Avapritinib (AYVAKIT) in Gastrointestinal Stromal Tumors (GISTs)
National Drug Monograph
November 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Tyrosine kinase inhibitor (TKI) with selectivity for platelet-derived growth factor receptor alpha (PDGFRA) and KIT (aka CD117) genes and the KIT D816V and PDGFRA D842V mutants. Avapritinib was a landmark treatment, being the first precision-targeted drug for GISTs driven by PDGFRA exon 18 mutations including multi-resistant PDGFRA D842V. PDGFRA exon 18 D842V mutations are generally insensitive to imatinib and carry a good prognosis.
Indication Under Review	Treatment of adults with unresectable or metastatic GIST (**umGIST**) harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations
Dosage Regimen	300 mg PO once daily
Dosage Forms Under Review	Tablets: 100 mg, 200 mg, 300 mg

EFFICACY CONSIDERATIONS

	NAVIGATOR[1,2,3]	**VOYAGER**[4]
Trial		
Design	MC, first-in-human, phase 1 single-arm, safety, antitumor activity, OL observational study (OBS). Tested null ORR ≤ 10% vs ORR ≥ 35% with 90% power.	Phase 3 MC OL RCT
Population	Adults with **umGISTs** and PDGFRA D842V mutation; ECOG PS ≤ 2. N = 56 efficacy, 82 safety	476 patients with molecularly unselected, locally advanced, unresectable, or metastatic GIST (**lumGIST**) who had prior imatinib therapy and one or two additional TKIs (95% sunitinib; 86% 2 TKIs, 14% 3 TKIs). ECOG PS 0 or 1.
Intervention	Avapritinib 30–600 mg QD	Avapritinib 300 mg QD in continuous 28-day, 4-weeks-on cycles
Comparator	None	Regorafenib 160 mg QD in 28-day, 3-weeks-on-and-1-week-off cycles
Results	Median follow-up: 15.9 mos	Median follow-up: 8.5 and 9.6 mos for avapritinib and regorafenib, respectively

Outcome	Avapritinib
ORR, n/N (%)	49/56 (88)*
95% CI	76,95
DOR-12, % (95% CI)	70 (54, 87)
mOS-24, % (95% CI)	81 (67, 94)
mOS, mos (95% CI)	NR

DOR-12, 12-mo duration of response; mOS, Median overall survival; mOS-24, mOS at 24 mos; NR, Not reached; ORR, Overall response rate (complete + partial)

* For reference: The manufacturer conducted a natural history study in which only one of 22 patients with GIST harboring a PDGFRA D842V mutation had a response in any line of therapy. The ORR (95% CI) was 4.5% (0, 23), representing a complete response with imatinib as first-line therapy.[5]

Outcome	Avapritinib	Regorafenib	Absolute Effect (95% CI)	Q
PFS, mos	4.2 (3.7, 5.6)	5.6 (3.8, 7.2)	Diff –1.4	L[α,β]
OS, n/N (%)	164/240 (68.2)	159/236 (67.4)	AAE 10 (–74, 94)	M[β]
mOS, mos (95% CI)	19.2 (19.2, NR)	17.4 (15.8, NR)	Diff 1.8	M[γ]
CFB in GHS	–5.7 (24.29)	–4.4 (20.74)	Diff –1.3 (–2.77, 5.37)	M[α]

See NAVIGATOR footnotes. PFS and OS in mos with 95% CI. AAE, Anticipated absolute effect per 1000; CFB, Change from baseline; GHS, Global health status score on the EORTC-QLQ-30, mean (SD); ND, No data. OS rate was the estimate at 12 mos, ITT.

α Downgraded for risk of bias (no blinding)

β Downgraded for indirectness (OS was estimated since data were immature at cutoff date; PFS is an image-based surrogate for OS)

γ Downgraded for imprecision (uncertain width of CI)

Subgroup analyses

- Avapritinib was better than regorafenib in median PFS time among 13 patients with PDGFRA D842V-mutant GIST. PFS times were not reached (95% CI 9.7 to not reached; n = 7) vs 4.5 months (1.7 to not reached; n = 6), respectively.
- Regorafenib was better than avapritinib in median PFS among ITT patients without PDGFRA D842V-mutant GIST: HR 1.34 (95% CI 1.06, 1.69); 5.6 vs 3.9 months, respectively.

