City of Hope®

Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Oncology for the Non–Oncologist

Principles of Cancer Care

Prep for Advances and Innovations in Endoscopic Oncology And Multidisciplinary Gastrointestinal Cancer Care



Disclosure

- This is a Non-CME Accredited session.

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ROADMAP

Ten modules, one goal: speaking the same language at the tumor board

1. **How oncologists think**
   intent, staging, the MDT
2. **NCCN guidelines**
   evidence and preference categories
3. **Local vs systemic therapy**
   surgery, radiation, sequencing
4. **Chemotherapy and dosing**
   regimens, toxicity, pharmacogenomics
5. **Dose escalation**
   phase I designs, dose optimization
6. **Genomics**
   germline vs somatic, biomarkers, ctDNA
7. **Targeted agents**
   kinase inhibitors, antibodies, ADCs
8. **Antiangiogenic agents**
   VEGF pathway, GI safety
9. **Immunotherapy**
   checkpoints, response, irAEs
10. **Assessing treatment and the patient**
    RECIST, endpoints, ECOG, QoL

1 · How oncologists think

Intent, staging and the multidisciplinary team

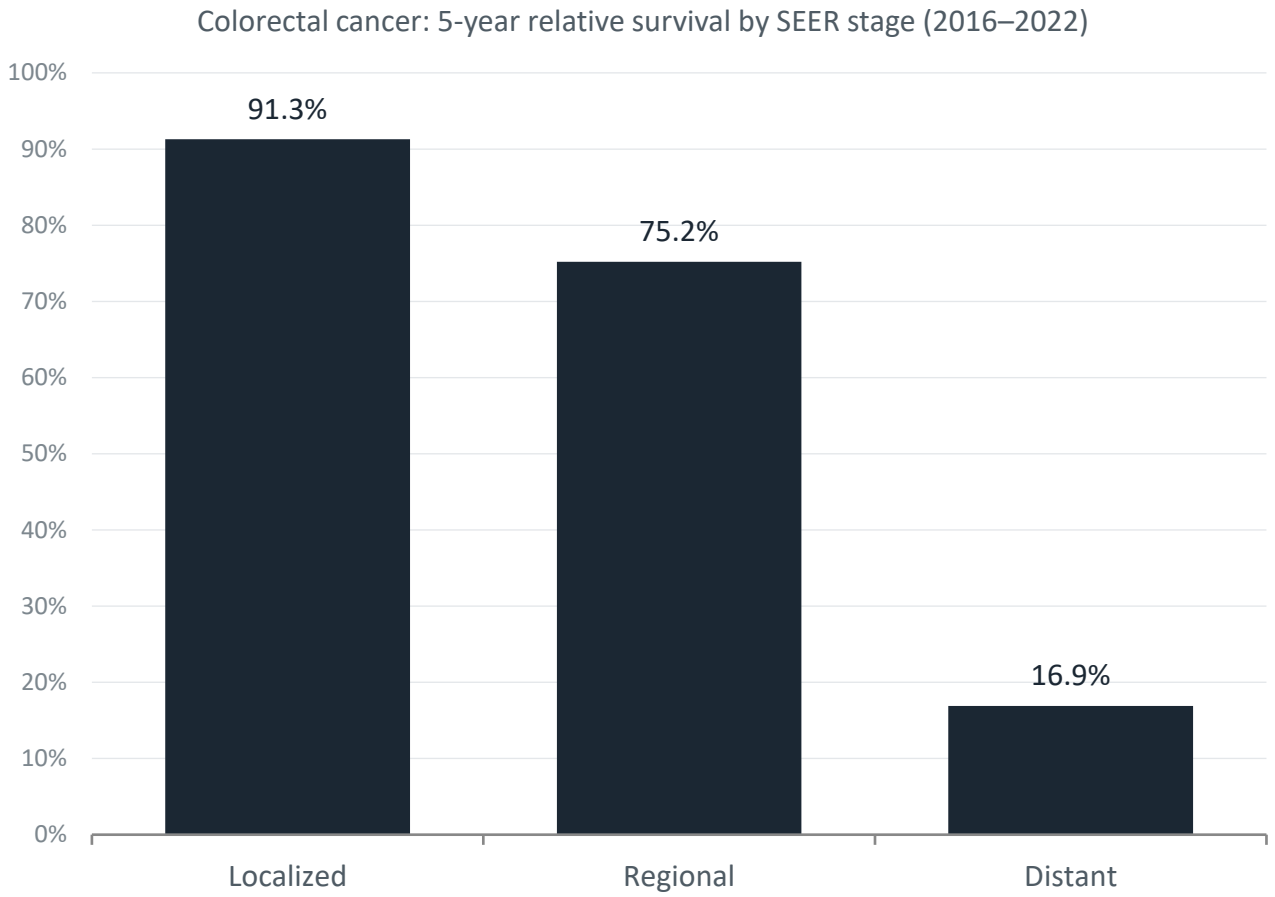
Every plan starts with one question: are we treating to cure or to control?

Curative intent
Localized or limited disease. Accept more toxicity for a chance of cure. Endpoints: overall survival, disease-free survival, pathologic response.

Palliative (disease-control) intent
Metastatic or unresectable disease in most solid tumors. Goal: longer life with good quality. Toxicity weighs more heavily.

Term	Meaning	GI example
Neoadjuvant	Before definitive local therapy	Chemoradiation before esophagectomy
Adjuvant	After complete resection, to kill micrometastases	FOLFOX/CAPOX after stage III colon resection
Perioperative	Both before and after surgery	FLOT around gastrectomy
Maintenance	Lower-intensity therapy after initial control	5-FU/capecitabine ± biologic in metastatic CRC

Stage drives intent, treatment and prognosis



TNM in one line

- **T** depth or size of the primary tumor
- **N** regional lymph node involvement
- **M** distant metastasis
- **Stage group** I–IV, from the AJCC manual; clinical (c), pathologic (p) and post-neoadjuvant (yp) prefixes

For GI:
EUS defines T and N in esophageal, gastric, pancreatic and rectal cancer; that staging decides who gets neoadjuvant therapy.

Sources: SEER Cancer Stat Facts: Colorectal Cancer (5-year relative survival 2016–2022; 34% localized, 37% regional, 23% distant at diagnosis); AJCC Cancer Staging Manual.

Cancer care is a team sport; the gastroenterologist touches every phase

Diagnose	Stage	Treat	Support	Survey
Endoscopy, biopsy, EUS-FNA/FNB; enough tissue for genomics	EUS T/N staging; ERCP/EUS for biliary obstruction	Endoscopic resection of early lesions; stents; nutrition access	Manage colitis, hepatitis and bleeding from systemic therapy	Colonoscopy after CRC resection; Lynch and high-risk programs

The tumor board (MDT)

Surgery, medical and radiation oncology, radiology, pathology, gastroenterology, genetics, nursing, palliative care and nutrition review each case to agree on intent, sequence and trial eligibility. Tissue adequacy at the first biopsy often decides how fast that can happen.

Cancer biology maps directly onto drug classes

Hallmark of cancer	What it means	Therapy that targets it	GI example
Sustained proliferative signaling	Growth pathways stuck "on"	Kinase inhibitors, anti-EGFR/HER2 antibodies	Cetuximab, trastuzumab
Inducing or accessing vasculature	Tumors recruit blood supply	Anti-VEGF antibodies, VEGFR TKIs	Bevacizumab, ramucirumab
Avoiding immune destruction	Tumors switch off T cells	Checkpoint inhibitors	Pembrolizumab, durvalumab
Genome instability and mutation	DNA repair defects	Immunotherapy (dMMR); PARP inhibitors (BRCA)	MSI-H CRC; BRCA pancreas
Resisting cell death	Apoptosis blocked	Cytotoxic chemotherapy, combinations	FOLFOX, FOLFIRINOX
Activating invasion and metastasis	Spread beyond the primary	Systemic therapy for micrometastases	Adjuvant chemotherapy

Source: Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov 2022;12:31–46 (selected hallmarks and enabling characteristics).

2 · NCCN guidelines

How to read the most-used oncology guideline in the US

NCCN: an alliance of leading US cancer centers that writes the guidelines most US oncologists use

1995

founded as a not-for-profit alliance

33

member cancer centers, most NCI-designated comprehensive centers

>16 million

guideline downloads per year

>190

countries where NCCN resources have been used

Clinical Practice Guidelines
Treatment by cancer type; screening, prevention and risk reduction; supportive care; specific populations

Drugs & Biologics Compendium
Drug and indication listings used by CMS and many commercial payers for coverage decisions

Evidence Blocks
Regimens rated 1–5 on efficacy, safety, evidence quality, consistency and affordability

Guidelines for Patients
Plain-language versions of the clinical guidelines, free to patients

Global resources
Harmonized guidelines for resource-limited settings; translations and international adaptations

JNCCN
Journal of the National Comprehensive Cancer Network, publishing guideline insights since 2003

Guidelines are written by multidisciplinary panels from member institutions (including a patient advocate) and updated at least annually.

