Fulfilling the potential of HER2-targeting in colorectal cancer: An update on detection and management

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Detecting HER2 amplification in CRC

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Could you give some background on HER2-positive tumours in CRC and outline the current testing methods?

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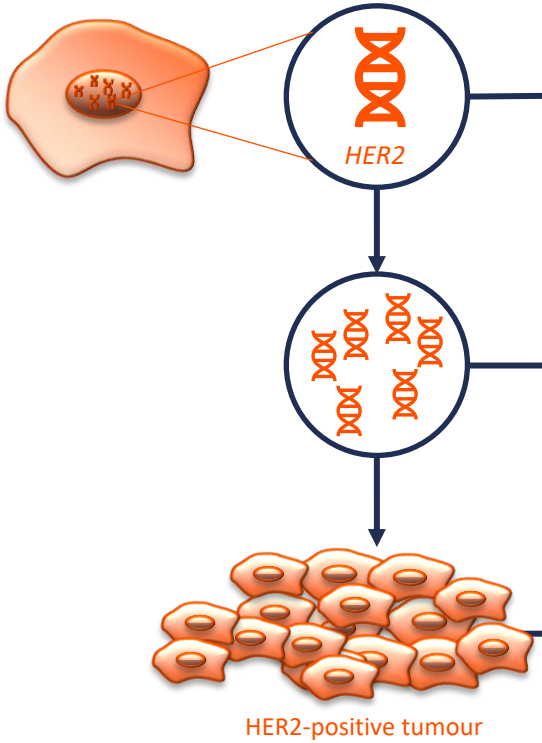
HER2-positive tumours in CRC



- 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

- Amplification of *HER2* oncogene or overexpression of its protein leads to hyperactivation of mitogenic signals and uncontrolled cell proliferation and tumourigenesis
- Activating mutations have also been identified in the *HER2* oncogene, sometimes coexisting with *HER2* amplification

HER2 overexpression in CRC:

- In approximately **2%** of all CRCs
- In **5–6%** of stage IV *KRAS* wild-type CRCs
- Higher prevalence in patients with left-sided tumours

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus.

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

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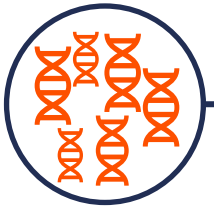
HER2 testing methods

- HER2 overexpression and amplification are routinely detected by **IHC** and **ISH**



- **NGS** is a molecular technique that can be used as an alternative tool to identify HER2 alterations
- Advantages of **NGS** include detecting a wide range of molecular alterations and quantifying the gene copy number, which could act as an additional biomarker to select patients who would benefit from HER2-targeted treatments

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NGS, next-generation sequencing.

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

What are the current guideline recommendations for HER2 testing?

Current EU/USA testing guidelines for HER2 in CRC

ESMO guidelines[1]	• Identification of HER2 amplification is recommended in *RAS* wild-type patients • Testing of HER2-activating mutations is not recommended outside of clinical trials • IHC and FISH are recommended as HER2 testing methods
NCCN guidelines[2,3]	• HER2 testing is recommended in patients unless there is a known *RAS* or *BRAF* mutation • IHC, FISH and NGS are recommended as HER2 testing methods
CAP guidelines[4]	• HER2 testing is not specifically included in testing guidelines for patients with CRC
NICE guidelines[5]	• HER2 testing is not specifically included in testing guidelines for patients with CRC

BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CAP, College of American Pathologists; CRC, colorectal cancer; ESMO, European Society for Medical Oncology; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NICE, National Institute for Health and Care Excellence; RAS, rat sarcoma virus.

1. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32; 2. NCCN. Colon cancer. V2.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 17 May 2023); 3. NCCN. Rectal cancer. V2.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 17 May 2023); 4. CAP. 2017. Available at: https://documents.cap.org/documents/colorectal-cancer-recommendations.pdf (accessed 17 May 2023); 5. NICE. 2020. Available at: www.nice.org.uk/guidance/ng151/evidence/b1-use-of-molecular-biomarkers-to-guide-systemic-therapy-pdf-7029391215 (accessed 17 May 2023).

