Fruquintinib (Fruzaqla) in Metastatic Colorectal Cancer
National Drug Mini-Monograph
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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	Fruquintinib is a small molecular inhibitor of vascular endothelial growth factors (VEGF) -1, -2, and -3, which inhibits tumor growth.
Indication Under Review[1]	Metastatic colorectal cancer previously treated with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapy, and anti-VEGF therapy/RAS wild-type anti-EGFR therapy if medically appropriate.
Dosage Regimen	5mg PO daily for days 1-21 of a 28-day cycle until progression of disease or intolerable toxicity
Dosage Forms Under Review	Oral capsules: 5mg & 1mg

EFFICACY CONSIDERATIONS

Trial	**FRESCO Trial[2]**	**NCT02314819**
Design	Multicenter, randomized, double-blind, placebo-controlled, phase III trial conducted in China	
Population	**Inclusion Criteria** • Age 18-75 • Histologically and/or cytologically confirmed metastatic colorectal cancer • Progression on/intolerant of at least two prior lines of standard with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapy • Body weight ≥ 40kg • ECOG Performance status ≤ 1 • Life expectancy > 12-weeks	**Exclusion Criteria** • Prior use of VEGF inhibitor (excluding bevacizumab) • Baseline cytopenias, liver dysfunction, renal dysfunction, proteinuria, uncontrolled hypertension, uncontrolled infection, or significant electrolyte abnormality. • CNS metastases • Persistent grade >1 toxicity from prior treatment
Demographics	**Fruquintinib Group (n=278)** • Median Age – 55.0 years • Men – 56.8; Women – 43.2% • K-Ras wild-type – 56.5% • Prior VEGF inhibitor – 30.2% • Prior EGFR inhibitor – 14.4%	**Placebo Group (n=138)** • Median Age – 57.0 years • Men – 70.3; Women – 29.7% • K-Ras wild-type – 53.6% • Prior VEGF inhibitor – 29.7% • Prior EGFR inhibitor – 13.8%
Intervention	Fruquintinib 5mg PO plus best supportive care for days 1-21 of a 28-day cycle until progression of disease or intolerable toxicity	
Comparator	Matched placebo plus best supportive care for days 1-21 of a 28-day cycle	
Results	**Primary Endpoint:** median overall survival (mOS) with fruquintinib vs. placebo - (9.3 vs 6.6 months HR 0.65, 95% CI 0.51-0.83; p<0.001) **Stratification (Primary Endpoint):** Prior VEGF inhibitor - Yes – HR 0.68, 95% CI 0.45-1.03 - No – HR 0.60, 95% CI 0.45-0.80 K-RAS Status - Wild Type – HR 0.56, 95% CI 0.40-0.78 - Mutated – HR 0.75, 95% CI 0.53-1.07 **Secondary Endpoints:** median progression free survival (mPFS) with fruquintinib vs. placebo - (3.7 vs 1.8 months HR 0.26, 95% CI 0.21-0.34; p<0.001) objective response rate (ORR) with fruquintinib vs. placebo - (4.7% vs 0% CI 2.1-7.2; p=0.01) disease control rate (DCR) with fruquintinib vs. placebo	

	- (62.2% vs 12.3% CI 42.0-57.8; p<0.001)
Conclusions/Summary	Use of fruquintinib with BSC was associated with an improved mOS, mPFS, ORR and DCR compared to placebo and BSC in a Chinese patient population with metastatic colorectal cancer who failed at least two prior lines of standard therapy that included fluoropyrimidine, oxaliplatin, or irinotecan-based chemotherapy. Benefit was demonstrated regardless of K-RAS mutational status or prior use of VEGF inhibitor.

