)

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## Abstract

In the present study we applied the software package "Genome Enhancer" to a data set that contains *genomics* data. The study is done in the context of *Colorectal Neoplasms*. The goal of this pipeline is to identify potential drug targets in the molecular network that governs the studied pathological process. In the first step of analysis pipeline discovers transcription factors (TFs) that regulate genes activities in the pathological state. The activities of these TFs are controlled by so-called master regulators, which are identified in the second step of analysis. After a subsequent druggability checkup, the most promising master regulators are chosen as potential drug targets for the analyzed pathology. At the end the pipeline comes up with (a) a list of known drugs and (b) investigational active chemical compounds with the potential to interact with selected drug targets.

From the data set analyzed in this study, we found the following TFs to be potentially involved in the regulation of the genes carrying sequence variations: NR3C1, MAFK and PAX8. The subsequent network analysis suggested

- Jak1
- Ubc9
- NCoR2
- YY1
- PDGFRbeta

as the most promising molecular targets for further research, drug development and drug repurposing initiatives on the basis of identified molecular mechanism of the studied pathology.

## 1. Introduction

Recording "-omics" data to measure gene activities, protein expression or metabolic events is becoming a standard approach to characterize the pathological state of an affected organism or tissue. Increasingly, several of these methods are applied in a combined approach leading to large "multiomics" datasets. Still the challenge remains how to reveal the underlying molecular mechanisms that render a given pathological state different from the norm. The disease-causing mechanism can be described by a re-wiring of the cellular regulatory network, for instance as a result of a genetic or epigenetic alterations influencing the activity of relevant genes. Reconstruction of the disease-specific regulatory networks can help identify potential master regulators of the respective pathological process. Knowledge about these master regulators can point to ways how to block a pathological regulatory cascade. Suppression of certain molecular targets as components of these cascades may stop the pathological process and cure the disease.

Conventional approaches of statistical "-omics" data analysis provide only very limited information about the causes of the observed phenomena and therefore contribute little to the understanding of the pathological molecular mechanism. In contrast, the "upstream analysis" method [1-4] applied here has been devised to provide a casual interpretation of the data obtained for a pathology state. This approach comprises two major steps: (1) analysing promoters and enhancers of genes carrying sequence variations for the transcription factors (TFs) involved in their regulation and, thus, important for the process under study; (2) re-constructing the signaling pathways that activate these TFs and identifying master regulators at the top of such pathways. For the first step, the database TRANSFAC® [5] is employed together with the TF binding site identification algorithms Match [6] and CMA [7]. The second step involves the signal transduction database TRANSPATH® [8] and special graph search algorithms [10-11] implemented in the software "Genome Enhancer".

The "upstream analysis" approach has now been extended by a third step that reveals known drugs suitable to inhibit (or activate) the identified molecular targets in the context of the disease under study. This step is performed by using information from HumanPSD™ database [11]. In addition, some known drugs and investigational active chemical compounds are subsequently predicted as potential ligands for the revealed molecular targets. They are predicted using a pre-computed database of spectra of biological activities of chemical compounds of a library of 2245 known drugs and investigational chemical compounds from HumanPSD™ database. The spectra of biological activities for these compounds are computed using the program PASS on the basis of a (Q)SAR approach [12-14]. These predictions can be used for the research purposes - for further drug development and drug repurposing initiatives.

## 2. Data

For this study the following experimental data was used:

Table 1. Experimental datasets used in the study

|              |           |
|--------------|-----------|
| File name    | Data type |
| CRC_variants | Genomics  |

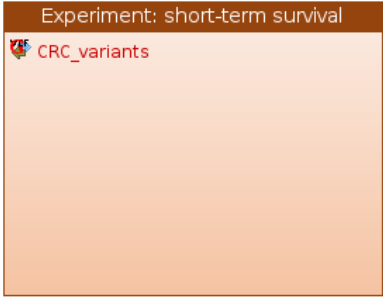


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

### 3. Results

We have analyzed the following condition: Experiment: short-term survival.

#### 3.1. Identification of target genes

In the first step of the analysis **target genes** were identified from the uploaded experimental data. The most frequently mutated genes were used as target genes.

Table 2. Top ten the most frequently mutated genes in Experiment: short-term survival.

[See full table](#) →

| ID              | Gene description                                           | Gene symbol | Gene schematic representation | Number of variations | Gene weight | Weighted score |
|-----------------|------------------------------------------------------------|-------------|-------------------------------|----------------------|-------------|----------------|
| ENSG00000132570 | pterin-4 alpha-carbinolamine dehydratase 2                 | PCBD2       |                               | 172                  | 430.35      | 645.52         |
| ENSG00000204525 | major histocompatibility complex, class I, C               | HLA-C       |                               | 71                   | 165.55      | 496.64         |
| ENSG00000169894 | mucin 3A, cell surface associated                          | MUC3A       |                               | 68                   | 160.61      | 481.82         |
| ENSG00000206503 | major histocompatibility complex, class I, A               | HLA-A       |                               | 73                   | 158.34      | 475.02         |
| ENSG00000228716 | dihydrofolate reductase                                    | DHFR        |                               | 56                   | 139.94      | 419.82         |
| ENSG00000196735 | major histocompatibility complex, class II, DQ alpha 1     | HLA-DQA1    |                               | 63                   | 134.8       | 404.4          |
| ENSG00000111700 | solute carrier organic anion transporter family member 1B3 | SLCO1B3     |                               | 51                   | 125.68      | 377.04         |
| ENSG0000013573  | DEAD/H-box helicase 11                                     | DDX11       |                               | 52                   | 120.65      | 361.94         |
| ENSG00000242086 | MUC20 overlapping transcript                               | MUC20-OT1   |                               | 147                  | 341.57      | 341.57         |
| ENSG00000234745 | major histocompatibility complex, class I, B               | HLA-B       |                               | 51                   | 111.84      | 335.51         |

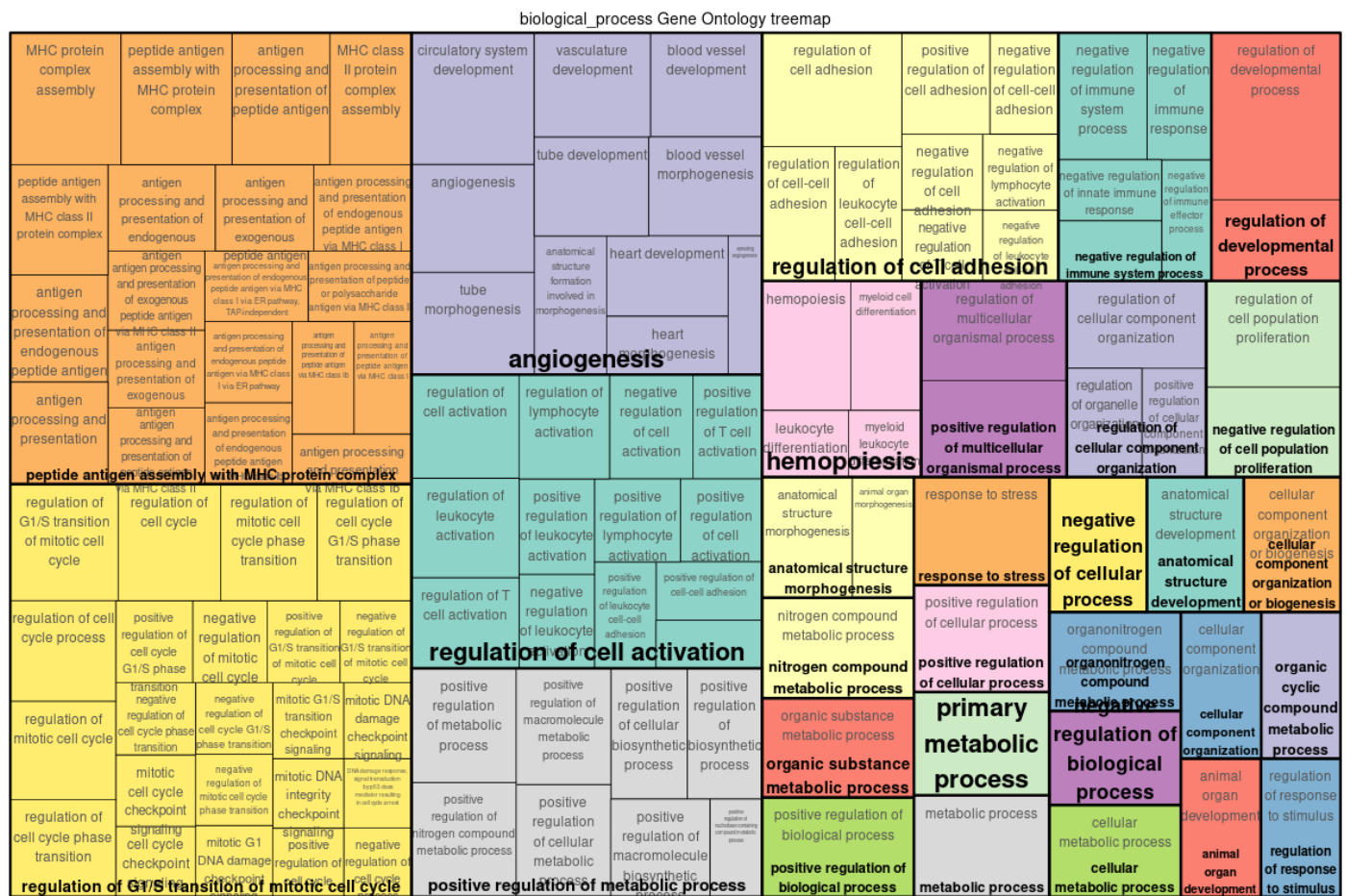
#### 3.2. Functional classification of genes

A functional analysis of genes carrying sequence variations was done by mapping the genes to several known ontologies, such as Gene Ontology (GO), disease ontology (based on HumanPSD™ database) and the ontology of signal transduction and metabolic pathways from the TRANSPATH® database. Statistical significance was computed using a binomial test.

Figures 2-4 show the most significant categories.

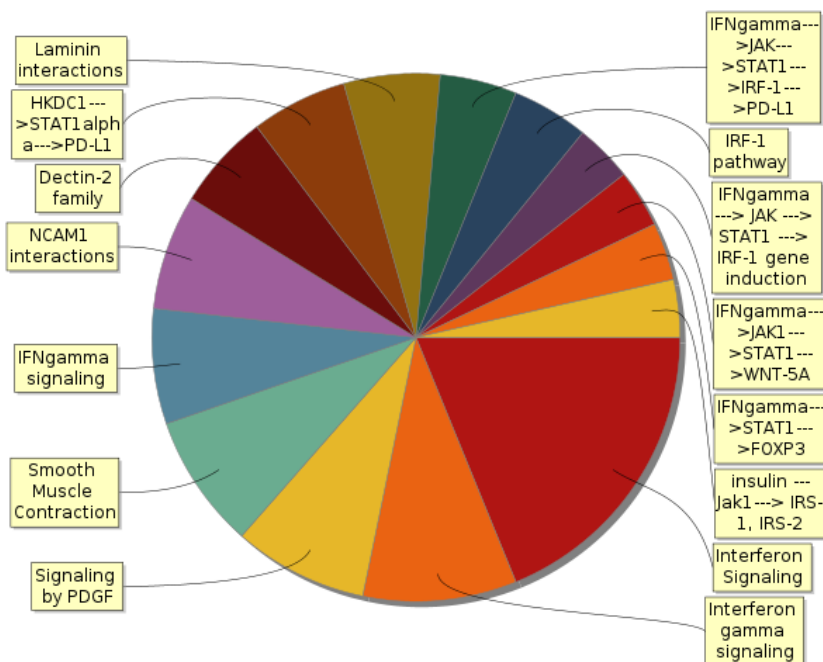
#### The most frequently mutated genes in Experiment: short-term survival:

300 top mutated genes were taken for the mapping.



**Full classification** →

## TRANSPATH® Pathways (2026.1)



**Full classification** →

HumanPSD(TM) disease (2026.1)

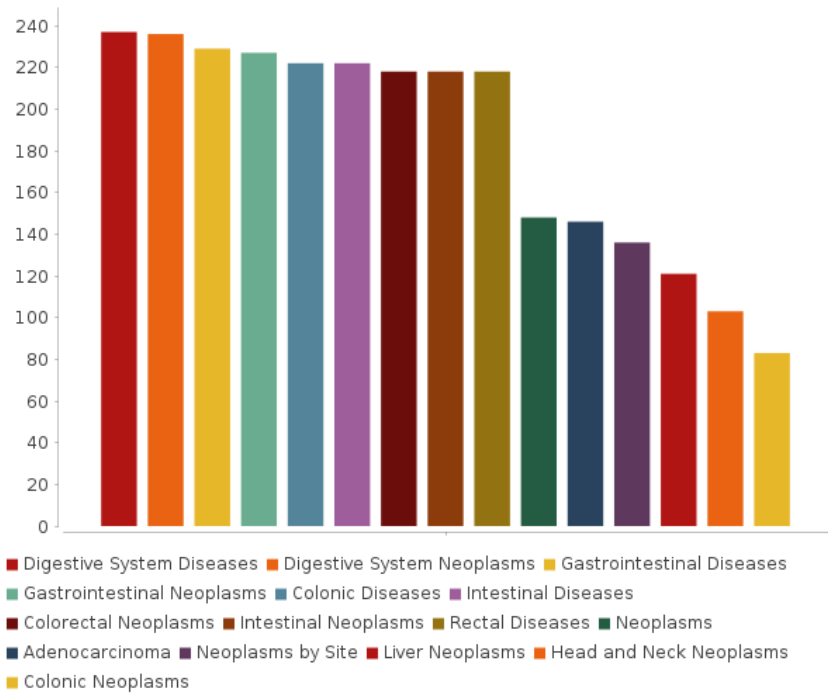
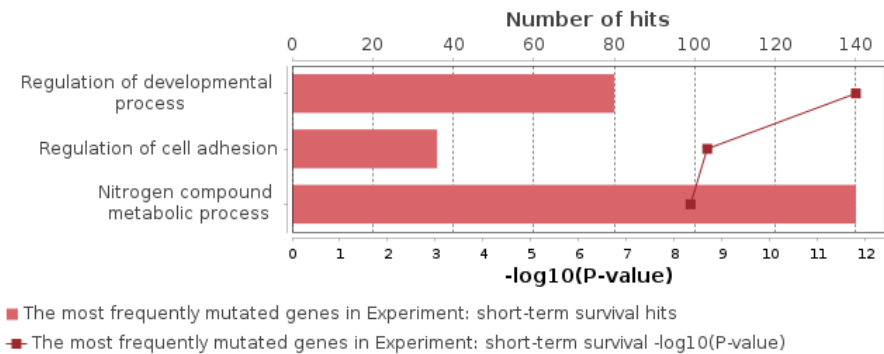


Figure 4. Enriched HumanPSD(TM) disease (2026.1) of the most frequently mutated genes in Experiment: short-term survival. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

[Full classification →](#)

The result of overall Gene Ontology (GO) analysis of the genes carrying sequence variations of the studied pathology can be summarized by the following diagram, revealing the most significant functional categories overrepresented among the observed (genes carrying sequence variations):



3.3. Analysis of enriched transcription factor binding sites and composite modules

In the next step a search for transcription factors binding sites (TFBS) was performed in the regulatory regions of the *target genes* by using the TF binding motif library of the TRANSFAC® database. We searched for so called **composite modules** that act as potential condition-specific **enhancers** of the *target genes* in their upstream regulatory regions (-1000 bp upstream of transcription start site (TSS)) and identify transcription factors regulating activity of the genes through such **enhancers**.

Classically, **enhancers** are defined as regions in the genome that increase transcription of one or several genes when inserted in either orientation at various distances upstream or downstream of the gene [7]. Enhancers typically have a length of several hundreds of nucleotides and are bound by multiple transcription factors in a cooperative manner [8].

In the current work, we use the Genomics data from the "Yes VCF track" track to predict positions of potential **enhancers** where the observed sequence variations may influence the gene expression in the pathology under study. We scan 5kb flanking regions and the body of all genes caring the variations, with a sliding window of 1100bp size and find the position of the window with the maximal sum of the mutation weights, where we then perform the search for potential condition-specific enhancers (CMA model search).

We analyzed mutations that were revealed in the potential enhancers located upstream, downstream or inside the *target genes* (see Table 3). We identified 24855 mutations potentially affecting gene regulation. Table 4 shows the following lists of PWMs whose sites were lost or gained due to these mutations. Weighting of mutations was done in respect to the significance of the change in TF affinity binding to the sequence. Mutations that maximally affected the change of binding affinity received higher weights. These PWMs were put in focus of the CMA algorithm that constructs the model of the enhancers by specifying combinations of TF motifs (see more details of the algorithm in the Methods section).

Table 3. Mutations revealed in the most frequently mutated genes

[See full table](#) →

| ID              | Gene symbol     | Gene schematic representation | Number of variations |
|-----------------|-----------------|-------------------------------|----------------------|
| ENSG00000132570 | PCBD2           |                               | 660                  |
| ENSG00000248923 | MTND5P11        |                               | 459                  |
| ENSG00000247627 | MTND4P12        |                               | 374                  |
| ENSG00000293331 | ENSG00000293331 |                               | 360                  |
| ENSG00000249119 | MTND6P4         |                               | 279                  |
| ENSG00000242086 | MUC20-OT1       |                               | 252                  |
| ENSG00000198868 | MTND4LP30       |                               | 245                  |
| ENSG00000263963 | ENSG00000263963 |                               | 245                  |
| ENSG00000154237 | LRRK1           |                               | 230                  |
| ENSG00000244921 | MTCYBP18        |                               | 225                  |

Table 4. PWMs whose sites were lost or gained due to mutations in the most frequently mutated genes

[See full table](#) →

| ID              | P-value (gains) | P-value (losses) | yesCount (gains) | yesCount (losses) |
|-----------------|-----------------|------------------|------------------|-------------------|
| V\$OTX2_06      | 3.65E-2         | 8.72E-14         | 25               | 70                |
| V\$GSC_04       | 3.12E-2         | 3.07E-11         | 5                | 82                |
| V\$RBAK_01      | 3.12E-2         | 5.35E-10         | 5                | 381               |
| V\$ZBTB33_07    | 1.06E-2         | 8.27E-12         | 13               | 611               |
| V\$ZBTB33_05    | 6.47E-3         | 6.92E-10         | 12               | 535               |
| V\$MATH1_Q2     | 1.99E-3         | 3.66E-12         | 204              | 389               |
| V\$E2A_03       | 1.6E-3          | 1.14E-12         | 231              | 387               |
| V\$MAFG_12      | 3.44E-5         | 3.47E-10         | 34               | 1295              |
| V\$E2F8_03      | 1.22E-6         | 1.32E-9          | 63               | 1618              |
| V\$CGBP_01      | 8.67E-23        | 4.62E-12         | 1755             | 1497              |
| V\$E2F4DP1_01   | 1.88E-25        | 1.14E-10         | 3568             | 4126              |
| V\$E2F1DP2_01   | 2.9E-31         | 1.81E-11         | 3552             | 3615              |
| V\$E2F3_12      | 1.1E-31         | 3.12E-2          | 1493             | 5                 |
| V\$AP2GAMMA_Q5  | 6.21E-33        |                  | 585              |                   |
| V\$E2F6_05      | 2.91E-34        | 4.61E-2          | 771              | 10                |
| V\$E2F_Q4_02    | 1.46E-35        | 2.93E-2          | 2015             | 55                |
| V\$E2F1_04      | 2.31E-36        |                  | 903              |                   |
| V\$GCM2SOX15_01 | 3.53E-39        |                  | 1927             |                   |
| V\$E2F3_09      | 1.41E-41        |                  | 3966             |                   |
| V\$TBX2_05      | 1.14E-41        |                  | 2457             |                   |

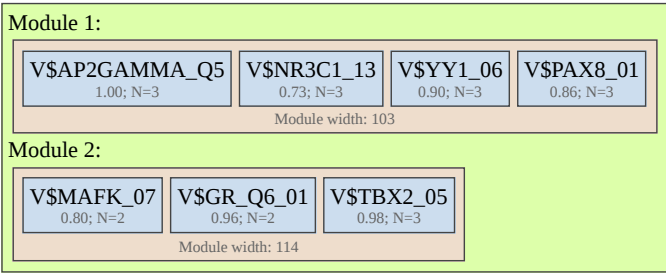
We applied the Composite Module Analyst (CMA) [7] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the enhancers by specifying combinations of TF motifs (from TRANSFAC®) whose sites are most frequently clustered together in the regulatory regions of the studied genes. CMA identifies the transcription factors that through their cooperation provide a synergistic effect and thus have a great influence on the gene regulation process.