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In your opinion, what are the biggest challenges currently surrounding HER2 testing in mCRC and how can they be overcome?

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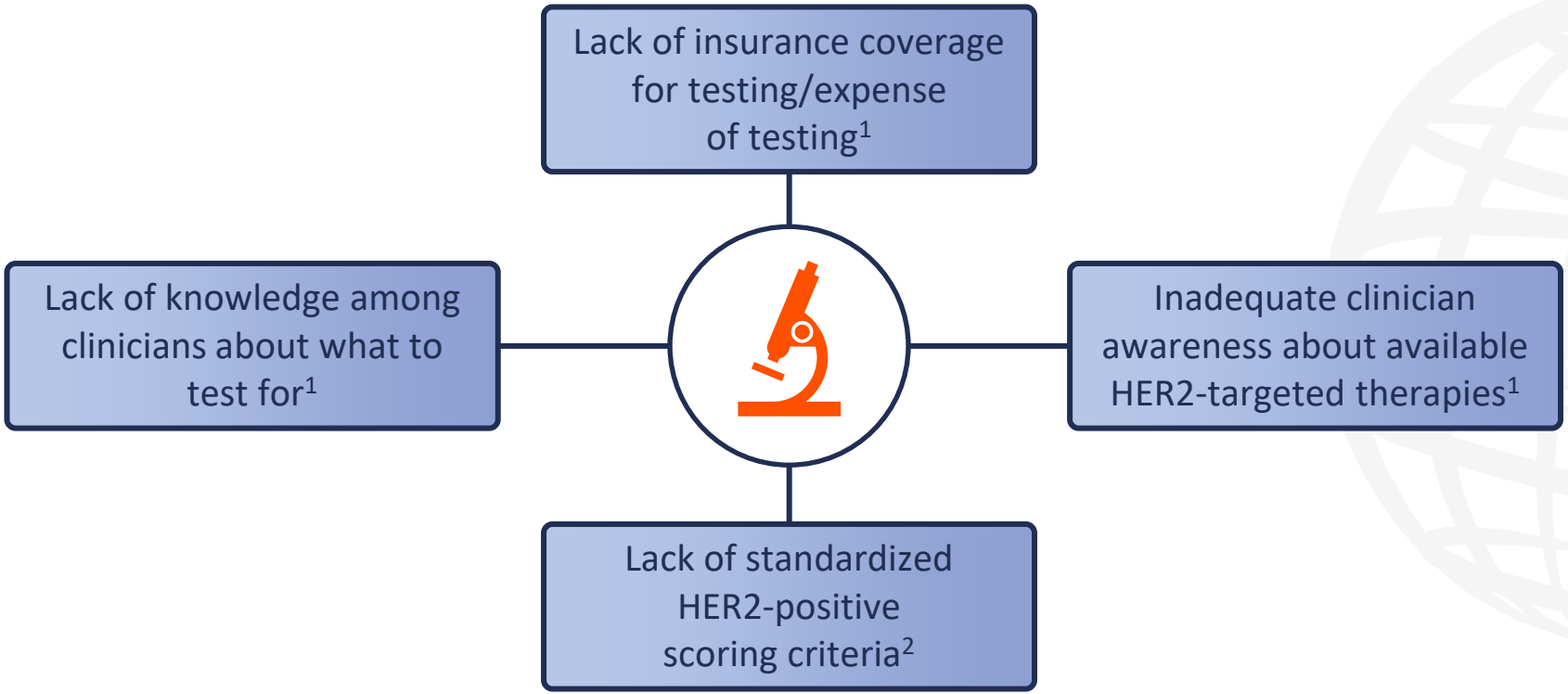
Challenges surrounding HER2 testing in mCRC



HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer.

1. AJMC® Insights. 2022. Available at: www.ajmc.com/view/improving-her2-biomarker-testing-in-metastatic-colorectal-cancer (accessed 17 May 2023);
2. Bellizzi AM. 2020. Available at: www.captodayonline.com/qa-column-0220/ (accessed 17 May 2023).

