Review Article

The role of ethnicity in personalized dosing of small molecule tyrosine kinase inhibitors used in oncology

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Abstract: Inter-ethnic differences in systemic exposure, efficacy and safety have been reported for some small molecule tyrosine kinase inhibitors (smTKIs). This variability in response related to ethnicity is due to a complex interplay of intrinsic and extrinsic factors that differ between people of different geographic ancestries, influencing the pharmacokinetics and pharmacodynamics of smTKIs. An example of intrinsic factor differences is the higher prevalence of epidermal-growth-factor receptor activating mutations in East Asians compared to Europeans with non-small cell lung cancer (NSCLC), which has been associated with significantly superior survival outcomes with erlotinib and gefitinib. A further example is the inter-ethnic difference reported in the susceptibility to erlotinib-induced adverse-events, which has been correlated to ethnic differences in the expression and activity of CYP3A5 as well as in P-glycoprotein and BCRP mediated transport. Differences in extrinsic factors, including tobacco smoking and complementary medicine use, may contribute to inter-ethnic differences in erlotinib treatment outcomes. Understanding the nature and mechanism of these inter-ethnic differences in smTKIs can help to guide treatment decisions to individualize treatments and improve patient outcomes.

Keywords: Ethnicity; inter-individual variation; precision medicine; tyrosine kinase inhibitors

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Introduction

The development of molecular targeted therapies, such as small molecule tyrosine kinase inhibitors (smTKIs), has revolutionized the treatment of some cancers, offering many patients a larger survival benefit with a lower toxicity profile and better quality of life, compared to traditional cytotoxic chemotherapy. However, despite their targeted mechanism of action, smTKIs exhibit large inter-individual variability in their systemic exposure (pharmacokinetics) and effects (pharmacodynamics) (1-3). Inter-individual variability in pharmacokinetics is particularly pertinent in oncology, as anticancer agents are frequently administered at doses close to maximally tolerable intensity, and most smTKIs are considered to have a narrow therapeutic index (3). Therefore, small changes in plasma concentrations may lead to serious adverse drug reactions or the potential for therapeutic failure (4). For some smTKIs, including axitinib, imatinib, sunitinib and pazopanib, there is sound evidence that systemic exposure correlates with clinical outcomes, thereby highlighting the importance of precision dosing (1,3,5). However, all smTKIs are still initiated at fixed doses, putting patients at risk of unpredictable efficacy and toxicity (3). Understanding reasons for variability in the pharmacokinetics and pharmacodynamics of smTKIs is fundamental to reducing the incidence of suboptimal

outcomes.

There is growing evidence to suggest that ethnicity may be a factor contributing to the inter-individual variability observed in the exposure and response to smTKIs (6,7). The same dose of a smTKI prescribed to people from different ethnic backgrounds can result in different systemic exposures, efficacy and toxicity (8,9). Outcomes from smTKI treatment are influenced by a complex interplay of both intrinsic and extrinsic factors affecting their pharmacokinetic and pharmacodynamic pathways (6,10). Thus, inter-ethnic differences in the outcomes of treatment with smTKIs are likely a reflection of population differences in these intrinsic and extrinsic determinants (6). Intrinsic factors are those relating to an individual's physiological characteristics, such as renal/hepatic function and body weight/composition, and genetic characteristics, considering both somatic and germline genetics (6,7). These include ethnic variation in the expression or activity of genes encoding for drug metabolizing enzymes and transporters (11-15), as well as genes involved in the mechanism of action of a drug, such as mutations in drug target proteins that cause particular sensitivities or resistance to the drug (15-19). Extrinsic factors, such as tobacco use, complementary and herbal medicine use and dietary habits, can vary between people of different geographic ancestries and can also influence the pharmacokinetics of a drug, its concentration at the target site, and thus drug response (6).

Recognition of inter-ethnic differences in anticancer treatment outcomes, as well as understanding reasons for these differences, can help identify populations that are predisposed to treatment resistance or susceptibility to adverse effects. The ethnicity of a patient could serve as a marker or predictor, alerting prescribers of patients who may need further investigation (e.g., genotyping critical pathways) to guide initial dose selection. It can also help identify patients who may need therapeutic drug monitoring to achieve adequate drug concentrations with minimal risk of harmful effects. Adverse drug reactions can greatly impact patient adherence, and may even result in cessation of treatment. Thus, identifying patients who are at risk of severe toxicities due to certain intrinsic/extrinsic factors, and personalizing their dose regimen with careful monitoring to reflect their pharmacokinetic and pharmacodynamic characteristics, can avoid treatment failure and improve a patients' quality of life. By incorporating knowledge of a patients' physiology, genetic predisposition and environmental influences into prescribing practices, we can move to a model of precision medicine and optimally utilize the life-changing drugs that are available. It may be possible to make earlier interventions, thereby reducing the likelihood of disease progression and ineffective treatment.

The aim of this review is to summarize the known information on inter-ethnic differences relevant for smTKIs in the treatment of cancer, discussing pharmacokinetic, efficacy and safety perspectives. This review will also illustrate how smTKI prescribing practices can be informed by considering a patients' ethnicity.

Inter-ethnic differences in tyrosine kinase inhibitor treatment outcomes

The efficacy of some smTKIs has been found to differ between European and East Asian populations (*Table 1*). There is good evidence that people of East Asian ancestry have significantly higher response rates and superior survival outcomes to erlotinib, gefitinib, lapatinib and regorafenib, when compared to non-East Asian patients (8,9,44-48,51,65,66,83-85). No inter-ethnic differences in treatment response have been reported for ruxolitinib and osimertinib (71,72,86,87,114-116). Additionally, there are known ethnic differences in the tolerability profile of some smTKIs (*Table 2*). Many studies have demonstrated that Asian patients, in particular East Asians, experience more severe and more frequent smTKI-related adverse events when compared to people of European ancestry (79,90,97,121,125), with the exceptions of ceritinib and crizotinib, where Asian patients appear less susceptible to adverse events (32,118), and osimertinib, which does not appear to display inter-ethnic differences in harmful effects (71). Accordingly, with most smTKIs, higher rates of toxicity-related dose reductions, dose interruptions and drug discontinuations have been reported in patients of East Asian than European ancestry (20,45,46,51,52,67,76,89,124,125).

Inter-ethnic differences in pharmacokinetic pathways

Tyrosine kinase inhibitor pharmacokinetics

Pharmacokinetics describes the relationship between the drug dose and the resulting plasma and tissue drug concentrations (126). The processes of absorption, distribution, metabolism and excretion of a drug all contribute to the concentration-time profile observed in a

Table 1 Small molecule tyrosine kinase inhibitor efficacy outcomes across ethnic groups

Tyrosine kinase Inhibitor	Summary of efficacy outcomes across ethnic groups	Reference
Afatinib	Japanese patients with EGFR-positive NSCLC have improved survival outcomes (OS and PFS) with afatinib, compared to other Asians and non-Asians[†]	(20,21)
Alectinib	Asian patients with crizotinib-refractory ALK-positive NSCLC show similar central nervous system response (ORR) to patients of European ancestry[‡]	(22)
	It is unknown if there are ethnic differences in systemic response to alectinib. Different dosing regimen and study methodology prevents cross-trial comparison of outcomes from a phase II North American trial and a phase II Japanese trial	(23,24)
Axitinib	Japanese patients with advanced RCC have improved outcomes (PFS and ORR) compared to other Asians and non-Asians[†]	(25-27)
Bosutinib	Although there are no head-to-head studies comparing clinical response to bosutinib in different ethnic groups with CP Ph-positive CML, outcomes from phase II studies suggest comparable response in Japanese and non-Japanese patients (MCyR, CHR and MMR)[§]	(28,29)
Cabozantinib	It is unknown if there are ethnic differences in cabozantinib outcomes in MTC or RCC. Over 90% of patients in the pivotal EXAM and METEOR phase III trials were of European ancestry, and there are currently no published studies in other ethnic groups	(30,31)
Ceritinib	Asian patients with ALK-positive NSCLC have a greater magnitude of benefit to ceritinib (ORR and PFS) than patients of European ancestry[†]	(32)
Cobimetinib	It is unknown if there are ethnic differences in cabozantinib outcomes in BRAF V600-positive melanoma. Over 95% of patients in the pivotal coBRIM study were of European ancestry, and there are currently no published phase II/III studies evaluating cobimetinib efficacy in other ethnic groups	(33)
Crizotinib	Asian patients with ALK-positive NSCLC have a greater magnitude of benefit to crizotinib (ORR and PFS) than non-Asians[†]	(34-36)
	It is unknown if there are ethnic differences in crizotinib outcomes in ROS1-positive NSCLC. Investigators of the pivotal PROFILE 1001 trial did not compare outcomes between Asians and non-Asian patients with ROS1-positive NSCLC	(37)
Dabrafenib	It is unknown if there are ethnic differences in dabrafenib outcomes in BRAF V600-positive melanoma. All patients enrolled in the pivotal BREAK-3 trial were of European ancestry, and there are currently no published phase II/III studies evaluating dabrafenib efficacy in other ethnic groups	(38)
Dasatinib	East Asians with CP Ph-positive CML may have numerically greater molecular and cytogenetic response rates to dasatinib (CCyR and MMR), as well as a shorter time to response, compared to non-East Asians[†]	(39-41)
	It is unknown if there are ethnic differences in dasatinib outcomes when used for Ph-positive ALL. Results from a phase I/II study in Japanese patients cannot be compared with those from non-Japanese cohorts, such as START-L, due to different study designs and patient characteristics	(42,43)
Erlotinib	East-Asian patients with NSCLC (+/– EGFR mutation) have better outcomes to erlotinib than patients of European ancestry (ORR, PFS and OS)[†,¶]	(44-48)
	Although there are no head-to-head studies comparing clinical response to erlotinib in different ethnic groups with pancreatic cancer, outcomes from phase III studies suggest greater response rates and survival outcomes in East Asians compared to Caucasian patients with pancreatic cancer[§]	(49,50)
Gefitinib	East-Asian patients with NSCLC (+/– EGFR mutation) have better outcomes to gefitinib than patients of European ancestry (ORR and OS)[†,¶]	(9,48,51-53)

