REVIEW ARTICLE

Genetic variants as potential predictive biomarkers in advanced colorectal cancer patients treated with oxaliplatin-based chemotherapy†

Running title: predictive biomarkers in advanced colorectal cancer patien

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Abstract

Chemotherapy regimen containing oxaliplatin is often the first-line treatment for patient with advanced colorectal cancer. Oxaliplatin binds to DNA, leading to the formation of crosslinks and bulky adducts. Approximately 50% of patients with CRC benefit from treatment with oxaliplatin. It is possible that genetic variants in biological pathways involved in drug transportation, drug metabolism, DNA damage repair, and cell cycle modulation might affect the activity, or efficacy of oxaliplatin. Because oxaliplatin resistance may be related to these genetic variants and may therefore be an important reason for treatment failure, we have summarized the genetic variations that have been reported to be predictive markers of the response to oxaliplatin based therapy in patients with advanced CRC.

Keywords: colorectal cancer, oxaliplatin, resistance, predictive biomarkers

1. Introduction:

Colorectal cancer (CRC) is the third most common diagnosed cancer and a major cause of cancer related mortality. CRC is a multistep process in which a combination of genetic and epigenetic factors leads to alterations in normal colonic mucosa to develop into invasive cancer. The major etiological and risk factors for CRC have been identified. Genetic and environmental alterations interact in a complex way. The overall heritability of CRC overall has been estimated to be 20-30%, and whilst important for familial CRC, the genetic factors have not been clarified (Vatandoost et al., 2016). Complete surgical removal of the tumor is the main treatment for CRC, particularly in its early stages (I/II). Patients with stage II/ III rectal cancers are usually treated with neo-adjuvant chemotherapy and radiation therapy. However, the benefits of neoadjuvant therapy in locally advanced CRC are still unclear. In stage III CRC in which there is involvement of ganglion, post-surgical chemotherapy is required to reduce the risk of recurrence. The use of adjuvant treatment in patients with stage II CRC is more controversial (Mirzaei et al., 2016).

During the past 50 years, 5-fluorouracil (5-FU) has been a major chemotherapeutic treatment in patients with CRC. More recently, 5-formyltetrahydrofolate (Leucovorin, LV) has been added to 5-FU, and has been shown to improve the response rate (RR) and the overall survival (OS). The use of capecitabine (an oral 5-FU pro-drug) alone was shown to have a greater efficacy with a lower adverse events profile compared to 5-FU itself (Bahrami et al., 2017).

Oxaliplatin, contains a 1, 2-diamino-cyclohexane ring and is the first cytotoxic platinum-based chemotherapeutic drug that has been shown to have antitumor efficacy in the treatment of CRC. It acts by forming DNA adducts and crosslinks that leads to an inhibition of cell replication, whilst promoting apoptosis. When added to either 5-FU (FOLFOX) or capecitabine (CAPOX or XELOX), it has been shown to improve disease free-survival (DFS)

and OS in patients with CRC in whom tumors have been completely resected. Oxaliplatin has a modest activity as a monotherapy, but has been shown to have a substantially better effect when used in conjugation with other agents such as fluoropyrimidines (Berretta et al., 2006). Treatment with FOLFOX has been reported to increase OS in the adjuvant setting in stage III patients compared to 5-FU/LV or 5-FU/ irinotecan combinations. Finally, these combination regimens are now considered to be the best choice for treatment of patients with stage III CRC, apart for patients in whom oxaliplatin is contraindicated (Madi et al., 2012)**.**

The efficacy of oxaliplatin may be affected by the intracellular availability of the drug, and this is dependent on the transportation of oxaliplatin into and out of the cells. Its efficacy is also dependent on its rate of cell metabolism (Marsh et al., 2009). The Food and Drug Administration (FDA) has reported that >60% of the subjects receiving oxaliplatin are affected by some degree of peripheral neuropathy (Ibrahim et al., 2004): these include ototoxicity and a dysphoric syndrome. Several approaches have been used to reduce oxaliplatin toxicity (Di Francia et al., 2013). A degree of oxaliplatin resistance may be due to the increased DNA-repair mechanisms, reduced glutathione conjugation, and enhanced drug efflux. Also, accumulating body of data suggests that functional genomic variations in drug target genes, DNA-repair enzymes, and metabolizing enzymes possibly contributed in drug sensitivity (Kang, 2003).

