What are the implications of the latest data for HER2-targeted therapies in HER2-tested patients with colorectal cancer?

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Agenda

Overview of current guidelines for the treatment of HER2+ CRC and testing methods used to identify patients with HER2+ CRC

How can we use efficacy data with HER2-targeted therapies in CRC to inform clinical practice?

How can the safety profile of HER2-targeted therapies in CRC inform clinical practice?

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

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Overview of current guidelines for the treatment of HER2+ CRC and testing methods used to identify patients with HER2+ CRC

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

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Current 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

NCCN guidelines[2,3]

- ✓ HER2 testing is recommended in all patients unless there is a known *RAS* or *BRAF* mutation

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

1. Cervantes A, et al. *Ann Oncol.* 2022; https://doi.org/10.1016/j.annonc.2022.10.003; 2. NCCN. Clinical Practice Guidelines in Oncology 2022. Colon cancer. Version 1.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 22 November 2022); 3. NCCN. Clinical Practice Guidelines in Oncology 2022. Rectal cancer. Version 1.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 22 November 2022).

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HER2 testing in CRC

HER2 testing is performed via the following methods:

- Immunohistochemistry (IHC)[1–3]
- Fluorescence in situ hybridization (FISH)[1–3]
- Next-generation sequencing (NGS; NCCN guidelines)[2,3]

According to the NCCN guidelines:[2,3]

- Positive IHC is defined as 3+ staining in >50% of tumour cells
- HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥2 in >50% of cells

CEP17, centromeric region of chromosome 17; CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network.

1. Cervantes A, et al. Ann Oncol. 2022; https://doi.org/10.1016/j.annonc.2022.10.003; 2. NCCN. Clinical Practice Guidelines in Oncology 2022. Colon cancer. Version 1.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 22 November 2022); 3. NCCN. Clinical Practice Guidelines in Oncology 2022. Rectal cancer. Version 1.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 22 November 2022).

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Current treatment guidelines for HER2+ CRC

ESMO guidelines[1]

HER2+ patients with metastatic CRC

Third- and further-line treatment:

- Trastuzumab + lapatinib or pertuzumab
- Trastuzumab deruxtecan monotherapy

NCCN guidelines[2,3]

HER2-amplified, *RAS* and *BRAF* wild-type, advanced or metastatic CRC

Initial therapy in patients who are not candidates for intensive therapy:

- Trastuzumab* + lapatinib or pertuzumab

Subsequent therapy:

- Trastuzumab* + lapatinib or pertuzumab
- Trastuzumab deruxtecan monotherapy

*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; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; RAS, rat sarcoma virus.

1. Cervantes A, et al. *Ann Oncol.* 2022; https://doi.org/10.1016/j.annonc.2022.10.003; 2. NCCN. Clinical Practice Guidelines in Oncology 2022. Colon cancer. Version 1.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 22 November 2022); 3. NCCN. Clinical Practice Guidelines in Oncology 2022. Rectal cancer. Version 1.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 22 November 2022).

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How can we use efficacy data with HER2-targeted therapies in CRC to inform clinical practice?

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Efficacy data for guideline-recommended* HER2-targeted therapies

Treatment	Clinical trial	No. of patients	ORR (%)	DCR (%)	Median PFS	Median OS
Trastuzumab + pertuzumab[1]	MYPATHWAY (phase IIa; NCT02091141)	57	32	44	2.9 months	11.5 months
Trastuzumab + lapatinib[2]	HERACLES-A (phase II; NCT03225937)	32	28	69	4.7 months	10.0 months
Trastuzumab deruxtecan[3]	DESTINY-CRC01† (phase II; NCT03384940)	53	45	83	6.9 months	15.5 months

*2022 ESMO and 2022 NCCN; †Data are shown for the HER2+ cohort only.
DCR, disease control rate; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
1. Meric-Bernstam F, et al. *Lancet Oncol*. 2019;20:518–30; 2. Tosi F, et al. *Clin Colorectal Cancer*. 2020;9:256–62;
3. Yoshino T, et al. Presented at: ASCO 2021 Annual Meeting. 4–8 June 2021.

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Efficacy data for investigational HER2-targeted therapies

Treatment	Clinical trial	No. of patients	ORR (%)	DCR (%)	Median PFS	Median OS
Trastuzumab + tucatinib[1]	MOUNTAINEER (phase II; NCT03043313)	86	38.1	71.4	8.2 months	24.1 months
Trastuzumab emtansine + pertuzumab[2]	HERACLES-B (phase II; NCT03225937)	31	9.7	77.4	4.1 months	NR
Trastuzumab + pyrotinib[3]	Phase II (NCT04380012)	11	27	45	NR	NR
Trastuzumab + pertuzumab[4]*	TRIUMPH (phase II; UMIN000027887)	27	30	67	4.0 months	10.1 months
Trastuzumab + pertuzumab[5]	TAPUR (phase II; NCT02693535)	28	25	54	17.2 weeks	60.0 weeks

*Data are shown for tissue positive subgroup only.

DCR, disease control rate; HER2, human epidermal growth factor receptor 2; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Strickler JH, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer. Abstract LBA-2, 29 June–2 July 2022; 2. Sartore-Bianchi A, et al. *ESMO Open*. 2020;5:e000911; 3. Yuan Y, et al. *J Clin Oncol.* 2021;39(Suppl. 15):e15554; 4. Nakamura Y, et al. *Nat Med.* 2021;27:1899–903; 5. Gupta R, et al. *JCO Precis Oncol.* 2022;6:e2200306.

