**Literature search terms**

(Cancer[tiab] OR "Neoplasms"[Mesh]) AND (“Chemotherapy, Adjuvant”[Mesh] OR “Chemotherap\*”[tiab] OR “Antineoplastic Agents”[Mesh]) AND (Neutropenia[tiab] OR Chemotherapy-induced neutropenia[tiab] OR "Neutropenia"[Mesh] OR "Agranulocytosis"[Mesh] OR Leukopenia[tiab] OR "Leukopenia"[Mesh]) AND (Pharmacogenomic\*[tiab] OR Pharmacogenetic\*[tiab] OR Polymorphism\*[tiab] OR single nucleotide polymorphism[tiab] OR "Genetic Variation"[Mesh] OR "Precision Medicine"[Mesh] OR Genome-wide association study[tiab] OR GWAS[tiab] OR "Genome-Wide Association Study"[Mesh]) AND (predict\*[tiab] OR independent predictor\*[tiab] OR risk prediction[tiab] OR “Risk Factors"[Mesh] OR Risk factor\*[tiab] OR determinant\*[tiab])

Table S1: Characteristics of the Included Studies

|  | **First author -year** | **Study Type** | **Cancer Type** | **Cancer Subtype** | **Main Drug Group (Regimen)** | **Main Drug Groupα** | **Gene** | **Variant\*** | **Allele Frequency** | **Patients No.** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Innocenti-2004 (1) |  | Advanced | Advanced and refractory | Other cytotoxic (topoisomerase I inhibitor) | Irinotecan | *UGT1A1* | promoter TA indel (*UGT1A1\*28*)  rs3064744 | 6 TA =0.0020, 8 TA =0.1943, 9 TA =0.0000, 10 TA =0.0000, 11 TA =0.0000 | 66 |
|  | Lamba-2014 (2) | Retrospective | Lung cancer | IIIB or IV NSCLC | Carboplatin or cisplatin + etoposide, gemcitabine or paclitaxel | Platinum-taxane based chemotherapy | *GTF2E1* | *rs447978*  *OR = 0.444 (95% CI: 1.531 − 0.093; P = 0.027)* | A=0.65974 | 90 |
| ERCC4 | *rs744154*  *OR = 2.176 (95% CI: 0.035- 1.52; P = 0.04)* | C=0.26886 |
| TMEM63A | *rs10158985*  *OR = 2.557 (95% CI: 0.087 to 1.79; P = 0.031)* | A=0.222785, T=0.000000 |
|  | Svedberg-2020 (3) | GWAS  (Whole-exome sequencing) | Lung cancer | I-IV NSCLC | Gemcitabine and carboplatin | Platinum and antimetabolites | *HFM1* | *rs17131429* | C=0.28656 | 212 |
| *LRRC8C* | *rs12032393* | G=0.141325 |
| *ABCB11* | *rs497692* | C=0.535827 |
| *ZNF512* | *rs11127071* | A=0.499159, G=0.000000 |
| *CGGBP1* | *rs7432838* | T=0.857151 |
| *FRAS1* | *rs34840208* | G=0.25542 |
| *PCDHB17* | *rs246697* | T=0.18669 |
| *GABRR2* | *rs282117* | C=0.592977 |
| *DNAH11* | *rs12536928* | G=0.000002, T=0.506236 |
| *IMPDH1* | *rs2288551* | T=0.02941 |
| *WEE2* | *rs6967301* | G=0.51282 |
| *PWWP2B* | *rs11817589* | A=0.07263 |
| *ITGB1* | *rs2230396* | C=0.000000, T=0.895080 |
| *MRE11A* | *rs535801* | T=0.307306 |
| *MUCL1* | *rs1048371* | T=0.462188 |
| *SSH1* | *rs34849596* | TT=0.29286 |
| *PSME1* | *rs11548692* | A=0.029562 |
| *BBS2* | *rs191207351* | G=0.01258 |
| *IL34* | *rs3813905* | G=0.33373 |
| *MBP* | *rs138484926* | A=0.00000, G=0.01399 |
| *MAST1* | *rs11085822* | G=0.145659, T=0.000000 |
| *ATP8B3* | *rs2385387* | A=0.000000, T=0.433866 |
| *PABPC1L* | *rs11780* | G=0.371990 |
| *SPATA2* | *rs495337* | A=0.415799, C=0.000000 |
| *MCM5* | *rs2307340* | G=0.07471, T=0.00000 |
| *MCM5* | *rs133427* | A=0.07322 |
| *MYO18B* | *rs133885* | A=0.447273, C=0.000000 |
| *PIK3IP1* | *rs4820044* | G=0.93649 |
|  | Vulsteke-2013 (4) | Observational | Breast cancer |  | FEC | Anthracyclines, alkylating agents and antimetabolites | *ABCC1/MRP1* | *rs4148350*  P 0.004 FDR 0.068 | T=0.058163 | 1012 |
| *UGT2B7* | *rs7668282*  P 0.001 FDR 0.045 | C=0.006545 |
