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FDA Approval Summary: Ripretinib for advanced gastrointestinal stromal tumor (GIST)

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Abstract

On May 15, 2020, the Food and Drug Administration (FDA) approved ripretinib for adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib. The approval was based on results from INVICTUS (NCT03353753), an international, multi-center, double-blind, placebo-controlled trial. Patients were randomly allocated (2:1) to receive either ripretinib 150 mg once daily (n=85) or matching placebo (n=44). The trial demonstrated a statistically significant improvement in progression-free survival (PFS) as assessed by modified RECIST v1.1 by blinded independent central review for patients randomized to ripretinib, with a median PFS of 6.3 months (95% confidence interval [CI]: 4.6, 6.9) compared with 1.0 month (95% CI: 0.9, 1.7) for placebo (hazard ratio [HR]: 0.15 (95% CI: 0.09, 0.25); p<0.0001, stratified log rank test). There was no statistically significant difference in objective response rate (ORR) in the ripretinib arm 9% (95% CI: 4.2, 18) compared to placebo 0% [(95% CI: 0, 8); p= 0.0504, Fisher's Exact Test]. The median overall survival (OS) in the ripretinib arm was 15.1 months (95% CI: 12.3, 15.1) compared with 6.6 months (95% CI: 4.1, 11.6) in the placebo arm. A formal statistical comparison of OS was not made due to the prespecified hierarchical analysis plan. The most common (≥20%) adverse events with ripretinib, in order of decreasing frequency, were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia, and vomiting. Other important risks of ripretinib include new primary cutaneous malignancies, hypertension, and cardiac dysfunction.

Introduction

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors arising predominantly from the stomach or small bowel (1). There are approximately 3,000-6,000 new cases of GIST diagnosed per year in the United States (2) with the majority of patients harboring activating mutations in either *KIT* (80-85%) or platelet derived growth factor receptor alpha

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(*PDGFRA*) (5-10%) proto-oncogenes (1, 3). April 2021 marked the 20th anniversary of the seminal description of the impact of a novel tyrosine kinase inhibitor (TKI), STI571 now known worldwide as imatinib, in the management of a 50-year-old patient with *KIT* mutated treatment-refractory GIST (4). Subsequently, based on the results of a single, multi-center, open-label clinical trial exploring 2 doses of imatinib, on February 1, 2002, the Food and Drug Administration (FDA) approved imatinib for the treatment of *KIT* positive metastatic and/or unresectable GIST (5).

Prior to the approval of imatinib, first-line therapy for GIST consisted of anthracycline-based regimens that were largely ineffective (6). In the ensuing two decades, the drug development and subsequent treatment landscape for GIST has transformed completely. Table 1 outlines the available TKIs approved for the treatment of advanced GIST, noting that the use of cytotoxic chemotherapy has largely become obsolete (7). As the treatment paradigm has shifted, so too have the challenges in therapeutic management, which now center around overcoming drug resistant mutations (8). The most common primary mutations in the *KIT* gene occur in exon 11 (approximately 70%) and exon 9 (approximately 10%), and for *PDGFRA,* in exon 18 (approximately 6%) (9). Reactivation of *KIT* signaling via a secondary *KIT* mutation is the predominant etiology for imatinib failure (10). These secondary *KIT* mutations can be broadly categorized as either affecting the ATP-binding pocket (exons 13 and 14) or the activation loop (exons 17 and 18) (11). There is significant heterogeneity in the secondary mutations encountered, and this may be associated with the variable clinical responses to treatment in the second- and third-line setting (11).

On May 15, 2020, FDA approved ripretinib for the treatment of advanced GIST for patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib. The approval was based on the results of INVICTUS (NCT03353753), an international, multi-center, randomized, double-blind, placebo-controlled trial, which demonstrated a statistically significant improvement in progression-free survival (PFS). The investigators' have published their primary analyses of the trial (12). Herein, we summarize the key findings from FDA's analyses of the data in the ripretinib marketing application and discuss regulatory insights that supported the approval of ripretinib.

Nonclinical Pharmacology and Toxicology

Ripretinib is a small molecule TKI, and *in vitro* assays of ripretinib demonstrated inhibition of the kinase activity of wild type *KIT*, *PDGFRA,* and *PDGFRB* as well as oncogenic *KIT* and *PDGFRA* variants. Anti-tumor activity of ripretinib was demonstrated using tumor xenograft models in mice implanted with cancer cell lines that had in frame-deletion in *KIT* exon 11or a *PDGFRA* amplification.

