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REVIEW

The Roles of Common Variation and Somatic Mutation in Cancer Pharmacogenomics

Hiu Ting Chan · Yoon Ming Chin · Siew-Kee Low

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ABSTRACT

Cancer pharmacogenomics is the science concerned with understanding genetic alterations and its effects on the pharmacokinetics and pharmacodynamics of anti-cancer drugs, with the aim to provide cancer patients with the precise medication that will achieve a good response and cause low/no incidence of adverse events. Advances in biotechnology and bioinformatics have enabled genomic research to evolve from the evaluation of alterations at the single-gene level to studies on the whole-genome scale using large-scale genotyping and next generation sequencing techniques. International collaborative efforts have resulted in the construction of databases to curate the identified genetic alterations that are clinically significant, and these are currently utilized in clinical sequencing and liquid biopsy screening/monitoring. Furthermore, countless clinical studies have accumulated sufficient evidence to match cancer patients to therapies by utilizing the information of clinical-relevant alterations. In this review we summarize the importance of germline alterations that act as predictive biomarkers for drug-induced toxicity and drug response as well as somatic mutations in cancer cells that function as drug targets. The integration of genomics into the medical field has transformed the era of cancer therapy from one-size-fits-all to cancer precision medicine.

Keywords: Cancer precision medicine; Germline variants; Next generation sequencing; Pharmacogenomics; Somatic mutations

INTRODUCTION

Cancer pharmacogenomics studies play an important role in evaluating the relationship between genomic alterations and its effect on modulating the pharmacokinetics and pharmacodynamics of anti-cancer drugs. Genetic alterations in the human genome can be divided into two major categories: germline and somatic alterations. Germline alterations include highly penetrant susceptible mutations and common genetic variants that are inheritable from generation to generation. These type of variations, particularly single-nucleotide polymorphisms (SNPs), are useful as predictive biomarkers for drug-induced adverse events and

Hiu Ting Chan and Yoon Ming Chin contributed equally to this manuscript.

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H. T. Chan · Y. M. Chin · S.-K. Low (✉)
Cancer Precision Medicine Center, Japanese Foundation for Cancer Research, Tokyo, Japan
e-mail: siewkee.low@jfcr.or.jp

drug response. Contrary, somatic mutations are acquired randomly following exposure to agents that have the potential to damage DNA in cells. In the context of cancer, these somatic mutations accumulate in the cancer cells and are commonly used as drug targets. For the past two decades, genomic technology has evolved from assessing a single mutation of a gene to the genome-wide perspective through large-scale genotyping and next generation sequencing (NGS). The emergence of abundant NGS data enables large-scale studies aimed at corroborating genomic sequencing and expression data to identify pathogenic germline variants that predispose to cancer [1].

The majority of germline variants are identified through candidate gene approaches or genome-wide association studies (GWAS), in which a GWAS is performed by genotyping up to millions of SNPs. Each approach has its own advantages and disadvantages. The candidate gene approach requires prior knowledge of the mechanism of action of the candidate gene and its target drug [2]. Despite the limitation of having a predefined gene set, candidate gene studies tend to have greater statistical power than GWAS to detect associations due to the lower number of multiple testing corrections performed [2]. The variants identified are relevant to the mode of action of a drug. This is in contrast to GWAS studies where large sample sizes are usually needed to confidently evaluate associations of thousands or even millions of variants in unison [3]. The advantage of GWAS studies is that they enable the identification of new and never before reported genes or variants with a potential effect on drug efficacy and toxicity. However, germline variants identified by both candidate gene studies and GWAS would require rigorous replication efforts to corroborate and confirm the associations [3].

The establishment of The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium has accelerated the identification of somatic mutations from cancer genomes by NGS. NGS is one of the key elements that has enabled the incorporation of genomic data into clinical practice. NGS utilizes the simultaneous sequencing of millions of DNA fragments to generate a large pool of genomic sequence data. The technique can be targeted to sequence a selected number of gene of interest (gene panel), the whole exome or the whole genome. With the constant advancement of technologies and bioinformatic pipelines, this procedure can now be conducted within an affordable cost and time frame [4, 5]. Numerous studies have been conducted to explore the mutational profile of different cancer types as a result of the availability of large-scale genomic sequencing via NGS. Large consortia and networks, such as COSMIC and GENIE, compile and collate somatic mutation data from various sources to deepen our understanding of the mutational landscape in cancer [6, 7]. These databases provide valuable knowledge on the possible associations of genomic information with different cancer subtypes, the development of metastasis and prognosis. More importantly, the increase in genomic knowledge of cancer also allows the identification of molecular targets which may enable the cancer patient to be started on an established targeted therapy or to be included into available clinical trials.

In this review, we have summarized the roles of both germline variants, particularly SNPs, and somatic mutations in cancer pharmacogenomics.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

PART I: ROLES OF COMMON GENETIC VARIATIONS IN CANCER PHARMACOGENOMICS

In this section, we highlight a few key cancer drug germline targets that have been extensively reported and discuss the current status of these targets as a potential marker for efficacy and toxicity. A summary of all germline variants is found in Table 1.

Table 1 Germline cancer pharmacogenomic variants

Drug	Cancer type	Phenotype	Study type	Population[a]	Discovery sample size	Replication sample size	SNP (*P* value; OR or HR)	Gene	Reference
Irinotecan (IROX)	Colon	Neutropenia	Candidate	North Americans	468	NA	*UGT1A1*28* (*P* = 0.003)	*UGT1A1*	[13]
		Neutropenia	Candidate	North Americans	520	NA	*UGT1A1*93* (*P* = 0.004)	*UGT1A1*	[13]
Irinotecan and cisplatin	Cervical or Ovarian	Neutropenia	Candidate	Japanese	30	NA	*UGT1A1*6* (*P* = 0.04)	*UGT1A1*	[14]
		Thrombocytopenia	Candidate	Japanese	30	NA	*UGT1A1*6* (*P* = 0.04)	*UGT1A1*	[14]
		Diarrhea	Candidate	Japanese	30	NA	*UGT1A1*6* (*P* = 0.005)	*UGT1A1*	[14]
Irinotecan	Lung	Neutropenia	Candidate	Korean	81	NA	*UGT1A1*6* (*P* = 0.044)	*UGT1A1*	[15]
	Lung	Diarrhea	Candidate	Korean	81	NA	*UGT1A9*22* (*P* = 0.037)	*UGT1A9*	[15]
Irinotecan, fluorouracil	Colon	Neutropenia	Candidate	Canadian and Italian	167	250	*UGT1A6* p.T181A-*UGT1A7* p.W208R-*UGT1A9* c.-688 (*P* = 0.03; OR 5.28; 95% CI 1.28–21.81)	*UGT1A6-UGT1A7-UGT1A9*	[16]
Irinotecan, S1, oxaliplatin	Colon	Vomitting	Candidate	Korean	43	NA	*UGT1A6*2* (*P* = 0.014)	*UGT1A6*	[17]
(TIROX)	Colon	Vomitting	Candidate	Korean	43	NA	*UGT1A7*3* (*P* = 0.014)	*UGT1A7*	[17]
Irinotecan (FOLFIRI)	Colon	Diarrhea	Candidate	Canadian	167	NA	rs3749438-T-rs10937158-C (*P* = 0.001; OR 0.43)	*ABCC5*	[19]
		Neutropenia	Candidate	Canadian	167	NA	rs225440-T-rs2292997-A (*P* = 0.0002; OR 5.93)	*ABCG1-ABCC5*	[19]

Table 1 continued

Drug	Cancer type	Phenotype	Study type	Population[a]	Discovery sample size	Replication sample size	SNP (*P* value; OR or HR)	Gene	Reference
Irinotecan	Acute lympho-blastic leukemia	PK	Candidate	Caucasian and Blacks	85	NA	rs6498588 ($P = 0.010$; $\beta = 0.111$; SE 0.042)	*ABCC1*	[20]
	Acute lympho-blastic leukemia	PK	Candidate	Caucasian and Blacks	85	NA	rs1272006 ($P = 0.005$; $\beta = -0.204$; SE 0.070)	*ABCB1*	[20]
	Acute lympho-blastic leukemia	Neutropenia	Candidate	Caucasian and Blacks	85	NA	rs17501331 ($P = 0.019$; $\beta = -0.255$; SE 0.106)	*ABCC1*	[20]
	Acute lympho-blastic leukemia	Neutropenia	Candidate	Caucasian and Blacks	85	NA	rs12720066 ($P = 0.030$; $\beta = 0.227$; SE 0.102)	*ABCB1*	[20]
Irinotecan	Multiple	Diarrhea	GWAS	Japanese	53	NA	rs9351963 ($P = 0.03$, OR 3.14, 95% CI 1.8–5.6)	*KCNQ5*	[21]
Irinotecan	Lung	Neutropenia	Candidate	Korean	107	NA	rs4149056 ($P = 0.007$; OR 3.8; 95% CI 1.4–10.0)	*SLCO1B1*	[18]
Irinotecan	Lung	Neutropenia	Candidate	Korean	101	146	rs11979430 ($P = 3.6 \times 10^{-5}$; OR 3.1; 95% CI 1.8–5.5)	*SEMA3C*	[25]
		Neutropenia	Candidate	Korean	101	146	rs7779029 ($P = 2.8 \times 10^{-5}$; OR 3.1; 95% CI 1.8–5.4)	*SEMA3C*	[25]
Irinotecan	Colorectal	hematological toxicities	Candidate	Unknown	109	NA	rs10934498 ($P = 0.009$, OR 0.17, 95% CI 0.04–0.08)	*NR1I2*	[26]
Irinotecan and cisplatin	Lung	Overall survival	GWAS	Korean	334	NA	rs16950650 (OS 2.5 months; 95% CI 0–5.9)	*ABCC4*	[27]
		Overall survival	GWAS	Korean	334	NA	rs17574269- (OS 12.2 months; 95% CI 10.9–13.5)	*DCBID1*	[27]