NCCN labels every recommendation by evidence and by panel consensus

Category	Evidence	Panel consensus	Vote required
1	High-level	Uniform consensus that it is appropriate	≥85%
2A (default)	Lower-level	Uniform consensus that it is appropriate	≥85%
2B	Lower-level	Consensus that it is appropriate	≥50% but <85%
3	Any level	Major disagreement that it is appropriate	≥25% to include

- **Most recommendations are 2A,** so "not category 1" does not mean "weak".
- **Panels** include specialists from member institutions, a patient advocate and a primary care physician; guidelines are reviewed at least annually, with interim updates when new data or approvals arrive.

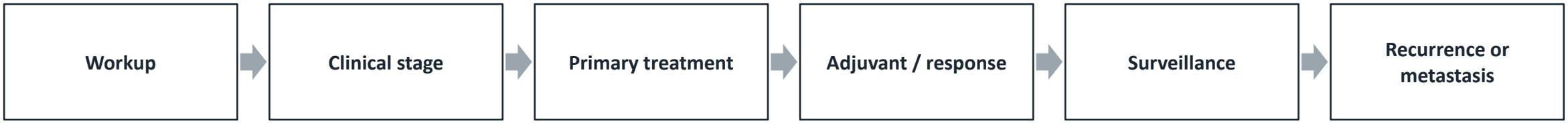
Source: NCCN. Development and update of guidelines; NCCN categories of evidence and consensus (nccn.org).

Preference labels and the algorithm structure tell you what the panel actually favors

Preferred
Best efficacy, safety and evidence; affordability considered where relevant

Other recommended
May be less effective, more toxic, less mature data, or much less affordable

Useful in certain circumstances
For specific patient populations, defined in the footnotes



Typical algorithm page sequence; footnotes carry much of the nuance (biomarker requirements, dosing, eligibility).

A note for industry partners:
the NCCN Drugs & Biologics Compendium is used by CMS and many payers to support coverage, including some off-label uses; listing and preference status matter commercially.

Sources: NCCN categories of preference; NCCN Drugs & Biologics Compendium (nccn.org).

Clinical trial phases: each answers a different question

Phase	Main question	Typical size	Typical endpoints
I	Is it safe? What dose?	Tens of patients	Dose-limiting toxicity, pharmacokinetics, early activity
II	Does it work well enough to test further?	Dozens to a few hundred	Response rate, PFS; sometimes randomized
III	Is it better than the standard?	Hundreds to thousands, randomized	OS, PFS, DFS/EFS, quality of life
IV	What happens in routine use?	Large populations	Rare toxicities, real-world effectiveness

Accelerated approval
FDA can approve on a surrogate endpoint (often response rate) when a confirmatory trial is required; common in targeted and tumor-agnostic approvals.

Sources: US FDA, Step 3: Clinical research (drug development process); FDA accelerated approval program.

Value frameworks ask a second question: how much benefit, at what cost?

NCCN Evidence Blocks
Rate each regimen 1–5 on efficacy, safety, quality and consistency of evidence, and affordability.

- **Statistically significant ≠ clinically meaningful:** a hazard ratio of 0.85 with a 3-week median gain may matter less than it sounds.
- **Industry relevance:** these scores increasingly inform formularies, payers and health-technology assessment outside the US.

Sources: Cherny NI, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit (ESMO-MCBS). Ann Oncol 2015;26:1547–73. NCCN Evidence Blocks (nccn.org).

3 · Local vs systemic therapy

Treating the tumor you can see and the cells you cannot

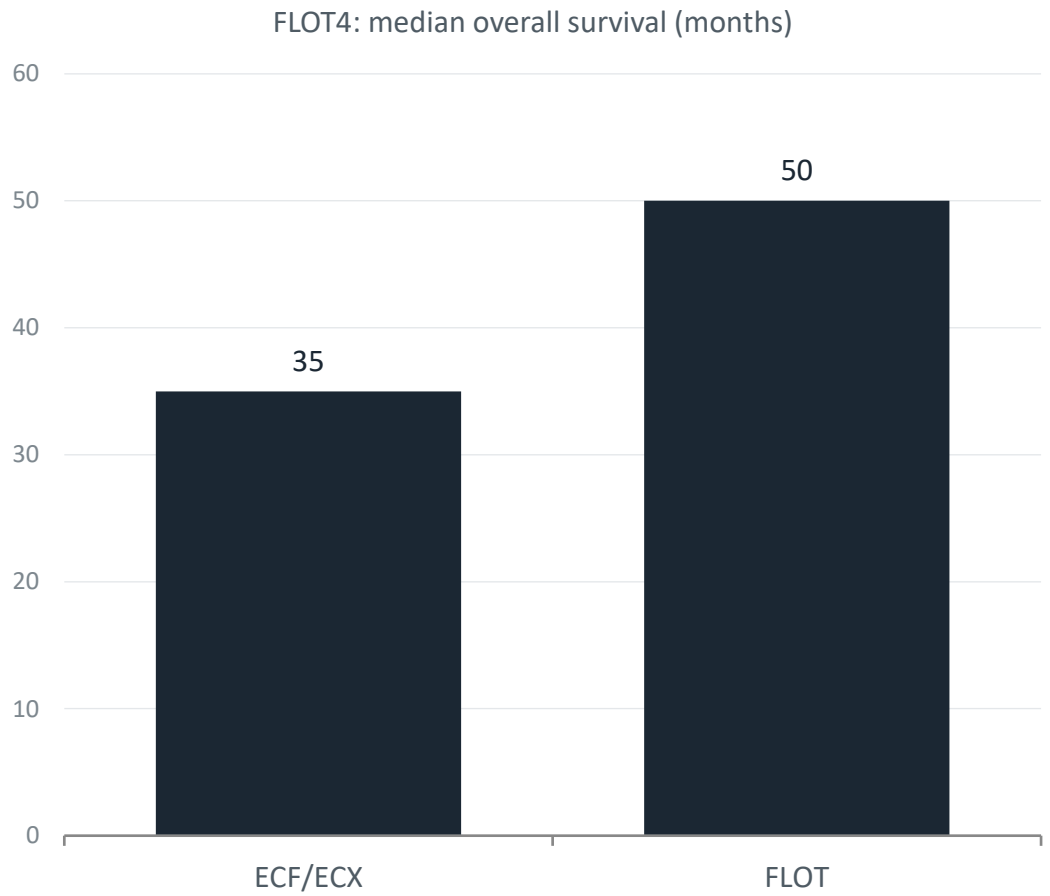
Local therapy treats a place; systemic therapy treats the whole body

	Local therapy	Systemic therapy
Modalities	Surgery, radiation (incl. SBRT), endoscopic resection, ablation, TACE/Y-90	Chemotherapy, targeted agents, immunotherapy, hormonal therapy
Goal	Remove or destroy visible disease	Treat micrometastases and widespread disease
Best when	Disease is confined to one site	Spread is present or likely
Main limits	Cannot reach occult spread; organ function	Resistance; whole-body toxicity

The modern trend

Combining both: systemic therapy first to shrink disease and test biology, then local therapy; and in selected oligometastatic disease, local therapy to metastases with curative intent (for example, colorectal liver metastases).

Perioperative systemic therapy raised survival in resectable gastric cancer



HR 0.71

MATTERHORN: event-free survival with durvalumab + perioperative FLOT vs FLOT alone (n=948)