Since the oxaliplatin resistance may be related to genetic mutations of genes in these pathways, and is now one of the main reasons of treatment failure, we have summarized the current data on the genetic variations identified as predictive markers of the response to oxaliplatin based therapy in advanced CRC patients.

2. Candidate Genes and Polymorphisms

2.1. Drug transporter

Several transporters located in the cell membrane determine the disposition and response to various drugs. Transporters have been classified into two main groups: (a) the ATP-binding cassette (ABC) family and (b) the class of solute carrier (SLC) membrane proteins. The ABC transporters (i.e. ABCB1, ABCC2, and ABCG2) are active efflux pumps, whereas SLC group members (i.e. SLCO1B1, SLC19A1) regulate the bidirectional or influx movement of substrates along the cell membranes. The concerted action of these carriers in the membranes of epithelial cells leads to drug translocation (Ho and Kim, 2005). Some recent studies have investigated the predictive power of variations in the ABC/SLC proteins on sensitivity to treatment with oxaliplatin combined with fluoropyrimidines (Mirakhorli et al., 2013). A study performed on 157 Taiwanese patients receiving first-line FOLFOX-4, reported a significant association between a ABCB1 variant (rs1045642) and poorer progression free survival (PFS) (Huang et al., 2011). Furthermore, a study in 50 Iranian cases with primary stage II/III CRC that received FOLFOX-4 regimen found an association between the ABCC2 polymorphism (rs2273697) with improved OS and DFS without an effect on primary relapse (Mirakhorli et al., 2013). The MRP2 transporter contributes to the detoxification of oxaliplatin, and also determines the resistance to platinum agents (Liu et al., 2012). However the phenotypic effect of the missense mutation (1249G>A) on the MRP2 activity is not fully understood (Cascorbi and Haenisch, 2010). Wu et al assessed the effects of ABCB1 polymorphisms in 1028 Chinese CRC patients receiving postoperative FOLFOX or XELOX regimen. They found the rs1045642 (CT genotype) was related to a higher recurrence free survival (RFS), whilst the rs1128503 (TT or CT genotype) was associated with a longer OS. Indeed, rs1128503 (TT), rs2032582 (TT) and rs1045642 (TT) haplotype carriers were found to have an unfavorable PFS. However these results have not been replicated in other studies conducted in 428 patients with the identical clinical characteristics (Yue et al., 2013). So, the predictive value of ABCB1 markers remains uncertain.

2.2. Metabolic enzymes

Among the metabolic enzymes involved in drug detoxification, there has been particular attention focused on glutathione-S-transferase (GSTs) (Watson et al., 1998). Polymorphisms of the GSTs are regarded as predictors of the effectiveness of oxaliplatin-based chemotherapy. GSTs are a superfamily of phase II enzymes that are involved in the inactivation of electrophilic xenobiotics by combination with glutathione (GSH), then facilitate excretion from the body. These proteins and the isoforms (e.g. GSTP1, GSTT1 and, GSTM1) participate directly in the detoxification of platinum compounds. For instance, GSTs adds a glutathione molecule to the electrophilic group of oxaliplatin and thus contributes to the determination of resistance to these drugs (Townsend and Tew, 2003).

