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PharmGKB summary: Sorafenib Pathways

Li Gong[1,*], **Marilyn M. Giacomini**[2,*], **Craig Giacomini**[3], **Michael L. Maitland**[4], **Russ B. Altman**[5,6], and **Teri E. Klein**[1]

[1]Department of Biomedical Data Science, Stanford, California

[2]Gilead Sciences, Foster City, California

[3]Evviva Sciences, San Francisco, California

[4]Inova Schar Cancer Institute and Therapeutics, Center for Personalized Health, Falls Church, Virginia

[5]Department of Biomedical Engineering, Stanford University, Stanford, California

[6]Department of Genetics, Stanford University, Stanford, California

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Background

Sorafenib (NEXAVAR®, BAY43-9006) is an oral anti-cancer drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma (RCC), unresectable or metastatic hepatocellular carcinoma (HCC), and locally recurrent or metastatic, progressive and differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment [1]. It is also being evaluated in acute myeloid leukemia (AML) and other solid tumors in adults and children. Sorafenib inhibits tumor cell proliferation and angiogenesis via targeting numerous serine/threonine and tyrosine kinases (RAF1, BRAF, VEGFR 1, 2, 3, PDGFR, KIT, FLT3, FGFR1, and RET) in multiple oncogenic signaling pathways [2–5]. The most common adverse effects associated with sorafenib include hand-foot skin reaction (HFSR), diarrhea, hypertension, rash, fatigue, abdominal pain and nausea [6–9]. Serious adverse effects (eg. liver failure, myocardial infarction) are rare but may arise in some cases. Adverse events may lead to compromised efficacy due to dose reduction or treatment interruptions. There is high interpatient variability in cumulative drug exposure and responses following sorafenib treatment [2, 3, 10, 11]. In this review, we discuss the

Corresponding Author: Dr. Teri E. Klein, Department of Genetics, Stanford University Medical Center, Shriram Center for Bioengineering and Chemical Engineering, 443 Via Ortega, Room 213, BioE Altman Lab MC: 4245 Stanford, CA 94305, Phone: (650)-725-0659, feedback@pharmgkb.org.

*Authors contributed equally to this work

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clinical pharmacology of sorafenib and highlight genetic variations that may contribute to the diverse pharmacological responses to sorafenib. Better understanding of the factors contributing to the high variability of response to sorafenib should improve the efficacy and safety of the drug, and help select patients who will benefit most from sorafenib therapy.

Pharmacokinetics

Sorafenib is a small lipophilic molecule with low-solubility and high permeability. After oral administration, it is rapidly absorbed from the gastrointestinal tract and reaches the liver via the portal vein. Sorafenib reaches peak plasma levels between 1 and 12 hours, with typically longer periods for the fed state, and reaches steady-state concentrations typically around 7 days [2, 12–14]. It has a relatively long mean half-life ranging from approximately 20 to 48 hours at the 400 mg bid dose. The majority (77%) of sorafenib is eliminated in the feces (51% unchanged) and about 19% is excreted in the urine (mostly as glucuronide conjugates of the parent drug and its metabolites) [15]. Full prescribing information about the drug is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021923s016lbl.pdf.

High interpatient pharmacokinetic variability was observed with multiple dosing of sorafenib. Clinical trials showed that sorafenib exposure (area under the plasma drug concentration-time curve (AUC)) varied from 18.0–24.0 mg*h/l on day 1 and 47.8–76.5mg*h/l on the last day of the dosing cycle, and the peak plasma concentrations (Cmax) ranged from 2.3–3.0 mg/l on day 1 and 5.4–10.0 mg/l on the last day of dosing [2, 12, 14, 16]. The median time to peak plasma concentration (Tmax) varied from 2–12 h. Additionally, sorafenib's AUC and Cmax values increased less than proportionally with increasing dose [2, 12, 14, 16]. Incidence and severity of sorafenib-induced side effects (eg.HFSR) were also related to cumulative dose and sorafenib exposure level [17–20]. The underlying mechanisms that led to these variabilities are not fully elucidated, and no validated markers have been found that can predict clinical outcome or tolerability for sorafenib [21–23].