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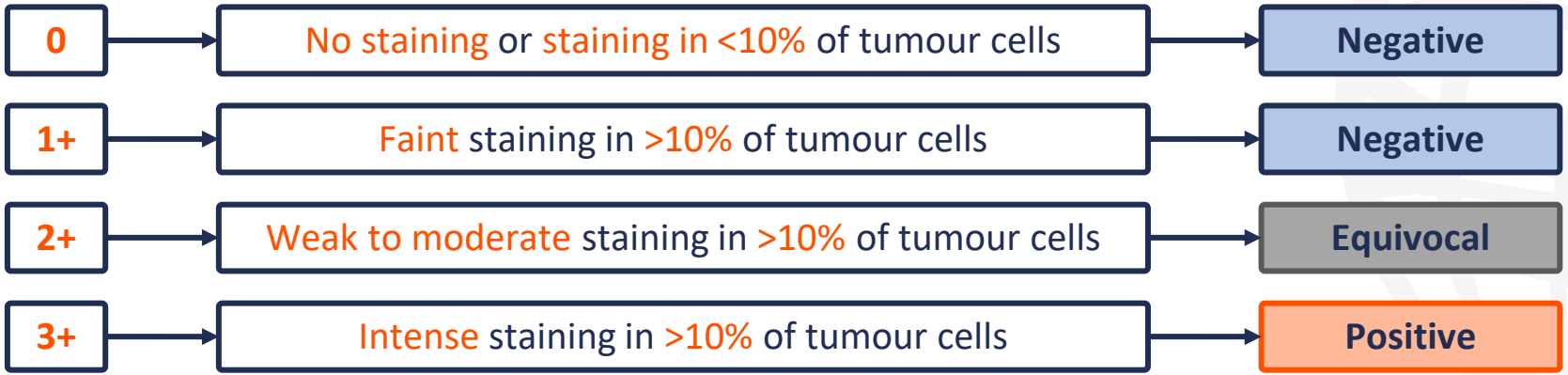
Diagnostic criteria for IHC HER2-positivity in CRC

- IHC expression is based on the pattern and intensity of membranous reactivity and the percentage of immunoreactive cells
- Both circumferential and basolateral/lateral patterns are considered
- Scoring ranges from 0 to 3+



- However, HER2 detection and scoring methods for CRC still lack standardization

CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
Ivanova M, et al. *Life*. 2022;12:1403.

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Individualizing therapy in HER2-amplified mCRC

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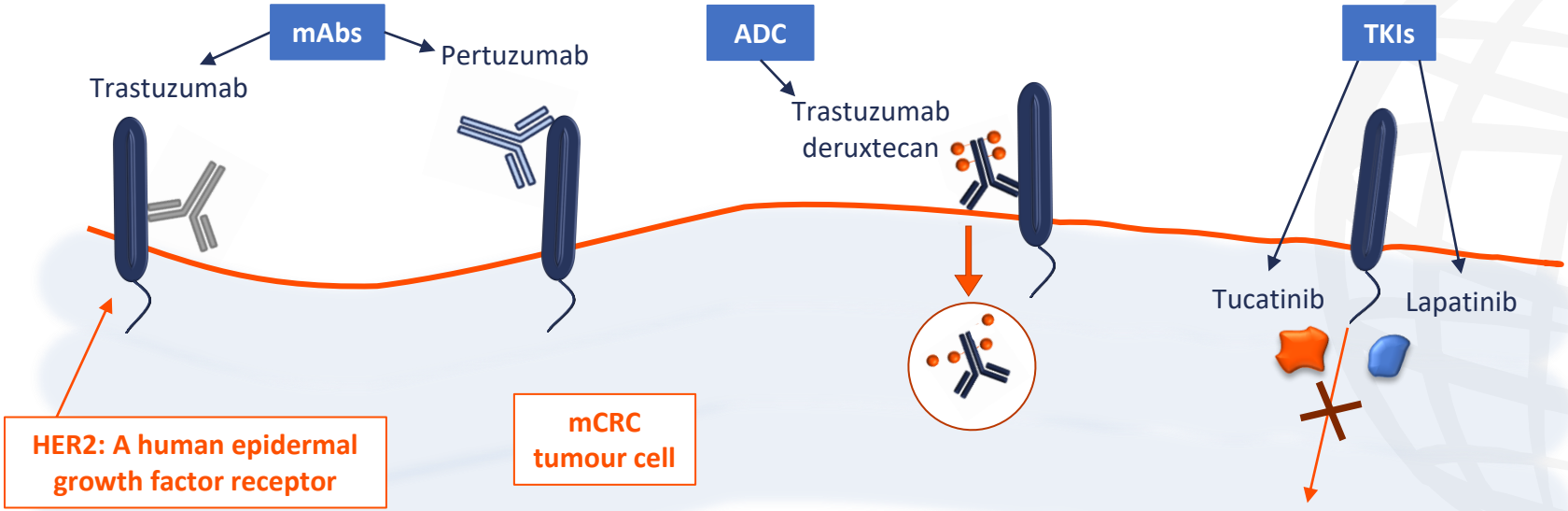
What are the current guideline-recommended HER2-targeted approaches for mCRC?

