

Advances in the Perioperative Management of Early Rectal Cancers

Olatunji B. Alese, MD FWACS

*Associate Professor & Director of GI Oncology
Winship Cancer Institute of Emory University*

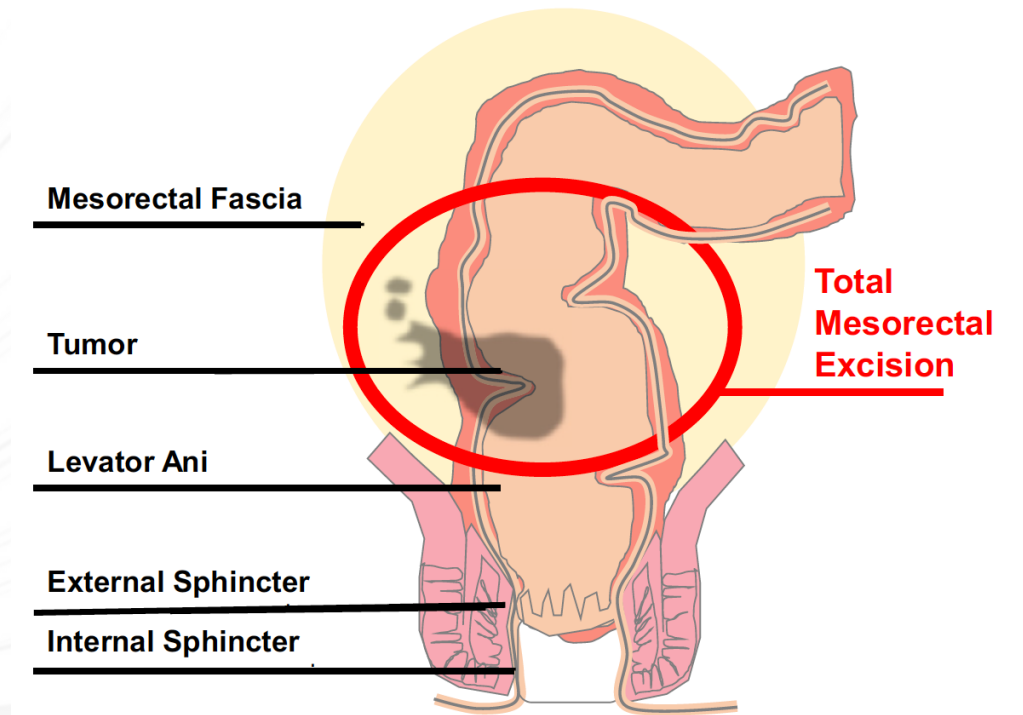
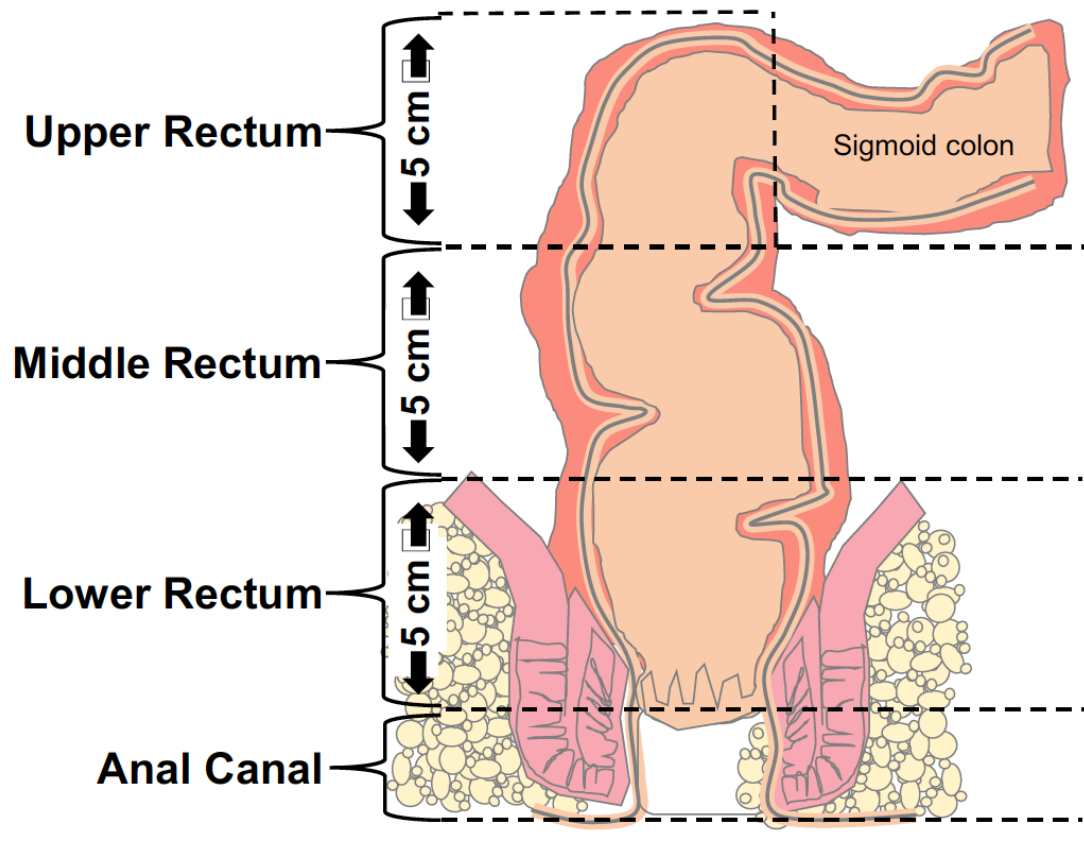
July 27, 2024

