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# Impact of baseline molecular alterations on the efficacy of tucatinib (TUC) plus trastuzumab (Tras) for HER2+, RAS WT metastatic CRC (mCRC) in MOUNTAINEER

**John H. Strickler, MD**
Duke University Medical Center, Durham, NC, USA

A. Cercek, K. Ng, S. Siena, T. André, E. Van Cutsem, C. Wu, A. Paulson, J. Hubbard, A. Coveler, C. Fountzilas, A. Kardosh, P. Kasi, H.J. Lenz, K. Ciombor, M.E. Elez Fernandez, M. Stecher, P. Cronin, M. Bieda, T. Bekaii-Saab

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# DECLARATION OF INTERESTS

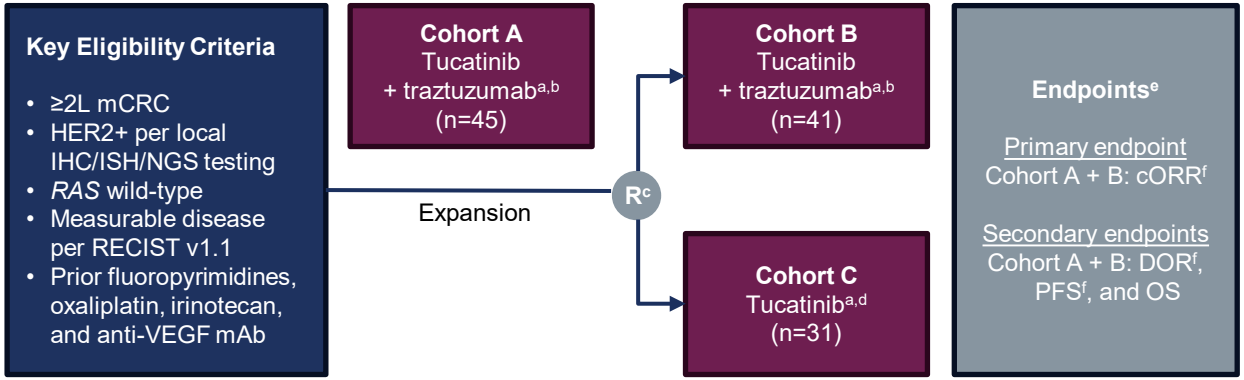
Dr. Strickler reports grants paid to the institution by Abbvie, Amgen, AStar D3, AstraZeneca, Bayer, Beigene, Curegenix, Daiichi Sankyo, Erasca, Leap Therapeutics, Nektar, Roche Genentech, Seagen Inc., and Silverback Therapeutics and grants paid to self by Abbvie, Amgen, AstraZeneca, Bayer, Beigene, Daiichi Sankyo, Eli Lilly, GSK, Natera, Pfizer, Pionyr Immunotherapeutics, Roche Genentech, Seagen Inc., Silverback Therapeutics, Taiho, Takeda, Viatris, and Zentalis. He also reports receiving consulting fees from GSK and Pionyr Immunotherapeutics; receiving other services from GSK and Pionyr Immunotherapeutics; being a member of advisory boards for Abbvie, Amgen, AstraZeneca, Bayer, Beigene, Daiichi-Sankyo, Eli Lilly, Natera, Pfizer, Roche Genentech, Seagen Inc., Silverback Therapeutics, Taiho, Takeda, Viatris, and Zentalis; being a Local PI for Abbvie, AStar D3, AstraZeneca, Bayer, Beigene, Curegenix, Daiichi Sankyo, Erasca, Leap Therapeutics, Nektar, Roche Genentech, and Silverback Therapeutics; and being a Coordinating PI for Amgen and Seagen Inc.