Table 1 continued

Drug	Cancer type	Phenotype	Study type	Population[a]	Discovery sample size	Replication sample size	SNP (*P* value; OR or HR)	Gene	Reference
Irinotecan (FOLFIRI)	Colon	Overall survival	Candidate	Spaniard	74	NA	rs11942466 (PFS 8.4 months, 95% CI 6.6–9.4, $P = 0.006$)	*AREG*	[29]
		PFS and OS	Candidate	Spaniard	74	NA	rs712829 (PFS 6.4 months, 95% CI 5.1–9.4, $P = 0.03$)	*EGFR*	[29]
Mercaptopurine	Leukemia	6-MP clearance	GWAS	Mixed[1]	1026	NA	rs1142345-A > G (*TPMT*3C*) ($P = 8.6 \times 10^{-61}$)	*TPMT*	[33]
	Leukemia	6-MP clearance	GWAS	Mixed[1]	1026	NA	rs1800460-G > A (*TPMT*3A*) ($P = 2.0 \times 10^{-44}$)	*TPMT*	[33]
Mercaptopurine	Acute lymphoblastic leukemia	GI toxicity	GWAS	European	87 HapMap CEU LCL	286	rs2413739 ($P = 0.04$; OR 2.09; 95% CI 1.0–4.6)	*PACSIN2*	[35]
Mercaptopurine	Acute lymphoblastic leukemia	6-MP dosage	GWAS	Mixed[2]	657	371	rs116855232 ($P = 8.8 \times 10^{-9}$; -TT 6.22 mg/m^2/day; -TC 47.25 mg/m^2/day; -CC 62.63 mg/m^2/day)	*NUDT15*	[40]
Mercaptopurine	Acute lymphoblastic leukemia	6-MP dosage	Candidate	Taiwan	404	NA	rs116855232 ($P < 1.0 \times 10^{-4}$; -TT 9.4 mg/m^2/day; -TC 30.7 mg/m^2/day; -CC 44.1 mg/m^2/day	*NUDT15*	[41]
Mercaptopurine	Acute lymphoblastic leukemia	6-MP dosage	Candidate	Mixed[3]	270	NA	rs116855232 ($P = 4.45 \times 10^{-8}$; Effect size = − 11.5)	*NUDT15*	[42]
Tamoxifen	Breast cancer	Recurrence-free survival	GWAS	Japanese	240	R1 = 105 R2 = 117	rs10509373 ($P = 6.29 \times 10^{-29}$; HR 4.51; 95% CI 2.72–7.51)	*C10orf11*	[48]
	Breast cancer	Endoxifen sensitivity	GWAS	Caucasian	60 HapMap CEU LCL	NA	rs478437 ($P < 0.05$)	*USP7*	[49]

Table 1 continued

Drug	Cancer type	Phenotype	Study type	Population[a]	Discovery sample size	Replication sample size	SNP (P value; OR or HR)	Gene	Reference
Erlotinib	Malignant brain tumor, head and neck carcinoma	PK-PD	Candidate	Europe	88	NA	*CYP3A5*1* ($P < 0.001$; 42% increase in CL)	*CYP3A5*	[51]
	Malignant brain tumor, head and neck carcinoma	PK-PD	Candidate	Europe	88	NA	*ABCB1* 2677G > T/A ($P < 0.001$; 19% decrease in CL)	*ABCB1*	[51]
Erlotinib and gefitinib	Lung cancer	Overall survival	Candidate	Chinese	100	NA	*ABCG2* 34-GG (OS = 18 months; 95% CI 14.9-21.1 months)	*ABCG2*	[52]
Erlotinib and gefitinib	Lung cancer	Skin rash and diarrhea	GWAS	Chinese	226	NA	rs884225-TT ($P = 0.001$)	*EGFR*	[53]
Erlotinib and gefitinib	Lung cancer	Progression free survival	GWAS	Chinese	128	R1 = 198, R2 = 153	rs3805383 ($P < 10^{-8}$; HR > 4)	*NMU*	[54]
Erlotinib	Lung cancer	Progression free survival	Candidate	Chinese	60	134	rs1042640 ($P = 0.009$; OR 1.7; 95% CI 0.7–4.1)	*UGT1A10*	[55]
	Lung cancer	Progression free survival	Candidate	Chinese	60	134	rs1060463 ($P = 0.001$; OR 0.2; 95% CI 0.07–0.5)	*CYP4F11*	[55]
	Lung cancer	Progression free survival	Candidate	Chinese	60	134	rs1064796 ($P = 0.013$; OR 3.1; 95% CI 1.2–7.8)	*CYP4F11*	[55]
	Lung cancer	Progression free survival	Candidate	Chinese	60	134	rs2074900 ($P = 0.001$; OR 5.8; 95% CI 1.8–18.5)	*CYP4F2*	[55]
Lapatinib	Breast cancer	Liver injury	Candidate	European	323	179	*HLA-DQA1*02:01* ($P < 0.001$; OR 9; 95% CI 3.2–27.4)	*HLA-DQA1*	[57]
Lapatinib	Breast cancer	Liver injury	GWAS	Unknown	844	NA	*HLA-DRB1*07:01* ($P = 2.0 \times 10^{-18}$)	*HLA-DRB1*	[58]

Table 1 continued

Drug	Cancer type	Phenotype	Study type	Population[a]	Discovery sample size	Replication sample size	SNP (*P* value; OR or HR)	Gene	Reference
Sunitinib	Renal cell carcinoma	Thrombo-cytopenia	Candidate	Japanese	219	NA	*ABCG2* 421C > A/ rs2231142 ($P = 8.41 \times 10^{-3}$, OR 1.86, 95% CI 1.17–2.94)	*ABCG2*	[68]
Sunitinib	Renal cell carcinoma	Thrombo-cytopenia	Candidate	Korean	65	NA	*ABCG2* 421C > A/ rs2231142 ($P = 0.04$, OR 9.90, 95% CI 1.16-infinity)	*ABCG2*	[70]
Anastrazole or exemestane	Breast cancer	Bone fractures	GWAS	Mixed[4]	1070	NA	rs10485828; $P = 2.56 \times 10^{-7}$	*CTSZ-SLMO2-ATP5E*	[74]
							rs6901146; $P = 1.15 \times 10^{-6}$	*TRAM2-TMEM14A*	[74]
							rs4550690; $P = 2.89 \times 10^{-6}$	*MAP4K4*	[74]
Anastrazole or exemestane	Breast cancer	MSAE	Candidate	Chinese	208	NA	rs7984870 ($P = 2.19 \times 10^{-4}$; OR 3.259; 95% CI 1.843–5.763)	*RANKL*	[75]
							rs2073618 ($P = 7.95 \times 10^{-4}$; OR 2.931; 95% CI 1.624–5.288)	*OPG*	[75]
Exemestane	Breast cancer	MSAE	Candidate	Dutch	737	NA	rs934635 ($P = 0.007$; OR 5.08; 95% CI 1.8–14.3)	*CYP19A1*	[79]
		VM	Candidate	Dutch	737	NA	rs934635 ($P = 0.044$; OR 2.78; 95% CI 1.02–7.56)	*CYP19A1*	[79]
Exemestane	Breast cancer	VM	Candidate	Unknown	1967	NA	rs10046 ($P = 0.03$; OR 0.78; 95% CI 0.63–0.97)	*CYP19A1*	[80]

Table 1 continued

Drug	Cancer type	Phenotype	Study type	Population[a]	Discovery sample size	Replication sample size	SNP (*P* value; OR or HR)	Gene	Reference
Letrozole	Breast cancer	Bone loss	Candidate	Unknown	122	NA	rs4870061 ($P = 3.0 \times 10^{-4}$; VT/VT%BMD change = − 10.94%; WT/WT,WT/VT%BMD change = − 3.76%)	*ESR1*	[81]
							rs10140457 ($P = 3.0 \times 10^{-4}$;WT/VT %BMD change = 3.08%; WT/WT%BMD change = − 3.43%)	*ESR2*	[81]
Letrozole	Breast cancer	Bone loss, fracture, osteoporosis	Candidate	Unknown	4861	NA	rs936308-CC (HR 1.37; 95% CI 1.01–1.85)	*CYP19A1*	[82]
Anastrazole, letrozole, exemestane	Breast cancer	Bone loss	Candidate	Mixed[5]	97	NA	rs700518 ($P = 0.03$)	*CYP19A1*	[83]

