HER2 in colorectal cancer

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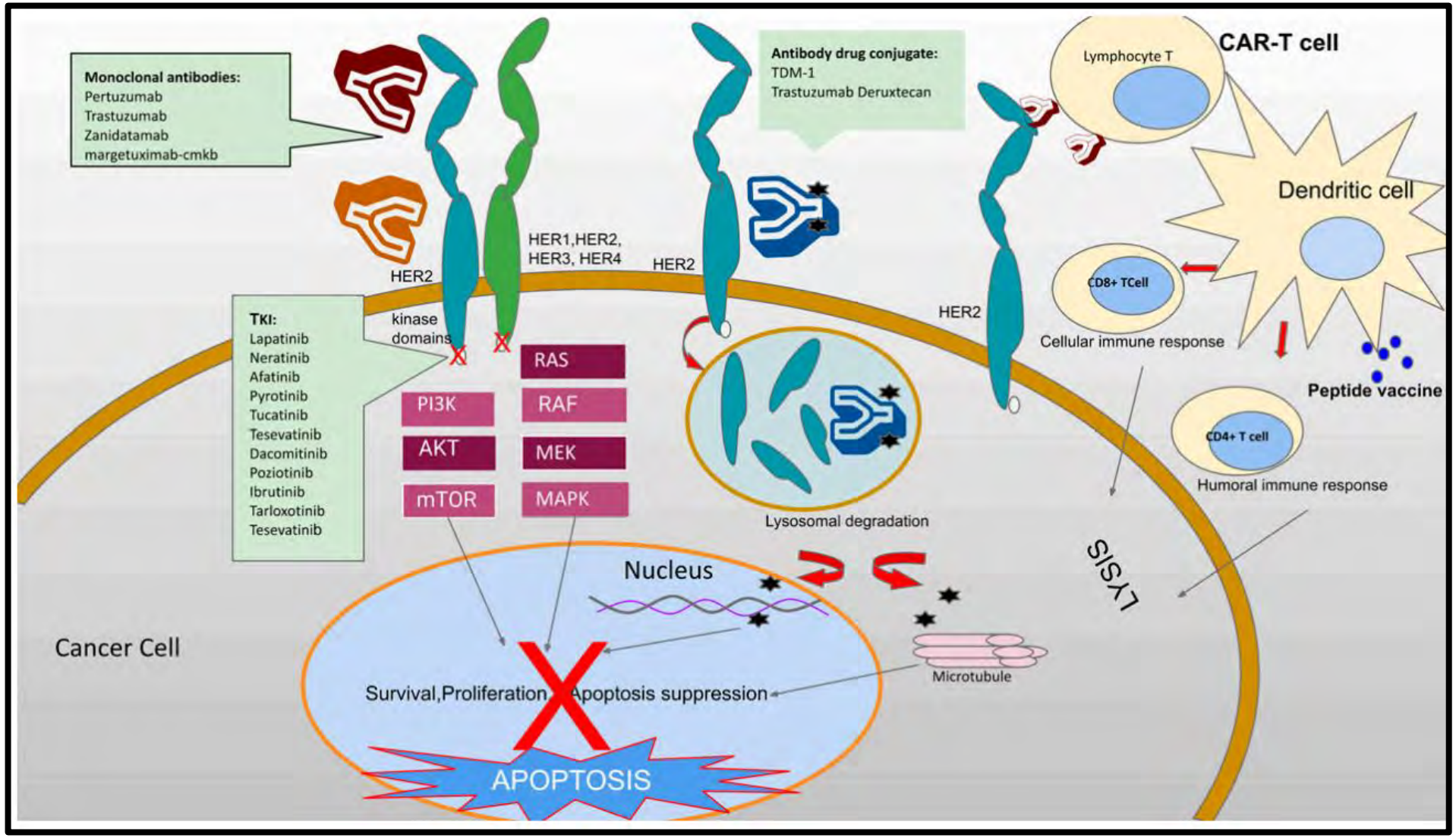
Disclosures

- **Speaker's bureau, consulting, advisory role or travel/conference**:
  - Bristol-Myers Squibb;
  - Ipsen
  - Merck Sharp & Dohme Corp.;
  - AstraZeneca.
  - A2Bio
  - Moderna

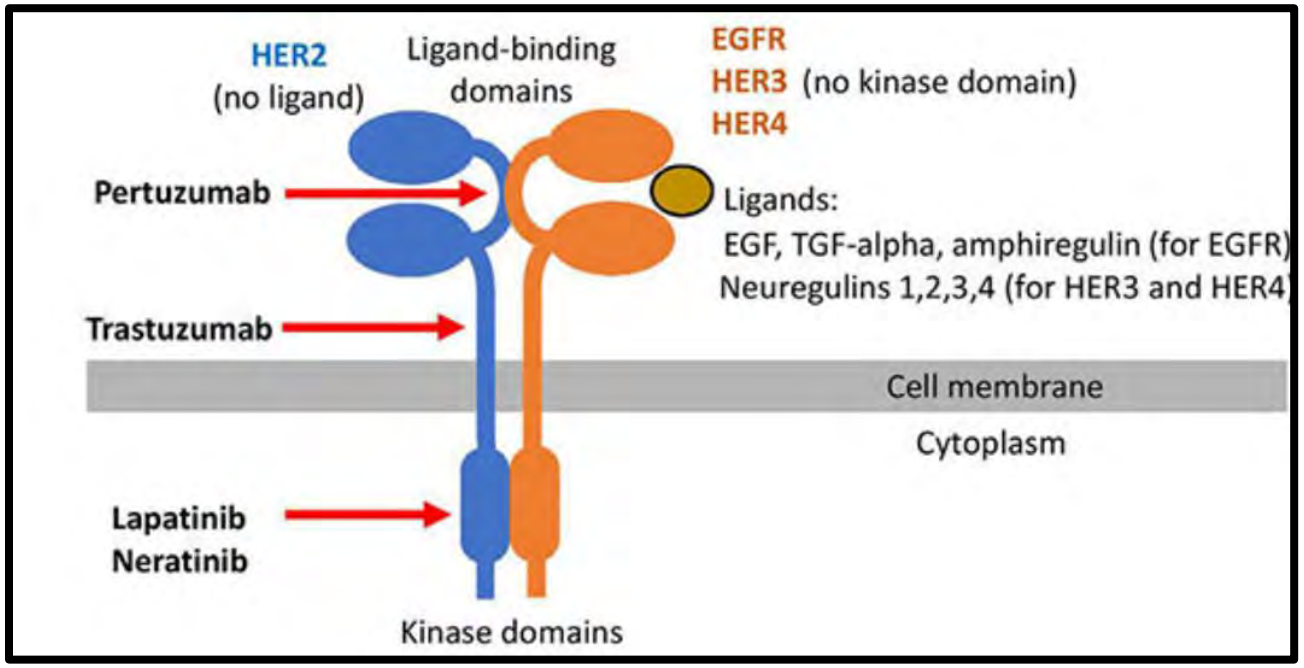
Background



Djaballah SA, et al. Am Soc Clin Oncol Educ Book. 2022;42:1–14.