**Enhancer model potentially involved in regulation of target genes (the most frequently mutated genes in Experiment: short-term survival).**

To build the most specific composite modules we choose top mutated genes as the input of CMA algorithm. The obtained CMA model is then applied to compute CMA score for all the most frequently mutated genes in Experiment: short-term survival.

The model consists of 2 module(s). Below, for each module the following information is shown:

- PWMs producing matches,
- number of individual matches for each PWM,
- score of the best match.



Model score (-p\*log10(pval)): 22.30  
Wilcoxon p-value (pval): 1.04e-40  
Penalty (p): 0.558  
Average yes-set score: 8.88  
Average no-set score: 7.40  
AUC: 0.75  
Separation point: 8.11  
False-positive: 32.84%  
False-negative: 26.00%

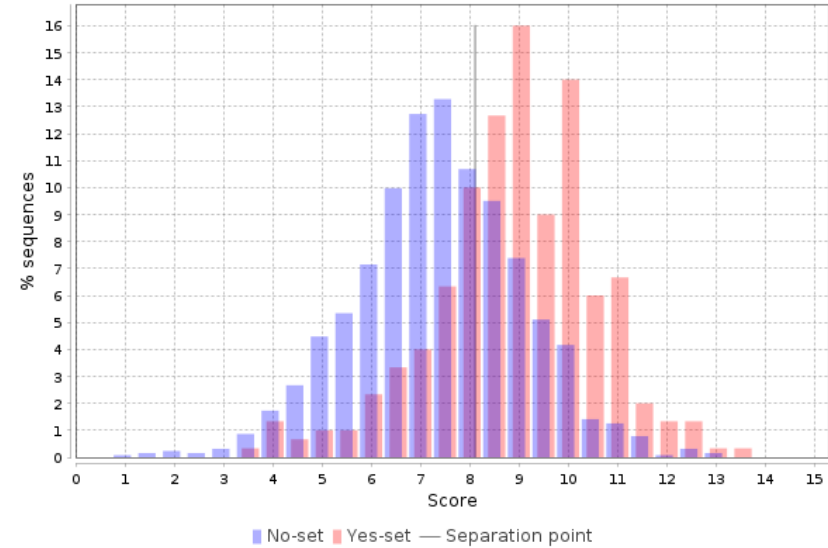


Table 5. List of top ten the most frequently mutated genes in Experiment: short-term survival with identified enhancers in their regulatory regions. **CMA score** - the score of the CMA model of the enhancer identified in the regulatory region.

See full table →

| Ensembl IDs     | Gene symbol | Gene description                                              | CMA score | Factor names                                            |
|-----------------|-------------|---------------------------------------------------------------|-----------|---------------------------------------------------------|
| ENSG00000074370 | ATP2A3      | ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 3 | 14.64     | MafK(h), YY1(h), AP-2gamma(h), Pax-8(h), TBX2(h), GR(h) |
| ENSG00000160256 | SLX9        | SLX9 ribosome biogenesis factor                               | 14.6      | GR(h), Pax-8(h), MafK(h), TBX2(h), AP-2gamma(h), YY1(h) |
| ENSG00000092529 | CAPN3       | calpain 3                                                     | 14.44     | TBX2(h), GR(h), MafK(h), Pax-8(h), YY1(h), AP-2gamma(h) |
| ENSG00000119522 | DENND1A     | DENN domain containing 1A                                     | 14.36     | YY1(h), Pax-8(h), AP-2gamma(h), GR(h), TBX2(h), MafK(h) |
| ENSG00000284031 | MIR4761     | microRNA 4761                                                 | 14.21     | AP-2gamma(h), MafK(h), YY1(h), Pax-8(h), GR(h), TBX2(h) |
| ENSG00000267080 | ASB16-AS1   | ASB16 antisense RNA 1                                         | 14.05     | MafK(h), TBX2(h), YY1(h), AP-2gamma(h), Pax-8(h), GR(h) |
| ENSG00000161664 | ASB16       | ankyrin repeat and SOCS box containing 16                     | 14.05     | MafK(h), TBX2(h), YY1(h), AP-2gamma(h), Pax-8(h), GR(h) |
| ENSG00000269604 |             | novel transcript, antisense to FEM1A                          | 13.98     | TBX2(h), GR(h), MafK(h), YY1(h), AP-2gamma(h), Pax-8(h) |
| ENSG00000106100 | NOD1        | nucleotide binding oligomerization domain containing 1        | 13.95     | Pax-8(h), YY1(h), TBX2(h), GR(h), AP-2gamma(h), MafK(h) |
| ENSG00000107736 | CDH23       | cadherin related 23                                           | 13.93     | MafK(h), TBX2(h), GR(h), Pax-8(h), AP-2gamma(h), YY1(h) |

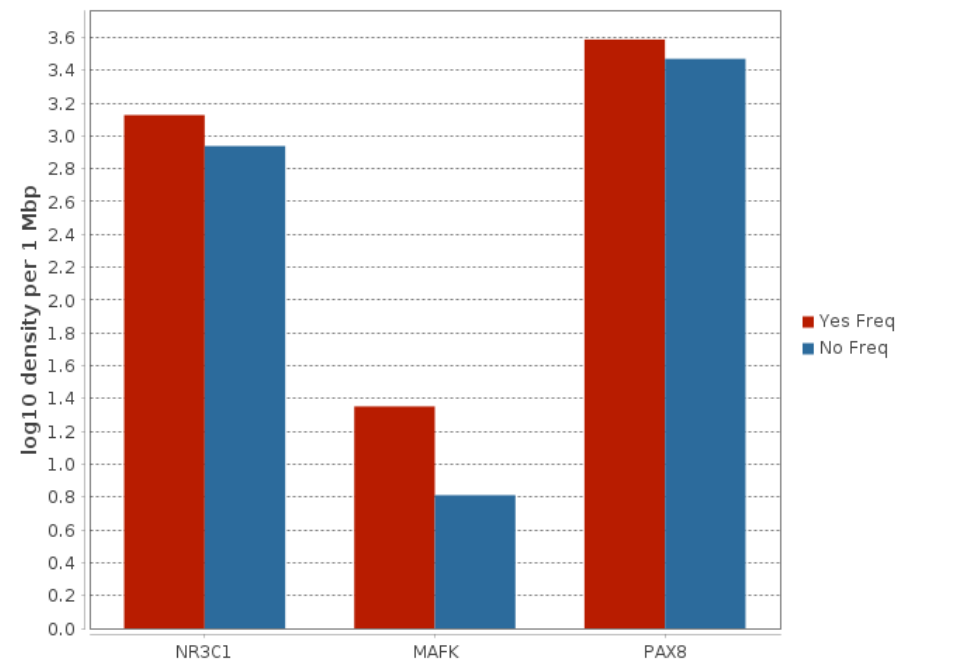
On the basis of the enhancer models we identified transcription factors potentially regulating the **target genes** of our interest. We found 6 transcription factors controlling expression of the genes associated with genomic variations (see Table 6).

Table 6. Transcription factors of the predicted enhancer model potentially regulating the genes carrying sequence variations (the most frequently mutated genes in Experiment: short-term survival). **Yes-No ratio** is the ratio between frequencies of the sites in Yes sequences versus No sequences. It describes the level of the enrichment of binding sites for the indicated TF in the regulatory target regions. **Regulatory score** is the measure of involvement of the given TF in the controlling of expression of genes that encode master regulators presented below (through positive feedback loops).

See full table →

| ID          | Gene symbol | Gene description                              | Regulatory score | Yes-No ratio |
|-------------|-------------|-----------------------------------------------|------------------|--------------|
| MO000031266 | NR3C1       | nuclear receptor subfamily 3 group C member 1 | 5.1              | 1.54         |
| MO000028668 | MAFK        | MAF bZIP transcription factor K               | 5.05             | 3.47         |
| MO000026866 | PAX8        | paired box 8                                  | 4.42             | 1.31         |
| MO000078913 | YY1         | YY1 transcription factor                      | 4.38             | 1.23         |
| MO000028209 | TBX2        | T-box transcription factor 2                  | 3.91             | 5.95         |
| MO000026449 | TFAP2C      | transcription factor AP-2 gamma               | 0                | 2.45         |

The following diagram represents the key transcription factors, which were predicted to be potentially regulating genes carrying sequence variations in the analyzed pathology: NR3C1, MAFK and PAX8.



3.4. Finding master regulators in networks

In the second step of the upstream analysis common regulators of the revealed TFs were identified. We identified 172 signaling proteins whose structure and function is highly damaged by the mutations (see Table 7).

Table 7. Signaling proteins whose structure and function are damaged by the mutations in the most frequently mutated genes

See full table →

| ID          | Title       | Mutation count | Consequence                               | Codons   |
|-------------|-------------|----------------|-------------------------------------------|----------|
| MO000019673 | p85alpha(h) | 22             | stop_gained                               | Cga/Tga  |
| MO000138949 | Drp1(h)     | 22             | NMD_transcript_variant,stop_gained        | Gaa/Taa  |
| MO000206935 | C11orf74(h) | 12             | stop_gained                               | Gaa/Taa  |
| MO000167580 | Sur-8(h)    | 11             | NMD_transcript_variant,stop_gained        | Gaa/Taa  |
| MO000168719 | GIPN(h)     | 10             | NMD_transcript_variant,frameshift_variant | aat/aaAt |
| MO000211774 | DPAGT1(h)   | 10             | NMD_transcript_variant,frameshift_variant | ttc/tTc  |
| MO000190658 | GPSM2(h)    | 9              | stop_gained                               | Gaa/Taa  |
| MO000093071 | chd8(h)     | 8              | stop_gained                               | taC/taA  |
| MO000113258 | MYPT1(h)    | 8              | NMD_transcript_variant,frameshift_variant | aga/aAga |
| MO000127741 | SMC4L1(h)   | 8              | stop_gained                               | Cga/Tga  |

Top 100 mutated proteins for the most frequently mutated genes were used in the algorithm of master regulator search as a list of nodes of the signal transduction network that are removed from the network during the search of master regulators (see more details about the algorithm in the Methods section). These master regulators appear to be the key candidates for therapeutic targets as they have a master effect on regulation of intracellular pathways that activate the pathological process of our study. The identified master regulators are shown in Table 8.

Table 8. Master regulators that may govern the regulation of the most frequently mutated genes in Experiment: short-term survival. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, genomics data.

See full table →

| ID          | Master molecule name                  | Gene symbol  | Gene description                                                   | Total rank | Weighted score |
|-------------|---------------------------------------|--------------|--------------------------------------------------------------------|------------|----------------|
| MO000031039 | NCoR2(h)                              | NCOR2        | nuclear receptor corepressor 2                                     | 126        | 191.29         |
| MO000019975 | Ubc9(h)                               | UBE2I        | ubiquitin conjugating enzyme E2 I                                  | 127        | 183.78         |
| MO001079984 | Ubc9(h){sumoC93}:sumo1(h){cICG97,93}  | SUMO1, UBE2I | small ubiquitin like modifier 1, ubiquitin conjugating enzyme E2 I | 129        | 183.78         |
| MO001080010 | Ubc9(h){sumo3C93}:sumo3(h){cICG92,93} | SUMO3, UBE2I | small ubiquitin like modifier 3, ubiquitin conjugating enzyme E2 I | 130        | 183.78         |
| MO001080002 | Ubc9(h){sumo2C93}:SUMO2(h){cICG93,93} | SUMO2, UBE2I | small ubiquitin like modifier 2, ubiquitin conjugating enzyme E2 I | 131        | 183.78         |
| MO000079234 | Ubc9(h)                               | UBE2I        | ubiquitin conjugating enzyme E2 I                                  | 133        | 183.78         |
| MO001088543 | Ubc9{sumoC93}:sumo1{cICG97,93}        | SUMO1, UBE2I | small ubiquitin like modifier 1, ubiquitin conjugating enzyme E2 I | 135        | 183.78         |
| MO001088545 | Ubc9{sumo3C93}:sumo3{cICG92,93}       | SUMO3, UBE2I | small ubiquitin like modifier 3, ubiquitin conjugating enzyme E2 I | 146        | 183.78         |
| MO001088544 | Ubc9{sumo2C93}:SUMO2{cICG93,93}       | SUMO2, UBE2I | small ubiquitin like modifier 2, ubiquitin conjugating enzyme E2 I | 147        | 183.78         |
| MO000481046 | Ubc9(h){aceK65}                       | UBE2I        | ubiquitin conjugating enzyme E2 I                                  | 295        | 183.78         |

The intracellular regulatory pathways controlled by the above-mentioned master regulators are depicted in Figure 5. This diagram displays the connections between identified transcription factors, which play important roles in the regulation of genes carrying sequence variations, and selected master regulators, which are responsible for the regulation of these TFs.

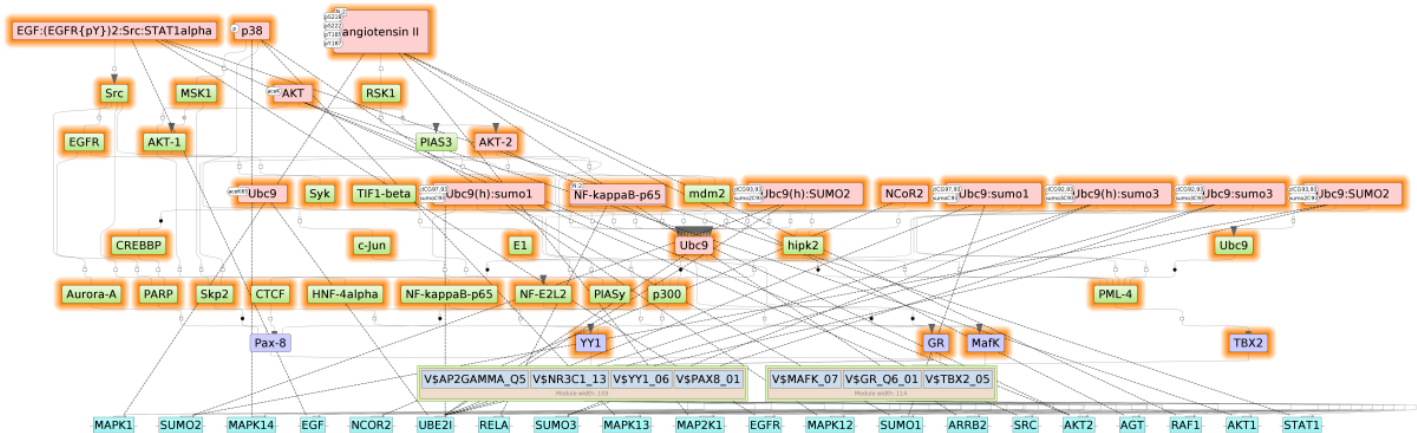


Figure 5. Diagram of intracellular regulatory signal transduction pathways of the most frequently mutated genes in Experiment: short-term survival. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have been added to the network during the search for master regulators from selected TFs. Orange frames highlight molecules presented in original mapping.

See full diagram →

#### 4. Finding prospective drug targets

The identified master regulators that may govern pathology associated genes were checked for druggability potential using HumanPSD™ [11] database of gene-disease-drug assignments and PASS [12-14] software for prediction of biological activities of chemical compounds on the basis of a (Q)SAR approach. Respectively, for each master regulator protein we have computed two Druggability scores: HumanPSD Druggability score and PASS Druggability score. Where Druggability score represents the number of drugs that are potentially suitable for inhibition (or activation) of the corresponding target either according to the information extracted from medical literature (from HumanPSD™ database) or according to cheminformatics predictions of compounds activity against the examined target (from PASS software).

The cheminformatics druggability check is done using a pre-computed database of spectra of biological activities of chemical compounds from a library of all small molecular drugs from HumanPSD™ database, 2507 pharmaceutically active known chemical compounds in total. The spectra of biological activities has been computed using the program PASS [12-14] on the basis of a (Q)SAR approach.

If both Druggability scores were below defined thresholds (see Methods section for the details) such master regulator proteins were not used in further analysis of drug prediction.

As a result we created the following two tables of prospective drug targets (top targets are shown here):

Table 9. Prospective drug targets selected from full list of identified master regulators filtered by Druggability score from HumanPSD™ database. **Druggability score** contains the number of drugs that are potentially suitable for inhibition (or activation) of the target. The drug targets are sorted according to the **Total rank** which is the sum of three ranks computed on the basis of the three scores: keynode score, CMA score and expression change score (logFC, if present). See Methods section for details.

See full table →

| Gene symbol | Gene Description                             | Druggability score | Total rank | Weighted score |
|-------------|----------------------------------------------|--------------------|------------|----------------|
| PDGFRB      | platelet derived growth factor receptor beta | 60                 | 242        | 108.52         |
| YY1         | YY1 transcription factor                     | 4                  | 293        | 66.12          |
| JAK1        | Janus kinase 1                               | 41                 | 351        | 146.11         |
| PRKCD       | protein kinase C delta                       | 31                 | 367        | 67.74          |
| VHL         | von Hippel-Lindau tumor suppressor           | 2                  | 407        | 293.02         |
| BRCA1       | BRCA1 DNA repair associated                  | 10                 | 417        | 117.01         |

 **Table 10.** Prospective drug targets selected from full list of identified master regulators filtered by Druggability score predicted by **PASS** software. Here, the **Druggability score** for master regulator proteins is computed as a sum of PASS calculated probabilities to be active as a target for various small molecular compounds. The drug targets are sorted according to the **Total rank** which is the sum of three ranks computed on the basis of the three scores: keynode score, CMA score and expression change score (logFC, if present). See Methods section for details.

