Harnessing the power of precision medicine for the treatment of colorectal cancer

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Module 1: Agenda

- Identifying patients for biomarker-targeted treatment in CRC
- Current CRC treatment landscape
- Clinical insights on anti-EGFR-rechallenge in the treatment of CRC

Identifying patients for biomarker-targeted treatment in CRC

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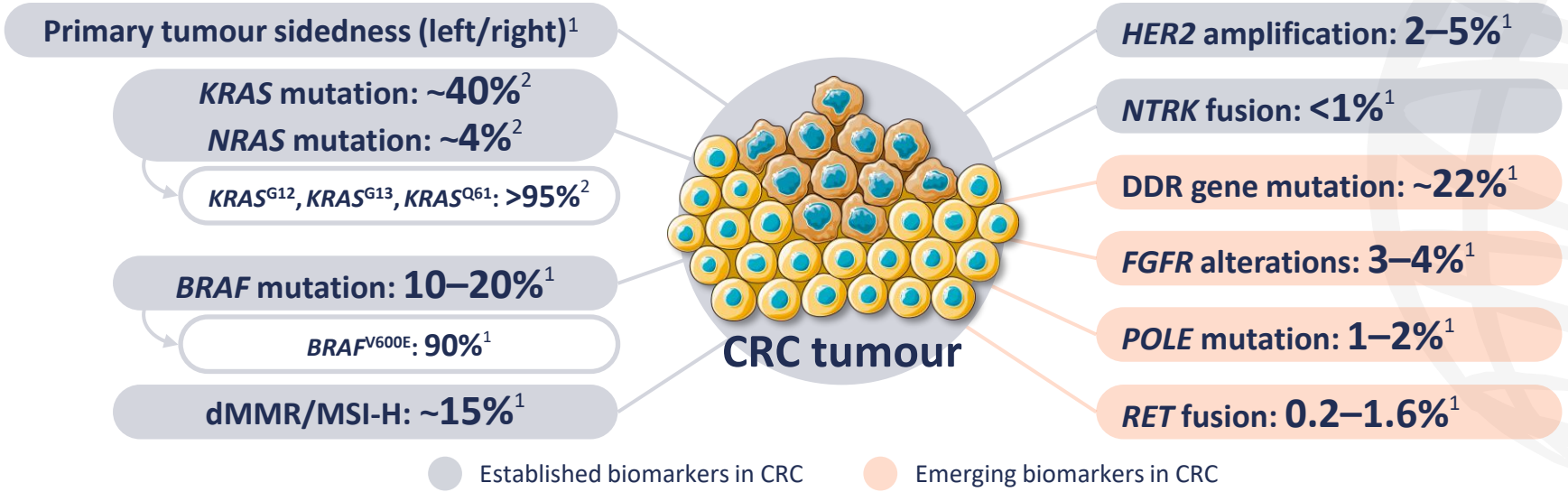
CRC biomarkers have sufficient actionable and clinical implications to warrant routine testing[1]

Prevalence of established and emerging biomarkers in patients with CRC



DDR, DNA damage repair; dMMR, deficient mismatch repair; FGFR, fibroblast-growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; POLE, DNA polymerase epsilon.