Table 1 *(continued)*

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Tyrosine kinase Inhibitor	Summary of efficacy outcomes across ethnic groups	Reference
Ibrutinib	Although there are no head-to-head studies comparing clinical response to ibrutinib in different ethnic groups with MCL, outcomes from phase II studies suggest that Japanese patients have superior outcomes than patients of European ancestry (ORR and time to response)[§]	(54-56)
Imatinib	East Asian patients with CP Ph-positive CML may have slightly greater cytogenetic and molecular response rates to imatinib (CCyR and MMR), as well as a shorter time to response, compared to non-East Asians[†]	(39-41, 57-59)
	Although there are no head-to-head studies comparing clinical response to imatinib in different ethnic groups with GIST, outcomes from phase II studies suggests that East Asian patients have superior outcomes than patients of European ancestry (ORR, DCR and 1-year survival rate)[§]	(60-64)
Lapatinib	There is significant variability in lapatinib survival outcomes between Asian and non-Asian patients with HER2-positive gastro-esophageal adenocarcinoma. Asian patients, in particular Korean and Chinese patients, show statistically significant improvements in OS with the addition of lapatinib to capecitabine and oxaliplatin[†]. Conversely, non-Asian patients do not demonstrate OS benefit with lapatinib[†]	(65,66)
Lenvatinib	Japanese patients with RR-DTC show similar benefit with lenvatinib (ORR and PFS) to patients of European ancestry[†]	(67,68)
	It is unknown if there are ethnic differences in lenvatinib outcomes when used in advanced RCC. Over 95% of patients enrolled in the pivotal phase II trial were of European ancestry, and there are currently no published studies investigating clinical outcomes of lenvatinib in other ethnic groups	(69)
Nilotinib	East Asians with CP Ph-positive CML may have slightly greater molecular response rates with nilotinib, as well as a shorter time to response, compared to non-East Asian patients[†]	(57-59)
Nintedanib	Asian patients with NSCLC may not experience a significant survival benefit with nintedanib over placebo, compared to non-Asian patients who do demonstrate survival benefits with nintedanib[†]	(70)
Osimertinib	Comparable efficacy (ORR and PFS) between Asian and non-Asian patients with EGFR T790M-positive NSCLC[†]	(71,72)
Pazopanib	When used for treatment naïve advanced RCC, pazopanib has comparable PFS benefits in Asians and patients of European ancestry[†]	(73)
	Although there are no head-to-head studies comparing clinical response to pazopanib in different ethnic groups with previously treated advanced RCC (i.e., second line), outcomes from phase II studies suggest comparable response in East Asians and Caucasians[§]	(74,75)
	Japanese patients with STS have a greater magnitude of survival benefit (PFS and OS) with pazopanib than non-Japanese patients[†]	(76)
Ponatinib	Comparison of ponatinib outcomes from phase II studies in different ethnic groups suggests higher response rates (MCyR and MHR) in Japanese patients compared to patients of European ancestry with CML or Ph-positive ALL[§]	(77,78)
Regorafenib	Comparison of regorafenib outcomes in phase III studies suggests that Chinese and Korean patients with mCRC have greater survival benefit (OS and PFS) compared to Japanese patients[§]. Regorafenib response rates and survival benefits are similar in Japanese patients and patients of European ancestry[†]	(79-82)
	East Asian patients with GIST show a greater PFS benefit with regorafenib compared to non-East Asians[†]	(83-85)

Table 1 *(continued)*

Table 1 *(continued)*

Tyrosine kinase Inhibitor	Summary of efficacy outcomes across ethnic groups	Reference
Ruxolitinib	Although there are no head-to-head studies comparing clinical response to ruxolitinib in different ethnic groups with myelofibrosis, comparison of phase II trials suggests comparable efficacy (percentage reduction from baseline spleen volume, and time to ≥35% reduction in spleen volume) in East Asians and patients of European ancestry[§]	(86,87)
	It is unknown if there are ethnic differences in ruxolitinib outcomes in patients with PV. Approximately 90% of patients in the pivotal RESPONSE trial were of European ancestry, and there currently are no studies in other ethnic groups	(88)
Sorafenib	Sorafenib is an effective second line treatment of advanced RCC in Asian and European cohorts. It is unknown whether there are ethnic differences in outcomes	(25-27,89)
	East Asians with HCC have a similar magnitude of benefit with sorafenib to patients of European ancestry[†,§]. However, East Asians (except Japanese patients) have numerically inferior survival outcomes compared to patients of European ancestry, as they are more likely to have etiological disease characteristics associated with poorer outcomes[†,§]	(90-96)
Sunitinib	In the treatment of metastatic RCC, South Asians may have poorer outcomes (ORR and PFS) compared to other Asians and patients of European ancestry[†]. Survival outcomes are similar between East Asians with metastatic RCC and patients of European ancestry (ORR, OS and PFS)[†,¶]	(73,97,98)
	Although no head-to-head comparison of clinical response to sunitinib in different ethnic groups with GIST are available, results from studies in East Asian patients suggest comparable efficacy (ORR, TTP) to patients of European ancestry[§]	(99-105)
Trametinib	It is unknown if there are ethnic differences in trametinib outcomes for BRAF V600E or V600K mutation-positive metastatic melanoma. Nearly all patients enrolled in the pivotal METRIC and COMBI-v trials were of European ancestry	(106-108)
Vandetanib	Ethnic differences in efficacy have not been investigated	(109,110)
Vemurafenib	Although there are no head-to-head studies comparing clinical response to vemurafenib in different ethnic groups, a small phase II study in Japanese patients reported similar ORR rates to that of a phase III study conducted in Europe, North America and Australia[§]. However, the Japanese study reported a shorter time to response and superior survival outcomes[§]	(111-113)

Current literature on tyrosine kinase inhibitor efficacy outcomes in different ethnic groups is presented. For some smTKIs, pre-specified subgroup analyses and adequate sample sizes have allowed comparison of outcomes between different ethnic groups. However, for most studies, the subpopulation analyses were not powered to measure the significance of the observed differences in clinical response between ethnic groups. Studies in larger numbers of subjects are required to confirm the trends observed. Furthermore, for many smTKIs, there are no studies directly comparing efficacy outcomes in different ethnic groups. Due to different study designs and baseline patient characteristics, cross-trial comparisons should be interpreted with caution. [†], based on a subgroup analysis by ethnicity of international trials; [‡], based on a pooled analysis of two phase II trials; [§], based on indirect comparisons of studies in different ethnic groups; [¶], based on a meta-analysis of randomized-controlled trials. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ALK, anaplastic lymphoma kinase; ORR, objective response rate; RCC, renal cell carcinoma; CP Ph-positive CML, chronic-phase Philadelphia positive chronic myeloid leukemia; MCyR, major cytogenetic response; CHR, complete haematological response; MMR, major molecular response; MTC, medullary thyroid cancer; ALL, acute lymphoblastic leukemia; MCL, mantle cell lymphoma; GIST, gastrointestinal stromal tumours; HER2, Human epidermal growth factor receptor 2; RR-DTC, radioactive iodine-refractory differentiated thyroid cancer; STS, soft tissue sarcoma; MHR, major haematological response; mCRC, metastatic colorectal cancer; PV, polycythemia vera; HCC, hepatocellular carcinoma; TTP, time to progression.

Table 2 Small molecule tyrosine kinase inhibitor adverse event reports across ethnic groups

Tyrosine kinase Inhibitor	Summary of ethnic difference in safety outcomes	Reference
Afatinib	Japanese patients are more susceptible to stomatitis and ILD compared to non-Japanese patients[†]	(20)
Alectinib	No head-to-head comparisons of safety profile in different ethnic groups	
Axitinib	Japanese patients are more susceptible than non-Japanese patients to AE including dysphonia, hypertension, HFS, hypothyroidism and stomatitis[†]	(25,27)
Bosutinib	Among all-grade non-haematological toxicities, Asians are more susceptible than non-Asians to diarrhea, rash, and pyrexia[†]. Asians are also more susceptible to grade ≥3 thrombocytopenia[†]. However, the incidences of other grade ≥3 hematological and laboratory abnormalities appear similar in Asians and non-Asians[†]	(117)
Cabozantinib	To date, no published studies evaluate the safety of cabozantinib in patients of non-European ancestry. Over 90% of patients enrolled in the pivotal EXAM and METEOR phase III trials were of European ancestry	
Ceritinib	Trend to higher incidence of ceritinib related grade ≥3 AE in patients of European ancestry compared to Asians[†]	(32)
Cobimetinib	To date, no published studies evaluate the safety of cobimetinib in patients of non-European ancestry. Around 95% of patients enrolled in the coBRIM study were of European ancestry	
Crizotinib	Trend to higher incidence of high-grade crizotinib-related AE in non-Asian patients, compared to Asians[†]. Non-Asian patients also appear to have a higher incidence of all-grade edema, fatigue and bradycardia[†,‡]. Conversely, Asian patients appear to have a greater incidence of gastrointestinal AE including constipation, dysgeusia, decreased appetite and neutropenia[†]. Further studies are required to confirm	(118,119)
Dabrafenib	No head-to-head comparisons of safety profile in different ethnic groups	
Dasatinib	East Asian patients are more susceptible than non-East Asian patients to dasatinib related non-hematological AE (including all grade fluid retention, superficial edema, pleural effusion, rash, nausea, and fatigue), hematological AE (neutropenia and thrombocytopenia), and biochemical abnormalities (decreased phosphate and decreased calcium)[†]	(39)
Erlotinib	Study comparisons indicate that African Americans have the lowest incidence of erlotinib-related AE, compared to Asians and patients of European ancestry[§]	(120)
	Higher incidence of erlotinib-related rash, diarrhea and ILD in East Asians compared to patients of European ancestry[†]. ILD risk is highest among Japanese patients, compared to non-Japanese Asians and non-Asians[¶]	(45,46,121)
Gefitinib	East Asian patients are more susceptible than patients of European ancestry to gefitinib-related AE, including rash, diarrhea, anorexia, pneumonia and ILD[†]. ILD risk is highest among Japanese patients, compared to non-Japanese Asians and non-Asians[¶]	(51,52,121)
Ibrutinib	No head-to-head comparison of safety profile in different ethnic groups	
Imatinib	East Asian patients, in particular Japanese patients, are more susceptible than non-East Asians to non-hematological AE including all grade fluid retention, rash, nausea, and fatigue[†]. Additionally, East Asian patients are more susceptible to grade ≥3 haematological /biochemical toxicities, including neutropenia, thrombocytopenia and hypokalaemia[†]	(39)
Lapatinib	No head-to-head comparisons of safety profile in different ethnic groups	
Lenvatinib	Japanese patients are more susceptible than patients of European ancestry to lenvatinib related hypertension, HFS, peripheral edema, stomatitis, proteinuria and thrombocytopenia[†]	(67,68)