# Background

- HER2 overexpression/amplification occurs in 3-5% of patients presenting with mCRC[1-5]
- Established regional guidelines for mCRC recommend HER2 testing and HER2-directed treatment options[1,6]
- Tucatinib is a highly selective HER2-directed TKI approved by the FDA in combination with trastuzumab for treatment of patients with RAS wild-type HER2+ unresectable or mCRC that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy[7]
- Treatment response to TUC+Tras was predicted by a HER2+ result from IHC, ISH, or NGS testing[8]
- Concomitant genomic alterations are common in patients with HER2+ mCRC[9] but the impact of these alterations on clinical outcomes is unknown

1. Benson AB. J Natl Compr Canc Netw. 2021: 329-59. 2. Kang A. J Manag Care Spec Pharm. 2021: S20-1. 3. Patel JN. J Precis Med. 2019: 3. 4. Sartore-Bianchi A. Oncologist. 2019: 1395-402. 5. Strickler J. J Clin Oncol. 2021: Abstract TPS153. 6. Cervantes A. Ann Oncol. 2023: 10-32. 7. TUKYSA. Prescribing Information. Seagen Inc. Jan 2023. Accessed Sep 11, 2023. 8. Strickler JH. J Clin Oncol. 2023;41(Suppl 16):Abstract 3528. 9. Cancer Genome Atlas Network. Nature. 2012;487(7407):330-7.
IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor

# MOUNTAINEER




[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

## Results: Cohorts A+B[1]

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

**Safety (n=86)**

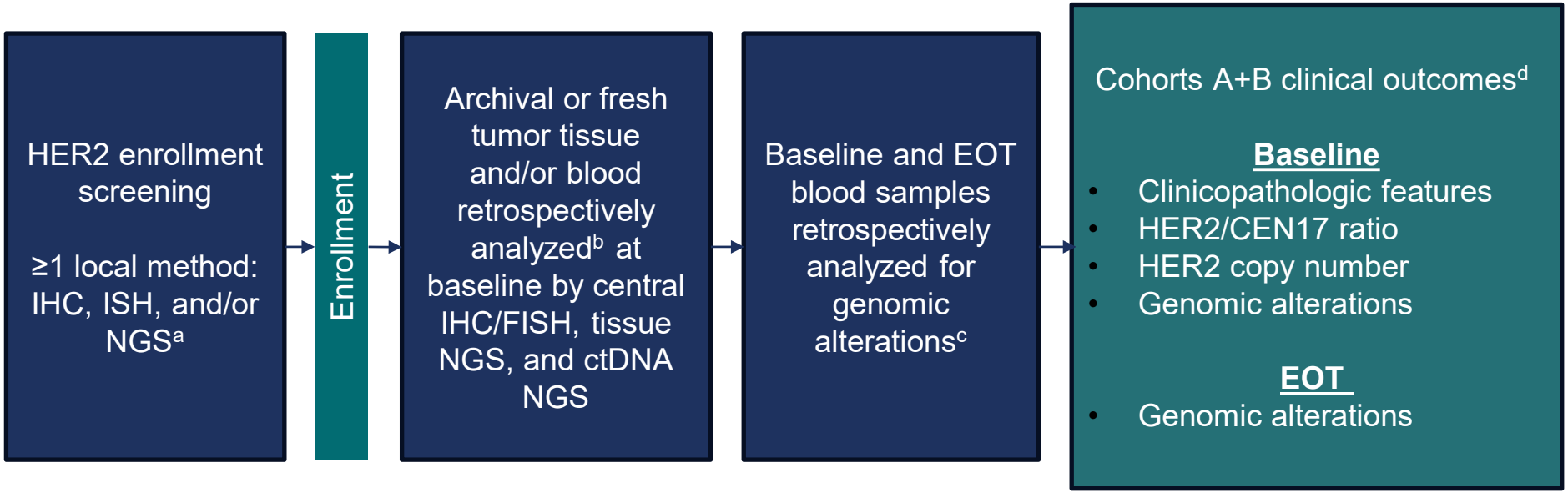
Diarrhea was most common AE
- Grade 1 or 2: 60.5%
- Grade 3: 3.5%

Results from the MOUNTAINEER primary analysis showed clinically meaningful activity and demonstrated tucatinib in combination with trastuzumab was well tolerated[1]

[1]Strickler JH. Lancet Oncol. 2023: 496-508.