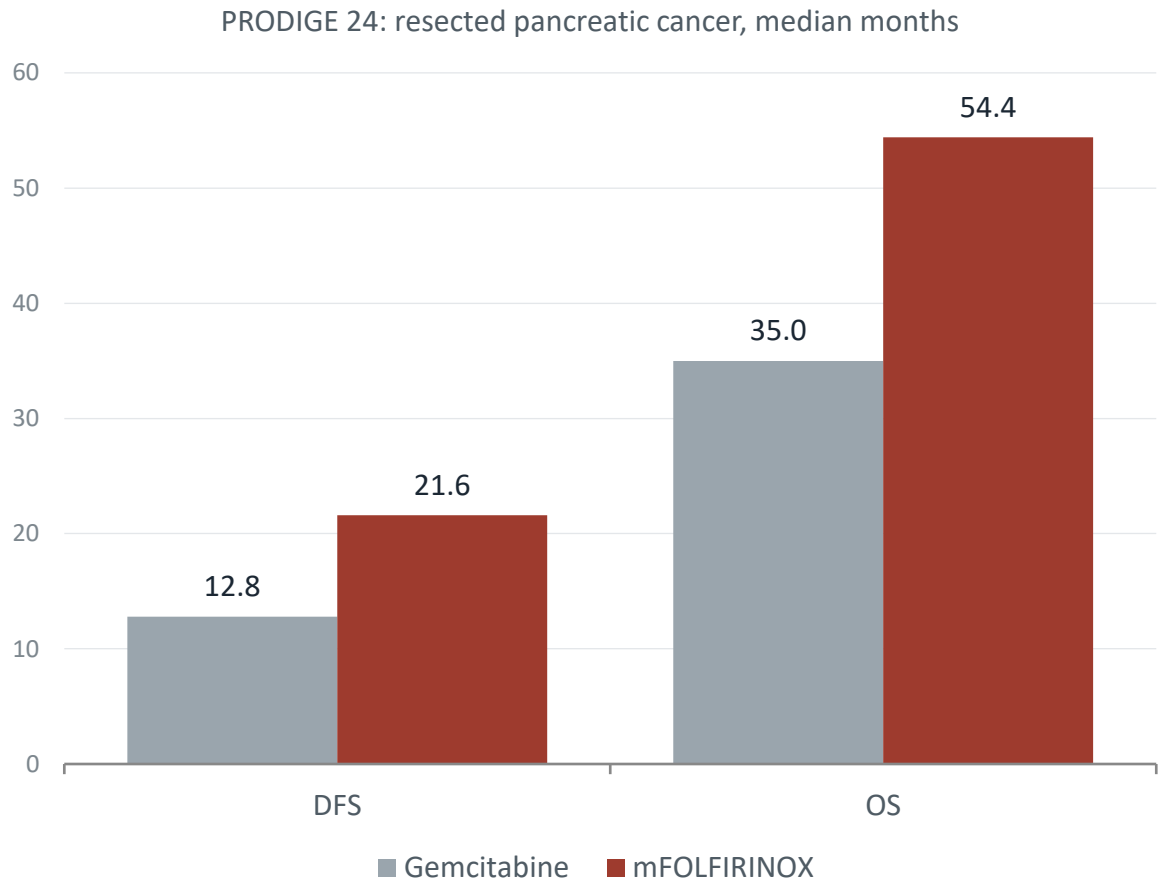
HR 0.78

MATTERHORN: overall survival; FDA approved November 2025

Principle:
treat micrometastases early, while the patient is fit and before surgery reduces tolerance.

Sources: Al-Batran SE, et al. FLOT4. Lancet 2019;393:1948–57. Janjigian YY, et al. MATTERHORN. N Engl J Med 2025;393:217–30; FDA approval Nov 25, 2025 (ASCO Post).

Adjuvant therapy after resection: large gains where micrometastases are common



CheckMate 577 (esophageal/GEJ)

22.4 vs 11.0

months median disease-free survival with adjuvant nivolumab vs placebo, for residual disease after neoadjuvant chemoradiation and resection

GI relevance:
adjuvant therapy is time-sensitive; delayed recovery from complications or poor nutrition after surgery can cost patients their adjuvant window.

Sources: Conroy T, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395–406. Kelly RJ, et al. Adjuvant nivolumab in resected esophageal or GEJ cancer. N Engl J Med 2021;384:1191–203.

Biology can replace surgery: immunotherapy for dMMR rectal cancer

49 of 49

patients with dMMR locally advanced rectal cancer had a clinical complete response to 6 months of dostarlimab

92%

recurrence-free at 2 years without surgery or radiation

65%

clinical complete response in 54 patients with other early dMMR cancers (gastroesophageal, hepatobiliary and others)

Why it matters

Avoids low anterior resection or abdominoperineal resection, ostomy, and pelvic radiation toxicity: organ preservation.

GI role

Endoscopic and MRI assessment of complete response, then close endoscopic surveillance for regrowth ("watch and wait").

Sources: Cercek A, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386:2363–76. Cercek A, et al. Nonoperative management of mismatch repair-deficient tumors. N Engl J Med 2025 (AACR 2025; ASCO Post).

Radiation therapy in brief

- **Dose** measured in Gray (Gy); split into daily fractions so normal tissue can repair between doses
- **Chemoradiation** 5-FU or capecitabine as radiosensitizers (rectal, esophageal, anal cancer)
- **Short-course** 5 Gy × 5 fractions in rectal cancer, often within total neoadjuvant therapy
- **SBRT** high-dose, few-fraction, highly conformal; used for oligometastases, pancreas, liver
- **Liver-directed** TACE and Y-90 radioembolization for HCC and liver metastases

Late GI effects to recognize
Radiation proctitis and enteritis, strictures, bleeding telangiectasias; months to years after pelvic radiation.

Total neoadjuvant therapy (TNT)
All chemotherapy and chemoradiation before rectal surgery: better delivery of systemic therapy and more complete responses.

General principles; see NCCN Rectal, Esophageal and Anal Cancer guidelines for regimen details.

4 · Chemotherapy and dosing

Regimens, toxicity and pharmacogenomics

The GI chemotherapy toolkit: a handful of drugs in named combinations

Class	Drugs	Signature toxicities
Fluoropyrimidines	5-FU, capecitabine (oral)	Mucositis, diarrhea, hand–foot syndrome; coronary vasospasm (rare)
Platinums	Oxaliplatin, cisplatin	Oxaliplatin: cold-induced and cumulative neuropathy; cisplatin: kidney, hearing
Topoisomerase I inhibitor	Irinotecan	Early cholinergic and late diarrhea; neutropenia
Taxanes	Docetaxel, paclitaxel, nab-paclitaxel	Neuropathy, neutropenia, hypersensitivity
Nucleoside analog	Gemcitabine	Myelosuppression, fatigue

Common regimens: FOLFOX / CAPOX (5-FU or capecitabine + oxaliplatin) · FOLFIRI · FOLFIRINOX · FLOT (5-FU, oxaliplatin, docetaxel) · gemcitabine + nab-paclitaxel

Regimen components per NCCN guidelines; toxicities per product labeling.

Toxicity is graded the same way everywhere: CTCAE

Grade	General definition	Diarrhea example (increase over baseline)
1	Mild; observation only	<4 stools/day
2	Moderate; limits instrumental daily activities	4–6 stools/day
3	Severe; limits self-care; hospitalization indicated	≥7 stools/day; incontinence
4	Life-threatening; urgent intervention	Life-threatening consequences
5	Death related to the adverse event	—

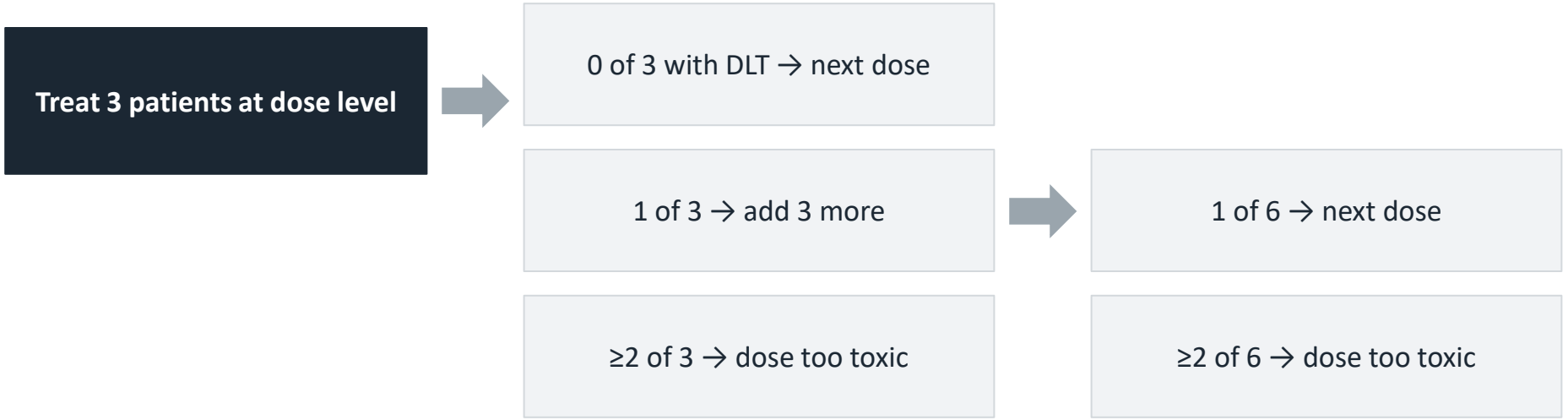
Sources: NCI Common Terminology Criteria for Adverse Events v5.0 (diarrhea grading); NCI DCTD, CTCAE updated to version 6 (2026).

5 · Dose escalation

How first-in-human trials find a dose, and why that is changing

DOSE ESCALATION

The classic 3+3 design escalates until toxicity appears



- **DLT** dose-limiting toxicity, defined in advance (usually grade ≥3) during cycle 1
- **MTD** maximum tolerated dose
- **RP2D** recommended phase 2 dose

MTD = highest dose with <2 of 6 DLTs → becomes RP2D

Standard 3+3 rule-based design as used in oncology phase I trials.