Guideline-recommended* therapeutic approaches for HER2-targeting in mCRC



*2022 ESMO and 2023 NCCN.

ADC, antibody–drug conjugate; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor.

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

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Current treatment guidelines for HER2-positive CRC

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

*An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CRC, colorectal cancer; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, metastatic; NCCN, National Comprehensive Cancer Network; RAS, rat sarcoma virus.

1. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32; 2. NCCN. Colon cancer. V2.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 2 June 2023); 3. NCCN. Rectal cancer. V3.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 2 June 2023).

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What is the supporting evidence for use of guideline-recommended HER2-targeted approaches in mCRC?

MyPathway and HERACLES trial efficacy data

MyPathway trial[1]

Assessed efficacy of trastuzumab + pertuzumab in patients with treatment-refractory mCRC with HER2 amplification

- Phase IIa, multiple basket trial in patients who have previously received standard first-line therapy for mCRC
- n=57
- **Trastuzumab + pertuzumab is active in HER2-amplified, *KRAS* wild-type mCRC**

ORR: 32%

mPFS: 2.9 months

mOS: 11.5 months

HERACLES trial[2]

Assessed the activity of trastuzumab + lapatinib in patients with HER2-positive, *KRAS* wild-type mCRC after failure of standard therapies

- Phase II, multicentre, open label
- n=27
- **Trastuzumab + lapatinib is active and well tolerated in treatment-refractory patients with HER2-positive mCRC**

ORR: 30%

mPFS: 21 weeks

mOS: 46 weeks

Direct comparisons between trials should not be made due to differences in trial design.

HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; m, median; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Meric-Bernstam F, et al. *Lancet Oncol*. 2019;20:518–30; 2. Sartore-Bianchi A, et al. *Lancet Oncol.* 2016;17:738–46.

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MOUNTAINEER and DESTINY-CRC01 trial efficacy data

MOUNTAINEER trial[1]

Assessed activity of trastuzumab + tucatinib (a tyrosine kinase inhibitor that is highly selective for HER2)

- Phase II, global, open-label trial in patients with chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or mCRC
- n=84
- **Trastuzumab + tucatinib had clinically meaningful antitumour activity**

ORR: 38.1%

mPFS: 8.2 months

mOS: 24.1 months

DESTINY-CRC01 trial[2*]

Assessed efficacy of trastuzumab deruxtecan (an ADC of humanized anti-HER2 antibody bound to a topoisomerase I inhibitor)

- Phase II, open-label, multicentre trial in patients with HER2-expressing mCRC
- n=53
- **Trastuzumab deruxtecan showed promising activity and durability with longer-term follow-up in patients with HER2-expressing mCRC**

ORR: 45.3%

mPFS: 6.9 months

mOS: 15.5 months

Direct comparisons between trials should not be made due to differences in trial design.