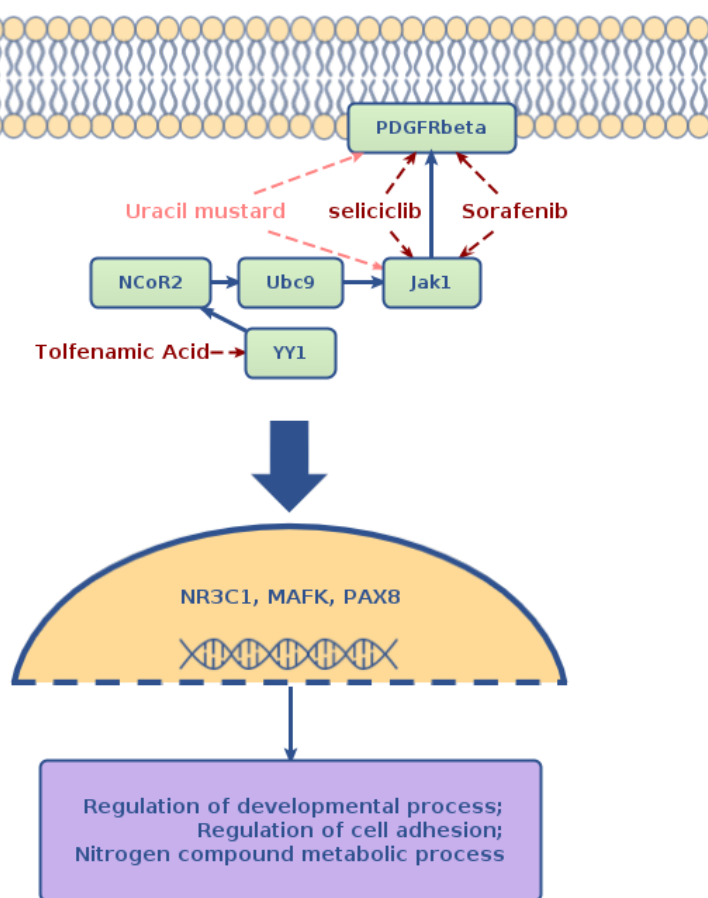
See full table →

| Gene symbol | Gene Description                             | Druggability score | Total rank | Weighted score |
|-------------|----------------------------------------------|--------------------|------------|----------------|
| PDGFRB      | platelet derived growth factor receptor beta | 8.9                | 242        | 108.52         |
| JAK1        | Janus kinase 1                               | 1.67               | 351        | 146.11         |
| PRKCD       | protein kinase C delta                       | 15.39              | 367        | 67.74          |
| BRCA1       | BRCA1 DNA repair associated                  | 17.24              | 417        | 117.01         |
| RPS6KA1     | ribosomal protein S6 kinase A1               | 4.17               | 458        | 74.63          |
| INSR        | insulin receptor                             | 3.03               | 465        | 104.22         |

Below we represent schematically the main mechanism of the studied pathology. In the schema we considered the top two drug targets of each of the two categories computed above. In addition we have added two top identified master regulators for which no drugs may be identified yet, but that are playing the crucial role in the molecular mechanism of the studied pathology. Thus the molecular mechanism of the studied pathology was predicted to be mainly based on the following key master regulators:

- Jak1
- Ubc9
- NCoR2
- YY1
- PDGFRbeta

This result allows us to suggest the following schema of affecting the molecular mechanism of the studied pathology:



Drugs which are shown on this schema: Sorafenib, Tolfenamic Acid, Uracil mustard and seliciclib, should be considered as a prospective research initiative for further drug repurposing and drug development. These drugs were selected as top matching treatments to the most prospective drug targets of the studied pathology, however, these results should be considered with special caution and are to be used for research purposes only, as there is not enough clinical information for adapting these results towards immediate treatment of patients. The drugs given in dark red color on the schema are FDA approved drugs or drugs which have gone through various phases of clinical trials as active treatments against the selected targets.

The drugs given in pink color on the schema are drugs, which were cheminformatically predicted to be active against the selected targets.

## 5. Identification of potential drugs

In the last step of the analysis we strived to identify known activities as well as drugs with cheminformatically predicted activities that are potentially suitable for inhibition (or activation) of the identified molecular targets in the context of specified human diseases(s).

Proposed drugs are top ranked drug candidates, that were found to be active on the identified targets and were selected from 4 categories:

1. FDA approved drugs or used in clinical trials drugs for the studied pathology;
2. Repurposing drugs used in clinical trials for other pathologies;
3. Drugs, predicted by PASS to be active against identified drug targets and against the studied pathology;
4. Drugs, predicted by PASS to be active against identified drug targets but for other pathologies.

Proposed drugs were selected on the basis of Drug rank which was computed from the ranks sum based on the individual ranks of the following scores:

- Target activity score (depends on ranks of all targets that were found for the selected drug);
- Disease activity score (weighted sum of number of clinical trials on disease(s) under study where the selected drug is known to be applied or PASS Disease activity score - cheminformatically predicted property of the compound to be active against the studied disease(s));
- Clinical validity score (applicable only for drugs predicted on the basis of literature curation in HumanPSD™ database (Tables 12 and 13), reflects the number of the highest clinical trials phase on which the drug was tested for any pathology).

You can refer to the Methods section for more details on drug ranking procedure.

Based on the Drug rank, a numerical value of Drug score was calculated, which reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. Drug score values belong to the range from 1 to 100 and are calculated as a quotient of maximum drug rank and the drug rank of the given drug multiplied by 100.

If sufficient information regarding the known associations between predicted drugs and variants identified in the studied pathology was found, this will be reflected in the **Somatic variants** column of the FDA approved and repurposed drugs used in clinical trials tables. Details on these variant-drug associations can be found in the [Molecular Tumor Board \(MTB\) report](#) generated for the studied pathology.

Top drugs of each category are given in the tables below:

## Drugs approved in clinical trials for Oncology



Table 11. Clinically approved (FDA, ENA, etc.) drugs for the studied pathology (most promising and clinically approved treatment candidates selected for the identified drug targets on the basis of literature curation in [HumanPSD™](#) database)

[See full table](#) →

| Name         | Target names                                                                                                                        | Drug score | Disease activity score | Disease trial phase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Approved                                                                                                                                        |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------|------------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Regorafenib  | KIT, MAPK1, ABL1, KDR, FGFR2, PDGFRB, FGFR1, BRAF, PDGFRA, RAF1, FLT4, FRS2, MAPK11, EPHA2, FLT1, AKT1, DDR2, TEK, MAPK3, RET, AKT2 | 95         | 6                      | Phase 3: Colorectal Neoplasms, Carcinoma, Hepatocellular, Gastrointestinal Stromal Tumors, Glioblastoma, Neoplasm Metastasis, Neoplasms, Parkinson Disease, Rectal Neoplasms, Recurrence, Spinocerebellar Degenerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Colorectal Neoplasms (FDA)                                                                                                                      |
| encorafenib  | MAPK10, MAPK1, MAPK8, MAPK9, MAPK7, MAPK6, LIMK1, BRAF, MAPK3, MAP2K4, RAF1                                                         | 86         | 5                      | Phase 3: Colorectal Neoplasms, Biliary Tract Neoplasms, Colonic Diseases, Colonic Neoplasms, Digestive System Diseases, Digestive System Neoplasms, Gastrointestinal Diseases, Gastrointestinal Neoplasms, Intestinal Diseases, Intestinal Neoplasms, Melanoma, Neoplasm Metastasis, Neoplasms, Rectal Diseases, Rectal Neoplasms, Skin Diseases, Skin Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, FDA)                                                                                      |
| Oxaliplatin  | CTNNB1, IGF2, CDH1, AKT1, AKT2                                                                                                      | 84         | 11                     | Phase 4: Colorectal Neoplasms, Colonic Neoplasms, Gastrointestinal Neoplasms, Intestinal Neoplasms, Neoplasms, Postoperative Complications, Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Colorectal Neoplasms (FDA, PUBMED)                                                                                                              |
| Fluorouracil | IL11, IL6R, ERCC1, CASP8, CASP3, BAX, FAS, BIRC5, CDKN1A                                                                            | 81         | 11                     | Phase 4: Colorectal Neoplasms, Bowen's Disease, Breast Neoplasms, Carcinoma, Carcinoma, Basal Cell, Carcinoma, Squamous Cell, Dermatitis, Dermatitis, Atopic, Gastrointestinal Neoplasms, Glaucoma, Head and Neck Neoplasms, Intestinal Neoplasms, Keratosis, Keratosis, Actinic, Liver Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms by Site, Neoplasms, Basal Cell, Neoplasms, Squamous Cell, Photosensitivity Disorders, Postoperative Complications, Psoriasis, Pterygium, Rectal Neoplasms, Skin Diseases, Skin Neoplasms, Vitiligo                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials)                                           |
| fruquintinib | KDR, FLT1, FLT4                                                                                                                     | 77         | 3                      | Phase 2: Colorectal Neoplasms, Breast Neoplasms, Burkitt Lymphoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Squamous Cell, Esophageal Neoplasms, Esophageal Squamous Cell Carcinoma, Hodgkin Disease, Lymphoma, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Neoplasms, Rectal Neoplasms, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Triple Negative Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Colorectal Neoplasms (FDA)                                                                                                                      |
| Aflibercept  | VEGFA, NOS3, PGF                                                                                                                    | 74         | 4                      | Phase 2: Colorectal Neoplasms, Angioid Streaks, Astrocytoma, Brain Neoplasms, Carcinoid Tumor, Carcinoma, Merkel Cell, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Central Nervous System Neoplasms, Central Serous Chorioretinopathy, Colonic Neoplasms, Diabetes Mellitus, Diabetic Retinopathy, Edema, Esophageal Neoplasms, Esophageal Squamous Cell Carcinoma, Eye Diseases, Glioblastoma, Hemorrhage, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Macular Degeneration, Macular Edema, Melanoma, Neoplasm Metastasis, Neoplasms, Nervous System Neoplasms, Pseudoxanthoma Elasticum, Pterygium, Rectal Neoplasms, Retinal Degeneration, Retinal Diseases, Retinal Vein Occlusion, Retinitis, Retinitis Pigmentosa, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Uterine Cervical Neoplasms, Vision Disorders, Vision, Low, Vitreous Hemorrhage, Wet Macular Degeneration, Xanthomatosis | Colorectal Neoplasms (FDA)                                                                                                                      |
| Irinotecan   | MAPK10, BIRC5, TOP1, RUNX3, CDKN1A                                                                                                  | 70         | 12                     | Phase 4: Colorectal Neoplasms, Neoplasms, Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA) |
| Bevacizumab  | FCGR2A, VEGFA, FCGR2B                                                                                                               | 60         | 12                     | Phase 4: Colorectal Neoplasms, Carcinoma, Ovarian Epithelial, Cataract, Corneal Diseases, Diabetic Retinopathy, Dilatation, Pathologic, Edema, Epistaxis, Fallopian Tube Neoplasms, Fibrosis, Glaucoma, Hemorrhage, Hypertension, Macular Edema, Neoplasm Metastasis, Neoplasms, Ocular Hypertension, Optic Nerve Diseases, Ovarian Neoplasms, Peritoneal Neoplasms, Pterygium, Rectal Neoplasms, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis, Vitreous Hemorrhage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Colorectal Neoplasms (FDA, FDA)                                                                                                                 |
| Cetuximab    | FCGR2A, EGFR, FCGR2B                                                                                                                | 45         | 11                     | Phase 4: Colorectal Neoplasms, Head and Neck Neoplasms, Liver Neoplasms, Neoplasm Metastasis, Neoplasms, Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Colorectal Neoplasms (FDA, FDA)                                                                                                                 |
| Panitumumab  | EGFR                                                                                                                                | 29         | 6                      | Phase 3: Colorectal Neoplasms, Neoplasm Metastasis, Neoplasms, Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Colorectal Neoplasms (FDA)                                                                                                                      |
| Capecitabine | CDKN2A                                                                                                                              | 26         | 11                     | Phase 4: Colorectal Neoplasms, Breast Neoplasms, Head and Neck Neoplasms, Neoplasms, Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)                                                 |

The **Disease trial phase** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

## Drugs approved in clinical trials



Table 12. Drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)  
See full table →

| Name      | Target names                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Drug score | Disease activity score | Disease trial phase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sorafenib | <p>BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, HIPK3, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, HUNK, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBF1, MAPKAPK3, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNK1, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RIPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBF2, DYRK2, FYN, PRKD2, RPS6KA4</p> | 98         | 3                      | <p>Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenocarcinoma, Follicular, Adenoma, Adenoma, Liver Cell, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Bile Duct Neoplasms, Biliary Tract Neoplasms, Brain Abscess, Brain Neoplasms, Burkitt Lymphoma, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Islet Cell, Carcinoma, Medullary, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Desmoplastic Small Round Cell Tumor, Gallbladder Neoplasms, Gastrinoma, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Glucagonoma, Head and Neck Neoplasms, Hemangiopericytoma, Hemangiosarcoma, Hepatitis, Hepatitis B, Hepatitis C, Hepatopulmonary Syndrome, Hodgkin Disease, Insulinoma, Kidney Diseases, Kidney Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Monocytic, Acute, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Chronic, Liposarcoma, Liver Neoplasms, Lymphoma, Lymphoma, B-Cell, Lymphoma, B-Cell, Marginal Zone, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Immunoblastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Cutaneous, Melanoma, Mesothelioma, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 2a, Multiple Endocrine Neoplasia Type 2b, Multiple Myeloma, Mycosis Fungoides, Myelodysplastic Syndromes, Myeloproliferative Disorders, Myosarcoma, Neoplasm Metastasis, Neoplasms, Neoplasms, Plasma Cell, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurologic Manifestations, Osteosarcoma, Pancreatic Neoplasms, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Sarcoma, Sezary Syndrome, Somatostatinoma, Thyroid Cancer, Papillary, Thyroid Diseases, Thyroid Neoplasms, Urinary Bladder Neoplasms, Vipoma, Waldenstrom Macroglobulinemia</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Sunitinib | <p>BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, HUNK, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBF1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, SIRT3, PRKCA, CSNK1E, SIRT2, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNK1, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, SIRT1, TGFBF2, FYN, PRKD2, RPS6KA4</p>                                                                                    | 98         | 3                      | <p>Phase 2: Colorectal Neoplasms, Acquired Immunodeficiency Syndrome, Adenocarcinoma, Adenocarcinoma, Bronchiolo-Alveolar, Adenoma, Adenoma, Islet Cell, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Ascites, Astrocytoma, Barrett Esophagus, Blast Crisis, Bone Neoplasms, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Carcinoma, Carcinoma, Embryonal, Carcinoma, Hepatocellular, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Transitional Cell, Central Nervous System Neoplasms, Chondrosarcoma, Colonic Neoplasms, Congenital Abnormalities, Cysts, Dermatofibrosarcoma, Desmoplastic Small Round Cell Tumor, Digestive System Diseases, Digestive System Neoplasms, Dysgerminoma, Endocrine Gland Neoplasms, Endocrine System Diseases, Endometrial Sinus Tumor, Endometrial Neoplasms, Esophageal Neoplasms, Fibroma, Fibromatosis, Aggressive, Fibrosarcoma, Fibrosis, Gastrointestinal Stromal Tumors, Germinoma, Glioblastoma, Glioma, Gliosarcoma, Hemangioblastoma, Hemangiopericytoma, Hemangiosarcoma, Hematologic Neoplasms, Histiocytoma, Histiocytoma, Malignant Fibrous, Hyperkalemia, Hyperoxaluria, Hyperoxaluria, Primary, Kidney Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Biphenotypic, Acute, Leukemia, Hairy Cell, Leukemia, Large Granular Lymphocytic, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Mast-Cell, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Accelerated Phase, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Chronic, Leukemia, Polymorphocytic, Liposarcoma, Liver Diseases, Liver Neoplasms, Lung Neoplasms, Lymphoma, Lymphoma, Non-Hodgkin, Melanoma, Meningioma, Multiple Myeloma, Myelodysplastic Syndromes, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Germ Cell and Embryonal, Neoplasms, Glandular and Epithelial, Neoplasms, Hormone-Dependent, Neoplasms, Nerve Tissue, Nervous System Neoplasms, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurofibroma, Neurofibromatosis, Neurofibromatosis 1, Neurofibromatosis 2, Neurofibrosarcoma, Osteosarcoma, Ovarian Neoplasms, Pancreatic Diseases, Pancreatic Neoplasms, Paraganglioma, Pathologic Processes, Pheochromocytoma, Pica, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Primary Myelofibrosis, Prostatic Neoplasms, Ranula, Rectal Neoplasms, Rhabdomyosarcoma, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Endometrial Stromal, Sarcoma, Kaposi, Sarcoma, Synovial, Seminoma, Small Cell Lung Carcinoma, Spina Bifida Occulta, Stomach Neoplasms, Teratoma, Testicular Neoplasms, Thymoma, Thymus Neoplasms, Thyroid Neoplasms, Urinary Bladder Neoplasms, Uterine Cervical Neoplasms, Uterine Neoplasms, von Hippel-Lindau Disease</p> |
| Vatalanib | <p>BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBF1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7,</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 97         | 3                      | <p>Phase 3: Colorectal Neoplasms, Colonic Neoplasms, Neoplasms, Rectal Neoplasms</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

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|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           | <p>MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, CDK1, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, HLA-A, TGFB2, FYN, PRKD2, RPS6KA4</p>                                                                                                                                                                                                                                                                                                                                                                                                             |    |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Erlotinib | <p>BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFB1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BIRC5, BMX, ERBB3, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K1, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, ILK, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, ERBB4, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFB2, FYN, PRKD2, NR1I2, RPS6KA4</p> | 96 | 2 | <p>Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenocarcinoma, Bronchiolo-Alveolar, Adenoma, Adenomatous Polyposis Coli, Adenomatous Polyps, Adrenal Gland Neoplasms, Astrocytoma, Biliary Tract Neoplasms, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Brenner Tumor, Carcinoid Tumor, Carcinoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Contracture, Diffuse Intrinsic Pontine Glioma, Digestive System Diseases, Ependymoma, Esophageal Diseases, Esophageal Neoplasms, Fallopian Tube Neoplasms, Fibrosarcoma, Glioblastoma, Glioma, Gliosarcoma, Head and Neck Neoplasms, Hyperkeratosis, Epidermolytic, Keratoderma, Palmoplantar, Keratosis, Laryngeal Neoplasms, Leukemia, Leukemia, Myelomonocytic, Acute, Lung Neoplasms, Lymphoma, Lymphoma, Non-Hodgkin, Melanoma, Mesothelioma, Multiple Endocrine Neoplasia, Multiple Myeloma, Nails, Malformed, Neoplasm Metastasis, Neoplasms, Neoplasms, Unknown Primary, Neuroblastoma, Neuroendocrine Tumors, Neurofibrosarcoma, Oligodendroglioma, Ovarian Neoplasms, Pachyonychia Congenita, Pancreatic Neoplasms, Paraganglioma, Paranasal Sinus Neoplasms, Pharyngeal Neoplasms, Pheochromocytoma, Polycythemia, Polycythemia Vera, Polyps, Psoriasis, Rectal Neoplasms, Sarcoma, Small Cell Lung Carcinoma, Thymoma, Thymus Neoplasms, Urinary Bladder Neoplasms</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Dasatinib | <p>BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFB1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, STAT5B, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, BCR, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFB2, FYN, PRKD2, RPS6KA4</p>                      | 95 | 2 | <p>Phase 2: Colorectal Neoplasms, Aging, Aging, Premature, Alzheimer Disease, Astrocytoma, Blast Crisis, Brain Abscess, Brain Stem Neoplasms, Breast Neoplasms, Bronchiolitis, Bronchiolitis Obliterans, Bronchiolitis Obliterans Syndrome, Burkitt Lymphoma, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Transitional Cell, Central Nervous System Neoplasms, Cholangiocarcinoma, Chondrosarcoma, Chordoma, Choroid Plexus Neoplasms, Cognitive Dysfunction, Colonic Neoplasms, Dendritic Cell Sarcoma, Interdigitating, Depressive Disorder, Depressive Disorder, Treatment-Resistant, Diffuse Intrinsic Pontine Glioma, Endometrial Neoplasms, Ependymoma, Esophageal Neoplasms, Fibrosarcoma, Frailty, Gastrointestinal Stromal Tumors, Germinoma, Giant Cell Tumor of Bone, Giant Cell Tumors, Glioblastoma, Glioma, Hemangiopericytoma, Hematologic Neoplasms, Hyper eosinophilic Syndrome, Immunoblastic Lymphadenopathy, Kidney Neoplasms, Leukemia, Leukemia, B-Cell, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Chronic, Leukemia, Prolymphocytic, Liver Neoplasms, Lung Neoplasms, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Non-Hodgkin, Mastocytosis, Medulloblastoma, Melanoma, Multiple Myeloma, Myelodysplastic Syndromes, Myosarcoma, Neoplasms, Neoplasms, Germ Cell and Embryonal, Nephroma, Mesoblastic, Nervous System Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neurofibrosarcoma, Oligodendroglioma, Optic Nerve Glioma, Osteosarcoma, Ovarian Neoplasms, Pancreatic Neoplasms, Polycythemia, Polycythemia Vera, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Primary Myelofibrosis, Prostatic Neoplasms, Rectal Neoplasms, Recurrence, Rhabdoid Tumor, Rhabdomyosarcoma, Rhabdomyosarcoma, Alveolar, Rhabdomyosarcoma, Embryonal, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Ewing, Schizophrenia, Solitary Fibrous Tumors, Spinal Cord Neoplasms, Stomach Neoplasms, Teratoma, Testicular Neoplasms, Thyroid Neoplasms, Triple Negative Breast Neoplasms, Urinary Bladder Neoplasms, Uterine Cervical Neoplasms, Uterine Neoplasms, Wilms Tumor</p> |

The **Disease trial phase** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

## Repurposing drugs



Table 13. Repurposed drugs used in clinical trials for other pathologies (prospective drugs against the identified drug targets on the basis of literature curation in HumanPSD™ database)

[See full table](#) →

| Name                                                                                            | Target names                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Drug score | Maximum trial phase                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| seliciclib                                                                                      | BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, HIPK3, MAP3K11, CDK4, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, MAPKAPK3, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, CDK1, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, DYRK2, FYN, PRKD2, RPS6KA4 | 92         | Phase 2: Cystic Fibrosis, Cysts                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea | BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, HIPK3, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, MAPKAPK3, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, DYRK2, FYN, PRKD2, RPS6KA4             | 91         | Phase 2: Arthritis, Arthritis, Rheumatoid, Psoriasis                                                                                                                                                                                                                                                                                                                                                                                                    |
| pi-103                                                                                          | BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, HIPK3, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, MAPKAPK3, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, DYRK2, FYN, PRKD2, RPS6KA4             | 91         | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| ruboxistaurin                                                                                   | BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, HIPK3, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, MAPKAPK3, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, DYRK2, FYN, PRKD2, RPS6KA4             | 91         | Phase 3: Diabetes Mellitus, Diabetes Mellitus, Type 1, Diabetic Retinopathy                                                                                                                                                                                                                                                                                                                                                                             |
| Flavopiridol                                                                                    | BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, CDK4, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, PIK3CB, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, CDK6, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, XIAP, MAP3K4, PAK1, CLK1, CDK5, NLK, PRKACB, RET, ABL2, CSF1R, PRKX, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, STK26, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, CDK1, LATS1, MAP2K4, PRKAA1, RPS6KA1,                                                                                                                                                                                                                                                                                                                | 91         | Phase 2: Burkitt Lymphoma, Carcinoma, Squamous Cell, Embolism, Head and Neck Neoplasms, Leukemia, Leukemia, Lymphoid, Lymphoma, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Immunoblastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Neoplasms, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Salivary Gland Neoplasms, Sarcoma, Squamous Cell Carcinoma of Head and Neck, Thromboembolism, Tumor Lysis Syndrome |

FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFB2, FYN, PRKD2, RPS6KA4

The **Maximum trial phase** column reflects the maximum clinical trials phase in which the drug was studied for any pathology.



