**Abstract**

Purpose: Pazopanib is an effective treatment for advanced renal cell carcinoma and soft-tissue sarcoma. Transaminase elevations have been commonly observed in pazopanib-treated patients. We conducted pharmacogenetic analyses to explore mechanistic insight into pazopanib-induced liver injury.

Experimental Design: The discovery analysis tested association between four-digit HLA alleles and alanine aminotransferase (ALT) elevation in pazopanib-treated patients with cancer from eight clinical trials (N = 1,188). We conducted confirmatory analysis using an independent dataset of pazopanib-treated patients from 23 additional trials (N = 1,002). Genome-wide association study (GWAS) for transaminase elevations was also conducted.

Results: The discovery study identified an association between HLA-B*57:01 carriage and ALT elevation [P = 5.0 × 10^-5 for maximum on-treatment ALT (MaxALT); P = 4.8 × 10^-4 for time to ALT > 5 × upper limit of normal (ULN) event; P = 4.1 × 10^-3 for time to ALT > 5 × ULN event] that is significant after adjustment for number of HLA alleles tested. We confirmed these associations with time to ALT elevation event (P = 8.1 × 10^-4 for ALT > 3 × ULN, P = 9.8 × 10^-3 for ALT > 5 × ULN) in an independent dataset. In the combined data, HLA-B*57:01 carriage was associated with ALT elevation (P = 4.3 × 10^-5 for MaxALT, P = 5.1 × 10^-4 for time to ALT > 3 × ULN event, P = 5.8 × 10^-4 for time to ALT > 5 × ULN event). In HLA-B*57:01 carriers and noncarriers, frequency of ALT > 3 × ULN was 31% and 19%, respectively, and frequency of ALT > 5 × ULN was 18% and 10%, respectively. GWAS revealed a possible borderline association, which requires further evaluation.

Conclusions: These data indicate that HLA-B*57:01 carriage confers higher risk of ALT elevation in patients receiving pazopanib and provide novel insight implicating an immune-mediated mechanism for pazopanib-associated hepatotoxicity in some patients.

**Introduction**

Pazopanib, a multitargeted tyrosine kinase inhibitor, is an effective treatment for advanced renal cell carcinoma (RCC) and soft-tissue sarcoma (STS; refs. 1–3). Hepatotoxicity is an established adverse event associated with pazopanib treatment, commonly presenting as isolated serum transaminase or total bilirubin elevations (4). Alanine aminotransferase (ALT) elevation >3 × upper limit of normal (ULN) occurs in approximately 20% of patients receiving pazopanib in clinical trials, with 91% of such events occurring within 18 weeks of commencing treatment (5). Concurrent elevations of ALT >3 × ULN and total bilirubin >2 × ULN were observed in approximately 1.8% of patients (5). After clinical adjudication, Hy's Law cases, a hallmark for significant risk of developing severe drug-induced liver injury (6), were seen in 0.4% of patients (5). Previous pharmacogenetic analyses in pazopanib-treated patients identified that Gilbert syndrome UGT1A1 variants were associated with bilirubin elevation (7, 8). A suggestive association between HFE polymorphisms and ALT was also reported (9).

Adverse drug reactions from off-target effects are generally unpredictable. Recent studies identified significant association between adverse drug reactions and specific human leukocyte antigen (HLA) alleles (10), suggesting that many such reactions involve immune mechanisms. In particular, specific HLA alleles are strongly associated with hepatotoxicity for amoxicillin clavulinate (HLA-DRB1*15:01, HL-A‘A*02:01; ref. 11), ticlopidine (HL-A‘A*33:03; ref. 12), ximelagatran (HLA-DRB1*07:01; ref. 13), fluvoxacillin (HLA-B*57:01; ref. 14), lumiracoxib (HLA-DRB1*15:01; ref. 15), and lapatinib (HLA-DRB1*07:01; ref. 16, 17), with ORs ranging from 2 to approximately 80. Here, we sought to characterize the molecular mechanisms of...
Translational Relevance

