

Colorectal cancer: biomarkers, regimens, rectal strategies and side effects

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Updated 9 October 2026 · No doses · Verify current approvals and product information

A. Biomarkers and matched therapy

Approximate frequency in metastatic colorectal cancer (overlaps exist; NTRK, RET and others are each under 1%).

RAS mutant ~45–50%

BRAF ~8%

MSI-H ~4%

HER2 ~3%

RAS/BRAF wild ~35%

RAS (KRAS, NRAS)

- Extended RAS test before any anti-EGFR
- Mutant: anti-EGFR harms or does not help
- KRAS G12C: sotorasib or adagrasib + anti-EGFR (later line)

BRAF V600E

- Aggressive; right-sided; peritoneal spread
- First line: encorafenib + cetuximab + FOLFOX
- Later: encorafenib + cetuximab

dMMR / MSI-high

- Immunotherapy first line (pembrolizumab, or nivolumab + ipilimumab)
- Localised: neoadjuvant IO trials, organ sparing in rectum

HER2 amplified

- IHC 3+ or ISH; usually RAS wild-type, left-sided
- Tucatinib + trastuzumab, or trastuzumab deruxtecan
- Predicts anti-EGFR resistance

All patients

- Sidedness + RAS/BRAF choose anti-EGFR vs bevacizumab
- NGS: KRAS G12C, NTRK, POLE (IO), PI3K (aspirin in stage I–III)
- DPYD and UGT1A1 where available

Test early

At diagnosis of metastatic disease: RAS, BRAF, MMR/MSI, HER2 (NGS panel preferred). Tissue first; plasma ctDNA if tissue is scant. MMR for every new cancer.

Biomarkers that change treatment. Each result points to a specific drug, or away from one: anti-EGFR antibodies help only RAS and BRAF wild-type tumours, ideally left-sided.

Table A. Biomarkers and matched therapy

Biomarker	Frequency	Test	What it changes	Key trials	Watch for
dMMR / MSI-high	~15% of stage II, ~4% of metastatic	IHC for MLH1, MSH2, MSH6, PMS2 (or PCR/NGS MSI) on every new cancer	Stage II: no fluoropyrimidine alone. Stage III: FOLFOX + atezolizumab. Localised: neoadjuvant IO (organ sparing in rectum). Metastatic: nivolumab + ipilimumab preferred; single-agent PD-1 if less fit	KEYNOTE-177, CheckMate 8HW, NICHE-2, Cercek 2022, ATOMIC	Lynch work-up; immune side effects; pseudoprogression early

Biomarker	Frequency	Test	What it changes	Key trials	Watch for
RAS (KRAS/NRAS exons 2, 3, 4)	~45–50%	Extended RAS by NGS or PCR before any anti-EGFR	Mutant → no cetuximab or panitumumab	PRIME, CRYSTAL	Do not use KRAS exon 2 alone
KRAS G12C	~3%	NGS	Sotorasib + panitumumab (or adagrasib + cetuximab) after chemotherapy and anti-VEGF	CodeBreak 300, KRYSTAL-1	Single-agent KRAS inhibitors work poorly in colorectal cancer
BRAF V600E	~8–10%	NGS or PCR; (also used to sort MLH1 loss)	First line (any side): encorafenib + cetuximab + FOLFOX (FOLFIRI alternative); later: encorafenib + cetuximab	BREAKWATER, BEACON	Rapid course; arthralgia, skin papillomas, fatigue
HER2 amplification	~3–5% (RAS wild-type, left)	IHC 3+, or 2+ with ISH; NGS copy number	After chemotherapy: tucatinib + trastuzumab preferred; trastuzumab deruxtecan later (or second line if RAS-mutant)	MOUNTAINEER, DESTINY-CRC01, DESTINY-CRC02	Predicts anti-EGFR resistance; ILD with deruxtecan
POLE / POLD1 proofreading mutation	About 1%; ultramutated (TMB often >50/Mb)	NGS (somatic); germline testing if suspected PPAP	Metastatic: immune checkpoint inhibitor first line, as for dMMR	Guideline-based	Germline PPAP: colonoscopy from 25–30
PI3K pathway (PIK3CA, PIK3R1, PTEN)	About a third	NGS on the resected tumour	Stage I–III after surgery: low-dose aspirin for 3 years	ALASCCA	Bleeding risk; not shown in unselected patients
NTRK, RET fusions	<1% (mostly MSI-high, right)	RNA NGS	Larotrectinib or entrectinib; selpercatinib (tumour-agnostic)	Basket trials	Rare: test if pan-wild-type
DPYD variants	A few per cent	Germline genotype (or phenotype) before fluoropyrimidines	Reduce or avoid 5-FU/capecitabine	Guidance (EMA, CPIC)	Severe mucositis, diarrhoea, neutropenia
UGT1A1*28	Common in South Asians (heterozygous)	Germline genotype	Lower irinotecan exposure in homozygotes	Guidance	Neutropenia, diarrhoea