Sorafenib is metabolized primarily in the liver via two pathways: phase I oxidation mediated by cytochrome P450 3A4 (CYP3A4), and phase II conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9) (Figure 1) [24, 25]. Eight metabolites of sorafenib have been identified (M1–8) [26–28]. The main circulating metabolite in the plasma is sorafenib N-oxide (M2) and it is produced through oxidation of sorafenib by CYP3A4 [29, 30]. Comprising 9 – 16% of the circulating analytes at steady-state, M2 exhibits an *in vitro* potency similar to sorafenib [16, 26, 30]. M2 also gets further metabolized to N-hydroxymethyl-sorafenib-N-oxide (M1), and glucuronidated to M8 [26]. The metabolite M7 (glucuronide of sorafenib) is produced through glucuronidation of the parent compound by UGT1A9 [26]. Glucuronidation accounts for clearance of about 15% of sorafenib dose in human, while oxidation accounts for only 5% [15]. Among the metabolites of sorafenib, M2, M4 (demethylation), and M5 (oxidative metabolite) were found to inhibit Vascular Endothelial Growth Factor Receptor (VEGFR) signaling pathway, Platelet-Derived Growth Factor Receptor (PDGFR) signaling pathway and members of the Mitogen-Activated Protein Kinase (MAPK) pathway [26].

Since the metabolism of sorafenib occurs through the CYP3A4 and UGT1A9 pathways, induction or inhibition of these pathways may affect the pharmacokinetics and effectiveness of sorafenib. Administration of the drug with CYP3A4 inducers, such as rifampin, St. John's Wort, phenytoin, carbamazepine, phenobarbital, and dexamethasone, has been shown to increase the metabolism of sorafenib and decrease exposure [31]. In contrast, administration of the drug with an inhibitor of CYP3A4, ketoconazole, did not significantly influence sorafenib exposure in healthy volunteers receiving a single dose of sorafenib, nor did it affect safety or tolerability of sorafenib [15, 24]. Though not a substrate for CYP2B6, CYP2C8, CYP2C9 and UGT1A1, sorafenib has been shown to inhibit their activities *in vitro* [25, 27]. The clinical significance of this inhibition is not clear, and drugs that are metabolized by these enzymes should be used with caution in patients receiving sorafenib due to a potential risk of drug interactions.

In addition to differences in metabolizing enzymes, inter-individual differences in hepatic transporters may also contribute to the substantial pharmacokinetic variability observed with sorafenib. *In vitro* and preclinical studies demonstrated that the hepatic uptake of sorafenib and its metabolites is mediated in part by organic cation transporter-1 (OCT1, encoded by gene *SLC22A1*) [32–36] and by organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3, encoded by gene *SLCO1B1, SLCO1B3*) [34, 35, 37]. Sorafenib also showed moderate affinity for the efflux transporter P-glycoprotein (p-gp, encoded by gene *ABCB1*) and breast cancer resistance protein (BCRP, encoded by gene *ABCG2*) [38–43]. Functional differences of both the influx and efflux transporters (either due to genetic variation or co-medication) may affect systemic exposure and response of sorafenib. Moreover, intra-tumoral *OCT1* mRNA expression has been shown to be a significant positive prognostic factor in hepatocellular carcinoma patients treated with sorafenib [44].

Pharmacodynamics

Sorafenib was initially identified as a Raf-1 kinase inhibitor [5, 45]. Further *in vitro* and *in vivo* studies demonstrated that it also targets multiple receptor tyrosine kinases in the cell membranes (eg. VEGFR 1, 2, and 3, PDGFR, stem cell factor receptor (KIT), FMS-related tyrosine kinase 3 receptor (FLT3), fibroblast growth factor receptor 1 (FGFR1), and RET proto-oncogene (RET)) as well as downstream intracellular serine/threonine kinases (eg. RAF1, wild-type BRAF and mutant BRAF carrying V600E) [2–5]. Blocking these kinases and their downstream signaling molecules in multiple oncogenetic pathways leads to potent inhibition of both tumor cell proliferation, apoptosis, as well as tumor angiogenesis (Figure 2).