Disclosure

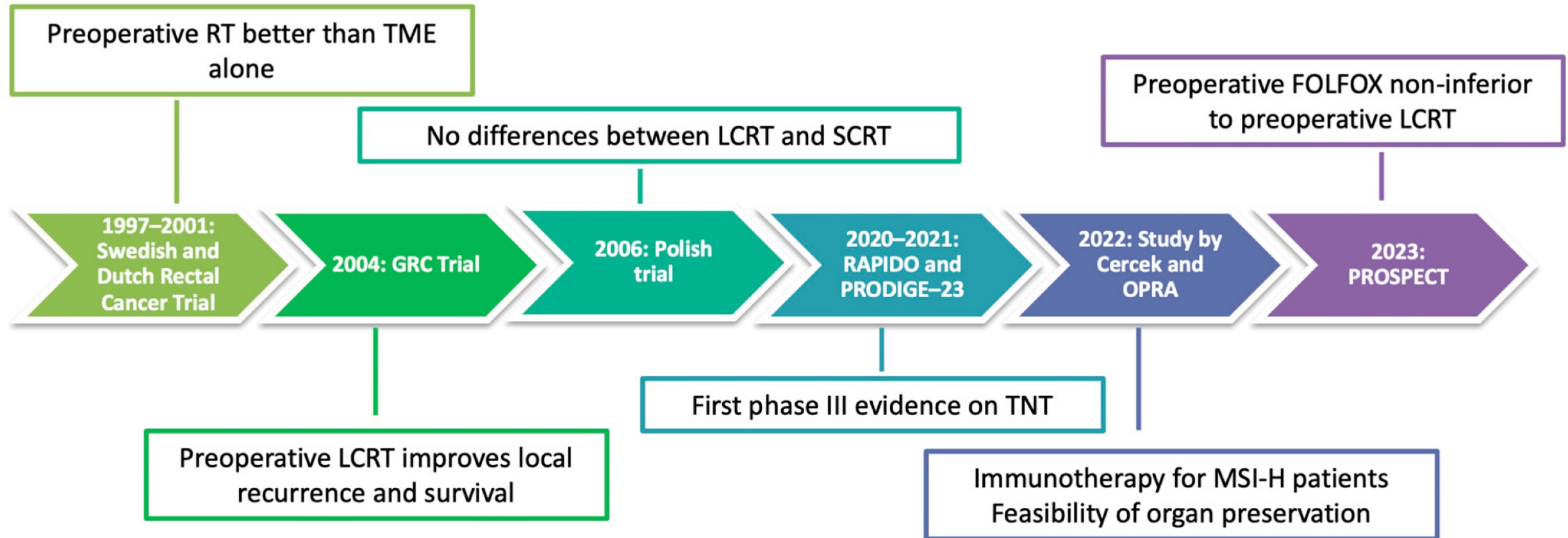
Research funding: Taiho Oncology, Ipsen Pharmaceuticals, GSK, Bristol Myers Squibb, PCI Biotech AS, ASCO, Calithera Biosciences, Inc., SynCore Biotechnology Co. Ltd., Suzhou Transcenta Therapeutics Co., Ltd, Corcept Therapeutics Inc., Hutchison MediPharma, Boehringer Ingelheim, Xencor Inc., Cue Biopharma, Inc., Merck, Syros Pharmaceuticals Inc., Inhibitex Inc, Arcus Biosciences Inc., ImmunoGen, Impact Therapeutics, Inc.

Consulting/Advisory Role: Ipsen Pharmaceuticals, Aadi Bioscience, Taiho, Pfizer, Seagen Inc., Bristol Myers Squibb, AstraZeneca, Exelixis, Takeda

Independent Data Monitoring Committee: Compass Therapeutics, Inc.

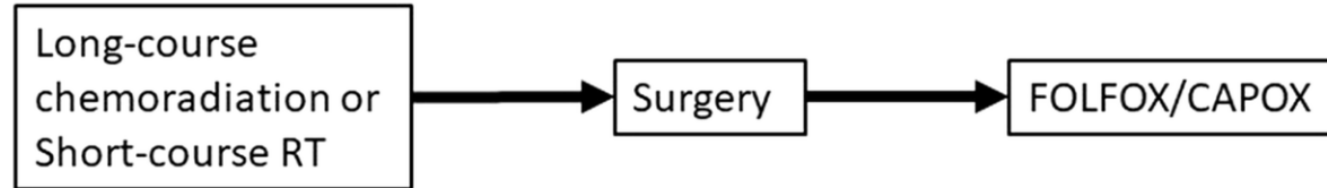


Rectal Cancer Treatment Timeline

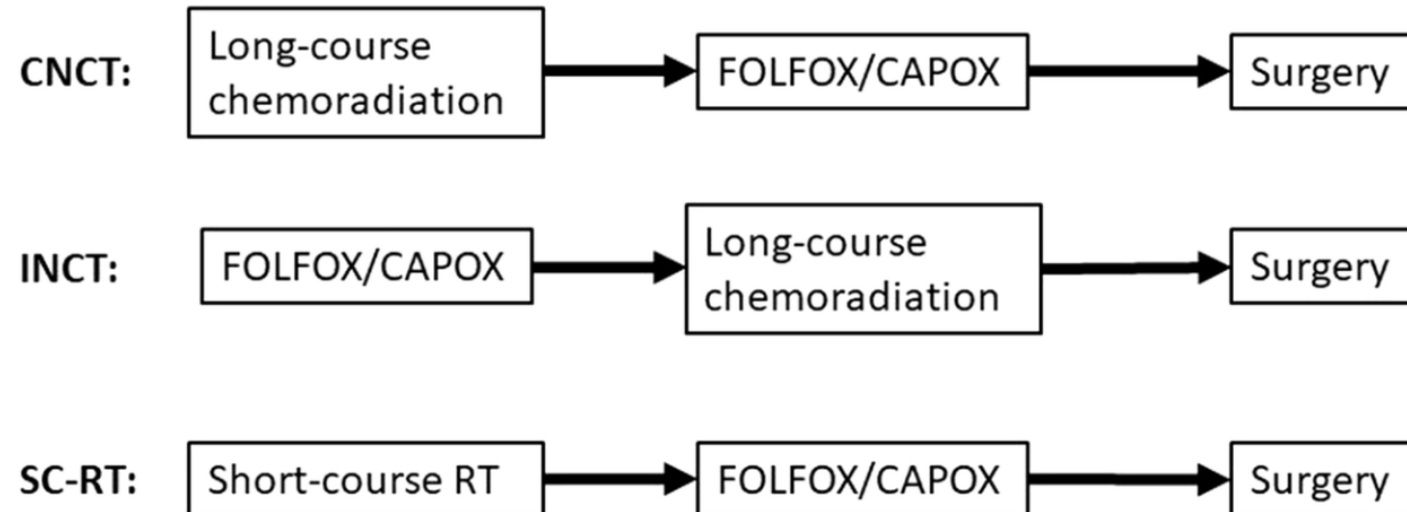


Total Neoadjuvant Therapy (TNT)