1. Puccini A, et al. *Cancers (Basel)*. 2022;14:4828; 2. Patelli G, et al. *ESMO Open.* 2021;6:100156.

Current CRC treatment landscape

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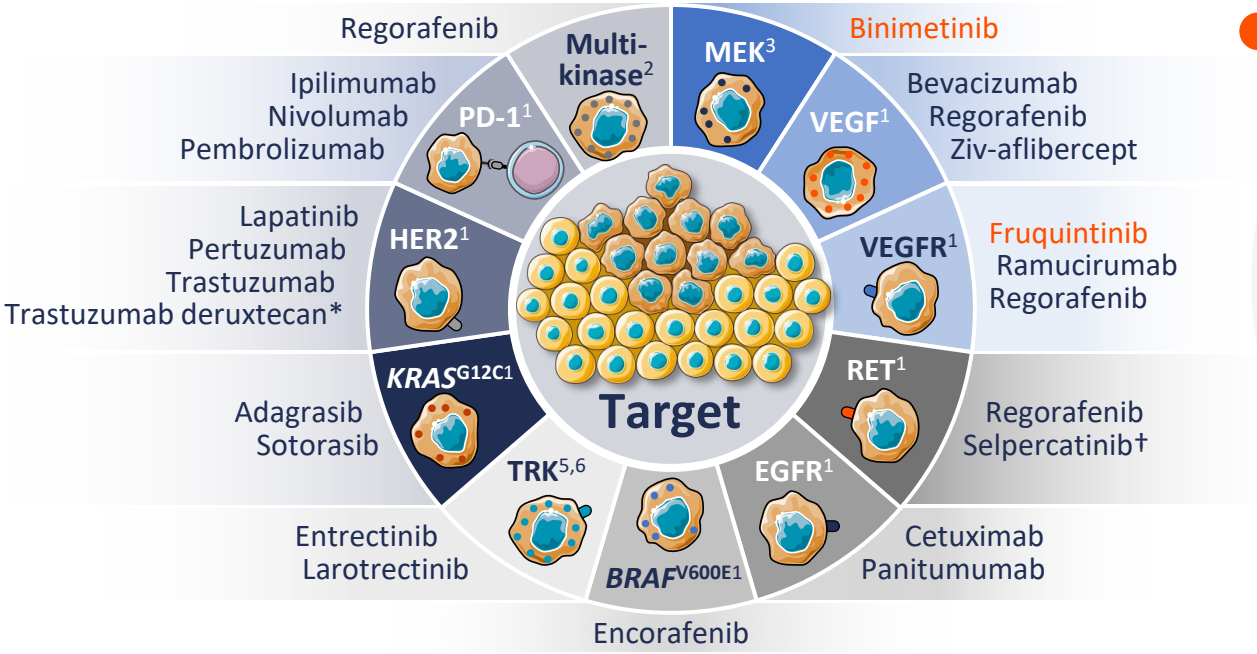
A range of biomarker-targeted therapies are available for the treatment of patients with CRC



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*HER2 amplification; †*RET* fusion. CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Alese OB, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389574; 2. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32;
3. Kopetz S, et al. *N Engl J Med.* 2019;381:1632–43; 4. Yoshino T, et al. *ESMO Open.* 2023;8:101558; 5. Entrectinib SmPC. Updated July 2023. Available at: https://bit.ly/3IMW5m8 (accessed 21 March 2024); 6. Larotrectinib SmPC. Updated September 2023. Available at: https://bit.ly/492kYEV (accessed 21 March 2023).

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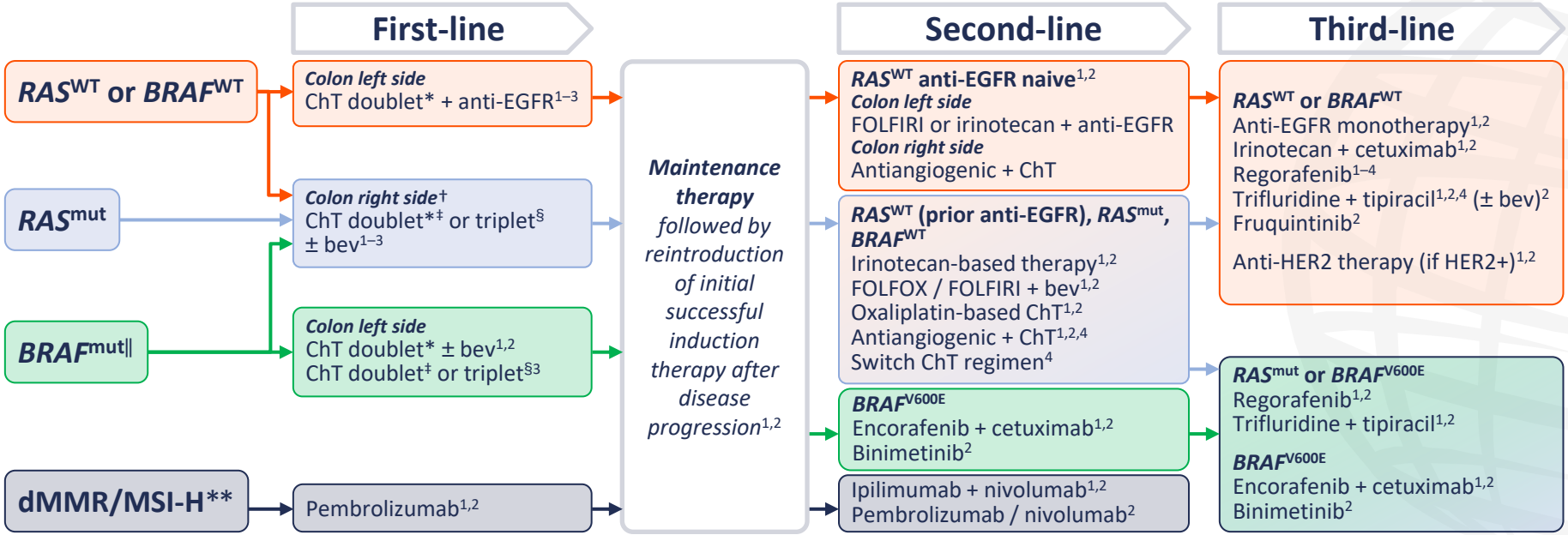
EU, Pan-Asian and Latin American recommendations for the management of unresectable mCRC generally align[1–3]