Hepatotoxicity is frequently observed in pazopanib-treated patients; however, the underlying mechanisms have not been elucidated. Because drug-induced liver injury is a potentially serious consequence of therapy, there is a growing need to identify biomarkers that could characterize causality and predict the patient population most likely to experience hepatotoxicity. Recent data linking adverse drug reactions to HLA alleles led us to test the hypothesis that specific HLA alleles may be related to transaminase elevations in pazopanib-treated patients. Our analysis, which was conducted in two large independent datasets (discovery and confirmatory), demonstrated that HLA-B*57:01 allele carriage is associated with increased alanine aminotransferase. Together with abacavir hypersensitivity syndrome and fluoxacillin-induced liver injury, pazopanib-induced hepatotoxicity is the third immune-mediated adverse effect involving HLA-B*57:01. Our results provide additional scientific insight into the mechanisms of pazopanib-related liver toxicity, support the determination of pazopanib causality of hepatotoxicity, and potentially could support safety management for patients receiving pazopanib.

Patients and Methods

Patients

This pharmacogenetic analysis included patients who provided written informed consent for the clinical study and genetic research and who received at least one dose of pazopanib in 31 GlaxoSmithKline (GSK)-sponsored clinical trials. The discovery analysis included patients from eight phase II to III clinical trials that evaluated efﬁcacy and safety of pazopanib monotherapy in patients with advanced RCC, advanced STS, or ovarian cancer (Supplementary Table S1, online only). The confirmatory analysis included patients from 23 additional phase I/II clinical trials that evaluated safety, tolerability, pharmacokinetics, and efﬁcacy of pazopanib as monotherapy or in combination with other agents in patients with solid tumors (Supplementary Table S2, online only). All trials were conducted in accordance with the Declaration of Helsinki; protocols and informed consent forms were reviewed and approved by Institutional Review Boards/Independent Ethics Committees according to local guidelines.

Genotyping

Germline DNA was extracted from peripheral blood using the Qiagen Autopure LS or QIAamp DNA Blood Kit by Quest Diagnostics and MDS Pharma Services. HLA genotyping using sequencing was conducted by Histogenetics and Beijing Anapure Bioscientiﬁc. Genome-wide SNP genotyping was performed using Illumina arrays (Human1M BeadChip, HumanOmni5-Quad BeadChip, or HumanOmniExpressExome BeadChip) by Expression Analysis, Illumina, and ShanghaiBio Corporation for patients in the discovery analysis, and using the Affymetrix Axiom Biobank Plus GSK custom array by BioStorage Technologies for patients in the confirmatory analysis. UGT1A1*28 genotyping was performed using Sanger sequencing by ShanghaiBio Corporation, Gen-Probe, and GSK, or using the Invader UGT1A1 Molecular Assay by LabCorp and Cogenics. All genotype calling and quality control were performed in accordance with the manufacturers’ protocols.

Liver chemistry measurement and monitoring

Serum liver chemistry assessments were performed by local institutional laboratories. Measured values (in IU/L) were converted to multiples of ULN by dividing by the institutional laboratory–speciﬁc ULN values. The details of liver chemistry monitoring were reported previously (5). Briefly, most studies had entry criteria of ALT/AST ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN. For isolated ALT > 3–8 × ULN, study treatment could continue with liver chemistry monitored until normalization or stabilization; for isolated ALT > 8 × ULN, dose would be interrupted and liver chemistry properly monitored. For concurrent ALT > 3 × ULN and total bilirubin > 2 × ULN with >35% direct bilirubin or with hypersensitivity (i.e., potential Hy’s Law cases), dosing was permanently discontinued.