BMD Bone mineral density, *CEU* Utah residents with Northern and Western European ancestry, *CI* confidence interval, *GI toxicity* Grade 3–4 mucositis and diarrhea, *GWAS* genome-wide association studies, *HR* hazards ratio, *LCL* lymphoblastoid cell line, *MSAE* musculoskeletal adverse events, *NA* not applicable *OR* odds ratio, *OS* overall survival, *PFS* progression free survival, *PK–PD* pharmacokinetics–pharmacodynamics, *SE* standard error, *SNP* single-nucleotide polymorphism, *VM* vasomotor, *VT* variant type, *WT* wild type

[a] Mixed[1]: White, Black, Hispanic, Asian, others. Mixed[2]: White, Black, Hispanic, Asian. Mixed[3]: Singapore, Guatemala, Japan. Mixed[4]: Asian, Black, Hawaiian, White, Unknown. Mixed[5]: Caucasians, African Americans, Asian

Irinotecan

Irinotecan is a campthotecin analog constantly used in the treatment of lung and colorectal cancer [8, 9]. It functions as a topoisomerase inhibitor and is activated to its active form SN-38 by carboxylesterases CES1 and CES2 [10]. SN-38 binds to the topoisomerase complex I, preventing the rewinding of the DNA double helix and eventually leading to DNA damage and cell death [11]. The active SN-38 is subsequently inactivated through glucuronidation by the uridine diphosphate-glucuronosyltransferase (UGT) family [11]. Diarrhea and neutropenia are the most common symptoms of irinotecan toxicity due to the accumulation of SN-38 [11].

The most extensively reported marker linked to irinotecan toxicity is *UGT1A1*. UGT1A1 is an important enzyme of the metabolic pathway for hepatic bilirubin glucuronidation [12]. Polymorphisms reported to be associated with irinotecan toxicity include *UGT1A1* SNPs and *UGT1A1* alleles [11]. Colorectal cancer patients carrying the homozygous *UGT1A1*28* and *UGT1A1*93* allele have shown an increased risk for neutropenia as compared to non-carriers ($P = 0.003$ and $P = 0.004$, respectively) [13]. Masashi and colleagues found that patients carrying *UGT1A1*28* and **6* alleles had an increased frequency of neutropenia, thrombocytopenia and diarrhea [14]. In another study involving patients with advanced non-small-cell lung cancer (NSCLC), homozygous carriers of *UGT1A1*6* were linked to higher risk for severe neutropenia and lower progression-free survival [15]; *UGT1A1*6/*6* carriers also had a lower tumor response [15]. *UGT1A9*22* has also been linked to a higher chance of diarrhea but not to tumor response [15]. Levesque and colleagues reported the haplotype combination of *UGT1A6* p.T181A–*UGT1A7* p.W208R–*UGT1A9* c.-688 to be the strongest predictor of severe neutropenia ($P = 0.03$; odds ratio (OR) 5.28; (95% confidence interval [CI] 1.28–21.81) [16]. In chemo-naïve metastatic colorectal cancer patients, patients carrying *UGT1A6*2* and *UGT1A7*3* show a higher tendency to vomit when treated using the combination TIROX treatment (S-1, irinotecan and oxaliplatin) [17]. In a separate study, NSCLC patients carrying the *UGT1A9* rs3832043 del/del genotype showed an increased risk of severe diarrhea [18].

Hepatic drug transporters are also known to play an important role in irinotecan toxicity [11]. Chen and colleagues evaluated the ABC transporter genes *ABCB1, ABCC1, ABCC2, ABCC5, ABCG1* and *ABCG2* as well as the solute carrier organic anion transporter *SLCO1B1* in metastatic colorectal cancer patients [19]. Their findings revealed that patients with the *ABCC5*-rs3749438-T-rs10937158-C haplotype had decreased risk of severe diarrhea ($P = 0.001$; OR 0.43) and those patients with the *ABCG1*-rs225440T-ABCC5-rs2292997A haplotype had an increased risk of severe neutropenia ($P < 0.0001$; OR 7.68) [19]. In a more recent study by Li and colleagues, cancer patients treated with monotherapy of irinotecan demonstrated an association of the *ABCC1* rs6498588 ($P = 0.010$; $\beta = 0.111$; standard error [SE] 0.042) and *ABCB1* ($P = 0.005$; $\beta = -0.204$; SE 0.070) SNPs to increased SN-38 exposure [20]. In addition, the *ABCC1* rs17501331 SNP ($P = 0.019$; $\beta = -0.255$; SE 0.106) and *ABCB1* gene ($P = 0.030$; $\beta = 0.227$; SE 0.102) were linked to increased risk of neutropenia [20]. A GWAS study evaluating the relationship between SNPs and irinotecan toxicity in Japanese cancer patients identified SNP rs9351963 in potassium voltage-gated channel subfamily KQT member 5 (*KCNQ5*) to be associated to an increased risk of diarrhea [21]. *KCNQ5* has been linked to irritable bowel syndrome and could be a possible predictor of irinotecan-induced diarrhea.

SLCO1B1 encodes the hepatic protein OATP1B1 whose function is to transport compounds from the blood to the liver where they will be metabolized and cleared from the body [22]. In patients with advanced NSCLC receiving irinotecan treatment, carriers of *SLCO1B1* rs4149056-TC or -CC are associated with a higher incidence of neutropenia ($P = 0.007$; OR 3.8; 95% CI 1.4–10.0) [18].

SEMA3C is a protein involved in cell survival [23]. *SEMA3C* variants have been linked to serum bilirubin levels, suggesting a possible link to irinotecan-induced neutropenia [24]. In a GWAS study in patients with advanced NSCLC, Han and colleagues identified *SEMA3C* SNPs

rs11979430 ($P = 3.6 \times 10^{-5}$; OR 3.1; 95% CI 1.8–5.5) and rs7779029 ($P = 2.8 \times 10^{-5}$; OR 1.8; 95% CI 1.8–5.4) to have a marginal association to severe neutropenia [25].

In a recent study on metastatic colorectal cancer patients, the xenobiotic sensing receptor *NR1I2* SNP rs10934498-A genotype was associated with increased degradation of SN-38 as well as increased risk for irinotecan-induced toxicity [26]. The authors of this study deemed the association of *NR1I2* to be independent from *UGT1A1*28* after adjusting for effects of the corresponding variant [26].

Genomic markers associated with irinotecan efficacy have been less extensively studied than toxicity. A GWAS study evaluating the survival of patients with SCLC receiving combination therapy of irinotecan + cisplatin observed a decreased overall survival (OS) in patients with the *ABCC4* SNP rs16950650-CT and the *DCBlD1* rs17574269-AG genotype [27]. Patients carrying the *ABCC4* SNP rs16950650-CT showed a median OS of 2.5 months (95% CI 0.0–5.9) while patients carrying -CC genotype showed median OS of 12.2 months (95% CI 10.9–13.5) [27]. Patients carrying the *DCBlD1* rs17574269-AG genotype showed median OS of 5.6 months (95% CI 3.4–7.8) while patients carrying the AA genotype had median OS of 12.7 months (95% CI 11.1–14.3) [27].

In metastatic colorectal patients treated with FOLFIRI regimen, patients with the *ABCG2* rs7699188-GG genotype show decreased tumor response [28]. In a separate study, metastatic colorectal patients carrying *AREG* rs11942466 C > A and rs9996584 C > T were associated with OS while those carrying *EGFR* rs712829 G > T were associated with progression-free survival (PFS) and OS [29]. For *AREG* rs11942466 C > A, patients carrying the C/C or C/A genotypes had a median PFS of 8.4 months (95% CI 6.6–9.4), while patients carrying an A/A genotype showed a median PFS of 3.0 months [29]. For patients carrying *EGFR* rs712829 G > T, the median PFS was 6.4 months (95% CI 5.1–9.4) for patients with a G/G genotype, 9 months (95% CI 6.6–9.9) for patients with a G/T genotype and 11.6 months for patients carrying the T/T genotype [29].

Mercaptopurine

6-Mercaptopurine (6-MP) is used to treat acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML) [30]. 6-MP has a similar structure to purine bases in the DNA. When incorporated into the DNA structure, it prevents cell division and inhibits DNA synthesis [31]. The clearance of 6-MP from the human body is highly dependent on the function of the enzyme thiopurine *S*-methyltransferase (TPMT) [32]. TPMT inactivates 6-MP through methylation. The side-effects of 6-MP toxicity include myelosuppression and pancreatitis [32]. A GWAS study conducted by Liu and colleagues in children with leukemia identified top *TPMT* SNPs rs1142345 or 719A > G ($P = 8.6 \times 10^{-61}$) and rs1800460 ($P = 2.0 \times 10^{-44}$) to be associated with TPMT activity [33]. The *TPMT* genotypes were also correlated with mercaptopurine clearance, as reduced TPMT activity would result in an accumulation of 6-MP [33]. The median dose intensities in *TPMT* heterozygotes who carried one **2, *3A* or **3C* allele was 63, 59 and 72%, respectively, which were lower than in those who carried the **1/*1* genotype (median 86%) [33]. The association of *TPMT* SNPs rs1800462 (G > C), rs1142345 (A > G) and rs1800460 (G > A) and their corresponding *TPMT* alleles *TPMT*2, TPMT*3A* and *TPMT*3C*, respectively, was also observed in a separate study [34].