Some GST gene variants are associated with variations in enzyme activity. Four common polymorphisms have been found to reduce GSTs functionality. Two common mis-sense mutations of the GSTP1 coding gene, are the 313A>G (rs1695) and the 341C>T (rs1138272) nucleotide substitutions (Watson et al., 1998). For the GSTT1 and GSTM1 isoforms the most common polymorphisms found were a deletion of a part of the gene (null-genotype) which leads to complete loss of the enzymatic activity in homozygous status (Rossini et al., 2002). These four GSTs markers are under assessment for their potential role in regulating the tumor sensitivity to oxaliplatin. There is substantial evidence for a role of GSTP1 (rs1695) mutation as a predictor of oxaliplatin efficacy. Until now, however the results have been inconsistent. A meta-analysis, including 1234 patients with advanced or metastatic CRC receiving xaliplatin-based treatment, did not find any significant association between the rs1695 polymorphism of GSTP1 and tumor response. However, this meta-analysis was limited due to the high heterogeneity among the 13 studies, and the technical difficulties of undertaking subgroup analysis on the specific regimen administered, or the effects of ethnicity (Ye et al., 2013).

The effect of the rs1695 of GSTP1 variant on OS has been less well established. A study on 335 advanced CRC patients treated with adjuvant FOLFOX-6 chemotherapy; the GSTP1 rs1695 variant (Val/Val genotype) was found to be related to a longer OS than the GSTP1 (IIe/Ile genotype) (Li et al., 2012). Consistent with this study, a cohort of 107 metastatic colorectal cancer (mCRC) patients (Stoehlmacher et al., 2004), administrating an oxaliplatin/ 5-FU as first or second line therapy, the GSTP1 (rs1695) Val allele was related to a better survival (Val/Val, 24.9 vs. Ile/Val, 13.3 vs. Ile/Ile 7.9 months). Despite these promising finding, a study with a larger sample size of 755 Caucasian CRC subjects at stage II/IV, did not observe a significant impact of the GSTP1 (rs1695) variant in OS, independent from oxaliplatin chemotherapy. Also, the authors did not find any significant association between the GST-T1 genotype and survival in either oxaliplatin or non-oxaliplatin treatment groups (Kap et al., 2014). However, the GSTT1-positive genotype was related with a significantly better RR in 170 mCRC patients receiving FOLFOX regimen as second-line therapy (Boige et al., 2010). Another similar study, revealed that the GST-M1 null genotype was associated with survival in patients receiving oxaliplatin therapy. In particular, homozygotes for the GST-M1 wild type had a poorer OS only in the patients treated with an oxaliplatin- based treatment. Other investigators failed to demonstrate any significant relationship between GSTT1 and GSTM1 variations and survival or sensitivity to oxaliplatin-containing treatment. But the small sample size of these studies make them difficult to interpret with any certainty (Stoehlmacher et al., 2002).

2.3.Folate pathway

Folate metabolism is a highly regulated and a complex process (Duthie, 2011). Folate, is a limiting factor in many crucial cellular pathways such as in DNA replication, repair and maintenance, and also in the methylation of DNA, RNA, and protein. In a cohort study conducted on 117 advanced CRC Caucasian patients treated with FOLFOX, the MTHFR

alleles (rs1801131-C and rs1801133-T) were associated with an improved tumor response (Etienne-Grimaldi et al., 2010).

2.4.DNA repair system

The cytotoxicity of oxaliplatin is due to the formation of DNA adducts, via intra- and inter-strand crosslinks, and these consequently result in the suppression of DNA replication and cell apoptosis. Sensitivity to drug treatment relies on the capacity of cell to repair this DNA damage. At least five molecular repair systems have been identified; each operate on particular type of DNA damage: (a) direct reversal, (b) base excision repair (BER), (c) nucleotide excision repair (NER), (d) DNA mismatch repair (MMR), and (e) Double-strand breaks repair (DSB). With respect to oxaliplatin, the BER, NER as well as MMR mechanisms are principally involved (Martin et al., 2008).