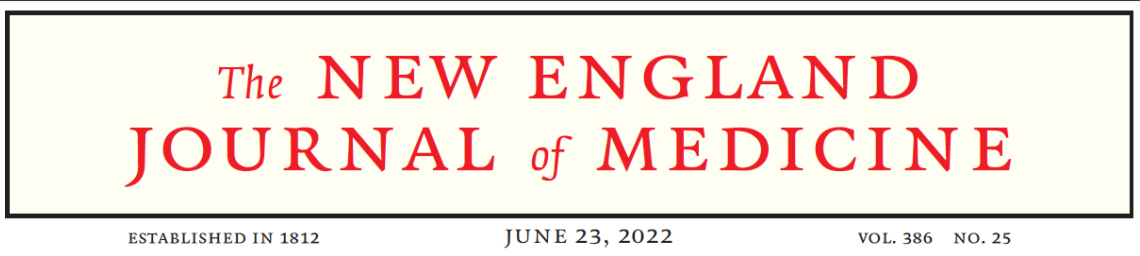
a) Standard treatment sequencing



b) Total neoadjuvant treatment sequencing

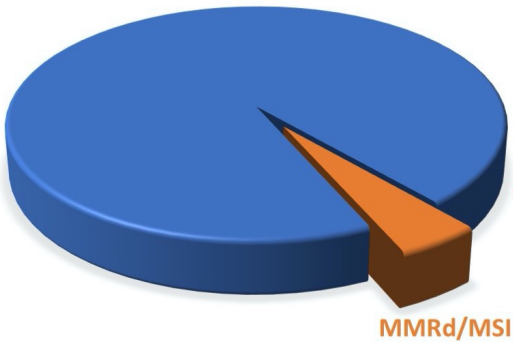
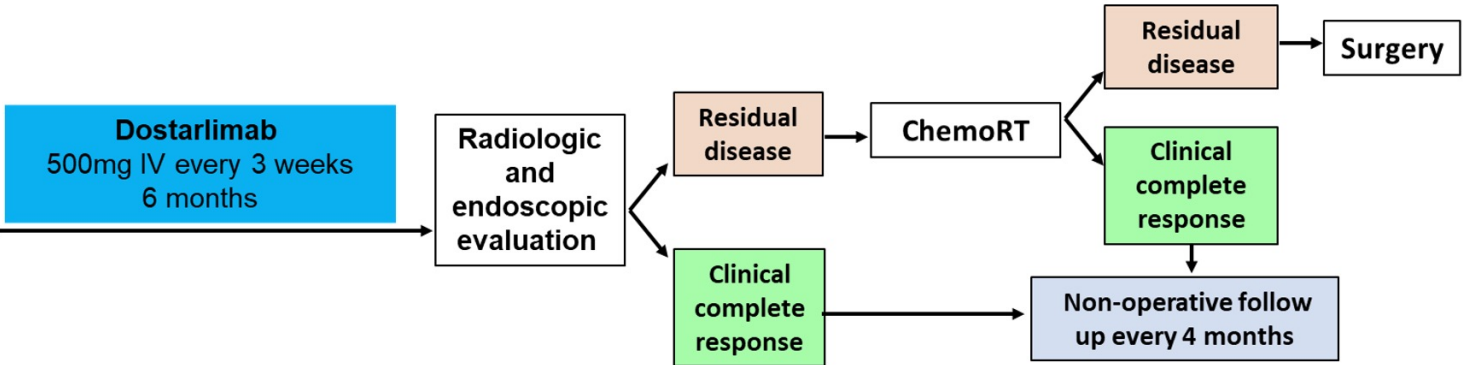


MSI-H/MMRd



PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.



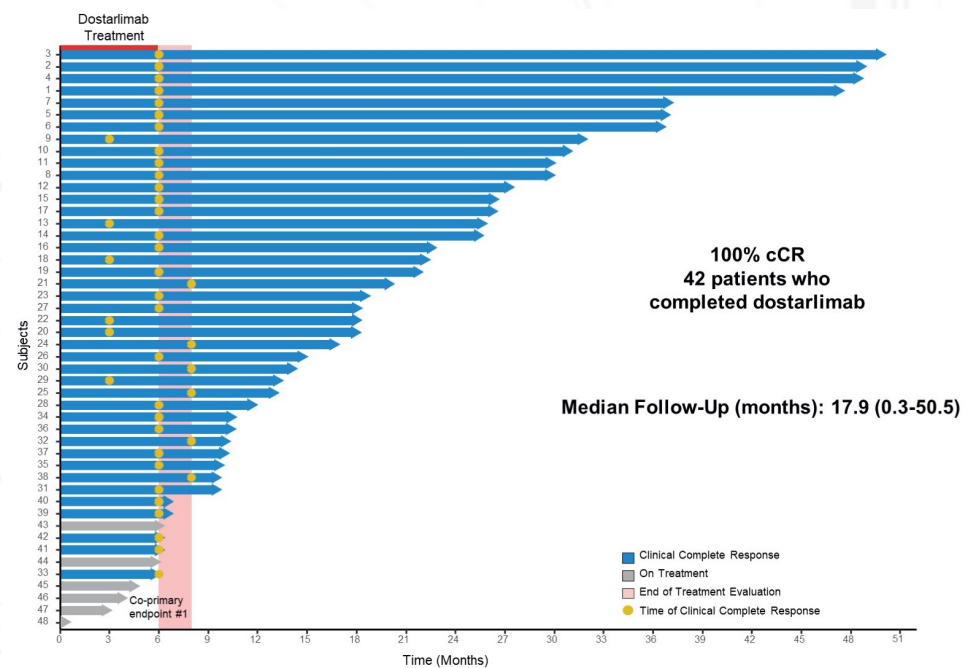
About 5-10% of all rectal cancers

Less sensitive to chemotherapy

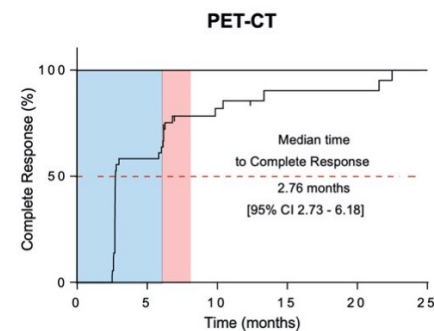
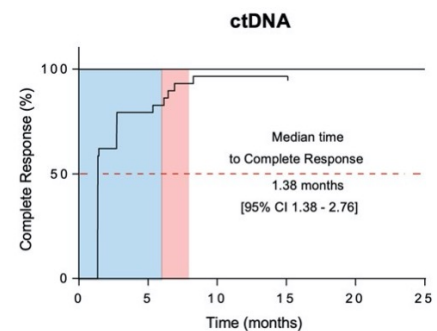
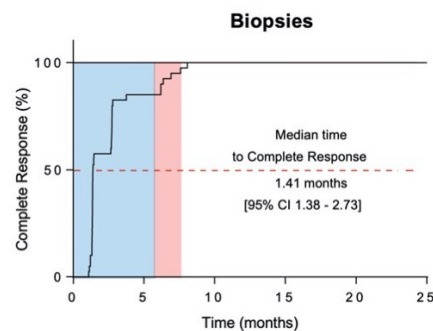
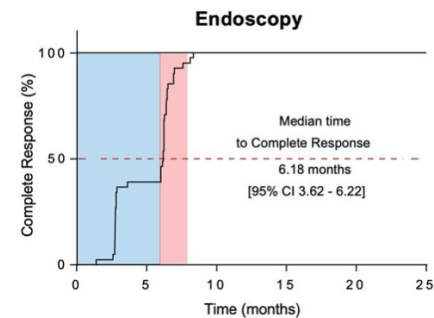
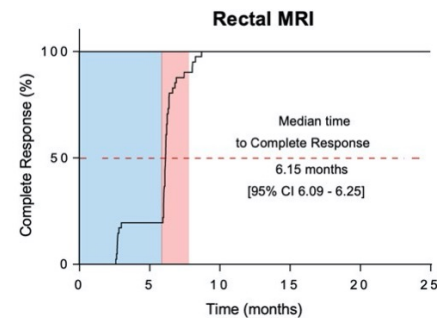
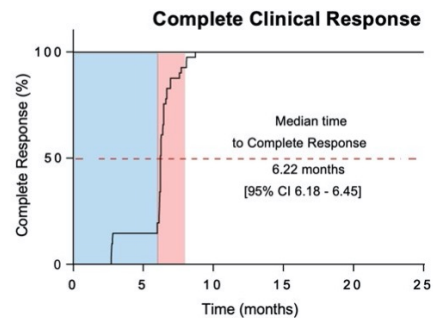
Rectal cancer treated with total neoadjuvant therapy chemotherapy and chemoRT followed by TME