Table 2 *(continued)*

Table 2 *(continued)*

Tyrosine kinase Inhibitor	Summary of ethnic difference in safety outcomes	Reference
Nilotinib	Trend to higher incidence of nilotinib-induced rash in Japanese patients, compared to patients of European ancestry[†]. Chinese patients appear more susceptible than patients of European ancestry to nilotinib-induced hyperbilirubinemia, thrombocytopenia and neutropenia[†]. Other adverse-events are comparable between Japanese, Chinese and European cohorts	(57-59)
Nintedanib	Study comparisons indicate a higher incidence of nintedanib-induced liver toxicity in Japanese patients compared to patients of European ancestry[§]	(122,123)
Osimertinib	Comparable safety profile between Asians and non-Asians[†]	(71)
Pazopanib	East Asian patients are more susceptible than patients of European ancestry to pazopanib-related AE including HFS, hypertension, thrombocytopenia, leukopenia, neutropenia, ALT elevation, AST elevation and proteinuria[†]. Conversely, Asians are less susceptible to gastrointestinal AE such as diarrhoea, mucositis, dysgeusia and vomiting[†]	(73)
Ponatinib	Cross-trial comparison of AE rates demonstrates a higher incidence of most ponatinib-induced AE in a small Japanese study compared to the PACE trial (of which 78% were of European ancestry), including hypertension, increased lipase, increased ALT/AST, thrombocytopenia and neutropenia[§]. Conversely, arterial occlusive events were less frequent in the Japanese study compared to the PACE population[§]	(77,78)
Regorafenib	East Asian patients experience more frequent and more severe toxicities compared to patients of European ancestry, including HFS, hypertension, proteinuria, thrombocytopenia, lipase elevation, hypophosphatemia, amylase elevation, ALT elevations, AST elevations and bilirubin elevations[†]	(79)
Ruxolitinib	Study comparisons indicate that East Asians, in particular Japanese patients, are more susceptible than patients of European ancestry to ruxolitinib related anaemia and grade ≥3 AE[§]	(86,87,114-116)
Sorafenib	East Asian patients are more susceptible than non-East Asians to sorafenib-related HFS, diarrhea, hypertension, alopecia and anorexia[†]	(89,90,124)
Sunitinib	East Asians are more susceptible than patients of European ancestry to sunitinib-related AE such as, ALT/AST elevation, proteinuria, hypertension, neutropenia, thrombocytopenia, leukopenia, anaemia and HFS[†,‡,¶]. South-Asians may be less susceptible to AE than East Asians[†]	(73,97,125)
Trametinib	No head-to-head comparison of safety profile in different ethnic groups	
Vandetanib	No head-to-head comparison of safety profile in different ethnic groups	
Vemurafenib	Japanese patients are more susceptible than patients of European ancestry to adverse-events including arthralgia, rash and alopecia[‡]	(111-113)

Current literature on tyrosine kinase inhibitor safety outcomes in different ethnic groups is presented. For some smTKIs, pre-specified subgroup analyses allowed comparison of adverse events between different ethnic groups. However, studies in larger numbers of subjects are required to confirm the trends observed. Furthermore, for many smTKIs, there are no studies directly comparing safety outcomes in different ethnic groups. Due to different reporting criteria, study designs, follow-up period and baseline patient characteristics, cross-trial comparisons could not be made. [†], based on a subgroup analysis by ethnicity of international trials; [‡], based on a pooled analysis of two phase II trials; [§], based on indirect comparisons of studies in different ethnic groups; [¶], based on a meta-analysis of randomized-controlled trials. ILD, interstitial lung disease; AE, adverse event; HFS, hand-foot syndrome.

patient undergoing smTKI treatment (4).

Absorption and bioavailability

For orally administered drugs, bioavailability influences systemic exposure (2), which is highly variable for most smTKIs (2). Bioavailability is a product of the fraction of the dose that is absorbed into enterocytes, the dose that reaches the hepatic portal vein unchanged, and the fraction that is not metabolized by enzymes in the liver (2,127). Therefore, membrane transporters and metabolizing enzymes can be important determinants of smTKI bioavailability (10,126,127). Once smTKIs enter

the enterocyte from the gut lumen, they can undergo metabolism (10,126,127). Subsequently the smTKI may either undergo efflux back into the gut lumen, or be transferred into the portal circulation via passive or active (efflux) transport (10,126,127). Upon presentation to the liver via the portal circulation, smTKIs can be taken into the hepatocytes where they can be metabolized, excreted into bile or transported back to the systemic circulation (10,126,127).

Membrane transport proteins include ATP-dependent (ABC) and solute carrier transporters (SLC) (1,2). ABC transporters mediate drug efflux, and include P-glycoprotein (P-gp; encoded by *ABCB1/MDR1*), Breast Cancer Resistant Protein (BCRP; encoded by *ABCG2*) and Multidrug Resistance Protein (MRP; encoded by *ABCC*) (1,2,128,129). ABC transporters are expressed on various cells, including the apical/luminal membrane of enterocytes, where they can act as a barrier to intestinal drug absorption (2,128,129). All TKIs except for cabozantinib, ibrutinib, regorafenib, ruxolitinib and trametinib are substrates for either P-gp or BCRP efflux transporters (*Table S1*) (1,130). SLC transporters mediate drug uptake into the cell and include organic anion transporters OATP1B1 (*SLC01B1*) and OATP1B3 (*SLC01B3*), and the organic cation transporter OCT1 (*SLC22A1*) (1,2,131). SLC transporters are expressed on various cells, including the apical and basolateral membranes of enterocytes, where they facilitate intestinal absorption (1,2,131). They are also expressed on the basolateral membrane of hepatocytes, where they promote hepatocellular drug uptake required for substrate metabolism and biliary excretion (1,2,131). *In vitro* studies suggest that most smTKIs cannot be considered significant substrates for uptake transporters, with the exception of axitinib for OATP1B1 and OATP1B3, regorafenib for OATP1B1 as well as nintedanib and dasatinib for OCT1 (*Table S1*) (1).

Distribution

Many smTKIs have extensive tissue distribution, with an apparent volume of distribution typically between 100 and 1,000 L, and a terminal half-life between 24 to 48 hours (*Table S1*) (3,132). Additionally, all smTKIs are extensively protein bound (>90%) to albumin or the acute phase protein α_1-acid glycoprotein (AGP) (3,132). Finally, membrane transporters play a key role in smTKI distribution (126). ABC transporters are expressed on capillary endothelial cells of tissue barriers (including the blood-brain barrier), acting as a barrier to penetration of substrate drugs (2,126,128,129). SmTKIs must also access cancer cells and intracellular molecular targets, in which case uptake into, and efflux out of, the target cell via transporters are key determinants of drug delivery and action (126). The ABC transporters may also contribute to multidrug resistance in tumors by removing substrates from cancer cells (133).

Metabolism

Drug metabolism usually occurs in the liver after distribution to the body, but some drugs undergo first-pass (pre-systemic) metabolism in the intestinal wall (enterocytes) and liver after oral administration prior to reaching the systemic circulation (134). SmTKIs are metabolized by phase 1 reactions, primarily catalyzed by cytochrome-P450 (CYP) enzymes, and phase 2 reactions catalyzed by enzymes including UDP-glucuronosyltransferases (UGTs) (*Table S1*) (134). Metabolism can render drug molecules inactive, or may produce a compound that is of equivalent or greater pharmacological activity (2). For example, sunitinib and imatinib are primarily metabolized by CYP3A4 to produce biologically active metabolites N-desethyl (SU12662) and N-demethylated piperizine, respectively, which have similar potencies to their parent drugs (135,136). Clinical responses must be considered in light of the concentrations of the parent drug and active metabolite. Sorafenib and erlotinib are also metabolized to pharmacologically active metabolites, sorafenib N-oxide and OSI-420, respectively (15,137). Since these metabolites are not present at high concentrations, they are not expected to play a major role in determining the clinical activity observed after administration of each parent compound (15,137).

Excretion

SmTKIs are primarily cleared through hepatic metabolism and P-gp mediated biliary excretion, with elimination of unchanged drug in urine accounting for less than 10% of total systemic clearance (*Table S1*) (134). Most smTKIs are extensively metabolized prior to biliary excretion, with the exception of afatinib, as it is mainly eliminated unchanged in feces (138). Membrane transporters play a role in the excretion of smTKIs. ABC transporters are expressed on bile caniculi of hepatocytes and are therefore involved in the biliary excretion of substrates. They are also expressed on renal epithelial cells, where they export substrates from the cytoplasm of the renal tubular cells to the urine (1,2,131).

Ethnic factors influencing pharmacokinetic determinants of TKIs

Expression levels and activities of drug transporters and metabolizing enzymes are influenced by genetic and environment factors, and may have important consequences for drug or metabolite(s) concentrations at the site of action and hence the efficacy and tolerability of smTKIs.

Genetic factors can be cis or trans acting elements (4). Cis acting elements include non-synonymous single nucleotide polymorphisms (SNPs), which are single nucleotide substitutions that lead to an amino acid change, a premature stop codon, or altered splicing (4). For example, the non-synonymous SNPs 34G>A (Val12Met) and 421C>A (Gln141Lys) in the coding regions (exon) of *ABCG2* are associated with decreased BCRP expression and activity, reduced efflux and increased plasma and cellular exposure of several BCRP substrates (130,139-141). SNPs in introns (non-coding region) can also have functional consequences. The 6986A>G SNP in *CYP3A5* (*CYP3A5*3*) creates an alternative splice acceptor site in intron 3, shifting the reading frame and causing a premature stop codon and non-functional protein (142). Conversely, the A allele is associated with the expresser phenotype of CYP3A5 (*CYP3A5*1*) (143). Synonymous SNPs can also affect the activity of the protein, and thus should not be disregarded (4,144). Although they do not result in an amino acid change, they can still cause "fitness consequences" and phenotypic differences (4,144). For example, the *ABCB1* 3435C>T SNP results in a synonymous change (ATC isoleucine, ATT isoleucine) that has been found to affect mRNA stability and the timing of co-translational folding, thereby altering P-gp conformation and the structure of interaction sites (144-146). However, its functional effect on P-gp expression is inconclusive, with studies associating the TT genotype with decreased P-gp expression (146-149), increased expression (150), or no effect (151). Haplotypes, which are SNPs that are inherited together in a particular pattern on the same chromatid, can also have pharmacokinetic implications (4). The *ABCB1* 3435T>C/1236T>C/2677T>G/A TTT haplotype combination results in decreased P-gp expression, and has been associated with increased plasma exposure of P-gp substrates (145). Furthermore, nucleotide insertions and deletions in exons and introns can affect protein structure and activity, by shifting the reading frame (4). Finally, sequence variations in the DNA binding site may affect the binding affinity of regulatory molecules (4). The presence of an additional TA repeat in the TATA sequence of the *UGT1A1* promotor (*UGT1A1*28*) results in reduced transcription and reduced UGT1A1 enzyme activity (152). Trans acting elements can also contribute to pharmacokinetic variability. They include the nuclear receptors, PXR (pregnane X receptor, *NR1I2*) and CAR (constitutive androstane receptor, *NR1I3*), which regulate the transcription of genes encoding drug metabolizing enzymes and transporters (4,126). Polymorphisms in *NR1I2* and *NR1I3* can affect the expression and activity of metabolizing enzymes and transporters (153).

Inter-ethnic differences in the pharmacokinetics of a drug can be due to variability in allele frequencies, and in the types of allelic variants of drug metabolizing enzymes, transporters and nuclear receptors in people from different ethnic backgrounds (4,126). Many variants in drug metabolizing enzymes and transporters have been described, which can result in either loss-of-function of the protein or increased activity. An ethnic group with a higher prevalence of an allelic variant of an efflux transporter that has impaired function, would have reduced drug efflux, and therefore increased plasma and cellular concentrations of the drug at a standard dose (4). This could potentially result in more frequent and severe adverse drug reactions, compared to people from other ethnic populations who have a lower frequency of this allelic variant (4). Additionally, an ethnic population with a higher frequency of a metabolizing enzyme with increased activity, would have higher mean clearance and lower mean plasma exposure, and thus possibly reduced efficacy and/or less frequent adverse events (4). The clinical relevance of these polymorphisms depends on whether the drug of interest is a substrate of the metabolizing enzyme or transporter, whether plasma or tissue concentrations correspond to efficacy and toxicity, and whether the metabolites produced are pharmacologically active. Additionally, since smTKIs have a narrow therapeutic index, polymorphisms contributing to aberrant drug metabolism and transport can result in clinically significant changes to drug response (126).

