Emerging Treatment Strategies in Colorectal Cancer

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No Disclosures

Aims:

Is conventional trimodality therapy necessary in all patients with stage II-III rectal adenocarcinoma?

Review treatments targeting Her-2 overexpression in CRC

Prospect Study: Phase III

Neoadjuvant chemoradiation vs neoadjuvant FOLFOX with selective use of chemoradiation, followed by TME for treatment of locally advanced rectal cancer

1194 pts randomized 1:1 to standard chemoRT → TME or 6 cycles of FOLFOX. For initial FOLFOX cohort, if tumor reduced by ≥ 20% → TME. If poor response/intolerance w FOLFOX → chemoRT → TME

Adjuvant FOLFOX x 6 cycles (initial chemo) or 8 cycles (initial chemoRT)

NEJM 389:322-334, 2023

Prospect Study: Phase III

Eligibility Criteria

cT2N+, cT3N-, cT3N+

Candidate for sphincter-sparing surgery

Exclusion Criteria

Need for APR

cT4

≥ 4 or pelvic nodes ≥ 1 cm in short axis

Prospect Study: Phase III

	FOLFOX + selective chemoRT	ChemoRT
Number	585	543
5 yr DFS	80.8%	78.6%
5 yr Local DFS	98.2%	98.4%
5 yr OS	89.5%	90.2%
# completing surgery	535	510
pCR	21.9%	24.3%
+ radial margin	1.2%	1.5%
Percent switch to chemo-RT	9.1%	NA

Prospect Study: Phase III

Conclusion:

In patients with locally advanced rectal cancer who were eligible for sphincter-sparing surgery, preoperative FOLFOX was noninferior to preoperative chemoradiotherapy with respect to disease-free survival.

90.9% patients receiving pre-op FOLFOX were spared from toxicities associated with radiation therapy.

Organ Preservation Rectal Adenocarcinoma (OPRA)

Randomized Phase II Trial

ChemoRT → Chemo vs Chemo → ChemoRT

50-56 Gy + capecitabine 825 mg/m² BID or 5-FU 225 mg/m²/d CI (physician choice)

CAPEOX: 1000 mg/m² BID d 1-14 + 130 mg/m² d 1 q 3 wk x 5 cycles or FOLFOX (ox 85 mg/m²; LV 400 mg/m²; 5-FU 400 mg/m² + 2400 mg/m²/46 hr q 2 wk x 8 cycles (physician choice)

J Clin Oncol 40:2546-56, 2022

OPRA study

Tumor restaging: DRE, endoscopic exam, MRI & CT CAP within 8 (± 4 wks) after TNT.

Complete or near complete response: watch & wait

Incomplete response: TME recommended

Watch & weight surveillance: DRE & flex sigmoidoscopy q 4 months for 1st 2 years, then q 6 months for years 3-5. Pelvic MRI q 6 months x 2 years, then yearly x 3 yr. CT Scan CAP yearly x 5 yr.

Organ Preservation: Rectal Adenocarcinoma

	Chemo → CRT	CRT → Chemo
Number	158	166
Number restaged	146	158
Surgery recommended	41	38
Watch & Wait	105	120
Local regrowth/surveillance TME Local excision Declined surgery Disease progression	42 (40%) 35 2 5 0	33 (27.5%) 27 3 1 2

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Organ Preservation: Rectal Adenocarcinoma

`	Chemo → CRT	CRT → Chemo
3 yr DFS	76% (95% CI 69-84)	76% (95% CI 69-83)
3 yr local DFS	94% (95% CI 89-99)	94% (95% CI 90-98)
3 yr distant MFS	84% (95% CI 77-91)	82% (95% CI 75-89)
TME-free Survival	47% (95% CI 39-56)	60% (95% CI 52-68)

Organ preservation is achievable in half of patients treated with total neoadjuvant chemotherapy without an apparent detriment in DFS compared to historical controls treated with CRT, TME & adjuvant chemotherapy.

Patient selection is critical: must be motivated to have careful surveillance.