Outcome	No. of patients (%)	
	dMMR	pMMR
FOLFOX as initial treatment	n = 21	n = 63
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	n = 16	n = 48
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

MSI-H/MMRd - Dostarlimab



Time to cCR



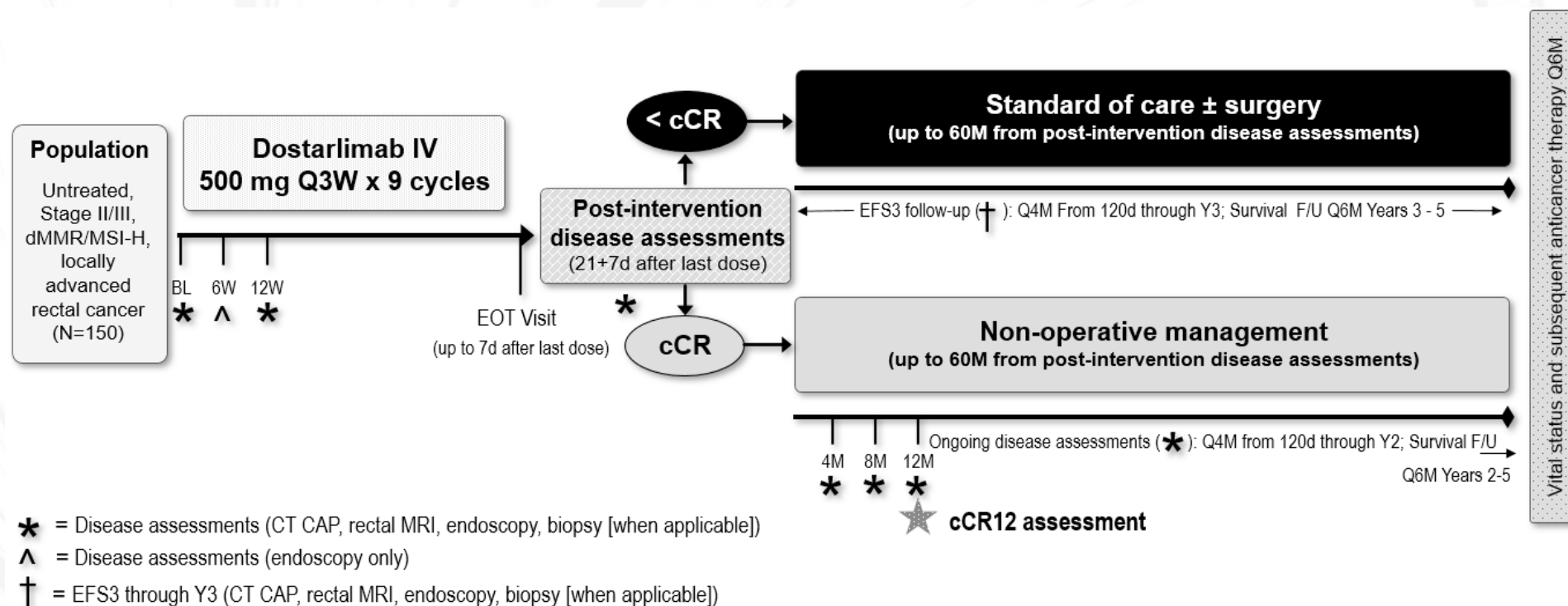
Time on Treatment
End of Treatment Evaluation

Ongoing Trials

AZUR-1: Phase 2, Single-Arm, Open-Label Study with Dostarlimab Monotherapy in Participants with Untreated Stage II/III dMMR/MSI-H Locally Advanced Rectal Cancer

- Primary objective:
To estimate the efficacy of Dostarlimab in Stage II/III (locally advanced) dMMR/MSI-H rectal cancer

- Endpoint: cCR12 - maintenance of cCR for 12 months.

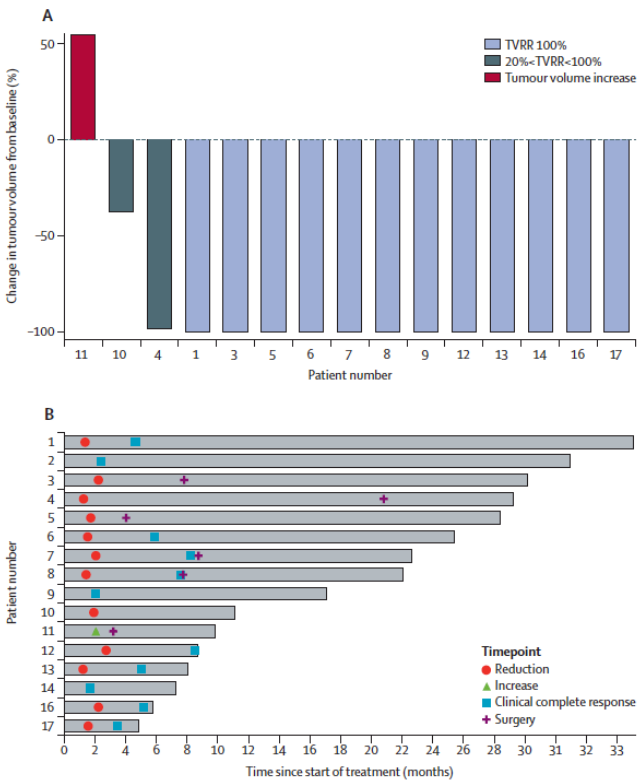


MSI-H/MMRd – Other ICI



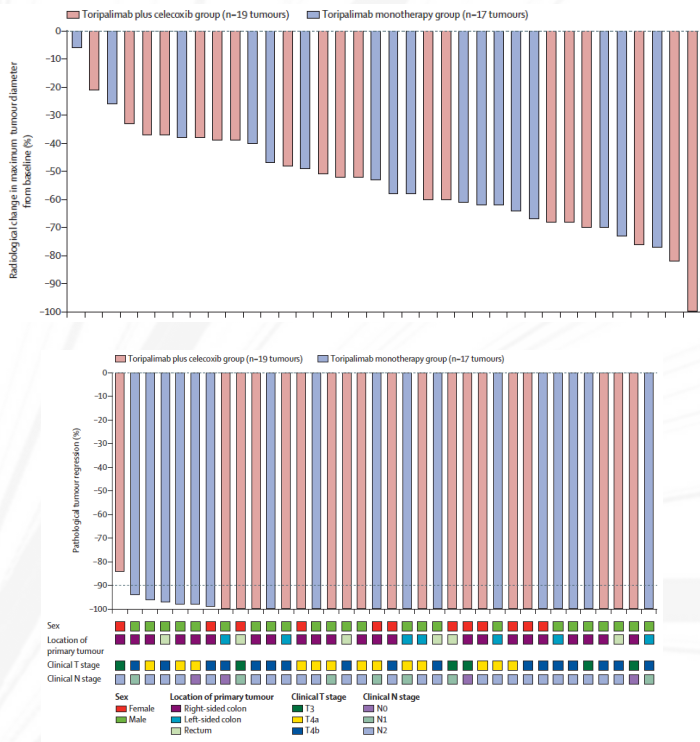
Neoadjuvant PD-1 blockade with sintilimab in mismatch-repair deficient, locally advanced rectal cancer: an open-label, single-centre phase 2 study