AE, adverse event; BICR, blinded independent central review; BID, twice a day; C1D1, Cycle 1 Day 1; cORR, confirmed objective response rate; CR, complete response; IHC, immunohistochemistry; ISH, in situ hybridization; DOR, duration of response; m, median; mAb, monoclonal antibody; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors

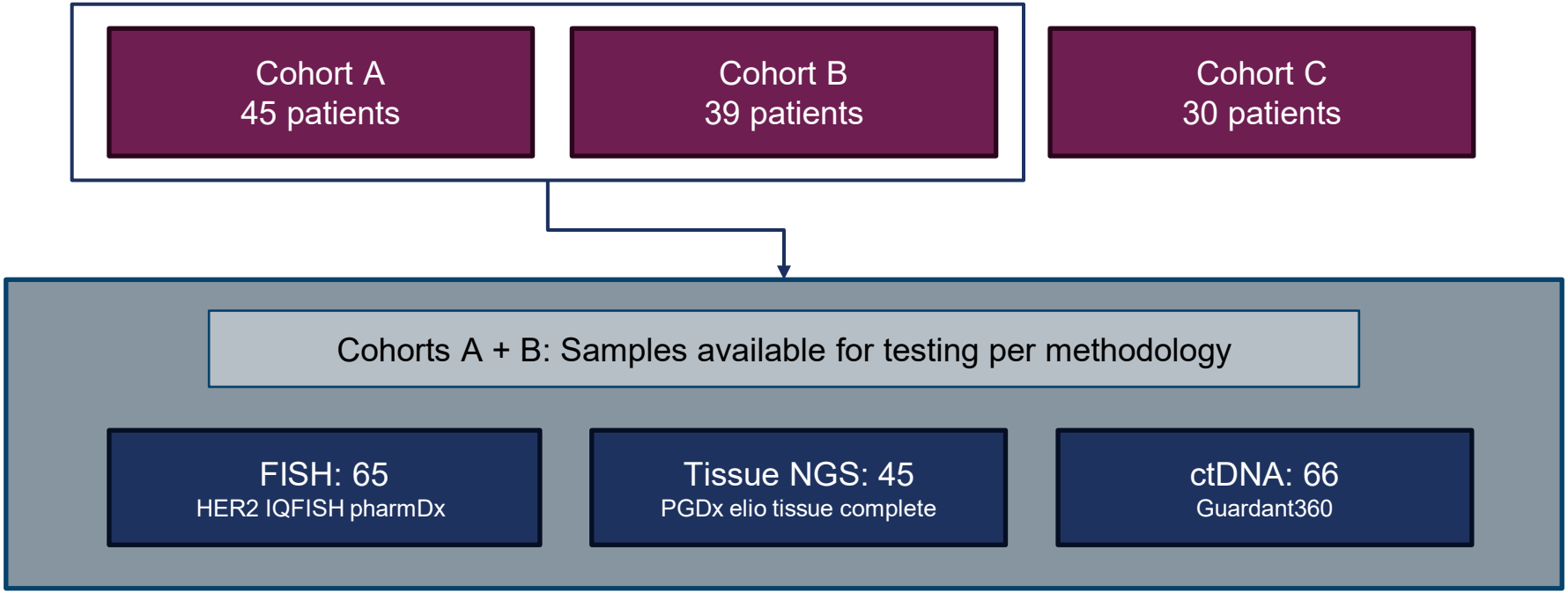
# Exploratory Biomarker Analyses




[a]Confirmed HER2-positive mCRC tested at CLIA-certified or ISO-accredited laboratory: IHC 3+ or 2+ with (F)ISH reflex by an FDA-approved or CE-marked test
[b]Analysis performed by sponsor-designated central laboratory
[c]Patients were required to have confirmed HER2 positive status via a retrospective HER2+ central lab test from one of the following methods: IHC/FISH, tissue NGS, or ctDNA
[d]cORR and DOR were calculated for SNVs and CNVs occurring in ≥5 patients; cORR was defined as the proportion of patients with complete response or partial response per RECIST v1.1 by BICR

