How can HER2-targeted therapies be incorporated into the management of patients with CRC?

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Discussion 1

Selecting the right treatment for the right patient

Prof. Andrea Sartore-Bianchi
Oncologist

Dr Evgeny Yakirevich
Pathologist

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
- IHC and FISH are recommended as HER2 testing methods

NCCN guidelines[2,3]

- HER2 testing is recommended in all patients unless there is a known *RAS* or *BRAF* mutation
- IHC, FISH and NGS are recommended as HER2 testing methods. HER2 positivity defined as:
  IHC 3+ staining in >50% of tumour cells
  FISH HER2:CEP17 ratio is ≥2 in >50% of cells

ASCO/CAP guidelines[4,5]

HER2 testing is not specifically included in guidelines for patients with CRC

ASCO, American Society of Clinical Oncology; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CAP, College of American Pathologists; CEP17, centromere 17; 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; RAS, rat sarcoma virus.

1. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32; 2. NCCN. Clinical Practice Guidelines in Oncology 2022. Colon cancer. Version 2.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 14 December 2022); 3. NCCN. Clinical Practice Guidelines in Oncology 2022. Rectal cancer. Version 3.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 14 December 2022); 4. Morris VK, et al. *J Clin Oncol.* 2023;41:678–700; 5. College of American Pathologists. Molecular Biomarkers for the Evaluation of Colorectal Carcinoma. Available at: https://documents.cap.org/documents/colorectal-cancer-recommendations.pdf (accessed 17 January 2022).

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Clinical case

PATIENT HISTORY

- 46 years old
- Sigmoidal tumour

CLINICAL EXAM

- **Clinical stage:** T3 M1, lung metastasis
- **Tumour biopsy:** Invasive adenocarcinoma, well differentiated
- **Initial molecular workup**: *KRAS* mutation wild-type, microsatellite stable by IHC

TREATMENT AND DISEASE PROGRESSION

Treatment received:

- 8 cycles of FOLFOX with partial response

Surgery:

- Rectosigmoid resection: ypT4b pN1a

Disease progression:

- 7 months later: multifocal lung metastases

Treatment received:

- FOLFIRI + bevacizumab

Disease progression:

- 9 months later: metastases in the lung, liver, nodes, femur

COMPREHENSIVE GENOMIC PROFILING

Genomic alterations:

- *HER2* amplification
- *FH:* L14fs*42
- *FUBP1:* Q550*
- *TP53:* R175H

PD-L1: TPS negative (0)
CPS negative (0)

TREATMENT AND DISEASE PROGRESSION

Treatment received:

- Trastuzumab deruxtecan, 14 cycles

Disease progression:

- Clinical benefit with improvement in dyspnoea and bone pain
- 12 months later: progression of lung metastases
- Liver, bone and node metastases appeared stable

CPS, combined positive score; FH, fumarate hydratase; FOLFIRI, leucovorin calcium (folinic acid), fluorouracil and irinotecan hydrochloride; FOLFOX, leucovorin calcium (folinic acid), fluorouracil and oxaliplatin; FUBP1, far upstream element binding protein 1; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; KRAS, Kirsten rat sarcoma virus; M, metastasis; PD-L1, programmed death-ligand 1; pN1a, 1 metastatic lymph node; T, tumour; TPS, tumour proportion score; TP53, tumour protein P53; yp, pathological.

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Discussion 2

Monotherapy and combination therapy of HER2-targeted treatment

Dr Kristen Ciombor
Oncologist

Prof. Andrea Sartore-Bianchi
Oncologist

Clinical trial efficacy data for guideline-recommended* HER2-targeted therapies

	MYPATHWAY Phase IIa NCT02091141	HERACLES Phase II NCT03225937	DESTINY-CRC01† Phase II NCT03384940	Phase I NCT02564900
Regimen	Trastuzumab + pertuzumab[1]	Trastuzumab + lapatinib[2]	Trastuzumab deruxtecan[3]	Trastuzumab deruxtecan[4]
No. of patients	57	27	53	20
ORR (%)	32	30	45	15
Median PFS	2.9 months	21 weeks	6.9 months	4.1 months
Median OS	11.5 months	46 weeks	15.5 months	NR