Trial	**FRESCO-2 Trial[3] NCT04322539**
Design	International, randomized, double-blind, placebo-controlled, phase III trial across 14 countries in North America, Europe, Asia, and Australia.
Population	**Inclusion Criteria** • Age 18-75 • Histologically and/or cytologically confirmed metastatic colorectal cancer • Progression or intolerance to on all standard lines of therapy including fluoropyrimidine, oxaliplatin, irinotecan, anti-EGFR, anti-VEGF therapies and PD or intolerant to trifluridine/tipiracil and/or regorafenib therapy • Body weight ≥ 40kg • ECOG Performance status ≤ 1 • Life expectancy > 12-weeks **Exclusion Criteria** • Baseline cytopenias, liver dysfunction, renal dysfunction, proteinuria, uncontrolled hypertension, uncontrolled infection, or significant electrolyte abnormality. • History severe bleed or thromboembolic events within 6-months • CNS metastasis • Persistent grade >1 toxicity from prior treatment (excluding neuropathy grade ≤2)
Demographics	**Fruquintinib Group (n=461)** • Median Age – 64 years • Men – 53; Women – 43.2% • White 80; Asian 9; Black 3% • K-Ras wild-type –87% • Median # prior tx: 4 (3-6) • Prior VEGF inhibitor – 97% • Prior EGFR inhibitor – 39% • Prior Trifluridine/tipiracil – 52% • Prior Regorafenib – 9% • Prior Trifluridine/tipiracil & Regorafenib – 39% **Placebo Group (n=230)** • Median Age – 64 years of age • Men – 61; Women – 29.7% • White 83; Asian 8; Black 3% • K-Ras wild-type – 86% • Median # prior tx: 4 (3-6) • Prior VEGF inhibitor – 97% • Prior EGFR inhibitor – 38% • Prior Trifluridine/tipiracil – 53% • Prior Regorafenib – 8% • Prior Trifluridine/tipiracil & Regorafenib – 40%
Intervention	Fruquintinib 5mg PO daily plus BSC for days 1-21 of a 28-day cycle until progression of disease or intolerable toxicity
Comparator	Matched placebo plus BSC for days 1-21 of a 28-day cycle
Results	**Primary Endpoints:** mOS with fruquintinib + BSC vs. placebo + BSC (@ median 11.3 vs. 11.2 months) (7.4 vs 4.8 months HR 0.66, 95% CI 0.55-0.80; p<0.0001) **Secondary Endpoints:** mPFS with fruquintinib arm vs. placebo - (3.7 vs 1.8 months HR 0.32, 95% CI 0.27-0.39; p<0.0001) ORR with fruquintinib arm vs. placebo - (2% vs 0% CI 0.4-2.7; p=0.059) NS DCR with fruquintinib arm vs. placebo - (56% vs 16% CI 32.8-46.0; p<0.0001) In the subgroup analysis for mPFS and mOS, the point estimates for those who also received prior tri-tipiracil, regorafenib or both favored fruquintinib.
Conclusion/Summary	Use of fruquintinib + BSC was associated with an improved mOS, PFS and DCR compared to placebo + BSC in heavily pretreated patients who have exhausted all other viable lines of therapy including fluoropyrimidine, oxaliplatin, irinotecan, anti-EGFR inhibitor, anti-VEGF, trifluridine/tipiracil or regorafenib-based therapy. No statistically significant difference was seen in terms of objective response rate.