B. Systemic therapy by setting

Table B. Systemic therapy by setting (indications only; no doses)

Setting	Preferred options	Alternatives / when to modify	Evidence
Stage II high-risk colon	CAPOX 3 months, or FOLFOX 6 months	Fluoropyrimidine alone if over 70 or unfit for oxaliplatin; none if dMMR	MOSAIC, QUASAR, IDEA
Stage III colon, low risk (T1–3 N1)	CAPOX 3 months	FOLFOX 6 months; capecitabine or 5-FU alone if oxaliplatin unsuitable	IDEA, X-ACT
Stage III colon, high risk (T4 or N2)	CAPOX or FOLFOX 6 months	CAPOX 3 months if neuropathy or poor tolerance	IDEA, MOSAIC OS
Stage III colon, dMMR	FOLFOX + atezolizumab	Standard FOLFOX/CAPOX where atezolizumab unavailable	ATOMIC
Stage I–III, PI3K-pathway altered	Low-dose aspirin for 3 years after surgery (with or after adjuvant therapy)	Unselected patients: discuss; trials negative	ALASCCA, ASCOLT
Locally advanced colon (radiological T4, bulky T3)	Neoadjuvant FOLFOX (6 weeks) then surgery	Neoadjuvant nivolumab + ipilimumab if dMMR (trial or expert setting)	FOxTROT, NICHE-2
Locally advanced rectum (pMMR)	Total neoadjuvant therapy: short-course RT → chemo, or CRT + consolidation chemo, or induction chemo → CRT	Selected cT2N1/cT3N0–1 with clear MRF: FOLFOX first, RT only if poor response	RAPIDO, OPRA, PRODIGE 23, PROSPECT
Locally advanced rectum, dMMR	Anti-PD-1 alone (dostarlimab) with close MRI/endoscopy follow-up	Chemoradiation if IO unavailable (response to chemotherapy is poorer)	Cercek 2022
Metastatic, first line, pMMR, RAS/BRAF wild-type, left	FOLFOX or FOLFIRI + panitumumab or cetuximab	Bevacizumab instead if anti-EGFR unaffordable or poorly tolerated	PARADIGM, FIRE-3, CALGB/SWOG 80405
Metastatic, first line, right-sided or RAS-mutant	FOLFOX / CAPOX / FOLFIRI + bevacizumab; FOLFOXIRI + bevacizumab if fit with high burden	Right, wild-type, bevacizumab contraindicated: chemotherapy alone (not anti-EGFR); FOLFIRI if oxaliplatin within 12 months; frail: capecitabine ± bevacizumab	Hurwitz, TRIBE, sidedness analysis
Metastatic, first line, dMMR / MSI-high or POLE-ultramutated	Nivolumab + ipilimumab	Pembrolizumab, nivolumab or dostarlimab alone if less fit; 1–2 years	CheckMate 8HW, KEYNOTE-177
Metastatic, first line, BRAF V600E	Encorafenib + cetuximab + FOLFOX	FOLFIRI backbone if neuropathy	BREAKWATER
Liver-only, potentially resectable (conversion)	RAS/BRAF wild-type: oxaliplatin doublet/triplet (± anti-EGFR if left); RAS/BRAF-mutant: FOLFOXIRI + bevacizumab	≤4 cycles before surgery; about 6 months in total	CAIRO5, EPOC
Maintenance	Fluoropyrimidine + bevacizumab after 4–6 months of induction; stop oxaliplatin at 3–4 months	Treatment break with close scans for selected patients	CAIRO3
Second line	Switch backbone (FOLFOX ↔ FOLFIRI) ± continue bevacizumab, or aflibercept / ramucirumab with FOLFIRI	Encorafenib + cetuximab (BRAF); KRAS G12C or HER2 options	BEACON
Older or less fit	Doublet without 5-FU bolus if fit; otherwise fluoropyrimidine ± bevacizumab or trifluridine–tipiracil + bevacizumab	ECOG 3–4: supportive care; avoid bevacizumab within 6–12 months of arterial events	Geriatric assessment