Preclinical studies have demonstrated that sorafenib inhibits tumor growth in a wide spectrum of human cancers (melanoma, renal, colon, pancreatic, hepatocellular, thyroid, ovarian, and non-small cell lung carcinomas (NSCLCs)) and in some cases induces tumor regression [46]. In Dec 2005, Sorafenib was approved for the treatment of advanced renal cell carcinoma (RCC) by the FDA after favorable progression-free survival (PFS) results (5.5 months for sorafenib vs. 2.8 months for placebo) were obtained in the pivotal double-blind, placebo-controlled Phase III TARGET trial (Treatment Approaches in Renal Cancer Global Evaluation Trial) [47]. Shortly after that in 2007, sorafenib was approved for the

treatment of advanced unresectable hepatocellular carcinoma (HCC) after it demonstrated significant survival benefits in two global phase III clinical trials (the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial and the Asia Pacific trial) [48, 49]. In 2013, sorafenib was also approved by the FDA to be the first-line treatment option in advanced, radioiodine-refractory differentiated thyroid carcinoma (DTC) [50]. The Phase III study conducted in radioiodine-refractory DTC showed that sorafenib significantly prolongs progression-free survival compared to placebo, 10.8 versus 5.8 months, respectively [51]. Though it prolongs overall survival (OS) or PFS in these trials, sorafenib's efficacy is modest with short survival prolongation periods of a few months. Following the approval of sorafenib, there have been various tyrosine kinase inhibitors (TKIs) investigated in phase II and III trials as first-line and second-line therapies to improve treatment outcomes of these advanced diseases. For advanced HCC, none of the TKIs have demonstrated superiority versus sorafenib in the front line setting or improved survival advantages over sorafenib used alone or in combination [52–55]. Sorafenib remains the only approved therapy for HCC and is one of the most commonly used kinase inhibitors for the treatment of solid tumors.

Sorafenib has a low response rate, but was demonstrated to improve progression-free and overall survival. However, small numbers of patients in individual trials have demonstrated significant reductions in tumor burden. Biomarkers that can predict sorafenib efficacy, especially these burden reduction effects, would be helpful to identify the group of patients that are likely to benefit most from the treatment. Numerous clinical studies have been published trying to identify biomarkers that may predict prognosis or efficacy for sorafenib [21–23, 56–59]. However, no predictive biomarker has yet been found or clinically validated. The candidate biomarkers that have been examined include molecular targets of sorafenib, ligands to those target receptors, as well as molecules that have been implicated in the pathogenesis of HCC. The clinical outcomes involved in biomarker analysis are PFS, OS and toxicities related to sorafenib treatment. The most convincing evidence evaluating plasma biomarkers to predict prognosis and response to sorafenib came from large randomized controlled trials. In the phase III randomized controlled SHARP trial involving 602 patients with HCC, Llovet et al found that plasma biomarkers (angiopoietin 2 (Ang2), VEGFA, HGF and IGF2) were predictors of prognosis in patients with HCC; however, none of the plasma biomarkers tested reached statistical significance to predict response to sorafenib, only high s-c-KIT or low HGF showed trends towards enhanced survival [23]. A recent exploratory biomarker study in 494 patients with advanced HCC treated with sorafenib with or without erlotinib in the phase III SEARCH (Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients With Hepatocellular Carcinoma) trial showed that high baseline plasma levels of HGF and VEGFA correlated significantly with shorter overall survival (OS), and high KIT concentration with longer OS. Additionally, high VEGF-C correlated with better time to progression (TTP) [21]. However, since the SEARCH trial did not include a non-sorafenib (placebo alone) arm, it is not possible to determine if any of these markers tested would be predictive of treatment benefit from sorafenib, was prognostic, or spurious. Similar findings were reported from analysis of patients with differentiated thyroid cancer (DTC) in the phase III DECISION trial (http://meetinglibrary.asco.org/content/169956-176). The authors reported that elevated baseline

serum thyroglubulin (Tg), VEGFA, VEGFC, TGF-β1, and low E-cadherin were correlated with poor prognosis in DTC. However, none of the biomarkers tested were able to predict benefit from sorafenib. In summary, despite the large number of plasma and tissue biomarkers that have been examined in various trials and clinical studies, unfortunately no predictive biomarkers of responsiveness to sorafenib have been validated for clinical use.