|  | van Erp-2009 (5) | Observational | Multiple | Renal cell carcinoma, Gastrointestinal stromal tumour and other | Sunitinib | Tyrosine kinase inhibitor | CYP1A1 | *2455A/G*  *rs1048943*  OR = 6.24; P =0.029) | C=0.034648 | 219 |
| FLT3 | *738T/C*  *rs1933437*  OR = 2.8; P = 0.008 | A=0.604445, T=0.000000 |
| NR1I3 | *5719C/T, 7738A/C, 7837T/G*  *rs2307424/ rs2307418/ rs4073054*  OR, 1.74; P = .041 | A=0.344024 / G=0.166105/ A=0.617214, G=0.000000, T=0.000000 |
|  | Gréen-2011 (6) | Observational | Ovarian cancer |  | Paclitaxel and carboplatin | Taxanes (paclitaxel) | CYP2C8-HapC | rs1113129  P value = 0.01 | A=0.00000, C=0.11746 | 33 |
| CYP3A5 / CYP2C8-HapC | CYP3A5\*3  rs776746 /rs1113129  P value 0.01 | C=0.930430 / A=0.00000, C=0.11746 |
|  | Melchardt-2015 (7) | Observational | Head and neck cancer | Advanced | Docetaxel, cisplatin and 5-fluorouracil | Platinum, antimetabolites and taxanes | CYP39A1 | rs7761731  *(p* = 0.01) | G=0.00000, T=0.25828 | 78 |
|  | Ongaro-2009 (8) | Observational | Blood cancer | Adult acute lymphoblastic leukaemia | Antimetabolite | Methotrexate (maintenance therapy) | *MTHFR* | 1298A>C  rs1801131  OR= 0.38, 95% CI: (1.6-90; *p*=0.028) | G=0.317025 | 122 |
|  | Senk-2019 (9) | Case-control study | Mesothelioma | MM of pleura or peritoneum | Cisplatin and gemcitabine or pemetrexed | cisplatin-based chemotherapy | *AQP1* | *rs1049305* | C=0.36931 | 231 |
|  | Tomao-2019 (10) | Retrospective | Ovarian cancer | High-grade epithelial ovarian cancer | Carboplatin and paclitaxel | Platinum-based chemotherapy | *BRCA* | *gBRCA1*  *P<0.001* |  | 176 |
| *BRCA* | *gBRCA2*  *P<0.001* |  |
|  | Chen-2015 (11) | Prospective observational | GIT | Metastatic CRC | Other cytotoxic drugs (FOLFIRI)  (Irinotecan is the main drug) | *Irinotecan* | *ABCG1/ ABCC5* | *rs225440T/ rs2292997A* | T=0.416035/  A=0.112657 | 417 |
| *ABCG1/ ABCC5/UGT1* | ***rs225440T/ rs2292997A /***[***UGT1A1\*28***](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab)***/UGT1 rs11563250G*** | T=0.416035/  A=0.112657, C=0.000000, T=0.000000/  3 AT = 0.0020, 16 AT = 0.1943, 17 AT = 0.0000, 18 AT = 0.0000 &19 AT = 0.0000/  G=0.136813 | 417 |
|  | Korver-2023 (12) | Retrospective | Solid cancers | Breast, colon, and upper GIT cancers | Fluoropyrimidine-based chemotherapy  (*ECF, EOF, FEC, FOLFOX, fluorouracil and leucovorin or*  *Capecitabine (± oxaliplatin))* | Fluoropyrimidines | *TGFB1* | [***rs1800469***](https://www.ncbi.nlm.nih.gov/snp/rs1800469) | G=0.677299 | 155 |
| *BDNF* | [***rs6265***](https://www.ncbi.nlm.nih.gov/snp/rs6265#frequency_tab) | T=0.193746 | 155 |
|  | Friedlaender-2019 (13) | Retrospective | Breast cancer | Non metastatic BC | Alkylating agents, anthracyclines, taxanes and platinum-based chemotherapies | *Not reported* | *BRCA* | *gBRCA1* |  | 221 |
|  | Bayraktar-2020 (14) | Retrospective | Breast cancer | Early BC | *Taxane-based chemotherapy*  *(regimen with paclitaxel, docetaxel, or nab-paclitaxel)* | *Taxanes* | *BRCA* | *gBRCA2* |  | 719 |
|  | Innocenti-2009 (15) | Retrospective | Not reported | Advanced cancer | *Irinotecan (single agent)* | *Irinotecan* | *UGT1A1* | *UGT1A1\*93 (rs1092302)* |  | 78 |
| *SLCO1B1* | [***SLCO1B1\*1b (rs2306283)***](https://www.ncbi.nlm.nih.gov/snp/rs2306283) | G=0.406101, T=0.000000 | 78 |