HER2 in CRC

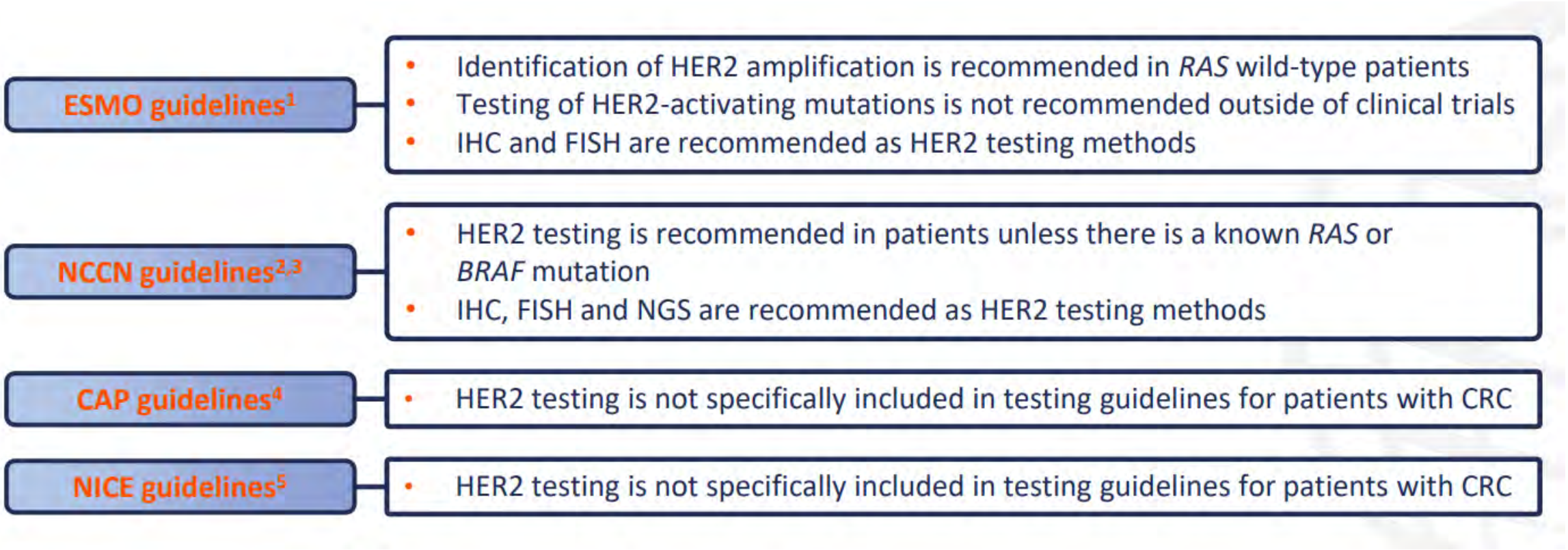
- A proto-oncogene (also known as ERBB2), located on chromosome 17q21
- Encodes for a transmembrane glycoprotein receptor with tyrosine kinase activity
- Linked to resistance to anti-EGFR therapies
- HER2 overexpression in 2% of all CRCs
- In 5–6% of stage IV KRAS wild-type CRCs
- Higher prevalence in patients with left-sided tumors



Djaballah SA, et al. Am Soc Clin Oncol Educ Book. 2022;42:1–14.

HER2 testing

Guidelines

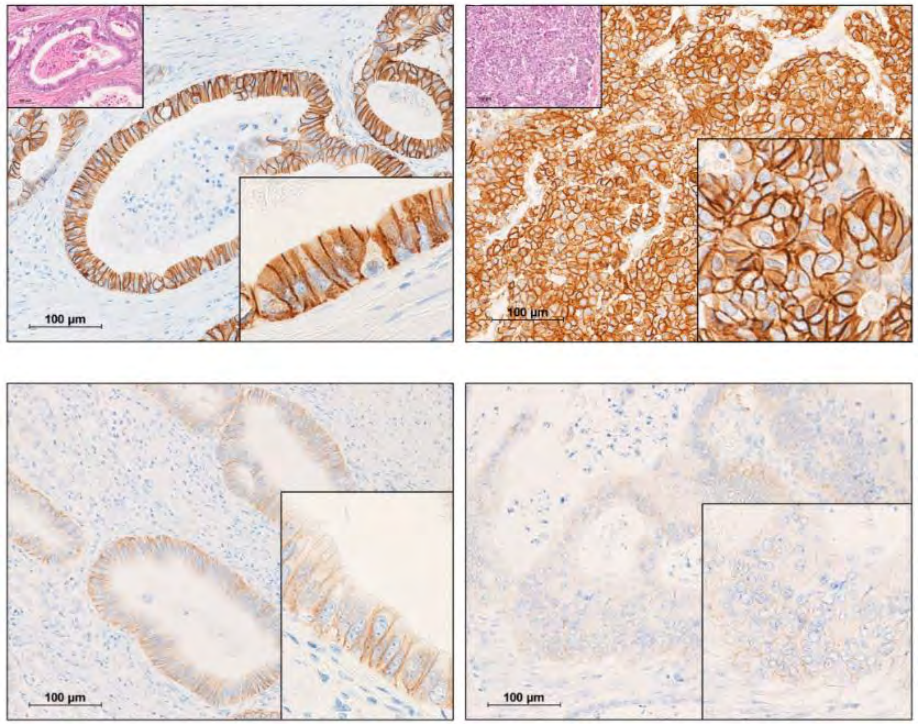


1) Cervantes A, et al. Ann Oncol. 2023;34:10–32.
2) NCCN. Colon cancer. V2.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
3) NCCN. Rectal cancer. V2.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
4) CAP. 2017. Available at: https://documents.cap.org/documents/colorectal-cancer-recommendations.
5) NICE. 2020. Available at: www.nice.org.uk/guidance/ng151/evidence/b1-use-of-molecular-biomarkers-to-guide-systemic-therapy-pdf-7029391215.

HERACLES criteria vs GE criteria

- In bold are the areas where the interpretation or subsequent testing/clinical consequences differ.
- Both sets of criteria recognize lateral membrane and basolateral staining as potentially positive staining patterns.

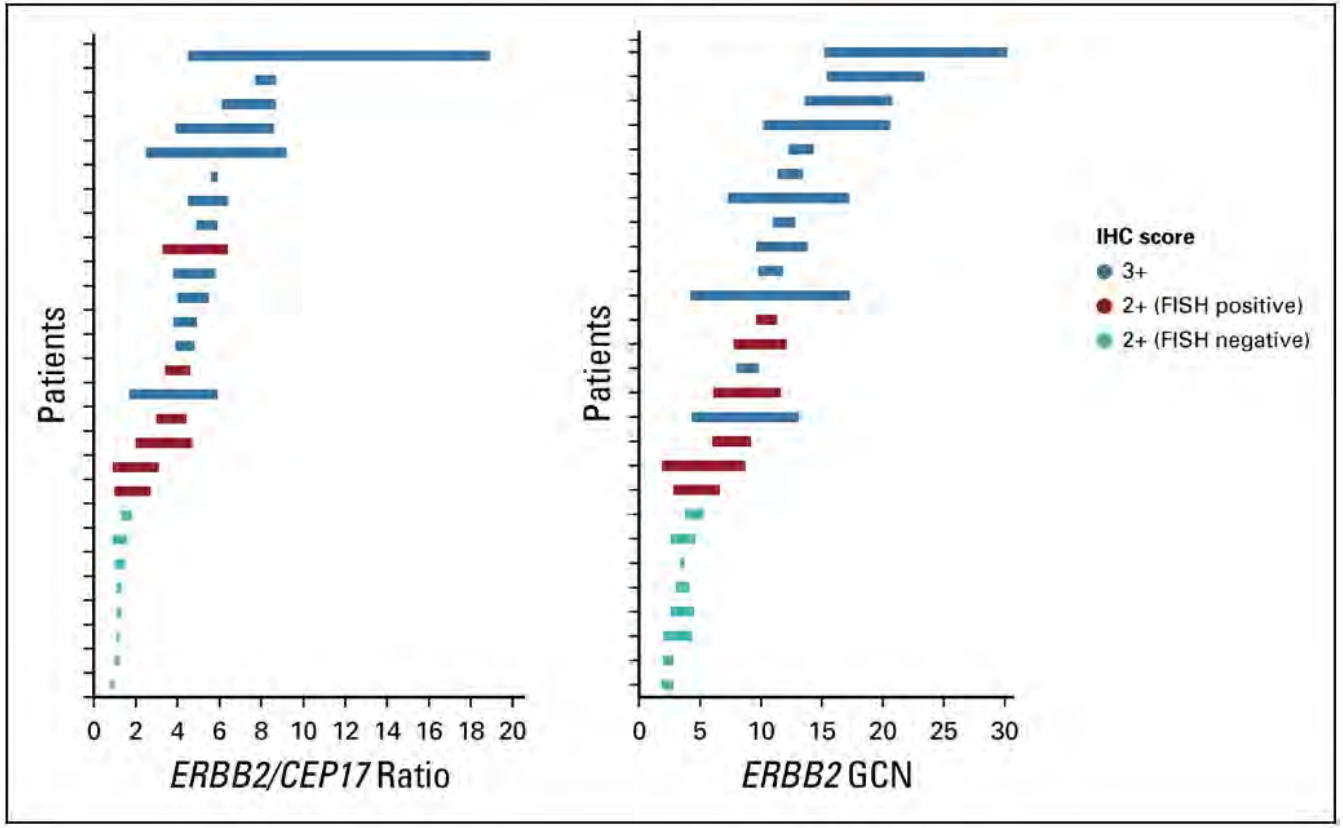
HER2 IHC Result	CAP/ASCP/ASCO Gastroesophageal Adenocarcinoma Guideline Interpretation (for resections)	Consequence	HERACLES Diagnostic Criteria Interpretation	Consequence
No reactivity or membranous reactivity in <10% of tumor cells	Negative (0)	No further testing required; not eligible for therapy	Negative	No further testing required; not eligible for therapy
Faint/barely perceptible reactivity in ≥10% of tumor cells	Negative (1+)	No further testing required; not eligible for therapy	Negative	No further testing required; not eligible for therapy
Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% but <50% of tumor cells	**Equivocal (2+)**	Perform ISH testing	**Negative**	No further testing required; not eligible for therapy
Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥ 50% of tumor cells	Equivocal (2+)	Perform ISH testing	Equivocal	**Mandatory IHC retesting to confirm staining in ≥50% of cells;** ISH testing required; eligible for therapy if ISH positive
Strong complete, basolateral, or lateral membrane staining in 10–50% of tumor cells	**Positive (3+)**	Eligible for therapy; no further testing required	**Conditionally positive**	**Mandatory IHC retesting to confirm staining in ≥10% of cells;** ISH testing required; eligible for therapy if ISH positive
Strong complete, basolateral, or lateral membrane staining in >50% of tumor cells	Positive (3+)	Eligible for therapy; no further testing required	Positive	Eligible for therapy; no further testing required