PD-1 Blockade in dMMR Locally Advanced Rectal Cancer

Stage II & III Rectal adenocarcinoma

Staging: CT CAP w contrast; MRI pelvis (T2 weighted & diffusion weighted); colonoscopy; PET CT Scan

1. Dostarlimab 500 mg IV q 3 weeks x 6 months

If cCR: surveillance

2. If no cCR → ChemoRT (5040 Gy/28 fx) + Cape

3. If no cCR → TME

N Engl J Med386:2363-76, 2022

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PDL-1 Blockade Locally Advanced Rectal Cancer

Staging:

Endoscopy & DRE baseline, 6 wks, 3 mo, 6 mo then every 4 months; Biopsy with each endoscopy

MRI pelvis, CT Scan CAP & PET CT scan baseline, 3 mo, 6 mo then every 4 months

cCR: absence of residual disease on digital and endoscopic rectal examination & absence of residual disease on rectal MRI (no restricted diffusion on T2-weighted imaging)

PDL-1 Blockade

16 patients enrolled

ECOG 0	12
ECOG 1	4
T1-T2	4
T3	9
T4	3
Node Neg	1
Node Pos	15

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PDL-1 Blockade: rectal

14 pts had PCR analysis

MSI-H	14
BRAF v600e	0
TMB	37.9 – 103 mut/Mb
Germline mut	8
cCR	12 of 12

AZUR-1 (NCT05723562)

Global, multicenter, single-arm, open-label, Phase II study of dostarlimab monotherapy in previously untreated patients with stage II/III dMMR/MSI-H locally advanced rectal cancer

Aim: To enroll 100 patients

Primary endpoint is cCR by independent central review (ICR) at 12 months, defined as achieving and maintaining cCR for 12 months (starting from first disease assessment after last dose of study intervention that demonstrates cCR by ICR).

Her-2 in Colorectal Cancer

HER2 overexpression
~ 2% of all CRCs
5% - 6% of stage IV KRAS wild-type CRCs

HER2 first emerged as a negative predictive biomarker in CRC: amplification or overexpression associated with a lack of response to anti-EGFR treatments

Her-2 overexpression CRC

HER2 overexpression by IHC: more than 10% of tumor cells with intense complete circumferential or lateral staining

Equivocal cases (IHC 2+) must be analyzed further by in situ hybridization

65% to 90% occurred in patients with left-sided or rectal tumors

Associated with a greater number of metastatic sites

About 20% will develop CNS metastasis

Amplification correlates with a lower incidence of KRAS mutations vs non-amplified CRC: 17% vs 50%

Her-2 Inhibitors for mCRC

Monoclonal antibodies that bind to Her-2

trastuzumab & pertuzumab

Tyrosine kinase inhibitors that bind to intracellular domain of Her-2

lapatanib & tucatinib

Antibody-drug Conjugates

fam-trastuzumab deruxtecan-nxki

Trastuzumab + Lapatinib

914 CRC pts w refractory disease screened

5% positive for Her-2 overexpression (KRAS exon 2 WT)

trastuzumab 4 mg/kg IV loading dose then 2 mg/kg q wk + oral lapatinib at 1000 mg per day until evidence of disease progression.

27 enrolled in trial

1 CR + 7 PR (RR 29.6%); 12 SD (44.4%)

Median PFS = 5.3 months

Median OS = 11.3 months

Her-2 3+ had higher RR than Her-2 2+/FISH+

Lancet Oncol 17:738-746; 2016

MyPathway “Basket” trial

Trastuzumab & Pertuzumab (IV)
Trastuzumab 8 mg/kg → 6 mg/kg q 3 wk
Pertuzumab 840 mg → 420 mg q 3 wk
57 patients with HER2-amplified mCRC
1 CR + 17 PR (overall RR 31.6%)
median PFS 2.9 months
median OS 11.5 months

Lancet Oncol 20(4): 518–530; 2019

Trastuzumab + Pertuzumab

TAPUR
Trastuzumab 8 mg/kg → 6 mg/kg q 3 wk
Pertuzumab 840 mg → 420 mg q 3 wk
28 patients with HER2-amplified mCRC
RR = 25%
Median PFS = 17.2 weeks
Median OS = 60.0 weeks

10 patients with ERBB2/3 mutations
RR = 0%
Median PFS = 9.6 weeks
Median OS = 28.8 weeks