| *ABCC1* | [***IVS11 −48C>T (rs3765129)***](https://www.ncbi.nlm.nih.gov/snp/rs3765129) | T=0.146620 | 78 |
|  | Tibaldi-2008 (16) | Observational | Lung cancer | NSCLC | *Cisplatin and gemcitabine* | *Not reported (platinum)* | *CDA* | [***Lys27Gln (rs2072671)***](https://www.ncbi.nlm.nih.gov/snp/rs2072671#frequency_tab) | C=0.351089 | 65 |
|  | Cortejoso-2013 (17) | Retrospective | GIT | CRC | *Oxaliplatin-based chemotherapy irinotecan-based chemotherapy* | *Oxaliplatin and irinotecan* | *ERCC1* | [***Asn118Asn (rs11615)***](https://www.ncbi.nlm.nih.gov/snp/rs11615) | G=0.379441 | 106 |
|  | Ruzzo-2017 (18) | Retrospective | GIT | CRC | Fluoropyrimidine-based chemotherapy  *(FOLFOX-4 or XELOX)* | Fluoropyrimidine | *DPYD* | [*\*6 (rs1801160)*](https://www.ncbi.nlm.nih.gov/snp/rs1801160) | T=0.051192 | 508 |
| *DPYD* | [*\*2A (rs3918290)*](https://www.ncbi.nlm.nih.gov/snp/rs3918290) | G=0.000000, T=0.004547 | 508 |
|  | Lee-2014 (19) | Retrospective | GIT | Colon cancer | *FOLFOX or FOLFIRI ± cetuximab* | *Fluorouracil* | *DPYD* | [*\*2A (rs3918290)*](https://www.ncbi.nlm.nih.gov/snp/rs3918290) | G=0.000000, T=0.004547 | 2886 |
| *DPYD* | [*D949V (rs67376798)*](https://www.ncbi.nlm.nih.gov/snp/rs67376798) | A=0.00561 | 2886 |
|  | Yao-2010 (20) | Retrospective | Breast cancer |  | *Anthracycline-based regimen or non-anthracycline-containing regimen (CMF or CAF) ± tamoxifen* | *Cyclophosphamide*  *(alkylating agents)* | *GSTP1* | [***Ile105Val (rs1695)***](https://www.ncbi.nlm.nih.gov/snp/rs977894) | G=0.326272, T=0.000000 | 458 |
|  | Furlanetto-2021 (21) | Retrospective  (clinical trial data) | Breast cancer | TNBC | *Anthracycline-taxane-based chemotherapy* | *Anthracyclines and taxanes* | *BRCA* | *gBRCA1/2* |  | 1171 |
|  | Joerger-2012 (22) | Prospective clinical study | Lung cancer | NSCLC | *platinum-gemcitabine chemotherapy* | *Platinum and gemcitabine* | *CDA* | [***A79C (rs2072671)***](https://www.ncbi.nlm.nih.gov/snp/rs2072671#frequency_tab) | C=0.351089 | 137 |
| *RECQ1* | [***A159C (rs13035)***](https://www.ncbi.nlm.nih.gov/snp/rs13035) | G=0.43661 | 137 |
|  | Garziera-2017 (23) | Retrospective | GIT | Non metastatic CRC | *(FOLFOX4)* | *Not reported*  *(platinum)* | *HLA-G* | [***rs1610696***](https://www.ncbi.nlm.nih.gov/snp/rs1610696) | G=0.31090 | 144 |
|  | Fasching-2022 (24) | GWAS | Breast cancer |  | *FEC* | *Not reported* | *NLRC5* | [***rs4784750***](https://www.ncbi.nlm.nih.gov/snp/rs4784750) | A=0.00000, T=0.15302 | 3276 |
| *TNFSF13B* | [***rs16972207***](https://www.ncbi.nlm.nih.gov/snp/rs16972207) | G=0.11770, T=0.00000 | 3276 |
|  | Huszno-2013 (25) | Retrospective study | Breast cancer | Early BC | *anthracycline-based chemotherapy* | *anthracyclines* | *BRCA* | *BRCA1/2* |  | 270 |
|  | Ludovini-2017 (26) | Prospective clinical study | Breast cancer | Early BC | *CMF or FEC* | *Not reported* | *TS* | *TS 2R/3R*  rs45445694 | CCGCGCCACTT=0.0000, CCGCGCCACTTGGCCTGCCTCCGTCCCGCCGCGCCACTT=0.2906, CCGCGCCACTTGGCCTGCCTCCGTCCCGCCGCGCCACTTGGCCTGCCTCCGTCCCGCCGCGCCACTTGGCCTGCCTCCGTCCCGCCGCGCCACTT=0.0001 | 244 |
|  | Yao-2010 (27) | Retrospective | Breast cancer |  | *CAF or CMF ± tamoxifen* | *Not reported* | *SOD2* | [***Val16Ala (rs4880)***](https://www.ncbi.nlm.nih.gov/snp/rs4880) | G=0.497902 | 458 |