*FOLFOX or FOLFIRI or CAPOX in the majority of patients (EU and Asia); FOLFIRI or mFOLFOX6 (Latin America). †ChT doublet + anti-EGFR may be considered if tumour shrinkage is the aim (EU and Asia).[1,2]
‡FOLFOX or FOLFIRI (Latin America).[3] §FOLFOXIRI;[1–3] ChT triplet alone recommended in Latin America.[3] ‖Pan-Asia guidelines recommend ChT doublet or triplet ± bev regardless of side.[2]
**No specific guidance for third-line treatment for patients with dMMR/MSI-H tumours.[1–3]
Bev, bevacizumab; ChT chemotherapy; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; FOLFIRI, leucovorine–5-fluorouracil–irinotecan; FOLFOX, leucovorine–5-fluorouracil–oxaliplatin; FOLFOXIRI, leucovorin–5-fluorouracil–oxaliplatin–irinotecan; MSI-H, microsatellite instability-high; mut, mutant; WT, wild type.

1. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32; 2. Yoshino T, et al. *ESMO Open.* 2023;8:101558;
3. Stefanon LR, et al. *J Pain Manage.* 2019;12:315–24; 4. López RI, et al. *ESMO Open.* 2018;3:e000315.

Clinical insights on anti-EGFR-rechallenge in the treatment of CRC

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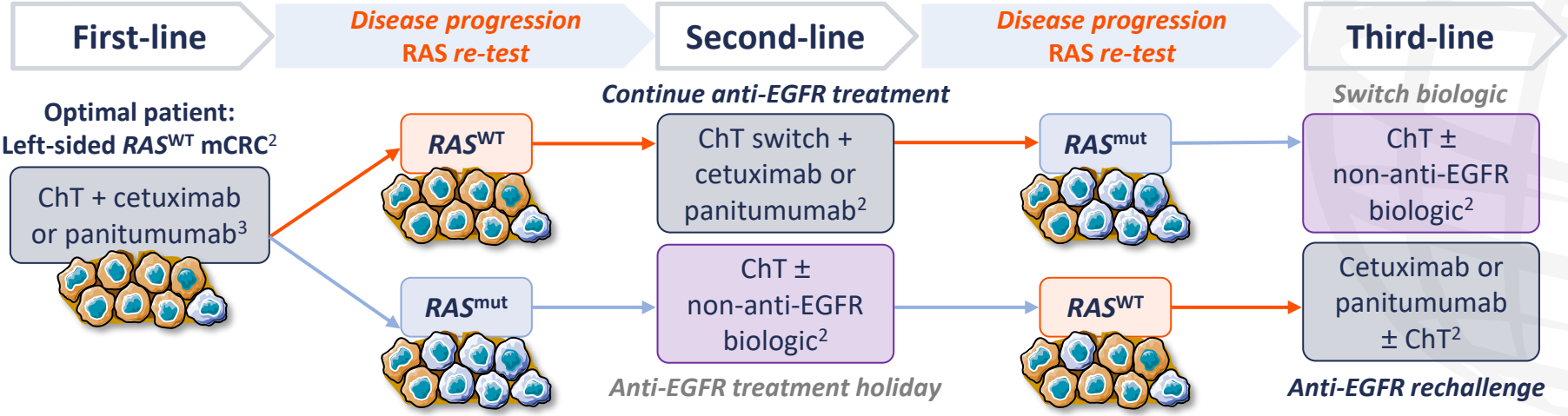
Anti-EGFR rechallenge has emerged as an active and well-tolerated therapeutic strategy[1,2]

Continuous anti-EGFR therapy can favour the proliferation of pre-existing, or insurgence of, new treatment-resistant mutant subclones of *RAS*^{WT} mCRC. These clones may decay with anti-EGFR treatment withdrawal, meaning the patient may become a candidate for anti-EGFR rechallenge[1]



Anti-EGFR rechallenge can offer tumour regression and disease stabilization for patients in the later-line setting[1]

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ChT, chemotherapy; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; mut, mutant; WT, wild type.

