HER2 TESTING IN COLORECTAL CANCER: CONCORDANCE ANALYSIS BETWEEN BREAST AND GASTRIC SCORING ALGORITHMS FROM THE MOUNTAINEER TRIAL

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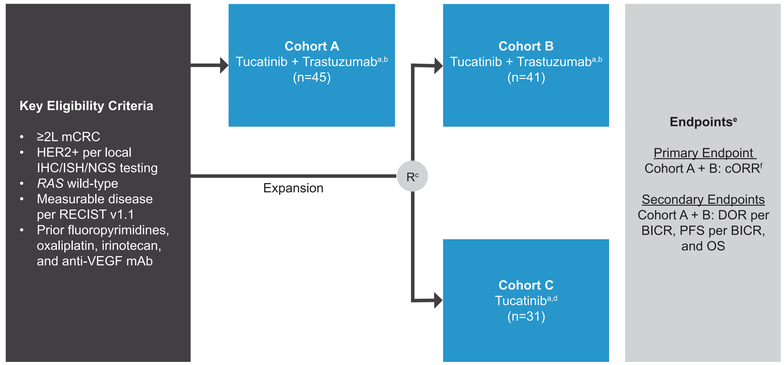
Background

- HER2 overexpression and/or amplification (HER2+) occurs in 3%–5% of patients with metastatic colorectal cancer (mCRC)[1–5]
  - Rates of HER2+ can increase to ~10% in patients with *RAS/BRAF* wild-type mCRC tumors
- The current standard of care for mCRC is multi-agent chemotherapy, with or without a VEGF- or EGFR-inhibitor[6,7]
  - Treatments are not curative and survival outcomes are poor
- HER2 positivity in mCRC is associated with primary resistance and poor response to anti-EGFR therapy[4,8–10]
- HER2 amplification has been identified as an oncogenic driver in breast and gastric cancers[11] and is an established and clinically relevant target in mCRC
- Established regional guidelines recommend HER2 testing and HER2-directed treatment options for mCRC[1]
  - There are several testing methods available to determine HER2 status
  - No currently established best practice for HER2 testing and interpretation in mCRC
  - No FDA-approved HER2-targeted therapies for mCRC
- The MOUNTAINEER trial (NCT03043313) evaluated the safety and efficacy of the investigational regimen of tucatinib in combination with trastuzumab in patients with HER2+ and *RAS* wild-type mCRC
  - Results from the primary analysis showed clinically meaningful activity and demonstrated tucatinib in combination with trastuzumab was well tolerated[12]

MOUNTAINEER: Global, Open-Label, Phase 2 Trial



a Tucatinib dose: 300 mg PO BID, Trastuzumab dose: 6 mg/kg Q3W (loading dose 8 mg/kg C1D1); each treatment cycle is 21 days
b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure
c Stratification: Left sided tumor primary vs other
d Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12
e Efficacy assessed in patients who received any amount of study treatment and had HER2+ tumors
f RECIST v1.1 per BICR

MOUNTAINEER: Tucatinib + Trastuzumab Topline Results

Efficacy (n=84)	
cORR per BICR	38.1%
mDOR	12.4 months
mPFS	8.2 months
mOS	24.1 months

Safety (n=86)
No deaths due to AEs
Diarrhea was most common AE • Grade 1 or 2: 60.5% • Grade 3: 3.5%
Low discontinuation rate: 5.8%

- Here we present the results from a concordance analysis comparing HER2 IHC analysis with the breast and gastric algorithms from the MOUNTAINEER trial in the mCRC setting

Methods

MOUNTAINEER: HER2 Testing and Analysis

a Confirmed HER2-positive mCRC tested at CLIA-certified or ISO-accredited laboratory: IHC: HER2 3+ IHC by an FDA-approved or CE-marked HER2 IHC test following interpretational manual for breast cancer, ISH: HER2 2+ IHC with amplification by an FDA-approved or CE-marked HER2 in situ hybridization assay (FISH or CISH) following interpretational manual for breast cancer, NGS: HER2 amplification by CLIA-certified or ISO-accredited NGS sequencing assay
b Testing was done per the package insert for Ventana HER2 (4B5) IHC and Dako HER2 IQFISH pharmDx assay and the reader was blinded to patient outcome

Breast and Gastric Scoring Criteria

IHC Score	IHC Status	FISH Result	FISH Status	Overall HER2 Status
0	Negative	Not Needed	N/A	Negative
1+	Negative	Not Needed	N/A	Negative
2+	Equivocal	HER2/CEN-17 ratio <2	Not Amplified	Negative
2+	Equivocal	HER2/CEN-17 ratio ≥2	Amplified	Positive
3+	Positive	Not Needed	N/A	Positive