A separate GWAS of children with ALL treated with mercaptopurine identified a new variant, *PACSIN2* SNP rs2413739, to be associated with gastrointestinal (GI) toxicity with increased GI toxicity for carriers of the *PACSIN2*-rs2413739-T allele [35]. This SNP is deemed to be independent of the effects of *TPMT* as the association was retained after adjusting for effects of *TPMT* SNPs [35]. In addition, *PACSIN2* was shown to be able to modulate *TPMT* activity through an effect on TPMT mRNA levels and/or TPMT protein degradation [35]. *PACSIN2* plays a role in autophagy that may be involved in the degradation of the TPMT protein expressed by variant *TPMT*3A* and to a lesser extent by wild-type (WT) *TPMT*1* [36].

6-MP-induced toxicities also occur in patients with WT *TPMT* variants, thus suggesting additional germ line variants contributing to 6-MP toxicity [37, 38]. Nudix hydrolase 15 (NUDT15) is another enzyme involved in 6-MP metabolism. It prevents the incorporation of thiopurine active metabolites thioguanine triphosphate (TGTP) and thioguanine diphosphate (TdGTP) into DNA by dephosphorylating them, thereby preventing the cytotoxic effects of 6-MP. In the presence of *NUDT15* variants or defective alleles, there will be an excess of thiopurine active metabolites TGTP and TdGTP, and this accumulation will lead to 6-MP toxicity [39].

One specific variant is rs116855232 (c.415C > T) in *NUDT15*; this variant shows a distinct population distribution, with a particularly higher occurrence of the rare allele rs116855232-T in East Asians (10%) compared to Hispanics, Europeans and Africans (http://www.internationalgenome.org/1000-genomes-browsers). A GWAS study on children with ALL reported an association of rs116855232 in *NUDT15* ($P = 8.8 \times 10^{-9}$) to mercaptopurine sensitivity in only East Asian patients, with a lower tolerance to mercaptopurine resulting in hematologic toxicities [40]. Patients carrying the rs116855232-TT genotype were less tolerant, with an average dose intensity of 8.3%, compared with those with TC and CC genotypes, who tolerated 63 and 83.5% of the planned dose of 75 mg/m^2 per day [40].

An association of rs116855232 to mercaptopurine sensitivity was also detected in a Taiwanese population through the candidate approach study ($P < 1.0 \times 10^{-4}$) [41]. The tolerable daily doses of mercaptopurine were 9.4 mg/m^2 per day for patients carrying rs116855232-TT, 30.7 mg/m^2 per day for those carrying rs116855232-TC and 44.1 mg/m^2 per day for those carrying rs116855232-CC. Moriyama and colleagues reported an association between *NUDT15* variant rs116855232 (c.415C > T) and increased 6-MP toxicity due to loss-of-function in the *NUDT15*-TT genotype ($P = 4.45 \times 10^{-8}$, effect size = − 11.5) based on the results of their meta-analysis combining data on children with ALL from Guatemala, Singapore and Japanese populations [42].

Tamoxifen

Tamoxifen is constantly used in the treatment of the estrogen receptor (ER+) subtype of breast cancer [43]. Tamoxifen itself has no affinity towards the estrogen receptor. It is a prodrug, requiring activation after being metabolized by cytochrome P450 (CYP) isoform *CYP2D6* and *CYP3A4* into its active form 4-hydroxytamoxifen (4-OHT) (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifene) [44]. The active forms of tamoxifen show markedly greater affinity for the estrogen receptors than does the parent drug tamoxifen [44]. The association of *CYP2D6* alleles towards efficacy and toxicity of tamoxifen have been well documented. Several studies have shown that women who are homozygous carriers of *CYP2D6*4* (poor metabolizers) have a higher risk of breast cancer relapse and a decreased disease-free survival, and they also experience less severe hot flashes [45–47]. In a GWAS study evaluating the effects of polymorphisms on the clinical outcomes of breast cancer patients receiving tamoxifen treatment, the rs10509373 SNP in the *C10orf11* gene was found to be associated with recurrence-free survival ($P = 1.26 \times 10^{-10}$), with carriers of the rs10509373-C allele linked to poorer recurrence-free survival (hazards ratio [HR] 4.51; 95% CI 2.72–7.51; $P = 6.29 \times 10^{-29}$) [48]. Weng and colleagues used a multi-platform approach and identified SNPs in the *USP7* (ubiquitin carboxyl-terminal hydrolase 7) gene that were associated with tamoxifen sensitivity [49]. Initial screening using HapMap lymphoblastoid cell lines identified an association between SNP rs478437 and *USP7* expression, with rs478437-T linked to lower *USP7* expression. Lower expression of *USP7* resulted in a higher resistance to endoxifen [49].

Erlotinib

Erlotinib is used in the treatment of several types of cancers, in particular NSCLC and pancreatic cancer. It is a receptor tyrosine kinase inhibitor (TKI) that specifically acts on the epidermal growth factor receptor (EGFR) [50]. Erlotinib binds to EGFR, preventing the

formation of EGFR homodimers that are needed to activate subsequent signaling cascades in the nucleus or other biochemical processes [50]. Koning and colleagues (2011) compared *ABCB1, ABCG2* and *CYP3A5* SNPs for their effects on erlotinib pharmacokinetics in both adults and children [51]. Their results indicate that *CYP3A5*1* and *ABCB1* (2677G > T/A) were associated with erlotinib clearance ($P < 0.001$), with *ABCB1* 2677G > T/A being associated with a 19% decrease in erlotinib clearance and the *CYP3A5*1* allele being linked to a 42% increase in erlotinib clearance [51].

In a study of advanced NSCLC Chinese patients receiving gefitinib or erlotinib treatment, Chen and colleagues identified *ABCG2* 34-GG carriers to have shorter OS (18 months; 95% CI 14.9–21.1 months) compared to carriers of the -GA or -AA genotype (OS 31 months; 95% CI 22.9–39.1 months) ($P < 0.05$) [52]. Patients undergoing erlotinib treatment are also prone to adverse drug reactions (ADRs) such as skin rash and diarrhea. A study investigating *EGFR* polymorphisms and theirs link to erlotinib ADRs in NSCLC patients identified rs884225-TC and -CC carriers to have a lower risk for erlotinib ADRs than did carriers of the WT rs884225-TT ($P = 0.001$) [53]. A GWAS study evaluating NSCLC patients receiving first-line EGFR-TKIs treatment of gefitinib or erlotinib identified SNPs at 4q12 to be associated with PFS at genome-wide significance ($P < 10^{-8}$), with an estimated HR of > 4. In particular, functional analyses of rs3805383 showed a positive correlation between SNPs and *EGFR* expression levels ($P = 0.04$; $\beta = 0.279$) [54].

Wang and colleagues performed targeted sequencing to evaluate the link between *EGFR* and *EGFR*-linked pathway gene SNPs with *EGFR*-TKI response and ADRs in patients with advanced NSCLC [55]. They identified rs1042640 in *UGT1A10*, rs1060463 and rs1064796 in *CYP4F11* and rs2074900 in *CYP4F2* as being associated with erlotinib treatment response, with improved an median PFS of 12.57 months compared to that of non-responders (median PFS 3.55 months) [55]. SNP rs1064796 in *CYP4F11* and SNP rs10045685 in *UGT3A1* were also linked to ADRs, with carriers of *CYP4F11*-rs1064796-C and *UGT3A1*-G showing an increased risk for skin rash or digestive track injury [55].

Lapatinib

Lapatinib is a human *EGFR* inhibitor administered to metastatic breast cancer patients found to be overexpressing *EGFR* [56]. Spraggs and colleagues conducted a candidate approach study to identify genetic variants associated with lapatinib-induced liver injury and identified the *HLA-DQA1*02:01* allele as being associated with liver enzyme alanine aminotransferase adverse effects ($P < 0.001$; OR 9; CI 3.2–27.4) [57]. They also reported that *HLA-DQA1*02:01* had negative and positive predictive values of 0.97 (95% CI 0.95–0.99) and 0.17 (95% CI 0.10–0.26), respectively, for liver risk. In a separate study, Parham and colleagues performed a GWAS study to identify genetic variants associated with liver injury [58]. The results identified *HLA-DRB1*07:01* to be associated with elevated levels of ALT ($P = 2.0 \times 10^{-18}$) [58].

Sunitinib

Sunitinib is a TKI and used as the first-line treatment for advanced renal cell carcinoma (RCC) as well as imatinib-resistant GI stromal tumor (GIST) [59]. It inhibits cellular signaling by targeting platelet-derived growth factors and vascular EGFRs, reducing tumor vascularization and subsequently causing cancer cell apoptosis and tumor shrinkage [60]. Sunitinib also inhibits CD117 (c-KIT) [61], the receptor tyrosine kinase that drives the majority of GISTs [62]. Patients receiving sunitinib exhibit a varying response to treatment, with several common sunitinib-induced adverse reactions reported, such as thrombocytopenia, hypertension, hand–foot syndrome, leucopenia and neutropenia [63–67].