DOSE ESCALATION

For targeted and immune therapies, "maximum tolerated" is often not "optimal"

Why the MTD paradigm is changing
Cytotoxics: more dose, more effect, so MTD made sense. Targeted agents and antibodies can saturate their target well below MTD, adding toxicity without benefit. Chronic dosing means low-grade toxicity also matters.

- **Model assisted/based designs** (e.g., BOIN, CRM) use all accumulating data and reach the target dose more efficiently than 3+3.
- **Expansion cohorts** test the chosen dose in specific tumor types or biomarker groups.
- **In clinic:** dose reductions for toxicity are common and expected; they do not necessarily reduce efficacy.

Sources: US FDA Oncology Center of Excellence, Project Optimus; FDA guidance, Optimizing the dosage of human prescription drugs and biological products for the treatment of oncologic diseases (2024). Liu S, Yuan Y. Bayesian optimal interval designs. J R Stat Soc C 2015.

6 · Genomics

Germline, somatic and circulating tumor DNA

Two genomes, two questions: is it inherited, and what drives this tumor?

Germline (inherited)
Present in every cell; tested in blood or saliva. Informs cancer risk for the patient and family, surveillance, and sometimes therapy (e.g., BRCA → PARP inhibitor or platinum). Examples: Lynch (MLH1, MSH2, MSH6, PMS2, EPCAM), BRCA1/2, PALB2, CDKN2A, APC.

Somatic (tumor)
Acquired in the tumor; tested on tissue or ctDNA by next-generation sequencing. Informs therapy choice and prognosis. Examples: KRAS, BRAF V600E, HER2 amplification, MSI/dMMR, FGFR2 fusion, NTRK fusion.

- **Tumor findings can reveal germline risk:** a dMMR tumor needs germline testing for Lynch syndrome.
- **Tissue vs liquid biopsy:** tissue remains standard; ctDNA is faster and less invasive but can miss low-shedding tumors.

See NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric; and Breast, Ovarian, Pancreatic, and Prostate.

GENOMICS

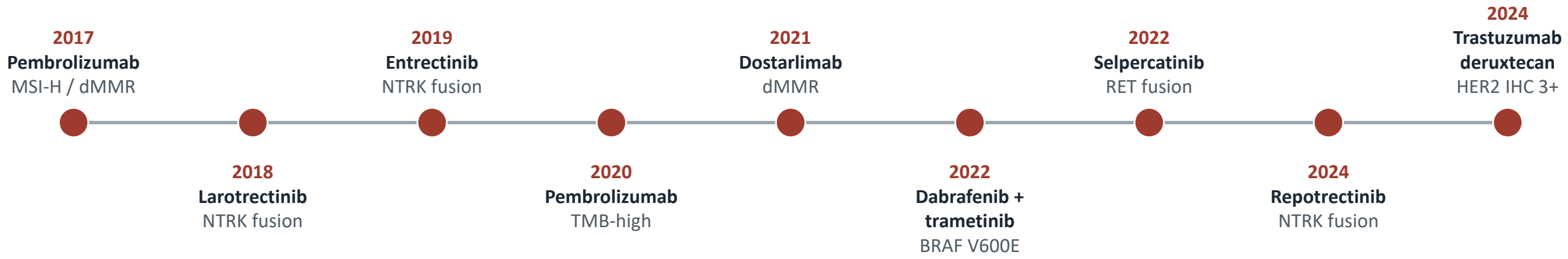
Biomarkers that change treatment in GI cancers today

Cancer	Test at diagnosis of advanced disease	Why
Colorectal	KRAS/NRAS, BRAF V600E, MSI/dMMR, HER2; consider NTRK, KRAS G12C	Anti-EGFR only if RAS wild-type; BRAF and HER2 targeted options; immunotherapy for dMMR
Gastric / GEJ / esophageal	HER2, PD-L1 (CPS), MSI/dMMR, Claudin 18.2	Trastuzumab; checkpoint inhibitors by CPS; zolbetuximab for CLDN18.2-positive
Pancreatic	Germline testing for all; tumor NGS (KRAS, BRCA, MSI, NTRK, NRG1)	Family risk; platinum/PARP for BRCA; rare targetable fusions
Biliary tract	FGFR2 fusions, IDH1, HER2, BRAF V600E, MSI	Multiple approved targeted agents
HCC	Usually no routine driver testing	Treatment guided by liver function and stage

Summarized from current NCCN Colon, Rectal, Gastric, Esophageal and EGJ, Pancreatic Adenocarcinoma, Biliary Tract, and Hepatocellular Carcinoma guidelines (2025–2026 versions).

GENOMICS

Tumor-agnostic approvals: the biomarker, not the organ, defines the indication

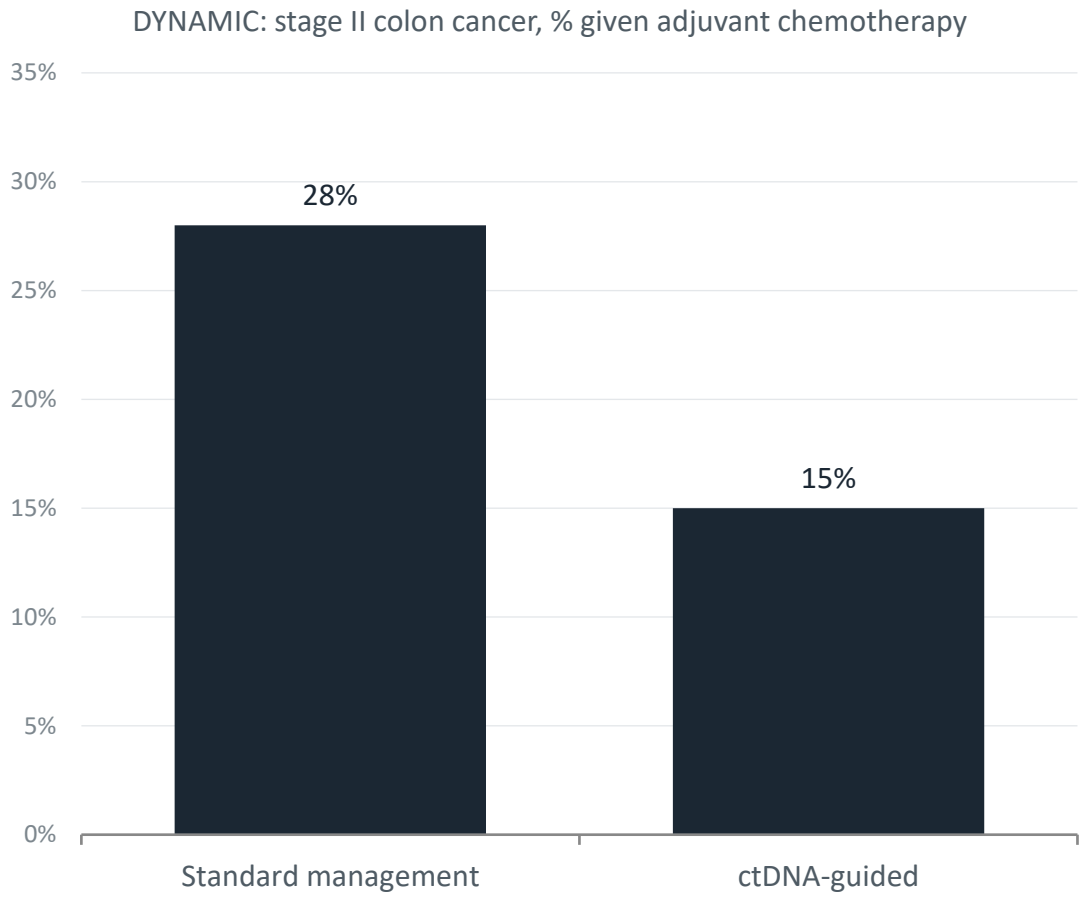


Implication:
broad next-generation sequencing (plus MMR/MSI and HER2 IHC) in advanced GI cancers, because rare targets appear across tumor types.

Sources: FDA approvals as summarized by OncLive (2024) and published reviews of tissue-agnostic approvals; years are first tumor-agnostic FDA approval.

GENOMICS

Circulating tumor DNA can guide who needs adjuvant chemotherapy



93.5% vs 92.4%

2-year recurrence-free survival, ctDNA-guided vs standard: non-inferior

- **MRD (minimal residual disease):** tumor DNA in blood after surgery predicts recurrence.
- **Today:** prognostic and increasingly used; trials are testing escalation for ctDNA-positive and de-escalation for ctDNA-negative patients.
- **Caveat:** a negative test does not exclude recurrence.

Source: Tie J, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. N Engl J Med 2022;386:2261–72.