Setting	Preferred options	Alternatives / when to modify	Evidence
Third line and later	Trifluridine–tipiracil + bevacizumab	Regorafenib; fruquintinib; anti-EGFR rechallenge if ctDNA RAS wild-type	SUNLIGHT, CORRECT, FRESCO-2, RECOURSE

C. Neoadjuvant strategies for rectal cancer

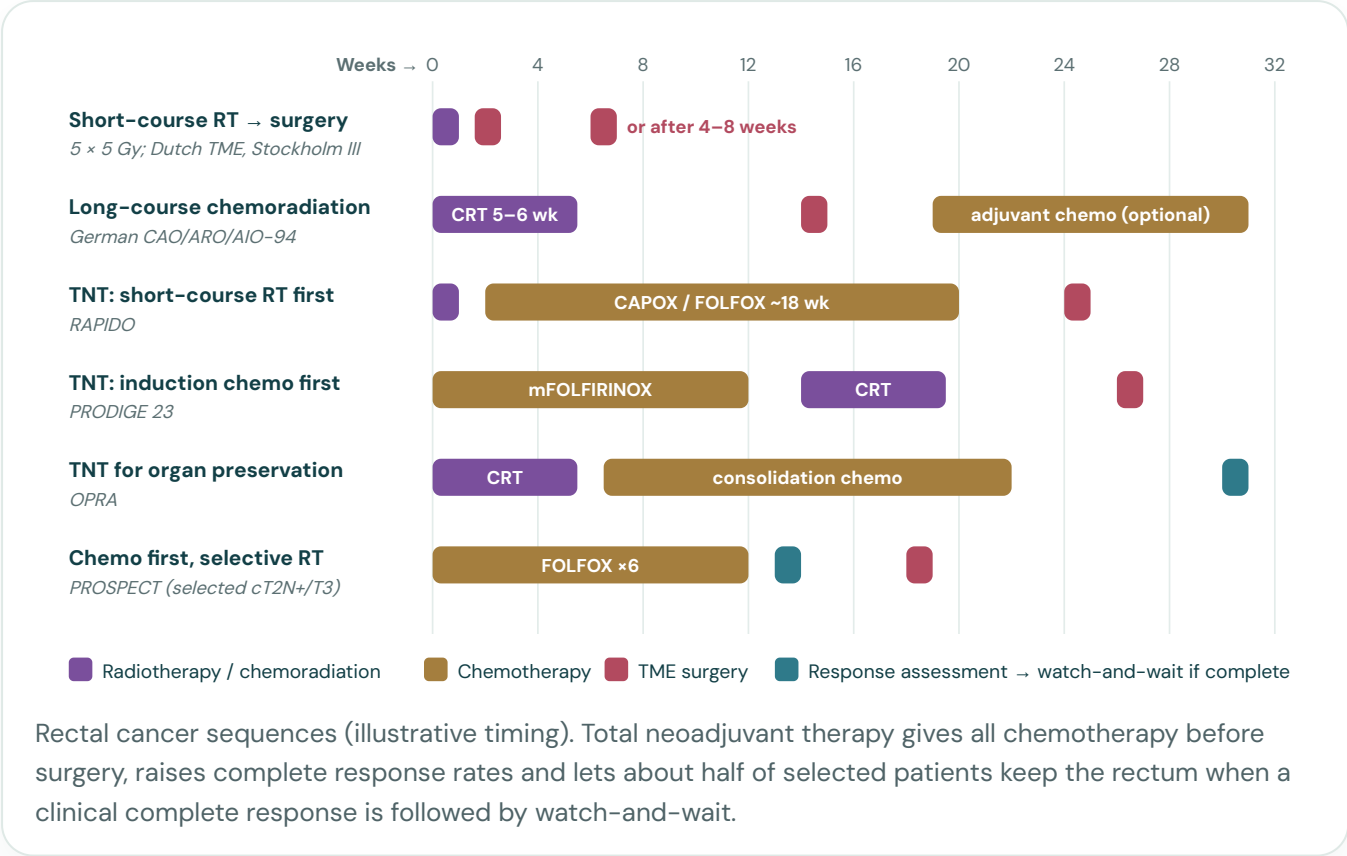
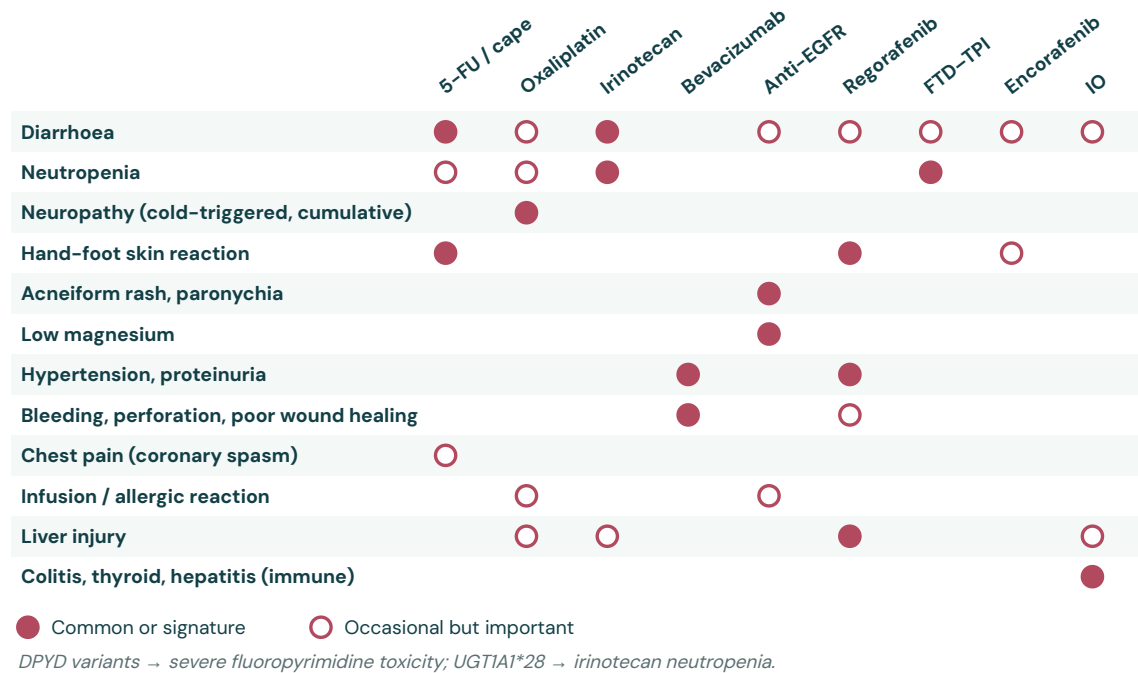