|  | Madi-2018 (28) | Retrospective (clinical trial data) | GIT | Advanced CRC | *oxaliplatin and fluoropyrimidines ± cetuximab* | *oxaliplatin and fluoropyrimidines* | *DPYD* | [*Asp949Val (rs67376798)*](https://www.ncbi.nlm.nih.gov/snp/rs67376798#frequency_tab) | A=0.00561 | 2183 |
|  | Goekkurt-2009 (29) | Retrospective | GIT | Advanced gastric cancer | *FLO or FLP* | *Platinum and fluorouracil* | *MTHFR* | *A2756G (****rs1805087)*** | G=0.190499 | 134 |
| *GSTP1* | [***Ile105Val (rs1695)***](https://www.ncbi.nlm.nih.gov/snp/rs1695#frequency_tab) | G=0.326272, T=0.000000 | 134 |
| *ERCC1* | ***C118T/* *C8092A***  ***(rs11615/ rs3212986)*** | G=0.376972/ A=0.246764 | 134 |
|  | McLeod-2010 (30) | Retrospective | GIT | Advanced CRC | *IROX, IFL, or FOLFOX* | *Platinum, fluorouracil and irinotecan* | *UGT1A1* | [***UGT1A1\*28***](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) (The wild type is 6 repeats while the variant is 7)  ***(6/6, 6/7, and 7/7 genotypes)*** | 3 AT = 0.0020, 16 **AT = 0.1943**, 17 AT = 0.0000, 18 AT = 0.0000 &19 AT = 0.0000 | 107 |
| *GSTM1* | [*GSTM1\*0*](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) | Gene deletion | 107 |
|  | Petty-2007 (31) | Prospective clinical study | Lung cancer | Advanced NSCLC | *Docetaxel and gemcitabine* | *Not reported*  *(mitotic inhibitors)* | *XPD* | [***K751Q (rs13181) (Lys751Gln)***](https://www.ncbi.nlm.nih.gov/snp/rs13181#frequency_tab) | A=0.000000, G=0.373251 | 49 |
|  | Grenda-2020 (32) | Observational | Lung cancer | NSCLC | *Platinum-based chemotherapy* | *platinum* | *ERCC1* | [***rs11615***](https://www.ncbi.nlm.nih.gov/snp/rs11615) | G=0.379441 | 113 |
|  | Riera-2018 (33) | Prospective clinical study | GIT | Metastatic CRC | *irinotecan‐containing chemotherapy* | *Irinotecan* | *UGT1A1* | [***UGT1A1\*28***](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) | 3 AT = 0.0020, 16 **AT = 0.1943**, 17 AT = 0.0000, 18 AT = 0.0000 &19 AT = 0.0000 | 308 |
|  | Ramchandani-2007 (34) | Retrospective | Advanced solid tumours or lymphoma |  | *Irinotecan* | *Irinotecan* | *UGT1A1* | [***UGT1A1\*28***](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) | 3 AT = 0.0020, 16 **AT = 0.1943**, 17 AT = 0.0000, 18 AT = 0.0000 &19 AT = 0.0000 | 86 |
|  | Martinez-Balibrea-2010 (35) | Retrospective | GIT | Metastatic CRC | *Irinotecan and fluorouracil* | *irinotecan/5FU* | *UGT1A1* | [***UGT1A1\*28***](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) | 3 AT = 0.0020, 16 **AT = 0.1943**, 17 AT = 0.0000, 18 AT = 0.0000 &19 AT = 0.0000 | 149 |
|  | Sawyer-2016 (36) | Prospective pharmacogenetic study | Breast cancer | Early BC | *Mainly FEC with other regimens* | *Epirubicin*  *(anthracyclines)* | *UGT2B7* | ***C***[***161T (rs7668258)***](https://www.ncbi.nlm.nih.gov/snp/rs7668258) | C=0.478377 | 132 |
|  | Gréen-2016 (37) | Exome-wide SNV association | Lung cancer | NSCLC | *Gemcitabine and carboplatin* | *Not reported* | *OR4D6* | [***rs1453542***](https://www.ncbi.nlm.nih.gov/snp/rs1453542) | A=0.00001, **C=0.28128** | (32 + 291) discovery and validation |
|  | Booton-2006 (38) | Retrospective  (clinical trial data) | Lung cancer | NSCLC | *Docetaxel and carboplatin, MIC, or MVP* | *platinum* | *XPD* | *Asp312Asn* ***/Lys751Gln***  ***rs1799793/ rs13181*** | **T=0.34727** / A=0.000000, **G=0.373251** | 98 |