Toxicology studies were conducted in both rats and dogs and safety was assessed with daily oral administration for up to 13 weeks. Skin was the main target organ of toxicity in both species. Specific skin toxicities included hyperkeratosis, skin erosions, skin discoloration, and alopecia. Dermatologic toxicity was attributed to the deaths of one main rodent study animal and two toxicokinetic study animals. Additional target organs identified in the rat were teeth, lungs, and male reproductive tracts. Ripretinib was not mutagenic or clastogenic.

Developmental studies demonstrated cardiovascular and skeletal fetal malformations at maternal exposures below the clinical AUC.

Clinical Pharmacology

The approved recommended dosage of ripretinib is 150 mg taken orally once daily with or without food until disease progression or unacceptable toxicities. The dosage of ripretinib was evaluated in a first-in-human (FIH) dose-escalation and expansion study using a 3+3 study design that assessed doses ranging from 20 mg twice daily to 200 mg twice daily and 100 mg once daily to 250 mg once daily. Though there were three observed dose-limiting toxicities (DLT), the maximum tolerated dose (MTD) was not reached. The recommended phase 2 dose (RP2D) of 150 mg once daily was selected by the sponsor based on the results of this FIH study. The sponsor considered the safety data and the preliminary anti-tumor activity, as well as the results of pharmacokinetic (PK) analyses which predicted its PK exposure above the efficacy threshold in greater than 90% of patients.

Ripretinib is hepatically metabolized, predominantly by CYP3A4. Thus, the dose recommendations for concomitant CYP3A4 modulators reflected in product labeling or U.S. Prescribing Information (USPI) include avoidance of concomitant use of strong and moderate CYP3A inducers; an increase of ripretinib dose frequency to twice daily if a moderate CYP inducer cannot be avoided; and monitoring more frequently for adverse reactions when used with strong CYP3A inhibitors. No large mean increase in QTc interval (i.e., >20 ms) was detected following treatment with ripretinib at the recommended dose of 150 mg taken orally once daily. Ripretinib exposure-response relationships and the time course of pharmacodynamics have not been fully characterized. At the time of approval, the effect of moderate and severe hepatic impairment on the PK of ripretinib was not fully established and a hepatic impairment study was a post-marketing requirement (PMR) following approval. Since less than 1% of ripretinib is eliminated in the urine, dose modification for renal impairment is not required.

Clinical Trial Design

INVICTUS was an international, multi-center, double-blind, randomized (2:1), placebo-controlled trial which enrolled patients who had received prior treatment with at least imatinib, sunitinib, and regorafenib. Patients were stratified according to number of prior therapies (three versus four or more) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 or 2).

The primary efficacy outcome measure was PFS based on assessment by blinded independent central review (BICR) using modified RECIST version 1.1 (mRECIST) (13) which mirrored the approach that was defined in the study that supported the approval of regorafenib for the treatment of locally advanced or metastatic GIST (14). Key secondary efficacy outcome measures included objective response rate (ORR) assessed by BICR and overall survival (OS). Patients received ripretinib 150 mg orally, with or without food, once daily in 28-day cycles until disease progression or unacceptable toxicity; efficacy was assessed at screening, every cycle for the initial 4 cycles, and every other cycle thereafter.

Patients were unblinded upon disease progression and those receiving placebo could cross-over to receive open-label ripretinib. Adverse events were rated by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. The trial also evaluated Patient Reported Outcomes using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30) (role and physical functioning questions only) and overall health was assessed using EuroQol visual analogue scale (EQ-VAS).

Efficacy Results

A total of 154 patients were screened for eligibility, and 129 patients were randomized; only one patient assigned to placebo did not receive the allocated treatment. Randomized patients were predominantly white (75%), male (57%), enrolled outside of the United States (53%) and had received 3 prior lines of systemic treatment (63%). The most common site of primary tumor was gastric (45%) followed by jejunum or ileum (22%), and *KIT* exon 11 mutations (58%) were the most frequently encountered primary mutations. Compared to patients randomized to placebo, those randomized to ripretinib were younger (median age 59 [range: 29-82] years versus 65 [range: 33-83] years), more likely to be Black or African American (9.4% versus 4.5%) and less likely to be Asian (4.7% versus 11%). The key baseline characteristics in the intention to treat (ITT) efficacy population enrolled into INVICTUS are shown in Table 2. The data cutoff date for the primary analysis was May 31, 2019.

