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

Practice aid for the treatment of patients with CRC

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Using biomarker testing to help inform treatment decisions

Biomarker testing is recommended in all patients at the time of mCRC diagnosis due to its relevance in selecting first-line therapy[1,2]

KEY BIOMARKERS[1,2]	***RAS* mutations** (exon 2, 3 and 4 in *KRAS* or *NRAS*)	***BRAF* mutations**	**MMR status**
Testing method	dPCR or NGS[1]	Sanger sequencing, dPCR or NGS[1]	PCR or IHC[1]

ADDITIONAL BIOMARKERS[1,2]	***HER2* amplification***	***NTRK* fusion†**
Testing method	IHC, ISH or NGS[1]	IHC; confirmation with NGS[1]

Drivers for first-line treatment[1]

TUMOUR CHARACTERISTICS
- Clinical presentation (tumour burden and localization)
- Tumour biology
- *RAS* and *BRAF* mutation status
- dMMR/MSI status

PATIENT CHARACTERISTICS
- Age and performance status
- Organ function
- Comorbidities
- Patient attitude, expectation and preference

TREATMENT CHARACTERISTICS
- Toxicity profile
- Flexibility of treatment administration
- Socioeconomic factors
- Quality of life

*Recommended in patients with *RAS*^{wt} tumours (and *RAS*^{mut} disease when feasible[2]) to detect those who may benefit from HER2 blockade in second or later lines.[1,2]
†Recommended when feasible to influence treatment decisions in third or later lines.[1,2]

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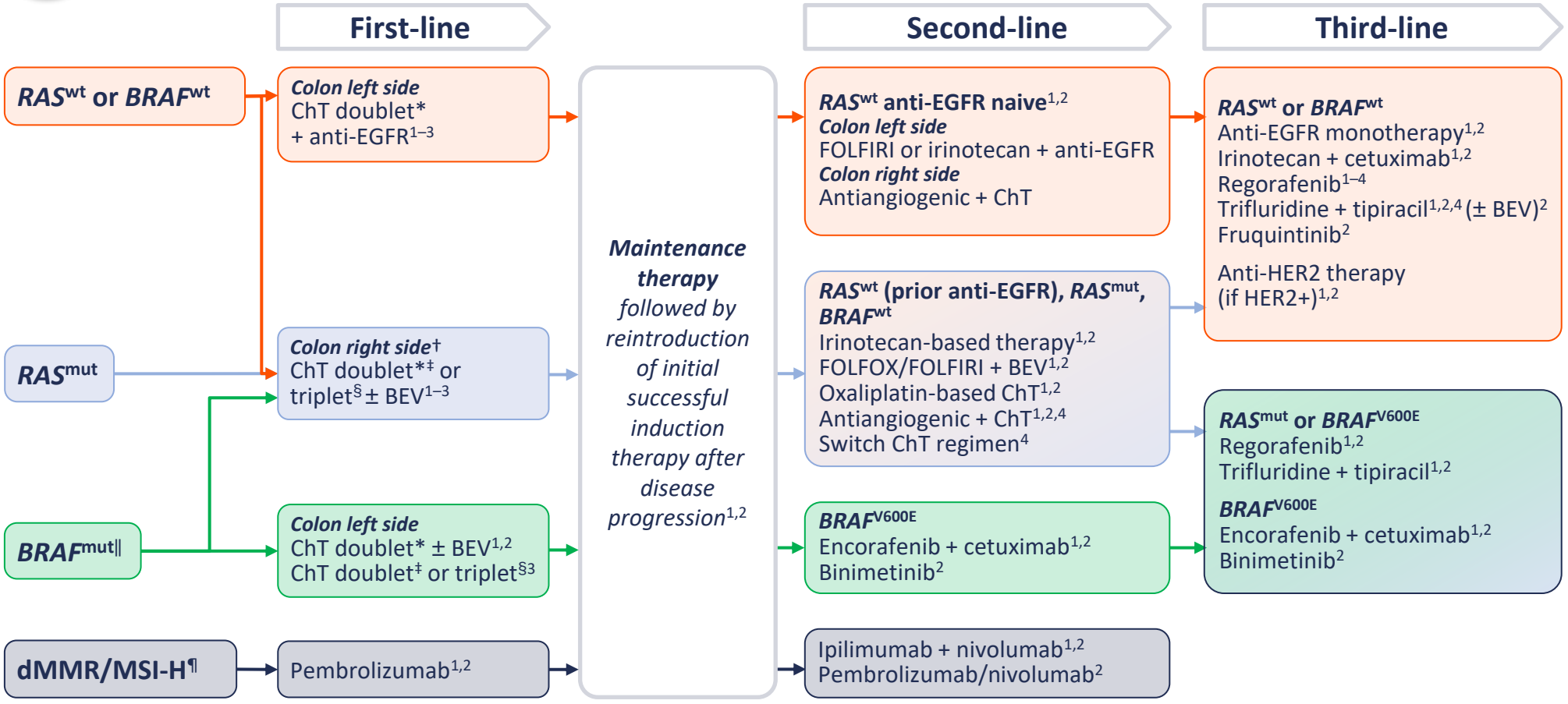
European, Pan-Asian and Latin American recommendations for the management of mCRC align[1–3]