*Data are shown for the HER2 IHC3+ or IHC2+/ISH+ cohort only.

ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; m, median; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma virus.

1. Strickler JH, et al. *Lancet Oncol.* 2023;24:496–508; 2. Yoshino T, et al. *J Clin Oncol.* 2021;39(Suppl. 15): Abstr 3505.

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What considerations are needed for individualizing therapy and treatment sequencing for mCRC in clinical practice?

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DESTINY-CRC02 trial data

DESTINY-CRC02 trial

Assessed the efficacy and safety of trastuzumab deruxtecan (5.4 mg/kg and 6.4 mg/kg doses)

- Phase II multicentre trial in patients with HER2-expressing mCRC
- Patients with *RAS* wild-type or mutant mCRC were eligible
- n=82 in 5.4 mg/kg cohort
- n=40 in 6.4 mg/kg cohort
- **Trastuzumab deruxtecan showed promising antitumour activity in patients with HER2-positive mCRC at both doses**
- **Antitumour efficacy was observed irrespective of *RAS* mutation status at the 5.4 mg/kg dose, and in those with prior anti-HER2 therapy**
- **Overall, safety was consistent with the known safety profile and favoured the 5.4 mg/kg dose**

cORR
5.4 mg/kg: 37.8%
6.4 mg/kg: 27.5%

mPFS
5.4 mg/kg: 5.8 months
6.4 mg/kg: 5.5 months

mOS
5.4 mg/kg: 13.4 months
6.4 mg/kg: NE

cORR, confirmed overall response rate; HER2, human epidermal growth factor receptor 2; m, median; mCRC, metastatic colorectal cancer; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma virus.

Raghav KPS, et al. *J Clin Oncol.* 2023;41(Suppl. 16): Abstr 3501.

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Future perspectives in HER2-amplified mCRC

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What further evidence supports HER2-targeted therapies working in combination with immunotherapies?

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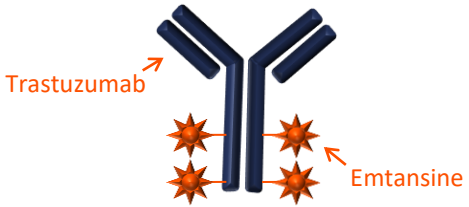
Trastuzumab emtansine + pertuzumab



- **Trastuzumab emtansine (T-DM1)** is an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a microtubule inhibitor[1]
- T-DM1 retains trastuzumab activity while providing intracellular delivery of DM1 to HER2-overexpressing cells[1]

HERACLES-B trial[2]

Assessed efficacy of a HER2-targeted combination of pertuzumab + T-DM1

- Phase II trial in patients with histologically confirmed *RAS*/*BRAF* wild-type and HER2-positive mCRC refractory to standard treatments
- HER2-positivity was assessed by IHC and ISH according to HERACLES criteria
- N=31, of which 48% of patients had received ≥4 lines of previous therapies

ORR: 9.7%

DCR: 77.4%

mPFS: 4.1 months

The HERACLES-B trial did not reach its primary endpoint of ORR; however, the anti-HER2 regimen provided good rates of sustained disease control with little toxicity

BRAF, v-Raf murine sarcoma viral oncogene homolog B1; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; m, median; mCRC, metastatic colorectal cancer; ORR, overall response rate; PFS, progression-free survival; RAS, rat sarcoma virus.

1. von Minckwitz G, et al. *N Engl J Med.* 2019;380:617–28; 2. Sartore-Bianchi A, et al. *ESMO Open*. 2020;5:e000911.