Reading an NGS report: not every variant is actionable

AMP/ASCO/CAP tier	Meaning	Action
Tier I	Strong clinical significance: FDA-approved or guideline-supported therapy	Usually acted on
Tier II	Potential clinical significance: other tumor types, trials, or emerging evidence	Consider trials or off-label use
Tier III	Unknown significance (VUS)	Do not act on; may be reclassified
Tier IV	Benign or likely benign	Ignore

- **Variant allele frequency (VAF):** the % of reads with the variant; ~50% in a high-purity tumor may suggest a germline variant needing confirmation.
- **Also reported:** TMB (mutations/Mb) and MSI status; ask whether the assay tests RNA for fusions.

Source: Li MM, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer (AMP/ASCO/CAP). J Mol Diagn 2017;19:4–23.

7 · Targeted agents

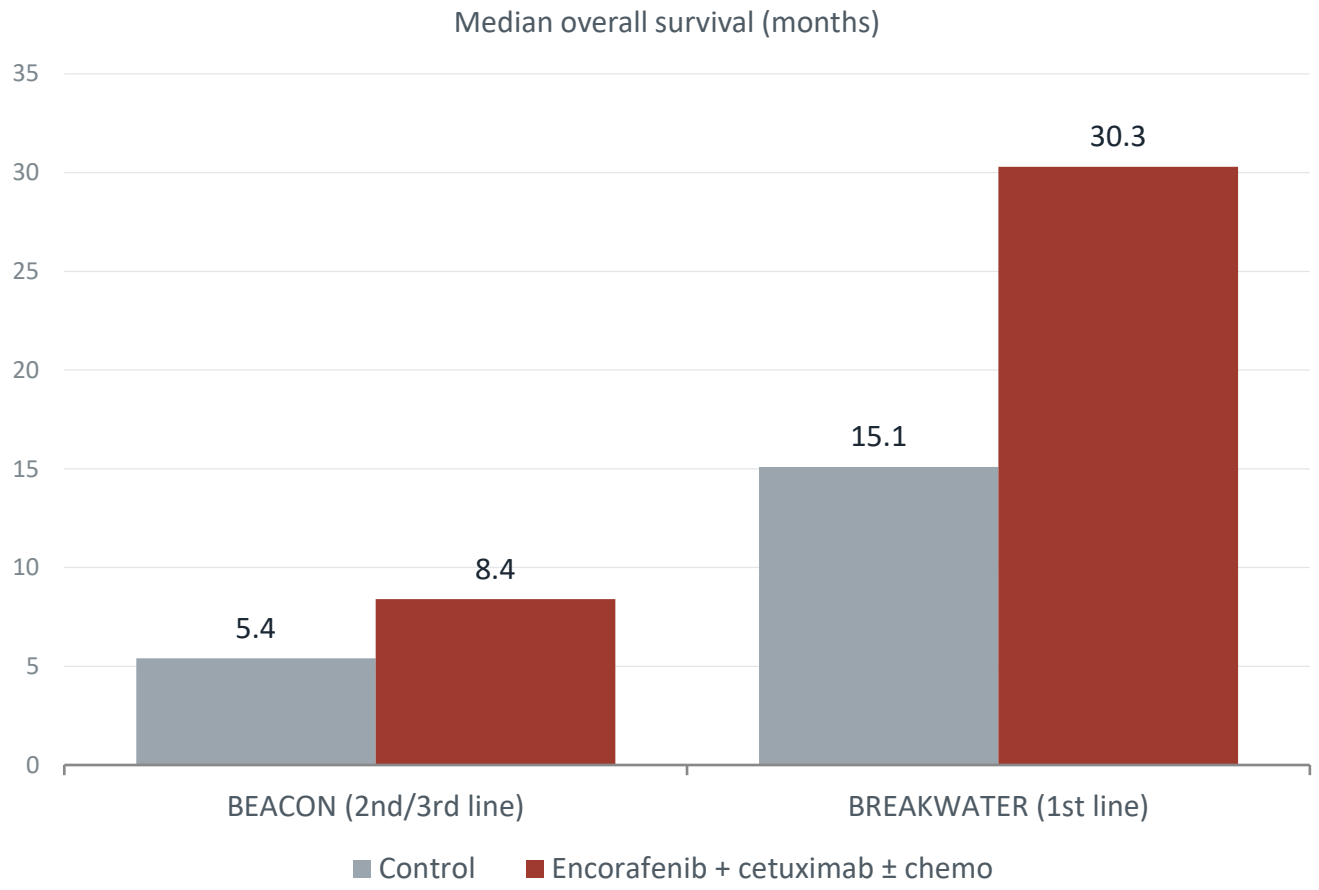
Kinase inhibitors, antibodies and antibody–drug conjugates

The drug name tells you the drug class

Suffix	Class	How it works	GI examples
-nib	Small-molecule kinase inhibitor (oral)	Enters cells, blocks kinase signaling	Regorafenib, fruquintinib, lenvatinib, pemigatinib
-mab	Monoclonal antibody (IV)	Binds receptor or ligand outside the cell; can recruit immune effectors	Cetuximab, panitumumab, trastuzumab, bevacizumab, zolbetuximab
-ximab / -zumab / -umab	Chimeric / humanized / human antibody	Less mouse sequence = less immunogenicity	Cetuximab / trastuzumab / panitumumab
ADC	Antibody–drug conjugate	Antibody delivers a cytotoxic payload into target cells	Trastuzumab deruxtecan
Bispecific	Antibody with two binding sites	Links two targets, e.g. tumor and T cell	Zanidatamab (HER2 biparatopic)

Naming conventions per USAN/INN monoclonal antibody nomenclature (pre-2022 scheme; newer antibodies use revised suffixes).

BRAF V600E colorectal cancer: from targeted rescue to first-line standard



HR 0.49

BREAKWATER overall survival: encorafenib + cetuximab + mFOLFOX6 vs standard chemotherapy ± bevacizumab

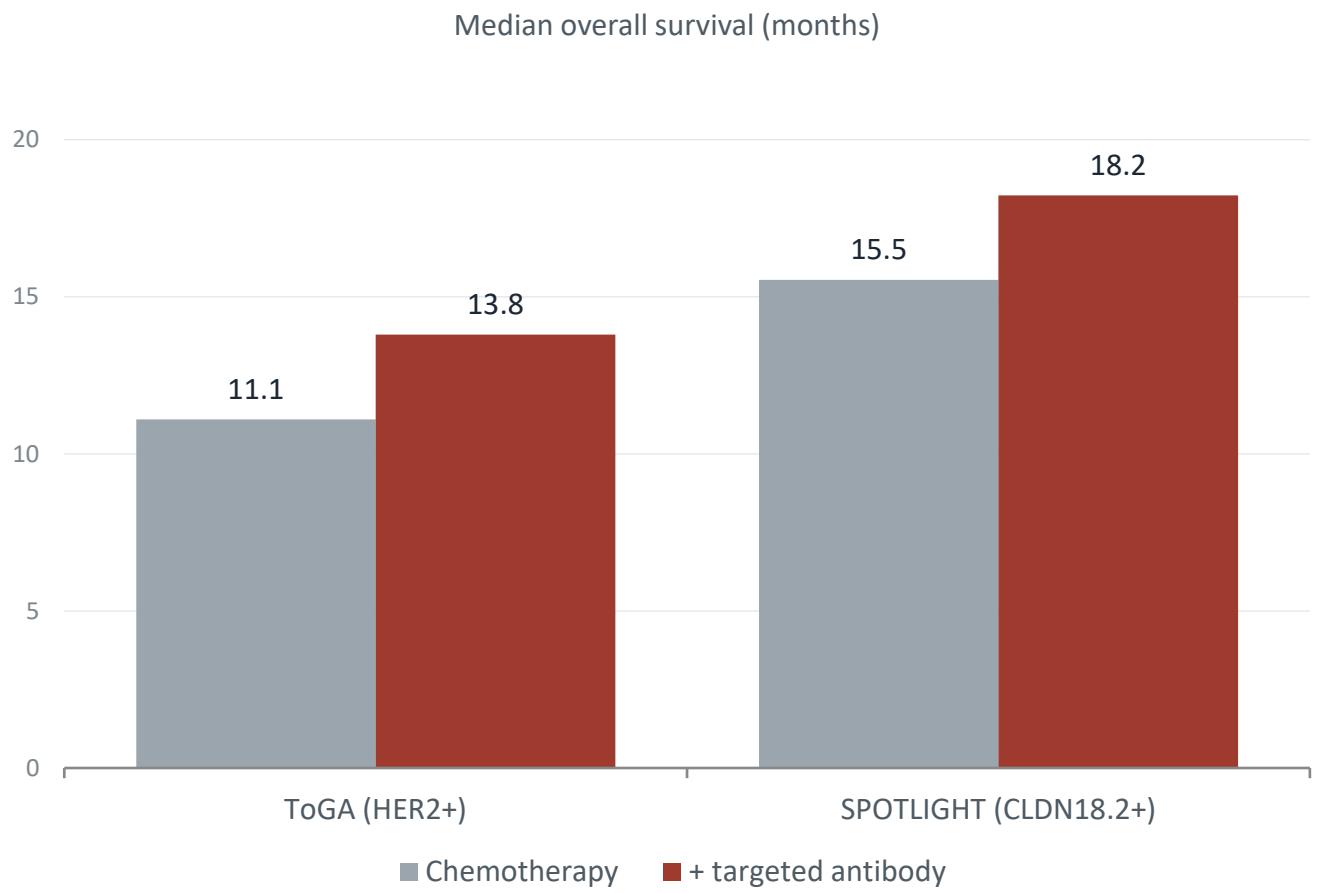
65.7% vs 37.4%

objective response rate

Lesson:
BRAF inhibitor alone fails in CRC because EGFR feedback reactivates the pathway; the combination blocks both.