Table 14. Prospective drugs, predicted by **PASS** software to be active against the identified drug targets with predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool PASS)

[See full table →](#)

| Name         | Target names                            | Drug score | Target activity score |
|--------------|-----------------------------------------|------------|-----------------------|
| LE-SN38      | HIF1A, TOP2A, CASP3, NFKB1, TOP1, TOP2B | 91         | 3.32                  |
| Camptothecin | HIF1A, TOP2A, CASP3, NFKB1, TOP1, TOP2B | 91         | 3.28                  |
| Topotecan    | HIF1A, TOP2A, CASP3, NFKB1, TOP1, TOP2B | 90         | 3.08                  |
| BNP 1350     | TOP2A, NFKB1, TOP1, TOP2B               | 87         | 2.16                  |
| Irinotecan   | HIF1A, TOP2A, TOP1, TOP2B               | 85         | 1.93                  |



Table 15. Prospective drugs, predicted by **PASS** software to be active against the identified drug targets, though without cheminformatically predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool PASS)

[See full table →](#)

| Name                                                                        | Target names                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Drug score | Target activity score |
|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------------|
| 2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One                                      | IRAK3, PAK2, SENP8, CDK4, SGK1, EPHA1, MAP2K3, CAMK2B, LIMK1, PKN1, MAP2K6, MAPK8, MAPKAPK3, PRKD3, CSNK1G2, DYRK1A, HSP90AB1, CLK4, CSNK1G1, CAMK2A, IRAK1, CHEK2, FES, AKT2, DAPK3, MAPK10, RPS6KA3, IRAK4, CDK6, CAMK2G, CSNK1A1, STAT1, EPHA4, CSNK1E, CDK1, MAP2K4, AURKB, CDK7, PRKAA1, HSP90AA1, CSNK1D, EE2F2K, PTK2B, AKT1, AURKA, CHEK1, MAPK9, EPHB2, DYRK1B, GSK3A, PAK4, EPHA3, PAK3, CAMK2D, EPHB1, SGK2, PAK1, CLK1, CDK5, DYRK2, RPS6KA4                                                                                                                                                                                                                                                                                                                | 96         | 20.25                 |
| Iodophenyl                                                                  | EIF2AK3, NEK7, PAK2, GSK3B, HIPK3, VRK1, NEK3, NEK6, EIF2AK2, LIMK1, HUNK, MELK, UHMK1, MAPKAPK3, RPS6KB2, CSNK1G2, MAP4K1, VRK2, TRIO, STK11, OBSCN, SMG1, CSNK1G1, NEK10, KALRN, IRAK1, CSNK2A1, CHEK2, AKT2, PDPK1, STK3, IRAK4, PINK1, CSNK1A1, CSNK1E, RAF1, AURKB, CSNK1D, CHEK1, TAF1, TAOK1, ATM, RIPK2, PIM2, HIPK2, PRPF4B, RPS6KA2, PAK4, PIM3, PRKDC, NUAK1, PASK, SGK2, PAK1, CDK5, TRPM7, PRKX, STK10, ROCK2, BCR, MAK, MAP4K4, CIITA, MARK3, IRAK3, SLK, NEK2, SGK1, TAOK2, RPS6KA5, MAPKAPK5, TNIK, STK26, BUB1B, CSNK2A2, TNK2, MAP4K3, RIPK1, STK4, MAP4K2, MAPKAPK2, TAOK3, DAPK3, RPS6KA3, RIPK3, PIK3CG, LATS1, PRKAA1, RPS6KA1, ILK, MASTL, HIPK1, AKT1, AURKA, LMTK2, PKMYT1, RPS6KB1, TBK1, ATR, MTOR, GSK3A, LATS2, PAK3, BRAF, MINK1, RPS6KA4 | 96         | 42.92                 |
| Rbt205 Inhibitor                                                            | RPS6KA3, CDK6, CAMK2G, GRK2, MAP3K10, PRKCQ, PRKACA, GSK3B, PRKCA, CDK1, MAP2K4, CDK4, CDK7, RPS6KA1, PRKAA1, SGK1, PRKCH, EE2F2K, CAMK2B, MAPKAPK5, PDP1, PRKD1, PKN1, MAP2K6, RPS6KA2, MAPKAPK3, GSK3A, GRK5, PRKD3, PDP2, PRKCE, PRKCZ, CAMK2D, PTK2, CAMK2A, SIRT1, SGK2, PRKCD, PRKCI, CDK5, PRKACB, DAPK3                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 95         | 27.07                 |
| 7-[4-(Dimethylamino)Phenyl]-N-Hydroxy-4,6-Dimethyl-7-Oxo-2,4-Heptadienamide | HDAC4, HDAC2, HDAC6, HDAC7, HDAC9, HDAC3, HDAC5, HDAC1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 94         | 9.98                  |
| Uracil mustard                                                              | ABL1, FGFR2, JAK3, INSR, SYK, EPHA1, EIF2AK2, EPHA2, ERBB2, TEK, CSK, AXL, TYK2, MELK, JAK1, IGF1R, SRC, PDGFRB, TNK2, ROR2, WEE1, PTK2, FLT1, PRKCD, LYN, FES, FGFR4, MET, KDR, EPHA4, PDGFRA, FLT4, MST1R, EGFR, EPHB3, PTK2B, DDR2, PTK6, JAK2, KIT, BMX, RIPK2, ERBB3, EPHB2, FGFR3, MTOR, NTRK2, TYRO3, MERTK, EPHB4, EPHA3, YES1, FGFR1, ERBB4, FER, ITK, EPHB1, FYN, RET, CSF1R, ABL2                                                                                                                                                                                                                                                                                                                                                                            | 94         | 11.2                  |

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Sorafenib, seliciclib, LE-SN38 and 2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One. These drugs were selected for acting on the following targets: PDGFRB, TOP1 and CDK1, which were predicted to be active in the molecular mechanism of the studied pathology.

The selected drugs are top ranked drug candidates from each of the four categories of drugs: (1) FDA approved drugs or used in clinical trials drugs for the studied pathology; (2) repurposing drugs used in clinical trials for other pathologies; (3) drugs, predicted by PASS software to be active against the studied pathology; (4) drugs, predicted by PASS software to be repurposed from other pathologies.

## Supplementary drug info

In addition to the approved and repurposed drugs proposed by Genome Enhancer, below the **Supplementary drug info** table is given, which contains an extended list of drugs used for treatment of neoplasms. Those drugs which were predicted by Genome Enhancer as prospective treatment candidates for the studied case (both approved and repurposed) have a respective **Predicted Drug Score** assigned to them. This value on a scale from 1 to 100 reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. The **Predicted Drug Score** column contains the "-" (Not Identified) value in case the drug targets of the respective treatment were not found in the molecular mechanism of the studied pathology.

Table 16. Supplementary drug info: extended list of drugs used for treatment of neoplasms with respective drug scores predicted for the studied pathology.

| Drug                 | Disease                                                                                                                                                                                                                                                                                                                                                                                                                             | Predicted Drug Score | Somatic variants |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------|
| Abarelix             | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                 | 10                   |                  |
| abemaciclib          | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                    | 62                   |                  |
| Abiraterone          | Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                           | -                    |                  |
| abiraterone acetate  | Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                       | -                    |                  |
| acalabrutinib        | Lymphoma, Mantle-Cell                                                                                                                                                                                                                                                                                                                                                                                                               | 42                   |                  |
| Acetaminophen        | Acute Pain Arthritis Back Pain Brain Injuries Common Cold Dysmenorrhea Fever Headache Hernia, Abdominal Hypertension Infections Influenza, Human Menigitis, Bacterial Migraine Disorders Muscle Cramp Nausea Neoplasms Obesity Obesity, Morbid Osteoarthritis Osteoarthritis, Knee Pain Pharyngitis Postoperative Nausea and Vomiting Streptococcal Infections Thrombotic Stroke Tonsillitis Toothache Vomiting Wounds and Injuries | 43                   |                  |
| Acetylsalicylic acid | Acute Coronary Syndrome Arthritis Asthma Atherosclerosis Atrial Fibrillation Back Pain Cardiovascular Diseases Cerebral Infarction Common Cold Coronary Artery Disease Coronary Disease Diabetes Mellitus Diabetes Mellitus, Type 2 Dysmenorrhea Fever Headache Heart Diseases Heart Failure Hypertension Internal                                                                                                                  | 82                   |                  |

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                                   | Hernia Ischemia Migraine Disorders Muscle Cramp Myalgia Myocardial Infarction Myocardial Ischemia Neoplasms Pain Peptic Ulcer Periodontitis Placental Insufficiency Pre-Eclampsia Scleroderma, Diffuse Scleroderma, Systemic Sclerosis Spasm ST Elevation Myocardial Infarction Stroke Thrombosis Toothache Ulcer Vascular Diseases                                                                                                                                         |    |
| ado-trastuzumab emtansine         | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 83 |
| Afatinib                          | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                              | 82 |
| afatinib dimaleate                | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| Aflibercept                       | Colorectal Neoplasms Macular Degeneration Macular Edema Retinal Detachment Retinal Diseases Retinal Vein Occlusion Wet Macular Degeneration                                                                                                                                                                                                                                                                                                                                 | 74 |
| Aldesleukin                       | Carcinoma Carcinoma, Renal Cell Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                    | 41 |
| Alectinib                         | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                              | 77 |
| Alemtuzumab                       | Leukemia, Lymphocytic, Chronic, B-Cell Nerve Degeneration                                                                                                                                                                                                                                                                                                                                                                                                                   | -  |
| Alfuzosin                         | Prostatic Hyperplasia                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| Alitretinoin                      | Sarcoma, Kaposi                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 59 |
| Allopurinol                       | Bipolar Disorder Colitis-Associated Neoplasms Diabetes Mellitus Gout Heart Failure Hypertension Hyperuricemia Internal Hernia Ischemia Leukemia Lymphoma Neoplasms Response Evaluation Criteria in Solid Tumors Stroke                                                                                                                                                                                                                                                      | -  |
| alpelisib                         | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Altretamine                       | Ovarian Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| Amifostine                        | Head and Neck Neoplasms Neoplasms Ovarian Neoplasms Xerostomia                                                                                                                                                                                                                                                                                                                                                                                                              | 61 |
| Aminoglutethimide                 | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -  |
| amivantamab                       | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                              | 56 |
| Amphotericin B                    | Aspergillosis Candidiasis Candidiasis, Invasive Cryptococcosis Histoplasmosis Infections Leishmaniasis Leishmaniasis, Visceral Leukemia Meningitis, Cryptococcal Mucormycosis Mycoses Sporotrichosis Zygomycosis                                                                                                                                                                                                                                                            | -  |
| Amsacrine                         | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 43 |
| Anastrozole                       | Breast Neoplasms Endometriosis Hypogonadism Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                       | 51 |
| apalutamide                       | Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                                                   | 15 |
| Aprepitant                        | Breast Neoplasms Nausea Neoplasms Postoperative Nausea and Vomiting Vomiting                                                                                                                                                                                                                                                                                                                                                                                                | -  |
| Aripiprazole                      | Alcoholism Alzheimer Disease Anxiety Attention Deficit Disorder with Hyperactivity Autistic Disorder Bipolar Disorder Child Development Disorders, Pervasive Colitis-Associated Neoplasms Depressive Disorder Depressive Disorder, Major Psychotic Disorders Schizophrenia Tourette Syndrome Weight Loss                                                                                                                                                                    | -  |
| Arsenic trioxide                  | Leukemia, Promyelocytic, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                              | 81 |
| arzoxifene                        | Endometrial Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 20 |
| asciminib                         | Leukemia, Myelogenous, Chronic, BCR-ABL Positive                                                                                                                                                                                                                                                                                                                                                                                                                            | 53 |
| Asparaginase Erwinia chrysanthemi | Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| atezolizumab                      | Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell Triple Negative Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                | -  |
| avapritinib                       | Gastrointestinal Stromal Tumors Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                   | 73 |
| avelumab                          | Carcinoma, Merkel Cell Carcinoma, Renal Cell Carcinoma, Transitional Cell                                                                                                                                                                                                                                                                                                                                                                                                   | -  |
| Avobenzone                        | Melanosis Skin Neoplasms Sunburn                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Axitinib                          | Carcinoma, Renal Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 93 |
| Azacitidine                       | Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes                                                                                                                                                                                                                                                                                                                                           | 71 |
| Azithromycin                      | Asthma Blepharitis Bronchiectasis Bronchiolitis Bronchiolitis Obliterans Bronchopulmonary Dysplasia Chlamydia Infections COVID-19 Cystic Fibrosis Diarrhea Endometritis Eye Diseases Fever Gonorrhea Infections Lung Diseases Malnutrition Mycobacterium avium-intracellulare Infection Otitis Media Pharyngitis Pneumonia Premature Birth Pulmonary Disease, Chronic Obstructive Sepsis Sinusitis Skin Diseases, Infectious Tonsillitis Urethritis Uterine Cervicitis Yaws | -  |
| belantamab mafodotin              | Multiple Myeloma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -  |
| Belinostat                        | Lymphoma, T-Cell, Peripheral                                                                                                                                                                                                                                                                                                                                                                                                                                                | 86 |
| belzutifan                        | Carcinoma, Renal Cell Hemangioblastoma Neuroendocrine Tumors von Hippel-Lindau Disease                                                                                                                                                                                                                                                                                                                                                                                      | 45 |
| Bendamustine                      | Leukemia Leukemia, Lymphocytic, Chronic, B-Cell                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Bevacizumab                       | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 60 |
| Bexarotene                        | Lymphoma Lymphoma, T-Cell, Cutaneous                                                                                                                                                                                                                                                                                                                                                                                                                                        | 68 |
| Bicalutamide                      | Neoplasms Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                               | 68 |
| binimetinib                       | Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 57 |
| Blinatumomab                      | Precursor B-Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Bortezomib                        | Multiple Myeloma Neoplasms Renal Insufficiency, Chronic                                                                                                                                                                                                                                                                                                                                                                                                                     | 75 |
| Bosutinib                         | Leukemia, Myelogenous, Chronic, BCR-ABL Positive                                                                                                                                                                                                                                                                                                                                                                                                                            | 83 |
| Brentuximab vedotin               | Hodgkin Disease Lymphoma, Large-Cell, Anaplastic Lymphoma, T-Cell, Peripheral                                                                                                                                                                                                                                                                                                                                                                                               | -  |
| brigatinib                        | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                              | 74 |
| Bupivacaine                       | Anesthesia Ankle Fractures Appendicitis Brain Neoplasms Dwarfism Fractures, Bone Hallux Valgus Headache Hemorrhage Hemorrhoids Hernia Hernia, Inguinal Hypotension Migraine Disorders Neoplasms Neuralgia Obesity Obesity, Morbid Opioid-Related Disorders Osteoarthritis Osteoarthritis, Hip Osteoarthritis, Knee Pain Rib Fractures Rotator Cuff Injuries Thoracic Injuries Thrombotic Stroke Wounds and Injuries                                                         | 47 |
| Bupropion                         | Alcoholism Attention Deficit Disorder with Hyperactivity Depressive Disorder Depressive Disorder, Major Lung Neoplasms Mood Disorders Neoplasms Schizophrenia Substance-Related Disorders Tobacco Use Disorder                                                                                                                                                                                                                                                              | -  |
| Buserelin                         | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Busulfan                          | Leukemia Leukemia, Myelogenous, Chronic, BCR-ABL Positive Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Cabazitaxel                       | Neoplasms Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                     | 81 |