**GIT**: gastrointestinal. **CRC**: colorectal cancer. **NSCLC**: non-small cell lung cancer. **BC:** breast cancer. **TNBC**: triple negative breast cancer. **SNV**: single nucleotide variant. **FOLFIRI:** folinic acid, fluorouracil, and irinotecan. **ECF:** epirubicin, cisplatin and fluorouracil. **EOF**: epirubicin, oxaliplatin and fluorouracil. **FOLFOX-4:** oxaliplatin, folinic acid and fluorouracil. **XELOX:** oxaliplatin and capecitabine. **CMF:** cyclophosphamide, methotrexate, and fluorouracil. **CAF:** cyclophosphamide, Adriamycin (doxorubicin), and fluorouracil. **FEC:** fluorouracil, epirubicin, and cyclophosphamide. **FLO:** fluorouracil, leucovorin, and oxaliplatin. **FLP:** fluorouracil, leucovorin, and cisplatin. **MIC:** mitomycin, ifosfamide, cisplatin. **MVP:** mitomycin, vinblastine, cisplatin. **IROX:** irinotecan and oxaliplatin. **IFL:** irinotecan and fluorouracil.

**Note: Variants** that were listed together were investigated as a haplotype**. Main drug group** as reported by the study. **Allele frequencies** were derived for the Allele Frequency Aggregator (ALFA) data in dpSNP (<https://www.ncbi.nlm.nih.gov/snp/>).