Gong Chen*, Ying Jin*, Wen-Long Guan*, Rang-Xin Zhang*, Wei-Wei Xiao*, Pei-Qiang Cai, Min Liu, Jun-Zhong Lin, Fu-Long Wang, Cong Li, Ting-Ting Quan, Shao-Yan Xi, Hui-Zhong Zhang, Zhi-Zhong Pan, Feng Wang†, Rui-Hua Xu†



Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial

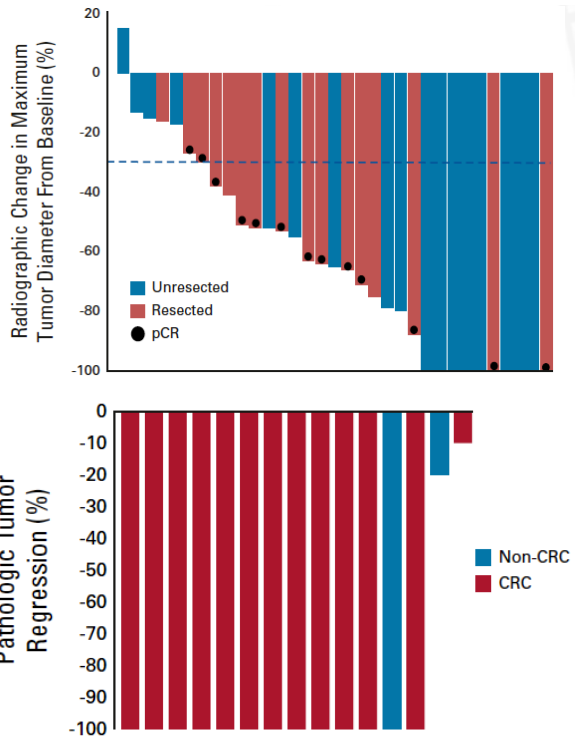
Huabin Hu*, Liang Kang*, Jianwei Zhang*, Zehua Wu*, Hui Wang, Meijin Huang, Ping Lan, Xiaojian Wu, Chao Wang, Wuteng Cao, Jiancong Hu, Yan Huang, Liang Huang, Huaiming Wang, Lishuo Shi, Yue Cai, Callu Shen, Jiaoyu Ling, Xiaoyu Xie, Yonghua Cai, Xiaowen He, Ruoxu Dou, Jiaming Zhou, Tenghui Ma, Xingwei Zhang, Shuangling Luo, Weihao Deng, Li Ling, Hao Liu, Yanhong Deng



original reports

Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors

Kaysia Ludford, MD^{1,2}; Won Jin Ho, MD³; Jane V. Thomas, MD²; Kanwal P.S. Raghav, MBBS²; Mariela Blum Murphy, MD²; Nicole D. Fleming, MD⁴; Michael S. Lee, MD²; Brandon G. Smaglo, MD²; Y. Nancy You, MD⁵; Matthew M. Tillman, MD⁶; Carlos Kamiya-Matsuoka, MD⁷; Selvi Thirumurthi, MD⁷; Craig Messick, MD⁸; Benny Johnson, DO²; Eduardo Vilar, MD, PhD⁸; Arvind Dasari, MBBS⁹; Sarah Shin, BS²; Alexei Hernandez, BS²; Xuan Yuan, MD²; Hongqi Yang²; Wai Chin Foo, MD⁹; Wei Qiao, MS, PhD¹⁰; Dipen Maru, MD²; Scott Kopetz, MD, PhD²; and Michael J. Overman, MD²



EA2201: Phase II Neoadjuvant Ipi/Nivo + SC radiation

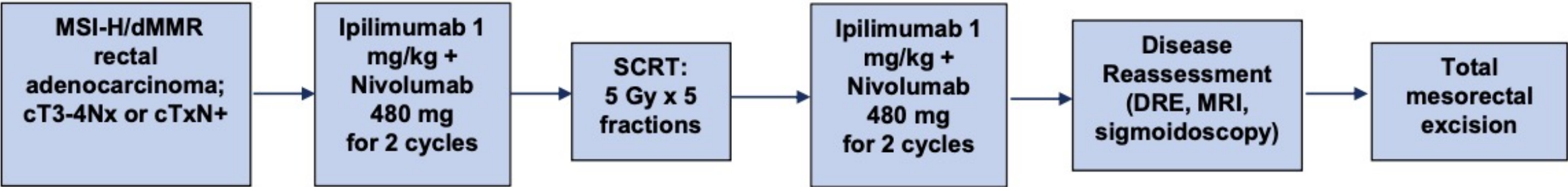
Prespecified interim analysis after completion of the first stage of enrollment (n=14)

Eligibility:

- cT3/4Nx or cTxN+ rectal adenocarcinoma (within 15 cm of anal verge)
- MSI-H and/or dMMR by local testing
- No active autoimmune disease
- No chronic prolonged systemic steroids

Protocol treatment received (n = 14):

- Nivo/ipi: 14/14 patients (range, 1-4 cycles; median 4; mean 3.29)
- SCRT: 12/14 patients
- TME: 3/14 patients



	n = 14
pCR plus cCR rate (95% CI)	8/14 57.1% (31.2%-83.1%)
pCR rate of those who underwent TME	3/3 (100%)