Statistical analysis

In this pharmacogenetic analysis, we used ALT for characterization of liver events as it is considered hepatic speciﬁc (18). To maximize the statistical power to detect a genetic association, we analyzed maximum ALT (MaxALT) within the pazopanib on-therapy window (deﬁned as ﬁrst day of therapy until 28 days after last day of therapy) and time-to-event endpoints. In the time-to-event analysis, events were deﬁned as ﬁrst ALT > 3 × ULN or >5× ULN within the on-therapy window; patients who never had on-therapy ALT > ULN (strict controls) were censored at the end of pazopanib treatment, and patients who neither had an event nor were strict controls were excluded. To characterize predictive values and cumulative incidence of events, we analyzed binary endpoints including all patients in the analysis (ever had on-therapy ALT > 3 × ULN or >5× ULN, vs. broad controls who never had on-therapy ALT > 3 × ULN or >5× ULN, respectively). We used linear regression to test genetic association with MaxALT, Cox regression to test genetic association with time-to-event endpoints, and logistic regression to test genetic association with binary (ever vs. never) endpoints. All regression models were adjusted for clinical study and arm, sex, age at baseline, baseline ALT, and ancestry principal components to control for population stratiﬁcation (19). Two-tailed P values are reported unless otherwise speciﬁed.

In the discovery analysis, we tested 92 HLA markers [minor allele frequency (MAF) ≥ 1%], initially assuming an additive genetic model for each allele, and used a Bonferroni adjusted signiﬁcance threshold P ≤ 5.4 × 10−4 (0.05/92). MaxALT and time to ALT > 3 × ULN were co-primary endpoints, with time to >5 × ULN as an exploratory endpoint. On the basis of results from the discovery analysis and the low frequency of HLA-B*57:01 homozygotes, all results for HLA-B*57:01 are reported assuming a dominant genetic model (carriers vs. noncarriers). Confirmatory analyses speciﬁed one-tailed tests with MaxALT as the primary endpoint and time to events (ALT > 3 × ULN and >5× ULN) as secondary endpoints. A post hoc analysis with the combined datasets further evaluated the HLA-B*57:01 association with ALT elevation and characterized predictive values and cumulative incidence of events.

Genome-wide analyses (GWAS) used a cosmopolitan reference panel of 2,048 haplotypes (20) to impute a common set of variants across the different genotyping platforms (21, 22). To control for pazopanib-induced ALT elevations and identify genetic markers that might predict the development of liver injury, using patient data and samples collected during pazopanib clinical trials.
technical batch effects, we analyzed the data in five subgroups according to genotyping platform and batch. Within each subgroup, we used Cox regression to test association for each genetic variant with time to ALT > 3 × ULN, adjusting for clinical study and arm, sex, age at baseline, baseline ALT, and ancestry principal components, and assuming an additive genetic model for each variant genome-wide. Analyses were combined across subgroups using a sample size weighted genome-wide meta-analysis (23). In total, 6,736,730 common variants (MAF > 5%) genome-wide were tested, and the conventional GWAS significance threshold \((P ≤ 5.0 \times 10^{-8})\) was applied. VARIants identified by the GWAS meta-analysis were further evaluated for association with all ALT elevation endpoints (MaxALT, time to ALT > 3 × ULN and > 5 × ULN, ever vs. never ALT > 3 × ULN and > 5 × ULN) in a pooled analysis using the combined dataset as described above.

Computational modeling

The binding of pazopanib to HLA-B*57:01 was modeled using Molecular Operating Environment (MOE) software version 2012.10 (Chemical Computing Group Inc.). Illing and colleagues demonstrated that the interaction of abacavir with HLA-B*57:01 altered antigen recognition and triggered immune self-reactivity by T-cell activation (24). The shared features between pazopanib and abacavir supported the use of the reported crystal structure of abacavir bound to HLA-B*57:01 (pdb ID 3VRJ) as a guide for modeling pazopanib binding. The structure was prepared using the Structure Preparation Tool in MOE. Atomic charges were assigned using the FFROST force-field parameters. Hydrogens were added and their positions optimized using the Protonate 3-dimensional (3D) tool. The observed binding mode of abacavir guided the manual placement of pazopanib in the antigen-binding cleft of HLA-B*57:01. Once a reasonable pose for pazopanib was obtained, LigX was used to minimize the ligand and nearby protein residues with the FFROST molecular mechanics force field. Born solvation model, and default settings to optimize favorable interactions and relieve remaining steric clashes between pazopanib and the HLA-B*57:01 receptor site residues.