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings	Hypertension (Any Grade – 49%) (Grade ≥3 – 19%) • Fruquintinib may cause/worsen hypertension with a median time to onset of 14 days. Anti-hypertensive therapy should be adjusted as appropriate and fruquintinib should be adjusted/discontinued if control cannot be achieved. Hemorrhagic Events (Any Grade – 6%) (Grade ≥3 – 1%) • Fruquintinib may cause serious hemorrhagic events including gastrointestinal hemorrhage. Fruquintinib should be permanently discontinued if serious hemorrhage occurs. Infections (Any 18%) (Fatal 1%) • Fruquintinib may increase the risk of infection including urinary tract infection respiratory infections, and sepsis. Fruquintinib should be held for grade 3-4 infections and resumed after resolution. Gastrointestinal Perforations (Grade ≥3 – 1.3%) • Fruquintinib should be permanently discontinued if gastrointestinal perforation occurs. Hepatoxicity (Any Grade – 48%) (Grade ≥3 – 5%) • Fruquintinib may cause elevations of liver function tests with a median time to onset of 29 days. Fruquintinib should be held and adjusted as appropriate depending on severity and persistence. Proteinuria (Any Grade – 36%) (Grade ≥3 – 2.5%) • Fruquintinib may cause proteinuria with a median time to onset of 22 days. Fruquintinib should be held and adjusted as appropriate depending on severity and persistence. Palmar-Plantar Erythrodysesthesia (PPE) (Any Grade – 35%) (Grade ≥3 – 8%) • Fruquintinib may cause PPE with a median time to onset of 19 days. Fruquintinib should be held and adjusted as appropriate depending on severity and persistence. Posterior Reversible Encephalopathy Syndrome (PRES) (0.1%) • Fruquintinib may cause PRES. Fruquintinib should be permanently discontinued if PRES develops. Impaired Wound Healing (Grade 2 – 0.1%) • Fruquintinib may lead to impaired wound healing. Fruquintinib should not be give within 2 weeks of a major surgery. Arterial Thromboembolic Events (Any – 0.8%) • Fruquintinib may increase the risk of arterial thromboembolic events. Caution should be taken in patients with recent thromboembolic events. Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF) (Incidence not defined) • Yellow No.5 & No. 6 dye are only present in 1mg capsule. Sensitivity to these dyes are more frequently seen in those with aspirin allergy. Embryo-Fetal Toxicity (Based on animal studies) • Fruquintinib was found to have embryo-fetal toxicity in animal studies. Fruquintinib should be avoid during pregnancy and precautions should be taken to avoid conception while on treatment.
Top 5 AEs	**<u>Toxicities – Any Grade (Grade 3-4)</u>** Hypertension – 38-61% (14-23%) Fatigue – 25-53% (2.5-12%) PPE– 19-49% (6-11%) Diarrhea – 24-25% (3.6-3.7%) Abdominal Pain – 25-29% (3.7-4%)
Drug Interactions	**Strong or Moderate CYP3A Inducers** – Concomitant use with a strong CYP3A inducer may decrease the efficacy of fruquintinib

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	CLINICAL GUIDELINES
Fruquintinib	TBD	TBD	mCRC in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.	**VHA Pathway** Replaced regorafenib; follows trifluridine-tipiracil **NCCN Guidelines** Category 2A recommendation for advanced/metastatic colorectal cancer that has progressed through fluoropyrimidine, oxaliplatin, irinotecan, EGFR targeting (if appropriate), and other biomarker directed therapy. **Outcomes Data[3]** (vs placebo) Overall Survival – 7.4 vs 4.8 months [HR 0.66; 95% CI 0.55-0.80; p<0.0001] Progression Free survival – 3.7 vs 1.8 months **Adverse Events[3]** All (Grade ≥ 3) vs placebo Any: 99 (63%) vs 93 (50%) Htn: 37 (14%) vs 9 (1%) Fatigue: 34 (8%) vs 23 (4%) Decr appetite: 27 (2%) vs. 17 (1%) Diarrhea: 24 (4%) vs. 10% (0) PPE: 19 (6%) vs 3% (0) Abd pain: 18 (3%) vs 16 (3%)
Trifluridine-tipiracil ± Bevacizumab	PA-F	Yes	Metastatic colorectal cancer as a single agent or in combination with bevacizumab in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti EGFR therapy.	**VHA Pathway** Third line therapy for advanced/metastatic colorectal cancer for patient who would not qualify for anti-EGFR therapy. Given alone or in combination with bevacizumab. **NCCN Guidelines** Category 2A recommendation for advanced/metastatic colorectal cancer that has progressed through fluoropyrimidine, oxaliplatin, irinotecan, EGFR targeting (if appropriate), and other biomarker directed therapy. Given alone or in combination with bevacizumab (combination preferred) **Outcomes data[4]** (Trifluridine-tipiracil + Bevacizumab vs Trifluridine-tipiracil) Overall Survival – 10.8 vs 7.5 months [HR 0.61; 95% CI 0.49-0.77; p<0.001] Progression Free Survival – 5.6 vs 2.4 months [HR 0.44; 95% CI 0.36-0.54; p<0.001] **Adverse Events[4]** All (Grade ≥ 3) (Trifluridine-tipiracil + Bevacizumab vs Trifluridine-tipiracil) Any: 98 (72.4%) vs 98 (69.5%) Neutropenia: 62 (43%) vs. 51 (32%) Nausea: 37 (1.6%) vs. 27.2 (1.6%) Anemia: 29 (6.1%) vs 31.7 (11.0%) Asthenia: 24.4 (4.1%) vs. 22.4 (4.1%) Fatigue: 21.5 (1.2%) vs. 16.3 (3.7%) Diarrhea: 20.7 (0.8%) vs. 18.7 (2.4%) Decr appetite: 20.3 (0.8%) vs. 15.4 (1.2%) Hypertension: 10.2 (5.7%) vs 2.0 (1.2%)