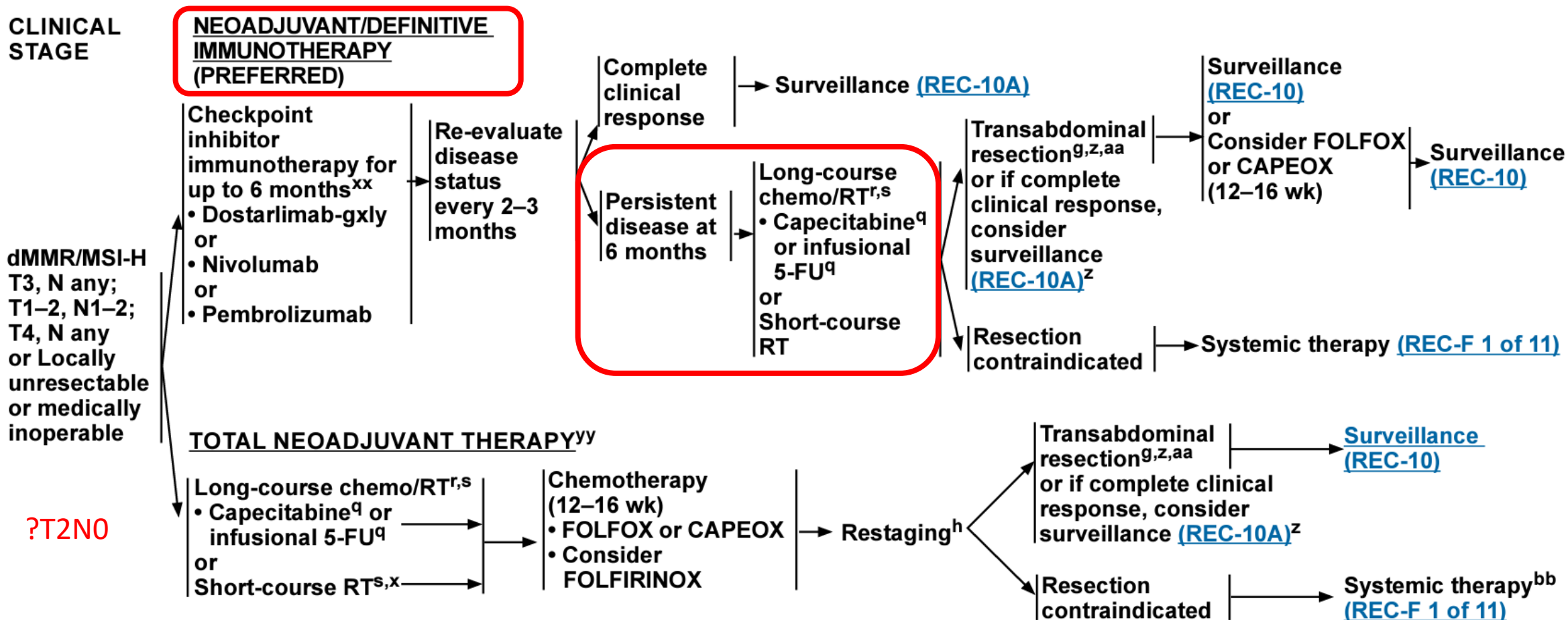
Event	Any	Grade 1 or 2	Grade 3 or 4	Grade 5
	n (%)	n (%)	n (%)	n (%)
TRAEs	14/14 (100%)	14/14 (100%)	5/14 (35.7%)	0/14 (0%)



NCCN Guidelines Version 3.2024

dMMR/MSI-H Rectal Cancer

CLINICAL STAGE



MSS/MMRp

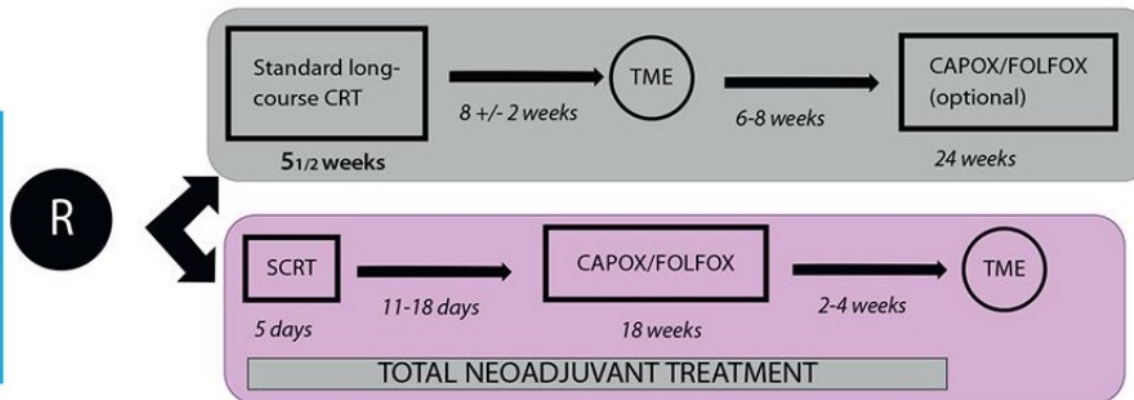
Study Name	Population	No.	Experimental Arm	Control Arm	Primary Outcome
RAPIDO ³	cT4, cN2, extramural vascular invasion, enlarged lateral LNs, or involved MRF	920	SCRT → CAPOX/FOLFOX → TME	LCRT → TME → optional CAPOX/FOLFOX	3-year DFS: 23.7% v 30.4%, HR 0.75, $P = .019$
PRODIGE-23 ⁴	cT3-T4	461	LCRT → mFOLFIRINOX → TME → FOLFOX/CAPOX	LCRT → TME → FOLFOX/CAPOX	3-year DFS: 76% v 69%, HR 0.69, $P = .034$
CAO/ARO/AIO-12 ⁵	cT3 <6 cm from AV, cT3 at 6-12 cm with invasion of mesorectal fat >5 mm, cT4, or cN+	311	FOLFOX → LCRT → TME	LCRT → FOLFOX → TME	pCR 17% v 25%, OR 1.69, $P = .071$
OPRA ⁶	cT3-4 or cN+	324	FOLFOX/CAPOX → LCRT → TME/WW	LCRT → FOLFOX/CAPOX → TME/WW	3-year DFS: 76% v 76%, $P = \text{NS}$
PROSPECT ⁷	cT3 or cT2N+	1,194	FOLFOX → LCRT (if <20% shrinkage or FOLFOX held) → TME → adjuvant chemo	LCRT → TME → FOLFOX/CAPOX	DFS HR 0.92, $P = .005$ (noninferiority)

RAPIDO vs. PRODIGE

RAPIDO

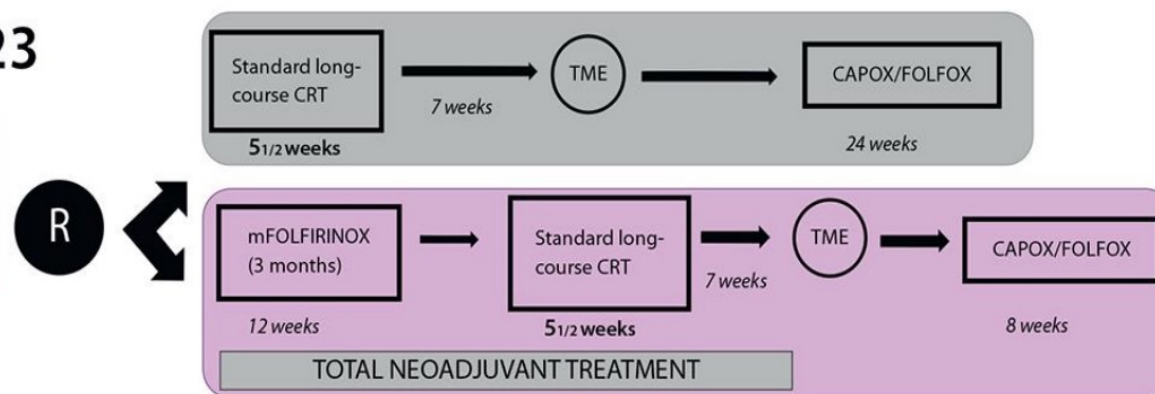
MRI staging
At least one of:
cT4a, cT4b, EMVI+,
N2, positive MRF, lat
LN+