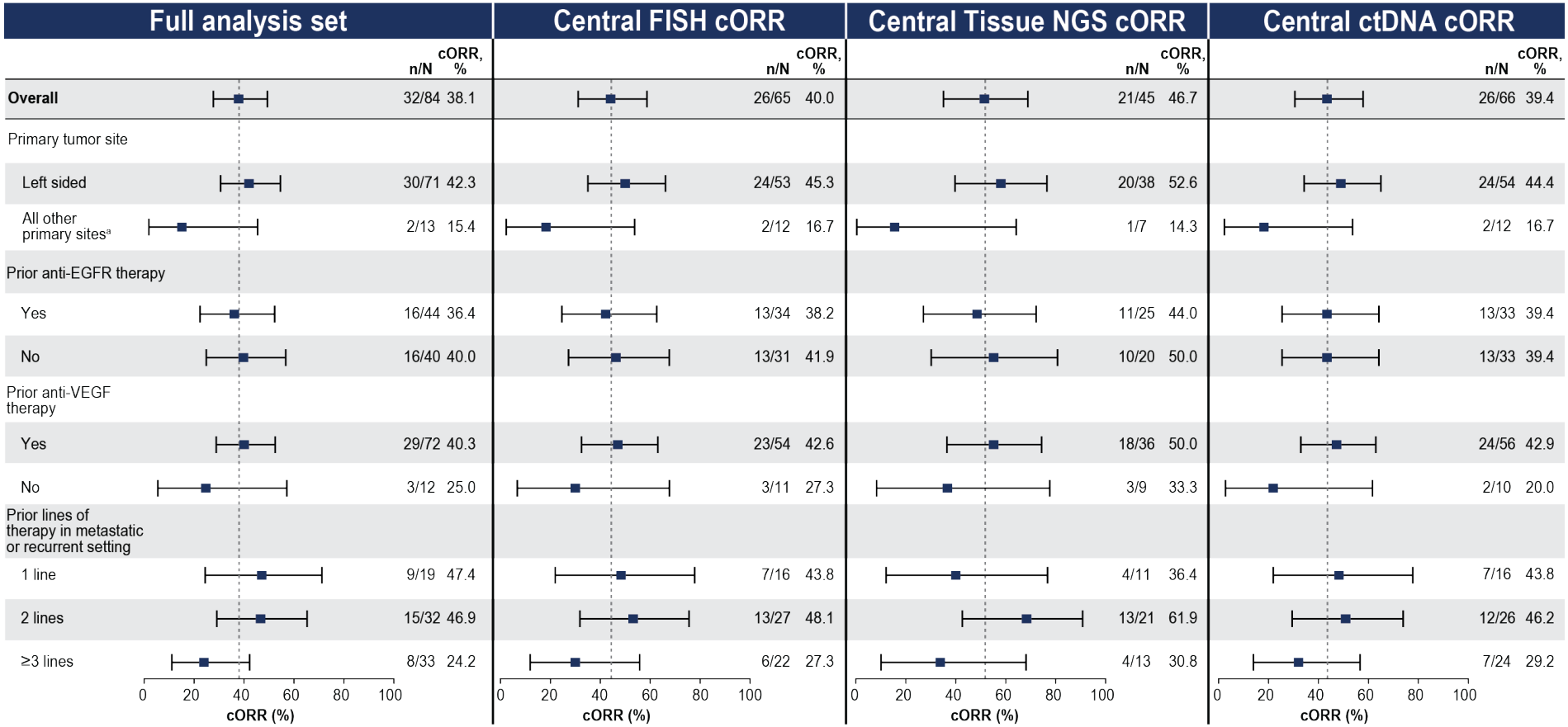
BICR, blinded independent central review; CEN17, centromere of chromosome 17; CNV; copy number variant; cORR, confirmed objective response rate; ctDNA, circulating tumor DNA; DOR, duration of response; EOT, end of treatment; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; RECIST; Response Evaluation Criteria in Solid Tumors; SNV, single nucleotide variant