	Regorafenib	NF	Yes	Metastatic colorectal cancer in patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy.	**VHA Pathway** Previously 3L therapy for advanced/metastatic colorectal cancer for patient who would not qualify for trifluridine-tipiracil; regorafenib is no longer on pathway **NCCN Guidelines** Category 2A recommendation for advanced/metastatic colorectal cancer that has progressed through fluoropyrimidine, oxaliplatin, irinotecan, EGFR targeting (if appropriate), and other biomarker directed therapy. **Outcomes data**[5] (vs placebo) Overall Survival – 6.4 vs 5.0 months [HR 0.77; 95% CI 0.64-0.94) Progression Free Survival – 1.9 vs 1.7 months DCR 41 vs. 15% **Adverse Events**[5] All (Grade ≥ 3) vs placebo Boxed warning for hepatotoxicity Any: 93 (54%) vs 61 (14%) Fatigue: 47 (9%) vs. 28 (5%) PPE: 47 (17%) vs 8 (<1%) Diarrhea: 34 (7%) vs 8 (1%) Anorexia: 30 (3%) vs. 15 (3%) Hypertension: 28 (7%) vs 6 (1%) Oral mucositis: 27 (3%) vs. 4% (0) Rash/desquamation: 26 (6%) vs 4% (0) Of note, a lower starting dose of regorafenib (80 vs. 160mg) with weekly titration based on tolerance has been shown to improve toxicity profile and allow a longer duration of therapy.[9]

VHA PLACE IN THERAPY	**Potential Use in VHA**	1. Patients with mCRC who have exhausted all standard treatment options with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti VEGF therapy, an anti-EGFR therapy (if RAS wild-type) and progressive disease or intolerance to trifluridine-tipiracil (with or without bevacizumab). 2. Toxicity profile limits regorafenib use. Fruquintinib may provide a more tolerable 3L agent for mCRC.

Prepared March 2024 by Nicholas G. Little, Pharm.D, PGY2 – Oncology Pharmacy Resident, Southern Arizona VA Health Care System.
Contact person: Berni Heron, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

References

1. FRUZAQLA (fruquintinib) capsules, for oral use [prescribing information online]. Lexington, MA: TAKEDA Pharmaceuticals America Inc. 11/2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217564s000lbl.pdf. Accessed 1/31/2024.
2. Li J, Qin S, Xu RH, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. *JAMA*. 2018;319(24):2486-2496. doi:10.1001/jama.2018.7855
3. Dasari A, Lonardi S, Garcia-Carbonero R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. *Lancet*. 2023;402(10395):41-53. doi:10.1016/S0140-6736(23)00772-9
4. Prager GW, Taieb J, Fakih M, et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. *N Engl J Med*. 2023;388(18):1657-1667. doi:10.1056/NEJMoa2214963
5. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312. doi:10.1016/S0140-6736(12)61900-X
6. LONSURF (trifluridine and tipiracil) tablets, for oral use [prescribing information online]. Princeton, NJ: Taiho Oncology, Inc. 8/2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/207981s012lbl.pdf. Accessed 1/31/2024.
7. MVASI (bevacizumab-awwb) Injection, for intravenous use [prescribing information online]. Thousand Oaks, CA: Amgen, Inc. 11/2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761028s008lbl.pdf. Accessed 2/21/2024.
8. STIVARGA (regorafenib) tablets, for oral use [prescribing information online]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc. 6/2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203085s013lbl.pdf. Accessed 1/31/2024.
9. Bakaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimization in patients with refractory metastatic colorectal cancer (ReDOS): a randomized, multicenter, open-label, phase 2 study. Lancet Oncol 2019; 20: 1070-1082.