|                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |    |                                     |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-------------------------------------|
| Cabergoline            | Infertility Infertility, Female Pituitary Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 18 |                                     |
| Cabozantinib           | Thyroid Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 84 |                                     |
| Capecitabine           | Adenocarcinoma Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms Neoplasms Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 26 |                                     |
| capiasertib            | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 90 |                                     |
| capmatinib             | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 87 |                                     |
| Carbamazepine          | Bipolar Disorder Cocaine-Related Disorders Colitis-Associated Neoplasms Depressive Disorder Epilepsies, Partial Epilepsy Glossopharyngeal Nerve Diseases Seizures Trigeminal Neuralgia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 6  |                                     |
| Carboplatin            | Breast Neoplasms Ovarian Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | -  | XRCC1:Q399R:sensitivity/response:B2 |
| Carfilzomib            | Brain Abscess Multiple Myeloma Neoplasms Neoplasms, Plasma Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 78 |                                     |
| Carmustine             | Astrocytoma Ependymoma Glioblastoma Glioma Hodgkin Disease Medulloblastoma Multiple Myeloma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 15 |                                     |
| Celecoxib              | Arthritis, Rheumatoid Hypertension Inflammation Low Back Pain Neoplasms Osteoarthritis Osteoarthritis, Hip Osteoarthritis, Knee Rectal Neoplasms Spondylitis, Ankylosing Wounds and Injuries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 58 |                                     |
| cemiplimab             | Carcinoma, Basal Cell Carcinoma, Squamous Cell Lung Neoplasms Neoplasms Skin Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 35 |                                     |
| Ceritinib              | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 86 |                                     |
| Cetuximab              | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 45 |                                     |
| Chlorambucil           | Hodgkin Disease Neoplasms Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 26 |                                     |
| Chlorotrianisene       | Carcinoma, Hepatocellular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 28 |                                     |
| Choline C 11           | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | -  |                                     |
| Cinacalcet             | Hyperparathyroidism, Primary Hyperparathyroidism, Secondary Parathyroid Neoplasms Renal Insufficiency, Chronic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -  |                                     |
| Cladribine             | Brain Abscess Leukemia Leukemia, Hairy Cell Multiple Sclerosis Sclerosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 78 |                                     |
| Clarithromycin         | Bacterial Infections Bronchitis, Chronic Duodenal Ulcer Helicobacter Infections Infections Mycobacterium avium-intracellulare Infection Neoplasms Otitis Media Periodontitis Pharyngitis Pneumonia Sinusitis Skin Diseases, Bacterial Stomach Neoplasms Tonsillitis Tuberculosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 15 |                                     |
| Clofarabine            | Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 76 |                                     |
| Clonidine              | Attention Deficit Disorder with Hyperactivity Cardiovascular Diseases Glaucoma Hypertension Migraine Disorders Neoplasms Neuralgia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | -  |                                     |
| Cobimetinib            | Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 78 |                                     |
| copanlisib             | Lymphoma, Follicular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 87 |                                     |
| Cortisone acetate      | Addison Disease Adrenal Hyperplasia, Congenital Anemia, Aplastic Anemia, Hemolytic Arthritis, Gouty Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Bursitis Dermatitis Herpetiformis Dermatitis, Atopic Dermatitis, Contact Dermatitis, Exfoliative Dermatitis, Seborrheic Dermatomyositis Enteritis Erythema Multiforme Eye Diseases Herpes Zoster Ophthalmicus Hypercalcemia Hypersensitivity Iridocyclitis Iritis Leukemia Lupus Erythematosus, Systemic Lymphoma Nephrotic Syndrome Ophthalmia, Sympathetic Osteoarthritis Peptic Ulcer Pneumonia Polymyositis Purpura, Thrombocytopenic, Idiopathic Stevens-Johnson Syndrome Synovitis Tennis Elbow Tenosynovitis Thrombocytopenia Thyroiditis, Subacute Tuberculosis, Meningeal Tuberculosis, Pulmonary Uveitis, Posterior | 34 |                                     |
| CP-4055                | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -  |                                     |
| Crizotinib             | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 92 |                                     |
| Cyclophosphamide       | Breast Neoplasms Hodgkin Disease Lupus Nephritis Lymphoma Lymphoma, Non-Hodgkin Multiple Myeloma Neoplasms Nephrotic Syndrome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 81 |                                     |
| Cyclosporine           | Acute Kidney Injury Anemia Anemia, Aplastic Arthritis, Rheumatoid Conjunctivitis, Allergic COVID-19 Dermatitis, Atopic Diabetes Mellitus Dry Eye Syndromes Eczema Eye Diseases Graft vs Host Disease Immune System Diseases Infections Inflammation Keratoconjunctivitis Keratoconjunctivitis Sicca Leukemia Meibomian Gland Dysfunction Myelodysplastic Syndromes Neoplasms Psoriasis Pterygium Renal Insufficiency Renal Insufficiency, Chronic Stevens-Johnson Syndrome Uveitis                                                                                                                                                                                                                                                                                                                      | 77 |                                     |
| Cyproterone acetate    | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 11 |                                     |
| Cytarabine             | Leukemia Leukemia, Lymphoid Leukemia, Myeloid, Acute Leukemia, Promyelocytic, Acute Meningeal Carcinomatosis Neoplasms Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 83 |                                     |
| Dabrafenib             | Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 56 |                                     |
| Dacarbazine            | Hodgkin Disease Melanoma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 47 |                                     |
| dacomitinib            | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 84 |                                     |
| Dactinomycin           | Neoplasms Wilms Tumor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 75 |                                     |
| Daratumumab            | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | -  |                                     |
| darolutamide           | Neoplasms Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 10 |                                     |
| Dasatinib              | Leukemia Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 95 |                                     |
| Daunorubicin           | Leukemia Leukemia, Lymphoid Leukemia, Myeloid, Acute Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 53 |                                     |
| Decitabine             | Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 69 |                                     |
| Degarelix              | Neoplasms Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 69 |                                     |
| Dehydroepiandrosterone | Arthritis, Rheumatoid Dysmenorrhea Hypogonadism Infertility Klinefelter Syndrome Neoplasms Orchitis Osteoarthritis Pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 73 |                                     |
| Denileukin diftitox    | Lymphoma, T-Cell, Cutaneous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 35 |                                     |
| Dexamethasone          | Acne Vulgaris Addison Disease Adrenal Hyperplasia, Congenital Adrenal Insufficiency Adrenocortical Hyperfunction Anemia, Aplastic Anemia, Hemolytic Arthritis, Gouty Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Brain Edema Bursitis Cataract Chorioretinitis Choroiditis Colitis, Ulcerative Conjunctivitis, Allergic Corneal Injuries COVID-19 Crohn Disease Dermatitis Dermatitis Herpetiformis Dermatitis, Atopic Dermatitis, Contact Dermatitis, Exfoliative Dermatitis, Seborrheic Diabetic Retinopathy Erythema Multiforme Eye Diseases Hemorrhoids Herpes                                                                                                                                                                                                            | 89 |                                     |

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                                | Simplex Herpes Zoster<br>Ophthalmicus Hypercalcemia Infections Inflammation Iridocyclitis Iritis Keratitis Laryngeal<br>Edema Leukemia Lupus Erythematosus, Systemic Lymphoma Macular Edema Multiple<br>Myeloma Multiple Sclerosis Mycosis Fungoides Myocarditis Nasal<br>Obstruction Nausea Neoplasms Nephrotic Syndrome Ophthalmia, Sympathetic Optic<br>Neuritis Osteoarthritis Pemphigus Peptic Ulcer Pneumonia Postoperative Nausea and<br>Vomiting Psoriasis Pulmonary Eosinophilia Purpura, Thrombocytopenic,<br>Idiopathic Respiratory Insufficiency Retinal Vein Occlusion Rhinitis, Allergic Rhinitis,<br>Allergic, Seasonal Sarcoidosis Serum Sickness Spondylitis, Ankylosing Stevens-Johnson<br>Syndrome Synovitis Tennis Elbow Tenosynovitis Thrombocytopenia Thyroiditis,<br>Subacute Transfusion Reaction Trichinellosis Tuberculosis, Meningeal Tuberculosis,<br>Pulmonary Uveitis, Intermediate Uveitis, Posterior Vomiting                                                                                                                                                                                                                                                                                                                                                                                  |    |
| dexamethasone sodium phosphate | Acne Vulgaris Addison Disease Adrenal Hyperplasia, Congenital Adrenal<br>Insufficiency Anemia, Aplastic Anemia, Hemolytic Arthritis, Gouty Arthritis,<br>Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Brain<br>Edema Bursitis Chorioretinitis Choroiditis Colitis, Ulcerative Conjunctivitis,<br>Allergic Corneal Injuries Crohn Disease Dermatitis Dermatitis Herpetiformis Dermatitis,<br>Atopic Dermatitis, Contact Dermatitis, Exfoliative Dermatitis, Seborrheic Erythema<br>Multiforme Eye Diseases Hemorrhoids Herpes Simplex Herpes Zoster<br>Ophthalmicus Hypercalcemia Inflammation Iridocyclitis Iritis Keratitis Laryngeal<br>Edema Leukemia Lupus Erythematosus, Systemic Lymphoma Macular Edema Multiple<br>Myeloma Mycosis Fungoides Myocarditis Nasal Obstruction Neoplasms Nephrotic<br>Syndrome Ophthalmia, Sympathetic Optic Neuritis Osteoarthritis Pemphigus Peptic<br>Ulcer Pneumonia Psoriasis Pulmonary Eosinophilia Purpura, Thrombocytopenic,<br>Idiopathic Rhinitis, Allergic Rhinitis, Allergic, Seasonal Sarcoidosis Serum<br>Sickness Spondylitis, Ankylosing Stevens-Johnson Syndrome Synovitis Tennis<br>Elbow Tenosynovitis Thrombocytopenia Thyroiditis, Subacute Transfusion<br>Reaction Trichinellosis Tuberculosis, Meningeal Tuberculosis, Pulmonary Uveitis,<br>Posterior | -  |
| Dexmedetomidine                | Acute Kidney Injury Brain Neoplasms Cognitive Dysfunction Cough Delirium Heart<br>Diseases Heart Septal Defects,<br>Atrial Hypertension Inflammation Neoplasms Pain Postoperative Cognitive<br>Complications Psychomotor Agitation Psychotic Disorders Respiratory<br>Insufficiency Shock, Septic Stomach Neoplasms Wounds and Injuries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | -  |
| Dexrazoxane                    | Breast Neoplasms Cardiomyopathies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 57 |
| Docetaxel                      | Breast Neoplasms Carcinoma Carcinoma, Non-Small-Cell Lung Carcinoma, Squamous<br>Cell Head and Neck Neoplasms Lung Neoplasms Neoplasms Prostatic<br>Neoplasms Squamous Cell Carcinoma of Head and Neck Stomach Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 76 |
| Dolasetron                     | Nausea Neoplasms Postoperative Nausea and Vomiting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Donepezil                      | Alzheimer Disease Amblyopia Aphasia Cognitive Dysfunction Colitis-Associated<br>Neoplasms Delirium Dementia Dementia, Vascular Multiple Sclerosis Parkinson<br>Disease Stroke                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 11 |
| dostarlimab                    | Endometrial Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 35 |
| Doxazosin                      | Hypertension Prostatic Hyperplasia Stress Disorders, Post-Traumatic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Doxercalciferol                | Hyperparathyroidism, Secondary Kidney Diseases Neoplasms Renal Insufficiency, Chronic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 75 |
| doxifluridine                  | Breast Neoplasms Colonic Neoplasms Neoplasms Stomach Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 18 |
| Doxorubicin                    | Breast Neoplasms Carcinoma Carcinoma, Hepatocellular Carcinoma, Ovarian<br>Epithelial Heart Failure Hodgkin Disease Leukemia, Myelomonocytic,<br>Acute Lymphoma Lymphoma, Non-Hodgkin Multiple<br>Myeloma Neoplasms Osteosarcoma Ovarian Neoplasms Sarcoma Sarcoma, Kaposi Urinary<br>Bladder Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 93 |
| durvalumab                     | Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| Dutasteride                    | Hypogonadism Prostatic Hyperplasia Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| duvelisib                      | Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 75 |
| elacestrant                    | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 28 |
| Elotuzumab                     | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 75 |
| elranatamab                    | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | -  |
| enasidenib                     | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| encorafenib                    | Colorectal Neoplasms Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 86 |
| enfortumab vedotin             | Carcinoma, Transitional Cell Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| entrectinib                    | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 51 |
| Enzalutamide                   | Neoplasms Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 18 |
| epcoritamab                    | Lymphoma, Large B-Cell, Diffuse                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -  |
| Epirubicin                     | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 75 |
| erdafitinib                    | Urinary Bladder Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 92 |
| Ergocalciferol                 | Bone Diseases, Metabolic Crohn Disease Cysts Diabetes Mellitus, Type 2 Fractures,<br>Bone Heart Failure Hip Fractures Hypoparathyroidism Hypophosphatemia, Familial Insulin<br>Resistance Muscular Diseases Neoplasms Osteoporosis Polycystic Ovary Syndrome Renal<br>Insufficiency, Chronic Rickets, Hypophosphatemic Syndrome Vitamin D Deficiency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 45 |
| Eribulin                       | Breast Neoplasms Neurotoxicity Syndromes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| Erlotinib                      | Carcinoma, Non-Small-Cell Lung Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 96 |
| Esomeprazole                   | Arthritis, Rheumatoid Croup Digestive System Diseases Duodenal<br>Ulcer Dyspepsia Esophagitis Esophagitis, Peptic Gastritis Gastroesophageal<br>Reflux Gastrointestinal Diseases Helicobacter Infections Hemorrhage Intestinal<br>Diseases Neoplasms Osteoarthritis Peptic Ulcer Spondylitis, Ankylosing Stomach<br>Ulcer Ulcer Zollinger-Ellison Syndrome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | -  |
| Estradiol                      | Atrophic Vaginitis Atrophy Breast<br>Neoplasms Dyspareunia Hypogonadism Menopause Osteoporosis Osteoporosis,<br>Postmenopausal Primary Ovarian Insufficiency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 71 |
| Estramustine                   | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 58 |
| estramustine phosphate         | Carcinoma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Ethinyl Estradiol              | Acne Vulgaris Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 51 |
| Etoposide                      | Carcinoma, Small Cell Lung Neoplasms Neoplasms Small Cell Lung Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 82 |
| Everolimus                     | Angiomyolipoma Astrocytoma Breast Neoplasms Carcinoma Carcinoma, Renal<br>Cell Kidney Diseases Neoplasms Neuroendocrine Tumors Polycystic Kidney                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 85 |

|                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                                 | Diseases Polycystic Kidney, Autosomal Dominant Renal Insufficiency Renal Insufficiency, Chronic Tuberous Sclerosis                                                                                                                                                                                                                                                                                                                                                                                                                           |    |
| Exemestane                      | Breast Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -  |
| Fentanyl                        | Acute Pain Chronic Pain Hemorrhage Hyperalgesia Low Back Pain Migraine Disorders Neoplasms Neuralgia Pain Respiratory Insufficiency                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| Finasteride                     | Prostatic Hyperplasia Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 42 |
| Flavopiridol                    | Leukemia, Lymphocytic, Chronic, B-Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 91 |
| Floxuridine                     | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 80 |
| Fludarabine                     | Leukemia, Lymphocytic, Chronic, B-Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 84 |
| fluoroestradiol f-18            | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Fluorouracil                    | Adenocarcinoma Carcinoma Carcinoma, Basal Cell Carcinoma, Squamous Cell Colonic Neoplasms Colorectal Neoplasms Esophageal Neoplasms Glaucoma Keratosi Keratosi, Actinic Neoplasms Rectal Neoplasms                                                                                                                                                                                                                                                                                                                                           | 81 |
| Fluoxymesterone                 | Breast Neoplasms Hypogonadism Puberty, Delayed                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 47 |
| Flutamide                       | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 72 |
| Formestane                      | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| Fosaprepitant                   | Neoplasms Postoperative Nausea and Vomiting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | -  |
| fruqintinib                     | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 77 |
| Fulvestrant                     | Breast Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 74 |
| futibatinib                     | Cholangiocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 82 |
| Geftitinib                      | Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 90 |
| Gemcitabine                     | Breast Neoplasms Carcinoma, Non-Small-Cell Lung Neoplasms Ovarian Neoplasms Pancreatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                             | 84 |
| Gemtuzumab ozogamicin           | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 24 |
| gilteritinib                    | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 78 |
| glasdegib                       | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 31 |
| glofitamab                      | Lymphoma, Large B-Cell, Diffuse                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| Goserelin                       | Breast Neoplasms Endometriosis Infertility Leiomyoma Neoplasms Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| Guanidine                       | Carcinoma, Small Cell Lambert-Eaton Myasthenic Syndrome Muscle Weakness                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 7  |
| Hexaminolevulinate              | Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| histrelin                       | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| Homoharringtonine               | Leukemia, Myelogenous, Chronic, BCR-ABL Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 85 |
| Hydrocortisone                  | Adrenal Hyperplasia, Congenital Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Bursitis Colitis, Ulcerative Conjunctivitis, Allergic Crohn Disease Dermatitis Dermatitis, Atopic Dermatitis, Seborrheic Eczema Endocrine System Diseases Exanthema Eye Diseases Hemorrhoids Herpes Labialis Inflammation Intertrigo Leukemia Lymphoma Nasal Obstruction Neoplasms Osteoarthritis Otitis Externa Pneumonia Pruritus Psoriasis Serum Sickness Shock, Septic Skin Diseases Spondylitis Tenosynovitis Wounds and Injuries | 80 |
| Hydromorphone                   | Acute Pain Low Back Pain Neoplasms Pain Substance-Related Disorders                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| hydroxyflutamide                | Carcinoma Neoplasms Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | -  |
| Hydroxyurea                     | Anemia, Sickle Cell Carcinoma, Squamous Cell Leukemia, Myelogenous, Chronic, BCR-ABL Positive Melanoma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                             | 69 |
| Ibandronate                     | Bone Diseases Bone Diseases, Metabolic Bone Neoplasms Neoplasm Metastasis Osteoporosis Osteoporosis, Postmenopausal                                                                                                                                                                                                                                                                                                                                                                                                                          | 4  |
| Ibritumomab                     | Lymphoma, B-Cell Lymphoma, Follicular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 24 |
| Ibrutinib                       | Graft vs Host Disease Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, B-Cell, Marginal Zone Lymphoma, Mantle-Cell Waldenstrom Macroglobulinemia                                                                                                                                                                                                                                                                                                                                                                                             | 86 |
| icotinib                        | Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 22 |
| Idarubicin                      | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 59 |
| Idelalisib                      | Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 75 |
| Ifosfamide                      | Neoplasms Testicular Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 52 |
| Imatinib                        | Gastrointestinal Stromal Tumors Leukemia, Myelogenous, Chronic, BCR-ABL Positive Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 90 |
| imatinib mesylate               | Breast Neoplasms Gastrointestinal Stromal Tumors Leukemia Leukemia, Myelogenous, Chronic, BCR-ABL Positive                                                                                                                                                                                                                                                                                                                                                                                                                                   | -  |
| Imiquimod                       | Carcinoma, Basal Cell Cheilitis Condylomata Acuminata Keratosi, Actinic Lentigo                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 53 |
| infigratinib                    | Cholangiocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 76 |
| inositol                        | Colitis-Associated Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 70 |
| inotuzumab ozogamicin           | Precursor B-Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Interferon Alfa-2a, Recombinant | Leukemia, Hairy Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 63 |
| Interferon Alfa-2b, Recombinant | Leukemia, Hairy Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 63 |
| Iopamidol                       | Glioma Pituitary Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -  |
| ipilimumab                      | Carcinoma, Renal Cell Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 31 |
| Irinotecan                      | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 70 |
| isatuximab                      | Multiple Myeloma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 21 |
| Isopropyl Alcohol               | Acromegaly Anemia Arthritis, Psoriatic Arthritis, Rheumatoid Burns Colitis, Ulcerative Constipation Eczema Infections Multiple Sclerosis Prostatic Neoplasms Psoriasis Spondylitis, Ankylosing                                                                                                                                                                                                                                                                                                                                               | -  |
| ivosidenib                      | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | -  |
| Ixabepilone                     | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 5  |
| Ixazomib                        | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Ketamine                        | Delirium Depression, Postpartum Depressive Disorder Depressive Disorder, Major Fractures, Bone Hemorrhage Lung Neoplasms Neoplasms Opioid-Related Disorders Pain Postoperative Complications Suicidal Ideation                                                                                                                                                                                                                                                                                                                               | -  |
| Lamotrigine                     | Bipolar Disorder Cocaine-Related Disorders Colitis-Associated Neoplasms Depressive Disorder Epilepsies, Partial Epilepsy Epilepsy, Tonic-Clonic Mental Disorders Mood Disorders Seizures                                                                                                                                                                                                                                                                                                                                                     | -  |
| Lanreotide                      | Acromegaly Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Lapatinib                       | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 91 |