Following the recording of this activity, the combination of tucatinib + trastuzumab is recommended in the NCCN guidelines[5,6]

*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; NR, not reported; 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; 3. Yoshino T, et al. Presented at: ASCO 2021 Annual Meeting. 4–8 June 2021; 4. Tsurutani J, et al. *Cancer Discov.* 2020;10:688–701; 5. NCCN. Clinical Practice Guidelines in Oncology 2022. Colon cancer. Version 3.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/colon.pdf (accessed 1 February 2023); 6. NCCN. Clinical Practice Guidelines in Oncology 2022. Rectal cancer. Version 4.2022. Available at: www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 1 February 2023).

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Clinical trial efficacy data for other HER2-targeted therapies

Tucatinib + trastuzumab granted accelerated approval by the FDA in January 2023[1]

	MOUNTAINEER phase II NCT03043313	HERACLES-B phase II NCT03225937	Phase II NCT04380012	TRIUMPH phase II UMIN000027887	TAPUR phase II NCT02693535	Phase II NCT03929666
Regimen	Trastuzumab + tucatinib[2]	Trastuzumab emtansine + pertuzumab[3]	Trastuzumab + pyrotinib[4]	Trastuzumab + pertuzumab[5]*	Trastuzumab + pertuzumab[6]	Zanidatamab (ZW25)[7]
No. of patients	86	31	11	27	28	34
ORR (%)	38.1	9.7	27.0	30.0	25	41
Median PFS	8.2 months	4.1 months	NR	4.0 months	17.2 weeks	NR
Median OS	24.1 months	NR	NR	10.1 months	60.0 weeks	NR

*Data are shown for tissue positive subgroup only. FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. FDA. Press release. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tucatinib-trastuzumab-colorectal-cancer (accessed 23 January 2023); 2. Strickler JH, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer. Abstract LBA-2, 29 June–2 July 2022; 3. Sartore-Bianchi A, et al. *ESMO Open.* 2020;5:e000911; 4. Yuan Y, et al. *J Clin Oncol.* 2021;39(Suppl. 15):e15554; 5. Nakamura Y, et al. *Nat Med.* 2021;27:1899–903; 6. Gupta R, et al. *JCO Precis Oncol.* 2022;6:e2200306; 7. Meric-Bernstam, et al. *Ann Oncol.* 2019;30(Suppl. 5):v159–v193.

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The landscape of HER2-targeted therapies

Antibody-drug conjugates[1]

Trastuzumab emtansine*
Trastuzumab deruxtecan*
Trastuzumab duocarmazine
ARX788
ALT-P7
MEDI-4276
MM-302
PF-06804103
XMT-1522

Antibodies[1]

Trastuzumab*
Trastuzumab-dkst*
Pertuzumab*
Zanidatamab (ZW25)

Small molecules[1]

Lapatinib*
Neratinib*
Tucatinib*[2]
Afatinib
Dacomitinib
Ibrutinib
Poziotinib
Pyrotinib
TAK-788
Sapitinib
Tarloxotinib
Tesevatinib
TAS0728

Other[1]

Bispecific antibodies targeting HER2 and immune cells:

- Margetuximab
- BTRC-4017A
- GBR-1302
- PRS-343

HER2 peptide vaccines:

- AVX901
- E75
- ETBX-021
- IMU-131

CAR T-cell therapy:

- HER2Bi-armed activated T cells

Designed ankyrin repeat protein[1]

MP0274

*Approved by European Medicines Agency or United States Food and Drug Administration. CAR, chimeric antigen receptor; HER2, human epidermal growth factor receptor 2.

1. Siena S, et al. *Cancer Cell*. 2020;38:317–9; 2. FDA. Press release. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tucatinib-trastuzumab-colorectal-cancer (accessed 23 January 2023).

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