CAP today. Available at: https://www.captodayonline.com/qa-column-0220/

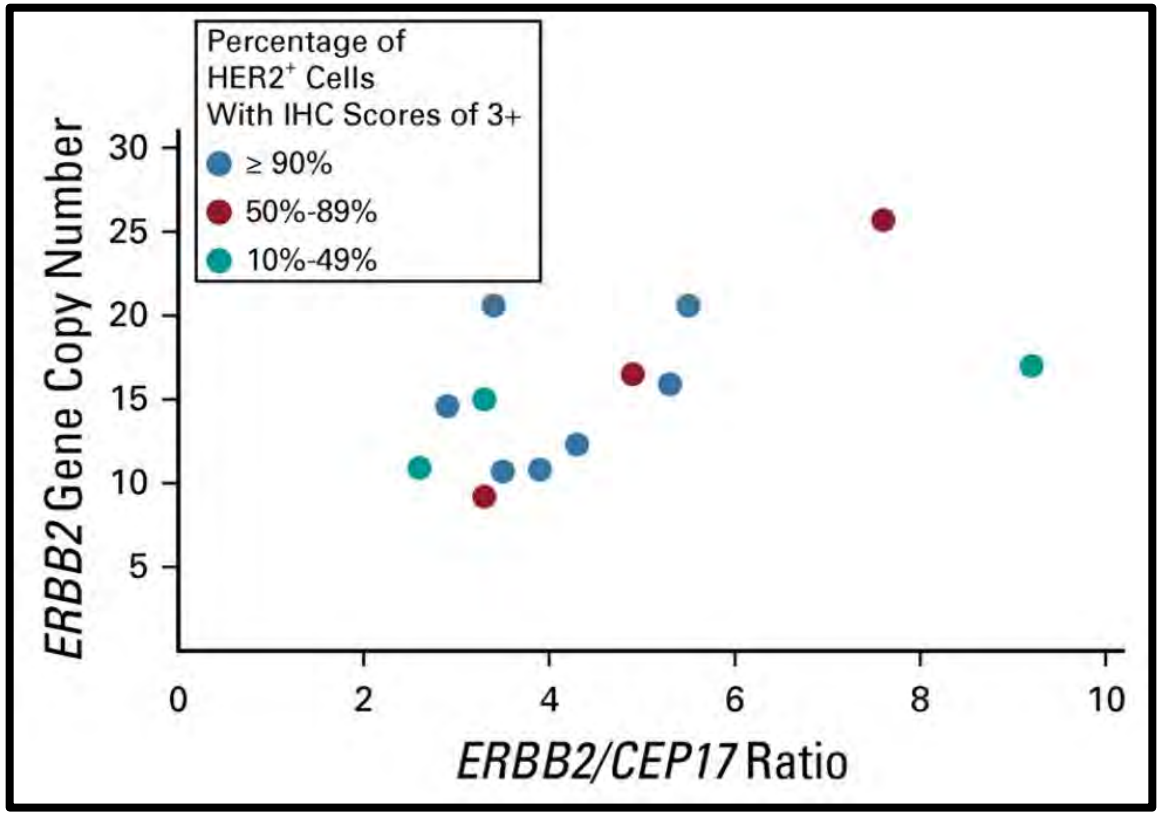
IHC, ISH and NGS correlation

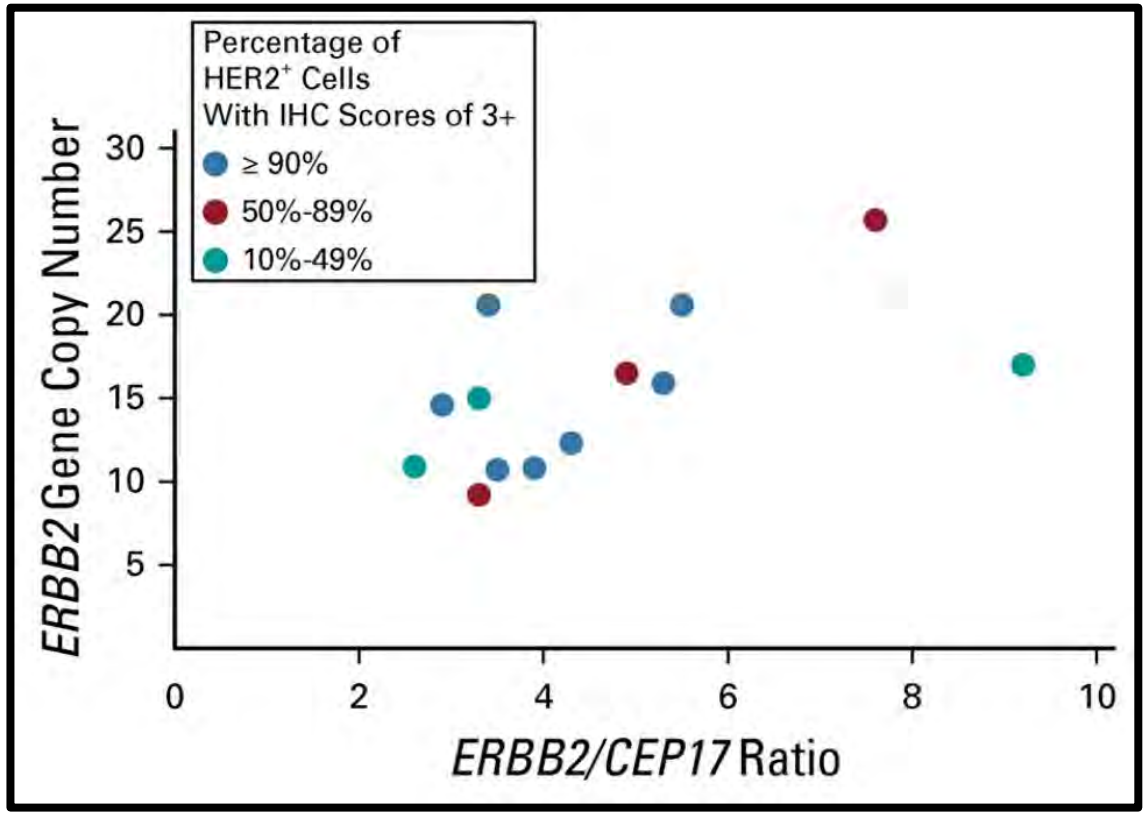
- ❑ Different trials with different eligibility criteria: HERACLES - IHC and FISH, MyPathway - IHC, FISH and NGS;
- ❑ Favor surgical samples if possible due to heterogeneous expression;
- ❑ CNV of ≥ 5.0: HER2 positive tumors (IHC/FISH), CNV of 4.0-4.9 needed to be confirmed by IHC/FISH



Fujii S et al. JCO Precis Oncol. 2020 Nov;4:6-19.

IHC, ISH and NGS correlation





Fujii S et al. JCO Precis Oncol. 2020 Nov;4:6-19.