|                             |                                                                                                                                                                                                                                                                                                                                                                                                                           |    |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Iarotrectinib               | Neoplasm Metastasis                                                                                                                                                                                                                                                                                                                                                                                                       | 55 |
| LE-SN38                     | Adenocarcinoma Carcinoma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                        | 26 |
| Lenalidomide                | Multiple Myeloma Myelodysplastic Syndromes Neoplasms                                                                                                                                                                                                                                                                                                                                                                      | 51 |
| Lenvatinib                  | Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms                                                                                                                                                                                                                                                                                                                                                         | 94 |
| Letrozole                   | Anovulation Breast Neoplasms Cardiac Complexes, Premature Infertility Leiomyoma Neoplasms Polycystic Ovary Syndrome Pregnancy, Ectopic                                                                                                                                                                                                                                                                                    | 28 |
| Leuprolide                  | Endometriosis Infertility Neoplasms Prostatic Neoplasms Puberty, Precocious                                                                                                                                                                                                                                                                                                                                               | -  |
| Levamisole                  | Colonic Neoplasms Helminthiasis                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| Levetiracetam               | Alcoholism Bipolar Disorder Brain Neoplasms Colitis-Associated Neoplasms Epilepsies, Partial Epilepsy Parkinson Disease Polyneuropathies Seizures                                                                                                                                                                                                                                                                         | -  |
| Levobupivacaine             | Muscle Weakness Neoplasms Paresis                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| levoleucovorin              | Anemia Colorectal Neoplasms Osteosarcoma                                                                                                                                                                                                                                                                                                                                                                                  | -  |
| Levonorgestrel              | Endometrial Hyperplasia Endometriosis Hemorrhage Menorrhagia                                                                                                                                                                                                                                                                                                                                                              | 36 |
| Levothyroxine               | Congenital Hypothyroidism Hypothyroidism Thyroid Neoplasms                                                                                                                                                                                                                                                                                                                                                                | 37 |
| Lidocaine                   | Anesthesia Arrhythmias, Cardiac Arthritis Back Pain Burns Bursitis Hemorrhoids Inflammation Insect Bites and Stings Muscle Cramp Myalgia Neuralgia Neuralgia, Postherpetic Osteoarthritis Pain Premature Ejaculation Prostatic Neoplasms Pruritus Rectal Diseases Sprains and Strains Sunburn Tendinopathy Urethritis                                                                                                     | 10 |
| lidocaine patch             | Breast Neoplasms Lung Diseases Pneumonia                                                                                                                                                                                                                                                                                                                                                                                  | -  |
| Liothyronine                | Depressive Disorder Hypothyroidism Myxedema Thyroid Neoplasms                                                                                                                                                                                                                                                                                                                                                             | 51 |
| lipegfilgrastim             | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                 | -  |
| Lomustine                   | Brain Neoplasms Hodgkin Disease                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| loncastuximab tesirine      | Lymphoma, B-Cell Lymphoma, Large B-Cell, Diffuse                                                                                                                                                                                                                                                                                                                                                                          | -  |
| lorlatinib                  | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                            | 74 |
| lurbinectedin               | Neoplasms Small Cell Lung Carcinoma                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| margetuximab                | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                          | 44 |
| Mechlorethamine             | Lymphoma, T-Cell, Cutaneous Neoplasms                                                                                                                                                                                                                                                                                                                                                                                     | 26 |
| Medroxyprogesterone Acetate | Carcinoma, Renal Cell Endometriosis Hemorrhage Hyperplasia Infertility Neoplasms Uterine Hemorrhage                                                                                                                                                                                                                                                                                                                       | 74 |
| Megestrol acetate           | Acquired Immunodeficiency Syndrome Anorexia Breast Neoplasms Cachexia                                                                                                                                                                                                                                                                                                                                                     | 65 |
| Melphalan                   | Carcinoma Multiple Myeloma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                      | 65 |
| melphalan flufenamide       | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                          | 79 |
| Mercaptopurine              | Leukemia Leukemia, Lymphoid Lymphoma Neoplasms Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                             | 1  |
| Mesna                       | Neoplasms Thrombocytopenia                                                                                                                                                                                                                                                                                                                                                                                                | -  |
| Methadone                   | Acute Pain Heroin Dependence HIV Infections Neonatal Abstinence Syndrome Neoplasms Neuralgia Opioid-Related Disorders Pain Scoliosis Substance-Related Disorders                                                                                                                                                                                                                                                          | -  |
| Methotrexate                | Adenoma Arthritis Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Breast Neoplasms Choriocarcinoma Communicable Diseases Crohn Disease Gout Immune System Diseases Lung Neoplasms Lymphoma Lymphoma, Non-Hodgkin Meningeal Carcinomatosis Multiple Sclerosis Mycosis Fungoides Neoplasms Osteoarthritis Precursor Cell Lymphoblastic Leukemia-Lymphoma Pregnancy, Ectopic Psoriasis Uveitis                | 62 |
| Methoxsalen                 | Lymphoma Lymphoma, T-Cell Mycosis Fungoides Psoriasis                                                                                                                                                                                                                                                                                                                                                                     | 7  |
| Methyl aminolevulinate      | Glioma Keratoses, Actinic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| Methylphenidate             | Alcoholism Alzheimer Disease Attention Deficit Disorder with Hyperactivity Bipolar Disorder Brain Injuries Brain Neoplasms Cocaine-Related Disorders Dementia Depressive Disorder Narcolepsy Neoplasms Parkinson Disease Substance-Related Disorders                                                                                                                                                                      | -  |
| Methylprednisolone          | Acne Vulgaris Anemia Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Bursitis Colitis, Ulcerative Crohn Disease Dermatitis Dermatitis, Atopic Endocrine System Diseases Fasciitis, Plantar Inflammation Leukemia Lymphoma Multiple Sclerosis Multiple Sclerosis, Relapsing-Remitting Osteoarthritis Pneumonia Purpura, Thrombocytopenic, Idiopathic Serum Sickness Tenosynovitis Uveitis, Posterior | 55 |
| Methyltestosterone          | Breast Neoplasms Hypogonadism Puberty, Delayed                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Metoclopramide              | Anorexia Digestive System Diseases Gastroparesis Heartburn Nausea Neoplasms Postoperative Nausea and Vomiting Renal Insufficiency Vomiting                                                                                                                                                                                                                                                                                | -  |
| midostaurin                 | Leukemia, Mast-Cell Leukemia, Myeloid, Acute Mastocytosis, Systemic                                                                                                                                                                                                                                                                                                                                                       | 91 |
| mirvetuximab soravtansine   | Ovarian Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Mitomycin                   | Adenocarcinoma Glaucoma Glaucoma, Neovascular Glaucoma, Open-Angle Myopia Neoplasms                                                                                                                                                                                                                                                                                                                                       | 77 |
| Mitotane                    | Adrenocortical Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                  | 36 |
| Mitoxantrone                | Leukemia, Myeloid, Acute Multiple Sclerosis Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                     | 77 |
| mobocertinib                | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                            | 59 |
| mogamulizumab               | Mycosis Fungoides Neoplasms Sézary Syndrome                                                                                                                                                                                                                                                                                                                                                                               | -  |
| Morphine                    | Abdominal Neoplasms Acute Pain Chronic Pain Dyspnea Low Back Pain Mucositis Myocardial Infarction Neoplasms Pain Pruritus Pulmonary Disease, Chronic Obstructive Scoliosis Stomatitis Substance-Related Disorders                                                                                                                                                                                                         | 35 |
| mosunetuzumab               | Lymphoma, Follicular                                                                                                                                                                                                                                                                                                                                                                                                      | -  |
| motixafortide               | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| moxetumomab pasudotox       | Leukemia, Hairy Cell Neoplasms                                                                                                                                                                                                                                                                                                                                                                                            | 26 |
| mrtx-849                    | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                            | 34 |
| nabilone                    | Nausea Neoplasms Postoperative Nausea and Vomiting                                                                                                                                                                                                                                                                                                                                                                        | -  |
| Necitumumab                 | Carcinoma, Non-Small-Cell Lung Neoplasms                                                                                                                                                                                                                                                                                                                                                                                  | -  |
| Nelarabine                  | Precursor T-Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                          | -  |
| neratinib                   | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                          | 85 |
| neratinib maleate           | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                          | -  |

|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Nilotinib               | Leukemia Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 86 |
| Nilutamide              | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 15 |
| niraparib               | Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 48 |
| Nivolumab               | Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| nogapendekin alfa       | Urinary Bladder Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 39 |
| Norepinephrine          | Carcinoma Carcinoma, Hepatocellular Cardiovascular Diseases Depressive Disorder Hypotension Hypotension, Orthostatic Multiple System Atrophy Poliomyelitis Sepsis Shock Shock, Septic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2  |
| Obinutuzumab            | Leukemia, Lymphocytic, Chronic, B-Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Octreotide              | Acromegaly Carcinoid Tumor Diarrhea Neoplasms Obesity Vipoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 56 |
| Ofatumumab              | Leukemia, Lymphocytic, Chronic, B-Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | -  |
| Olaparib                | Breast Neoplasms Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Neoplasms Ovarian Neoplasms Pancreatic Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 60 |
| olaratumab              | Sarcoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Ondansetron             | Alcoholism Breast Neoplasms Gastroenteritis Hypotension Irritable Bowel Syndrome Nausea Neoplasms Obsessive-Compulsive Disorder Postoperative Nausea and Vomiting Vomiting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 6  |
| Osimertinib             | Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 89 |
| Oxaliplatin             | Colorectal Neoplasms Liver Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 84 |
| Oxycodone               | Low Back Pain Neoplasms Pain Substance-Related Disorders                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| Paclitaxel              | Adenocarcinoma Breast Neoplasms Carcinoma, Non-Small-Cell Lung Constriction, Pathologic Coronary Restenosis Ischemia Neoplasms Ovarian Neoplasms Peripheral Arterial Disease Peripheral Vascular Diseases                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 91 |
| Palbociclib             | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 42 |
| palifosfamide           | Neoplasms Testicular Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | -  |
| Palonosetron            | Nausea Neoplasms Postoperative Nausea and Vomiting Vomiting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | -  |
| Pamidronate             | Bone Diseases Breast Neoplasms Hypercalcemia Osteitis Deformans Osteogenesis Imperfecta                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 7  |
| Panitumumab             | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 29 |
| Panobinostat            | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 80 |
| Papaverine              | Digestive System Diseases Erectile Dysfunction Kidney Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1  |
| Paricalcitol            | Diabetic Nephropathies Hyperparathyroidism, Secondary Kidney Diseases Neoplasms Renal Insufficiency, Chronic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 36 |
| Pazopanib               | Carcinoma, Renal Cell Sarcoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 92 |
| pazopanib hydrochloride | Carcinoma, Renal Cell Sarcoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | -  |
| Pegaspargase            | Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | -  |
| Pembrolizumab           | Carcinoma, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Non-Small-Cell Lung Carcinoma, Renal Cell Carcinoma, Transitional Cell Hodgkin Disease Melanoma Neoplasms Stomach Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Pemetrexed              | Carcinoma, Non-Small-Cell Lung Lung Neoplasms Mesothelioma Neoplasms Renal Insufficiency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | -  |
| pemigatinib             | Cholangiocarcinoma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 81 |
| Pentostatin             | Leukemia, Hairy Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 4  |
| Pertuzumab              | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 87 |
| Pipobroman              | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| pirtobrutinib           | Lymphoma, Mantle-Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| Pixantrone              | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 54 |
| Plerixafor              | Lymphoma Lymphoma, Non-Hodgkin Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| Podofilox               | Carcinoma, Squamous Cell Condylomata Acuminata Virus Diseases                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 50 |
| polatuzumab vedotin     | Lymphoma, Large B-Cell, Diffuse Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| Pomalidomide            | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 17 |
| Ponatinib               | Leukemia, Myelogenous, Chronic, BCR-ABL Positive Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 89 |
| Porfimer                | Esophageal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | -  |
| Posaconazole            | Aspergillosis Candidiasis Leukemia Leukemia, Myeloid, Acute Mycoses Neutropenia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| Potassium Citrate       | Acidosis, Renal Tubular Kidney Calculi Neoplasms Stomach Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | -  |
| Povidone-iodine         | Breast Neoplasms Surgical Wound Surgical Wound Infection Wound Infection Wounds and Injuries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| Pralatrexate            | Lymphoma, T-Cell, Peripheral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -  |
| pralsetinib             | Carcinoma, Medullary Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -  |
| Prednicarbate           | Adrenal Hyperplasia, Congenital Anemia Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Brain Neoplasms Bursitis Conjunctivitis, Allergic Dermatitis, Atopic Endocrine System Diseases Inflammation Multiple Sclerosis Neoplasms Osteoarthritis Peptic Ulcer Rhinitis, Allergic Skin Diseases Spondylitis Tenosynovitis Uveitis, Posterior                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 19 |
| Prednisolone            | Addison Disease Adrenal Hyperplasia, Congenital Anemia Anemia, Aplastic Anemia, Hemolytic Arthritis Arthritis, Gouty Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Berylliosis Brain Neoplasms Bursitis Chorioretinitis Choroiditis Colitis, Ulcerative Conjunctivitis, Allergic Crohn Disease Dermatitis Herpetiformis Dermatitis, Atopic Dermatitis, Contact Dermatitis, Exfoliative Dermatitis, Seborrheic Dermatomyositis Endocrine System Diseases Erythema Multiforme Eye Diseases Hemorrhoids Herpes Zoster Ophthalmicus Hypercalcemia Inflammation Iridocyclitis Iritis Keratitis Leukemia Lung Diseases Lupus Erythematosus, Systemic Lupus Nephritis Lymphoma Multiple Sclerosis Mycosis Fungoides Myocarditis Nasal Obstruction Neoplasms Nephrotic Syndrome Ophthalmia, Sympathetic Optic Neuritis Osteoarthritis Pain Pemphigus Peptic Ulcer Pneumonia Polymyositis Psoriasis Pulmonary Disease, Chronic Obstructive Pulmonary Eosinophilia Pulpitis Purpura, Thrombocytopenic, Idiopathic Rhinitis, Allergic Rhinitis, Allergic, Seasonal Sarcoidosis Serum Sickness Sinusitis Skin Diseases Spondylitis Spondylitis, Ankylosing Stevens-Johnson Syndrome Synovitis Tennis Elbow Tenosynovitis Thrombocytopenia Thyroiditis, | 57 |

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                              | Subacute Trichinellosis Tuberculosis, Meningeal Tuberculosis, Pulmonary Uveitis Uveitis, Posterior                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |
| prednisolone phosphoric acid | Anemia Asthma Conjunctivitis, Allergic Corneal Injuries Idiopathic Pulmonary Fibrosis Inflammation Leukemia Multiple Sclerosis Nephrotic Syndrome Pulmonary Disease, Chronic Obstructive Pulmonary Fibrosis Rhinitis, Allergic Uremia Uveitis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 34 |
| Prednisone                   | Addison Disease Adrenal Hyperplasia, Congenital Anemia, Aplastic Anemia, Hemolytic Arthritis Arthritis, Gouty Arthritis, Juvenile Arthritis, Psoriatic Arthritis, Rheumatoid Asthma Berylliosis Bursitis Chorioretinitis Choroiditis Colitis, Ulcerative Conjunctivitis, Allergic Crohn Disease Dermatitis Herpetiformis Dermatitis, Atopic Dermatitis, Contact Dermatitis, Exfoliative Dermatitis, Seborrheic Dermatomyositis Erythema Multiforme Giant Cell Arteritis Heart Failure Hematologic Diseases Herpes Zoster Ophthalmicus Hypercalcemia Hypereosinophilic Syndrome Infections Iridocyclitis Iritis Keratitis Leukemia Lung Diseases Lupus Erythematosus, Systemic Lymphoma Multiple Sclerosis Mycosis Fungoides Myocarditis Nephrotic Syndrome Ophthalmia, Sympathetic Optic Neuritis Osteoarthritis Pemphigus Pneumonia Polymyalgia Rheumatica Polymyositis Psoriasis Pulmonary Disease, Chronic Obstructive Pulmonary Eosinophilia Purpura, Thrombocytopenic, Idiopathic Respiratory Tract Infections Rhinitis, Allergic, Seasonal Sarcoidosis Serum Sickness Spondylitis, Ankylosing Stevens-Johnson Syndrome Synovitis Tennis Elbow Tenosynovitis Thrombocytopenia Thyroiditis, Subacute Trichinellosis Tuberculosis, Meningeal Tuberculosis, Pulmonary Uveitis, Posterior Vestibular Neuritis | 33 |
| Procarbazine                 | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 44 |
| Progesterone                 | Amenorrhea Endometrial Hyperplasia Hemorrhage Infertility Premature Birth Uterine Hemorrhage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 82 |
| Propofol                     | Breast Neoplasms Coronary Artery Disease Heart Diseases Inflammation Neoplasms Obesity, Morbid Psychomotor Agitation Respiratory Insufficiency Scoliosis Wounds and Injuries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 31 |
| Quetiapine                   | Alcoholism Anxiety Bipolar Disorder Cocaine-Related Disorders Colitis-Associated Neoplasms Delirium Dementia Depressive Disorder Depressive Disorder, Major Mental Disorders Mood Disorders Obsessive-Compulsive Disorder Parkinson Disease Phobia, Social Psychomotor Agitation Psychotic Disorders Schizophrenia Sleep Initiation and Maintenance Disorders Stress Disorders, Post-Traumatic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | -  |
| quizartinib                  | Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 85 |
| Radium Ra 223 Dichloride     | Neoplasm Metastasis Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| Raloxifene                   | Breast Neoplasms Osteoporosis Osteoporosis, Postmenopausal Psychotic Disorders Schizophrenia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 47 |
| Raltitrexed                  | Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 43 |
| Ramucirumab                  | Stomach Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| Rasburicase                  | Leukemia Lymphoma Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -  |
| Regorafenib                  | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 95 |
| relugolix                    | Prostatic Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | -  |
| Remifentanyl                 | Hypotension Neoplasms Respiratory Insufficiency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -  |
| repotrectinib                | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 20 |
| retifanlimab                 | Carcinoma, Merkel Cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 35 |
| Ribavirin                    | Fibrosis Hepatitis Hepatitis C Hepatitis C, Chronic HIV Infections Infections Kidney Diseases Liver Cirrhosis Neoplasms Renal Insufficiency Renal Insufficiency, Chronic Respiratory Syncytial Virus Infections Virus Diseases                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 51 |
| ribociclib                   | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 51 |
| ripretinib                   | Gastrointestinal Stromal Tumors Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 85 |
| Risperidone                  | Aggression Alzheimer Disease Anxiety Attention Deficit and Disruptive Behavior Disorders Autistic Disorder Bipolar Disorder Child Development Disorders, Pervasive Colitis-Associated Neoplasms Dementia Developmental Disabilities Psychotic Disorders Schizophrenia Stress Disorders, Post-Traumatic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Rituximab                    | Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Lymphoma, B-Cell Lymphoma, Follicular Vasculitis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 24 |
| rivoceranib mesylate         | Lymphoma Neoplasms Ovarian Neoplasms Stomach Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Romidepsin                   | Lymphoma, T-Cell, Cutaneous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 84 |
| Ropivacaine                  | Acute Pain Appendicitis Breast Neoplasms Fractures, Bone Hallux Valgus Joint Diseases Muscle Weakness Neoplasms Osteoarthritis Osteoarthritis, Knee Pain Paralysis Paresis Rotator Cuff Injuries                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | -  |
| Rosuvastatin                 | Acute Coronary Syndrome Atherosclerosis Cardiovascular Diseases Coronary Artery Disease Coronary Disease Diabetes Mellitus Diabetes Mellitus, Type 2 Dyslipidemias Heart Failure HIV Infections Hypercholesterolemia Hyperlipidemia, Familial Combined Hyperlipidemias Hyperlipoproteinemia Type II Hyperlipoproteinemia Type IV Hypertension Hypertriglyceridemia Internal Hernia Ischemia Metabolic Diseases Neoplasms Periodontitis Prostatic Neoplasms Renal Insufficiency Stroke                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| rucaparib                    | Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 79 |
| sacituzumab govitecan        | Breast Neoplasms Triple Negative Breast Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -  |
| Salicylic acid               | Acne Vulgaris Callosities Dandruff Dermatitis, Seborrheic Eye Diseases Fever Inflammation Melanosis Pain Pruritus Psoriasis Skin Diseases Skin Neoplasms Sunburn Warts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 21 |
| Sargramostim                 | COVID-19 Leukemia, Myeloid, Acute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 69 |
| selinexor                    | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 66 |
| selpercatinib                | Carcinoma, Medullary Carcinoma, Non-Small-Cell Lung Lung Neoplasms Thyroid Neoplasms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 80 |
| Sildenafil                   | Diabetes Mellitus Emphysema Erectile Dysfunction Familial Primary Pulmonary Hypertension Heart Diseases Heart Failure Hypertension Hypertension, Pulmonary Lung Diseases Parkinson Disease Persistent Fetal Circulation Syndrome Prostatic Hyperplasia Pulmonary Arterial Hypertension Pulmonary Edema                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | -  |
| Silodosin                    | Prostatic Hyperplasia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -  |
| Siltuximab                   | Giant Lymph Node Hyperplasia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -  |