primary endpoint:
DrTF



PRODIGE 23

MRI staging
cT3 with risk of local
recurrence or cT4,
primary endpoint:
DFS



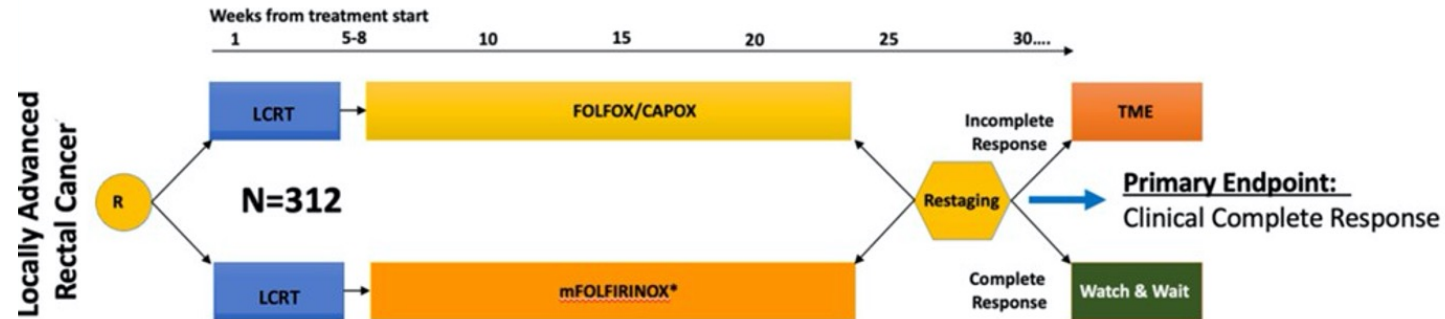
RAPIDO vs. PRODIGE

	RAPIDO TNT; n=920	PRODIGE TNT; n=461
Design experimental arm	SCRT (5x5) → FOLFOX or CAPOX (18 wks) → TME	FOLFIRINOX (18 wks) → CRT (50.4) → TME → (adj. FOLFOX)
Inclusion criteria	cT4a/b, EMVI, cN2, CRM+, lat Ln. +, CRM+ (by MRI): 61%	cT3 „at risk for local recurrence“, T4, N any, CRM+ (by MRI): 27%
Disease free survival (vs. SOC)	HR 0.75 (0.60-0.95)	HR 0.69 (0.47-0.97)
pCR	28%	28%
Local relapses	9% vs. 6% (ns)	5% vs. 7% (ns)

RAPIDO trial: Longer follow-up

	RAPIDO TNT	CRT
OS	81.7%	80.2%
Disease-related tx. failure	27.8%	34%
Distant mets.	23%	30.4%
Locoregional failure	12% (54/460)	8% (36/446)
Locoregional recurrence	10% (44/431)	6% (26/428)
Breached Rectum	21% (9/44)	4% (1/26)

ALLIANCE A022104/NRG-GI010: Janus Rectal Cancer Trial



- Expands on the findings of modern rectal cancer trials to provide further evidence for cCR as an endpoint
- Improved organ preservation rates utilizing a consolidation chemotherapy approach
- ctDNA levels as an exploratory biomarker in the context of a prospective randomized trial
- Determine generalizability of a WW approach across a more diverse population of patients, practice sites, and providers

Alvarez J...Alese O... ALLIANCE A022104/NRG-GI010. BMC Cancer – in press

PROSPECT

2023 ASCO[®]
ANNUAL MEETING

Preoperative Chemotherapy with Selective Chemoradiation versus Chemoradiation for Locally Advanced Rectal Cancer:

The PROSPECT Trial (Alliance N1048)

D Schrag MD MPH Q Shi PhD MR Weiser MD MJ Gollub MD LB. Saltz MD BL Musher MD J. Goldberg MD T. Al Baghdadi MD KA Goodman MD RR McWilliams MD MSc JM Farma MD TJ George MD HF Kennecke MD A Shergill MD M Montemurro MD GD Nelson MS B Colgrove BS V Gordon MD AP Venook MD EM O'Reilly MD JA Meyerhardt MD MPH AC Dueck PhD E. Basch MD MSc GJ Chang MD HJ Mamon MD PhD

ClinicalTrials.gov Identifier: NCT01515787



2023 ASCO[®]
ANNUAL MEETING

#ASCO23

PRESENTED BY: Deb Schrag MD MPH FASCO, Attending, Gastrointestinal Oncology Service, Memorial Sloan Kettering NY, NY USA

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KNOWLEDGE CONQUERS CANCER

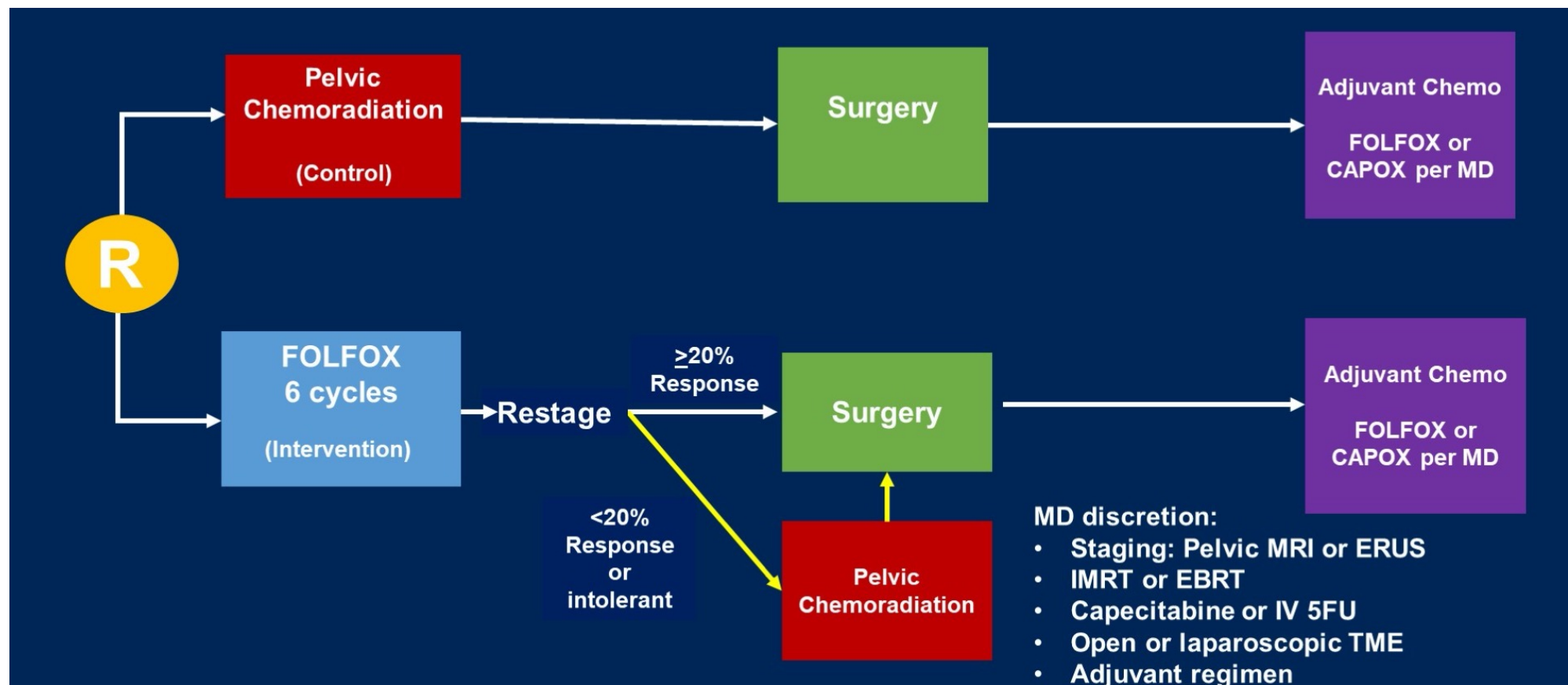
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Treatment of Locally Advanced Rectal Cancer