IHC, ISH and NGS correlation

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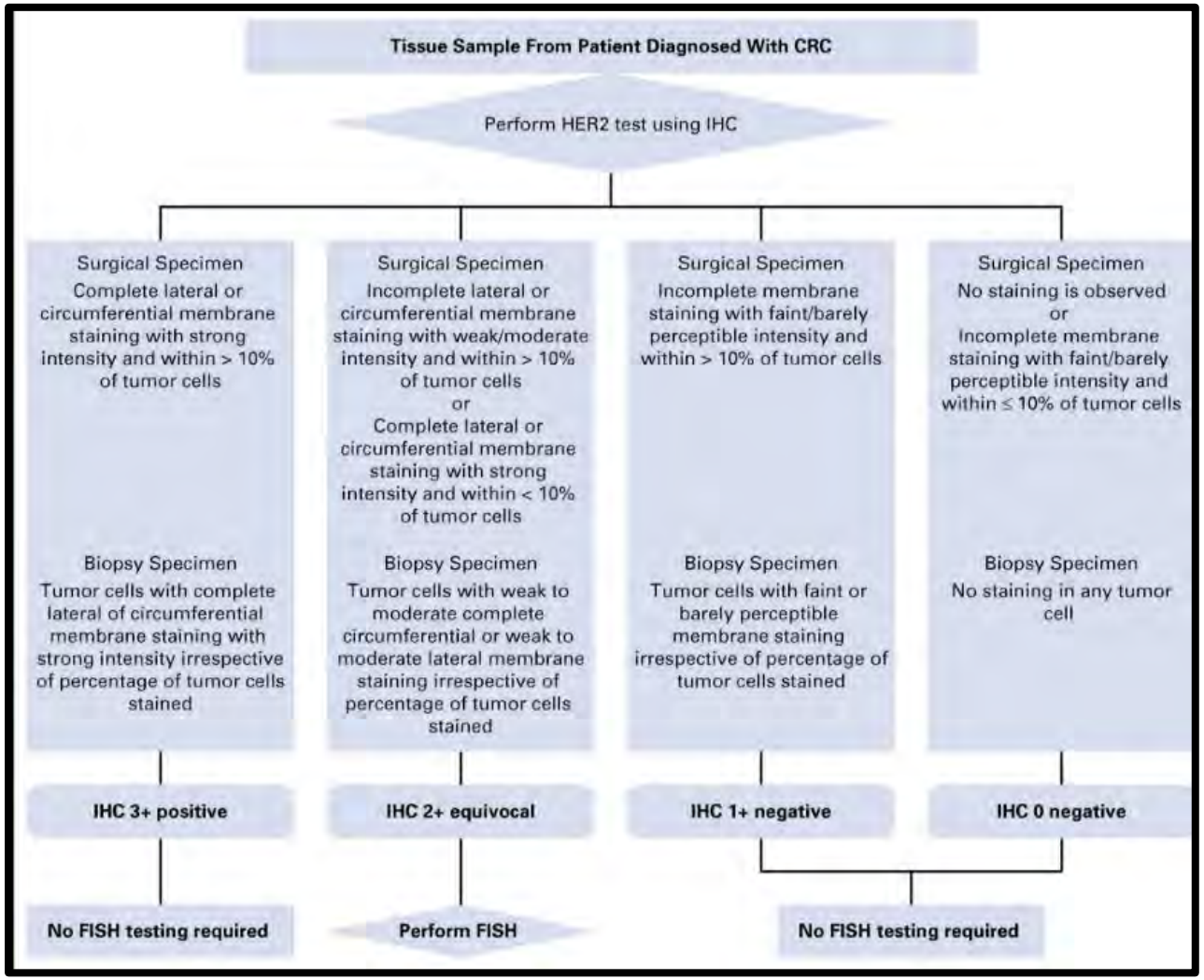
ORIGINAL REPORTS | January 07, 2020

International Harmonization of Provisional Diagnostic Criteria for *ERBB2*-Amplified Metastatic Colorectal Cancer Allowing for Screening by Next-Generation Sequencing Panel

Authors: Satoshi Fujii, MD, PhD, Anthony M. Magliocco, MD, FRCPC, FCAP, Jihun Kim, MD, PhD, Wataru Okamoto, MD, PhD, Jeong Eun Kim, MD, PhD, Kentaro Sawada, MD, PhD, Yoshiaki Nakamura, MD, PhD, ... SHOW ALL ..., and Takayuki Yoshino, MD, PhD AUTHORS INFO & AFFILIATIONS

Publication: JCO Precision Oncology • Volume 4 • https://doi.org/10.1200/PO.19.00154



Fujii S et al. JCO Precis Oncol. 2020 Nov;4:6-19.

NCCN recommendation

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Colon Cancer

PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

HER2 Testing

- **Diagnostic testing is via IHC, fluorescence in situ hybridization (FISH), or NGS.**
- **Positive by IHC is defined as: 3+ staining in more than 50% of tumor cells. 3+ staining is defined as an intense membrane staining that can be circumferential, basolateral, or lateral. Those who have a HER2 score of 2+ should be reflexed to FISH testing.[62-64] HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥2 in more than 50% of the cells.[62-64] NGS is another methodology for testing for HER2 amplification.[65]**
- **Anti-HER2 therapy with signal transduction inhibition (eg, trastuzumab/pertuzumab, trastuzumab/tucatinib, trastuzumab/lapatinib) is only indicated in HER2-amplified tumors that are also *RAS* and *BRAF* wild-type.**
- **Fam-trastuzumab deruxtecan-nxki is only indicated in HER2-amplified tumors (IHC 3+).**

NCCN Guidelines Version 5.2024 Colon Cancer.

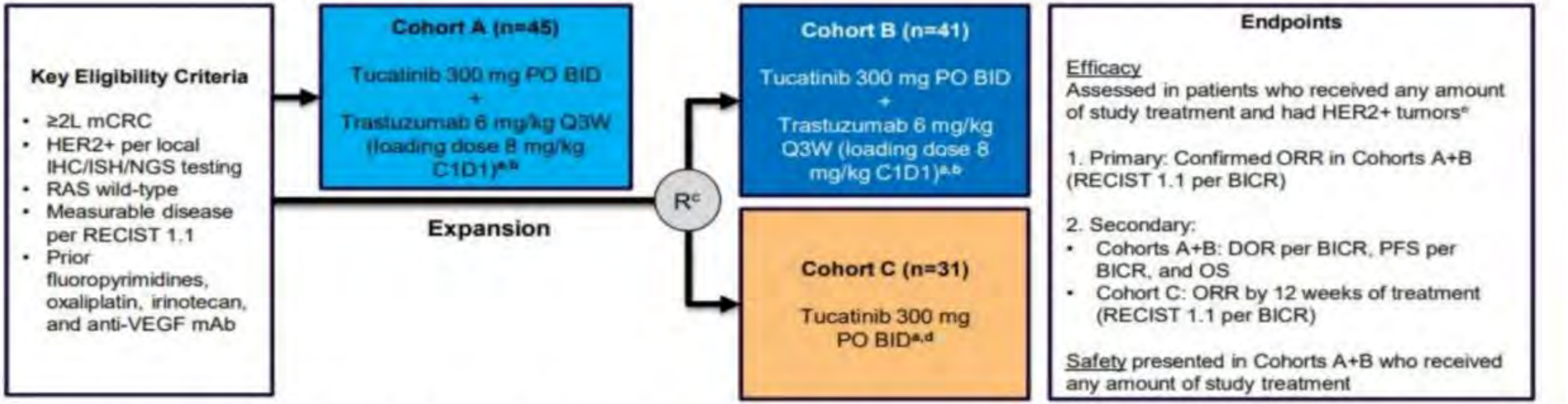
HER2 therapies

Treatment guidelines

Trial and Design	Treatment Arms	Eligibility Criteria	Line of Treatment	Results
HERACLES-A phase II (single arm)	Trastuzumab plus lapatinib	HERACLES diagnostic criteria by IHC and FISH, KRAS exon 2 (codon 12 and 13) wild-type	≥ second	ORR: 30% mPFS: 21 weeks mOS: 46 weeks
HERACLES-B phase II (single arm)	Pertuzumab plus T-DM1	HERACLES diagnostic criteria by IHC and FISH, RAS wild-type	≥ second	ORR: 9.7% mPFS: 4.1 months mOS: not reported
My pathway phase II (basket trial)	Trastuzumab plus pertuzumab	HER2 overexpression and/or amplification by CISH, FISH, or NGS, RAS wild-type	≥ second	ORR: 32% mPFS: 2.9 months mOS: 11.5 months
Triumph phase II (single arm)	Trastuzumab plus pertuzumab	The patients who received standard therapy (including HER2-targeted therapy) with HER2 amplification by IHC and/or FISH on tissue and/or ctDNA	≥ second	Tissue-positive patients: ORR: 30% mPFS: 4 months mOS: 10.1 months ctDNA-positive patients: ORR: 28% mPFS: 3.1 months mOS: 8.8 months

Karan C, et al. JCO Oncol Pract. 2022;18:545–54.