The most commonly reported variant associated with sunitinib-induced adverse response is *ABCG2* 421C > A (rs2231142). According to the 1000 Genomes Project database, this variant is more common in Asians (Japanese, 32%; Chinese Han Southern China, 26%; Chinese

Han Beijing, 31%) than in Caucasians (Utah residents of European descent, 12%; British, 14%; Iberian in Spain, 7%) (http://www.internationalgenome.org/1000-genomes-browsers). This ethnic difference in allele frequency could explain the ethnic difference in sunitinib toxicity.

Low and colleagues conducted a candidate approach study on adverse reactions of sunitinib treatment in Japanese patients with RCC and reported the association of *ABCG2* 421C > A with severe thrombocytopenia ($P = 8.41 \times 10^{-3}$; OR 1.86; 95% CI 1.17–2.94) [68]. The ABCG2 functions as a half transporter of sunitinib. *ABCG2* 421C > A encodes ABCG2 Q141K, a variant associated with lower expression of *ABCG2*; this lower expression may in turn affect the oral absorption and/or elimination of sunitinib, thereby increasing patient toxicity to sunitinib [69]. Similar findings were also reported by Kim and colleagues, who found *ABCG2* 421C > A to be associated with severe thrombocytopenia in Korean patients with metastatic RCC ($P = 0.04$; OR 9.90; 95% CI 1.16–∞) [70]. Kim and colleagues also reported the association of *ABCG2* 421C > A with neutropenia ($P = 0.02$; OR 18.20; 95% CI 1.49–222.09) as well as hand–foot syndrome ($P = 0.01$, OR 28.46, 95% CI 2.22–364.94) [70]. *ABCG2* 421C > A has also been associated with sunitinib-induced neutropenia, with *ABCG2* 421-AA linked with poorer clearance of sunitinib ($P = 0.03$; OR 0.3; 95% CI 0.1–0.9) [71].

Aromatase Inhibitor

In contrast to tamoxifen that requires activation through a metabolic process, third-generation aromatase inhibitors (AIs) are active in their parent form, with metabolism resulting in inactivation of the drug. Common adverse effects associated with AI treatment include bone loss, musculoskeletal adverse events (MSAEs), such as arthralgia, osteoporosis, and bone fractures, as well as vasomotor symptoms (VMSs) such as hot flashes and night sweats [72, 73].

Ingle and colleagues performed a GWAS to identify genomic variants associated with AI-induced bone fractures in postmenopausal ER+ breast cancer patients [74]. After initial GWAS discovery and imputation, the study identified SNPs near *CTSZ-SLMO2-ATP5E* (rs10485828; $P = 2.56 \times 10^{-7}$), *TRAM2-TMEM14A* (rs6901146; $P = 1.15 \times 10^{-6}$) and *MAP4K4* (rs4550690; $P = 2.89 \times 10^{-6}$) that were moderately associated with risk for bone fracture [74]. These associations did not overcome the genome-wide significance threshold ($P < 5.0 \times 10^{-8}$). It is possible that these SNPs are involved in SNP-dependent and estrogen-dependent regulation of the corresponding genes, with possible downstream influence on the *RANK/RANKL/OPG* genes related to osteoporosis [74].

Wang and colleagues evaluated the association of *RANKL/RANK/OPG* gene polymorphisms with AI-induced MSAEs in early-stage, hormone-sensitive breast cancer patients [75]. Patients received either letrozole or anastrazole treatment. The *RANKL/RANK/OPG* signaling pathway plays an important role in bone health [76, 77]. Wang and colleagues found that the *RANKL* SNP rs7984870 ($P = 2.19 \times 10^{-4}$; OR 3.259; 95% CI 1.843–5.763) and OPG SNP rs2073618 ($P = 7.95 \times 10^{-4}$; OR 2.931; 95% CI 1.624–5.288) were associated with an increased risk of AI-related MSAEs [75].

In a separate study involving patients from the B-ABLE study, Garcia-Gira and colleagues investigated the association of SNPs with AI-induced arthralgia and found that SNPs in the *CYP17A1* and *VDR* genes showed significant association ($P < 0.01$) [78]. In a study involving hormone receptor-positive early-breast cancer patients from the TEAM trial, patients receiving exemestane treatment experienced known side-effects of AIs, such as MSAEs and VMSs. Patients carrying the aromatase gene variant *CYP19A1* rs934635-AA were associated with a significantly higher odds of having MSAEs ($P = 0.007$; OR 5.08; 95% CI 1.8–14.3) and VMSs ($P = 0.044$; OR 2.78; 95% CI 1.02–7.56) [79].

In the TEXT trial study involving premenopausal hormone receptor (HR)-positive breast cancer patients, the aromatase gene variant *CYP19A1* rs10046-TT was associated with a reduced incidence of hot flashes/sweating in patients receiving exemestane treatment

($P = 0.03$; OR 0.78; 95% CI 0.63–0.97). A stronger association was observed in the combination treatment of exemestane and suppression of ovarian function (TT vs. CT/CC: OR 0.65; 95% CI 0.48–0.89) [80].

In a randomized trial comparing exemestane and letrozole in early-stage HR-positive breast cancer patients, patients in the letrozole treatment arm of the study showed significantly greater bone loss than did those receiving exemestane [81]. Letrozole-treated patients carrying variant genotype *ESR1* rs4870061 ($P = 3.0 \times 10^{-4}$; VT/VT%BMD change − 10.94%; WT/WT,WT/VT%BMD change − 3.76%) and *ESR2* rs10140457 ($P = 3.0 \times 10^{-4}$; WT/VT %BMD change 3.08%; WT/WT%BMD change − 3.43%) were associated with decreased BMD [81].

In the BIG1-98 trial, which compared tamoxifen and letrozole treatment, letrozole-treated patients carrying the *CYP19A1* rs936308-CC genotype showed a higher risk of bone adverse effects (bone fractures, osteoporosis, arthralgia, and myalgia) (HR 1.37; 95% CI 1.01–1.85) [82].

Napoli and colleagues reported the association of *CYP19A1* variant rs700518 with bone loss in postmenopausal women with ER+ breast cancer treated with the third-generation AIs anastrazole, letrozole and exemestane [83]. Carriers of the rs700518-AA genotype developed significant bone loss at the lumbar spine and total hip at 12 months when compared to carriers of the WT GA/GG genotypes ($P = 0.03$) [83].

PART II: ROLES OF SOMATIC MUTATIONS IN CANCER PHARMACOGENOMICS

The use of genomic data to facilitate the development of molecularly targeted therapy was first demonstrated in the use of imatinib in CML patients. CML is characterized by the presence of the *BCR-ABL* fusion gene, which leads to the formation of a constitutively active tyrosine kinase, resulting in uncontrolled cell proliferation and malignant transformation. Imatinib, a first-generation ABL1 TKI, was approved by the U.S. Food and Drug Administration (FDA) in 2001 with the indication of CML for both newly diagnosed patients and for those with a failed interferon-alpha (IFα) response [84]. Imatinib was soon considered to be the first-line therapy for CML as it achieved a better response rate and tolerability among patients than did the existing therapy at the time, IFα [85]. More importantly, imatinib has dramatically improved the prognosis of CML, with a sustained OS rate and PFS of > 80% after 10 years of treatment [86]. The success of imatinib opened the era of molecular-targeted therapy for cancer. In recent years, the availability of NGS for in-depth genomic characterization has allowed the increasing identification of genomic biomarkers that could be targeted by FDA-approved therapies (Table 2) [87, 88]. Some of the most extensively studied genomic markers, *EGFR*, *ALK*, *BRAF* and *MEK*, will be further reviewed in this paper.

Epidermal Growth Factor Receptor

The superiority of personalized, genomic-based targeted therapy is most evident in the use of EGFR inhibitors in NSCLC treatments. Somatic mutations in *EGFR* are some of the most extensively studied targets due to their high prevalence (15–50%) in NSCLC patients. The two most common *EGFR* mutations are exon 19 deletions and exon 20 substitution (-L858R), together accounting for up to 90% of total EGFR mutations. These alterations result in a mutated tyrosine kinase that is under constant phosphorylation and activates downstream signals (RAS/MAPK and P13K/Akt), leading to tumorigenesis. More importantly, these two mutations, also recognized as sensitizing mutations, were found to predict the response rate of TKIs in NSCLC patients [89, 90]. Data from several clinical trials have shown that up to 67% of NSCLC patients who harbored a sensitizing mutation achieved objective response from erlotinib or gefitinib (FDA-approved first-generation TKIs) [91]. Similarly, the superiority of TKIs over traditional chemotherapy in response rate and PFS was also only observed in patients who harbored a sensitizing mutation [92, 93].