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Trastuzumab + pertuzumab

TRIUMPH trial[1]

Assessed efficacy of trastuzumab + pertuzumab in patients with HER2 amplification prospectively confirmed by tumour tissue or ctDNA analysis

- Phase II trial in patients with mCRC with HER2-positive *RAS* wild-type tumours
- n=27 tissue+ group and n=25 ctDNA+ group
- **Patients with HER2 amplification identified by ctDNA genotyping benefited from dual-HER2 blockade similarly to patients identified by conventional tissue analysis**

mOS (months)
Tissue+: 10.1
ctDNA+: 8.8

mPFS (months)
Tissue+: 4.0
ctDNA+: 3.1

TAPUR trial[2]

Assessed efficacy of trastuzumab + pertuzumab in patients with HER2 amplification or HER2/3 mutation

- Phase II trial in patients with heavily pre-treated advanced CRC
- n=28 HER2 amplification and n=10 HER2/3 mutation
- **The combination treatment does not have antitumour activity in patients with HER2/3 mutation, but benefit is seen in patients with HER2 amplification**

mOS (weeks)
HER2 amplification: 60.0
HER2/3 mutation: 28.8

mPFS (weeks)
HER2 amplification: 17.2
HER2/3 mutation: 9.6

Direct comparisons between trials should not be made due to differences in trial design.

CRC, colorectal cancer; ctDNA, circulating tumour DNA; HER2/3, human epidermal growth factor receptor 2/3; m, median; mCRC, metastatic CRC; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma virus.

1. Nakamura Y, et al. *Nat Med.* 2021;27:1899–903; 2. Gupta R, et al. *JCO Precis Oncol.* 2022;6:e2200306.

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What other approaches are being investigated for patients with HER2-amplified mCRC?

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Trastuzumab + pyrotinib

Pyrotinib: Irreversible dual pan-ErbB tyrosine kinase inhibitor[1]

HER2-FUSCC-G trial[2]

Assessed the therapeutic efficacy of trastuzumab + pyrotinib in patients with HER2-positive CRC

- Phase IIa trial in patients with mCRC refractory to standard chemotherapies
- n=11
- The combination of trastuzumab + pyrotinib showed a promising antitumour response and prolonged long-term survival benefit in *RAS* wild-type and HER2-positive mCRC with acceptable tolerance

ORR
Whole cohort: 45.5%
***RAS* wt cohort: 55.6%**

mPFS (whole cohort): 7.80 months

mOS (whole cohort): 14.97 months

CRC, colorectal cancer; ErbB, epidermal growth factor receptor B; HER2, human epidermal growth factor receptor 2; mCRC, metastatic CRC; m, median; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma virus; wt, wild-type.

1. Ivanova M, et al. *Life (Basel)*. 2022;12:1403; 2. Li W, et al. *J Clin Oncol.* 2022;40(Suppl.):97.

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Trastuzumab + neratinib or cetuximab + neratinib

Neratinib: Small-molecule, irreversible pan-inhibitor of the EGFR, HER2, and HER4 members of the ErbB tyrosine kinase family[1]

NSABP FC-11 trial[2]

Evaluated the activity of dual MAPK pathway inhibition based on HER2 status: amplified, non-amplified or mutated

- A phase II study of trastuzumab + neratinib or cetuximab + neratinib in patients with quadruple wild-type (*KRAS, NRAS, BRAF, PIK3CA*) mCRC based on HER2 status
- 21 patients enrolled (HER2 non-amplified or HER2 amplified without prior anti-EGFR therapy)
- ORR, CBR and PFS compare favourably to patients previously relapsed following oxaliplatin and irinotecan and treated with single-agent anti-EGFR therapy

ORR for all patients who received at least one dose of therapy: 33%

BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; EGFR, epidermal growth factor receptor; ErbB, epidermal growth factor receptor B; HER2/4, human epidermal growth factor receptor 2/4; KRAS, Kirsten rat sarcoma virus; MAPK, mitogen-activated protein kinase; mCRC, metastatic colorectal cancer; NRAS, neuroblastoma rat sarcoma virus; ORR, overall response rate; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Zhao M, et al. *Clin Cancer Res.* 2021;27:1681–94; 2. Jacobs SA, et al. *J Clin Oncol.* 2022;40(Suppl.):3564.