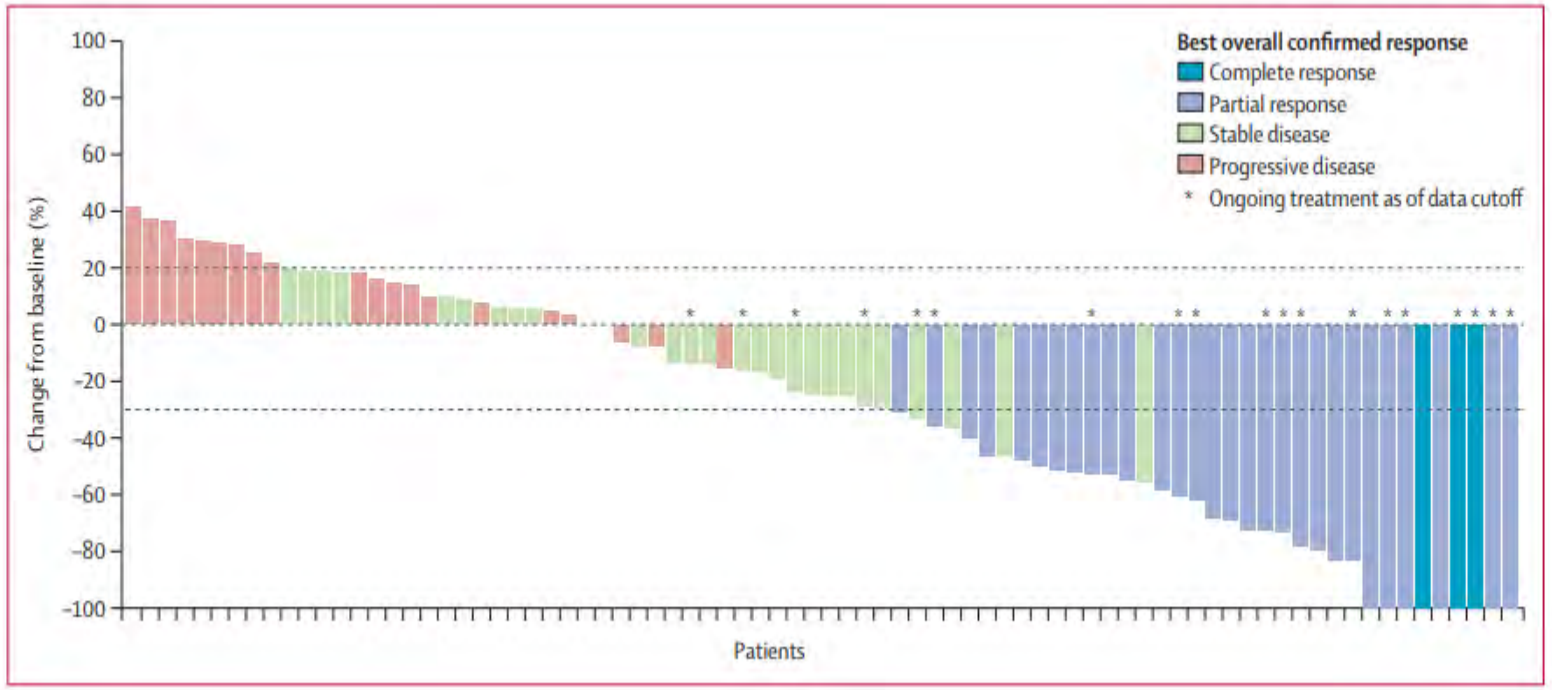
MOUNTAINEER trial



MOUNTAINEER began as a US investigator-sponsored trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomized to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Strickler JH et al. Lancet Oncol. 2023 May;24(5):496-508.

MOUNTAINEER trial



	Tucatinib plus trastuzumab (cohorts A and B; n=84)
Confirmed objective response rate (95% CI)*	38·1% (27·7–49·3)
Complete response†	3 (4%)
Partial response†	29 (35%)
Stable disease†‡	28 (33%)
Progressive disease†	22 (26%)
Not available§	2 (2%)
Disease control rate (post hoc)¶	60 (71%)
Median duration of response, months (IQR)	12·4 (8·3–25·5)

ORR: 38.1%

mPFS: 8.2 months

mOS: 24.1 months

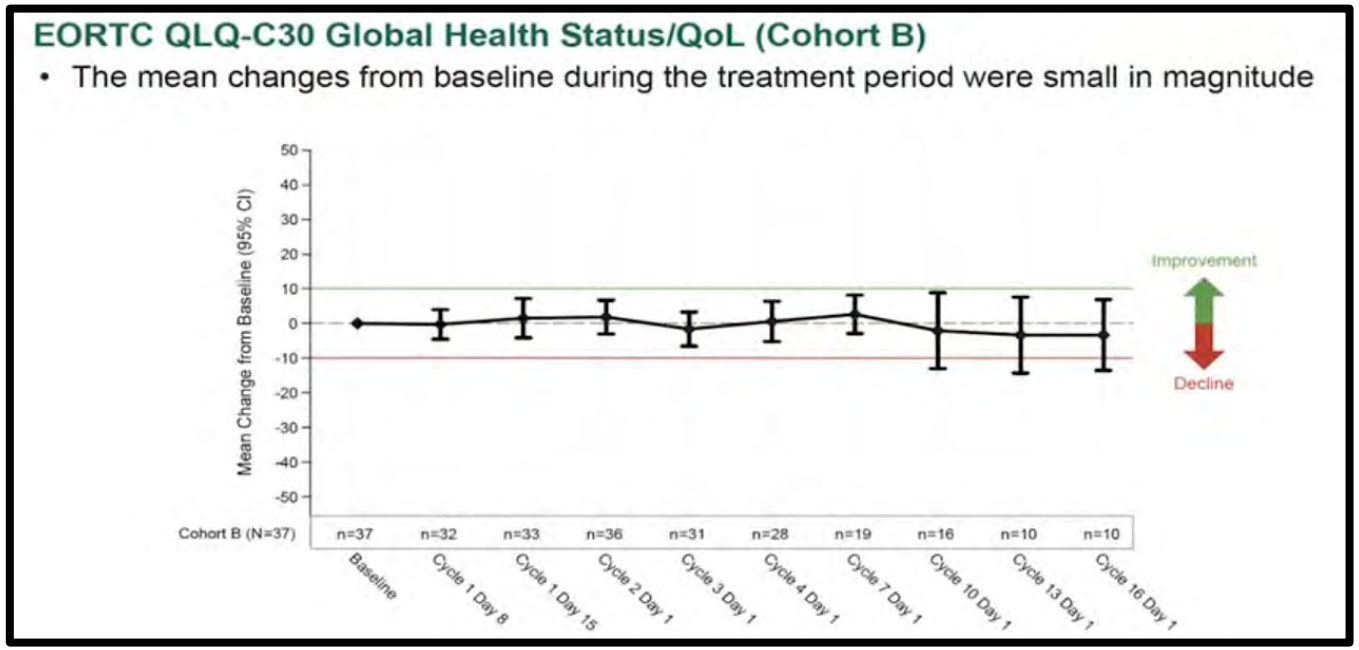
- ORR in cohort C (tucatinib monotherapy): 3.3%

- Pts in combination therapy with centrally confirmed HER2 status: ORR 46% for IHC 3+ and 20% with IHC 2+/FISH+

Strickler JH et al. Lancet Oncol. 2023 May;24(5):496-508.

MOUNTAINEER trial

	Grade 1–2	Grade 3	Grade 4
Any adverse event	20 (67%)	8 (27%)	0
Diarrhoea	10 (33%)	0	0
Abdominal pain	6 (20%)	0	0
Fatigue	6 (20%)	0	0
Asthenia	5 (17%)	0	0
Nausea	5 (17%)	0	0
Urinary tract infection	4 (13%)	1 (3%)	0
Constipation	4 (13%)	0	0
Decreased appetite	3 (10%)	1 (3%)	0
Headache	3 (10%)	0	0
Stomatitis	3 (10%)	0	0
Decreased weight	3 (10%)	0	0
Hypokalaemia	2 (7%)	1 (3%)	0
Pyrexia	2 (7%)	1 (3%)	0
Increased aspartate aminotransferase	1 (3%)	2 (7%)	0
Increased alanine aminotransferase	0	2 (7%)	0
Cholecystitis	0	1 (3%)	0
Duodenal obstruction	0	1 (3%)	0
Flank pain	0	1 (3%)	0
Kidney infection	0	1 (3%)	0
Pyelonephritis	0	1 (3%)	0



Strickler JH et al. Lancet Oncol. 2023 May;24(5):496-508.