1. Ciardello D, et al. *Cancer Treat Rev*. 2024;124:102683; 2. Goldberg RM, et al. *ESMO Open.* 2018;3:e000353; 3. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32.

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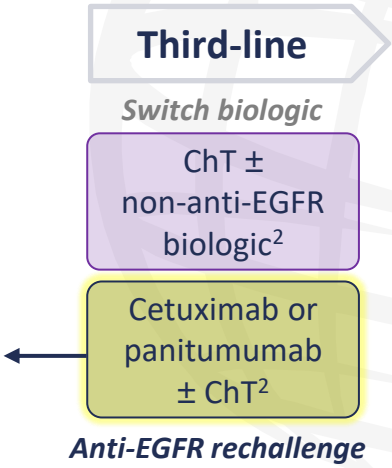
Various anti-EGFR rechallenge regimens have been investigated:[1]

- Cetuximab monotherapy
- Panitumumab monotherapy
- Cetuximab + irinotecan-based ChT
- Panitumumab + irinotecan-based ChT
- Panitumumab + trifluridine–tipiracil
- Cetuximab + avelumab

However, despite a small difference in the safety profile depending on the anti-EGFR mAb therapeutic partner, optimal regimens are yet to be identified[1]



Anti-EGFR rechallenge can offer tumour regression and disease stabilization for patients in the later-line setting[1]

ChT, chemotherapy; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; WT, wild type.

1. Ciardello D, et al. *Cancer Treat Rev*. 2024;124:102683; 2. Goldberg RM, et al. *ESMO Open.* 2018;3:e000353; 3. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32.

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Module 2: Agenda

- Biomarker-driven treatment sequencing in CRC
- Practical challenges in biomarker-targeted treatment of CRC
- Emerging targeted therapies for patients with CRC

Biomarker-driven treatment sequencing in CRC

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The mCRC treatment sequence is based on patient-, disease- and tumour-specific characteristics[1]

Factors affecting treatment choice[1,2]

Patient characteristics

- Symptoms
- Age
- Performance status
- Comorbidities
- Preferences
- Quality of life

Tumour biology

- Primary tumour location
- Location of metastases
- Mutational status
- Tumour burden

Treatment factors

- Treatment goal
- Toxicity
- Physician preference
- Type and timing of prior therapy

First- and second-line setting

Standard treatment is generally **ChT**, often combined with **VEGF- or EGFR-targeted therapies** (*RAS*^{WT}), or **immunotherapy** (dMMR/MSI-H)[1]

Third-line setting and beyond

Anti-EGFR ± ChT (*RAS*^{WT} and *BRAF*^{WT})[2,3]*
Trifluridine–tipiracil or regorafenib (*RAS*^{mut})[2,3]*
Encorafenib + cetuximab (*BRAF*^{V600E})[2,3]*
Anti-HER2 (HER2+)[2,3]

Despite multiple treatment options in the first-, second-, third- and further-line settings, there is currently no defined optimal treatment sequence for mCRC across multiple lines of therapy[1]

*Pan-Asian adapted ESMO guidelines also recommend trifluridine–tipiracil ± bevacizumab or fruquintinib (*RAS*^{WT}, *BRAF*^{WT}, *RAS*^{mut}, *BRAF*^{V600E}) and encorafenib + cetuximab ± binimetinib or regorafenib (*BRAF*^{V600E}).[3]

ChT, chemotherapy; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; WT, wild type.

1. Babajanyan S, et al. *Colorectal Cancer.* 2022;10:1; 2. Cervantes A, et al. *Ann Oncol.* 2023;34:10–32; 3. Yoshino T, et al. *ESMO Open.* 2023;8:101558.