Results

In total, we evaluated clinical and genetic data from 2,190 pazopanib-treated patients in 31 clinical trials (Table 1; Supplementary Table S3, online only). In the discovery analysis, using data from eight clinical trials of pazopanib 800 mg monotherapy \((N = 1,188), HLA-B^*57:01, HLA-C^*06:02, \) and HLA-C^*04:01 were significantly associated with ALT elevations (multiple-test corrected threshold \(P ≤ 5.4 \times 10^{-4}\)). The strongest association was between HLA-B^*57:01 and MaxALT \((P = 5.0 \times 10^{-7}; \) Table 2), and a similar strength of association \((P = 4.1 \times 10^{-7})\) was seen for time to ALT > 5 × ULN event (NCI CTC AE v4 grade 3 ALT elevation). Multivariate analyses showed that the associations of HLA-C^*06:02 and HLA-C^*04:01 with ALT were not statistically significant after conditioning on HLA-B^*57:01, indicating a single independent genetic effect best explained by HLA-B^*57:01.

We therefore attempted to confirm the HLA-B^*57:01 association with ALT in an independent dataset of 1,002 patients who received pazopanib (at various doses, either as monotherapy or in combination with other agents) for solid tumors. HLA-B^*57:01 was borderline significantly associated with MaxALT in this data-set \((P = 0.042 \text{ for prespecified one-tailed test}; \) Table 2 reported the two-tailed \(P\) value as \(P = 0.085\)) and demonstrated a statistically significant replication of the association with time to ALT > 5 × ULN event [HR, 4.6; 95% confidence interval (CI), 1.7–12.6; \(P = 9.8 \times 10^{-3}\)] and time to ALT > 3 × ULN event (HR, 3.3; 95% CI, 1.7–6.2; \(P = 8.1 \times 10^{-3}\); Table 2).

In the combined dataset of discovery and confirmatory studies, HLA-B^*57:01 was significantly associated \((P ≤ 5.4 \times 10^{-4})\) with ALT elevation in pazopanib-treated patients for all three ALT endpoints \((P = 4.3 \times 10^{-3} \text{ for MaxALT}, P = 5.1 \times 10^{-3} \text{ for time to ALT > 5 × ULN, and } P = 1.8 \times 10^{-3} \text{ for time to ALT > 5 × ULN}). In HLA-B^*57:01 carriers \((n = 131)\) and non-carriers \((n = 2,059)\), the median values (25th–75th percentiles) of MaxALT were 1.7 \((0.9–3.5)\) × ULN and 1.2 \((0.7–2.2)\) × ULN, respectively (Fig. 1), consistent with the 1.4-fold increase in carriers estimated by regression (Table 2). The frequency of ALT > 3 × ULN was 31% in HLA-B^*57:01 carriers and 19% in non-carriers, and the frequency of ALT > 5 × ULN was 18% in HLA-B^*57:01 carriers and 10% in non-carriers (Fig. 2).

As reported previously (5), baseline ALT was associated with ALT elevation in pazopanib-treated patients in the combined data analyzed here (Spearman rank correlation, \(r = 0.40, P = 10^{-5}\)). However, HLA-B^*57:01 was not associated with baseline ALT \((r = 0.52)\), indicating that the association with ALT elevation is specific for response to treatment. In post hoc sensitivity analyses, we excluded 192 patients with baseline ALT > ULN and observed slightly stronger associations between HLA-B^*57:01 and ALT elevation (Supplementary Table S4) compared with the main analyses that modeled the effect of baseline ALT as a covariate (Table 2).

Within the combined data, ALT > 3 × ULN and > 5 × ULN events occurred in 20% and 11% of pazopanib-treated patients, respectively, with HLA-B^*57:01 carriers having a higher risk of experiencing ALT elevation than non-carriers (OR, 2.0; 95% CI, 1.3–3.1 for ALT > 3 × ULN and OR, 2.1; 95% CI, 1.3–3.6 for ALT > 5 × ULN; Table 2). Consistent with the low carriage frequency for HLA-B^*57:01 \((6\% \text{ in the combined data})\) and modest effect size, the fraction of patients with ALT elevation potentially attributable to HLA-B^*57:01 is modest: 10% for ALT > 3 × ULN and 10% for ALT > 5 × ULN. As a predictor of ALT elevation in pazopanib-treated patients \((\text{ALT > 3 × ULN vs. ALT ≤ 3 × ULN}), HLA-B^*57:01\) carriage improves the positive predictive value (PPV), 31% \((95\% \text{ CI, 23%–40%})\) compared with 20% in all