Sources: Kopetz S, et al. Encorafenib, binimetinib and cetuximab in BRAF V600E–mutated colorectal cancer (BEACON). N Engl J Med 2019;381:1632–43 (doublet vs control). Élez E, et al. BREAKWATER. ASCO 2025 LBA3500; N Engl J Med 2025.

Gastric cancer: HER2 and Claudin 18.2 as targets

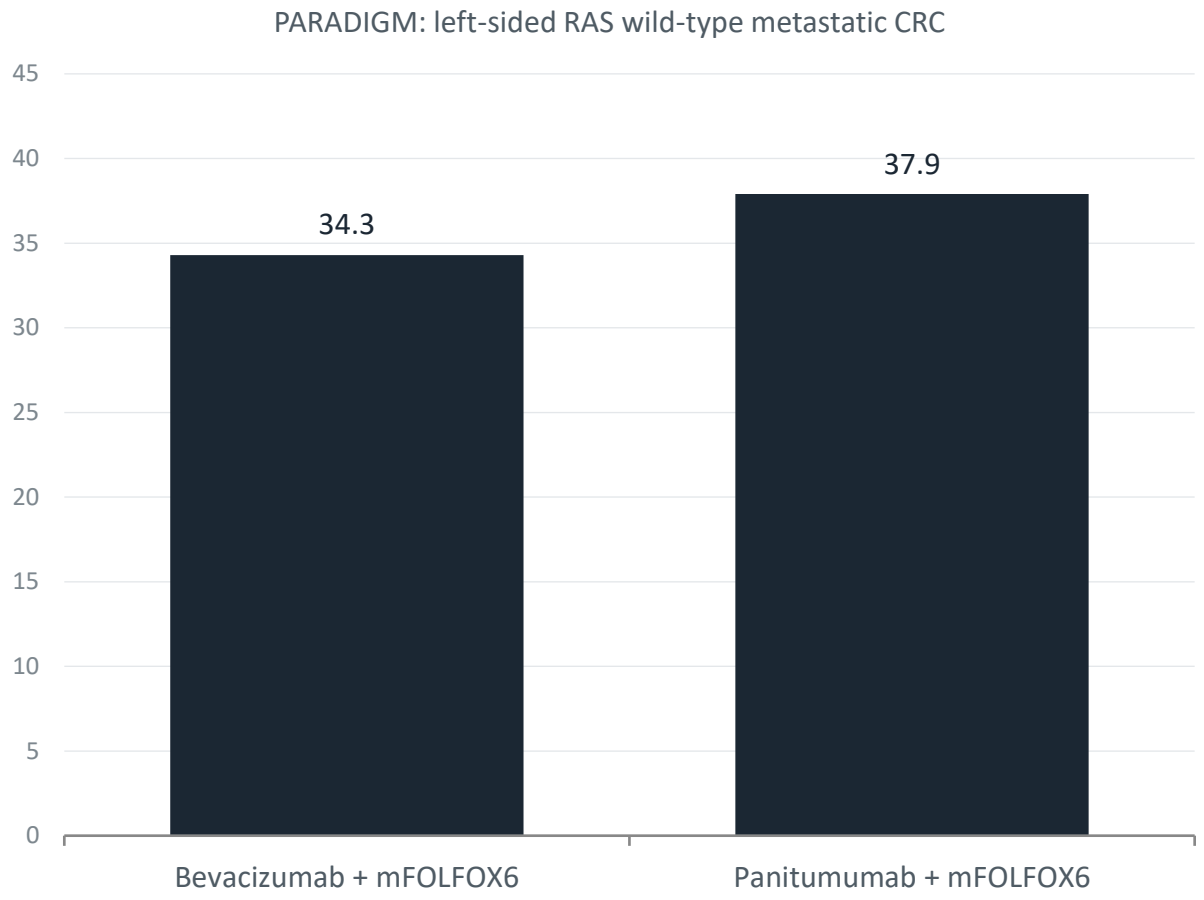


- **HER2:** trastuzumab + chemotherapy (ToGA); pembrolizumab added for PD-L1–positive disease (KEYNOTE-811).
- **Claudin 18.2:** zolbetuximab + chemotherapy for CLDN18.2-positive (≥75% of tumor cells, moderate–strong staining), HER2-negative disease; FDA approved 2024.

Watch for:
nausea and vomiting are the main early toxicities of zolbetuximab (claudin is expressed in normal gastric mucosa).

Sources: Bang YJ, et al. ToGA. Lancet 2010;376:687–97. Shitara K, et al. SPOTLIGHT. Lancet 2023;401:1655–68. Janjigian YY, et al. KEYNOTE-811. Nature 2021 / Lancet 2023.

Anti-EGFR therapy: RAS status and tumor sidedness both matter



- **RAS mutant:** anti-EGFR antibodies do not work and may harm.
- **Left-sided, RAS wild-type:** anti-EGFR + chemotherapy preferred first line (HR 0.82 for OS in PARADIGM).
- **Right-sided:** bevacizumab-based regimens generally preferred.

Toxicities to recognize:
acneiform rash (correlates with benefit), paronychia, hypomagnesemia, diarrhea.

Source: Watanabe J, et al. Panitumumab vs bevacizumab added to standard first-line chemotherapy and overall survival among patients with RAS wild-type, left-sided metastatic colorectal cancer (PARADIGM). JAMA 2023;329:1271–82.

Targeted therapy works until the tumor adapts

- **Primary resistance** pathway bypass from the start (e.g., RAS mutation blocks anti-EGFR effect)
- **Acquired resistance** new mutations in the target or downstream (e.g., emerging RAS clones on anti-EGFR therapy)
- **Monitoring** ctDNA can detect resistance clones before imaging progression
- **Rechallenge** resistant clones can decay off therapy, allowing later re-use in selected patients

Practical message for partners

Targeted agents rarely cure metastatic solid tumors alone. The field is moving to combinations (targeted + chemotherapy, + immunotherapy), earlier lines, and repeated molecular testing at progression.

General principles of targeted-therapy resistance in GI oncology.