# Results: Samples Available for Testing at Baseline




FISH testing utilized the gastric criteria for purposes of this analysis
Final sample sizes for FISH, Tissue NGS, and ctDNA consist of patients with ≥1 positive central test result regardless of modality
ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization

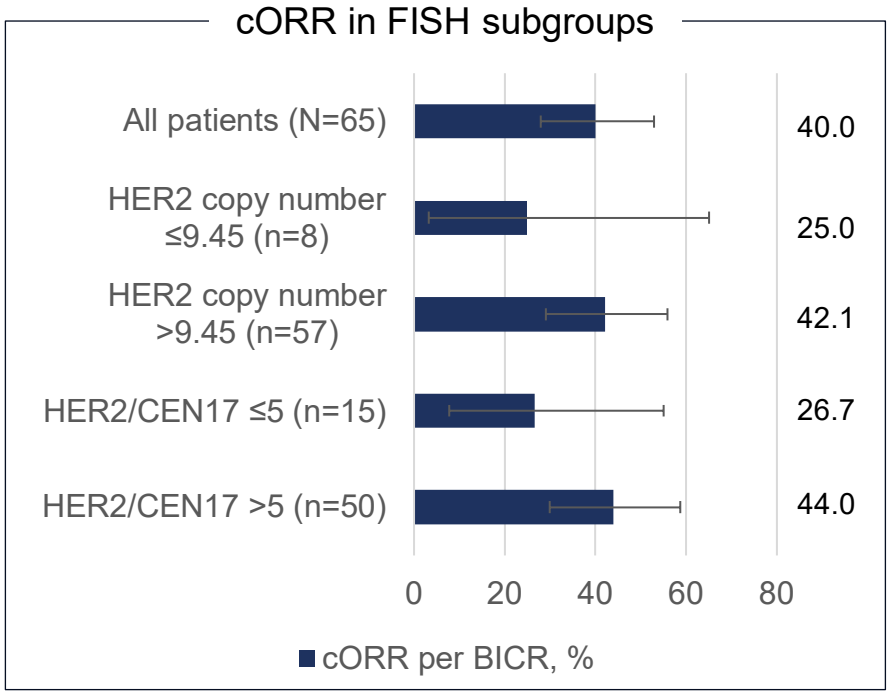
# cORR by Clinicopathologic features and Testing Method

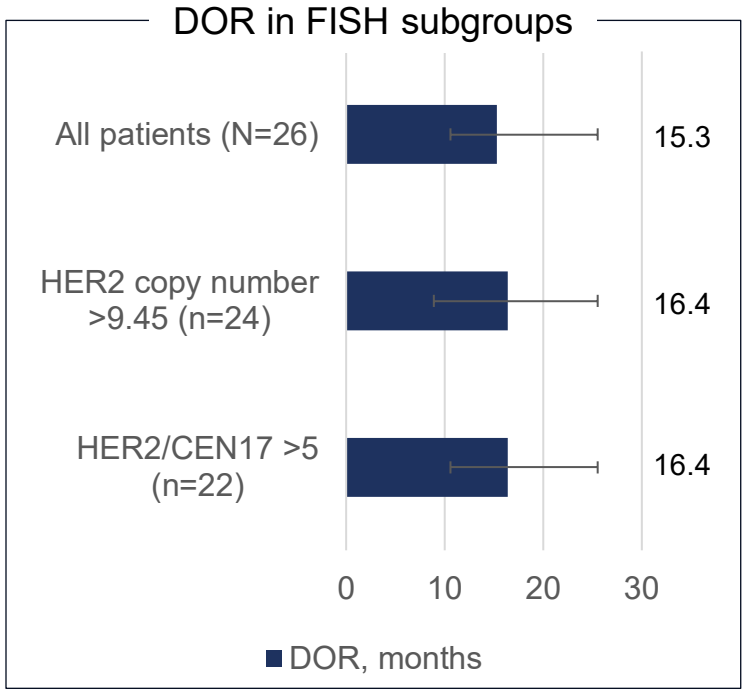



[a]Transverse, right-sided, and multiple primaries
cORR, confirmed objective response rate