Table 1. Baseline characteristics for patients in the pharmacogenetic analyses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Discovery ((n = 1,188))</th>
<th>Confirmatory ((n = 1,002))</th>
<th>Total ((n = 2,190))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>59 (18–86)</td>
<td>56 (18–86)</td>
<td>58 (18–86)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 557 (47)</td>
<td>359 (36)</td>
<td>916 (42)</td>
</tr>
<tr>
<td></td>
<td>Female 631 (53)</td>
<td>643 (64)</td>
<td>1,274 (58)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White 844 (71)</td>
<td>811 (81)</td>
<td>1,655 (76)</td>
</tr>
<tr>
<td></td>
<td>Asian 325 (27)</td>
<td>114 (11)</td>
<td>439 (20)</td>
</tr>
<tr>
<td></td>
<td>Othera 19 (2)</td>
<td>77 (8)</td>
<td>96 (4)</td>
</tr>
<tr>
<td>Baseline liver metastasis, n (%)</td>
<td>Yes 165 (14)</td>
<td>208 (21)</td>
<td>373 (17)</td>
</tr>
<tr>
<td>Baseline ALT, × ULN</td>
<td>Median (range)</td>
<td>0.46 (0.07–2.82)</td>
<td>0.48 (0.06–6.91)</td>
</tr>
</tbody>
</table>

\*Includes 9 individuals with “unknown” race.
| \*Baseline liver lesion data not available for VEGI09603, VEGI09599, VEGI0190, and VEGI02857.
Table 2. Association between HLA-B*57:01 carriage and maximum on-treatment ALT in pazopanib-treated patients from the combined data (N = 2,190).

<table>
<thead>
<tr>
<th>ALT Measure</th>
<th>Discovery Study N</th>
<th>Combined Analysis N</th>
<th>Effect (95% CI)</th>
<th>Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarriers, n</td>
<td>Carriers, n</td>
<td>Noncarriers, n</td>
<td>Carriers, n</td>
<td>Noncarriers, n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>1,383</td>
<td>1,924</td>
<td>0.085</td>
<td>0.035</td>
</tr>
<tr>
<td>&gt;5 × ULN</td>
<td>1,060</td>
<td>1,276</td>
<td>2.09</td>
<td>2.01</td>
</tr>
<tr>
<td>Time to ALT &gt;5 × ULN</td>
<td>234</td>
<td>279</td>
<td>1.60</td>
<td>1.41</td>
</tr>
<tr>
<td>Time to ALT &gt;3 × ULN</td>
<td>262</td>
<td>307</td>
<td>1.53</td>
<td>1.32</td>
</tr>
</tbody>
</table>

*Carriers are patients who carry one or two HLA-B*57:01 alleles, and the Gilbert syndrome (UGT1A1) genotypes. Eight patients (33%) had the Gilbert UGT1A1 genotypes and three patients (12%) were HLA-B*57:01 carriers. No patients carried both the Gilbert UGT1A1 and HLA-B*57:01 risk genotypes. We also made detailed causality assessments according to DILIN criteria (definite, highly likely, probable, possible, unlikely; ref. 25) for all 26 cases based on available clinical, laboratory, and UGT1A1 genotyping data (Supplementary Table S5, online only). This assessment adjudicated four cases that met criteria for Hy’s Law of these, two carried HLA-B*57:01 alleles. Although the numbers are very small, the point estimate 50% (2 of 4) is notably greater than approximately 10% of isolated ALT elevations potentially attributable to HLA-B*57:01. Evaluation of other HLA genotypes (HLA-A, -B, -C, DRB1, DQB1, and DPB1) in patients with combined ALT and bilirubin elevation did not reveal additional robust significant association.