Table 2 U.S. Food and Drug Administration-approved molecular-targeted drugs

Molecular targets[a]	Drugs	Cancer type[b]	Specific mutations approved for patient selection	References
ALK	Alectinib	NSCLC	*ALK* mutation	[120]
	Brigatinib	NSCLC	*ALK* mutation	[122]
	Ceritinib	NSCLC	*ALK* mutation	[119]
ALK, MET, ROS1	Crizotinib	NSCLC	*ALK* fusion or *ROS1* fusion	[113]
BCR-ABL1	Bosutinib	CML	*BCR-ABL1* fusion	[159]
	Dasatinib	CML	*BCR-ABL1* fusion	[160]
	Imatinib	CML and ALL	*BCR-ABL1* fusion	[161, 162]
	Nilotinib	CML	*BCR-ABL1* fusion	[163]
	Ponatinib	CML	*BCR-ABL1* fusion	[164]
BRAF	Dabrafenib	NSCLC, melanoma, anaplastic thyroid cancer	*BRAF* V600/K	[130–132]
CDK4/6	Abemaciclib	ER+ HER2− breast cancer		[139]
	Palbociclib	HR+ HER2− breast cancer		[165]
	Ribociclib	HR+ HER2− breast cancer		[137, 166]
EGFR	Cetuximab	Colorectal cancer, squamous head and neck cancer	EGFR expressing and *KRAS* wild type for colorectal cancer	[167]
	Erlotinib	NSCLC, pancreatic cancer	*EGFR* (exon 19 deletions/L858R) for NSCLC	[98, 168, 169]
	Gefitinib	NSCLC	*EGFR* (exon 19 deletions/L858R)	[170]
	Necitumumab	Squamous NSCLC		[104]
	Osimertinib	NSCLC	*EGFR* (T790M/exon 19 deletions/L858R)	[171–173]
	Panitumumab	Colorectal cancer	*KRAS* and *NRAS* wild type	[174, 175]
EGFR/ ERBB2	Afatinib	NSCLC	*EGFR* (exon 19 deletions/L858R/ S768I/L861Q/ G719X)	[96]

Table 2 continued

Molecular targets[a]	Drugs	Cancer type[b]	Specific mutations approved for patient selection	References
ERBB2	Ado-Trastuzumab Emtansine	HER2+ breast cancer		[176, 177]
	Trastuzumab	HER2+ breast cancer, HER2+ gastric cancer		[178–180]
	Pertuzumab	HER2+ breast cancer		[181]
	Lapatinib	HER2+ breast cancer		[182]
	Neratinib	HER2+ breast cancer		[183, 184]
KIT	Imatinib	Aggressive systemic mastocytosis	Lack of D816V *c-Kit* mutation	[185]
		Gastrointestinal stromal tumors	*Kit* (CD117) positive	[186]
MEK	Trametinib	NSCLC, melanoma, anaplastic thyroid cancer	*BRAF* V600E/K	[130, 131]
mTOR	Everolimus	HR+ HER2− breast cancer; renal cell carcinoma; pancreatic, gastrointestinal or lung origin of neuroendocrine tumor; subependymal giant cell astrocytoma		[187–191]
PDGFR	Imatinib	Myelodysplastic/myeloproliferative disorders	*PDGFR* gene rearrangements	[192]
		Dermatofibrosarcoma protuberans	*COL1A1-PDGFB* fusion	[193]
		Hypereosinophilic syndrome and Eosinophilic leukemia	*FIP1L1-PDGFRA* fusion	[194]
VEGF	Bevacizumab	NSCLC; colorectal cancer; cervical cancer; glioblastoma; ovarian epithelial, fallopian tube or primary peritoneal cancer; renal cell carcinoma		[195, 196]
VEGFR2	Ramucirumab	NSCLC, metastasized colorectal cancer, advanced gastric or gastro-esophageal junction adenocarcinoma		[197]

[a] *ALK* Anaplastic lymphoma kinase, *BRAF* Proto-oncogene B-Raf, *CDK4/6* Cyclin-dependent kinase 4/6, *EGFR* Epidermal growth factor receptor, *ERBB2* Erb-B2 Receptor Tyrosine Kinase 2, *KIT* Tyrosine-protein kinase Kit, *MEK* Mitogen-activated protein kinase kinase, *mTOR* Mammalian target of rapamycin, *MET* Tyrosine-protein kinase Met, *PDGFR* Platelet-derived growth factor receptors, *ROS1* Proto-oncogene tyrosine-protein kinase, *VEGF* Vascular endothelial growth factor, *VEGFR2* Vascular Endothelial Growth Factor Receptor 2

[b] *ALL* Acute lymphocytic leukemia, *CML* chronic myeloid leukemia, *ER+* estrogen receptor subtype of breast cancer, *HER* human epidermal growth factor receptor 2, *HR* hormone receptor, *NSCLC* non-small-cell lung cancer

These positive results have secured the role of TKIs as the first-line treatment for metastatic NSCLC patients who harbor *EGFR* sensitizing mutations. Although TKIs achieved a remarkable initial response, up to 50% of the patients acquired resistance after 1 year of treatment, with the secondary -T790M mutation accounting for the majority of the resistance cases [94]. Second-generation TKIs, such as afatinib and dacomitinib, were initially designed to overcome the resistance by increasing the inhibition potency. Unfortunately, they did not overcome the resistance caused by the -T790M mutation [95]; instead, afatinib was found to be effective against three other rare *EGFR* mutations, namely, - S768I/L861Q/G719X, with 78% of the patients who harbored one of these three mutations having an objective response [96]. Osimertinib, a third-generation TKI has recently been approved for advanced NSCLC patients with a T790 M mutation. The approval was based on the promising results from a phase II clinical trial that assessed the efficacy of osimertinib in patients who harbored either an intrinsic or acquired *EGFR*-T790M mutation. Up to 70% of the patients achieved an objective response with manageable side effects [97]. In addition to being a treatment for NSCLC, erlotinib is also currently approved as a combination therapy with gemcitabine for metastatic pancreatic cancer patients based on findings showing that this combination therapy achieved an improved PFS and disease control rate [98].

In addition to EGFR inhibitors, anti-EGFR monoclonal antibodies have also been developed to inhibit EGFR auto-phosphorylation and further downstream signaling. Anti-EGFR monoclonal antibodies are most commonly used for treating metastatic colorectal cancer [99]. Cetuximab and panitumumab are currently approved to be used either as combination treatment with irinotecan or as monotherapy for advanced EGFR-positive colorectal cancer patients due to their superior response rate, disease control rate and longer PFS compared to existing chemotherapy treatment [100–102]. In more recent years, a second-generation anti-EGFR monoclonal antibody, necitumumab, has been approved for use in combination with gemcitabine and cisplatin as the first-line treatment for patients with metastatic squamous NSCLC [103]. The approval was based on the promising results obtained from a large randomized, multicenter study that involved 1093 patients with squamous NSCLC across 26 countries [104]. These patients were divided into two treatment arms: gemcitabine + cisplatin with or without necitumumab. Significant improvement in the OS and PFS rates was observed in patients who were treated with necitumumab [104]. Anti-EGFR monoclonal antibodies have shown clinical benefits over traditional chemotherapy in NSCLC and colorectal cancer patients; however, unlike EGFR inhibitors, the predictive biomarker for such clinical response is still unclear. Several clinical trials have shown EGFR-positive patients (identified using fluorescence in situ hybridization [FISH] or immunohistochemistry [IHC]) to have a more favorable outcome from necitumumab and cetuximab than those who did not express EGFR; however, this difference was found to be non-significant [105, 106]. The limited sensitivity of FISH and IHC to detect EGFR expression also questions the predictivity of EGFR expression for treatment response to anti-EGFR monoclonal antibodies. Future studies using assays with higher sensitivity, such as NGS, are required to verify and quantify such a relationship. In contrast to EGFR expression, *KRAS* mutation status has been well established as a predictor of response to cetuximab and panitumumab [99]. *KRAS* mutations result in a constitutively active guanine nucleotide-binding (GTP)-binding protein, allowing the tumor to escape from the inhibition effect of EGFR-targeted therapies. Such effects have been demonstrated in several clinical trials where the improved PFS and response rate of anti-EGFR monoclonal antibodies were only observed in *KRAS* WT groups [107, 108]. Recently, *NRAS* and *BRAF* mutation status were found to predict the response rate of cetuximab and panitumumab in colorectal cancer patients. Cumulative evidence shows that patients whose tumor harbors mutations in *NRAS* exons 2, 3 and 4 and *BRAF*-V600E are unlikely to respond to anti-EGFR monoclonal antibodies [109]. *RAS* mutation testing is currently mandatory before the

initiation of cetuximab and panitumumab treatment as they are not indicated for patients whose tumor harbor somatic mutations in exon 2, 3 and 4 of either *KRAS* or *NRAS*.

In recent years, in vitro studies have been conducted to explore the possibility of targeting *EGFR* in NSCLC patients using immunotherapy. In a pre-clinical study, the authors developed an adoptive T-cell treatment with chimeric antigen receptor (CAR) that targets EGFR. The modified CAR T cells showed great anti-cancer efficacy with significant regression of EGFR-positive human lung cancer xenografts [110]. Future clinical studies are required to confirm their efficacy in humans. The feasibility of CAR T cells that target EGFR in patients with metastatic colorectal cancer is currently under a phase I/II clinical trial (ClinicalTrials.gov Identifier: NCT03152435).