# Tissue FISH Assay

## Impact of baseline HER2/CEN17 ratio and HER2 copy number




DOR subgroups not shown had <5 responders and analyses were not performed

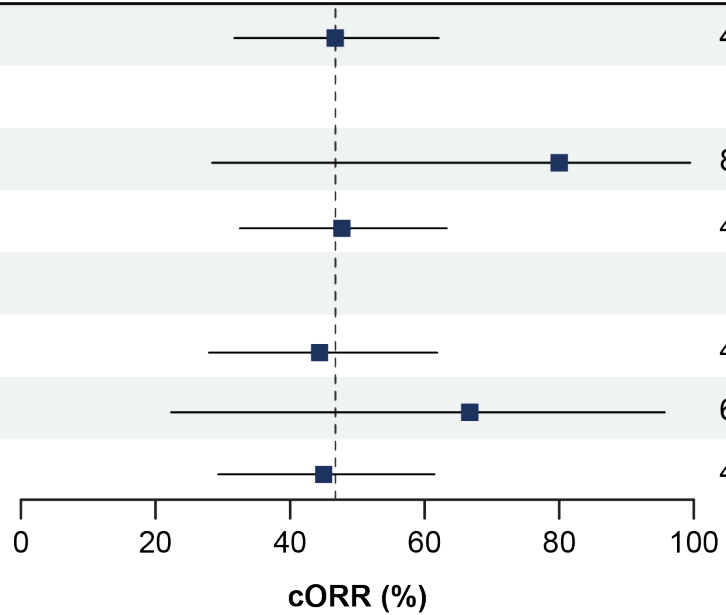
HER2 copy number of 9.45 used in Sartore-Bianchi A. Lancet Oncol. 2016;17(6):738-46; HER2/CEN17 ratio used in Raghav KPS. J Clin Oncol 41, 2023 (suppl4; abstr 140)

Error bars represent 95% CIs

CEN17, centromere of chromosome 17; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescence in situ hybridization

# Tissue NGS: Impact of Baseline Co-Amplifications and Co-Mutations

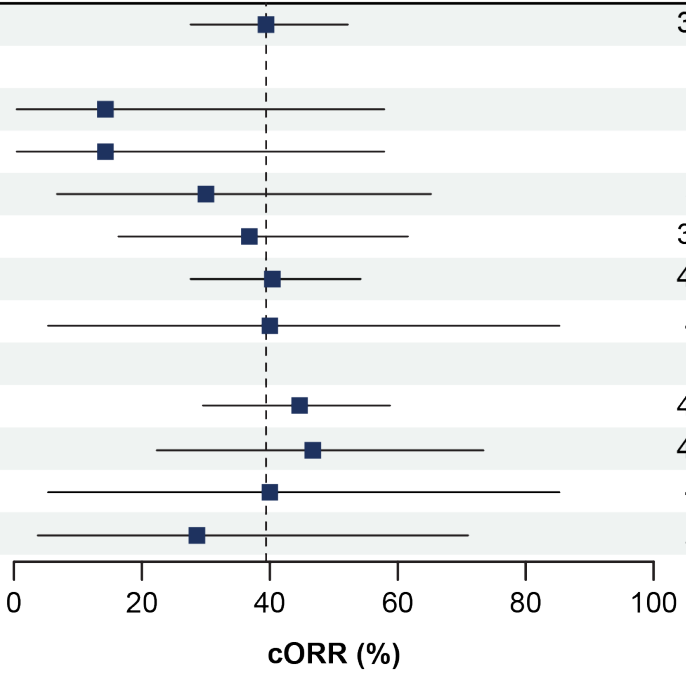
| Category | Total | Responders | cORR (95% CI) | DOR, months (95% CI) |
|---|---|---|---|---|
| Tissue NGS | 45 | 21 | 46.7 (31.7-62.1) | 15.3 (8.9-25.5) |
| **Amplifications** | | | | |
| BRCA2 | 5 | 4 | 80.0 (28.4-99.5) | – |
| ERBB2 | 44 | 21 | 47.7 (32.5-63.3) | 15.3 (8.9-25.5) |
| **Mutations** | | | | |
| APC | 36 | 16 | 44.4 (27.9-61.9) | 16.6 (6.1-NE) |
| ERBB2 | 6 | 4 | 66.7 (22.3-95.7) | – |
| TP53 | 40 | 18 | 45.0 (29.3-61.5) | 16.6 (8.9-NE) |