	Avapritinib vs Other TKIs[6]	
Trial		
Design	Indirect, retrospective OBS	
Population	Adults with PDGFRA D842V-mutant **umGIST**	
Intervention	Avapritinib in NAVIGATOR (N = 56)	
Comparator	Other TKIs in natural history study (Study 1002; real-world data; N = 19)	
Results	*Overall Population* maOS: NR vs 12.6 mos	*Subgroup of Avapritinib 300/400 mg (n = 38) vs Study 1002 (n = NS)* maOS: NR vs ~25 mos

[redacted]	maOS-6: 100% vs 56% maOS-48: 63% vs 17%	maOS-6: 100% vs 68% maOS-36: 73% vs 20%

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maOS-6, -36, -48, Median adjusted overall survival at 6, 36, or 48 months

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings	Intracranial hemorrhage (ICH), cognitive effects (e.g., memory impairment, amnesia, somnolence, speech disorder), photosensitivity, embryofetal toxicity
Top 5 and Grade 3/4 (G3/4) AEs (NAVIGATOR)	Top 5 AEs: Edema, nausea, fatigue / asthenia, cognitive impairment, vomiting. Top 5 G3/4 AEs: Fatigue / asthenia, abdominal pain, diarrhea, cognitive impairment, nausea Top 5 G3/4 Lab Abnormalities: Decreased hemoglobin, decreased phosphate, increased bilirubin, decreased sodium, decreased neutrophils, decreased potassium
Drug Interactions	Strong CYP3A inHIBitors: Avoid (increased avapritinib effects). Moderate CYP3A inHIBitors: Avoid or reduce dose of avapritinib. Strong or moderate CYP3A inDUCers: Avoid (decreased avapritinib effects)
Undesirable Effects Size	VOYAGER: Similar to regorafenib except for increased risk of treatment-related cognitive effects: RR 5.7 (2.4, 12.2); ARI 22.1 (16.0, 28.2); NNH 5 (4, 6). In addition, low but potentially serious risk of ICH.

PLACE IN THERAPY					
DRUG	**VANF**	**CFU**	**FDA**	**NCCN GIST GUIDELINES (v1.2023)[7]†**	**ESMO GIST GUIDELINES (2022)[8]**
Avapritinib	TBD	TBD	1st-line therapy for **umGIST** with PDGFRA exon 18 mutations	Preferred (1st-line) option for unresectable, progressive, or metastatic GISTs (**upmGISTs**; including recurrent GIST post-resection) harboring PDGFRA D842V or other PDGFRA exon 18 mutations insensitive to imatinib. Preferred (1st-line) **neoadjuvant therapy for resectable GIST** with significant morbidity and harboring PDGFRA exon 18 mutations insensitive to imatinib including PDGFRA D842V. Additional (5th-line) option useful in certain circumstances after **progression** on approved therapies (imatinib, sunitinib, regorafenib, ripretinib) for **upmGISTs** with sensitive mutations excluding PDGRA exon 18 mutations that are insensitive to imatinib including D842V.	Standard 1st-line therapy for advanced / metastatic GIST (**amGIST**) with PDGFRA exon 18 D842V mutation May be considered for neoadjuvant therapy of **localized GIST** with PDGFRA D842V mutation *Localized GIST with PDGFRA exon 18 D842V mutation should not be treated with adjuvant therapy (lack of evidence).*
Dasatinib	NF	NA	Off-label use[9,10]	2nd-line (other recommended option) after avapritinib for **upmGISTs** with PDGFRA D842V or other PDGFRA exon 18 mutations insensitive to imatinib	Not mentioned
Ripretinib	NF	4th line for **GIST** after imatinib, sunitinib, and regorafenib	4th-line for **advanced GIST** after ≥ 3 kinase inhibitors including imatinib	Additional option useful in certain circumstances after progression on avapritinib and dasatinib for GIST with PDGFRA exon 18 mutations insensitive to imatinib including D842V. (Ripretinib's clinical efficacy needs to be confirmed.)	No recommendation on use of ripretinib for PDGFRA D842V GIST

† Regorafenib was not recommended for GIST with PDGFRA exon 18 mutations.

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. Unresectable or metastatic GISTs harboring PDGFRA exon 18 mutations insensitive to imatinib including PDGFRA D842V. 2. Progressive GIST after trials of imatinib and 3 other kinase inhibitors such as sunitinib, regorafenib, and dose-escalated ripretinib.

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