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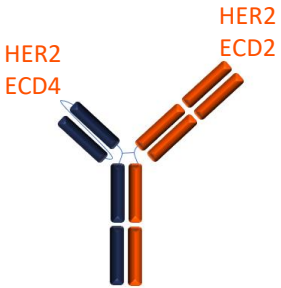
Zanidatamab (ZW25)



- **ZW25: Bispecific antibody targeting two epitopes of HER2: ECD2 (pertuzumab binding domain) and ECD4 (trastuzumab binding domain)[1,2]**
- **Multiple differentiated and unique mechanisms of action, including improved receptor internalization and downregulation relative to trastuzumab[3]**

NCT03929666[2–4]

Investigating safety, tolerability and anti-tumour activity of ZW25 + standard first-line combination chemotherapy regimens for selected gastrointestinal cancers

- Phase II, open-label, two-part, first-line study
- n=43 with HER2-positive tumours who had progressed on all standard therapies, including 17 with gastro-oesophageal adenocarcinoma, 6 with biliary tract cancers, 10 with CRC, and 10 with other cancers
- **ZW25 was well tolerated with promising activity in heavily pre-treated patients**

ORR for response evaluable patients: 41%

CRC, colorectal cancer; ECD, extracellular domain; HER2, human epidermal growth factor receptor 2; ORR, overall response rate.

1. Antonarelli G, et al. *Pharmaceuticals (Basel).* 2021;14:884; 2. Ivanova M, et al. *Life (Basel).* 2022;12:1403; 3. Meric-Bernstam F, et al. *Ann Oncol.* 2019;30(Suppl. 5):v167–v168; 4. ClinicalTrials.gov. NCT03929666. Available at: https://clinicaltrials.gov/ct2/show/NCT03929666 (accessed 9 June 2023).

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What considerations are needed around HER2-targeted therapies and what are potential future strategies?

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Resistance to anti-HER2 therapy

In CRC, preliminary data suggest that mechanisms activating *HER2* parallel pathways or downstream effectors, such as *RAS* and *PIK3CA*, are implicated in primary and secondary resistance to *HER2* blockade[1]

Understanding resistance mechanisms is important to better select patients most likely to benefit from anti-HER2 agents and to develop new therapeutic strategies to overcome resistance[1]

The HERACLES RESCUE trial (NCT03418558) aims to investigate the activity of trastuzumab emtansine in patients who have been previously treated and progressed with lapatinib + trastuzumab in the HERACLES-A trial[2]

CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RAS, rat sarcoma virus.

1. Djaballah SA, et al. *Am Soc Clin Oncol Educ Book.* 2022;42:1–14; 2. ClinicalTrials.gov. NCT03418558. Available at: https://clinicaltrials.gov/ct2/show/NCT03418558 (accessed 24 May 2023).

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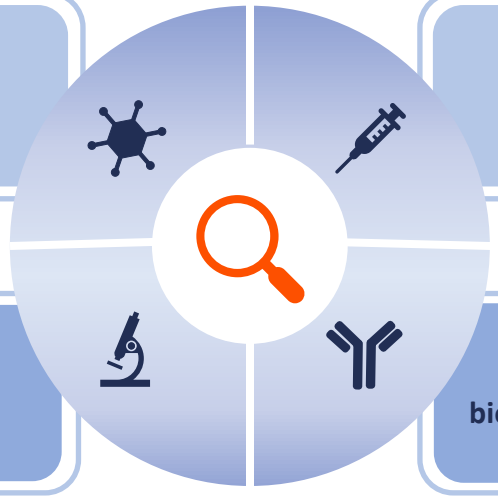
Potential strategies for HER2-targeted therapies in CRC in early-phase trials

- Chimeric antigen receptor (CAR) T cells targeting HER2 in combination with an intra-tumour injection of CAdVEC, an oncolytic adenovirus
- Cancer vaccines including HER2 peptides recognized by T-lymphocytes
- Natural killer cell products targeting HER2 expressing solid tumours
- Immune-stimulating antibody conjugate consisting of a trastuzumab biosimilar chemically conjugated to a toll-like receptor 7/8 agonist



CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2.
Ivanova M, et al. *Life (Basel)*. 2022;12:1403.

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