Other environmental (non-genetic) factors may also contribute to ethnic variability in pharmacokinetics and therefore response to tyrosine kinase inhibitors, such as tobacco smoking, diet and the use of complementary and herbal medicines (4). These factors are discussed below.

Ethnic differences in genetic determinants of TKI pharmacokinetics

Many studies have correlated polymorphisms in genes encoding metabolizing enzymes or transporters with toxicity and efficacy of smTKIs. Variability in the frequency and the types of these genetic variants among people from different ethnic populations can, in part, explain the inter-ethnic differences observed in smTKI exposure, efficacy and adverse drug outcomes (*Table 3*).

Sunitinib

High sunitinib systemic exposure has been correlated with an increased risk of adverse events, as well as improved tumor response rates, time to progression (TTP) and overall survival (OS) in patients with gastrointestinal stromal tumors (GIST) and metastatic renal cell carcinoma (RCC) (209). A number of population pharmacokinetic studies have demonstrated that Asian patients have lower clearance of sunitinib and greater sunitinib plasma exposure compared to people from a non-Asian background (209-211). Accordingly, many studies have demonstrated that East Asians are more susceptible than people from a European background to sunitinib-related adverse events (*Figure 1*) (97,98,157,212-214).

This altered pharmacokinetic profile in East Asian patients can be explained in part by the higher prevalence of the *ABCG2* 421C>A allele and the *ABCB1* 3435CC genotype in East Asians than Europeans (154). Both variants are independently associated with significantly lower clearance and higher plasma exposure of sunitinib (143,158,159,169,171,215). The *ABCG2* 421AA genotype has also been correlated with a significantly higher risk of sunitinib-induced toxicities, including thrombocytopenia [odds ratio (OR) =9.90, P=0.04], neutropenia (OR =18.20, P=0.02) and Hand-Foot Syndrome (HFS) (OR =28.46, P=0.01) in Asian cohort studies (157-159). A case report in 2014 described a Japanese patient with RCC who was homozygous for *ABCG2* 421AA and developed severe thrombocytopenia, transaminase elevation, hypoxia, and pleural effusion on a 50 mg daily dose of sunitinib, due to elevated sunitinib and metabolite (SU12662) plasma concentrations (160). Additionally, Asian patients carrying the *ABCB1* 3435CC genotype had a significantly higher risk of all-grade rash [relative risk (RR) =3.00] and mucositis (RR =1.60), compared to T allele carriers (169). A separate study demonstrated a 10-fold reduction in the risk of neutropenia (P=0.01) and 3-fold reduction in the risk of diarrhoea (P=0.02) in patients expressing the *ABCB1* 3435T allele (171). Furthermore, the *ABCB1* TTT haplotype (3435T>C/1236T>C/2677T>G/A), which is more prevalent in East Asians and South Asians than Europeans, has been associated with an increased risk of sunitinib-induced HFS (0R =2.56, P=0.035) (175). Recently, a case was reported of a Japanese patient that developed severe toxicities with sunitinib and gemcitabine, including grade 3 thrombocytopenia, neutropenia, respiratory distress, and elevated transaminases (173). The patient was found to have the *ABCB1* TTT haplotype, as well as high sunitinib and SU12662 concentrations (173).

Metabolizing enzymes also play an important role in the inter-ethnic variability of sunitinib exposure and response. An exploratory study in patients with GIST and RCC found a significant correlation between the *CYP1A1* 2455A>G variant and an increased risk of leukopenia (OR =6.24, P=0.029) and mucosal inflammation (OR =4.03, P=0.021) (175). This G allelic variant is associated with increased CYP1A1 catalytic activity, and therefore is hypothesized to increase sunitinib conversion to the SU12662 metabolite (154). Excessive accumulation of SU12662 has been associated with grade 3 thrombocytopenia and leukopenia (216). Additionally, *CYP3A5*1* has been associated with an increased risk of sunitinib dose reductions secondary to toxicity (180,181), and increased progression-free survival (PFS) in RCC patients treated with sunitinib [hazard ratio (HR) =0.266, P<0.05] (179). The increased catalytic activity of CYP3A5 associated with this variant results in increased conversion of sunitinib to SU12662 (143). It is hypothesized that this increased conversion to SU12662, which has a longer elimination half-life than sunitinib, results in increased exposure and therefore altered clinical outcomes (143). Furthermore, the *CYP3A4* rs4646437G>A SNP has been correlated with an increased risk of hypertension in sunitinib treated RCC patients (OR =2.4, P=0.021) (177). It is hypothesized that hypertension is due to inhibition of vascular endothelial growth factor receptor-2 (VEGFR-2), leading to a reduced amount of nitric oxide and therefore vasoconstriction (177,217). All these CYP variants are more prevalent in South Asian and East Asian, compared to European populations (154), a possible explanation for the greater incidence of sunitinib-induced adverse events observed in Asians.

It has been suggested that people of Asian ancestry are started on lower doses of sunitinib to reduce the likelihood

Table 3 Pharmacogenetic variants linked to ethnic differences in small molecule tyrosine kinase inhibitor outcomes

Gene	Polymorphism (*rs number*)	Variation type/ class	Functional consequence	Ethnic difference in allele/ genotype frequencies	Associations with ethnic differences in tyrosine kinase inhibitor outcomes		
					Exposure	Efficacy	Toxicity
Genes involved in TKI pharmacokinetics							
ABCG2	34G>A Val12Met (*rs2231137*)	SNP/ missense	A allele results in decreased expression and activity of membrane efflux protein BCRP	GG genotype more common in Caucasians (0.97) than East Asians (0.42–0.66) (154)	–	Imatinib (155)	Gefitinib (156)
ABCG2	421C>A Gln141Lys (*rs2231142*)	SNP/ missense	A allele results in decreased expression and activity of membrane efflux protein BCRP	AA genotype more common in East Asians (Japanese 0.341, Chinese 0.292–0.321) than Caucasians (0.074–0.111) A allele: 0.29 East Asian, 0.09 European, 0.01 African American, 0.10 South Asians (154)	Sunitinib (157-160); imatinib (141, 161-163)	Imatinib (155,164)	Sunitinib (157-160) Erlotinib (165) Gefitinib (166,167)
ABCB1	3435C>T (*rs1045642*)	SNP/ synonymous	Affects mRNA stability and timing of co-translational folding, thereby altering P-gp conformation. However, functional effects on P-gp expression are inconclusive, with studies associating the TT genotype with decreased P-gp expression, increased expression, or no effect (168)	CC genotype more common in East Asians than Europeans (0.29 *vs.* 0.125) T allele: South Asians 0.57, Europeans 0.52, East Asians 0.40, African American 0.15 (154)	Sunitinib (169)	Imatinib (170)	Sunitinib (169,171)
ABCB1	2677T>G/A Ser893Ala/Thr (*rs2032582*)	SNP/ missense	Phenotypic effects are inconclusive, with some studies correlating the polymorphism with altered P-gp activity and expression, and other studies showing no association (168)	G allele: Europeans 0.53, East Asians 0.38 (154)	–	Imatinib (170)	–
ABCB1 haplotype	3435T>C (*rs1045642*) 1236T>C (*rs1128503*) 2677T>G/A (*rs2032582*)	SNP/ Synonymous SNP/ Synonymous SNP/ missense	TTT haplotype results in decreased expression of P-gp transporter	TTT haplotype in 56% of South Asians, 49% of East Asians, 35–42% of European, and <8.5% African-Americans (172)	Sunitinib (173); erlotinib (171,174)	–	Sunitinib (173,175); Erlotinib (171,174)
CYP1A1	CYP1A1*2C 2455A>G Ile462Val (*rs1048943*)	SNP/ missense	G allele results in two-fold higher CYP1A1 catalytic activity	G allele more common in East Asians (0.252) and South Asians (0.13) than Europeans (0.035), and low in African-Americans (0.007) (154)	Erlotinib (176)	–	Sunitinib (175)

Table 3 *(continued)*

Table 3 *(continued)*

Gene	Polymorphism (*rs number*)	Variation type/ class	Functional consequence	Ethnic difference in allele/ genotype frequencies	Associations with ethnic differences in tyrosine kinase inhibitor outcomes		
					Exposure	Efficacy	Toxicity
CYP3A4	99767460G>A (*rs4646437*)	Intronic SNP	Unclear whether this variant results in increased or decreased CYP3A4 activity	A allele most prevalent in African Americans (0.85), followed by South Asians (0.38), East Asians (0.16) and Europeans (0.09) (154)	Sunitinib (177)	–	Sunitinib (177)
CYP3A5	CYP3A5*3 6986A>G (*rs776746*)	Intronic SNP	G allele creates a cryptic splice site in intron 3, resulting in altered mRNA splicing; alternatively spliced isoform has an insertion from intron 3, which changes the reading frame and results in a premature termination codon and hence a non-functional protein	G allele more frequent in Europeans (0.82–0.95), followed by East Asians (Japanese 0.85, Chinese 0.65), and South Asians (0.67). Lowest prevalence in African Americans (0.18–0.33) (178)	Erlotinib (176)	Sunitinib (179)	Sunitinib (180,181)
	CYP3A5*1 6986G>A	NA	A allele results in the expresser phenotype of CYP3A5	A allele most prevalent in African Americans (0.82), followed by South Asians (0.33) and East Asians (0.29). Lowest prevalence in Europeans (0.06) (178)	–	–	–
UGT1A1	UGT1A1*28 TA6>TA7 (*rs8175347*)	Short tandem repeat variation in promoter	Reduced gene transcription, and reduced transcriptional activity by 70%, and thus reduced UGT1A1 enzyme activity	Most prevalent in African Americans (0.42–0.56) and Europeans (0.26–0.31). Low prevalence in Asians (0.09–0.16) (182)	–	–	–
UGT1A9	IVS1-37431A>G (*rs7574296*)	Intronic SNP Synonymous	Unknown	A allele: Han Chinese 0.80, Japanese 0.73, European 0.59, and African Americans 0.10 (182)	–	–	Sorafenib (183)
NR1I2	-1135C>T (*rs3814055*)	Upstream SNP	T allele associated with increased CYP3A4 transcription and metabolic activity	T allele; Europeans 0.37, South Asians 0.35, African-Americans 0.31, and East Asians 0.22 (154)	Imatinib (184)	–	Imatinib (184)