MOUNTAINEER trial – HER2 testing

	Central IHC + FISH (n = 70)			PGDx tissue NGS (n = 50)		Guardant ctDNA (n = 71)	
Response	Positive (IHC3+) (n = 45)	Positive (IHC2+/ ISH+) (n = 15)	Negative (n = 10)	Positive (n = 44)	Negative (n = 6)	Positive (n = 56)	Negative (n = 15)
CR	3	0	0	1	0	1	1
PR	18	3	1	20	0	22	2
SD[a]	17	5	4	16	2	18	7
PD	7	6	5	7	4	14	4
NA	0	1	0	0	0	1	1
cORR, n, (%) (95% CI)	**21, (46.7%)** (31.7-62.1)	**3, (20.0%)** (4.3-48.1)	**1, (10.0%)** (0.3-44.5)	**21, (47.7%)** (32.5-63.3)	**0, (0%)** (0-45.9)	**23, (41.1%)** (28.1-55)	**3, (20.0%)** (4.3-48.1)
mDOR, months (95% CI)	**16.4** (10.6, 25.5)		-	**15.3** (8.9, 25.5)	-	**12.4** (6.2, 38.3)	-
mPFS, months (95% CI)	**10.1** (4.2, 15.2)		**2.8** (1.2, 6.3)	**10.9** (7.0, 20.7)	**2.1** (1.3, -)	**8.1** (3.1, 10.2)	**10.9** (2.0, 18.4)

- **HER2 testing concordance:**
- 81.0% (95%CI, 68.6-90.1) between blood and tissue NGS
- 92.6% (95%CI,83.7-97.6) between IHC/FISH and tissue NGS
- 79.5% (95%CI,69.2-87.6) between IHC/FISH and blood NGS

Strickler JH et al. Meeting Abstract: 2023 ASCO Annual Meeting.

DESTINY-CRC 01 trial

	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A *n* = 53	HER2 IHC 2+/ISH− Cohort B *n* = 15	HER2 IHC 1+ Cohort C *n* = 18
Confirmed ORR by ICR	24 (45.3) [95% CI, 31.6–59.6]	0 [95% CI, 0.0–21.8]	0 [95% CI, 0.0–18.5]
Complete response	0	0	0
Partial response	24 (45.3)	0	0
Stable disease	20 (37.7)	9 (60.0)	4 (22.2)
Progressive disease	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
DCR	83.0 (70.2–91.9)	60.0 (32.3–83.7)	22.2 (6.4–47.6)
Median DoR, months	7.0 (5.8–9.5)	NE (NE–NE)	NE (NE–NE)
Median treatment duration, months	5.1 (3.9–7.6)	2.1 (1.4–2.6)	1.4 (1.3–1.5)