8 · Antiangiogenic agents

Starving the tumor of blood supply, and what that means for the gut

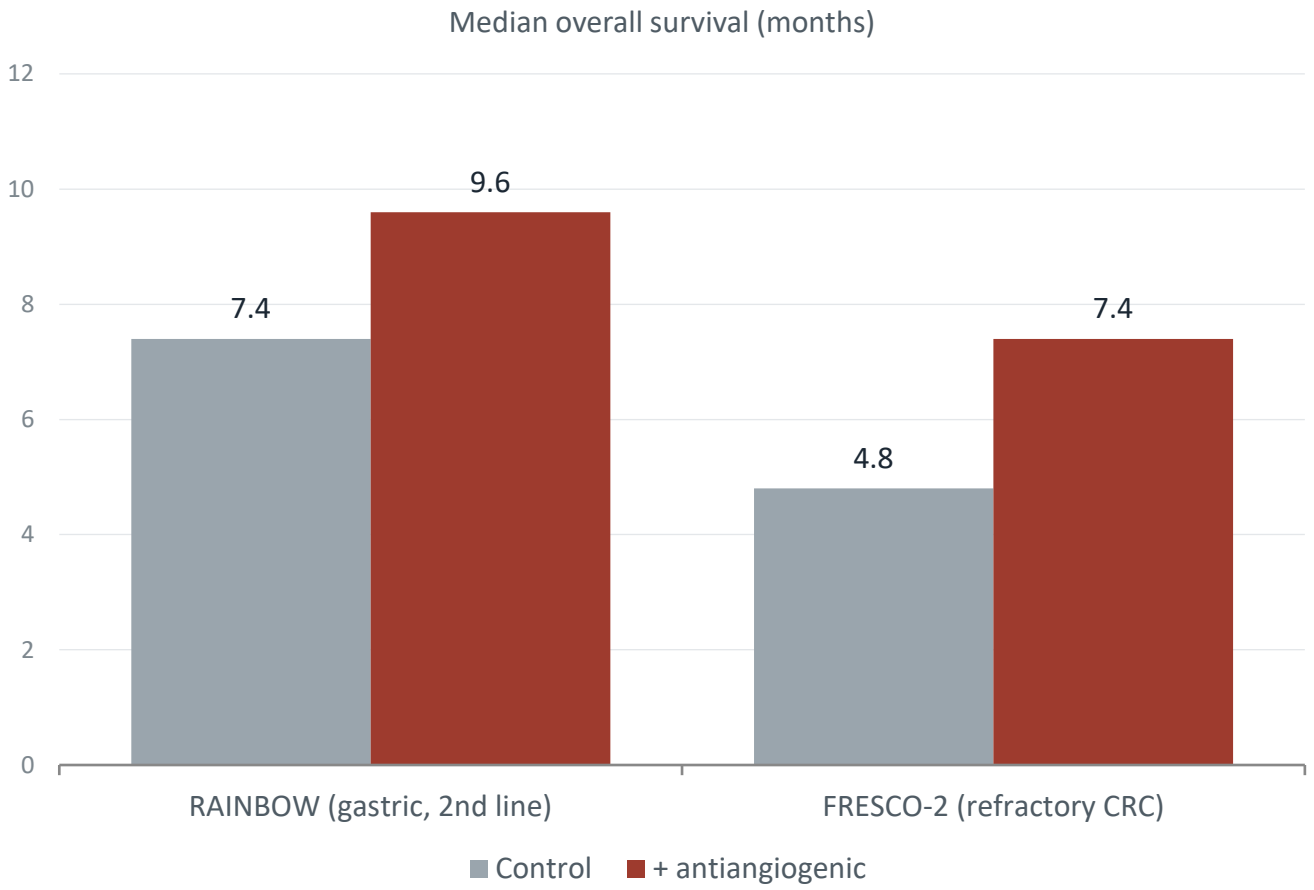
ANTIANGIOGENIC AGENTS

Antiangiogenic drugs block VEGF signaling at the ligand or the receptor

Agent	Type	Target	Main GI indications
Bevacizumab	Antibody	VEGF-A ligand	Metastatic CRC; HCC (with atezolizumab)
Ramucirumab	Antibody	VEGFR-2	Gastric/GEJ 2nd line; CRC; HCC (AFP ≥400)
Ziv-aflibercept	Fusion protein ("VEGF trap")	VEGF-A, VEGF-B, PlGF	CRC 2nd line with FOLFIRI
Regorafenib	Multikinase TKI	VEGFR and others	Refractory CRC, GIST, HCC
Fruquintinib	Selective TKI	VEGFR-1, -2, -3	Refractory CRC
Lenvatinib / sorafenib / cabozantinib	Multikinase TKIs	VEGFR, FGFR, MET and others	HCC

Indications summarized from FDA labeling and NCCN guidelines (Colon/Rectal, Gastric, Hepatocellular Carcinoma).

Benefits are real but measured in months in refractory disease



HR 0.58

IMbrave150 (HCC): overall survival with atezolizumab + bevacizumab vs sorafenib

Reading these numbers

Hazard ratios of ~0.65–0.8 and median gains of 2–3 months in later lines. Clinically meaningful for many patients, but toxicity and quality of life must be weighed.

Sources: Wilke H, et al. RAINBOW. Lancet Oncol 2014;15:1224–35 (ramucirumab + paclitaxel). Dasari A, et al. FRESCO-2. Lancet 2023;402:41–53 (fruquintinib). Finn RS, et al. IMbrave150. N Engl J Med 2020;382:1894–905.

What every gastroenterologist should know about VEGF inhibitors

Issue	What to do
GI perforation	Rare but serious; higher risk with active ulceration, recent surgery or obstruction
Wound healing	Hold bevacizumab ≥28 days before elective surgery; do not restart for ≥28 days after and until the wound is healed
Colonic stenting	ESGE does not suggest stenting while on antiangiogenic therapy; bevacizumab can be considered after stenting
Bleeding	Increased mucosal bleeding risk; consider timing of polypectomy or variceal therapy
Hypertension and proteinuria	Common class effects; monitor blood pressure and urine protein

Sources: Bevacizumab (Avastin) prescribing information. van Hooft JE, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: ESGE guideline update 2020. Endoscopy 2020;52:389–407.

9 · Immunotherapy

Releasing the brakes on T cells, and managing what follows

IMMUNOTHERAPY

Checkpoint inhibitors release the brakes tumors put on T cells

Target	Agents	Biology
PD-1	Pembrolizumab, nivolumab, dostarlimab, tislelizumab, toripalimab	Blocks the "off" signal on T cells in the tumor
PD-L1	Atezolizumab, durvalumab	Blocks the ligand expressed by tumor and immune cells
CTLA-4	Ipilimumab, tremelimumab	Acts at T-cell priming in lymph nodes; more toxicity

Who benefits most in GI cancers	Example evidence
MSI-H / dMMR tumors (any stage)	KEYNOTE-177: PFS 16.5 vs 8.2 months, pembrolizumab vs chemo, metastatic CRC
PD-L1–positive gastric/esophageal (CPS)	CheckMate 649: nivolumab + chemo, OS 14.4 vs 11.1 months (CPS ≥5)
HCC	IMbrave150 (atezolizumab + bevacizumab); HIMALAYA (durvalumab + tremelimumab)

Sources: André T, et al. KEYNOTE-177. N Engl J Med 2020;383:2207–18. Janjigian YY, et al. CheckMate 649. Lancet 2021;398:27–40. Finn 2020 (IMbrave150); Abou-Alfa GK, et al. HIMALAYA. NEJM Evid 2022.

Immunotherapy responds differently: slow, durable, and sometimes misleading on scans

Delayed response
Responses can take 2–3 months; early scans may look stable or worse.

Pseudoprogression
Apparent growth from immune infiltration before shrinkage; uncommon (well under 10% in most solid tumors).

Durable "tail"
A subset has long-lasting control, so survival curves flatten; medians understate this.

iRECIST
Adapts RECIST for immunotherapy: first progression is "unconfirmed" (iUPD) and must be confirmed on a scan 4–8 weeks later (iCPD) if the patient is clinically stable, avoiding premature discontinuation.

Source: Seymour L, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.

Immune-related adverse events can hit any organ, often the gut and liver

Organ	irAE	Practical point
Colon	Colitis, diarrhea	Most common reason for GI consult; more frequent with CTLA-4 combinations
Liver	Hepatitis	Rising AST/ALT; exclude viral, drug and progression causes
Endocrine	Thyroiditis, hypophysitis, adrenal insufficiency, diabetes	Often permanent; hormone replacement
Skin	Rash, pruritus, vitiligo	Usually mild
Lung	Pneumonitis	Can be fatal; new cough or dyspnea
Heart / nerve / muscle	Myocarditis, myositis, myasthenia	Rare, high mortality; urgent evaluation

Sources: Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021;39:4073–126. NCCN Management of Immunotherapy-Related Toxicities.

Checkpoint-inhibitor colitis: graded management, with early GI involvement

Grade	Checkpoint inhibitor	Treatment
1	Continue or hold briefly	Hydration, diet; loperamide if infection excluded
2	Hold until ≤ grade 1	Prednisone 1 mg/kg/day; GI consult; stool studies; consider endoscopy
3	Hold; stop CTLA-4 permanently; PD-1/PD-L1 may resume after recovery	Prednisone/IV methylprednisolone 1–2 mg/kg/day; infliximab if no response in 3–5 days; often admit
4	Permanently discontinue	IV methylprednisolone 1–2 mg/kg/day; early infliximab; vedolizumab if refractory

GI role:
endoscopy with biopsy for grade ≥2 helps confirm the diagnosis and gauge severity (ulceration predicts steroid-refractory course); steroids are tapered over at least 4–6 weeks.

Source: Schneider BJ, et al. ASCO guideline update. J Clin Oncol 2021;39:4073–126 (summarized via MDCalc irAE colitis tool).

10 · Assessing treatment and the patient

Response, endpoints, performance status and quality of life

RECIST 1.1: response is a change in the sum of target-lesion diameters

Complete response (CR)	All target lesions gone; nodes <10 mm short axis
Partial response (PR)	≥30% decrease from baseline sum
Stable disease (SD)	Neither PR nor PD
Progressive disease (PD)	≥20% increase from smallest sum and ≥5 mm absolute, or new lesions

- **Target lesions:** up to 5 total, 2 per organ; ≥10 mm (nodes ≥15 mm short axis)
- **Other criteria:** mRECIST for HCC (viable, enhancing tumor); iRECIST for immunotherapy
- **Tumor markers** (CEA, CA19-9, AFP) support but do not define response

Source: Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Trial endpoints: what each one tells you

Endpoint	Definition	Strength	Limitation
Overall survival (OS)	Time to death from any cause	Unambiguous; gold standard	Needs large, long trials; diluted by later therapies
Progression-free survival (PFS)	Time to progression or death	Earlier readout; not affected by later lines	Depends on scan timing; may not translate to OS
DFS / EFS	Time to recurrence (or event) after curative-intent therapy	Standard in adjuvant and perioperative trials	Surrogate for cure; validated in some cancers
ORR	% with CR or PR	Fast; basis for accelerated approval	Shrinkage ≠ longer life
pCR	No residual invasive cancer at surgery	Early signal in neoadjuvant trials	Patient-level, not always trial-level, surrogate
Quality of life / PROs	Patient-reported symptoms and function	What patients feel	Missing data; often secondary

General endpoint definitions as used in FDA oncology guidance and clinical trial reporting.