The variations in the BER, NER and MMR enzymes may potentially affect the resistance to oxaliplatin; so, these are excellent candidates for pharmacogenetic analyses. The most frequently studied variation has been the missense mutation at 28152A>G (rs25487) of XRCC1, as a member of BER system. This variation has been associated with a reduced repair activity in vitro (Vodicka et al., 2004). While the in vivo data obtained were more heterogeneous because of the confounding effects of environmental factors. A germline mutation of Arg399Gln (rs25487) of the gene coding XRCC1 has been related to a lower risk of toxicity. Patients possessing the G mutant allele (homozygous or heterozygous) had a 5.2 fold higher risk of treatment failure with 5-FU/oxaliplatin therapy (Stoehlmacher et al., 2000). However, a meta-analysis assessed 1234 advanced/ metastatic CRC patients (64% Asians and 46% Whites) treated with chemotherapy regimen that included oxaliplatin found that the rs25487-Gln allele of XRCC1 was significantly related with a moderately increased tumor response, without impact on PFS (Ye et al., 2013).

Concerning the NER system, research has focused on the pharmacogenetic significance of variations in genes coding for ERCC1 and ERCC2. In particular, the most frequent mutation was the synonymous substitution at 19007T>C (rs11615) of ERCC1 that negatively impacted the expression level of mRNA (Bostick-bruton and Reed, 2000).Also, the missense mutation 35931T>G (rs13181) of ERCC2 was linked with a suboptimal capacity of DNA repair (Duell et al., 2000).

In a meta-analysis that included 1550 patients with advanced/metastatic CRC (45% Asians and 55% Caucasians) treated with oxaliplatin-based chemotherapy, Yin et al showed that the ERCC1 (rs11615-T allele) was markedly associated with a reduced response, shorter OS and PFS in only Asians (Yin et al., 2011). Whereas the ERCC2 (rs13181-G allele) was a predictor of poorer OS and PFS with a greater effect being found in Caucasian compared to Asian patients. The ERCC1 (rs11615-T allele) was found to be associated with over-expression of mRNA and the ERCC2 (rs13181- G allele) with a reduced DNA damaged rate (Lunn et al., 2000). These findings suggest that both markers are associated with a positive effect on the repair functionality and provide plausible explanation for the functional mechanism of the two polymorphisms.

Some pharmacogenetic studies have investigated variants in genes coding for other elements of the DNA repair systems, specifically ERCC5, an enzyme play role in NER system. Chen and colleagues analyzed data from 83 Chinese patients with advanced CRC receiving 5-FU/ oxaliplatin-based treatment and reported that these regimen had a significant positive effect on RR for the ERCC5 (rs2016073-G and rs751402-A markers) (Chen et al., 2009). Another study on 42 Hispanic patients indicated an association between ERCC5 (rs1047768-CC genotype) and a longer OS and time–to-progression (TTP). This effect was greater when combined with the rs18 00975-C allele of XPA gene, another member of the NER pathway (Monzo et al., 2008). Kweekel *et al*. investigated 91 Caucasians patients with CRC who were

allocated to oxaliplatin-based chemotherapy, and found strong evidence for a predictive role of ERCC5 variations on PFS (Kweekel et al., 2009). The ERCC5 rs1047768-CC genotype was related with a poor PFS, without affecting OS. Another larger study, comprising 432 Chinese CRC patients also suggested a potential role of the ERCC5 (rs17655-GG genotype) as predictor of higher PFS post oxaliplatin-based therapy (Liu et al., 2012). In a similar cohort on 718 patients, the ERCC5 rs17655-C allele was associated with a longer DSF without an effect on OS. Indeed, the rs2228000-C allele of XPC (another NER member) may be considered to be a predictor of favorable DFS (Sun et al., 2015). The genetic analysis conducted on 94 Korean mCRC patients treated with oxaliplatin, reported that rs3732183-G allele of MSH2 (a member of MMR pathway) and rs4937-TT genotype of POLR2C (the largest subunit of MGMT), participated in the defense against the biological adverse effects of O-6-methylguanine in DNA, and were significantly related with a favourable response. Whereas the rs1625649-TT genotype of MGMT was related with a poorer PFS. No difference in terms of survival was observed with respect to the genotypes of MSH2 or POLR2C (Park et al., 2010).