cORR was calculated for genomic alterations with a minimum sample size of 5 subjects. DOR was not calculated for genomic alterations with <5 responders
cORR, confirmed objective response rate; DOR, duration of response; NE, not evaluable; NGS, next-generation sequencing

# ctDNA NGS: Impact of Baseline Co-Amplifications and Co-Mutations

| Category | Total | Responders | cORR (95% CI) | DOR, months (95% CI) |
|---|---|---|---|---|
| ctDNA NGS | 66 | 26 | 39.4 (27.6-52.2) | 12.4 (8.3-20.5) |
| **Amplifications** | | | | |
| BRAF | 7 | 1 | 14.3 (0.4-57.9) | – |
| CCND1 | 7 | 1 | 14.3 (0.4-57.9) | – |
| CDK6 | 10 | 3 | 30.0 (6.7-65.2) | – |
| EGFR | 19 | 7 | 36.8 (16.3-61.6) | 12.5 (4.2-NE) |
| ERBB2 | 57 | 23 | 40.4 (27.6-54.2) | 12.4 (6.2-38.3) |
| PIK3CA | 5 | 2 | 40.0 (5.3-85.3) | – |
| **Selected Mutations*** | | | | |
| APC | 42 | 18 | 42.9 (27.7-59.0) | 15.3 (6.2-38.3) |
| ERBB2 | 15 | 7 | 47.1 (23.0-72.2) | 11.4 (6.1-NE) |
| KRAS/NRAS | 5 | 2 | 40.0 (5.3-85.3) | – |
| PIK3CA | 7 | 2 | 28.6 (3.7-71.0) | – |




cORR was calculated for genomic alterations with a minimum sample size of 5 subjects. DOR was not calculated for genomic alterations with <5 responders

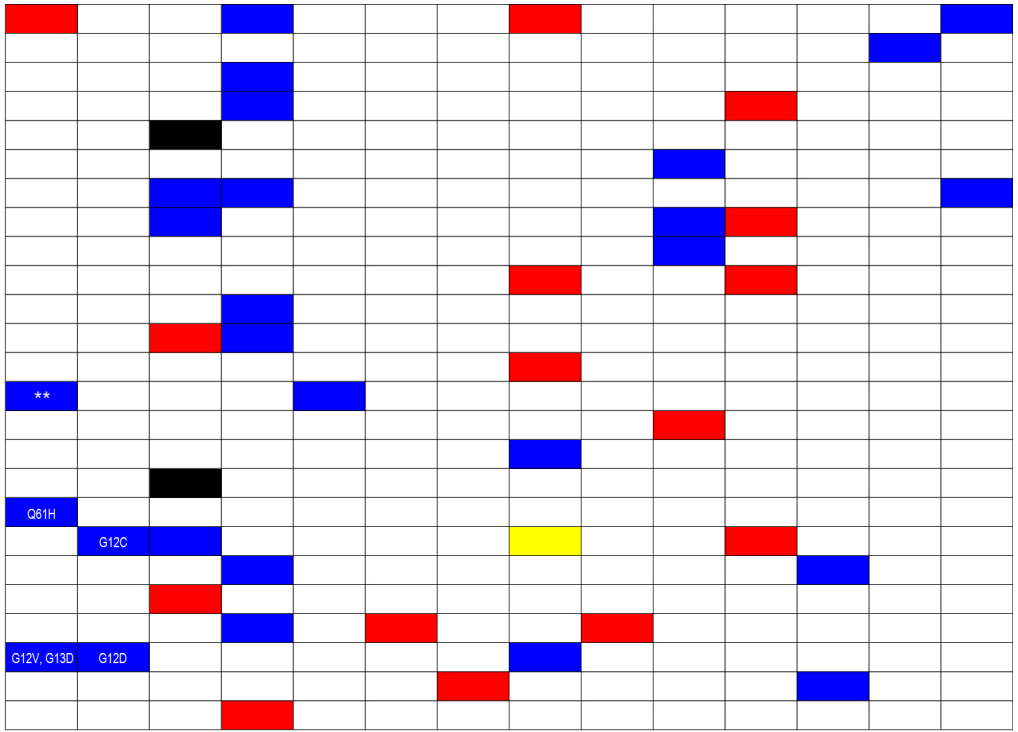
*Additional genes with ≥5 patients with mutations (gene, responders/total): CDK12 6/11; BRCA2 4/6; BRCA1 1/5; FBXW7 4/6; ATM 1/6. For CDK12, DOR (95% CI) is 12.5 (4.2-NE).2 patients had KRAS mutations and 0/2 were responders; 3 patients had NRAS mutations and 2/3 were responders.