Table C. Neoadjuvant strategies for rectal cancer compared

Strategy	Best suited to	Main result	Caveat
Short-course RT (5 × 5 Gy) → surgery	Elderly or frail; when chemotherapy is not planned	Halved local recurrence vs surgery alone (Dutch TME)	Little downstaging if surgery is immediate; delay 4–8 weeks lowers complications (Stockholm III)
Long-course chemoradiation → surgery → adjuvant	Traditional standard	Preoperative better than postoperative for local control and toxicity (German CAO/ARO/AIO-94)	No survival gain; adjuvant chemotherapy often not completed
TNT: short-course RT → 18 weeks chemo → TME	High risk: T4, N2, threatened CRM, EMVI, lateral nodes	Fewer disease-related treatment failures; pathological complete response doubled (RAPIDO)	Higher local recurrence at 5 years than CRT in the trial: careful surgery and follow-up
TNT: induction FOLFIRINOX → CRT → TME	Fit patients, high distant risk	Better disease-free and overall survival (PRODIGE 23)	Intensive; needs good performance status

Strategy	Best suited to	Main result	Caveat
TNT: CRT → consolidation chemo → watch-and-wait if cCR	Low tumours where keeping the rectum matters	About half keep the rectum at 3–5 years (OPRA)	Regrowth in about a third of watch-and-wait patients; strict surveillance
FOLFOX → selective CRT → TME	cT2N1, cT3NO–1, MRF clear, suitable for sphincter-sparing surgery	Non-inferior disease-free survival; most avoid pelvic RT (PROSPECT)	Not for T4, threatened margin or low tumours
Anti-PD-1 alone	dMMR / MSI-high rectal cancer	Clinical complete response in nearly all patients in the first series (Cercek 2022)	Small numbers; confirm MMR status; surveillance as for watch-and-wait

D. Managing common side effects



Side effects by drug (schematic). Signature toxicities guide counselling: cold-triggered neuropathy with oxaliplatin, rash and low magnesium with anti-EGFR antibodies, hypertension and bleeding with anti-VEGF drugs.

Table D. Managing common side effects (principles; follow local protocols)

Problem	Usual cause	Do	Hold or stop when
Cold-triggered tingling, cramps; later persistent numbness	Oxaliplatin	Warn about cold drinks and metal; check function every cycle; stop-and-go strategy	Persistent numbness affecting function (grade 2 lasting, or 3): stop oxaliplatin, continue the rest
Diarrhoea	Irinotecan, fluoropyrimidines, IO	Loperamide plan given in advance; fluids; check for neutropenia	Severe, bloody, febrile or with dehydration: admit; on IO consider colitis (stool tests, steroids)
Severe toxicity in cycle 1 (mucositis, diarrhoea, neutropenia)	DPD deficiency	Stop fluoropyrimidine; supportive care; uridine triacetate where available	Do not rechallenge at full intensity; genotype DPYD

Problem	Usual cause	Do	Hold or stop when
Chest pain on infusion or capecitabine	Fluoropyrimidine coronary vasospasm	Stop, ECG and troponin	Recurrence is common: switch to raltitrexed or non-fluoropyrimidine regimen
Painful red palms and soles	Capecitabine; regorafenib (hand-foot skin reaction)	Emollients, urea cream, avoid friction; dose delay	Blistering or limits self-care
Acneiform rash, paronychia	Cetuximab, panitumumab	Pre-emptive doxycycline/minocycline, moisturiser, sunscreen; rash often tracks with benefit	Severe or infected rash; hold then resume at lower intensity
Low magnesium, cramps, arrhythmia	Anti-EGFR antibodies	Check magnesium, calcium, potassium regularly; replace	Symptomatic or refractory hypomagnesaemia
Hypertension, proteinuria	Bevacizumab, regorafenib, fruquintinib	BP every visit; urine dipstick	Uncontrolled BP, nephrotic-range proteinuria
Bleeding, perforation, wound problems	Anti-VEGF drugs	Stop 4–6 weeks before elective surgery; restart after wound heals	Perforation, major bleeding, arterial thrombosis: stop permanently; avoid with an uncovered stent
Neutropenia	Irinotecan, trifluridine–tipiracil, FOLFOXIRI	Count before each cycle; G-CSF per risk	Febrile neutropenia: emergency antibiotics
Colitis, hepatitis, thyroid, adrenal problems	Pembrolizumab, nivolumab ± ipilimumab	Baseline and periodic TSH, cortisol, liver tests; report diarrhoea early	Grade ≥2 colitis or hepatitis: hold, steroids; grade 4: stop