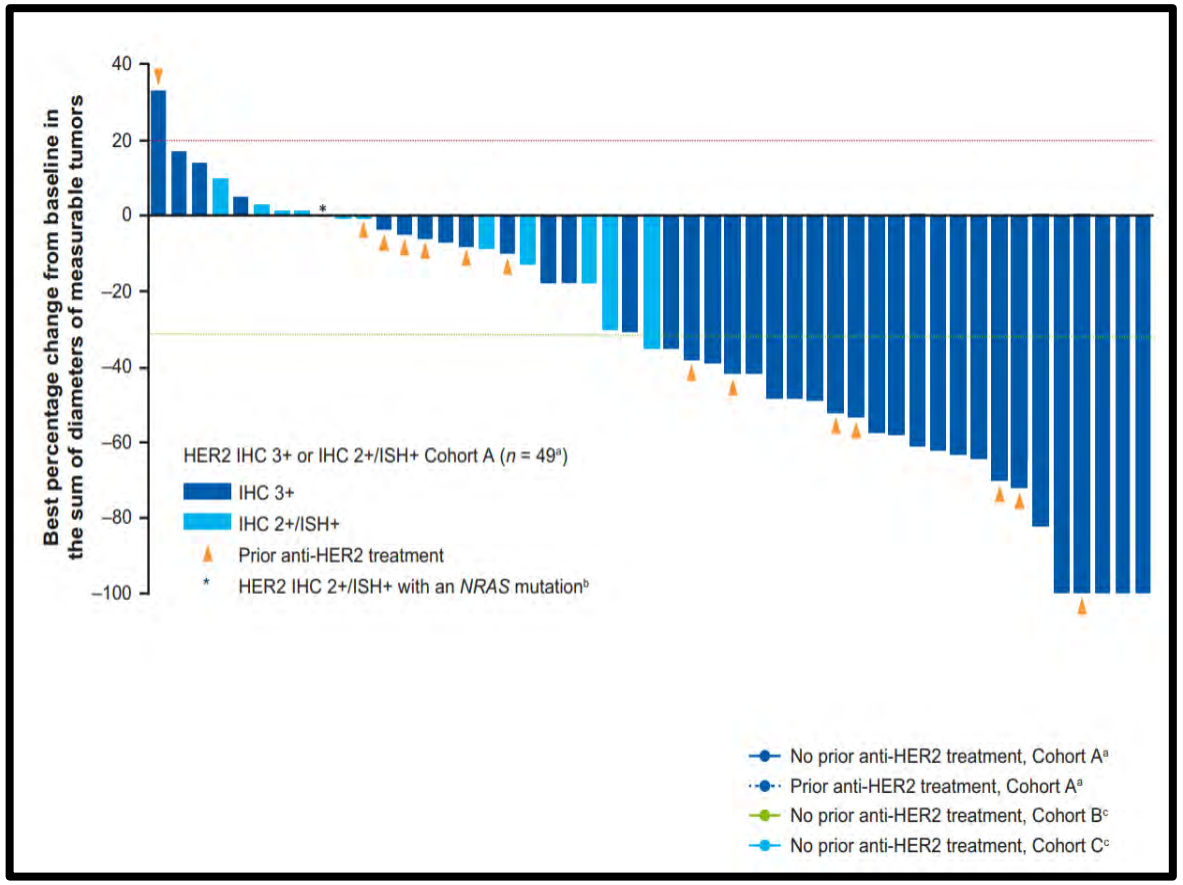
ORR: 45.3%

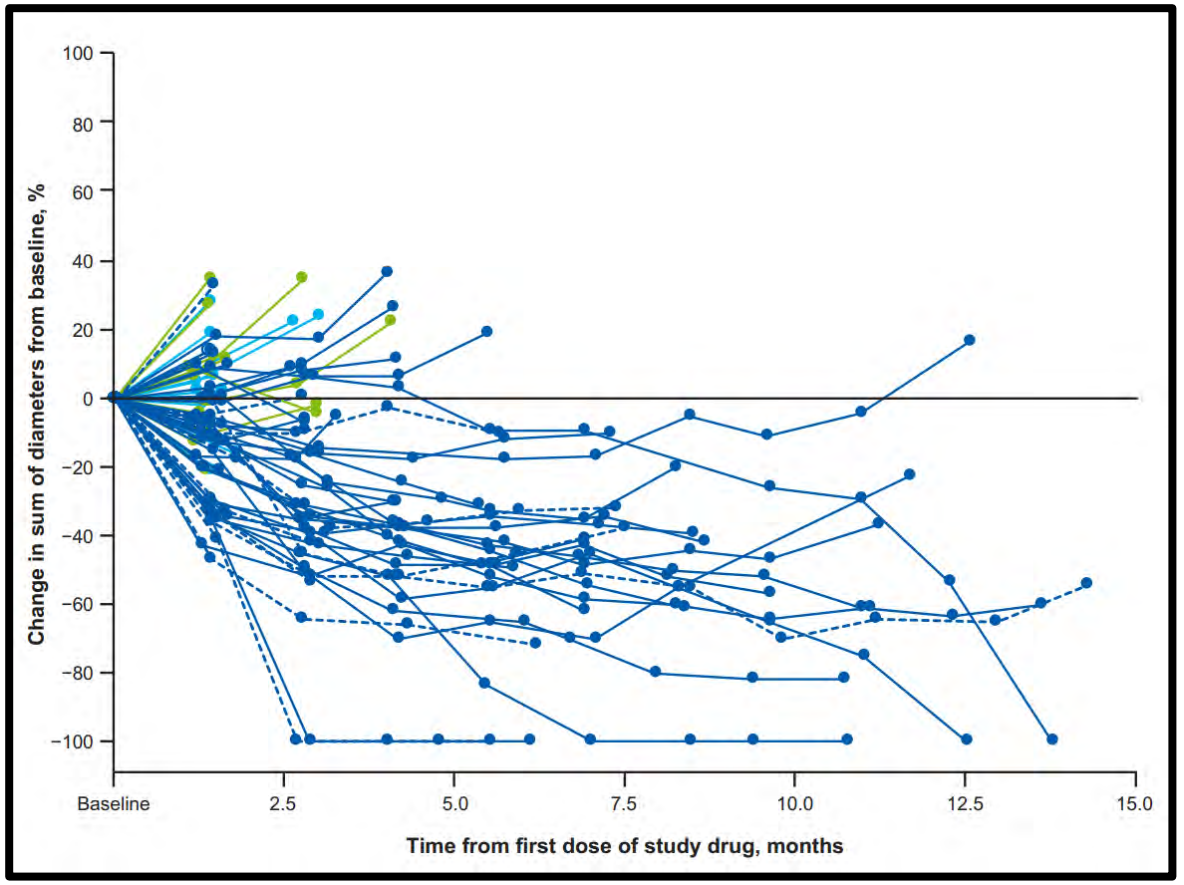
mPFS: 6.9 months

mOS: 15.5 months

Yoshino T et al. Nat Commun. 2023 Jun 7;14(1):3332.

DESTINY-CRC 01 trial





Yoshino T et al. Nat Commun. 2023 Jun 7;14(1):3332.

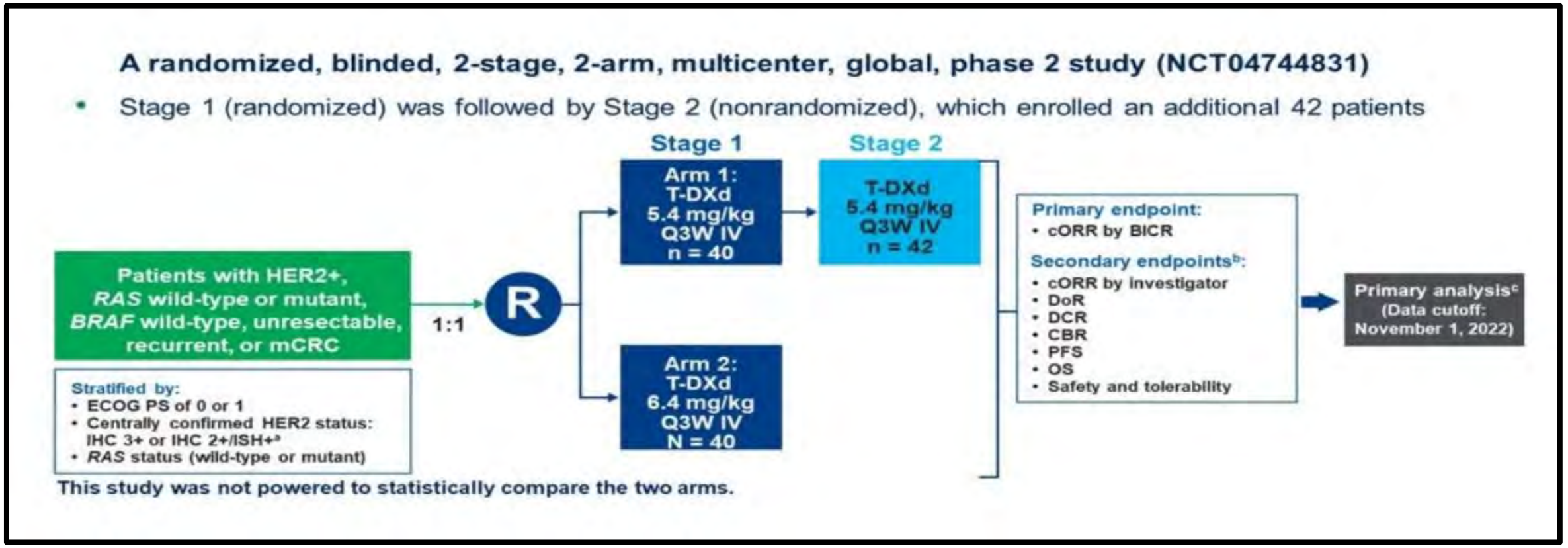
DESTINY-CRC 01 trial

| TEAEs reported in at least 20% of patients in the overall cohort (safety analysis set)

Preferred term	HER2 IHC 3+ or IHC 2+/ ISH+ Cohort A *n* = 53		HER2 IHC 2+/ISH− Cohort B *n* = 15		HER2 IHC 1+ Cohort C *n* = 18		Overall *N* = 86	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any TEAE	53 (100)	35 (66.0)	15 (100)	7 (46.7)	18 (100)	14 (77.8)	86 (100)	56 (65.1)
Nausea	37 (69.8)	5 (9.4)	9 (60.0)	0	7 (38.9)	0	53 (61.6)	5 (5.8)
Anemia	21 (39.6)	8 (15.1)	4 (26.7)	1 (6.7)	6 (33.3)	3 (16.7)	31 (36.0)	12 (14.0)
Fatigue	21 (39.6)	1 (1.9)	7 (46.7)	0	3 (16.7)	0	31 (36.0)	1 (1.2)
Decreased appetite	18 (34.0)	0	5 (33.3)	0	7 (38.9)	0	30 (34.9)	0
Platelet count decreased	17 (32.1)	6 (11.3)	4 (26.7)	0	7 (38.9)	2 (11.1)	28 (32.6)	8 (9.3)
Vomiting	23 (43.4)	1 (1.9)	3 (20.0)	0	1 (5.6)	0	27 (31.4)	1 (1.2)
Neutrophil count decreased	20 (37.7)	13 (24.5)	2 (13.3)	2 (13.3)	4 (22.2)	4 (22.2)	26 (30.2)	19 (22.1)
Diarrhea	19 (35.8)	0	0	0	4 (22.2)	1 (5.6)	23 (26.7)	1 (1.2)

Yoshino T et al. Nat Commun. 2023 Jun 7;14(1):3332.

DESTINY-CRC 02 trial



Raghav K et al. Lancet Oncol. 2024 Sep;25(9):1147-1162.

DESTINY-CRC 02 trial

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

Raghav K et al. Lancet Oncol. 2024 Sep;25(9):1147-1162.

DESTINY-CRC 02 trial

	MOUNTAINEER	DESTINY-CRC02
Agents	Tucatinib 300 mg PO BID Trastuzumab 6 mg/kg IV Q3W (loading dose 8 mg/kg C1D1)	T-DXd 5.4 mg/kg IV Q3W T-DXd 6.4 mg/kg IV Q3W
ORR	38.1%	37.8% (5.4 mg/kg) 27.5% (6.4 mg/kg)
mPFS	8.2 months	5.8 months (5.4 mg/kg) 5.5 months (6.4 mg/kg)
RAS Status	N/A	82.9% wild-type (5.4 mg/kg) 17.1% mutant (5.4 mg/kg) 85% wild-type (6.4 mg/kg) 15% mutant (6.4 mg/kg)
Received Prior HER2 Directed Therapy	N/A	20.7% (5.4mg/kg) 25% (6.4 mg/kg)

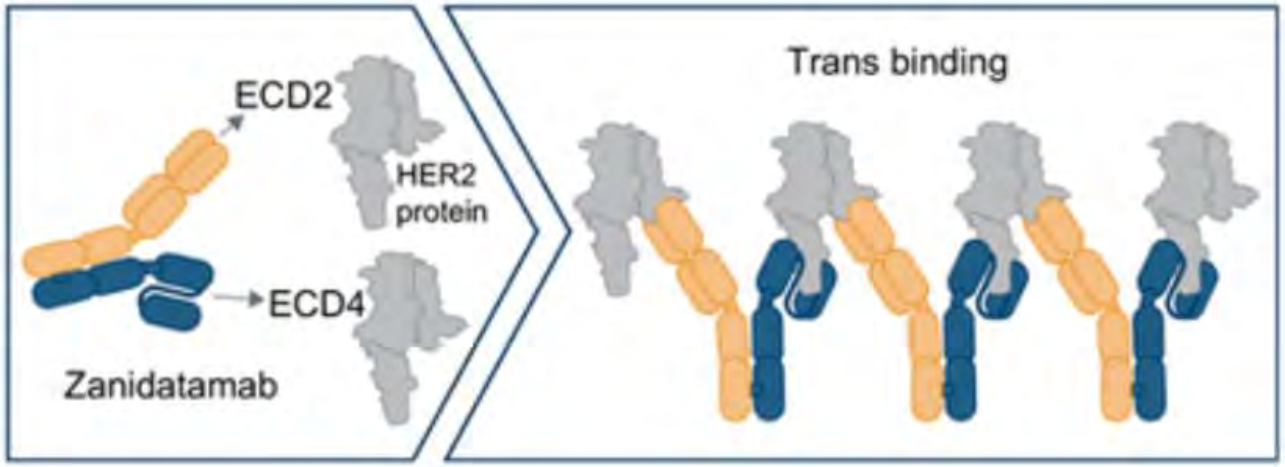
Strickler JH et al. Lancet Oncol. 2023 May;24(5):496-508.
Raghav K et al. Lancet Oncol. 2024 Sep;25(9):1147-1162.