The molecular mechanism for the observed HLA association with pazopanib ALT elevation is unknown. The reported crystal structure of abacavir bound to HLA-B*57:01 guided our computational model of pazopanib binding with HLA-B*57:01 (Fig. 3). The resulting model suggests that the pyrimidine ring of pazopanib can make a pi-methyl stacking interaction with Val97 and a pi-edge stacking interaction with Trp147, whereas the N1 pyrimidine nitrogen is predicted to form a hydrogen bond with the side chain of Asp114, similar to the observed interactions of the purinyl group of abacavir in the E pocket of HLA-B*57:01. In this binding mode, the N-methyl of pazopanib occupies a similar

![Figure 1](image-url)

Association between HLA-B*57:01 carriage and maximum on-treatment ALT in pazopanib-treated patients from the combined data (N = 2,190).
region as the cyclopropyl of abacavir, whereas the indazole of pazopanib fills more of the F pocket relative to abacavir by making additional hydrophobic contacts with Asn77, Ile80, Tyr84, Thr143, and Trp147. Finally, the phenyl group of pazopanib is predicted to bind in a similar region as the cyclopentene group of abacavir in the D pocket of HLA-B*57:01 and make hydrophobic contacts with Tyr9, Tyr99, Leu156, and Tyr159. The sulfonamide group of pazopanib is directed toward solvent and is predicted to form a water-mediated interaction with the side-chain hydroxyls of Tyr9 and Ser70. Our computational modeling therefore suggests that pazopanib is able to make similar interactions with HLA-B*57:01 compared with abacavir.

An exploratory GWAS meta-analysis for time to ALT > 3× ULN event using data from all patients in the combined dataset (N = 1,379) did not reveal any common variant associations at genome-wide significance (i.e., no common variant with \( P < 5.0 \times 10^{-8} \), Supplementary Fig. S1). The most significant GWAS signal was at SNP rs1800625 (GWAS meta-analysis \( P = 1.5 \times 10^{-7} \)), which was further evaluated using the combined dataset in a pooled analysis (\( P = 7.7 \times 10^{-5} \), Supplementary Table S6). This SNP maps to the MHC class II region, ~800 kb away from HLA-B, and is weakly correlated with HLA-B*57:01 carriage (\( r^2 = 0.07 \)). A joint analysis of rs1800625 and HLA-B*57:01 indicates that the two associations are mostly independent (Supplementary Table S7).

**Discussion**

In this large pharmacogenetic study using data from all completed GSK-sponsored pazopanib clinical trials available at the time, HLA-B*57:01 is associated with pazopanib-induced ALT elevation. In the discovery analysis, MaxALT and time to event were considered co-primary endpoints. With hindsight, specifying MaxALT as the sole primary endpoint in the confirmatory analysis may have been a suboptimal choice. Because the discovery \( P \) values for MaxALT (5.0 \( \times 10^{-5} \)) and time to 5× ULN (4.1 \( \times 10^{-5} \)) were similar, either or both could have been chosen as (co-)primary endpoints in the confirmatory analysis. A more objective approach is to evaluate all endpoints in the full (combined) sample size, and this approach demonstrates compelling evidence for the association.

HLA-B*57:01 carriers have approximately 1.5- to 2.0-fold greater risk of experiencing ALT increases (\( > 3 \times \) ULN, \( > 5 \times \) ULN) compared with non-carriers. As expected for a common adverse event (20% for ALT > 3× ULN, 11% for ALT > 5× ULN) and a less common risk marker (6% HLA-B*57:01 carriage), the NPV of 81% for ALT > 3× ULN and 90% for ALT > 5× ULN is very close to the overall frequency of non-cases in the population studied. HLA-B*57:01 provides some modest improvements on PPV (ALT > 3× ULN, 11% for ALT > 5× ULN).
Within this dataset, HLA-B^{57:01} accounted for approximately 10% of patients who experienced ALT > 3 × ULN or ALT > 5 × ULN when receiving pazopanib, suggesting there are additional factors contributing to the observed ALT elevations. Previous meta-analyses of pazopanib clinical trials showed older age and concomitant use of simvastatin were associated with increased risk of transaminase elevations (5, 30). In a previous study using data from n = 243 patients (a subset of ∼10% of the patients analyzed here), we reported that two SNPs in the HFE gene were associated with ALT elevation, with an estimated 12% probability that this observation occurred by chance (9). We tested the association between these two HFE SNPs and ALT elevation in the full dataset now available (n = 2,190) and were unable to validate this previous finding.