|                          |                                                                                                                                                                                                                                                                                                                                                            |    |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Sodium Chloride          | Acid-Base Imbalance Cerebral Palsy Common Cold Corneal Edema Diabetes Mellitus Dry Eye Syndromes Electrolytes Eye Diseases Fractures, Bone Graves Ophthalmopathy Heart Failure Hemorrhage Hypothermia Kidney Diseases Muscle Spasticity Neoplasms Osteoarthritis Osteoarthritis, Knee Paralysis Renal Insufficiency Tennis Elbow Wounds and Injuries       | 68 |
| Solifenacin              | Prostatic Hyperplasia Urinary Bladder, Overactive Urinary Incontinence Urinary Incontinence, Urge                                                                                                                                                                                                                                                          | -  |
| Sonidegib                | Carcinoma, Basal Cell                                                                                                                                                                                                                                                                                                                                      | 22 |
| Sorafenib                | Carcinoma Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms                                                                                                                                                                                                                                                                                | 98 |
| sotorasib                | Carcinoma, Non-Small-Cell Lung                                                                                                                                                                                                                                                                                                                             | 34 |
| Strontium chloride Sr-89 | Neoplasm Metastasis                                                                                                                                                                                                                                                                                                                                        | -  |
| Sugammadex               | Hypothermia Neoplasms Postoperative Complications                                                                                                                                                                                                                                                                                                          | -  |
| Sunitinib                | Adenoma, Islet Cell Carcinoma Carcinoma, Renal Cell Gastrointestinal Stromal Tumors Neoplasms Neuroendocrine Tumors                                                                                                                                                                                                                                        | 98 |
| Tadalafil                | Diabetes Mellitus, Type 2 Erectile Dysfunction Hypertension Hypertension, Pulmonary Insulin Resistance Lower Urinary Tract Symptoms Muscular Dystrophies Muscular Dystrophy, Duchenne Prostatic Hyperplasia Pulmonary Arterial Hypertension Scleroderma, Systemic                                                                                          | -  |
| tafasitamab              | Lymphoma Lymphoma, Large B-Cell, Diffuse Neoplasms                                                                                                                                                                                                                                                                                                         | -  |
| talazoparib              | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                           | 62 |
| talquetamab              | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                           | -  |
| Tamoxifen                | Adenoma Breast Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                         | 84 |
| Tamsulosin               | Hyperplasia Nocturia Prostatic Hyperplasia Ureterolithiasis Urinary Retention Urination Disorders                                                                                                                                                                                                                                                          | -  |
| tarlatamab               | Small Cell Lung Carcinoma                                                                                                                                                                                                                                                                                                                                  | -  |
| tazemetostat             | Lymphoma, Follicular Sarcoma                                                                                                                                                                                                                                                                                                                               | 40 |
| tebentafusp              | Uveal Neoplasms                                                                                                                                                                                                                                                                                                                                            | -  |
| teclistamab              | Multiple Myeloma                                                                                                                                                                                                                                                                                                                                           | 8  |
| Tegafur                  | Neoplasms                                                                                                                                                                                                                                                                                                                                                  | 91 |
| Temozolomide             | Astrocytoma Brain Neoplasms Central Nervous System Neoplasms Glioblastoma Neoplasms                                                                                                                                                                                                                                                                        | 43 |
| Temsirolimus             | Carcinoma, Renal Cell Lymphoma Lymphoma, Mantle-Cell Lymphoma, Non-Hodgkin                                                                                                                                                                                                                                                                                 | 86 |
| Teniposide               | Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                                                                             | 77 |
| tepotinib                | Carcinoma, Non-Small-Cell Lung Neoplasms                                                                                                                                                                                                                                                                                                                   | 80 |
| Terazosin                | Hypertension Prostatic Hyperplasia                                                                                                                                                                                                                                                                                                                         | 29 |
| Testosterone             | Brain Injuries Brain Injuries, Traumatic Erectile Dysfunction Hypogonadism Insulin Resistance Klinefelter Syndrome Neoplasms Obesity Orchitis Sarcopenia Wounds and Injuries                                                                                                                                                                               | 74 |
| testosterone cypionate   | Hypogonadism Neoplasms Orchitis                                                                                                                                                                                                                                                                                                                            | -  |
| testosterone undecanoate | Hypogonadism Klinefelter Syndrome Neoplasms Orchitis                                                                                                                                                                                                                                                                                                       | 36 |
| Thalidomide              | Immune System Diseases Multiple Myeloma Neoplasms                                                                                                                                                                                                                                                                                                          | 81 |
| Thiotepa                 | Adenocarcinoma Carcinoma Hodgkin Disease Neoplasms                                                                                                                                                                                                                                                                                                         | 50 |
| thyrotropin alfa         | Thyroid Neoplasms                                                                                                                                                                                                                                                                                                                                          | -  |
| Tioguanine               | Neoplasms                                                                                                                                                                                                                                                                                                                                                  | 20 |
| Tipiracil                | Colorectal Neoplasms                                                                                                                                                                                                                                                                                                                                       | -  |
| tirabrutinib             | Lymphoma                                                                                                                                                                                                                                                                                                                                                   | -  |
| tisagenlecleucel         | Neoplasms                                                                                                                                                                                                                                                                                                                                                  | -  |
| tislelizumab             | Esophageal Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                         | 39 |
| tisotumab vedotin        | Uterine Cervical Neoplasms                                                                                                                                                                                                                                                                                                                                 | -  |
| tivozanib                | Carcinoma, Renal Cell                                                                                                                                                                                                                                                                                                                                      | 85 |
| Topotecan                | Small Cell Lung Carcinoma                                                                                                                                                                                                                                                                                                                                  | 47 |
| Toremifene               | Breast Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                 | 68 |
| toripalimab              | Nasopharyngeal Carcinoma                                                                                                                                                                                                                                                                                                                                   | 33 |
| Tositumomab              | Lymphoma, Follicular                                                                                                                                                                                                                                                                                                                                       | 27 |
| Trabectedin              | Leiomyosarcoma Liposarcoma                                                                                                                                                                                                                                                                                                                                 | -  |
| Trametinib               | Carcinoma, Non-Small-Cell Lung Melanoma                                                                                                                                                                                                                                                                                                                    | 92 |
| Tranexamic Acid          | Blood Coagulation Disorders Epistaxis Femoral Neck Fractures Fractures, Bone Gastrointestinal Hemorrhage Hematoma Hematoma, Subdural Hematoma, Subdural, Chronic Hemophilia A Hemorrhage Hip Fractures Joint Diseases Menorrhagia Neoplasms Osteoarthritis Osteoarthritis, Knee Placenta Accreta Placenta Previa Postpartum Hemorrhage Wounds and Injuries | -  |
| Trastuzumab              | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                           | 81 |
| trastuzumab deruxtecan   | Breast Neoplasms Neoplasms                                                                                                                                                                                                                                                                                                                                 | 80 |
| tremelimumab             | Carcinoma, Hepatocellular                                                                                                                                                                                                                                                                                                                                  | 30 |
| treosulfan               | Neoplasms                                                                                                                                                                                                                                                                                                                                                  | -  |
| Triclosan                | Breast Neoplasms Gingivitis Periodontal Diseases Periodontitis                                                                                                                                                                                                                                                                                             | 88 |
| Trifluridine             | Colorectal Neoplasms Eye Infections Herpes Simplex Keratoconjunctivitis Neoplasms                                                                                                                                                                                                                                                                          | -  |
| trilaciclib              | Small Cell Lung Carcinoma                                                                                                                                                                                                                                                                                                                                  | 45 |
| Triptorelin              | Endometriosis Infertility Neoplasms Prostatic Neoplasms                                                                                                                                                                                                                                                                                                    | 82 |
| tucatinib                | Breast Neoplasms                                                                                                                                                                                                                                                                                                                                           | 87 |
| umbralisib               | Lymphoma, B-Cell, Marginal Zone Lymphoma, Follicular                                                                                                                                                                                                                                                                                                       | 73 |
| Uracil mustard           | Neoplasms                                                                                                                                                                                                                                                                                                                                                  | -  |
| Valganciclovir           | Acquired Immunodeficiency Syndrome Cytomegalovirus Infections Cytomegalovirus Retinitis Infections Leukemia, Lymphocytic, Chronic, B-Cell Retinitis Virus Diseases                                                                                                                                                                                         | -  |
| Valproic Acid            | Alzheimer Disease Anorexia Autistic Disorder Bipolar Disorder Colitis-Associated Neoplasms Depressive Disorder Depressive Disorder, Major Epilepsy Epilepsy, Absence Epilepsy, Complex Partial Migraine Disorders Mitochondrial Diseases Mood Disorders Schizophrenia Seizures Vomiting                                                                    | 83 |
| Valrubicin               | Urinary Bladder Neoplasms                                                                                                                                                                                                                                                                                                                                  | 54 |

|                                       |                                                                                                                                                                                                                                                                                                 |    |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Vandetanib                            | Thyroid Neoplasms                                                                                                                                                                                                                                                                               | 94 |
| Vemurafenib                           | Melanoma Neoplasms                                                                                                                                                                                                                                                                              | 75 |
| venetoclax                            | Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Myeloid, Acute                                                                                                                                                                                                                                 | 46 |
| Vincristine                           | Precursor Cell Lymphoblastic Leukemia-Lymphoma                                                                                                                                                                                                                                                  | 57 |
| vincristine                           | Neoplasms                                                                                                                                                                                                                                                                                       | -  |
| vinflunine                            | Neoplasms                                                                                                                                                                                                                                                                                       | -  |
| Vinorelbine                           | Breast Neoplasms Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms                                                                                                                                                                                                                        | 61 |
| vipivotide tetraxetan lutetium lu-177 | Prostatic Neoplasms, Castration-Resistant                                                                                                                                                                                                                                                       | 30 |
| Vismodegib                            | Carcinoma Carcinoma, Basal Cell                                                                                                                                                                                                                                                                 | 26 |
| Vorinostat                            | Lymphoma, T-Cell, Cutaneous                                                                                                                                                                                                                                                                     | 85 |
| zanubrutinib                          | Lymphoma, Mantle-Cell                                                                                                                                                                                                                                                                           | 77 |
| Ziprasidone                           | Anxiety Bipolar Disorder Colitis-Associated Neoplasms Depressive Disorder Depressive Disorder, Major Mood Disorders Psychotic Disorders Schizophrenia                                                                                                                                           | -  |
| Zoledronate                           | Bone Diseases Bone Diseases, Metabolic Bone Neoplasms Breast Neoplasms Carcinoma, Non-Small-Cell Lung Carcinoma, Renal Cell Multiple Myeloma Neoplasm Metastasis Osteitis Deformans Osteoarthritis, Hip Osteoporosis Osteoporosis, Postmenopausal Pain Prostatic Neoplasms Spinal Cord Injuries | 3  |

## 6. Conclusion

We applied the software package "Genome Enhancer" to a data set that contains *genomics* data. The study is done in the context of *Colorectal Neoplasms*. The data were pre-processed, statistically analyzed and genes carrying sequence variations were identified. Also checked was the enrichment of GO or disease categories among the studied gene sets.

We propose the following drugs as most promising candidates for treating the pathology under study:



**Sorafenib, seliciclib, LE-SN38 and 2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One**

These drugs were selected for acting on the following targets: PDGFRB, TOP1 and CDK1, which were predicted to be involved in the molecular mechanism of the pathology under study.

The identified molecular mechanism of the studied pathology was predicted to be mainly based on the following key drug targets:



**Jak1, Ubc9, NCoR2, YY1 and PDGFRbeta**

These potential drug targets should be considered as a prospective research initiative for further drug repurposing and drug development purposes. The following drugs were predicted as, matching those drug targets: Sorafenib, Tolfenamic Acid, Uracil mustard and seliciclib. These drugs should be considered with special caution for research purposes only.

In this study, we came up with a detailed signal transduction network regulating genes carrying sequence variations in the studied pathology. In this network we have revealed the following top master regulators (signaling proteins and their complexes) that play a crucial role in the molecular mechanism of the studied pathology, which can be proposed as the most promising molecular targets for further drug repurposing and drug development initiatives.

- Jak1
- Ubc9
- NCoR2
- YY1
- PDGFRbeta

Potential drug compounds which can be affecting these targets can be found in the "Finding prospective drug targets" section.

## 7. Methods

### Databases used in the study

Transcription factor binding sites in promoters and enhancers of genes carrying sequence variations were analyzed using known DNA-binding motifs described in the **TRANSFAC®** library, release 2026.1 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transfac>).

The master regulator search uses the **TRANSPATH®** database (BIOBASE), release 2026.1 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transpath>). A comprehensive signal transduction network of human cells is built by the software on the basis of reactions annotated in **TRANSPATH®**.

The information about drugs corresponding to identified drug targets and clinical trials references were extracted from **HumanPSD™** database, release 2026.1 (<https://genexplain.com/humanpsd>).

The Ensembl database release Human112.38 (hg38) (<http://www.ensembl.org>) was used for gene IDs representation and Gene Ontology (GO) (<http://geneontology.org>) was used for functional classification of the studied gene set.

### Genomic data processing

When analyzing a list of genomic variations (from input vcf file or computed by Genome Enhancer from SNP list or from fastq files), first of all, we compute a specific mutation weight ( $w_1$ ) for each variation depending on it's location in gene body and gene flanking regions (-1000 upstream and +1000 downstream of the gene body).

$w_1 = 0.7$  for variations in exon area  
 $w_1 = 1.3$  for variations in promoter region (-1000bp upstream and 100bp downstream of TSS),  
 $w_1 = 1.0$  for variations in other locations.

Next, VCF track (Yes track), provided as input or created by Genome Enhancer from SNP list or fastq files, is compared to Random VCF track (No track) of 10000 random human variations. On both tracks we calculate the score delta values (differences between PWM score values of the TF sites with the reference or with the alternative allele of the considered variation). For each variation we find then the maximal score delta values at each PWM leading either to the gain or to the loss of TF site (with the alternative allele). For selecting the maximum score delta values we consider both directions of DNA strand. Next, by going through all variations we compute two p-values for each PWM – the p-value of site losses and p-value of site gains. The p-values are computed using cumulative Binomial distribution estimating the random chances to observe the found high number of lost or gained TF sites in Yes track in the comparison to the No track. The PWM cut-offs are optimized to obtain the most extreme p-values. We further take top 20 best matrices by p-value from each: gained and lost sites and calculate the mutation weights on the Yes track on the basis of the obtained 40 matrices. Each mutation is assigned with a respective matrix that got the maximum delta value either for the site gain or for the site loss (changed the binding affinity most significantly). This delta is then compared to other delta values that were computed for the respective matrix on the No track. The eventual weight that reflects the transcription factor binding affinity change caused by the mutation is calculated as follows:

$w_2 = -\log_{10}(\text{NoGr} / \text{NoAll})$ , if  $\text{NoGr} > 0$   
 $w_2 = -\log_{10}(1.0 / (2.0 * \text{NoAll}))$ , if  $\text{NoGr} = 0$

where NoGr is the number of deltas from the No track that appeared to be greater than the inspected delta and NoAll is the total number of deltas in the No track. The resulting track is then constructed that contains all sites of the initial Yes track together with the additional weights reflecting the transcription factor binding affinity change caused by the mutation.

The list of 40 matrices most affected by variations will be further used in composite modules search described in the next section.

Total Gene mutation weight is the sum of the weights  $w_1$  of all variations located inside the gene body and in the gene flanking regions summed up with the weight  $w_2$  that reflects the transcription factor binding affinity change caused by the mutation. This weight is calculated by estimating the importance of a certain mutation in terms of gains or losses of binding sites caused by it.

Next, a weighted score is calculated for all genes with the following formula:

Weighted score =  $\text{In\_disease} * \text{In\_transpath} * \text{Gene mutation weight}$ , where

$\text{In\_disease} = 2.0$  for genes assigned to selected diseases,  
 $\text{In\_transpath} = 1.5$  for genes mapped to Transpath pathways,  
 and  $\text{In\_disease} = \text{In\_transpath} = 1.0$  in all other cases.

At the next step, 300 genes with highest weighted score are selected for further CMA model search.

The mutation weights ( $w = w_1 + w_2$ ) are also used to find the regulatory regions of the genes most affected by the variations/SNP. A sliding window of 1100 bp is used to scan through the intronic, 5' and 3' regions of the genes and a region is selected with the highest sum of the mutation weights.

## Methods for the analysis of enriched transcription factor binding sites and composite modules

Transcription factor binding sites in promoters and enhancers of disease affected genes were analyzed using known DNA-binding motifs. The motifs are specified using position weight matrices (PWMs) that give weights to each nucleotide in each position of the DNA binding motif for a transcription factor or a group of them. The matrix profile used to identify potential transcription factor binding sites is a collection of 3390 TRANSFAC® vertebrate matrices carefully selected for the purpose of enrichment analysis.

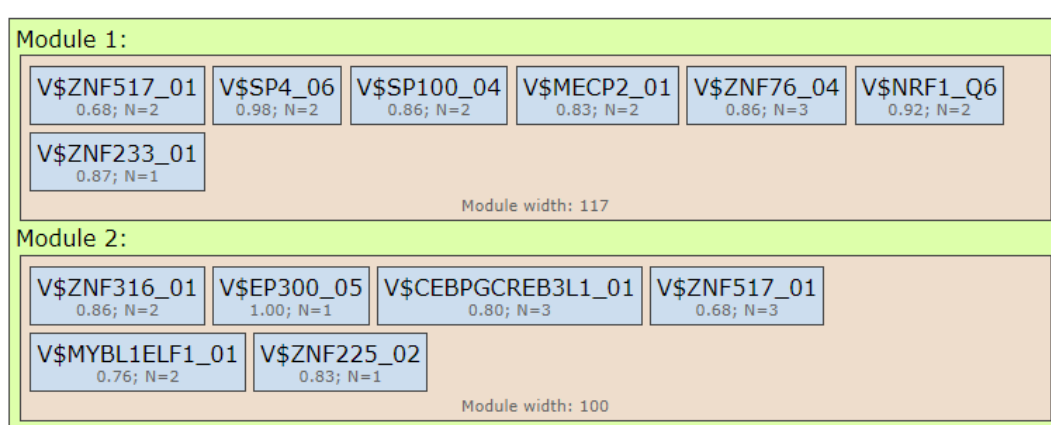
We search for transcription factor binding sites (TFBS) that are enriched in the enhancers under study as compared to a background set of promoters of housekeeping genes. We denote study and background sets briefly as Yes and No sets. In the current work we used a workflow considering promoter sequences of a length 1100bp (-1000 to +100). The error rate in this part of the pipeline is controlled by estimating the adjusted p-value (using the Benjamini-Hochberg procedure) in comparison to the TFBS frequency found in randomly selected regions of the human genome (adj.p-value < 0.01).

We have applied the CMA algorithm (Composite Module Analyst) for searching composite modules [6] in the promoters and enhancers of the Yes and No sets. We searched for a composite module consisting of a cluster of 10 TFs in a sliding window of 200-300 bp that statistically significantly separates sequences in the Yes and No sets (minimizing Wilcoxon p-value). Each composite module is forced to include at least one matrix that was identified as matrix causing the significant change in the transcription factor binding affinity as the result of the observed mutation.

CMA constructs a generalized model of the regulatory regions of the studied genes by specifying combinations of potential TFBSs that are most frequently clustered together. CMA identifies the transcription factors that through their cooperation are able to provide a synergistic effect and, thus, are likely to have a great influence on the gene regulation process.