Table S2: Literature-search excluded variants

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study** | **Gene** | **Variant** | **Allele frequency** | **Exclusion reason** |
|  | Tomao-2019 (10) | *BRCA* | *gBRCA1*  *gBRCA2* | **-** | gBRCA1 and gBRCA2 positive status are determined by the presence of any germline pathogenic variant in the BRCA1 or BRCA2 genes. These variants have very low frequency in the European population. |
|  | Friedlaender-2019 (13) |
|  | Bayraktar-2020 (14) |
|  | Furlanetto-2021 (21) |
|  | Ruzzo-2017 (18) | *DPYD* | [*\*2A (rs3918290)*](https://www.ncbi.nlm.nih.gov/snp/rs3918290) | G=0.000000, T=0.004547 | MAF < 1% |
|  | Lee-2014 (19) | *DPYD*  *DPYD* | [*\*2A (rs3918290)*](https://www.ncbi.nlm.nih.gov/snp/rs3918290) | G=0.000000, T=0.004547 |
|  | [*D949V (rs67376798)*](https://www.ncbi.nlm.nih.gov/snp/rs67376798) | A=0.00561 |
|  | Madi-2018 (28) | *DPYD* | [*Asp949Val (rs67376798)*](https://www.ncbi.nlm.nih.gov/snp/rs67376798#frequency_tab) | A=0.00561 |
|  | Innocenti-2004 (1) | *UGT1A1* | promoter TA indel (*UGT1A1\*28*)  rs3064744 | 6 TA =0.0020, 8 TA =0.1943, 9 TA =0.0000, 10 TA =0.0000, 11 TA =0.0000 | The variant is tandem repeat (TA repeats) not a single nucleotide variant. In addition, it was reported for the uncommon drug in study data irinotecan. |
|  | Riera-2018 (33) |
|  | Ramchandani-2007 (34) |
|  | McLeod-2010 (30) | *UGT1A1* | [***UGT1A1\*28***](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) (The wild type is 6 repeats while the variant is 7)  ***(6/6, 6/7, and 7/7 genotypes)*** | 6 TA =0.0020, 8 TA =0.1943, 9 TA =0.0000, 10 TA =0.0000, 11 TA =0.0000 | The variant is tandem repeat (TA repeats) not a single nucleotide variant. |
|  | Martinez-Balibrea-2010 (35) | *UGT1A1* |
|  | McLeod-2010 (30) | [*GSTM1\*0*](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) | Gene deletion | [*GSTM1\*0*](https://www.ncbi.nlm.nih.gov/snp/rs3064744#frequency_tab) | Because it is a gene deletion. |
|  | 1454109860 | *PTPN2* | *rs11664064* | C=0.04717 | This variant was reported in patients treated with azathioprine, which, although it can be classified as an antimetabolite, is not a cancer drug. |
|  | 1452563360 | *MIR23A; MIR24-2; MIR27A* | *rs895819* | C=0.321606 | The study investigated the impact of this variant on other *DPYD* variants (gene-gene interaction) which is out of the scope of this study (39). |
|  | 981398678 | *DPYD* | *rs2297595* | C=0.098205 | In the study, they sequenced *DPYD* cDNA to identify the haplotypes and investigated its association with neutropenia in another cohort classified as: high‐risk patients, low-risk patients and control based on the presence of certain haplotypes (40). |
|  | 1451206444 | *UGT1A1* | *UGT1A1\*1; UGT1A1\*28* |  | The variant is tandem repeat (TA repeats) not a single nucleotide variant. |