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Practical challenges in biomarker-targeted treatment of CRC

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Opportunities exist to address practical challenges with biomarker-targeted therapies in CRC

Addressing patient concerns and raising awareness[1]

- Fear of side effects
- Personal preferences
- Education status
- Lack of awareness
- Understanding treatment efficacy and outcomes

Developing genomic testing infrastructure[2,3]

- Improved access to testing
- Harmonized assays
- Workforce and training
- Available techniques and new technologies

Understanding CRC molecular pathology[4,5]

- Identifying new actionable targets
- Target pathway complexity
- Tumour heterogeneity
- Tumour microenvironment

CRC, colorectal cancer. 1. Liu Y, et al. *Int J Public Health.* 2023;68:1606091; 2. Roberts TJ, et al. *JAMA Network Open.* 2023;6:e2310809; 3. Rzadkowska P, Lawler M. Access to Genomic Tumour Testing. 2024. Available at www.europeancancer.org/policy/13-policy/48-time-to-accelerate-access-to-genomic-tumour-testing (accessed 18 March 2024); 4. Batis N, et al. *Adv Drug Deliv Rev.* 2021;176:113854; 5. Kim SY, Kim TW. *ESMO Open.* 2020;5:e000634.

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Emerging targeted therapies for patients with CRC

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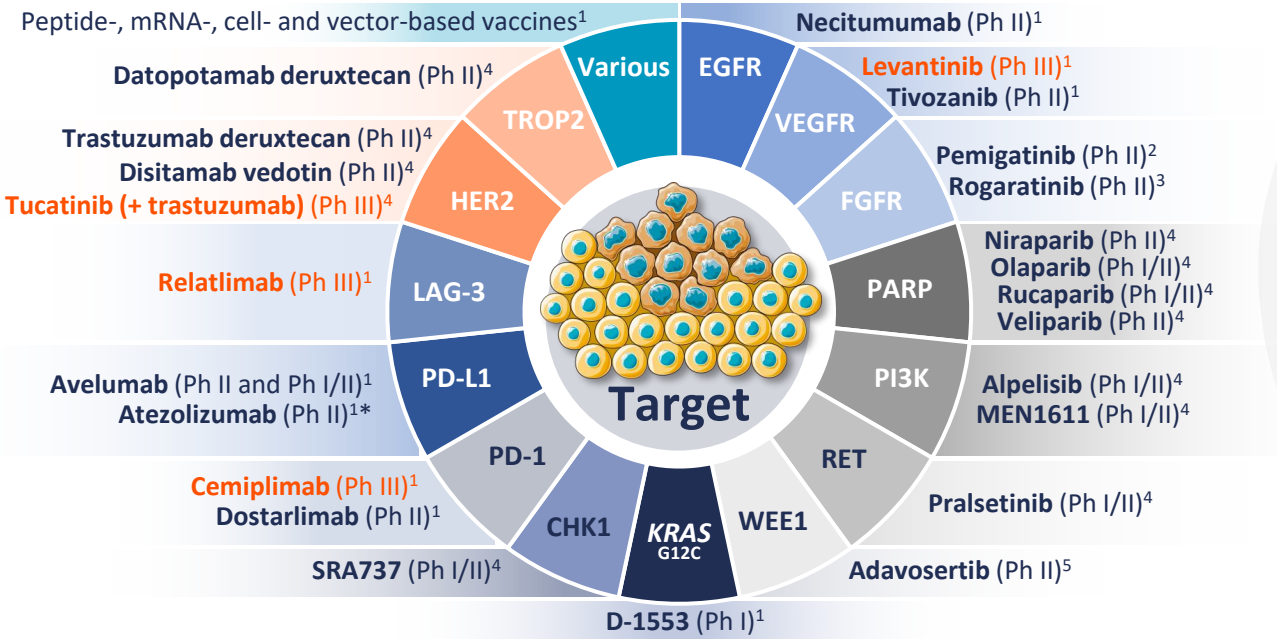
An extensive range of targeted treatments are being evaluated for the management of CRC



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*The phase III clinical trial, atezolizumab ± cobimetinib vs regorafenib in previously treated patients with mCRC failed to meet the primary endpoint.[1] ADC, antibody-drug conjugate; CHK1, checkpoint kinase 1; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; LAG-3, lymphocyte activation gene 3; PARP, poly(ADP-ribose)polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Ph, phase; PI3K, phosphoinositide 3-kinase; TRK, tropomyosin receptor kinase; TROP2, trophoblast antigen 2; VEGFR, vascular endothelial growth factor receptor.

1. Kumar A, et al. *World J Gastrointest Surg.* 2023;15:495–519; 2. ClinicalTrials.gov. NCT05202236; 3. ClinicalTrials.gov. NCT04595747; 4. Alese OB, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389574; 5. Seligmann JF, et al. *J Clin Oncol.* 2021;39:3705–15.

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