Our GWAS meta-analysis and subsequent analysis of the most strongly associated variant (rs1800625) suggests the possibility of a second independent association within the MHC region. Rs1800625 is located in the promoter region of the AGER (RAGE) gene, encoding the advanced glycosylation end product receptor, and has been associated with promoter activity and expression (31). This finding awaits confirmation in an independent dataset.

Strengths of the present pharmacogenetic study include the large datasets and frequent laboratory assessment of ALT levels for patients receiving pazopanib. Prospective collection of germline DNA samples during clinical trials enabled this genetic evaluation of pazopanib-induced liver toxicity, and all available data from completed GSK-sponsored pazopanib clinical trials (as of August 1, 2014) were included. The discovery study included patients who received pazopanib as monotherapy for cancers, whereas the confirmatory study included patients who received pazopanib as monotherapy as well as in combination with other anticancer agents. The confirmation study had similar sample size compared with the discovery study but had greater heterogeneity of patients analyzed (including multiple tumor types, different pazopanib dosages and treatment durations, and presence of combination therapies, all of which could dilute the pazopanib-specific genetic signal). Confirmation of the association despite the heterogeneity of the confirmatory dataset may, therefore, demonstrate the robustness of the signal.

In summary, these data indicate that HLA-B^{57:01} carriers have a higher risk of ALT elevation than non-carriers when receiving pazopanib treatment. Our results provide new insights that implicate an immune-mediated mechanism for at least some cases of pazopanib-induced hepatotoxicity. This finding, and the established widespread availability of HLA testing, could potentially support the determination of pazopanib causality of hepatotoxicity during pazopanib treatment. Additional studies to further understand the immune-mediated mechanism and further evaluate the rs1800625 association are warranted.

Disclosure of Potential Conflicts of Interest

T. Johnson, C. Carpenter, A. Graves, Z. Xue, D.I. Fraser, L.N. Pandite, and M.R. Nelson have ownership interest (including patents) in GlaxoSmithKline. L. Warren is an employee of OmicsSoft and Parexel. I.P. Britley is an employee of Parexel and has ownership interest (including patents) in GlaxoSmithKline. A. du Bois is a consultant/advisory board member for AstraZeneca, MSD, Pharmamar, and Roche. T. Powles reports receiving commercial research grants from Novartis, Pfizer, and Roche, and speakers bureau honoraria from Novartis and Pfizer. N. Kaplowitz is a consultant/advisory board member for Daiichi Sankyo, GlaxoSmithKline, Johnson & Johnson, and Pfizer, Sanofi, and Takeda. No potential conflicts of interest were disclosed by the other authors.
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.-F. Xu, Z. Xue, L.P. Briley, I. Mitrica, H. Tada, A. du Bois, T. Powles
Study supervision: C.-F. Xu, T. Johnson, M.R. Nelson, L.N. Pandite

Acknowledgments

The authors thank the investigators and their patients who made this study possible. Medical editorial assistance for this article was provided by William Sinkins, PhD, of ProEd Communications, Inc., Beachwood, OH, and was funded by GlaxoSmithKline, Philadelphia, PA.

Grant Support

This study was sponsored by GlaxoSmithKline.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received August 21, 2015; revised October 16, 2015; accepted October 23, 2015, published OnlineFirst November 6, 2015.

References

HLA-B*57:01 Confers Susceptibility to Pazopanib-Associated Liver Injury in Patients with Cancer

Chun-Fang Xu, Toby Johnson, Xiaojing Wang, et al.


Updated version
Access the most recent version of this article at:

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2015/11/06/1078-0432.CCR-15-2044.DC1

Cited articles
This article cites 30 articles, 8 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/22/6/1371.full.html#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
/content/22/6/1371.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.