**MAF:** minor allele frequency

Table S3: PharmGKB Reported variants for the main drug groups

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PharmGKB ID** | **Gene** | **Variant** | **Allele frequency** | **Phenotype** | **Section** | **Drug group** |
|  | *-* | ***XRCC1*** | ***rs25487*** | **C=0.642131** | **Efficacy (treatment response)** | **Clinical Annotations**  **Level 2B** | **Platinum** |
|  | 655386620 | *ERCC2* | *rs1799793* | T=0.35200 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | 655386329 | *TP53* | *rs1042522* | C=0.73664 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | 981201312 | *MSH6* | *rs3136228* | G=0.364580 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | - | *ERCC5* | *rs17655* | C=0.22121 |  |  |  |
|  | 1184348675 | *RAD52* | *rs11226* | A=0.45611 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | 1184348683 | *MUTYH* | *rs3219484* | T=0.070132 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | 655386624 | *XRCC1* | *rs25487* | C=0.642131 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | 1184348667 | *LIG3* | *rs1052536* | T=0.462444 | Toxicity (neutropenia) | Variant Annotations | Platinum |
|  | 1449270852 | *PERP* | *rs78428806* | A=0.04808 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270824 | *CBR3* | *rs74743371* | T=0.01301 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270831 | *CYP2C8* | *rs117458836* | A=0.01393 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270838 | *TP53AIP1* | *rs118088833* | T=0.01316 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270845 | *GNL3* | *rs112242273* | T=0.03345 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270787 | *PERP* | *rs117101815* | T=0.02783 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270794 | *PERP* | *rs9402944* | T=0.05261 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270801 | *TOP2A* | *rs181501757* | A=0.00353, T=0.00000 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270808 | *NOS1* | *rs149212925* | G=0.0002 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270815 | *CBR3* | *rs112783657* | T=0.02814 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449271386 | *RBX1* | *rs141084494* | A=0.00259 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270625 | *PIK3R2* | *rs56022120* | T=0.011439 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270634 | *PIK3R2* | *rs150688309* | G=0.0016, T=0.0000 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270643 | *PIK3R2* | *rs58695150* | T=0.01364 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270650 | *HMMR* | *rs299293* | T=0.12878 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270601 | *FOXO1* | *rs144991623* | T=0.00252 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270611 | *PERP* | *rs9389568* | C=0.04934 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270618 | *PIK3R2* | *rs8110364* | A=0.01533 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270755 | *PIK3R2* | *rs148013902* | T=0.01519 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270764 | *PIK3R2* | *rs55633228* | T=0.01220 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270773 | *INSR* | *rs41412545* | A=0.03334 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270780 | *PPP2R5D* | *rs3805945* | C=0.04254 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270725 | *PIK3R2* | *rs79430272* | T=0.011613 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270732 | *PIK3R2* | *rs118129530* | A=0.01617 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270739 | *CCNK* | *rs77769901* | G=0.01218 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270746 | *PIK3R2* | *rs145623321* | T=0.01156 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270690 | *HMMR* | *rs299313* | A=0.08407 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270697 | *IRS1* | *rs115457081* | A=0.013147 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270704 | *PIK3R2* | *rs117341846* | T=0.01568 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270711 | *TP53* | *rs4968187* | T=0.002917 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270718 | *INSR* | *rs142244113* | T=0.03388 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270657 | *PIK3R2* | *rs138602176* | A=0.01596 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270667 | *PIK3R2* | *rs148235907* | A=0.01589 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270674 | *PIK3R2* | *rs117951771* | T=0.00997 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1449270683 | *HMMR* | *rs299314* | C=0.13400 | Toxicity (neutropenia) | Variant Annotations | Anthracyclines |
|  | 1184348675 | *RAD52* | *rs11226* | A=0.45611 | Toxicity (neutropenia) | Variant Annotations | Alkylating Agents |
|  | 1184348683 | *MUTYH* | *rs3219484* | T=0.070132 | Toxicity (neutropenia) | Variant Annotations | Alkylating Agents |
|  | 655386620 | *ERCC2* | *rs1799793* | T=0.35200 | Toxicity (neutropenia) | Variant Annotations | Alkylating Agents |
|  | 655386329 | *TP53* | *rs1042522* | C=0.73664 | Toxicity (neutropenia) | Variant Annotations | Alkylating Agents |
|  | 655386624 | *XRCC1* | *rs25487* | C=0.642131 | Toxicity (neutropenia) | Variant Annotations | Alkylating Agents |
|  | 1184348667 | *LIG3* | *rs1052536* | T=0.462444 | Toxicity (neutropenia) | Variant Annotations | Alkylating Agents |
|  | 1444935324 | *ERCC2* | *rs13181* | G=0.375417 | Toxicity (neutropenia) | Variant Annotations | Taxanes |
|  | 1451719260 | *ABCB1* | *rs1045642* | G=0.478393 | Toxicity (neutropenia) | Variant Annotations | Taxanes |
|  | 1454109860 | *PTPN2* | *rs11664064* | C=0.04717 | Toxicity (Leukopenia) | Variant Annotations | Anti-metabolites |
|  | 1184514055 | *NUDT15* | *rs116855232* | T=0.003814 | Toxicity (Leukopenia) | Variant Annotations | Anti-metabolites |
|  | 981201312 | *MSH6* | *rs3136228* | G=0.364580 | Toxicity (neutropenia) | Variant Annotations | Anti-metabolites |
|  | 655387891 | *MTHFR* | *rs1801133* | A=0.343070 | Toxicity (Leukopenia) | Variant Annotations | Anti-metabolites |
|  | 1452563360 | *MIR23A; MIR24-2; MIR27A* | *rs895819* | C=0.321606 | Toxicity (neutropenia) | Variant Annotations | Anti-metabolites |
|  | 981398678 | *DPYD* | *rs2297595* | C=0.098205 | Toxicity (neutropenia) | Variant Annotations | Anti-metabolites |
|  | 1451206444 | *UGT1A1* | *UGT1A1\*1; UGT1A1\*28* |  | Toxicity (neutropenia) | Variant Annotations | Anti-metabolites |
|  | 1446907551 | *NA* | *rs2292997* | A=0.114556 | Toxicity (neutropenia) | Variant Annotations | Anti-metabolites |
|  | 1446907535 | *ABCG1* | *rs225440* | T=0.413504 | Toxicity (neutropenia) | Variant Annotations | Anti-metabolites |
|  | 1452616240 | *DPYD* | *DPYD* c.2194G>A (\**6)* *rs1801160* | T=0.049261 | Toxicity (neutropenia and Leukopenia) | Variant Annotations | Anti-metabolites |