Future perspective

Zanidatamab

Zanidatamab's unique binding geometry

- Biparatopic binding targets two distinct HER2 epitopes and results in HER2 binding across a range of expression levels (low to high)
  - The geometry of zanidatamab prevents it from binding to the same HER2 molecule
  - Binding occurs on 2 separate HER2 molecules in *trans*



Dual HER2-binding of zanidatamab drives unique MOA

- HER2-receptor cross-linking, clustering, internalization, and downregulation
  - Enhanced receptor clustering on cell surface (cluster internalization, receptor downregulation) compared to trastuzumab ± pertuzumab
  - Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC

Weisser NE et al. Nat Commun. 2023 Mar 13;14(1):1394.

Zanidatamab

	Part 1: dose escalation (n=46)		Part 2: dose expansion (n=86)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Diarrhoea	24 (52%)	0	36 (42%)	1 (1%)
Infusion reaction	20 (43%)	0	29 (34%)	0
Nausea	9 (20%)	0	8 (9%)	0
Fatigue	8 (17%)	1 (2%)	8 (9%)	0
Vomiting	5 (11%)	0	6 (7%)	0
Decreased appetite	2 (4%)	1 (2%)	2 (2%)	0
Arthralgia	1 (2%)	1 (2%)	0	0
Hypertension	0	1 (2%)	0	0
Hypophosphataemia	0	1 (2%)	0	0

	Biliary tract cancer (n=21)	Colorectal cancer (n=26)	Other cancer types (n=36)	Total (n=83)
Confirmed objective response, n (% [95% CI])	8 (38% [18 to 62])	10 (38% [20 to 59])	13 (36% [21 to 54])	31 (37% [27 to 49])
Partial response, n (%)	8 (38%)	10 (38%)	13 (36%)	31 (37%)
Stable disease, n (%)	5 (24%)	10 (38%)	16 (44%)	31 (37%)
Progressive disease, n (%)	8 (38%)	6 (23%)	7 (19%)	21 (25%)
Clinical benefit rate*	38% (18 to 62)	58% (37 to 77)	53% (35 to 70)	51% (39 to 62)
Disease control rate†	62% (38 to 82)	77% (56 to 91)	81% (64 to 92)	75% (64 to 84)
Median duration of response, months‡	8·5 (3·2 to not estimable)	5·6 (2·8 to 16·7)	9·7 (3·7 to not estimable)	6·9 (5·6 to 16·7)
Had event, n/n (%)	6/8 (75%)	9/10 (90%)	7/13 (54%)	22/31 (71%)
Censored, n/n (%)	2/8 (25%)	1/10 (10%)	6/13 (46%)	9/31 (29%)
Progression-free survival, months§	3·5 (1·8 to 6·7)	6·8 (3·5 to 7·8)	5·5 (3·6 to 8·3)	5·4 (3·7 to 7·3)
Had event, n (%)	19/22 (86%)	24/28 (86%)	28/36 (78%)	71/86 (83%)
Censored, n (%)	3/22 (14%)	4/28 (14%)	8/36 (22%)	15/86 (17%)

Meric-Bernstam F et al. Lancet Oncol. 2022 Dec;23(12):1558-1570.

Zanidatamab

516MO **Zanidatamab (Zani) + chemotherapy (CT) in first-line (1L) human epidermal growth factor receptor 2-positive (HER2+) advanced/metastatic colorectal cancer (mCRC)**

- N = 13
- Zani + mFOLFOX6 (n=6) or zani + mFOLFOX6-2 + bev (n=7)
- Three pts had DLTs (GI toxicity, nausea, vomiting and diarrhea)
- No pts discontinued zani due to a DLT.
- Grade 3-4 TRAEs occurred in 5 (38%) pts, 3 (23%) of whom experienced diarrhea.
- In 11 evaluable pts, there were 10 confirmed partial responses (ORR 91%; 1 pt had stable disease.

Rha SY et al. ESMO 2024.

Ongoing efforts

Title	Phase	Status	Interventions	HER2 %
A Safety and Efficacy Study of ZW25 (Zanidatamab) Plus Combination Chemotherapy in *HER2*-Expressing Gastrointestinal Cancers, Including Gastroesophageal Adenocarcinoma, Biliary Tract Cancer, and Colorectal Cancer (NCT03929666)	II	Recruiting	Zanidatamab + chemotherapy	IHC 3+ or gene amplification
ACE1702 in Subjects With Advanced or Metastatic *HER2*-Expressing Solid Tumors (NCT04319757)	I	Recruiting	ACE1702-001 (anti-*HER2* oNK cells) Cyclophosphamide Fludarabine	IHC 2+ or 3+
CAR-Macrophages For the Treatment of *HER2*-Overexpressing Solid Tumors (NCT04660929)	I	Recruiting	CT-0508 (anti-*HER2* CAR macrophages)	Missing
A First-in-Human Study Using BDC-1001 as a Single Agent and in Combination With Nivolumab in Advanced *HER2*-Expressing Solid Tumors (NCT04278144)	I/II	Recruiting	BDC-1001 (anti-*HER2* monoclonal antibody conjugated to a TLR7/8 dual agonist) Nivolumab	Missing
A Study of SBT6050 Alone and in Combination With PD-1 Inhibitors in Subjects With Advanced *HER2*-Expressing Solid Tumors (NCT04460456)	I/Ib	Recruiting	SBT6050 Pembrolizumab Cemiplimab	IHC 2+ or 3+
Binary Oncolytic Adenovirus in Combination With *HER2*-Specific Autologous CAR VST, Advanced *HER2* Positive Solid Tumors (VISTA) (NCT03740256)	I/Ib	Recruiting	CAdVEC	IHC 2+ or 3+
TAEK-VAC-HerBy Vaccine for Brachyury and *HER2* Expressing Cancer (NCT04246671)	I	Recruiting	TAEK-VAC-HerBy	Missing

Djaballah SA, et al. Am Soc Clin Oncol Educ Book. 2022;42:1–14.

Treatment guidelines

ESMO guidelines[1]

- Anti-HER2 inhibition is optionally recommended in third and later lines of therapy using a combination of trastuzumab + lapatinib or trastuzumab + pertuzumab, especially in *RAS* wild-type tumours
- Monotherapy with trastuzumab deruxtecan is another recommended option

NCCN guidelines[2,3]

- Trastuzumab* + [pertuzumab, lapatinib or tucatinib] or trastuzumab deruxtecan are recommended as options for subsequent therapy of patients with HER2-amplified and *RAS*/*BRAF* wild-type advanced or mCRC
- Trastuzumab* + [pertuzumab, lapatinib or tucatinib] may also be appropriate for initial therapy for patients who are not suitable for intensive therapy

1. Cervantes A, et al. Ann Oncol. 2023;34:10–32.
2. NCCN Guidelines Version 5.2024 Colon Cancer.
3. NCCN Guidelines Version 5.2024 Rectal Cancer.

Take home messages

- Detection of HER2 amplification by ctDNA is useful; however, pts w/o HER2 amplification should be confirmed with a tissue-based assay;
- Trastuzumab/tucatinib (HER2+, RAS wt) and trastuzumab deruxtecan (HER2+) as preferred treatment in HER2 mCRC;
- MOUNTAINEER-03 is an ongoing a phase 3 study of tucatinib, trastuzumab, and mFOLFOX6 as first-line treatment in HER2+ mCRC;
- New agents like zanidatamab and targeting HER2 in early/upfront lines as promising approaches.

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