AHFS Final Determination of Medical Acceptance: Off-label Use of Ripretinib as Second-line Treatment for Gastrointestinal Stromal Tumor (GIST)

Drug: Ripretinib

Off-label Use: Second-line treatment for GIST

Criteria Used in Selection of Off-label Use for Review:

- Results from the open-label, multicenter, randomized, phase 3, INTRIGUE study

Strength of Evidence: Level 2 (moderate strength/quality)

Grade of Recommendation: Not fully established

Narrative Summary:

Gastrointestinal stromal tumors (GISTs) occur rarely but are the most common sarcomas of the GI tract.[10001] For localized GIST, complete surgical resection is standard therapy.[10001] For advanced GIST, tyrosine kinase inhibitors (TKIs) are the cornerstone of treatment since the majority of GISTs (80 to 90%) are driven by activating genomic alterations in *KIT* or platelet-derived growth factor α (*PDGFRA*).[10001,10002] Imatinib is the first-line TKI in the advanced GIST setting for most patients; however, nearly all patients experience disease progression with continued treatment.[10001,10002] Sunitinib is the preferred second-line TKI for those with progressive disease on imatinib.[10001] Ripretinib may be another second-line option for patients with advanced GIST; ripretinib was compared to sunitinib in the open-label, multicenter, randomized, phase 3, INTRIGUE study.[10002]

Adult patients (≥18 years of age) with histologically confirmed GIST and at least 1 measurable lesion within 21 days prior to study drug administration were eligible for study enrollment.[10002] Enrolled patients also experienced disease progression on or an intolerance to first-line imatinib therapy and an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2.[10002] Patients were initially stratified by mutational status and imatinib intolerance and subsequently randomized to ripretinib 150 mg orally once daily on a continuous basis or sunitinib 50 mg orally once daily for 4 weeks followed by 2 weeks without taking the drug.[10002]

Ripretinib dose reduction to 100 or 50 mg once daily was allowed; sunitinib dose modifications occurred per the approved prescribing information or institutional guidelines.[10002] If a patient required therapy interruption for >28 consecutive days, treatment was discontinued.[10002]

Of the 541 patients assessed for eligibility, 453 were randomized to ripretinib (n=226) or sunitinib (n=227).[10002] Of all enrolled patients, 62% were male, 66.2% were White, and the median age was 60 years (range, 18 to 88 years).[10002] Most patients (99.1%) enrolled in the study had a baseline ECOG performance status of ≤1.[10002] Regarding mutation status, 327 patients had a primary *KIT* exon 11 mutation, 60 had a primary *KIT* exon 9 mutation, 33 were *KIT/PDGFRA* wild type, and 33 had a primary mutation in another *KIT* exon or a *PDGFRA* mutation.[10002] Imatinib intolerance was reported in 9.9% of patients.[10002] The primary end point was progression-free survival (PFS), defined as time from randomization to initial disease progression or death from any cause (whichever occurred first), as determined by independent radiologic review using mRECIST v1.1.[10002] Imaging assessments of the tumor were conducted at screening, day 1 of cycles 2 to 7, every other cycle thereafter, and at the end-of-treatment visit.[10002] Key secondary end points included objective response rate (ORR) and overall survival (OS).[10002] The primary and key secondary end points were analyzed in 2 intention-to-treat populations: *KIT* exon 11 patients and the overall study population.[10002]

Results revealed that ripretinib therapy was not associated with a significant improvement in PFS over sunitinib in either the overall ITT population (median 8.0 versus 8.3 months, respectively; hazard ratio [HR]: 1.05; 95% confidence interval [CI], 0.82 to 1.33) or the *KIT* exon 11 ITT population (median 8.3 versus 7.0 months, respectively; HR: 0.88; 95% CI, 0.66 to 1.16).[10002] The ORR was significantly improved with ripretinib in the *KIT* exon 11 ITT population (23.9% vs. 14.6%), but not in the overall ITT population (21.7% vs. 17.6%).[10002] Median duration of response for ripretinib and sunitinib in both populations was 16.7 and 20.1 months, respectively.[10002] Data for OS were highly immature and the median OS was not reached in either arm during this study.[10002] The most common adverse events of any grade severity with ripretinib included alopecia (64.1%), fatigue (37.7%), myalgia (36.3%), and constipation (35%).[10002] The most common adverse events of any grade severity with sunitinib were hand-foot syndrome (51.1%), diarrhea (48%), hypertension (47.1%), and stomatitis (36.2%).[10002] A more favorable safety profile, fewer grade 3/4 treatment-emergent adverse events (41.3% vs. 65.6%) and improved scores on patient-reported tolerability outcome measures were observed with ripretinib as compared to sunitinib.[10002]

Based on current evidence, ripretinib as a second-line treatment for adult patients with advanced GIST has Level 2 (moderate strength/quality) evidence supporting its use.[10002] Ripretinib demonstrated similar clinical activity with a more favorable safety profile as compared to sunitinib for patients with advanced GIST previously treated with imatinib, especially for those with *KIT* exon 11.[10002] Clinicians may consider preferential use of ripretinib over sunitinib in patients who are frail or have severe cardiovascular complications or uncontrolled hypertension.