**Variants** no. 10–44 were also reported for alkylating agents and antimetabolites in the variant annotation of the fluorouracil, epirubicin, and cyclophosphamide (FEC) regimen. **Variant** no. 5 (ERCC5 rs17655) was added from the same study that reported the variants no. 6, 7 & 9.

**Variants** that were listed together were investigated as a haplotype. **Main drug group** as reported by the study. **Allele frequencies** were derived for the Allele Frequency Aggregator (ALFA) data in dpSNP (<https://www.ncbi.nlm.nih.gov/snp/>).

Table S4: PharmGKB excluded variants

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **PharmGKB ID** | **Gene** | **Variant** | **Allele frequency** | **Exclusion reason** |
|  | 1449270801 | *TOP2A* | *rs181501757* | A=0.00353, T=0.00000 | MAF < 1% |
|  | 1449270808 | *NOS1* | *rs149212925* | G=0.0002 |
|  | 1449271386 | *RBX1* | *rs141084494* | A=0.00259 |
|  | 1449270634 | *PIK3R2* | *rs150688309* | G=0.0016, T=0.0000 |
|  | 1449270601 | *FOXO1* | *rs144991623* | T=0.00252 |
|  | 1449270711 | *TP53* | *rs4968187* | T=0.002917 |
|  | 1449270674 | *PIK3R2* | *rs117951771* | T=0.00997 |
|  | 1184514055 | *NUDT15* | *rs116855232* | T=0.003814 |
|  | 1444935324 | *ERCC2* | *rs13181* | G=0.375417 | The variant was significant in specific subgroup who were lacking CYP3A4 and CYP3A5 expression (41). |
|  | 1451719260 | *ABCB1* | *rs1045642* | G=0.478393 | A meta-analysis that included studies with Asian populations (42). |
|  | 1454109860 | *PTPN2* | *rs11664064* | C=0.04717 | This variant was reported in patients treated with azathioprine, which, although it can be classified as an antimetabolite, is not a cancer drug. |
|  | 1452563360 | *MIR23A; MIR24-2; MIR27A* | *rs895819* | C=0.321606 | The study investigated the impact of this variant on other *DPYD* variants (gene-gene interaction) which is out of the scope of this study (39). |
|  | 981398678 | *DPYD* | *rs2297595* | C=0.098205 | In the study, they sequenced *DPYD* cDNA to identify the haplotypes and investigated its association with neutropenia in another cohort classified as: high‐risk patients, low-risk patients and control based on the presence of certain haplotypes (40). |
|  | 1451206444 | *UGT1A1* | *UGT1A1\*1; UGT1A1\*28* |  | The variant is tandem repeat (TA repeats) not a single nucleotide variant. |

**MAF:** minor allele frequency**.**

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