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**NCCN Guidelines Panel:** Soft Tissue Sarcoma

**Attention: NCCN Guideline Panel for Soft Tissue Sarcoma**

**Submission 1 of 2 for Ripretinib (4<sup>th</sup> line)**

On behalf of Deciphera, I respectfully request the NCCN Soft Tissue Sarcoma Panel to consider the inclusion of ripretinib as a **4L treatment option** (Category 1, preferred) in patients with advanced gastrointestinal stromal tumor (GIST) based upon the FDA approval and the pivotal Phase 3 clinical study (INVICTUS) of ripretinib.<sup>1,2</sup> The suggested changes to the NCCN Soft Tissue Sarcoma Guidelines (Version 1.2020 – May 15, 2020) are listed below.

**Requested changes to page GIST-5, TREATMENT FOR PROGRESSIVE DISEASE**

**Progression: Limited**

Middle column, add the following after “Change to sunitinib (category 1)”:

- If progression on or intolerance to sunitinib, then ripretinib (category 1, preferred)

**Progression: Generalized (widespread systemic)**

Middle column, modify 2<sup>nd</sup> bullet:

- If progression on or intolerance to sunitinib, then regorafenib (category 1)

Middle column, add new bullet after 2<sup>nd</sup> bullet:

- If progression on or intolerance to regorafenib, then ripretinib (category 1, preferred)<sup>1,2</sup>

**Last column:** Modify first sentence:

- If disease is progressing despite prior imatinib/sunitinib/regorafenib/ripertinib, consider the following options:

**Footnotes:**

- Request removal of footnote “aa” as ripretinib has been shown to be effective after 3 to 7 prior therapies in the pivotal Phase 3 study.

**Requested changes to GIST-D 1 of 2, SYSTEMIC THERAPY AGENTS AND REGIMENS for GIST (changes in red)**

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
First-line therapy for unresectable recurrent or metastatic disease	<ul style="list-style-type: none"><li>• Imatinib<sup>a</sup> (category 1)</li><li>• Avapritinib<sup>a,b</sup> (for GIST with <i>PDGFRA</i> exon 18 mutation, including <i>PDGFRA</i> D842V mutations)</li></ul>		
Second-line therapy for unresectable or metastatic disease (progressive disease or intolerance to imatinib)	<ul style="list-style-type: none"><li>• Sunitinib<sup>a</sup> (category 1)</li></ul>		
Third-line therapy for unresectable or metastatic disease (progressive disease or intolerance to imatinib and sunitinib)	<ul style="list-style-type: none"><li>• Regorafenib<sup>a</sup> (category 1)</li></ul>		
Fourth-line therapy for unresectable or metastatic disease (progressive disease or	<ul style="list-style-type: none"><li>• <b>Ripretinib<sup>a,d</sup> (category 1)</b></li></ul>		



intolerance to imatinib, sunitinib, and regorafenib)			
Fifth-line therapy for unresectable or metastatic disease (progressive disease or intolerance to imatinib, sunitinib, regorafenib, and ripretinib)			<ul style="list-style-type: none"><li>• Sorafenib</li><li>• Nilotinib</li><li>• Dasatinib (for patients with <i>PDGFRA</i> D842V mutation)</li><li>• Pazopanib</li><li>• Everolimus + TKI<sup>c</sup></li><li>• Avapritinib<sup>a,b</sup></li></ul>

<sup>a</sup>FDA-approved TKIs for the treatment of GIST.

<sup>b</sup>Indicated for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations.

<sup>c</sup>TKIs to be considered for use in combination with everolimus include imatinib, sunitinib, or regorafenib.

<sup>d</sup>Ripretinib is indicated for use in patients who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

**FDA Approval:** Ripretinib is approved for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib.<sup>1</sup>

#### **Rationale for inclusion of ripretinib as a 4L treatment option**

In the pivotal, Phase 3 clinical trial INVICTUS, ripretinib demonstrated meaningful clinical benefit in patients with  $\geq 4$ L GIST where there is a high unmet medical need.

#### **Pivotal Phase 3 INVICTUS Trial<sup>2</sup>**

Approval of ripretinib was based on INVICTUS<sup>2</sup>, a Phase 3 randomized, placebo-controlled, double-blind trial that enrolled 129 patients with  $\geq 4$ L GIST. In the trial, 63% of patients received 3 prior therapies and 37% received 4 or more prior therapies (range 4 to 7). Patients were randomized 2:1 to ripretinib 150 mg once daily (QD) orally (n=85) or placebo (n=44). Upon progression, patients randomized to placebo could cross over to ripretinib treatment. Upon progression on ripretinib 150 mg QD, patients could dose escalate to ripretinib 150 mg BID. The primary endpoint was progression-free survival (PFS) and secondary endpoints included objective response rate (ORR) and overall survival (OS).

- Ripretinib significantly improved PFS versus placebo (median 6.3 months vs 1.0 month; HR 0.15; 95% CI 0.09–0.25;  $P < 0.0001$ ).
- The confirmed ORR was 9.4% for ripretinib vs 0.0% for placebo ( $p = 0.0504$ ). The median duration of response for ripretinib had not been reached.
- The ripretinib arm showed higher overall survival (OS) versus placebo (median 15.1 vs 6.6 months; HR 0.36; 95% CI 0.21–0.62). This clinically meaningful benefit was demonstrated despite 66% of patients in the placebo arm crossing over to ripretinib treatment.
- Ripretinib was well tolerated; most adverse events (AEs) were grade 1 or 2. The rates of grade 3 or 4 treatment emergent adverse events (TEAEs) were similar between ripretinib and placebo (49.4% vs 44.2%, respectively).
- Rates of discontinuation, dose interruption, and dose reduction with ripretinib due to TEAEs were low (discontinuation 8% ripretinib vs. placebo 12%; dose interruption 24% ripretinib vs. placebo 21%; dose reduction 7% ripretinib vs. placebo 2%).

Ripretinib is a novel switch-control tyrosine kinase inhibitor (TKI) that broadly inhibits KIT and *PDGFRA* kinase signaling through a unique dual mechanism of action. Ripretinib is designed to precisely and durably bind to both the switch pocket and the activation switch to lock the kinase in the inactive state, preventing downstream signaling and cancer cell proliferation. This dual mechanism of action provides broad inhibition of KIT and *PDGFRA* kinase activity, including wild type and the multiple primary and secondary mutations known to drive disease progression in GIST.<sup>1,3</sup> In preclinical studies, ripretinib demonstrated potent activity in GIST patient cell lines harboring both primary and secondary KIT and *PDGFRA* mutations.<sup>3</sup>

In summary, ripretinib provides an effective, well-tolerated, FDA-approved treatment for advanced GIST patients in the 4<sup>th</sup> line setting with clinically meaningful improvements in both PFS and OS. We respectfully request that NCCN include ripretinib with a *Category 1 preferred* designation for the treatment of 4L GIST.

Sincerely yours,

Matthew L. Sherman, MD  
Phone: 781-209-6408



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**References:**

1. QINLOCK™ [Prescribing Information]. Waltham, MA: Deciphera Pharmaceuticals LLC; 2020.
2. von Mehren V, Bauer S, George S, et al. INVICTUS: A phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as  $\geq 4$ th line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). Oral presentation at ESMO Congress, September 27-October 1, 2019; Barcelona, Spain.
3. Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. *Cancer Cell*. **2019**; 35: 738-51.

**References 1 and 2 are enclosed. Please note the INVICTUS manuscript has been submitted for publication and will be forwarded upon acceptance.**