A total of 60% of patients had PFS events in the ripretinib arm versus 84% in the placebo arm. The trial met its primary endpoint of PFS in the ITT population. The median PFS with ripretinib was 6.3 months (95% confidence interval [CI]: 4.6-6.9) versus 1.0 month (95% CI: 0.9-1.7) with placebo (hazard ratio [HR] 0.15, 95% CI: 0.09-0.25, $p<0.001$). Table 3 highlights the key efficacy results of the INVICTUS trial. Overall response rate and then OS were planned to be tested in hierarchical order as pre-specified in the statistical analysis plan. As such, although 8 (9.4%) patients in the ripretinib arm had a partial response compared to no responses in the placebo arm, this difference was not statistically significant ($p=0.0504$; compared to a stopping boundary of 0.047). There was an 8-month difference in the median OS between arms favoring the ripretinib arm though statistical significance for this cannot be claimed due to the pre-specified hierarchical testing order per statistical analysis plan.

Safety Results

The safety evaluation was based on 85 patients who received at least one dose of ripretinib during the double-blind period of the INVICTUS trial. Cumulative supportive safety data reflect exposure to ripretinib as a single agent in 351 patients with advanced solid tumors enrolled in either an open-label dose finding with cohort expansion trial (NCT02571036) or INVICTUS (NCT03353753). Dose reductions were made in 6 patients (7.1%) receiving ripretinib and 1 patient (2.3%) receiving placebo; 8.2% of patients discontinued ripretinib during the double-blind period as a result of an adverse event. The majority of the treatment emergent adverse events (TEAEs) in patients receiving ripretinib versus those on placebo

during the double-blind period of the study were of either of grade 1 or 2 severity. The most common TEAEs (≥20%) being alopecia (52%), fatigue (42%), nausea (39%), abdominal pain (36%), constipation (34%), myalgia (32%), diarrhea (28%), decreased appetite (27%), palmar-plantar erythrodysesthesia syndrome (21%), and vomiting (21%) in those receiving ripretinib. Grade 3 or 4 TEAEs were seen in 49% versus 44% in the ripretinib and placebo arms, respectively. The most common Grade 3 or 4 TEAEs (≥4%) were anemia (9.4%), abdominal pain (7.1%), hypertension (7.1%), hypophosphatemia (4.7%), and increase in lipase (4.7%).

Among the 351 patients included in the overall safety population, adverse events of special interest included cardiac dysfunction (1.7%), hypertension (17%), new primary cutaneous malignancies (either squamous cell carcinoma of the skin and/or keratoacanthoma) (9%), and palmar-plantar erythrodysesthesia (29%). There were three cases of melanoma, including two cases of melanoma in-situ in patients randomized to receive ripretinib in the INVICTUS trial identified in the overall safety population. No cases of Steven Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN) were reported in the INVICTUS trial, although one case was observed in the overall safety population. Although no formal study on wound healing was conducted, interruption of ripretinib is recommended prior to elective surgery based on in vitro inhibition of the vascular endothelial growth factor (VEGF) signaling pathway and the potential for impaired wound healing.

Patient Reported Outcomes

Although the analyses of patient reported outcomes (PROs) as assessed using EORTC-QLQ-C30 and EQ-VAS were generally supportive of a favorable risk-benefit assessment these analyses were considered descriptive due to the prespecified hierarchical testing.

Regulatory Insights

During development, ripretinib was granted fast track designation. Breakthrough therapy designation was granted after the results of the INVICTUS study became available (15). Ripretinib is the fifth TKI approved for the treatment of patients with GIST, and its approval addressed an unmet medical need for patients following at least three prior lines of treatment. FDA reviewed the application under priority review and granted approval on the application 3 months ahead of the review goal date. The application was also part of the Real Time Oncology Review (RTOR) program and Project Orbis collaboration with Health Canada and Australia Therapeutic Goods Administration.

Ripretinib was approved for the treatment of patients who received at least three lines of prior TKI therapy including imatinib. The approval of ripretinib, like those for sunitinib and regorafenib, was based on the clinically meaningful and statistically significant improvement in PFS compared to placebo (14, 16, 17). While overall survival (OS) remains the preferred endpoint for demonstration of clinical efficacy, PFS is an acceptable endpoint in oncology including for approval of drugs to treat GIST when the results are statistically robust, clinically meaningful, and in the context of an acceptable benefit-risk profile (18). Although OS was not formally tested due to the hierarchical testing design, FDA evaluated the results

of the OS analysis, as part of a safety assessment to determine whether the data indicate possible detrimental effects on survival.