Table 3 *(continued)*

Table 3 *(continued)*

Gene	Polymorphism (*rs number*)	Variation type/ class	Functional consequence	Ethnic difference in allele/ genotype frequencies	Associations with ethnic differences in tyrosine kinase inhibitor outcomes		
					Exposure	Efficacy	Toxicity
Genes involved in TKI pharmacodynamics							
EGFR	E746_A750del in exon 19	In frame deletion	Confers increased sensitivity	In NSCLC, the pooled prevalence of these two mutations is 30% in East Asians *vs.* 7% in Europeans	NA	Erlotinib Gefitinib (185-200)	–
	2573T>G Leu858Arg, in exon 21 (*rs121434568*)	SNP/ missense	Confers increased sensitivity	In lung adenocarcinoma, pooled prevalence of these two mutations is 57% in East Asians, 22% in African Americans and 20% in Europeans (201,202)			
	L778P and I821T in exon 20, K728R and W731X in exon 19	SNP/ missense		In pancreatic adenocarcinoma, prevalence is 56% in Chinese, 0% in Europeans (50,203)	NA	Erlotinib (50)	–
BCL2L11	c465T>C (*rs724710*)	Synonymous/ SNP	May impact speed of BIM translation and consequently BIM folding and activity (204). May also exist in linkage disequilibrium with other polymorphisms in the promotor region, therefore interfering with miRNA binding and reducing BIM expression (204)	Variant more common in South Asians (0.569) than Europeans (0.296–0.407) and East Asians (Chinese 0.128–0.146, Japanese 0.084) (154)	NA	Imatinib (204)	–
IFNG	-1616C>T (*rs2069705*)	5' Flanking/ SNP		CC genotype frequency; 0.78 in Japanese, 0.53–0.66 in Chinese, 0.10 in Europeans and 0.06 in South Asians (154)	NA	Imatinib (205)	–
HIF1A	1790G>A Ala588Thr (*rs11549467*)	Missense/ SNP	Higher transcriptional activity of the hypoxia-inducible factor-1 (HIF1) protein, a transcription factor that upregulates genes involved in angiogenesis including VEGF and PDGF	AG genotype more common in East Asians (Han Chinese 0.14, Japanese 0.06) than Europeans (0.03) (154)	NA	Pazopanib (206)	–
HLA	*A*24*			C Allele frequency; Japanese 0.37, Korean 0.23, South Asians 0.13–0.21, Chinese 0.14–0.18, and Europeans 0.07–0.16 (154)	NA	–	Sorafenib (207)

Table 3 *(continued)*

Table 3 *(continued)*

Gene	Polymorphism (*rs number*)	Variation type/ class	Functional consequence	Ethnic difference in allele/ genotype frequencies	Associations with ethnic differences in tyrosine kinase inhibitor outcomes		
					Exposure	Efficacy	Toxicity
VEGFR2	1191C/T (*rs2305948*)	Missense/ SNP	T allele associated with lower binding efficiency of VEGF to the polymorphic VEGFR-2	T allele frequency; 0.17 in East Asians, 0.12 South Asians, 0.09 Europeans (154)	NA	–	Sunitinib (175)
TNF-alpha	-308G>A (*rs1800629*)	5' Flanking/ SNP	G allele associated with higher levels of TNF-alpha cytokine The G>A polymorphism affects the binding of transcription factors, reducing TNF-alpha expression	GG genotype more prevalent in East Asians (Japanese 0.95, Chinese 0.93) and South Asians (0.89) than Europeans (0.57–0.67) (154)	NA	–	Sorafenib (183,208)
FLT3	738T>C (*rs1933437*)	Missense/ SNP		TT genotype more common in East Asians (0.64 Japanese, 0.56 Chinese) than Europeans (0.40) (154)	NA	–	Sunitinib (171,175)

SNP, single nucleotide polymorphism; BCRP, breast cancer resistant protein; P-gp, P-glycoprotein; VEGF, vascular endothelial growth factor; CYP, cytochrome-P450; UGT, UDP-glucuronosyltransferase; PDGF, platelet derived growth factor; NSCLC, non-small cell lung cancer; NA, not applicable.

of severe toxicities (218). A study in Singapore evaluated sunitinib outcomes at an attenuated dosing regimen of 37.5 mg/day (4 weeks on, 2 weeks off), which is lower than the conventional dosing of 50 mg daily (4 weeks on, 2 weeks off) (218). Both regimens demonstrated comparable survival outcomes, however, there was a significantly lower rate of toxicities (P=0.0088) and toxicity-related dose reductions (P=0.005) with the attenuated dose regimen (218).

Imatinib

Higher imatinib systemic exposure is associated with improved response rates, time to response, and event-free survival in patients with chronic-myeloid leukaemia (CML) (161,219-222). In patients with GIST, imatinib systemic exposure is correlated to clinical response and disease progression (223). There is a growing body of evidence to suggest that East Asian patients with GIST or CML are more susceptible to imatinib-related adverse events, and are more likely to respond to treatment (39,60-63,224-228). This variability in response is possibly a reflection of inter-ethnic differences in imatinib exposure, due to inter-ethnic variability in the activity and expression of BCRP and P-gp.

A study conducted in Chinese patients with GIST correlated the T allele of *ABCB1* 3435T>C with significantly higher steady-state imatinib plasma concentrations (184). They hypothesized that this polymorphism resulted in reduced P-gp production, thereby lowering drug clearance (184). In a meta-analysis of *ABCB1* gene polymorphisms, the T allele of *ABCB1* 3435T>C and G allele of *ABCB1* 2677T>G/A were predictors of worse imatinib response in patients with chronic-phase CML (170). Both of these allelic variants are more common in Europeans than East Asians, which could contribute to the observed inter-ethnic differences in imatinib outcomes (154). The *ABCG2* 421C>A allelic variant has also been correlated with decreased imatinib clearance, and increased imatinib plasma and cellular concentrations (141,161-163). A study in Korean patients with GIST demonstrated a significantly superior 5-year PFS rate in patients with the *ABCG2* 421AA genotype (92.3% *vs.* 65%, P=0.047) (164). Similarly, in CML patients, this AA genotype has been associated with increased major molecular response (MMR) rates (155). The *ABCG2* 34GG genotype, which is more prevalent in Europeans than East Asians, has also been correlated with significantly poorer cytogenetic response rates

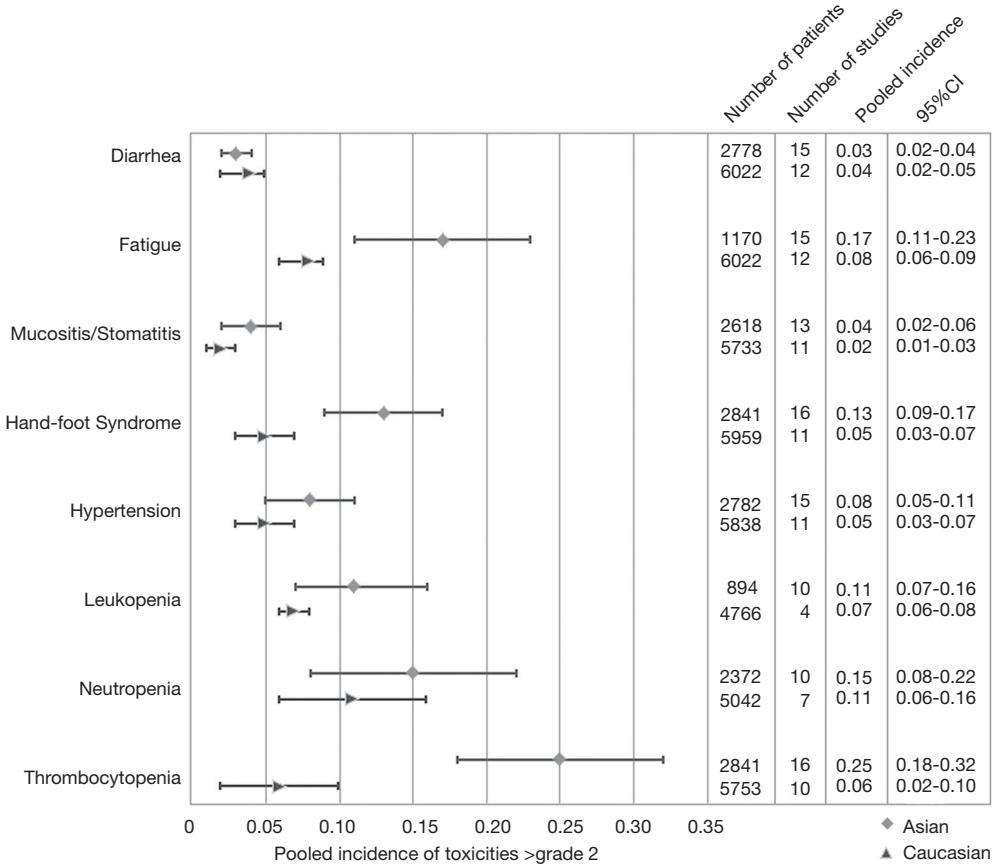

Figure 1 Incidence (95% confidence interval) of grade 3 or more adverse events in Asian and Caucasian patients with metastatic renal cell carcinoma administered sunitinib, as calculated by a meta-analysis of 28 clinical studies (97).

(major: MCyR, complete: CCyR) (155). This variant is associated with normal BCRP expression, thus reducing imatinib intestinal absorption and systemic exposure (229). Together, these studies indicate that genotyping for *ABCG2* 421C>A and 34G>A, as well as *ABCB1* 2677T>G/A and 3435T>C, may be useful in identifying patients at risk of sub-therapeutic response and toxicity, particularly among Asian populations. This may identify patients who will benefit from therapeutic drug monitoring, or dose-adjustment.

Variability in the activity of nuclear receptors can contribute to variability in treatment outcomes. A study in Chinese GIST patients correlated the CC wild-type genotype of *NR1I2 rs3814055*, with significantly higher imatinib trough plasma concentrations (P=0.0066) and a higher incidence of imatinib-induced edema (OR =13.48, P=0.003), compared to T allele carriers (184). The T allelic variant of *rs3814055*, which is more frequent in Europeans than East Asians (154), is associated with increased CYP3A4 and ABCB1 transcription and metabolic activity, and therefore increased imatinib clearance (153).

Erlotinib

There are known inter-ethnic differences in erlotinib pharmacokinetics and outcomes. East Asians are more susceptible than Europeans to erlotinib-related adverse events (45,46,121). Additionally, African Americans are reported to have higher erlotinib clearance and lower erlotinib systemic exposure, when compared to East Asians and people of European ancestry, as reflected in their substantially lower incidence of adverse events (120,230). It is known that erlotinib trough concentrations are an independent risk factor for the development of grade ≥2 diarrhea (P=0.037) and skin rash (P=0.031) (165), and therefore ethnic variability in erlotinib pharmacokinetic determinants has the potential to result in inter-ethnic

differences in toxicity.