Performance status: the single most important patient factor

ECOG	Description	Karnofsky
0	Fully active, no restrictions	90-100
1	Restricted in strenuous activity; ambulatory, able to do light work	70–80
2	Ambulatory and capable of self-care; up and about >50% of waking hours; unable to work	50–60
3	Limited self-care; confined to bed or chair >50% of waking hours	30–40
4	Completely disabled; no self-care; totally confined to bed or chair	10–20
5	Dead	0

- **Eligibility:** most trials require ECOG 0–1
- **Prognosis:** PS is independently prognostic across cancers
- **Tolerance:** PS ≥3 generally argues against cytotoxic chemotherapy
- **Caution:** PS is subjective; patients and clinicians often rate differently

Source: Oken MM, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55. ECOG–Karnofsky mapping per ECOG-ACRIN.

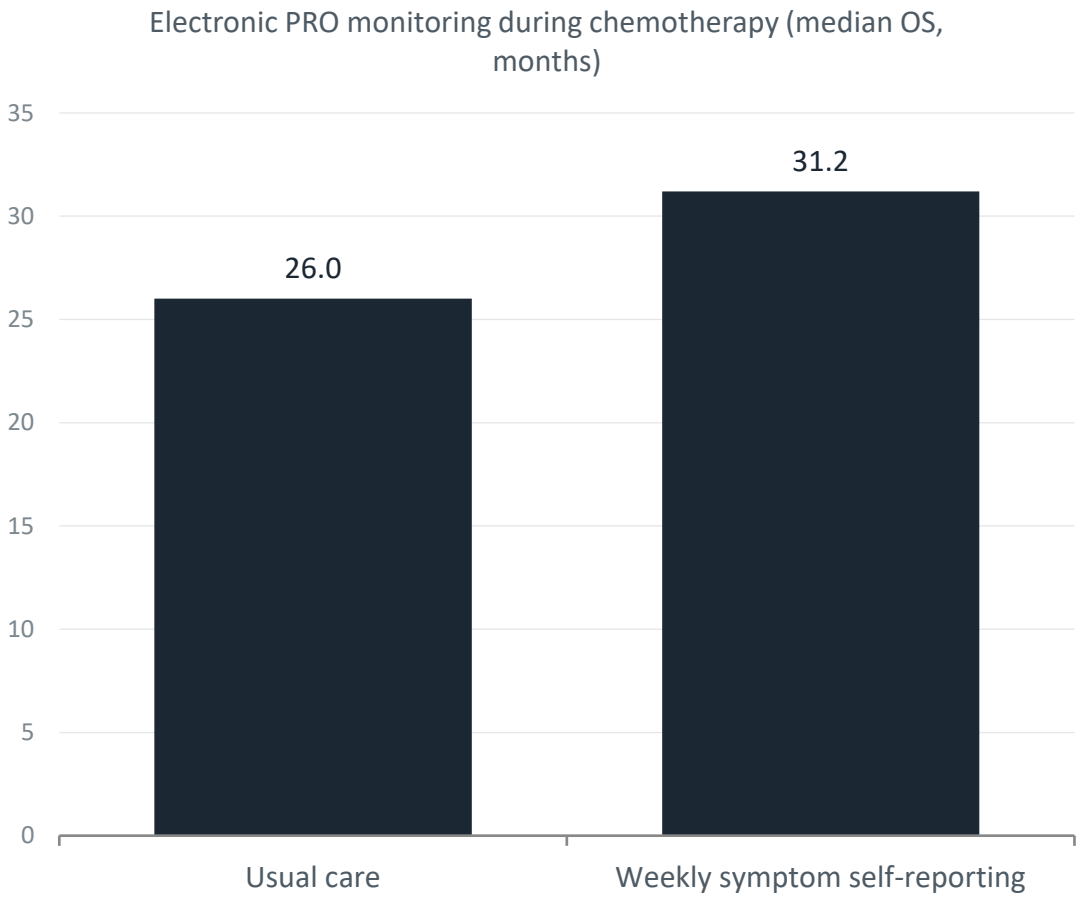
Quality of life is measured with validated, patient-reported instruments

Instrument	What it measures	GI-specific versions
EORTC QLQ-C30	Function (physical, role, emotional, cognitive, social), symptoms, global health	Modules: OES18, STO22, CR29, PAN26, HCC18
FACT-G	Physical, social, emotional and functional well-being	FACT-C (colorectal), FACT-Hep, FACT-E
PRO-CTCAE	Patient-reported frequency and severity of symptomatic toxicities	—
ESAS	Quick symptom screening in clinic (pain, fatigue, nausea, appetite…)	—

Interpreting scores:
on EORTC QLQ-C30 (0–100 scales), changes of about 5–10 points are small, 10–20 moderate and >20 large, as perceived by patients.

Sources: Aaronson NK, et al. EORTC QLQ-C30. J Natl Cancer Inst 1993;85:365–76. Osoba D, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44. NCI PRO-CTCAE.

Listening to patients changes outcomes



11.6 vs 8.9 mo

median survival with early integrated palliative care vs standard oncology care, metastatic NSCLC

- **Mechanism:** earlier recognition of symptoms and complications, fewer emergency visits, better tolerance of treatment
- **For partners:** PRO and supportive-care endpoints are increasingly part of regulatory and value assessments

Sources: Basch E, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318:197–98. Temel JS, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–42.

Putting it together

A case walk-through

CASE

A 62-year-old with metastatic colon cancer

Presentation

- Iron-deficiency anemia, weight loss 6 kg
- Colonoscopy: obstructing-appearing sigmoid mass; biopsy adenocarcinoma
- CT: 3 liver metastases (largest 4 cm), no other disease
- CEA 48 ng/mL
- ECOG 1; works part-time; normal renal and liver function

Questions for the room

- What is the treatment intent?
- Which tests do we need before choosing therapy?
- Should the gastroenterologist place a stent?
- How will we judge whether treatment is working?
- What would make us change course?

Hypothetical teaching case.

CASE

How the principles apply

Question	Answer	Module
Intent	Potentially curative: limited liver metastases may become resectable after systemic therapy	Local vs systemic
Tests	RAS, BRAF, MSI/dMMR, HER2 on tissue; germline testing if dMMR; DPYD before fluoropyrimidines	Genomics; chemotherapy
Result: left-sided, RAS/BRAF wild-type, MSS	FOLFOX + panitumumab (anti-EGFR) preferred; bevacizumab avoided if stenting likely	Targeted; antiangiogenic
Stent?	Only if obstructed; coordinate timing with any VEGF inhibitor (ESGE)	Antiangiogenic
Assessment	CT every ~8 weeks by RECIST 1.1; CEA trend; rash and magnesium monitoring	Assessment
Patient	ECOG, weight and PROs at each visit; nutrition support	Patient
Next	Tumor board re-review for liver resection after response	MDT

Teaching synthesis; consistent with NCCN Colon Cancer guideline principles. If dMMR, first-line pembrolizumab would be preferred (KEYNOTE-177).

Take-home points

1. Intent (cure vs control) and stage drive every decision; the MDT coordinates it.

2. NCCN: most recommendations are category 2A; read the preference labels and the footnotes.

3. Biomarkers decide therapy in GI cancers: RAS, BRAF, MSI/dMMR, HER2, PD-L1, CLDN18.2, FGFR2, IDH1; test germline when indicated.

4. Know the class: chemotherapy, targeted (-nib, -mab, ADC), antiangiogenic and immunotherapy each have signature toxicities, many in the GI tract.

5. Judge treatment with RECIST and the right endpoint; judge the patient with ECOG, geriatric assessment and patient-reported outcomes.

Questions and discussion

REFERENCE

Glossary for quick reference

ADC Antibody–drug conjugate

CPS PD-L1 combined positive score

ctDNA Circulating tumor DNA

DFS / EFS Disease- / event-free survival

DLT Dose-limiting toxicity

dMMR / MSI-H Mismatch repair deficient / microsatellite instability-high

ECOG PS Eastern Cooperative Oncology Group performance status

HR Hazard ratio

irAE Immune-related adverse event

MTD / RP2D Maximum tolerated / recommended phase 2 dose

NGS Next-generation sequencing

ORR Objective response rate

OS / PFS Overall / progression-free survival

pCR Pathologic complete response

PRO Patient-reported outcome

RECIST Response Evaluation Criteria in Solid Tumors

TKI Tyrosine kinase inhibitor

TMB Tumor mutational burden

TNT Total neoadjuvant therapy

VUS Variant of unknown significance