INVICTUS was a global trial conducted in 29 sites across 12 different countries; close to half of the study participants (47%) were enrolled in the United States. The demographics of patients enrolled in INVICTUS were generally similar to those of patients enrolled in the pivotal trials that led to the approval of sunitinib (NCT00075218), and regorafenib (NCT01271712) for the treatment of patients with advanced GIST. Notably, 8% of study participants in INVICTUS were Black or African American versus 0.5% in the GRID study (regorafenib). While the enrollment in INVICTUS represents a step forward, we note that 18.2% of GISTs in the United States are diagnosed in African American patients (19). The diversity of study participants improves generalizability of study results to the real-world patient population who are likely to receive the drug once it is approved (20).

Both avapritinib and ripretinib were granted approval for the management of advanced GIST in 2020 (17, 21). The drug development and subsequent approvals used different study designs and target patient populations. Avapritinib was approved based on the results of the NAVIGATOR trial (21), a multi-center, single-arm, open-label trial, where the efficacy analysis was based on 43 patients whose tumors harbored a PDGFRA exon 18 mutation, including the PDGFRA D842V mutation. Avapritinib demonstrated an ORR (84% [95% CI: 69, 93]) and the approval was in keeping with FDA recommendations on developing targeted therapies in low-frequency molecular subsets of a disease (22). The INVICTUS study included a treatment refractory patient population, all of whom had either progressed on or intolerant to at least imatinib, sunitinib, and regorafenib. There was greater heterogeneity in the molecular profile of the INVICTUS study participants, including ten (8%) patients who were *KIT* and *PDGRA* wild-type. In addition to the magnitude of the PFS benefit, the absence of detriment in the OS analysis provided supportive evidence of the favorable benefit risk assessment (Supplementary Table S1). The approval of ripretinib provides an additional treatment option for patients with treatment-refractory advanced GIST.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Summary of FDA approved TKI for advanced GIST

FDA APPROVED TKI	YEAR OF INITIAL FDA APPROVAL	INDICATION
IMATINIB	2002	Malignant metastatic and/or unresectable GISTs
SUNITINIB	2006	Imatinib refractory or intolerant locally advanced GISTs
REGORAFENIB	2013	Advanced GIST previously treated with imatinib and sunitinib
AVAPRITINIB	2020	Advanced GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutation
RIPRETINIB	2020	Advanced GIST who have received 3 or more prior TKIs including imatinib

Source: FDA Approval Dates

Abbreviations: FDA: Food and Drug Administration; GIST: Gastrointestinal Stromal Tumor; PDGFRA: platelet derived growth factor alpha; TKI: Tyrosine Kinase Inhibitor

Table 2:

Demographics and Clinical Characteristics of Patients in the Efficacy Intention-to-Treat population*

	RIPRETINIB (N = 85)	PLACEBO (N = 44)
SEX [N(%)]		
FEMALE	38 (45)	18 (41)
MALE	47 (55)	26 (59)
AGE [YEARS]		
[MEDIAN (RANGE)]	59 (29-82)	65 (33-83)
AGE GROUP [N (%)]		
18 – 64 YEARS	57 (67)	22 (50)
65 – 74 YEARS	20 (24)	12 (27)
75 YEARS OR OLDER	8 (9)	10 (23)
RACE [N (%)]		
ASIAN	4 (5)	5 (11)
BLACK	8 (9)	2 (5)
WHITE	64 (75)	33 (75)
NOT REPORTED	8 (9)	4 (9)
OTHER	1 (1)	0
REGION [N (%)]		
US	40 (47)	20 (46)
NON-US	45 (53)	24 (54)
ECOG PS [N (%)]		
0	37 (44)	17 (39)
1	40 (47)	24 (55)
2	8 (9)	3 (7)

Source: FDA Analysis

Abbreviations: US – United States; ECOG PS: Eastern Cooperative Oncology Group Performance Status

* Percentages may not total 100 due to rounding

Table 3:

Efficacy Results

EFFICACY PARAMETER	RIPRETINIB (N = 85)	PLACEBO (N = 44)	P-VALUE	HR (95% CI)
PROGRESSION FREE SURVIVAL [MEDIAN, MONTHS (95% CI)]	6.3 (4.6-6.9)	1.0 (0.9-1.7)	<0.0001[a]	0.15 (0.09-0.25)
OBJECTIVE RESPONSE RATE [% (95% CI)]	9.4[b] (4.2-17.7)	0	0.0504[c]	n/a
OVERALL SURVIVAL [MEDIAN, MONTHS (95% CI)]	15.1 (12.3-15.1)	6.6 (4.1-11.6)	n/a	0.36 (0.21-0.62)

Source: FDA Analysis

[a]– p-value is based on 2-sided stratified log rank test

[b]– 8 patients had a partial response

[c]– p-value is based on Fisher's exact test

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval, n/a: Not applicable