Written By: Matthew Arango, PharmD, BCOP
The Ohio State University James Comprehensive Cancer Center

Positive Quality Intervention: Tucatinib (TUKYSA®) and trastuzumab in HER2-positive Metastatic Colorectal Cancer

Description: Understand how to identify eligible patients and manage adverse effects of tucatinib treatment for patients with metastatic colorectal cancer.

Background: The optimal treatment of metastatic colorectal cancer (mCRC) is increasingly dependent upon anatomical, histopathological, and molecular features. Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 1-4% of mCRC cases.[1] Multiple treatment regimens targeting HER2 had previously demonstrated benefit in the treatment of this population.[2-5] (Supplemental Information, Table 1) Tucatinib, an oral, selective, small molecule inhibitor of HER2, in combination with trastuzumab is the first FDA-approved treatment for patients with HER2-positive mCRC previously treated with chemotherapy. This is an accelerated approval supported by the phase II MOUNTAINEER trial.[6]

The MOUNTAINEER trial enrolled 86 patients who were treated with tucatinib and trastuzumab. Patients had HER2-positive mCRC (defined as 3+ via immunohistochemistry (IHC), or 2+ via IHC with a positive result via in-situ hybridization (ISH), or HER2 amplification by next-generation sequencing (NGS) sequencing assay and RAS wild-type. Patients must have previously been treated with chemotherapy including fluoropyrimidine, oxaliplatin, and irinotecan (median prior therapies = 2).[7] Key efficacy endpoints included an objective response rate (ORR) of 38%, median duration of response of 12.4 months, median progression-free survival (PFS) of 8.2 months, and median overall survival (OS) of 24.1 months. Common adverse events included diarrhea (64% any grade/3.5% Grade 3), fatigue (44%/2.3%), nausea (35%/0%), and abdominal pain (21%/2.3%).[5] An ongoing phase III trial, MOUNTAINEER-03, will compare tucatinib in combination with trastuzumab and mFOLFOX6 chemotherapy versus mFOLFOX6 ± bevacizumab or cetuximab in previously untreated patients with HER2-positive, RAS wild-type mCRC.[8]

PQI Process: Upon receipt of an order for tucatinib

- Ensure the patient has mCRC and has been previously treated with, or has a contraindication to, a fluoropyrimidine, oxaliplatin, and irinotecan
- Evaluate molecular testing to make sure patient is HER2-positive (IHC 3+ or IHC 2+/ISH positive or NGS), RAS and BRAF wild type, and not MSI-H
- Recommend baseline labs (serum chemistry, liver function, and complete blood count) and cardiac function (echocardiogram or multigated acquisition scan) if not already completed and when:
    - Initial dose of tucatinib requires dose reduction for patients with severe hepatic impairment (Child Pugh class C) (Supplemental Information, Table 2)
    - Treatment with trastuzumab may worsen pre-existing cardiac dysfunction, and tucatinib monotherapy is not recommended based upon limited efficacy
- Assess medication list for potential drug-drug interactions
    - Avoid concomitant use of tucatinib with a strong CYP3A4 inducer or a strong or moderate CYP2C8 inducer
    - Avoid concomitant use of tucatinib with a strong CYP2C8 inhibitor
    - Avoid concomitant use of tucatinib with CYP3A4 substrates with narrow therapeutic indexes; if concomitant use cannot be avoided, reduce the dose of the CYP3A4 substrate and monitor
    - If using tucatinib with a concomitant P-gp substrate with a narrow therapeutic index, consider reducing the dose of the P-gp substrate and monitor

- Recommended dose is 300 mg twice daily with or without food; supplied as 150 mg and 50 mg tablets, therefore patients will take multiple pills multiple times per day
- Ensure female patients are not pregnant nor breastfeeding prior to starting tucatinib
- Patients should be monitored for diarrhea, which may be severe and contribute to dehydration, acute kidney injury, and death; pre-emptive antidiarrheals are not routinely recommended
    - Evaluate any diarrhea to rule out infectious or other causes. Diarrhea not caused by infection should be treated with antidiarrheals
    - Withhold tucatinib for Grade 3 or 4 diarrhea (Supplementary Information, Table 3)
- Monitor liver function labs at least every 3 weeks during treatment (Supplementary Information, Table 3)

Patient-Centered Activities:

- Provide the Oral Chemotherapy Education (OCE) Sheet
- Counsel patients to take tucatinib doses approximately 12 hours apart, at consistent times each day, and consistently in regard to food
    - Do not chew, crush, or split tablets and do not ingest tablets which are not intact
    - If a dose is missed or vomited, do not make it up
- Store tucatinib at room temperature, in the original bottle, and discard unused tablets 3 months after opening the bottle
- Advise patients that their oncologist will monitor labs, cardiac function, and disease response periodically during treatment with tucatinib and trastuzumab
- Counsel patients on the use of antidiarrheals, if needed or if recommended pre-emptively by their oncologist; patients should contact their prescriber if they experience a change in bowel function, signs/symptoms of hepatic dysfunction, or any symptom which limits activities of daily living
- Confirm that patients of reproductive potential, or patients with partners of reproductive potential, use effective contraception and inform their oncologist of a known or suspected pregnancy
- Advise patients of reproductive potential that the effects of tucatinib on fertility are not completely known and fertility may be impaired

References:

1. Yoshikawa, A., & Nakamura, Y. (2022). Molecular basis of HER2-targeted therapy for HER2-positive colorectal cancer. Cancers, 15(1), 183.
2. Sartore-Bianchi, A., Trusolino, L., Martino, C., et al. (2016). Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. The Lancet. Oncology, 17(6), 738–746.
3. Meric-Bernstam, F., Hurwitz, H., Raghav, K. P. S., et al. (2019). Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. The Lancet. Oncology, 20(4), 518–530.
4. Gupta R, Meric-Bernstam F, Rothe M, et al. Pertuzumab plus trastuzumab in patients with colorectal cancer with ERBB2 amplification or ERBB2/3 mutations: results from the TAPUR Study. JCO Precis Oncol. 2022;6:e2200306.
5. Siena, S., Di Bartolomeo, M., Raghav, K., et al. (2021). Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. The Lancet. Oncology, 22(6), 779–789.
6. Tukysa (tucatinib) [package insert].
7. Strickler JH, Cercek A, Siena S, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. The Lancet. Oncology, 24(5), 496-508.
8. ClinicalTrials.gov. NCT05253651. A study of tucatinib with trastuzumab and mFOLFOX6 versus standard of care treatment in first-line HER2+ metastatic colorectal cancer. Accessed March 3, 2023.

Supplemental Information:

Table 1: Additional anti-HER2 treatments in mCRC				
Intervention	Trastuzumab + lapatinib[2]	Trastuzumab + pertuzumab[3,4]		fam-Trastuzumab deruxtecan[5]
Patients Evaluated	27	57	28	53
Median Prior Therapies	5	4	1	4
ORR	30%	32%	25%	45.3%
Median PFS	21 weeks	2.9 months	17.2 weeks	6.9 months
Median OS	46 weeks	11.5 months	60.0 weeks	Not reached*

*Median follow up 5.4 months

Table 2: Tucatinib dose levels	
Initial recommended dose*	300 mg twice daily
Dose level -1	250 mg twice daily
Dose level -2	200 mg twice daily
Dose level -3**	150 mg twice daily

*For patients with severe hepatic dysfunction (Child Pugh class C) initiate tucatinib at 200 mg twice daily
**Permanently discontinue tucatinib for patients unable to tolerate 150 mg twice daily

Table 3: Recommended dose modifications for adverse reactions		
Adverse Reaction	**Severity**	**Management**
Diarrhea	Grade 3 without antidiarrheals	Hold tucatinib and initiate antidiarrheals. Resume tucatinib at same dose level once improved to Grade ≤ 1
	Grade 3 with antidiarrheals	Hold tucatinib. Intensify antidiarrheals, if appropriate. Resume tucatinib at next lower dose level once improved to Grade ≤ 1
	Grade 4	Permanently discontinue tucatinib
Hepatotoxicity	Grade 2 bilirubin (>1.5 to 3x ULN)	Hold tucatinib until recovery to Grade ≤ 1, then resume at the same dose level
	Grade 3 AST or ALT (>5 to 20x ULN) or bilirubin (>3 to 10x ULN)	Hold tucatinib until recovery to Grade ≤ 1, then resume at the next lower dose level
	Grade 4 AST or ALT (> 20 × ULN) OR bilirubin (> 10 × ULN)	Permanently discontinue tucatinib
	AST or ALT > 3x ULN AND bilirubin > 2x ULN	Permanently discontinue tucatinib
Other adverse reactions	Grade 3	Hold tucatinib until recovery to Grade ≤ 1, then resume at the next lower dose level
	Grade 4	Permanently discontinue tucatinib