Dosage

When ripretinib is used for the second-line treatment of advanced GIST, the usual dosage administered is 150 mg orally once daily.[10002] In the double-blind, randomized, placebo-controlled, phase 3, INVICTUS trial that compared ripretinib to placebo in patients with previously treated, advanced GIST, dose escalation of ripretinib to 150 mg twice daily was permitted upon further disease progression.[10003] In INVICTUS, ripretinib 150 mg twice daily doses were well tolerated without clinically meaningful dose-limiting adverse reactions.[10003]

References:

10001. Zalcberg JR. Ripretinib for the treatment of advanced gastrointestinal stromal tumor. *Ther Adv Gastroenterol*. 2021;14:1-12.

10002. Bauer S, Jones RL, Blay JY, et al. Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial. *J Clin Oncol*. 2022;40:3918-28.

10003. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomized, placebo-controlled, phase 3 trial. *Lancet Oncol*. 20220;21(7):923-934.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote (6 of 7 committee members returned the initial ballot):

Proposed Level of Evidence: Level 2 (Moderate strength/quality)

Concur with rating: 6 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 4 votes

Reasonable choice (Accepted, with possible conditions): 2 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Reviewer Comments on Level of Evidence and Grade of Recommendation

Ripretinib 150 mg oral daily had comparable PFS compared with sunitinib as a second line option for GIST with KIT exon 11 mutations and overall ITT population after imatinib. A benefit of the use of ripretinib over sunitinib for a second line option is the more favorable side effect profile, less instances of dose reduction and interruption, and the tolerability of the effects. Sunitinib had more Gr3/4 TEAEs and arguably more impactful side effects like hypertension,

neutropenia, and palmar-plantar erythrodysesthesia. Overall survival information was incomplete and will be necessary to follow up on as more data become available. Ripretinib is a reasonable choice as a second line option in GIST after imatinib. When stratified by mutation type KIT exon 11 was more widely represented and those with KIT exon 9 mutation were more likely to respond to sunitinib, which should be noted for decision making.

May be used in this general patient population (2nd line after imatinib for GIST patients); however, consider avoiding use in KIT Exon 9 mutations at this time. Patients who are frail, have severe cardiovascular complications, or uncontrolled hypertension, may be considered as more appropriate subpopulations to receive ripretinib over sunitinib. The phase III INTRIGUE trial studied the efficacy and safety of ripretinib vs sunitinib, in the setting of GIST patients that were previously on imatinib. The primary endpoint was not met, and therefore neither superiority nor non-inferiority can be established. However, the similarity of efficacy outcomes to sunitinib and safety profile exhibited in the INTRIGUE trial suggests that it is a viable option that is supported by moderate quality of evidence.

Ripretinib had a favorable toxicity profile with fewer severe (grade 3/4) treatment-related adverse events, demonstrated with statistical significance (41.3% for ripretinib vs 65.6% for sunitinib, $p < 0.0001$). Relatedly, there were less QoL (quality-of-life) issues with ripretinib than with sunitinib. Therefore, there are subpopulations where ripretinib may be the preferable choice over sunitinib. One subpopulation to consider using ripretinib over sunitinib are patients with poor performance status that clinicians may evaluate as unlikely to tolerate sunitinib. Another subpopulation to consider ripretinib over sunitinib would be patients with poor cardiovascular health, severe cardiovascular complications, or baseline uncontrolled severe hypertension. As sunitinib has a severe hypertension rate of 26.7% (vs 8.5% for ripretinib), it may be unsafe to use sunitinib in the aforementioned patient group as it may further exacerbate cardiovascular morbidities. Although data are limited and no subgroup analysis was completed, ripretinib has demonstrated in the INTRIGUE that its efficacy in patients with KIT exon 9 mutations may be especially limited. Until further study is completed, it may be advisable to avoid the use of ripretinib in these patients at this time.

Consensus Vote (5 of 7 committee members returned the consensus ballot):

Proposed Level of Evidence: Level 2 (Low strength/quality)

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 3 votes

Reasonable choice (Accepted, with possible conditions): 2 votes

Not fully established (Equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Final Grade of Recommendation: Not fully established – consensus was not reached after 2 ballots

Reviewer Comments on Level of Evidence and Grade of Recommendation:

Based on supported evidence and randomized, placebo-controlled trial recommended/acceptable use in second line setting

Reasonable choice as a second line option in GIST after imatinib. Patients with KIT exon 11 variants are more likely to benefit. Patients with cardiovascular morbid illnesses are ideal candidates due to the more favorable side effect profile compared with sunitinib. Those with KIT exon 9 variants are more likely to respond to sunitinib, as such this should continue to be the second line choice for this subpopulation with GIST.

Exon 9 mutation patients should refrain from utilizing ripretinib while patients with a history of uncontrolled cardiovascular disease should favor the use of ripretinib. I voted for "Reasonable choice" as this option takes into consideration certain subgroups that may be more appropriate for use. From my review, I noted that (which is now included in the narrative summary) Exon 9 mutation patients should refrain from utilizing ripretinib while patients with a history of uncontrolled cardiovascular disease should favor the use of ripretinib. Given that there are conditions that should be considered before deciding the therapy, I see that this fits with the language under "Reasonable choice" of "it is reasonable to use the drug under certain conditions [e.g. patient subgroups].

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): John Villano MD, PhD; Eve Segal PharmD, BCOP; Andrew Li PharmD, BCOP; Caroline Clark MSN, APRN; Jason Bergsbaken PharmD, MBA, BCOP; Christine Gegeckas RPh, BCOP, FFSHP; Kirollos Hanna PharmD, BCPS, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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