Clinical pharmacodynamics biomarkers such as treatment adverse effects have also been examined. Hypertension and HSFR are two of the common side effects associated with sorafenib in cancer patients, and the occurrence of these events have been associated with more favorable clinical outcomes [17, 60–62]. These adverse events are also commonly seen with other anti-angiogenic therapies (eg. pazopanib, sunitinib, lenvatinib etc.) and are considered a class-specific toxicity [63–67]. The mechanism behind sorafenib-induced toxicities is not clear and may involve simultaneous disruptions of multiple signaling pathways including VEGF, PDGF, RAF1, BRAF, KIT, and FLT3 in normal organs [68–70].

Pharmacogenomics

The role of genetic factors in predicting response and toxicity to sorafenib has been the subject of many publications. *In vitro* and clinical data have associated polymorphisms in the genes regulating pharmacokinetics (PK) and pharmacodynamics (PD) of sorafenib with high interpatient pharmacokinetic variability and clinical outcomes [2, 12, 14, 16, 26, 29]. However, due to the lack of replication, small sample size and marginally significant associations in many of these studies, none of the genetic variants identified have emerged as clinically meaningful or useful to select patients most likely to respond to sorafenib treatment.

Pharmacogenetic research on sorafenib published so far has mainly focused on SNPs selected based on the knowledge of PK or PD of the drug. CYP3A4 and UGT1A9 regulate the metabolism and clearance of sorafenib [24, 25]. In a study examining genetic variations in metabolizing enzymes in a cohort of 111 patients with solid tumors treated with sorafenib, Jain et al. observed no significant effect on sorafenib exposure in patients with polymorphisms *CYP3A4*1B, CYP3A5*3C, UGT1A9*3*, and *UGT1A9*5* [71]. Later, a study by Boudou-Rouquette et al. examined additional SNPs in *UGT1A9* along with variants in *CYP3A5, UGT1A9, ABCB1* and *ABCG2* for their association with sorafenib-induced toxicity in 54 patients with solid tumor [18]. Similar to the previous study, no genetic variants of metabolizing enzymes and efflux transporters were related to sorafenib exposure.

Though UGT1A1 is not involved in sorafenib metabolism, its activity is inhibited by sorafenib [25]. In a study that examined the effect of *UGT1A1, UGT1A9* and *ABCC2* polymorphisms on the pharmacokinetics of sorafenib and the risk of developing hyperbilirubinemia in 120 cancer patients dosed with sorafenib, Peer et al. found that patients carrying at least one copy of *UGT1A1*28* had increased plasma bilirubin concentrations and greater sorafenib exposure [25]. This is consistent with earlier case reports showing that sorafenib induced hyperbilirubinemia in individuals carrying the *UGT1A1*28* polymorphism and inhibited UGT1A1-mediated bilirubin glucuronidation [25,

72, 73]. A recent study by Bins et al. in 114 cancer patients also confirmed that cancer patients carrying the *UGT1A1*28/*28* (rs8175347) had over five-fold higher odds of acute hyperbilirubinemia within 2-months of sorafenib treatment [74]. Patients carrying at least one *UGT1A1* variant allele also had a 3.4 fold higher odds of interrupting treatment.

In addition to metabolizing enzymes, genetic polymorphisms in drug transporters have also been associated with sorafenib toxicity and response. In a recent study with 114 cancer patients treated with sorafenib, patients with at least one variant allele of rs2306283 in *SLCO1B1* (*1B, increased transporter function) had almost eight fold lower odds of developing diarrhea than patients with wild type genotype following sorafenib treatment [74]. Another variant in *SLCO1B1*, rs4149651 (*5, reduced transporter function), was associated with 4.2-fold higher odds of developing thrombocytopenia. On the other hand, genetic variations in *SLCO1B3* (rs4149117), *ABCC2* (rs717620), *ABCG2* (rs2231142) and *UGT1A9* (rs17868320, rs6714486) were not found to be associated with either toxicity or response to sorafenib in this study [74]. In contrast to this study, a previous report in Japanese patients with advanced renal cell carcinoma showed that the CC genotype of *ABCC2* rs717620 and *HLA-A*24* were associated with a higher risk of sorafenib-induced high-grade skin rash [75].