*FOLFOX or FOLFIRI or CAPOX in the majority of patients (Europe and Asia);[1,2] FOLFIRI or mFOLFOX6 (Latin America).[3] †ChT doublet + anti-EGFR may be considered if tumour shrinkage is the aim (Europe 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]

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Phase III clinical evidence for treatment options in mCRC

First-line immunotherapy in patients with MSI-H/dMMR mCRC

KEYNOTE-177[5]

PEMBRO vs **ChT** (± BEV or CETUX)

Median follow-up **44.5 months**

mPFS, months

PEMBRO	16.5	n=153
ChT	8.2	n=154

Grade ≥3 TRAEs

22% (33/153) vs 66% (95/143)

CHECKMATE 8HW[6]

NIVO + IPI vs **ChT**

Median follow-up **24.3 months**

mPFS, months

NIVO + IPI	NR	n=171
ChT	5.8	n=84

Grade 3 or 4 TRAEs

23% (46/200) vs 48% (42/88)

NIVO + IPI vs ChT 79% **risk reduction** (disease progression/death)

Second- or later-line targeted therapy in patients with *BRAF*^{V600E}-mutant mCRC

BEACON[7,8]

ENCO + CETUX vs **CTRL** (investigators' choice)

Median follow-up **12.8–14.9 months***

mPFS, months

ENCO + CETUX	4.3	n=220
CTRL	1.5	n=221

AEIs: Association with PFS†

Arthralgia/myalgia
Diarrhoea
Dermatological

Grade ≥2 nephrotoxicity: Rare cases observed

BREAKWATER safety lead-in[9–11]

ENCO + CETUX + FOLFIRI vs **ENCO + CETUX + mFOLFOX6**[9–11]

Safety lead-in data (N=57) (trial ongoing)[10,11]

mPFS in 2L, months[9–11]

+ FOLFIRI	12.6	n=18
+ mFOLFOX6	10.8	n=8

Grade ≥3 TRAEs[10]

50% vs 78%

*Median duration of follow-up 12.8 months for survival[7] and 14.9 months for the safety analysis.[8] All p<0.02.[8]

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Practical challenges associated with the treatment of mCRC

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

First- and second-line setting

Standard treatment:

- **ChT**, often combined with **VEGF- or EGFR-targeted therapies** (*RAS*^{wt}), or
- **Immunotherapy** (dMMR/MSI-H)[12]

Third-line setting and beyond

- **Anti-EGFR ± ChT** (*RAS*^{wt} and *BRAF*^{wt})[1,2]*
- **Trifluridine–tipiracil or regorafenib** (*RAS*^{mut})[1,2]*
- **Encorafenib + cetuximab** (*BRAF*^{V600E})[1,2]*
- **Anti-HER2** (HER2+)[1,2]

Despite multiple treatment options in all settings, **there is currently no defined optimal treatment sequence for mCRC** across multiple lines of therapy[12]

Anti-EGFR rechallenge can offer tumour regression and disease stabilization for patients in the later-line setting[13]

Optimal patient: Left-sided *RAS*^{wt} mCRC[14]

First-line

ChT + cetuximab or panitumumab[1]

Disease progression RAS re-test

***RAS*^{mut}**

Second-line

ChT ± non-anti-EGFR biologic[14]

Disease progression RAS re-test

***RAS*^{wt}**

Third-line

Cetuximab or panitumumab ± ChT[14]

Continuous anti-EGFR therapy can favour the proliferation of pre-existing, or insurgence of, new treatment-resistant mutant subclones of *RAS*^{wt} mCRC[13]

Anti-EGFR treatment holiday[14]

Mutant clones may decay upon anti-EGFR treatment withdrawal[13]

Anti-EGFR rechallenge[14]

*Pan-Asian adapted ESMO guidelines also recommend fruquintinib or trifluridine–tipiracil ± BEV (*RAS*^{wt}, *BRAF*^{wt}, *RAS*^{mut}, *BRAF*^{V600E}) and regorafenib or encorafenib + cetuximab ± binimetinib (*BRAF*^{V600E}).[2]

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Abbreviations and references

Abbreviations

2L, second line; AE, adverse event; AEI, AE of interest; BEV, bevacizumab; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CAPOX, oxaliplatin and capecitabine; CETUX, cetuximab; ChT chemotherapy; CTRL, control; dMMR, deficient MMR; dPCR, digital polymerase chain reaction; EGFR, epidermal growth factor receptor; ENCO, encorafenib; ESMO, European Society for Medical Oncology; FOLFIRI, leucovorine–5-fluorouracil–irinotecan; FOLFOX, leucovorine–5-fluorouracil–oxaliplatin; FOLFOXIRI, leucovorin–5-fluorouracil–oxaliplatin–irinotecan; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IPI, ipilimumab; ISH, in situ hybridization; m, median; mCRC, metastatic colorectal cancer; mFOLFOX6, modified leucovorin–5-fluorouracil–oxaliplatin; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; mut, mutant; NGS, next-generation sequencing; NIVO, nivolumab; NR, not reached; NTRK, neurotrophic tyrosine receptor kinase; PEMBRO, pembrolizumab; PFS, progression-free survival; RAS, rat sarcoma virus; TRAE, treatment-related AE; VEGF, vascular endothelial growth factor; wt, wild type.

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