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How can the safety profile of HER2-targeted therapies in CRC inform clinical practice?

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Most common TEAEs for guideline-recommended* HER2-targeted therapies

Trastuzumab + pertuzumab[1] MYPATHWAY (phase IIa; NCT02091141) N=57 Grades 1–3	Trastuzumab + lapatinib[2] HERACLES-A (phase II; NCT03225937) N=32 Grades 1–3	Trastuzumab deruxtecan[3] DESTINY-CRC01 (phase II; NCT03384940) n=53† Any grade
• Diarrhoea: 33% • Fatigue: 32% • Nausea: 30% • Anaemia: 25% • Abdominal pain: 23% • Chills: 23% • Dyspnoea: 21% • Vomiting: 19%	• Diarrhoea: 84% • Fatigue: 59% • Rash: 56% • Paronychia: 38% • Nausea: 31% • Dry skin: 25% • Conjunctivitis: 19% • Abdominal pain: 16% • Vomiting: 16%	• Nausea: 70% • Vomiting: 43% • Fatigue: 40% • Anaemia: 40% • Neutrophil count decreased: 38% • Diarrhoea: 36% • Decreased appetite: 34% • Platelet count decreased: 32%

*2022 ESMO and 2022 NCCN; †Data are shown for the HER2+ cohort only.
ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; TEAE, treatment-emergent adverse event.
1. Meric-Bernstam F, et al. *Lancet Oncol*. 2019;20:518–30; 2. Tosi F, et al. *Clin Colorectal Cancer*. 2020;9:256–62;
3. Yoshino T, et al. Presented at: ASCO 2021 Annual Meeting. 4–8 June 2021.

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AEs of special interest for guideline-recommended* HER2-targeted therapies

Cardiotoxicity TEAEs

Trastuzumab + pertuzumab[1] MYPATHWAY (phase IIa; NCT02091141) N=57	Trastuzumab + lapatinib[2] HERACLES-A (phase II; NCT03225937) N=32	Trastuzumab deruxtecan[3] DESTINY-CRC01 (phase II; NCT03384940) n=53†
• Left ventricular dysfunction (grade 4): 2%	• Decrease in LVEF (grade 3): 6%	• None reported

Interstitial lung disease with trastuzumab deruxtecan (DESTINY-CRC01)[3]

Interstitial lung disease seen in 8 (9.3%) patients, including 3 (3.5%) grade 5 (N=86)

*2022 ESMO and 2022 NCCN; †Data are shown for the HER2+ cohort; only TEAEs in ≥20% of patients reported.
AE, adverse event; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; NCCN, National Comprehensive Cancer Network; TEAE, treatment-emergent adverse event.
1. Meric-Bernstam F, et al. *Lancet Oncol*. 2019;20:518–30; 2. Tosi F, et al. *Clin Colorectal Cancer*. 2020;9:256–62;
3. Yoshino T, et al. Presented at: ASCO 2021 Annual Meeting. 4–8 June 2021.

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Most common TEAEs for investigational HER2-targeted therapies

Trastuzumab + tucatinib[1] MOUNTAINEER (phase II; NCT03043313) n=86 Grades 1–3	Trastuzumab emtansine + pertuzumab[2] HERACLES-B (phase II; NCT03225937) N=31 Grades 1 and 2	Trastuzumab + pyrotinib[3] (phase II; NCT04380012) N=11 Grade ≥3	Trastuzumab + pertuzumab[4] TRIUMPH (phase II; UMIN000027887) N=30 Any grade	Trastuzumab + pertuzumab[5] TAPUR (phase II; NCT02693535) N=38 Grade 3
• Diarrhoea: 64% • Fatigue: 44.2% • Nausea: 34.9% • IRR: 20.9% • Pyrexia: 19.8%	• Fatigue: 18% • Hyperbilirubinaemia: 9% • Thrombocytopenia: 8% • Pruritus: 8% • Nausea/vomiting: 8% • Muscular pain: 8%	• Diarrhoea: 73%	• IRR: 47% • Diarrhoea: 37% • Stomatitis: 13% • Malaise: 10% • Decreased appetite: 7% • Nausea: 7%	• 11% (including: anaemia, infusion reaction, diarrhoea, left ventricular systolic dysfunction, and decreased lymphocyte count)

Cardiotoxicity TEAEs

• Asymptomatic LVEF decrease: 3.5%*	• Hypertension (grades 1 and 2): 1%	• None reported	• Ejection fraction decreased (grade 3): 3%	• Left ventricular systolic dysfunction

*Proportion in which LVEF decrease led to dose modification or discontinuation.

HER2, human epidermal growth factor receptor 2; IRR, infusion-related reaction; LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event.

1. Strickler JH, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer. Abstract LBA-2, 29 June–2 July 2022; 2. Sartore-Bianchi A, et al. *ESMO Open*. 2020;5:e000911; 3. Yuan Y, et al. *J Clin Oncol.* 2021;39(Supple. 15):e15554; 4. Nakamura Y, et al. *Nat Med.* 2021;27:1899–903; 5. Gupta R, et al. *JCO Precis Oncol.* 2022;6:e2200306.

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