In summary, numerous publications in the past decade have investigated multiple gene variants in candidate genes and found associations with sorafenib efficacy or toxicity. However, many of these studies have small sample sizes, lack reproducibility, and can only be considered as exploratory. The clinical significance of these findings will only be revealed through study of larger observational cohorts. At this time, none of the reported associations meet the current standard of evidence for genotype/drug effect relationships [76, 77].

Conclusion

The multi-kinase inhibitor, sorafenib, is currently approved for the treatment of metastatic or advanced liver, kidney, and thyroid cancers. Although many new targeted therapies have been tested over the past decade, sorafenib remains the standard of care for these diseases due to its modest efficacy and acceptable tolerability. The pharmacokinetics and pharmacodynamics of sorafenib have been well studied, but there is still incomplete understanding of the high variability in sorafenib exposure and clinical responses. Although numerous studies have been conducted to identify biomarkers that can predict response to sorafenib therapy, no predictive biomarkers for sorafenib response have been identified.

This experience with pharmacogenomic and biomarker studies of sorafenib should be instructive for investigation of predictive biomarkers for anti-cancer drugs in the future. Sorafenib has high inter-individual variance in pharmacokinetic parameters. The dose of sorafenib is therefore a poor predictor of individual exposure. Without the measured exposure, the power to detect meaningful associations between pre-treatment markers and on-treatment events is greatly reduced. In this setting, it becomes difficult to detect reproducible and clinically meaningful relationships even in the largest clinical trials. Karovic et al demonstrated a systematic method to detect a clinically meaningful

relationship between sorafenib dose and a rapidly detectable and precisely measurable pharmacodynamic biomarker-blood pressure [67]. Their results suggested that although blood pressure had many favorable properties as a pharmacodynamic biomarker, it would be unlikely to be useful in the clinical setting. Perhaps more systematic evaluation of candidate biomarkers will enable our community to better conserve our precious resources so that we might focus our efforts on development of biomarkers that have the greatest likelihood to improve care of patients who receive narrow therapeutic index treatments.

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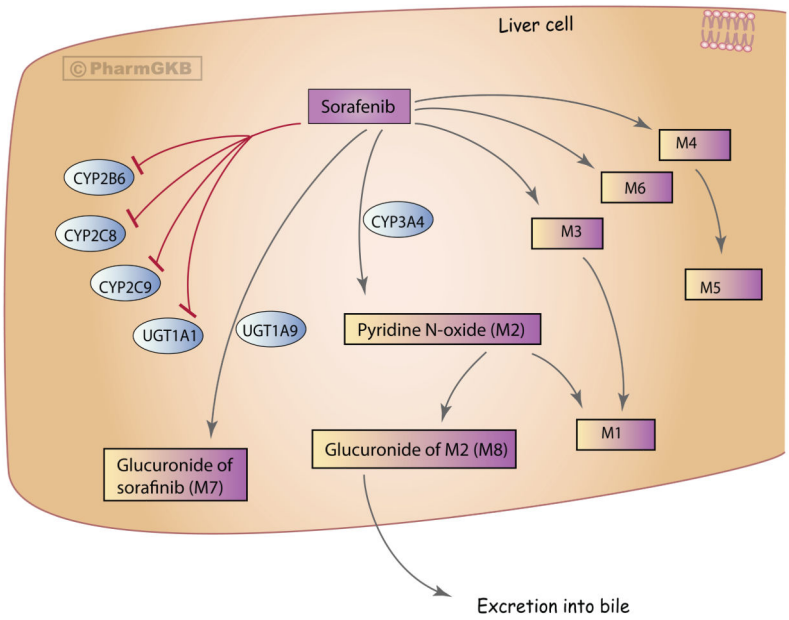

Figure 1.

Sorafenib pharmacokinetics pathway.