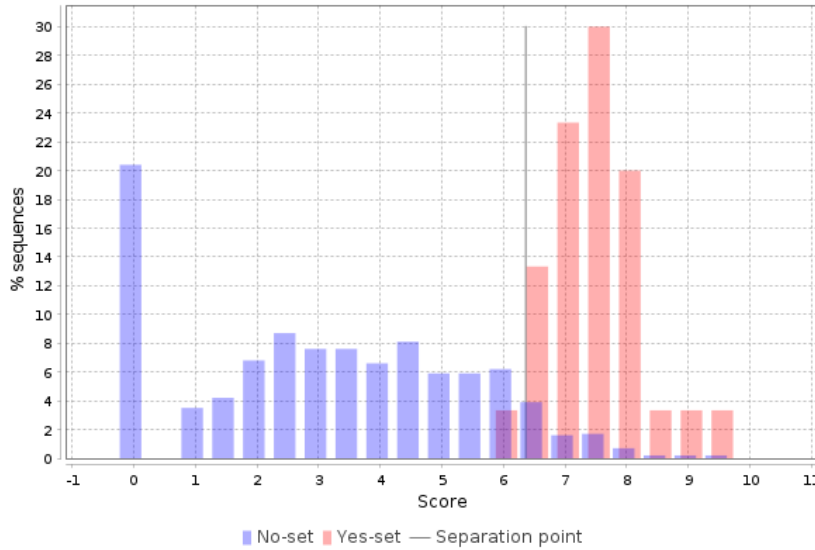
Composite modules can have a complex hierarchical structure consisting of two levels: site models and modules. The highest hierarchical level contains two modules and corresponds to the whole promoter model. The first level, site model, corresponds to the individual site model, based on one PWM. Names of the site models are the same as the matrix names (site models are taken from the profile that was used in the site search). In the resulting schema (see example below) the site models are shown by blue boxes. Within these boxes, there are two values below each site model. The first value is the threshold value for the score of the respective site model, which is determined by the genetic algorithm during the optimization process. The second value is the maximum number of best individual matches (sites) found for this site model and taken into account for calculating the score of the module.

Promoter model example:



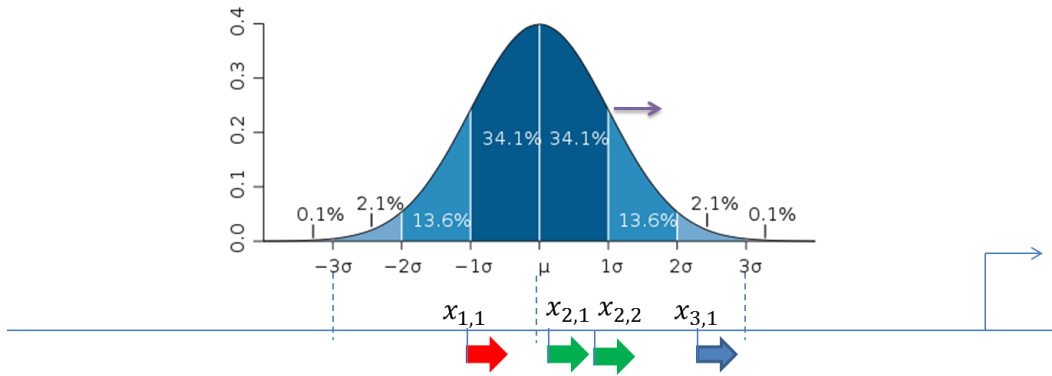
The next level, module, may contain several site models, shown within the light brown boxes. The module is characterized by its width, the average length of DNA window containing matches for the mentioned site models. In the resulting schemas modules are shown in green boxes, and they are numbered: Module 1 and Module 2. The complexity of the promoter model to be constructed is defined by the number of units of each level: number of modules, number of site models, as well as the maximum number of individual sites to be considered. In the Genome Enhancer workflow we limit the number of modules to 2, the number of site models from 6 to 8, and the maximum number of individual sites to be considered from 1 to 3.

The CMA score is calculated for each promoter depending on the number of modules, site models, sites, their scores and other statistical parameters. The higher is the CMA score of a promoter, the better is the differentiation of this promoter from the promoters of the NO set. The distribution of scores for individual promoters is shown on an example histogram below:



The CMA score of the promoters is shown on the X axis of the histogram and the percentage of promoters (% sequences) having this score is shown on the Y axis. The separation point shown in gray corresponds to the average value. Promoters from the NO set with a score above the separation point (blue bars to the right of the separation point) are referred to as false positives. Promoters from the YES set with a score below the separation point (red bars to the left of the separation point) are referred to as false negatives. The YES promoters with a score above the separation point are well separated from the NO promoters, meaning that for these promoters the constructed composite model is most suitable.

The figure below demonstrates the calculation of the score value for the composite modules in the promoter sequences. The TSS is shown as a thin arrow on the right side of the figure. Four thick arrows exemplify four sites found in this promoter. The color of the arrows exemplifies the site model which these sites belong to (three site models – red, green and blue).



A promoter model consists of  $K$  modules. The score of each module  $M_k$  ( $Score(M_k)_{k=1,...,K}$ ) is calculated according to the following formula:

$$Score(M_k) = \max_{\mu=1,L} \sum_{t=1}^{T_k} \sum_{i=1}^{m_t} SiteScore(t,i) \times f(x_{t,i}, \mu, \sigma^2)$$

Here,

- $SiteScore(t,i)$  is the site score for the sites found in the promoter, which is calculated by the MATCH algorithm.
- $m_t$  – the number of sites of the site model  $t$  found in the promoter.
- $T_k$  – the number of site models in the module  $M_k$ , and
- $f(x; \mu, \sigma^2) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2}$

The final promoter score is calculated as the sum of the module scores  $M_k$

Standard deviation ( $\sigma$ ) of the normal distribution is subject to optimization by the genetic algorithm and represents the width of the module in the result of the composite module analysis.

Transcription factors that correspond to the PWMs of the composite modules are further taken to the next step of finding master regulators in networks.

## Methods for finding master regulators in networks

We searched for master regulator molecules in signal transduction pathways upstream of the identified transcription factors. The master regulator search uses a comprehensive signal transduction network of human cells. The goal of the algorithm is to find nodes in the global signal transduction network that may potentially regulate the activity of a set of transcription factors found at the previous step of the analysis. Such nodes are considered as most promising drug targets, since any influence on such a node may switch the transcriptional programs of hundreds of genes that are regulated by the respective TFs. [3,4]

The signal transduction network is represented as a weighted graph, which is defined as  $\Theta = (M, E, S)$ , where  $M$  is the set of nodes (all molecules in the database),  $E$  is the set of edges (all reactions between molecules in the database) and  $S: E \rightarrow R+ \cup \{0\}$  is the cost function that defines a non-negative value for every edge. In the simplest variant of the algorithm, the initial values of the cost functions for each direct reaction are defined as 1.0. So, the cost of any path through the consequent reactions will be equal to the number of reactions. In our application of the algorithm in Genome Enhancer, we used a weighted graph, which encodes the types of reactions (direct or indirect) from TRANSPATH® database into different edge weights (costs).

The core of the algorithm is the Dijkstra's shortest-path algorithm. The upstream search starts from each molecule of the input set (subset  $M_x$  of  $M$ ; e.g. transcription factors found on the previous step) and constructs the shortest-path to all nodes  $i$  of  $M$ , limited by a specified radius. After evaluating all nodes of  $M_x$  the algorithm calculates the number of visits  $N_i$  for each node  $i$  of  $M$ . This corresponds to the number of molecules of the input set  $M_x$  that can receive the signal from the node  $i$ . The values  $N_i$  are required to calculate the "master-regulator" score. The higher the value  $N_i$  the better chances has molecule  $i$  to transduce its signal to the molecules of the initial list  $M_x$ . However, if to use the value of  $N_i$  as a straightforward "master-regulator" score would be too simplistic since it would rank those molecules high that are in general highly connected within the network and thus are likely to be false positives (so called "hub" molecules). So, in our score we incorporate the full number of TF nodes in the whole network  $M$  that can be reached from the molecule  $i$ . The score is computed for each potential master regulator and it reflects a certain balance between sensitivity and specificity of signal transduction from this master node to the downstream effector TFs:

$$S(k) = \sum_{k=1}^{k_{\max}} \frac{M_k}{\left(1 + \kappa \cdot \frac{N_k}{N_{\max,k}}\right) \cdot M_{\max,k}}$$

where  $k$  is the radius of pathway steps from the master node to the effector nodes,  $M_k$  is the number of input TFs reached by a signal from the master node within  $k$  steps, and  $N_k$  is the total number of all potential TFs in the database reached by a signal from the master node within  $k$  steps.  $M_{\max,k}$  and  $N_{\max,k}$  are the highest values among all possible master regulator nodes which helps to normalize the score to the (0,1)-interval. The higher this score, the more sensitive and more specific this master regulator is for the set of input TFs. The parameter  $\kappa$  is the penalty which is set to 0.1 in the Genome Enhancer workflow.

Incorporation of proteomics data into the analysis of master regulators is done through application of the so called "Context algorithm", which is described below.

When we have additional experimental information about the activity of certain components of the signal transduction network (additional context information) we can use this information to adapt the search for master regulators. To do that, the context algorithm encodes this additional context information as modified edge costs in the signaling network. For instance, the proteomics data gives information about proteins that are expressed in the cell. We call them "context proteins". The idea of the approach is to attract the key node search (e.g. the underlying Dijkstra algorithm for shortest paths) towards context proteins by decreasing the costs of those edges that are close to the context proteins in the network. There are two major aspects of this algorithm:

1. Attraction ("gravity") of the shortest-paths towards context proteins. The gravity is achieved by decreasing the costs of the incoming and outgoing edges in the graph for the nodes corresponding to the context proteins. The zero cost of the edges gives the maximal "gravity" for the nodes. During the search the path that follows through this node will be always "cheaper" than other alternative paths. This way we push the search algorithm to construct its paths maximally through the context proteins when it is possible.

2. "Decay" factor. It is necessary to extend the attraction power of the "gravity" to a wider area of the network around the context proteins in order to attract the search algorithm to go as close as possible to the context proteins in case there is no path that goes through the context gene directly. To enable such "long distance" attraction power we distribute the gravity to edges of the next neighboring nodes. This pushes the shortest path algorithm to find alternative paths still at least close to the context proteins. The gravity strength reduces with increasing distance by a decay factor. The decay factor is set to 0.1 in the Genome Enhancer workflow.

The context algorithm is based on creating a graph  $G$  consisting of gravity factors [0..1], which reflect both aspects described above by modifying edge costs. Graph  $G$  is used to modify the costs of  $S$  of original graph  $\Theta$  resulting in  $S'$  which can be then used for any subsequent key node analysis or possibly other shortest path based analysis.

Initially the graph  $G$  is created as a copy of original signaling graph  $\Theta$ , where all edges get initialized with weight zero, while the edges linked to context proteins are initialized by value 1.0. If quantitative proteomics data are available the algorithm allows to use the absolute protein expression values as the graph weights instead of 1.0. In such case the protein expression values are normalized to the range [0..1] (in such case these expression values will represent different context strengths). As the result we obtain a vector  $\vec{c}$  representing the "expression" values of context proteins. The initial graph  $G$  reflects the gravity of the context proteins in the closest proximity only. The gravity is then propagated through the whole graph in downstream and upstream directions as follows. The gravity for the closest edge subsequently forwarded to the next adjacent edge by multiplying it by a user defined decay factor  $d$ .

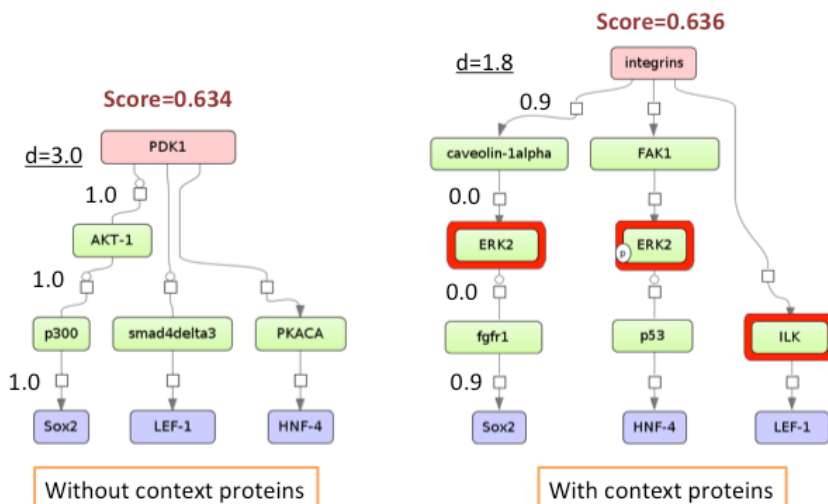
$$D = \sum_{k=1} d^{k-1} \cdot \vec{c} \cdot S^k \quad U = \sum_{k=1} d^{k-1} \cdot \vec{c} \cdot (S^T)^k$$

The first graph  $D$  is the result of the downstream direction and  $U$  is the result of the upstream direction of the gravity propagation through the graph  $G$ . These are two independent feed-forward runs. Both are added together, normalized to [0..1] and each weight  $(D+U)_{ij}$  is replaced by  $(1-(D+U)_{ij})$ , such that the weights become compatible to the cost paradigm. So, the final graph  $G$  is constructed as follows:

$$G = \begin{pmatrix} 1 & \dots & 1 \\ \vdots & & \vdots \\ 1 & \dots & 1 \end{pmatrix} - \frac{(D+U)}{\|D+U\|_{\max}}$$

At the final step, the costs of the edges of the initial signaling graph  $\Theta$  are modified by the context protein information stored in the gravity graph  $G$  by simple multiplication. The factor  $r$  scales the new edge costs such that they are equal to the initial costs of graph  $\Theta$  in average.  $S'_{ij} = S_{ij} \cdot G_{ij} \cdot r$  for all  $i$  and  $j$ .

The Context algorithm is illustrated in the figure below.



In our analysis, we have run the algorithm with a maximum radius of 12 steps upstream of each TF in the input set. The error rate of this algorithm is controlled by applying it 10000 times to randomly generated sets of input transcription factors of the same set-size. Z-score and FDR value of ranks are calculated then for each potential master regulator node on the basis of such random runs (see detailed description in [8]). We control the error rate by the FDR threshold 0.05.

To identify feed forward loops in transduction network we calculate regulatory scores for transcription factors from CMA result and keynodes analysis. The matrices from the CMA model are converted to TFs. Keynode analysis is then performed on these TFs and resulting keynodes are sorted by keynode score. Then the keynodes, which are regulated by the model, are selected.

$$S_j = \sum_{j=1}^{M_j} \frac{1}{D_{ij}}; D_{ij} = \sum_{k=1}^{C_{ij}} d_k$$

Here:

- j – TF (Transcription Factor),
- i – MR (Master Regulator),
- $S_j$  – Regulatory score of the TF,
- $D_{ij}$  – Cumulative distance between MR i and TF j,
- $M_j$  – Number of MRs whose signal can reach the TF j and whose gene is regulated by TF j,
- $C_{ij}$  – Number of steps in the network from between MR i and TF j (shortest path),
- $d_k$  – Distance of the step k in the shortest path between MR i and TF j.

In unweighted TRANSPATH network  $d_k = 1$  for each direct signaling reaction (like  $A+B-C = D$ ),  $d_k \geq 3$  for each semantic reaction (like  $A \rightarrow B$ ).  $d_k$  depends on the type of reaction, on basic or orthology level of its components, and on species of its components.

In weighted TRANSPATH network  $d_k$  is changed after applying the Context Algorithm as described in [ 4].

## Methods for analysis of pharmaceutical compounds

We seek for the optimal combination of molecular targets (key elements of the regulatory network of the cell) that potentially interact with pharmaceutical compounds from a library of known drugs and biologically active chemical compounds, using information about known drugs from HumanPSD™ and predicting potential drugs using PASS program.

### Method for analysis of known pharmaceutical compounds

We selected compounds from HumanPSD™ database that have at least one target. Next, we sort compounds using "Drug rank" that is the sum of the following ranks:

1. ranking by "Target activity score" ( $T\text{-score}_{PSD}$ ),
2. ranking by "Disease activity score" ( $D\text{-score}_{PSD}$ ),
3. ranking by "Clinical validity score".

"Target activity score" ( $T\text{-score}_{PSD}$ ) is calculated as follows:

$$T\text{-score}_{PSD} = - \frac{|T|}{|T| + w(|AT| - |T|)} \sum_{t \in T} \log_{10} \left( \frac{\text{rank}(t)}{1 + \max \text{Rank}(T)} \right),$$

where  $T$  is set of all targets related to the compound intersected with input list,  $|T|$  is number of elements in  $T$ ,  $AT$  and  $|AT|$  are set set of all targets related to the compound and number of elements in it,  $w$  is weight multiplier,  $\text{rank}(t)$  is rank of given target,  $\max \text{Rank}(T)$  equals  $\max(\text{rank}(t))$  for all targets  $t$  in  $T$ .

We use following formula to calculate "Disease activity score" ( $D\text{-score}_{PSD}$ ):

$$D\text{-score}_{PSD} = \begin{cases} \sum_{d \in D} \sum_{p \in P} \text{phase}(d, p) \\ 0, D = \emptyset \end{cases},$$

where  $D$  is the set of selected diseases, and if  $D$  is empty set,  $D\text{-score}_{PSD} = 0$ .  $P$  is a set of all known phases for each disease,  $\text{phase}(p, d)$  equals to the phase number if there are known clinical trials for the selected disease on this phase and zero otherwise.

The clinical validity score reflects the number of the highest clinical trials phase (from 1 to 4) on which the drug was ever tested for any pathology.

### Method for prediction of pharmaceutical compounds

In this study, the focus was put on compounds with high pharmacological efficiency and low toxicity. For this purpose, comprehensive library of chemical compounds and drugs was subjected to a SAR/QSAR analysis provided by the PASS software version 2020. This library contains 13040 compounds along with their pre-calculated potential pharmacological activities of those substances, their possible side and toxic effects, as well as the possible mechanisms of action. All biological activities are expressed as probability values for a substance to exert this activity ( $Pa$ ).

We selected compounds that satisfied the following conditions:

1. Toxicity below a chosen toxicity threshold (defines as  $Pa$ , probability to be active as toxic substance).
2. For all predicted pharmacological effects that correspond to a set of user selected disease(s)  $Pa$  is greater than a chosen effect threshold.
3. There are at least 2 targets (corresponding to the predicted activity-mechanisms) with predicted  $Pa$  greater than a chosen target threshold.

The maximum  $Pa$  value for all toxicities corresponding to the given compound is selected as the "Toxicity score". The maximum  $Pa$  value for all activities corresponding to the selected diseases for the given compound is used as the "Disease activity score". "Target activity score" ( $T\text{-score}$ ) is calculated as follows:

$$T\text{-score}(s) = \frac{|T|}{|T| + w(|AT| - |T|)} \sum_{m \in M(s)} \left( pa(m) \sum_{g \in G(m)} IAP(g) \text{optWeight}(g) \right),$$

where  $M(s)$  is the set of activity-mechanisms for the given structure (which passed the chosen threshold for activity-mechanisms  $Pa$ );  $G(m)$  is the set of targets (converted to genes) that corresponds to the given activity-mechanism ( $m$ ) for the given compound;  $pa(m)$  is the probability to be active of the activity-mechanism ( $m$ ),  $IAP(g)$  is the invariant accuracy of prediction for gene from  $G(m)$ ;  $\text{optWeight}(g)$  is the additional weight multiplier for gene.  $T$  is set of all targets related to the compound intersected with input list,  $|T|$  is number of elements in  $T$ ,  $AT$  and  $|AT|$  are set set of all targets related to the compound and number of elements in it,  $w$  is weight multiplier.

"Druggability score" ( $D\text{-score}$ ) is calculated as follows:

$$D\text{-score}(g) = IAP(g) \sum_{s \in S(g)} \sum_{m \in M(s, g)} pa(m),$$

where  $S(g)$  is the set of structures for which target list contains given target,  $M(s, g)$  is the set of activity-mechanisms (for the given structure) that corresponds to the given gene,  $pa(m)$  is the probability to be active of the activity-mechanism ( $m$ ),  $IAP(g)$  is the invariant accuracy of prediction for the given gene.

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## Thank you for using the Genome Enhancer!

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## Supplementary material

1. [Supplementary table 1 - Detailed report. Composite modules and master regulators \(the most frequently mutated genes in Experiment: short-term survival\).](#)
2. [Supplementary table 2 - Detailed report. Pharmaceutical compounds and drug targets.](#)

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