2.5.VEGF and EGF pathway

The treatment for CRC was greatly improved with the emergence of biological compounds targeting VEGF (i.e. bevacizumab) and EGFR (i.e. cetuximab) pathways or multiple-kinase inhibition (i.e. regorafenib). Bevacizumab and cetuximab are monoclonal antibodies (mAbs), used either as monotherapy or combined with the standard chemotherapy, and represent a significant outcome benefit, but only in selected patients. Somatic variations are important for personalized medicine with biological drugs. But germ-line polymorphisms were extensively also investigated for their involvement in determining the effectiveness of targeted compounds (Schmoll and Stein, 2014).

The rs2227983 EGFR polymorphism was assessed in 109 mCRC patients treated with 5-FU/ Folinic Acid (FA) and oxaliplatin regimen as a first-line treatment. The rs2227983-A allele appeared to be a predictor of a higher RR and increased OS (Wang et al., 2007). The same polymorphism was investigated in 132 mCRC patients treated with oxaliplatin-based therapy plus bevacizumab, and demonstrated that the EGFR rs2227983-A allele was associated with an improved RR. Furthermore, in 130 mCRC cases receiving cetuximab (CTX) as monotherapy, the heterozygous rs2227983-AG genotype appeared to be a strong predictor of higher PFS compared to wild-type and homozygous genotypes (Lurje et al., 2008)..

The rs4444903 variant of EGF has consistently shown an effective predictive role in various treatment regimens. Furthermore, the rs4444903-GG genotype was found to be related with a higher PFS in a study in mCRC patients who received CTX alone, after failing to respond in two previous lines of therapy (Lurje et al., 2008). In a cohort of mCRC subjects treated with oxaliplatin-based therapy plus bevacizumab, the rs4444903-G allele recognized as a strong predictor of an improved OS.

Variants in genes encoding the IL-8 receptors (CXCR-1 and CXCR-2) may be able to predict response and invasion in mCRC cases treating with oxaliplatin-based therapy independent from bevacizumab (Gerger et al., 2011).

Some genetic polymorphisms in the ILb/IL1RA network may possibly be of value in personalized CRC treatment. In a cohort of 180 mCRC patients on treatment with second-line irinotecan or oxaliplatin with or without CTX, the ILRA (rs579543 and rs4251961) markers were genotyped. The TT carriers (rs579543-TT, or rs4251961-TT, or both) showed a better response with respect to OS, compared to others (Graziano et al., 2009).

2.6. CRC pathway

2.6.1 .Microsatellite instability (MSI)

MSI is one of the most common tumor alterations related with colorectal carcinogenesis. The MSI pathway is caused by a mismatch repair (MMR) defect, and may be of relevance in 15% of CRCs (Lengauer et al., 1997). MSI has been suggested to affect the outcome of CRC. The prognostic and predictive value of MSI was evaluated in two populations of patients with CRC received 5-FU/oxaliplatin-based chemotherapy (Des Guetz et al., 2007; Müller et al., 2008). Although both studies failed to find a relationship between the MSI status of CRC patients and the OS. However, Zanaan *et al*. reported that whilst the number of CRC patients with MSI tumors was low, the DFS rate among CRC patients who were treated with FOLFOX was higher than when treated with 5-fluorouracil combined leucovorin (Zaanan et al., 2010). Additionally, no relapse was observed in the CRC patients with MSI tumors who received FOLFOX; multivariate analysis was undertaken to examine whether MSI was considered as an independent factor. The findings indicated that patients with CRC with MSI tumors had greater benefit from FOLFOX rather than 5-fluorouracil and leucovorin regimen.

2.6.2.Chromosomal instability (CIN)

Two principal types of genomic instability have been identified as alternative mechanisms of colon tumorgenesis. The more frequent, chromosomal instability (CIN), is present in nearly 65-70% of CRCs. CIN is poorly characterized as the presence of multiple numerical or structural chromosome alterations in cancer cells, and, in practice, is usually inferred from finding polyploidy and/or aneuploidy (Miyazaki et al., 1999). In a meta-analysis of sixty-three studies reported CIN is linked with a poor prognosis in CRC. CIN should be evaluated as a prognostic marker, combined with MSI status, in clinical studies, in particular those

involving adjuvant therapies. Altogether, CIN is related with a worse prognosis, regardless of type of adjuvant chemotherapy (Walther et al., 2008).