Stylized cells depicting genes involved in the metabolism of sorafenib. A fully interactive version is available online at: https://www.pharmgkb.org/pathway/PA165959537

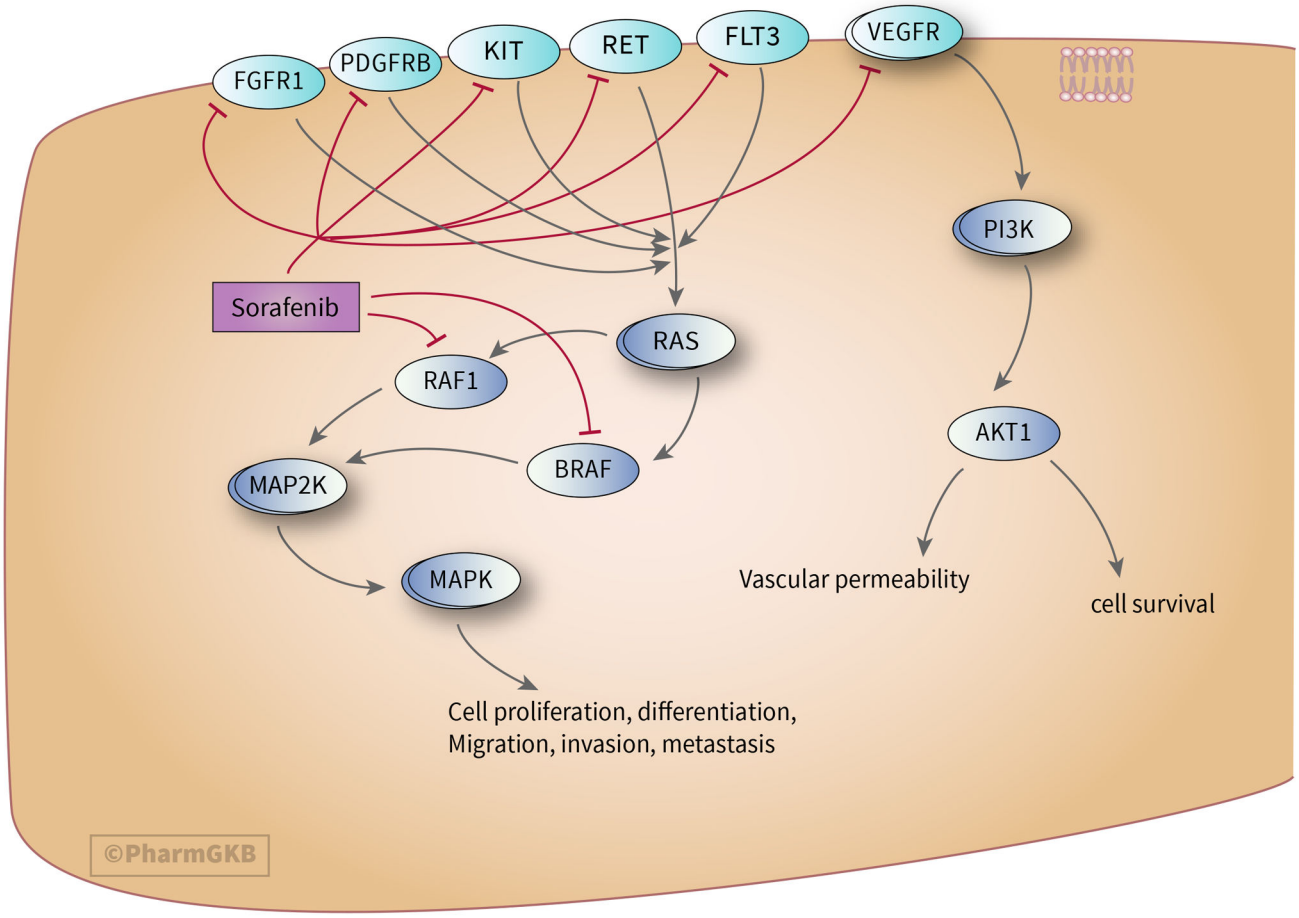

Figure 2.

Sorafenib pharmacodynamics pathway.

Stylized cells depicting the mechanism of action of sorafenib. An interactive version is available online at: https://www.pharmgkb.org/pathway/PA165959584