ctDNA, circulating tumor DNA; cORR, confirmed objective response rate; DOR, duration of response; NE, not evaluable; NGS, next-generation sequencing

# ctDNA NGS: Genomic Landscape of Acquired Alterations at Progression Timepoint or EOT

| Response | PFS |
|---|---|
| PR | 16.5 |
| PR | 15.2 |
| PR | 13.1 |
| PR | 12.6 |
| PR | 12.5 |
| PR | 10.3 |
| PR | 8.3 |
| PR | 8.3 |
| SD | 8.1 |
| PR | 8.1 |
| PR | 8 |
| PR | 6.8 |
| SD | 4.4 |
| SD | 3.1 |
| SD | 2.8 |
| SD | 2.7 |
| SD | 2.7 |
| SD | 2.6 |
| SD | 2.6 |
| SD | 2.6 |
| SD | 2.1 |
| PD | 2.1 |
| PD | 1.7 |
| PD | 1.5 |
| PD | 1.1 |

**KRAS G13C, G12C, I24N




n=31; 1 patient removed from analysis due to no detected alterations at baseline, leading to analysis set of 30; 23/30 showed alteration gains; 2/30 showed ERBB2 loss; 5/30 showed no alteration gains and no ERBB2 loss.

- SNV/INDEL
- Amplification
- SNV/INDEL and amplification
- Loss of amplification

Note: a single BLUE or YELLOW box can represent multiple SNV/INDEL detections in the same gene

DDR: DNA Damage Response; EOT, end of treatment; PFS, progression-free survival; RTK: Receptor Tyrosine Kinase; SNV, single nucleotide variation

# Conclusions

- In this exploratory analysis, TUC+Tras had broad clinical activity in all clinicopathologic and genomic subgroups
- Earlier lines of treatment (≤2L), left sided primary tumors, higher gene copy number, and increased HER2/CEN17 ratio might be associated with greater clinical benefit – additional study is needed
- In the baseline tissue and ctDNA NGS analysis, *RAS* and *ERBB2* mutations did not predict primary treatment resistance
- At the time of progression (EOT), ctDNA demonstrated the following patterns:
  - Most patients acquired multiple heterogeneous resistance alterations
  - Common acquired genomic alterations included *PIK3CA*, *RTKs*[a], and *KRAS/NRAS*
  - Loss of *ERBB2* amplification was rare
- Understanding the genomic drivers of primary and acquired resistance may inform future therapeutic opportunities



[a]EGFR, FGFR1, FGFR2, MET

CEN17, centromere of chromosome 17; ctDNA; circulating tumor DNA; DOR, duration of response; EOT, end of treatment; FISH, fluorescence in situ hybridization

# Acknowledgement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**European Society for Medical Oncology (ESMO)**
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

**esmo.org**