Anaplastic Lymphoma Kinase

In addition to EGFR, several other targeted inhibitors have been approved for NSCLC patients who harbor alterations in the gene for anaplastic lymphona kinase (*ALK*). *ALK* mutations, are found in 3–7% of patients with NSCLC, which include gene fusion, point mutation and amplification, with gene fusion accounting for majority of these cases. Several fusion partners of *ALK* have been identified, and the gene that encodes *EML4* has been found to be most abundant in NSCLC. Other fusion partners include *KIF5B*, *TFG*, *DCTN1*, *SQSTM1*, *Nucleoprotein TPR*, *CRIM1*, *STRN*, *HIP1*, *PTPN3*, *KLC1*, *CLTC* and *FBX036* [111]. *ALK* rearrangements lead to the formation of a constitutively active oncogenic fusion protein that activates downstream signaling pathways, such as the mitogen-activated protein kinase (MAPK) or JAK-STAT pathways [112]. Several *ALK* inhibitors are now available, and these are considered to be first-line therapy for NSCLC patients who harbor *ALK* mutations due to their superior efficacy. In a randomized phase III clinical trial, the median PFS in NSCLC patients who were treated with crizotinib, a first-generation ALK/ROS1/MET inhibitor, was significantly longer than that in patients treated with the standard chemotherapy (7.7 vs. 3.0 months, respectively) [113]. Also, the objective response rate was 46% higher in the crizotinib treatment arm than in the chemotherapy arm [113]. Unfortunately, similar to EGFR inhibitors, the majority of the patients treated with crizotinib experienced relapse within 12–24 months, with the resistance mechanisms being either *ALK* dependent or *ALK* independent [114]. Around 30% of the resistance cases developed due to the presence of a secondary mutation in the ALK tyrosine kinase domain that led to reactivation of the fusion protein [114]. Some of the reported secondary point mutations include L1196M, C1156Y, F1174L and F1174V [115]. Second- and third-generation ALK inhibitors (ceritinib, alectinib and brigatinib) have been designed to overcome such resistance by increasing the potency and selectivity to *ALK* fusion proteins [116]. In two studies, both ceritinib and alectinib demonstrated an overall response rate of $>$ 50% in patients who progressed or were intolerant to crizotinib [117, 118]. Furthermore, these agents have also been shown to have superior efficacy in ALK inhibitor-naïve patients compared to chemotherapy; this efficacy led to their recent approval as first-line treatment for NSCLC patients carrying the *ALK* mutation [119, 120]. In a pre-clinical study, brigatinib, a recently FDA-approved ALK inhibitor, showed inhibition activity against several *ALK* acquired resistance mutations, such as *ALK* C1156Y, I1171S/T, V1180L, L1196M, L1152R/P, E1210K and G1269A [121]. This finding was confirmed in a phase II clinical trial, where the overall response rate to brigatinib was observed to be $>$ 53% in *ALK*-positive, crizotinib-treated patients with metastatic NSCLC [122].

Serine–Threonine Protein Kinase and Mitogen-Activated Protein Kinase

Approximately half of advanced melanomas harbor a serine–threonine protein kinase *BRAF* mutation, with V600E being the most common mutation (90% of total *BRAF* mutations). The mutated BRAF phosphorylates and activates MEK proteins, which in turn activates the MAPK pathway, leading to an uncontrolled cell

growth and proliferation [123]. The high prevalence of the *BRAF* mutation in melanoma makes it a perfect candidate for targeted therapies for melanoma patients. Dabrafenib and vemurafenib, both BRAF inhibitors, were both found to exhibit improved PFS or OS compared to the empirical chemotherapy agent dacarbazine in patients with *BRAF*-V600 metastatic melanoma [124, 125]. Unfortunately, the majority of the patients who received monotherapy with the BRAF inhibitor developed resistance within 6–7 months of treatment [126]. Resistant melanoma cells may arise from either preexisting resistant clones that were undetected in the single biopsy specimen or acquired through secondary mutation [127]. Some of the known acquired resistance mutations for BRAF inhibitors include alternative splicing of *BRAF*, *BRAF* copy number amplification, *NRAS* mutations (Q61, Q12 and Q13 on codon 12 or 61) and alterations in *PI3K*. The secondary mutations allow reactivation of the MAPK pathway, thus permitting the melanoma cells to escape BRAF inhibition [128]. In addition to BRAF inhibitors, the MEK inhibitor trametinib has also been approved to intervene the amended MAPK pathway in melanoma patients with *BRAF*-V600 mutations. In one study, trametinib demonstrated improved OS at 6 months compared to the empirical chemotherapy agents (81% and 67%, respectively); however, resistance quickly emerged with a median PFS of 4.8 months [129]. More importantly, combination therapy of trametinib + dabrafenib has shown superior clinical effects with durable benefit which overcomes the frequent occurrence of resistance that was observed in monotherapies [130]. Combination targeted therapy has led to significant improvement in the 3-year PFS (22 vs. 12%) and 3-year OS (44 vs. 32%) compared to dabrafenib monotherapy [130]. Combination therapies of trametinib + dabrafenib or of vemurafenib + cobimetinib are currently approved for the treatment of advanced melanoma that harbors the *BRAF* V600E or V600K mutation. Combination therapy of dabrafenib + trametinib has also shown superior efficacy in NSCLC and anaplastic thyroid cancer with *BRAF* V600 mutations [131, 132].

Other Molecular Targets: c-Met Tyrosine Kinase and Cyclin Dependent Kinases 4/6

In addition to the approved biomarkers mentioned above, which can be utilized for treatment selection, several other targets have also been validated to expand treatment availability for cancer patients. However, further studies are warranted to identify the specific genomic markers for selecting sensitive patients. c-Met tyrosine kinase (MET) dysregulations, in particular *MET* exon 14 splice site mutations, are detected in approximately 3–4% of lung adenocarcinomas [112]. *MET* amplification has also been reported in cases with acquired resistance to EGFR inhibitors in NSCLC patients [133]. The possibility of MET inhibition as a treatment option was suggested in several early clinical trials that tested the effectiveness of MET inhibitor in combination therapies. Cabozantinib and onartuzumab in combination with erlotinib, an EGFR TKI, showed significantly improved PFS compared to monotherapy with erlotinib [134, 135]. Unfortunately, these promising results could not be replicated in a phase III clinical trial where superior clinical benefits of MET inhibitor were not observed in NSCLC patients who harbored the *MET* mutation [136]. However, it should be noted that the patients participating in this trial were selected based on the tumor overexpressing MET, as determined by IHC. It is unclear whether IHC is a sufficiently sensitive selection tool to identify MET-positive patients. Further studies with accurate molecular profiling using NGS are warranted to validate the implication of MET in NSCLC patients.

The importance of cyclin dependent kinases 4/6 (CDK4 and CDK6, respectively) in cell division and their hyperactivation in multiple cancer types has been well established. Great efforts have been expended to develop drugs targeting CDK activity, and three of these are now approved for ER+ advanced or metastatic breast cancer in combination with an AI. The addition of a CDK4/6 inhibitor (ribociclib, palbociclib and abemaciclib) to the hormone therapy has successfully increased PFS when compared to AI monotherapy [137–139]. Despite their superior efficacy in cancer

treatments, the determinants of sensitivity of CDK4/6 inhibitors are still unknown. The association of cyclin D1 amplification and the response to CDK4/6 have been extensively studied in both pre-clinical and clinical trials across different cancer types. Patients with mantle cell lymphoma whose tumor harbors cyclin D1 deregulation were found to be sensitive to CDK4/6 inhibitors; however, such a specific response was not observed in breast cancer patients [140, 141]. It should be noted that the frequency of cyclin D1 genetic alteration is strongly disease specific; therefore, CDK4/6 inhibitors are most likely to be sensitive in tumors with a strong dependence on cyclin D1 alterations [142]. Similarly, the association of *CDK4/6* amplification with the sensitivity of CDK4/6 inhibitors has been assessed in several tumors. In a phase II clinical trial, palbociclib was found to be sensitive in patients with *CDK4* amplified liposarcoma [143]; however, this study was not powered to assess whether *CDK4* amplification can be used as a biomarker to identify sensitive patients due to the lack of a control arm. Furthermore, contradicting results have been reported in pre-clinical studies where *CDK4* and *CDK6* amplifications were associated with acquired resistance of CDK4/6 inhibitors in breast cancer and renal cancer [144, 145]. Several clinical trials are currently underway to confirm the association of these genetic markers with the efficacy of CDK4/6 inhibitors (ClinicalTrials.gov Identifier: NCT03310879 and NCT02187783).