For example, the *ABCB1* TTT haplotype (3435T>C/1236T>C/2677T>G/A) has been correlated with significantly higher erlotinib plasma exposure (P=0.021), and a greater risk of erlotinib-related grade 2/3 toxicities including skin rash (P=0.012) (171,174). Additionally, a population pharmacokinetic-pharmacodynamic model in Japanese patients noted a significantly higher incidence of grade ≥2 diarrhea in patients with the *ABCG2* 421C>A allelic variant (P=0.035) (165). This reduced function variant of BCRP is uncommon in African-Americans (154), and has been correlated with decreased erlotinib and OSI-420 clearance, higher erlotinib plasma exposure, and higher erlotinib cerebrospinal fluid penetration (165,231). Furthermore, a study in Japanese patients with non-small cell lung cancer (NSCLC) noted significantly higher erlotinib plasma exposure in patients carrying the *CYP1A1* 2455GG genotype (P=0.0151) and *CYP3A5* 6986GA/GG genotypes (P=0.0198) (176). These variants are more prevalent in East Asians than Europeans and African-Americans (154), a possible explanation for inter-ethnic differences in erlotinib adverse-event susceptibility. Conversely, the AA genotype of *CYP3A5 (*1/*1)* is found in 50% of African-Americans, compared to only 5.8% of East Asians and 4.5% of people of European ancestry (154).

Gefitinib

Inter-ethnic differences in BCRP expression may contribute to the ethnic disparities observed in gefitinib-related adverse events. The *ABCG2* 34G>A allelic variant has been correlated with gefitinib-induced skin toxicity (P=0.046) (156), and the *ABCG2* 421C>A allelic variant with grade ≥2 diarrhea (P=0.0046) (166,167). Both variants are associated with higher gefitinib plasma concentration at steady-state (166,167), an independent risk factor for developing gefitinib-induced diarrhea (P=0.006) and hepatotoxicity (P=0.024) (232). These variants are more prevalent in East Asians than Europeans (154), which is in line with the higher incidence of gefitinib-related adverse events observed in East Asians (51,52,121).

Sorafenib

East Asian patients have increased susceptibility to sorafenib-induced HFS (89-93,124,233-236). A study in Korean patients with hepatocellular carcinoma (HCC) identified the UGT1A9 IVS1-37431 AA variant as an independent risk factor for the development of high-grade HFS (OR =18.7, P=0.02) (183). Given that this genotype is more prevalent in East Asians than Europeans (154), it could explain some of the observed inter-ethnic variability in sorafenib toxicity (90).

Ethnic differences in physiological factors determining TKI pharmacokinetics

Plasma protein binding

Plasma protein binding has an important role in the distribution of anticancer drugs, including smTKIs (4,237-240). Many studies have demonstrated that a reduction in AGP concentration leads to an increase in the unbound fraction of imatinib and a reduction in total plasma imatinib concentrations, due to the rapid distribution of unbound imatinib into extravascular space and effects on hepatic clearance (238-240). Serum AGP concentrations have also been correlated with imatinib efficacy in CML, with a study suggesting that AGP concentrations (an inflammatory marker) are associated with the *in vivo* load of leukemic cells (240). There are inter-ethnic differences in plasma protein binding, with East Asian healthy subjects reported to have lower AGP concentrations than Europeans (241). A recent study in people with breast cancer noted significantly lower AGP concentrations in Chinese patients when compared to Malays and Indians (242). It could therefore be postulated that the greater toxicity and efficacy observed in East Asian patients treated with imatinib, could be a reflection of lower AGP concentrations, correlating to increased imatinib cellular and tissue distribution.

Body size and weight

For many drugs, body size (usually assessed by total body weight) can explain the inter-ethnic differences observed in pharmacokinetics. Generally, South Asian and East Asian populations have a higher portion of body fat with a lower body-mass-index (BMI), lean body mass (LBM), and body surface area (BSA), when compared to people of European ancestry (243-246). These factors have the potential to affect drug distribution and elimination. For lipophilic drugs, such as some smTKIs, apparent volume of distribution (V/F) can increase in people with a higher portion of body adipose tissue (247). For some drugs, lower LBM has been associated with lower clearance, related to organ size and blood flow (247). In population pharmacokinetic studies of imatinib, higher total body weight (TBW) has been correlated with increased V/F and clearance, consistent with increased body fat and body mass (248-250). Low TBW

and BSA have also been correlated with higher imatinib plasma trough concentrations, and correspondingly improved response rates with increased toxicities (221,251). Additionally, low BMI and muscle mass have been identified as significant predictors of sorafenib (252) and sunitinib-related dose-limiting toxicities (253). Recently, LBM was also identified as a predictor of sunitinib plasma exposure and toxicities (215). Furthermore, lenvatinib clearance has been correlated to TBW (254). A subgroup analysis of patients enrolled in the SELECT trial demonstrated no difference in lenvatinib plasma exposure between the Japanese and non-Japanese subgroups after adjusting for TBW (67). For all aforementioned smTKIs, there is good evidence that East Asian patients are more susceptible than Europeans to drug-related adverse events (39,67,68,73,89,90,97,124) (*Table 2*). The lower LBM and higher body-fat percentage of East Asians could be a factor contributing to this inter-ethnic variability in tolerability. Therapeutic drug monitoring and body-weight based dosing may help reduce the incidence of severe smTKI-related adverse events, particularly in Asian patients.

Ethnic differences in extrinsic factors and TKI pharmacokinetics

Extrinsic factors should be considered as a possible source of inter-ethnic differences in drug response, as they can influence the pharmacokinetics and pharmacodynamics of smTKIs.

Complementary and herbal medicine use

The use of complementary and herbal medicines varies between people from different ethnic groups, due to different cultural and health beliefs, with the highest level of complementary and herbal medicine use reported in Asians (255,256). A study by Hsiao *et al.* noted greater use of green tea, ginseng, and soy products among Asian Americans compared to Americans of European ancestry (255). Additionally, complementary and herbal medicines are commonly used among cancer patients, with studies in Europe, America, Malaysia and Korea reporting use in 35.9%, 63%, 70.2% and 78.5% of patients, respectively (257-260). Importantly, many cancer patients are using complementary and herbal medicines in combination with their conventional anticancer therapy, with most patients (up to 72%) not informing their physicians about their complementary medicines (261). A study in patients undergoing treatment for melanoma demonstrated that 85.1% of patients that were using complementary and herbal medicine with their anticancer agent were at risk of drug interactions (262). Considering the narrow therapeutic index of most smTKIs, drug- drug interactions could lead to serious adverse events or reduced therapeutic effect of the smTKI.

Most smTKIs are metabolized primarily by CYP3A4, and are substrates of P-gp and BCRP membrane transporters (*Table S1*) (10,263). Therefore, there is a high potential for serious interactions when smTKIs are co-administered with complementary and herbal medicines that have modulatory effects on P-gp, BCRP and CYP3A4 (*Figure 2*) (10,263). Some herbal medicines that are inducers of CYP3A4, BCRP or P-gp have the potential to increase smTKI metabolism, and promote hepatic and renal excretion (10,263). The increased elimination and reduced plasma exposure of the smTKI could result in therapeutic failure. Conversely, inhibition of BCRP, P-gp or CYP3A4 by complementary and herbal medicines could result in enhanced intestinal absorption, reduced metabolism, and reduced renal and hepatic excretion (10,263). The increased smTKI exposure could result in severe drug-related toxicities. Case reports of these complementary medicine or herbal TKI interactions are presented in *Table S2*. Physicians must consider a patients' use of complementary and herbal medicines prior to smTKI treatment, to ensure appropriate doses are initiated for efficacy and safety. Understanding inter-ethnic differences in the use of complementary and herbal medicines can also assist clinicians in educating patients, and in identifying possible reasons for suboptimal treatment outcomes.

Tobacco smoking

Tobacco smoking prevalence differs by ethnicity, both within and between countries. For example, in the US, the Center for Disease Control and Prevention reported that in 2010–2013 cigarette smoking prevalence was lowest in Asian Americans (10.9%) and highest in Native Americans (38.9%) (287). In addition, in many countries, including in Asia, smoking prevalence is higher in men than women. For example, in China in 2010 52.9% of men and 2.4% of women were reported to be current tobacco smokers (288).

Polycyclic aromatic hydrocarbons in tobacco smoke have the potential to affect drug metabolism, as they are potent CYP1A1 and CYP1A2 inducers (289). A pharmacokinetic study of erlotinib reported a 2.8-fold lower area under the concentration-time curve (AUC) in smokers and a 8.3-fold lower median steady-state plasma concentration (C_{24h}) in smokers compared to

Tyrosine kinase inhibitors with clinically significant changes in exposure with co-administered drugs		Common complementary and herbal medicines implicated in potential CYP3A4-mediated interactions	
CYP3A4 inducers (rifampicin or carbamazepine)	CYP3A4 inhibitors (including ketoconazole)	CYP3A4 inducers (264)	CYP3A4 inhibitors (264)
Axitinib (265)	Axitinib (280)	Echinacea	Black pepper extract
Bosutinib (266)	Bosutinib (281)	Garlic	Black cohosh
Cabozantinib (267)	Cabozantinib (267)	Ginkgo biloba	Chamomile
Crizotinib (268)	Crizotinib (268)	Grape seed/leaf	Dehydroepiandrosterone (DHEA)
Dasatinib (269)	Dasatinib (282)	Licorice root extract	Devil's claw
Erlotinib (270)	Erlotinib (283)	St John's Wort (hyperforin constituent)	Echinacea
Gefitinib (271)	Gefitinib (271)		Feverfew
Iburitinib (272)	Iburitinib (272)		Garlic
Imatinib (273)	Imatinib (284)		Ginkgo biloba
Lapatinib (274)	Lapatinib (274)		Ginseng (Asian, American and Siberian)
Nilotinib (275)	Nilotinib (275)		Grape seed/leaf
Regorafenib (276)	Pazopanib (285)		Green tea catechins
Ruxolitinib (277)	Regorafenib (276)		Ginger
Sunitinib (278)	Ruxolitinib (277)		Hawthorn (quercetin constituent)
Vandetanib (279)	Sunitinib (286)		Licorice root extract
			Milk Thistle
			Peppermint oil
			Red clover
			Soy extract
			Turmeric

Figure 2 Potential drug-drug interactions for tyrosine kinase inhibitors with complementary and herbal medicines (264-286).

non-smokers (290). Erlotinib is metabolized in part by CYP1A2 and CYP1A1, thereby resulting in greater erlotinib clearance and lower plasma concentrations in smokers. In a population pharmacokinetic analysis of NSCLC patients, the median C_{24h} and clearance of erlotinib in current smokers were 60% and 143% of the values in a non-smoking group (291). Non-smokers also had a greater incidence of adverse events compared to smokers, consistent with higher erlotinib exposure (178). A meta-analysis of epidermal growth factor receptor (EGFR)-positive NSCLC patients treated with EGFR-smTKIs (erlotinib or gefitinib) demonstrated that non-smoking was associated with significantly prolonged PFS (HR=0.73, P=0.001) compared to ever smokers (292). The ethnic variability in cigarette smoking prevalence may be a factor contributing to superior response rates and greater toxicity observed in East Asian patients treated with these EGFR-smTKIs. Therefore, lower starting doses are recommended in heavy smokers (>20 cigarettes/day). A study in head and neck cancer patients' demonstrated comparable efficacy outcomes in current smokers receiving an adjusted erlotinib dose of 300 mg daily, and in non-smokers receiving standard doses of 150 mg daily (293). With tobacco smoking potentially influencing drug