2.6.3.CpG island methylator phenotype (CIMP)

CIMP refers to a subset of CRCs that present with wide-spread hypermethylation of promoter CpG islands. This aberrant methylation transcriptionally inactivates tumor suppressor genes and thereby promotes carcinogenesis. CIMP is related to MSI-high tumors and clinicopathologic characteristics, such as proximal location, female gender and poor differentiation (Dahlin et al., 2010; Kim et al., 2009). It has been shown that DFS was better in patients with CIMP (-)/MSI (+) and poor in patients with CIMP (+)/MSI (+), following adjuvant FOLFOX treatment. Additionally, concurrent methylation of two CpG island loci (NEUROG1 and CDKN2A) is associated with relapse following adjuvant FOLFOX in stages II/III CRCs (Han et al., 2013).

2.6.4. mutY homologue (MUTYH)-associated polyposis (MAP)

A subset of patients with clinical familial adenomatous polyposis (FAP) and attenuated FAP (AFAP), without a significant multigenerational family history, do not carry a detectable APC gene mutation. In these patients, MUTYH associated polyposis (MAP), an autosomal recessive disease is frequently observed. This condition is caused through a biallelic mutation in the BER gene MUTYH. Approximately 30% of subjects will developed polyps involving the upper gastrointestinal tract, however no extra-intestinal manifestations are observed (Bosetti et al., 2011). These patients have about 80% risk for developing CRC as well as the mean age of diagnosis is 40-60 years old (von Karsa et al., 2013). To best our knowledge until now no investigation has been conducted about response to chemotherapy in this mutation.

2.7. Other candidate gene related to oxaliplatin therapy

Additional candidate gene polymorphisms affecting oxaliplatin-based therapy have been identified. These include GRHPR that contributes to the metabolism of toxins. AGXT encodes the hepatic enzyme alanineglyoxylate aminotransferase, phosphatase and tensin homolog (PTEN) gene as a tumor suppressor gene and, several transporter genes (ATP1A1, ATP1B2 and ATP8B3). Some other genes and polymorphisms and their effects on outcomes of patients who received oxaliplatin-based chemotherapy are summarised in table 1 .Several other gene variations have been identified by Genomic wide Association studies (GWAS), but these have not been validated yet. So, more evidences in confirmatory researches need with other populations and platforms.

3. Gene related to response to the Radiotherapy

Radiotherapy injures genetic material and increases apoptosis in tumor cells. Until now, polymorphisms in DNA repair genes and in metabolic enzymes have been found to be correlated to treatment response in cervical (Britten et al., 2000), lung (Rosell et al., 2002), colon (Stoehlmacher et al., 2002), and other cancers (Goode et al., 2002). Although, there are few studies assessing the association between polymorphisms and clinical outcome in CRC.

Wartanabe and coworker have identified 33 novel discriminating genes that were differentially expressed between responders and non-responders to radiotherapy in rectal cancer. These discriminating genes included cell proliferation, growth factor, apoptosis, signal transduction, or cell adhesion genes. Apoptosis inducers (galectin-1, lumican, and thrombospondin 2) showed over-expression in responders while apoptosis inhibitors (glutathione peroxidase and cyclophilin 40) showed over-expression in non-responders. This study suggests the possibility that gene expression profiling may be potential to predicting

radiotherapy response to establish an individualized appropriate therapy for rectal cancer. (Watanabe et al., 2006).

4. Conclusion:

In recent years there has been increasing attention on the identification of prognostic or predictive genetic markers to improve management of CRC patients. In particular, several pharmacogenetic studies have reprted that germline genetic variants may be involved in determining tumor sensitivity toward chemotherapy. However, despite the large number of published studies, it has not been possible to identify strong germline mutations that can be used as predictive markers in clinical practice. Further studies in larger population samples is required to establish the best treatment for cancer patients, together with other markers, such as microRNA, mRNA, or protein. Further work is also, required to elucidate the mechanism behind the variations and chemotherapy effectiveness, further functional evaluations are required.