HER2 Test	Breast Guidelines	Gastric Guidelines[a]
IHC 0	No staining or membrane staining in ≤10% of tumor cells	No reactivity or membranous activity <10% of tumor cells
IHC 1+	Incomplete/faint membrane staining >10% of cells	Faint/barely perceptible membranous reactivity in ≥10% of tumor cells
IHC 2+	Weak to moderate complete membrane staining in >10% of tumor cells, ISH mandatory	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells
IHC 3+	>10% strong complete membrane staining	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumor cells

Breast Guidelines developed from: Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018;142(11):1364-82.
Gastric Guidelines developed from: Bartley AN, Washington MK, Ventura CB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med. 2016;140(12):1345-63.

a Based on surgical specimen

Abbreviations

AE, adverse event; BICR, blinded independent central review; BID, twice a day; BRAF, proto-oncogene B-Raf; C1D1, cycle 1 day 1; CE, Conformité Européenne; CEN-17, chromosome 17 centromere; CISH, chromogenic in situ hybridization; CLIA; Clinical Laboratory Improvement Amendments; cORR, confirmed objective response rate; CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; FDA, United States Food and Drug Administration; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ISO, International Organization for Standardization; mCRC, metastatic colorectal cancer; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; Q3W, every 3 weeks; R, randomization; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; VEGF, vascular endothelial growth factor

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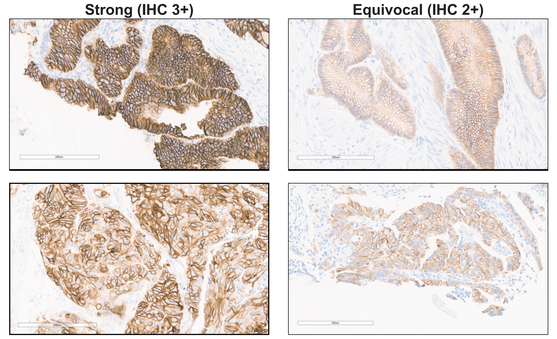
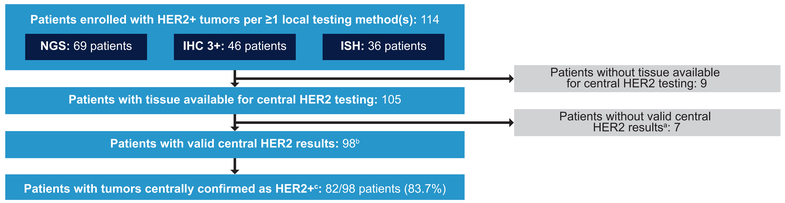
Results

HER2 IHC Staining Examples



HER2 Testing



a Of the 7 patients that did not have valid central HER2 results, 3 were tested outside of the manufacturer-specified 28-day stability window and had HER2 inconclusive results and 4 had tissue that was deemed not-evaluable by the central lab pathologist
b Ten patients were tested outside of the manufacturer-specified 28-day stability window and were considered HER2 positive with an IHC of 3+ or 2+/FISH-amplified based on the scientific rationale that HER2 IHC staining intensity would be expected to decrease over time
c HER2+ results include all tissue samples analyzed with an IHC of 3+ or 2+/FISH-amplified result

Concordance of Central Laboratory-confirmed HER2 Status by Breast and Gastric Algorithms

	Gastric Algorithm (N=105)		
Breast Algorithm (N=105)	Negative	Positive	Not Determined
Negative	**16**	0	0
Positive	0	**82**	0
Not Determined	0	0	7[a]

- Tissue samples had a 100% concordance rate of HER2 status between breast and gastric algorithms
- HER2 IHC score was 99% concordant between algorithms

a One patient had an IHC score of 2+ and subsequently did not have a valid FISH result, resulting in 7 "Not Determined" for HER2 status but only 6 "Not Determined" for IHC score

Concordance of Central Laboratory-confirmed HER2 IHC Score by Breast and Gastric Algorithms

	Gastric Algorithm (N=105)				
Breast Algorithm (N=105)	0	1+	2+	3+	Not Determined
0	**5**	1	0	0	0
1+	0	**8**	0	0	0
2+	0	0	**22**	0	0
3+	0	0	0	**63**	0
Not Determined	0	0	0	0	6[a]

a One patient had an IHC score of 2+ and subsequently did not have a valid FISH result, resulting in 7 "Not Determined" for HER2 status but only 6 "Not Determined" for IHC score

Conclusions

- Without established best practices, both the breast and gastric algorithms are commonly used by pathologists to determine HER2 status in the CRC patient population to determine HER2 status in mCRC
- This concordance analysis supports the use of either algorithm to identify patients that may respond to treatment with tucatinib in combination with trastuzumab until an FDA-approved HER2 assay is available for mCRC

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