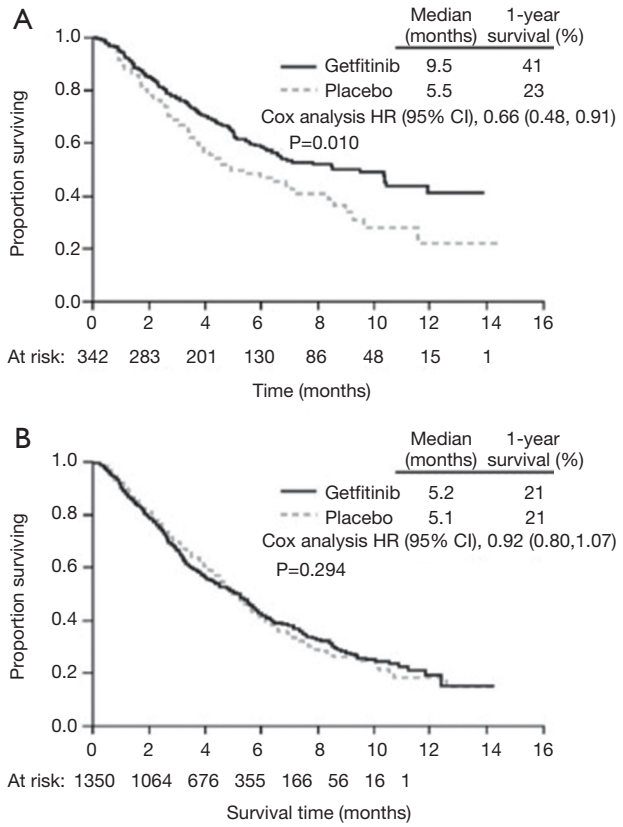

Figure 3 Overall survival benefit with gefitinib or placebo in (A) patients of Asian ancestry and (B) patients of non-Asian ancestry enrolled in the phase III placebo-controlled ISEL (IRESSA Survival Evaluation in Lung Cancer) trial (51).

response, population differences in the incidence of smoking can contribute to the inter-ethnic difference in efficacy and safety reported for some smTKIs.

Inter-ethnic differences in pharmacodynamic pathways

Pharmacodynamics refers to the relationship between drug concentrations and effects (126). Individuals with similar drug plasma or tissue concentrations can have significantly different responses, indicating that non-pharmacokinetic mechanisms can be involved in variable drug action (126). Pharmacodynamic variability can arise from genetic variability in the activity or expression of target genes or candidate genes involved in the therapeutic pharmacological pathway of a drug (10,126). The prevalence and activity of smTKI target variants in different ethnic populations can contribute to inter-ethnic differences in smTKI treatment outcomes.

Erlotinib and gefitinib

Many studies have demonstrated superior response rates and survival outcomes with erlotinib and gefitinib in East Asian patients compared to Europeans with NSCLC (*Figure 3*) (8,9,44-48,51-53,294-297). This variation in response has been correlated to inter-ethnic differences in the frequency of EGFR activating mutations, namely the in-frame deletion in exon 19 and L858R point mutation in exon 21 (201,202). These activating mutations are found in approximately 30% of East Asian patients with NSCLC, compared to only 8% of Europeans (201,202). EGFR-positive NSCLC patients show significantly greater tumor shrinkage, objective response rates (ORR), OS and PFS with gefitinib and erlotinib, compared to EGFR-negative patients (185-198), irrespective of the mutation type (197,199,200). However, studies selective for EGFR-positive NSCLC still show significantly superior outcomes with gefitinib and erlotinib in East Asians compared to other ethnic groups, indicating that other factors are also contributing to variable response (48). Similarly, East Asian patients with pancreatic cancer show more profound benefits with erlotinib than non-East Asians (49,50). This is likely due to inter-ethnic differences in EGFR mutation profiles, with EGFR activating mutations (L778P and I821T in exon 20, K728R and W731X in exon 19) significantly more common in Chinese than European patients with pancreatic cancer (50,203). These mutations are associated with significantly greater disease control rates (DCR), longer PFS and longer OS (50).

Imatinib

It appears that South Asian patients with CML do not respond as well as patients with an East Asian or European ancestry to imatinib treatment (224). Ethnic diversity in the expression of genes involved in imatinibs' apoptotic pathway can explain some of the observed inter-ethnic variability in response. Bcl-2-like protein-1 (encoded by *BCL2L11/BIM)* plays a central role in the apoptosis of BCR-ABL cells, a pathway essential to imatinib-induced cell death (298). In a French cohort study, the T allelic variant of *BCL2L11* 465T>C significantly delayed MMR achievement (P=0.0407) and increased the risk of imatinib resistance (P=0.0049) (204). This variant is more common

in South Asians than Europeans and East Asians (154), mirroring the poorer outcomes observed in South Asians. It is hypothesized that this polymorphism may reduce BIM activity and expression (204). Another candidate pathway involved in imatinib response is interferon (IFN) signaling. Variability in IFN-gamma expression affects hematopoietic stem cell expansion and proliferation, thereby altering the sensitivity of CML to imatinib (205). A study in CML patients correlated the CC genotype of *IFNG* rs2069705 with higher CCyR rates (HR =1.727, P=0.005) and MMR rates (HR =1.912, P=0.002) (205). Inter-ethnic differences in the frequency of the CC genotype correlate with the lower response rates observed in South Asian patients with chronic-phase CML (154).

Pazopanib

Pazopanib is an angiogenesis inhibitor targeting VEGFR, platelet-derived growth factor receptors (PDGFR) and the stem cell factor receptor, c-Kit. When pazopanib is used as second line treatment of advanced RCC, it appears that people of European ancestry have superior response rates and survival outcomes compared to East Asians (74,75). A polymorphism in the *HIF1A* gene (1790G>A) has been correlated with pazopanib efficacy, with the AG genotype associated with poorer PFS (20 *vs.* 44 weeks, P=0.03) and ORR (30% *vs.* 43%, P=0.02) compared to the GG wild-type (206). This variant results in higher transcriptional activity of the hypoxia-inducible factor-1 (HIF1) protein, which is a transcription factor that upregulates genes involved in angiogenesis, including vascular endothelial growth factor (*VEGF)* and platelet derived growth factor (*PDGF)* (299,300). Therefore, patients with this variant have increased angiogenesis capability, rendering anti-angiogenesis agents like pazopanib less effective (299). The AG genotype is more common in East Asians than Europeans (154), which could potentially explain the inferior outcomes observed.

Sorafenib

East Asians are more susceptible than people with European ancestry to sorafenib-induced adverse events such as HFS and hypertension, and are therefore more likely to discontinue treatment (90). Inter-ethnic differences in genes relevant to tumor angiogenesis can explain some of the ethnic variability observed in sorafenib response. A cohort study in Korean patients with HCC identified the GG genotype of tumor-necrosis factor-α (*TNF*-α) -308G>A as an independent risk factor for developing high-grade sorafenib-induced HFS (OR =44, P=0.02) (183). This genotype is associated with higher levels of the TNF-α cytokine (183), resulting in increased anti-vascular and anti-angiogenic activity, and reduced tumor blood-flow (301,302). It is hypothesized that the poor vascular exchange associated with increased TNF-α, leads to an inflammatory response that manifests as HFS (183). This genotype is more prevalent in East Asians than Europeans (154), which may explain their enhanced susceptibility to sorafenib-induced HFS. In a small cohort study in Japanese patients with RCC, patients with the *HLA-A*24* variant were at a significantly higher risk of sorafenib-induced HFS (207). Furthermore, a Korean case-series described three cases of sorafenib cutaneous reactions, of which two patients expressed *HLA-A*24* (208). Binding of an antigenic drug to the human leukocyte antigen (HLA) protein activates cytotoxic T lymphocytes, a possible mechanism for skin toxicities (207). Interestingly, *HLA-A*24* is more common in populations of Japanese ancestry than European ancestry (303), another explanation for the increased susceptibility to sorafenib-induced HFS in East Asians. However, larger studies are required to validate these associations.

Sunitinib

Genetic polymorphisms in sunitinib target proteins, such as VEGFR-2 and FMS-like tyrosine kinase-3 (FLT3), have been linked to increased sunitinib-induced toxicity (175). In an exploratory study of patients with GIST and RCC, the risk of sunitinib-induced high-grade toxicity was increased with the *VEGFR-2* 1191C>T allelic variant (OR =2.39, P=0.046) (175). This variant is associated with a lower binding efficiency of VEGF to the VEGFR-2 (304), and is more prevalent in East Asians than Europeans (154). This study also correlated leukopenia with the *FLT3* 738C>T allelic variant (OR =2.8, P=0.008) (175), which is also more prevalent in East Asians than Europeans (154). Similarly, a retrospective study of Asian RCC patients demonstrated a significantly increased risk of leukopenia (OR =8.0, P=0.03) and neutropenia (OR =2.7; P=0.04) in patients expressing the *FLT3* 738TT genotype (171). These studies suggest that Asian patients comprise a

subgroup with increased potential for target-related adverse events when treated with sunitinib.

Challenges for clinical practice

Ethnicity is an important factor accounting for inter-individual differences in smTKI response. However, there are challenges faced by prescribers when translating this evidence into clinical practice. The concept of ethnicity is complex, and there is a lack of concordance across studies in the descriptions of ethnic groups. Some studies define patients as White *vs.* non-White, whilst others nominate nationality (e.g., Korean) or geographic ancestry. Another challenge faced is the limited sample size of many studies, which have insufficient patient numbers from each ethnic group to perform statistical analyses of potential inter-ethnic differences in treatment outcomes. Additionally, small sample sizes may allow potentially important but uncommon genetic polymorphisms to be missed. Furthermore, comprehensive datasets on smTKI outcomes, pharmacokinetic profiles and genetic variants in all ethnic groups are not available. Almost all research has described East Asian, European and African-American populations, and information on many other ethnic groups who utilize these treatments is not available. Moreover, there may be undefined factors which affect an individual's response to treatment and which contribute to ethnic differences across populations. Understanding all of these factors is fundamental to precision medicine, in order to assist with drug and dose selection for a specific patient of a particular ancestry.

Conclusions

It is clear that ethnicity is an important factor accounting for some of the inter-individual differences observed in smTKI treatment outcomes. Identifying factors that influence outcomes of anticancer drugs, including smTKIs, is a crucial step toward enabling physicians to make personalized treatment decisions. Receiving an appropriate first-line treatment after a cancer diagnosis is critical, as early response has been shown to predict long-term PFS and OS (305-310). We know certain ethnic groups have altered expression/activity of metabolizing enzymes and transporters, thereby influencing smTKI pharmacokinetics and response. Additionally, some ethnic populations have a higher frequency of mutations in candidate genes or biological pathways associated with sensitivity to smTKIs, while others are more likely to have a higher frequency of mutations associated with smTKI resistance. Knowledge of these genetic polymorphisms involved in smTKI pharmacokinetic and pharmacodynamic pathways, and how they influence response, can enable personalized medicine using genotype-based drug and dose selection. Ethnicity could be used as a surrogate to identify patients at risk of severe toxicities or suboptimal treatment, triggering genotype testing. When considered in conjunction with non-genetic factors, such as body weight and extrinsic influences, ethnicity can be used to individualize therapy in terms of both initial drug and dose selection, and to identify patients who would benefit from therapeutic drug monitoring. Finally, understanding the influence of ethnicity on drug pharmacokinetics and pharmacodynamics will better inform the design of future targeted therapies, and also help improve the dose rationale for clinical trials of smTKIs.