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Table 1. Other genetic variants related to the response to oxaliplatin based therapy in CRC

Gene	Chromosome	Variation	Effect when patient receive oxaliplatin	References
MTHFR	1p36.22	rs1801133	In patients carrying 2–4 of these variants those who received oxaliplatin-based chemotherapy achieved a higher RR and PFS than irinotecan-based therapy. But, patients carrying 0 or 1 of these variants represented better outcomes after treatment with FOLFIRI compared to FOLFOX/XELOX	(Zhao et al., 2014)
		rs1801131		
ABCG2	4q22.1	rs2231137		
		rs2231142		
MTHFR	1p36.22	rs1801133	The combination of these variants was associated with a higher risk of recurrence	(Custodio et al., 2014)
SELE	1q24.2	rs3917412		
ABCA9	17q24.2	rs1860447	Associated with an reduced OS	(Kap et al., 2016)
ABCB1	7q21.12	rs1128503	Associated with longer OS	(Wu et al., 2013)
		rs2032582	rs1128503-rs2032582-rs1045642 haplotype carriers showed a worse PFS and RFS	
		rs1045642		
ABCB11	2q31.1	rs2287618	Associated with an reduced OS	(Kap et al., 2016)
		rs3770591	Associated with an increased OS	
		rs853778	Associated with an increased OS	
ABCC10	6p21.1	rs2125739	Associated with an reduced OS	(Kap et al., 2016)
PTEN	10q23.31	rs701848	C allele associated with better prognosis	(Lin et al., 2014)
ATP1A1	1p13.1	rs4839524	Associated with a reduced risk of dying	(Kap et al., 2016)
		rs975351	Associated with a reduced risk of dying	
ATP1B2	17p13.1	rs1642763	Associated with higher risk of dying	(Kap et al., 2016)
XPC	3p25.1	rs1043953	Associated with longer OS after	(Kap et al., 2015)
ERCC2	19q13.32	rs238406	Associated with longer PFS	(Kjersem et al., 2016)
ATP8B3	19p13.3	rs7249302	Associated with a reduced risk of dying	(Kap et al., 2016)
		rs8100856	Associated with higher risk of dying	
AGXT	2q37.3	rs34116584	Associated with longer PFS and OS	(Kjersem et al., 2016)
GSTM5	1p13.3	rs11807	Minor alleles associated with decreased OS	(Kap et al., 2016)
MNAT1	14q23.1	rs3783819	Associated with longer OS	(Kap et al., 2015)
GRHPR	9p13.2	rs10814535	Associated with an increased OS	(Kap et al., 2016)
		rs11793053	Minor alleles associated with decreased OS	
		rs17502738	Minor alleles associated with decreased OS	

Abbreviations: methylenetetrahydrofolate reductase (MTHFR); Selectin E (SELE); ATP-binding cassette sub-family A member 9 (ABCA9); ATP-binding cassette sub-family B member 1 (ABCB1); ATP-binding cassette sub-family B member 11 (ABCB11); ATP-binding cassette sub-family C member 10 (ABCC10); ATP-binding cassette sub-family C member 10 (ABCC10);ATP-binding cassette sub-family G member 2 (ABCG2); Phosphatase and tensin homolog (PTEN); ATPase, Na+/K+ transporting, Alpha-1 polypeptide (ATP1A1); ATPase, Na+/K+ transporting, Beta-2 polypeptide (ATP1B2); XPC gene (XPC); Excision repair, complementing defective, in Chinese hamster, 2(ERCC2); ATPase, Class I, type 8B, member 3 (ATP8B3); Alanine-glyoxylate aminotransferase (AGXT); Glutathione S-transferase, MU-5 (GSTM5); Menage A Trois 1 (MNAT1); Glyoxylate reductase/hydroxypyruvate reductase (GRHPR); overall survival(OS); response rate (RR); Recurrence-free survival (RFS); progression-free survival (PFS)