DOI: 10.1200/PO.22.00306 JCO Precision Oncology no. 6 (2022) e2200306

Trastuzumab + Pertuzumab

TRIUMPH Trial

Refractory CRC patients HER-2 amplified

Trastuzumab 8 mg/kg → 6 mg/kg q 3 wk

Pertuzumab 840 mg → 420 mg q 3 wk

	Tissue-positive	ctDNA-positive
Number	27	25
RR	30%	28%
Median PFS	4.0 months	3.1 months
Median OS	10.0 months	8.8 months

Nature Med 27,1899–1903; 2021

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Mountaineer Trial

Trastuzumab + tucatinib in refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer

cohort A: tucatinib 300 mg PO BID + trastuzumab IV 8 mg/kg → 6 mg/kg every 21 days

Cohort B (expansion phase): same as cohort A

Cohort C (expansion phase): tucatinib alone [cross-over to cohort B allowed if PD: 60% crossed over]

Lancet Oncol 24(5):496-508; 2023

Mountaineer trial

	Trastuzumab + Tucatinib	Trastuzumab + Tucatinib	Tucatinib
No. enrolled No. received Rx	45 45	41 39	31 30
RR	3 CR + 29 PR (38%)		3.3%
Median PFS	8.2 months		Not reported
Median OS	24.1 months		21.1 months in cross-over pts

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Mountaineer trial: toxicity

	Grade 1-2	Grade 3	Grade 4
Diarrhea	60%	3%	0%
Fatigue	42%	2%	0%
Nausea	35%	0%	0%
Infusion reaction	21%	0%	0%
Pyrexia	20%	0%	0%
Decreased appetite	19%	0%	0%
Dermatitis acneiform	19%	0%	0%
Chills	17%	1%	0%
Cough	16%	0%	0%
Vomiting	16%	0%	0%
Back pain	15%	1%	0%
Arthralgia	15%	2%	0%

Ongoing trial: NCT05253651

Tucatinib + Trastuzumab + Chemo vs Standard Care in HER2+ CRC as First-line Therapy

Standard arm:

mFOLFOX6 or mFOLFOX6 + bevacizumab or mFOLFOX6 + cetuximab

Experimental arm:

mFOLFOX6 + tucatinib + trastuzumab

Primary Endpoint: PFS per RECIST v1.1 by Blinded Independent Central Review (BICR)

Destiny CRC01

Fam-Trastuzumab deruxtecan-nxki (an antibody-drug conjugate of humanized anti-HER2 antibody + topoisomerase I inhibitor payloads)

6.4 mg/kg q 3 weeks: 3 cohorts

No responses in IHC 2+/FISH- (n=7) or IHC 1+ (n= 18)

IHC 3+ & IHC 2+/FISH+

N = 53

RR = 45.3%

Median PFS = 6.9 mo

Median OS = 15.5 mo

Activity was not impaired in a subgroup of patients harboring RAS mutation–positive ctDNA

Lancet Oncol 22(6):779-789; 2021

Destiny CRC02

HER2-overexpressing, RAS WT or mutant mCRC

Trastuzumab deruxtecan	5.4 mg/kg	6.4 mg/kg
Number	82	40
RR	37.7%	27.5%
Median PFS	5.8 mo	5.5 mo
RR Prior anti-Her2 Her2 IHC 3+ Her 2 IHC 2+/FISH+ RAS WT RAS mutant	 7/17 (41.2%) 30/64 (46.9%) 1/18 (5.6%) 27/68 (39.7%) 4/14 (28.6%)	 4/10 (40.0%) 10/34 (29.4%) 1/6 (16.7%) 11/34 (32.4%) 0/6 (0%)
≥ Grade 3 AEs Interstitial lung disease	41/83 (49.4%) 7/83 (8.4%)	23/39 (59.0%) 5/39 (12.8%)

DOI: 10.1200
JCO.2023.41.16_suppl.3501

FDA-Approved Anti-Her2 Agents for mCRC

For RAS/BRAF WT + Her-2 over-expression

In No Order of Preference:

Trastuzumab (or FDA approved biosimilar) given with either lapatinib, pertuzumab or tucatinib

For unresectable or metastatic HER2 positive (IHC 3+) metastatic colorectal cancer who have received two or more prior regimens:

Fam-Trastuzumab deruxtecan-nxki

** May have activity in patients who received prior anti-Her2 therapy*

** May have activity in patients with RAS mutations*

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