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Supplementary

Table S1 Targets, pharmacokinetic determinants and pharmacokinetic properties of small molecule tyrosine kinase inhibitors

Drug	Targeted kinases[†]	Metabolizing enzymes[†]	Transporters[†]	Plasma protein binding[†], %	Excretion (%)[†,‡]		Half-life (h)[†]
					Fecal	Renal	
Afatinib	EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4	Covalent adducts to proteins, minimal metabolism	ABCB1, ABCG2	95	85	4	37
Alectinib	ALK, RET	Major: CYP3A4	Metabolite ABCB1 substrate	>99	97.8	0.5	32.5
Axitinib	VEGFR1–3, PDGFR, KIT	Major: CYP 3A4/5 Minor: CYP1A2, CYP2C19, UGT1A1	OATP, ABCB1, ABCG2	>99	41	23	2.5–6.1
Bosutinib	BCR–ABL, SRC, LYN, HCK	Major: CYP3A4	ABCB1	94–96	91	3	22.5
Cabozantinib	RET,MET, VEGFR1–3, KIT, TRKB, FLT3, AXL, TIE2	Major: CYP3A4 Minor: CYP2C9	ABCC2	99.7	54	27	55
Ceritinib	EML4-ALK, IGF-1R, INSR, ROS1	Major: CYP3A4	ABCB1	>97	92	1.3	31–41
Cobimetinib	MEK	Major: CYP3A4 Minor: CYP3A5, UGT2B7	ABCB1	95	76	17.8	44
Crizotinib	EML4-ALK, MET, ROS1, MST1R	CYP3A4, CYP3A5	OATP, ABCB1	91	63	22	42
Dabrafenib	BRAF	CYP3A4, CYP2C8	ABCB1, ABCG2	>99	71	23	8
Dasatinib	BCR-ABL, c-Kit, PDGFR-β, Src, LCK, YES, FYN, EPHA2	Major: CYP3A4 Minor: FMO-3 and UGT	ABCB1, ABCG2, OATP Suggested: OCT1	96	85	4	3–5
Erlotinib	EGFR	Major: CYP3A4 and CYP3A5 Minor: CYP1A1, CYP1A2, CYP2C8 and CYP2D6	ABCB1, ABCG2	93	83	8	36.2
Gefitinib	EGFR	Major: CYP3A4 Minor: CYP3A5, CYP2D6	ABCB1, ABCG2,	90	86	4	30–41
Ibrutinib	BTK	Major: CYP3A Minor: CYP2D6	Transporters not identified	97.3	80	10	4–6
Imatinib	KIT, PDGFRa domain & BCR-ABL	Major: CYP3A4, CYP3A5, CYP2C8 Minor: CYP1A2, CYP2D6, CYP2C9, CYP2C19	ABCB1, ABCG2, ABCC4 Suggested: OCT1	95	68	13	18
Lapatinib	ErbB-1 (EGFR), ErbB-2 (HER2)	Major: CYP3A4, CYP3A5 Minor: CYP2C19, CYP2C8	ABCB1, ABCG2, OATP	>99	Median 27 [3–67]	<2	24
Lenvatinib	VEGFR1–3, PDGFRα, FGFR1–4, KIT, RET	Major: CYP3A4	ABCB1, ABCG	98–99	64	25	28
Nilotinib	BCR-ABL, KIT, CSF1R, PDGFR, DDR1	Major: CYP3A4 Minor: CYP2C8, CYP1A2, CYP2J2	ABCB1, ABCG2, OATP	98	94	5	17
Nintedanib	VEGFR1–3, PDGFRα/β, FGFR1–3, RET, Flt3	Major: Esterases Minor: UGT1A1, UGT1A7, UGT1A8, UGT1A10	ABCB1 Suggested: OCT1	97.8	93	1	10–15
Osimertinib	EGFR T790M	Major: CYP3A4, CYP3A5	ABCB1, ABCG2	99	68	14	48
Pazopanib	VEGFR1–3, PDGFR-α/β, FGFR1/3, KIT, LCK, CSF1R, ITK	Major: CYP3A4 Minor: CYP1A2, CYP2C8, and UGT	ABCB1, ABCG2, OATP	>99	82	3	30.9
Ponatinib	BCR-ABL, BCR-ABL-T315I, SRC, FLT3, FGFR, VEGFR, PDGFR, KIT, RET, TIE2, EPH	Major: CYP3A4 Minor: CYP2C8, CYP2D6, CYP3A5	ABCB1, ABCG2	>99	83	5	24
Regorafenib	FGFR1/2, PDGFR-α/β, VEGFR1–3, KIT, RET, RAF1, BRAF, BRAF-V600E, ABL1, TIE2, EPH2A, MAPK11, FRK, NTRK1	Major: CYP3A4, UGT1A9	ABCC2, OATP1B1	>99	71	19	28
Ruxolitinib	JAK1/2	Major: CYP3A4 Minor: CYP2C9	Not a substrate	97	22	74	3
Sorafenib	VEGFR1–3, BRAF, BRAF-V600E, RAF1, KIT, FLT3, RET, PDGFRb	Major: CYP3A4 & UGT1A9	OATP, ABCC2, ABCB1, ABCG2	>99	77	19	25–48
Sunitinib	VEGFR1–3, PDGFR-α/β, KIT, FLT3, CSF-1R, RET	Major: CYP3A4	OATP, ABCB1, ABCG2	95	61	16	40–60
Trametinib	MEK1/MEK2	Major: hydrolytic enzymes, such as carboxyl-esterases or amidases	Not a substrate	97.4	80	19	3.9–4.8 days
Vandetanib	EGFR, RET, VEGFRs, PTK6, TIE2, EPHRs, SRCs	CYP3A4, FMO1, FMO3	OATP, ABCB1, ABCG2	90	44	25	10 days
Vemurafenib	BRAF	CYP3A4	ABCB1	>99	95	<1	57

[†], data extracted from product information of respective drugs, and review articles by Neul *et al.* 2016 (1) and Rowland *et al.* (3); [‡], percentage excretion of metabolites and unchanged drug. ABL1, ABL proto-oncogene1,non-receptortyrosinekinase; ALK, anaplastic lymphoma kinase; AXL, AXL receptor tyrosine kinase; BCR-ABL, break point cluster region–Abelson murine leukemia viral oncogene homolog; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BTK, Bruton's tyrosine kinase; CSF1R, colony stimulating factor 1receptor; DDR1, discoid in domain receptor 1; EGFR, epidermal growth factor receptor; EML4–ALK, echinodermmicrotubule-associatedprotein-like4–anaplastic lymphoma kinase; EPHA2, ephrin type-A receptor 2; EPH, ephrin receptors; ERBB2, Erb-b2 receptor tyrosine kinase 2; FGFR1–4, fibroblast growth factor receptors 1–4; FLT3, Fms-related tyrosine kinase 3; FRK, Fyn-related Src family tyrosine kinase; FYN, proto-oncogene tyrosine-protein kinase Fyn; HCK, hematopoietic cell kinase proto-oncogene, Src family tyrosine kinase; HER1–4, human epidermal growth factor receptors 1–4; IGF-1R, insulin-like growth factor 1 receptor; INSR, insulin receptor kinase; ITK, IL2 inducible T-cell kinase; JAK1–3, januskinase1–3; KIT, mast/stem cell growth factor receptor; LCK, Lckproto-oncogene, Src family tyrosine kinase; LYN, Lynproto-oncogene, Src family tyrosine kinase; MAPK11, mitogen-activated protein kinase11; MET, hepatocyte growth factor receptor; MST1R, macrophage stimulating 1 receptor; NTRK1, neurotrophic receptor tyrosine kinase 1; PDGFR, platelet-derived growth factor receptor; PTK6, protein tyrosine kinase 6; RAF1, rapidly accelerated fibrosarcoma 1proto-oncogene,serine/threonine kinase; RET, retproto oncogene receptor tyrosine kinase; ROS1, Rosproto-oncogene1, receptor tyrosine kinase; SRC, Srcproto-oncogene, non-receptor tyrosine kinase; TIE2, TEK receptor tyrosine kinase; TRKB, tropomyosin receptor kinase B; VEGFR1–3, vascular endothelial growth factor receptors 1–3; YES, YES proto-oncogene1, Src family tyrosine kinase.

Table S2 Case reports of tyrosine kinase inhibitor drug-drug interactions with complementary and herbal medicines

Complementary Medicine(s)	Tyrosine kinase Inhibitor	Case	Mechanism of interaction
Ginseng	Imatinib	Severe hepatotoxicity in a patient with CML (311)	Ginseng is a CYP3A4 inhibitor (311). Imatinib is predominantly metabolized by CYP3A4, thus concomitant administration of a CYP3A4 inhibitor could result in increased plasma exposure and potentially toxicity
St John's Wort (*Hypericum perforatum*)	Imatinib	Imatinib clearance increased by 43% ($P<0.001$), median area under the curve ($AUC_{0-\infty}$) decreased by 30% ($P<0.001$), maximum concentration (Cmax) by 15% ($P<0.009$), and half-life by 33% ($P<0.0018$) (312)	St John's Wort is a CYP3A4 and P-gp inducer (313). Thus concomitant administration will increase imatinib metabolism, whilst facilitating biliary and renal excretion
	Imatinib	The $AUC_{0-\infty}$ decreased by 32%, with Cmax and half-life reduced by 29% and 21%, respectively (314)	
Ginseng, *Fomes fomentarius*, Chaga mushroom (*Inonotus obliquus*), Black hoof fungus (*Phellinus linteus*) and Selenium	Gefitinib	Treatment failure when initiated (315). After discontinuation, symptoms improved and revealed partial response of NSCLC with gefitinib treatment	Unknown
Green tea	Sunitinib	Green tea consumption disturbed symptom control of mRCC patient taking sunitinib (316)	Epigallocatechin gallate (EGCG), a major tea polyphenol, directly binds with sunitinib to form a precipitate in solution and sticky semisolid contents in the stomach, therefore reducing sunitinib bioavailability and plasma concentrations (316,317). This interaction with green tea has been confirmed in experiments with erlotinib and lapatinib in rats (318)
			Green tea and its constituents (including EGCG), inhibit OATB1, OATB3, OCT1 and OCT2 transporters. Thus, green tea could inhibit the uptake of sunitinib into cells, reducing absorption and cellular uptake (319)

CML, chronic-myeloid leukaemia; NSCLC, non-small cell lung cancer.

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