Efficacy of Genomic-Based Therapies

The increased availability of targeted drugs and the increased use of genomic-based therapies have driven the urgency to conduct trials to assess whether genomic-based molecular targeted therapies are clinically superior to empirical therapies. SHIVA, conducted in 2012–2014, was the first prospective, randomized phase II trial to assess the efficacy of molecularly targeted therapies in refractory solid tumors based on the patient's genomic data compared to clinician's choice [146]. In this trial, the genomic DNA of 741 patients were screened using the AmpliSeq cancer panel (Thermo Fisher Scientific, Waltham, MA, USA). Alterations in the gene copy number were assessed using the CytoScan® HD cytogenetic microarray system (Thermo Fisher Scientific), and expression of the hormone receptors was assessed using IHC. Of the screened patients, 40% contained at least one molecular alteration that could be targeted by one of the 11 pre-selected molecularly targeted agents. 26% of the patients were randomly assigned into one of the two treatment arms: molecularly targeted therapy or clinician's choice. Interestingly, no differences in PFS was observed between the two arms. However, it should be noted the main aim of the study was to assess the efficacy of the off-label use of marketed drugs in patients harboring invalidated genomic alteration in multiple cancer types. Furthermore, the study was not powered to assess the efficacy of a specific drug in a specific subgroup of patients with certain molecular alteration patterns. The negative results from this study prompted the need for more narrowly focused studies that would evaluate the efficacy of one molecularly targeted drug in one specific subgroup of patients compared to a non-targeted empirical treatment. In contrast to the results obtained from SHIVA, genomic-based therapies assessed in a recent retrospective trial showed improved treatment outcome [147]. This trial (IMPACT/COMPACT) involved 1640 patients with advanced solid tumors who were molecular profiled in the study; overall response rate was observed to be higher in patients with the genotyped-matched treatment than in those with the genotype-unmatched treatment (19 vs. 9%, respectively) [147]. Similar benefits were also observed in several other smaller trials: the iCat study [148] and the NEXT-1 study [149]. In addition to the trials mentioned above, NCI-MATCH, an-ongoing clinical trial has attracted much attention as this is to date one of the largest precision medicine trial based on molecular alteration targeted therapies. This phase II clinical trial is being conducted across 1173 sites for patients with relapsed/refractory solid tumors, lymphomas and myelomas. Enrolled patients are assigned to one of the 30 treatment arms based on their tumor molecular

alterations. The results from this study would provide a better understanding of the feasibility and efficacy of genomic-based therapies.

Development of Basket Trial

One of the biggest limitations of genomic-based therapies is the limited availability of validated genomic markers. The American Association for Cancer Research (AACR) project, GENIE, is one of the biggest consortium that explores the linkage of cancer genomic data with clinical outcomes. It contains over 19,000 genomic and clinical records that were obtained from multiple international institutes. Of these, 7.3% of tumors harbored a level 1 or 2A molecular alteration that is indicative of treatment with an FDA-approved drug or standard care in the same disease type. An additional 6.4% tumors contained Level 3A alterations, which are those with clinical evidence for response to investigational therapies in the same disease type; and a further 17.8% of tumors had level 2B (FDA-approved target in another disease type) or 3B alterations (target with clinical evidence in another disease type). In total, up to 30% of the patients harbored at least one potential actionable target [7]. As observed from these figures, through the expansion of targeted therapies across different disease types, an additional 20% of patients may benefit from such therapies. This gives rise to the necessity of basket trials. Basket trials incorporate different tumor types with the same genetic alteration into one study. These trials are extremely beneficial for studying low prevalent mutations and diseases for which it is often difficult to recruit sufficient patients to collate clinically meaningful data. The successful targeting of BRAF inhibitors and EGFR inhibitors across different cancer types reinforces the importance of validating biomarkers on other patient groups who share the same molecular alterations. This may broaden the number of patients who can benefit from genomic-based therapy.

The *AKT1*-E17K mutation is found in a broad range of tumor types, but it is infrequent in all individual tumor lineages. This makes the testing of AKT inhibitors in this patient population in one tumor type difficult, which makes *AKT1*-E17K mutation an ideal candidate for a basket trial. A total of 52 patients with advanced solid tumors who carried the *AKT1* mutation were recruited in this trial and were treated with AZD5363, an ATP-competitive pan-AKT kinase inhibitor. Durable responses and tumor regression were observed across a variety of tumor types harboring the E17K mutation: breast cancer, both ER+ and ER-triple negative; endometrial cancer; cervical cancer; and lung cancer. Furthermore, patients carrying *AKT1*-Q79K (a rare mutation) also responded to AZD5363 [150].

Basket trials also allow exploration of the underlying biology of diverse but rare mutations, such as *HER2* and *HER3* alterations. The efficacy of neratinib, a pan-HER kinase inhibitor, in HER2+ breast cancer has been well established, however, due to the diversity of HER2 and HER3 mutations and its low prevalence in one tumor type, little is known about the therapeutic importance of these genomic alterations in the efficacy of pan-HER inhibitors. In a basket trial conducted by Hyman et al., neratinib showed the greatest activity in breast, cervical and biliary cancers where the tumors contained HER2 kinase domain missense mutations [151].

Future Directions

The development and availability of NGS has allowed genomic profiling through somatic mutation identification to be more easily achieved. However, several factors should be taken into consideration when using this information for the selection of genomic-based targeted therapies.

One of the major drawbacks with the identification of somatic mutations using single biopsy specimen is the underdetection of the clonal heterogeneity of cancer. Biomarker sampling in a single tumor region may underdetect or even not detect at all some biomarkers that may be crucial for targeted therapy selection. Undetected heterogeneity may result in potential escaping mechanisms being overlooked, possibly accounting for the resistance that is

commonly observed in targeted therapies. Furthermore, improved understanding of the clonal heterogeneity may allow the development of combination target therapies to reduce the incidences of resistance. The success of the combination therapy using BRAF and MEK inhibitors to reduce disease recurrence for melanoma patients reinforces the potential importance of combining targeted therapies. Current understanding of the clonal heterogeneity of tumors may be enhanced by the use of liquid biopsy where it reflects the global, both primary and metastatic sites, molecular status of the patient. However, further studies are required to confirm the concordance rates of the mutation profile obtained using liquid biopsy and tumor tissue, respectively [152].

The current standard for somatic variant calling is achieved through the alignment of genomic information from the tumor with either the reference DNA or the paired-blood/normal sample. However, recent studies have found that alignment with the reference DNA may incorrectly identify a germline mutation, in particular clonal hematopoiesis (CH), as a somatic mutation. CH is the somatic acquisition of genomic alterations in hematopoietic stem and/or progenitor cells that leads to clonal expansion. They are usually associated with aging, smoking and radiation therapy. When NGS is carried out in an unpaired setting, CH can potentially be incorrectly identified as somatic mutations, as illustrated in a recent large retrospective study in which NGS, using the MSK-IMPACT platform, was performed on matched tumor and blood samples from 17,469 patients across 69 cancer types [153]. Up to 14.1% of the CH-associated mutations identified were also detectable in the matched tumor. Without matched blood samples, 5.2% of the patients would have at least one CH-associated mutation mistakenly considered to be a tumor-derived somatic mutation [153]. Similar results were reported in a smaller retrospective study where up to 8% of the identified clonal hematopoiesis-related genes from tumor samples were also identified in the paired blood sample. Some of these identified mutations were also considered to be actionable mutations [154]. These results highlight the importance of using paired tumor and blood samples to prevent incorrect target identification, which in turn may lead to inappropriate clinical management.

To date, only a limited number of studies have been conducted to explore the variable frequency of somatic mutations across different ethnic groups. In a study conducted by Nagahashi et al., *ERBB2*, *APC*, *TP53* and *NRAS* mutations were found to be significantly higher in Japanese colorectal cancer patients than in the data obtained from TCGA which were based on the U.S. population [155]. The same study also found that close to 50% of *BRAF* mutations occurred outside the hotspot V600E, which is the most common *BRAF* mutation in the Western population [155]. Similarly, *EGFR* mutationd were more frequently observed in the non-smoking Asian population than in the Western population. Up to 59.7% of East Asian never or light smokers had tumors harboring an *EGFR* mutation while only 11% of the Western patients with lung adenocarcinoma possessed an *EGFR* mutation [156, 157]. The variable frequencies of certain variants between different ethnic groups bring into question the applicability of the same gene panels to be used across all populations. This challenge may be met by using a customized panel of genes, increasing specific genes that are more applicable for the situation.

The recent development of liquid biopsy to detect circulating tumor cells or cell-free tumor DNA from patients' blood further enhances the utilization of genomic information to improve patient outcome. The minimal invasiveness of liquid biopsy in combination with NGS allow ongoing monitoring of disease progression, drug response and resistance development [158]. Overall, NGS has allowed the translation of genomic information into clinical practice and the development of cancer precision therapy.

CONCLUSION

The integration of genomics into the medical field has transformed the era from one-size-fits-all to cancer precision medicine, in which cancer precision medicine aims to provide the right

dose of the right drug, to the right patient, at the right time. In particular, clinical trials now request the pre-screening of genetic mutations in individual medical institutions to refine patients' selection before enrolment, enhancing the pivotal role of genetic mutation in the clinical settings. Also, the establishment of basket trials that evaluate the same genetic alteration in different tumor types provide the possibility of drug repurposing to treat cancer patients based on the mutation status in the near future. It is hopeful that the incorporation of genetic information could improve treatment precision, leading to a better quality of life for cancer patients.

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