Deborah Schrag, M.D., M.P.H., Qian Shi, Ph.D., Martin R. Weiser, M.D.,
Marc J. Gollub, M.D., Leonard B. Saltz, M.D., Benjamin L. Musher, M.D.,
Joel Goldberg, M.D., Tareq Al Baghdadi, M.D., Karyn A. Goodman, M.D.,
Robert R. McWilliams, M.D., Jeffrey M. Farma, M.D., Thomas J. George, M.D.,
Hagen F. Kennecke, M.D., Ardaman Shergill, M.D., Michael Montemurro, M.D.,
Garth D. Nelson, M.S., Brian Colgrove, B.S., Vallerie Gordon, M.D.,
Alan P. Venook, M.D., Eileen M. O'Reilly, M.D., Jeffrey A. Meyerhardt, M.D., M.P.H.,
Amylou C. Dueck, Ph.D., Ethan Basch, M.D., George J. Chang, M.D.,
and Harvey J. Mamon, M.D., Ph.D.

PROSPECT



2023 ASCO
ANNUAL MEETING

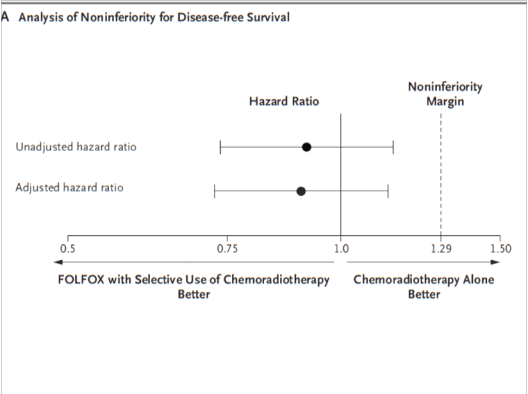
#ASCO23

PRESENTED BY: Deb Schrag MD MPH FASCO

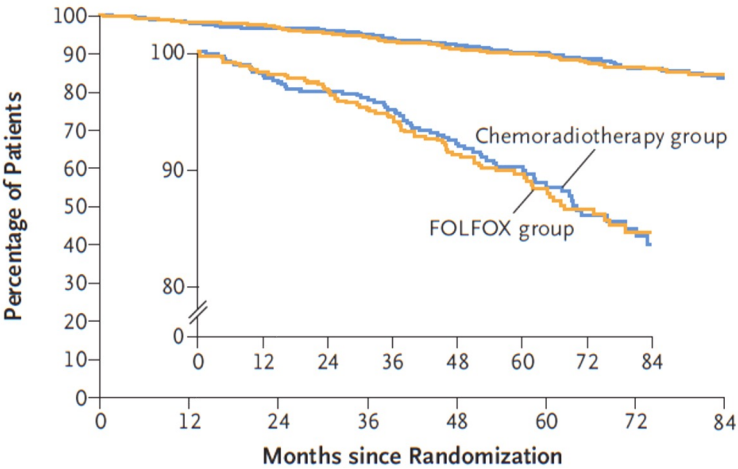
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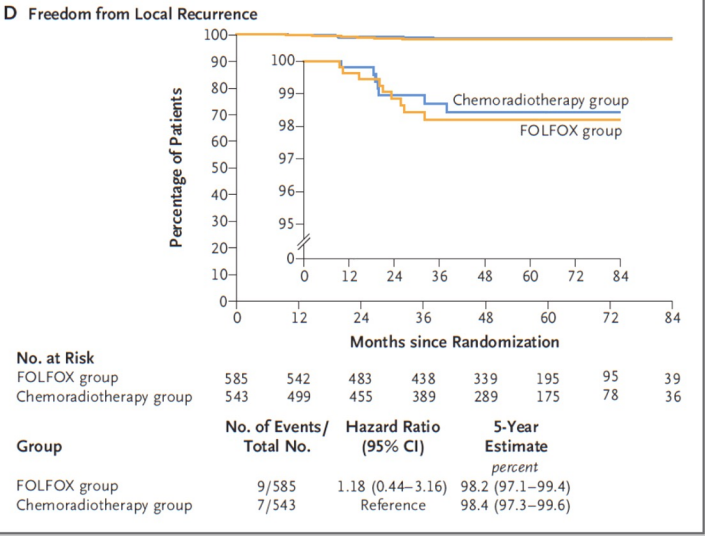
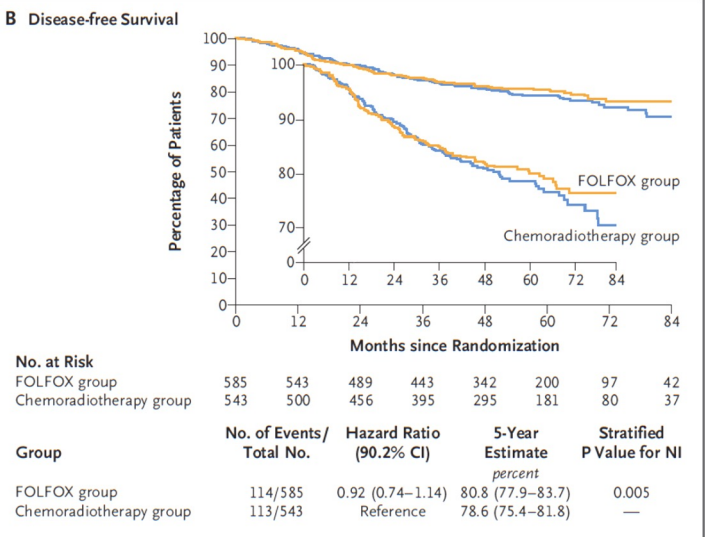
PROSPECT



C Overall Survival



No. at Risk									
FOLFOX group		585	565	551	531	429	287	212	120
Chemoradiotherapy group		543	527	513	486	380	273	182	107
Group		No. of Events/ Total No.		Hazard Ratio (95% CI)		5-Year Estimate percent			
FOLFOX group		74/585		1.04 (0.74–1.44)		89.5 (87.0–92.2)			
Chemoradiotherapy group		67/543		Reference		90.2 (87.6–92.9)			





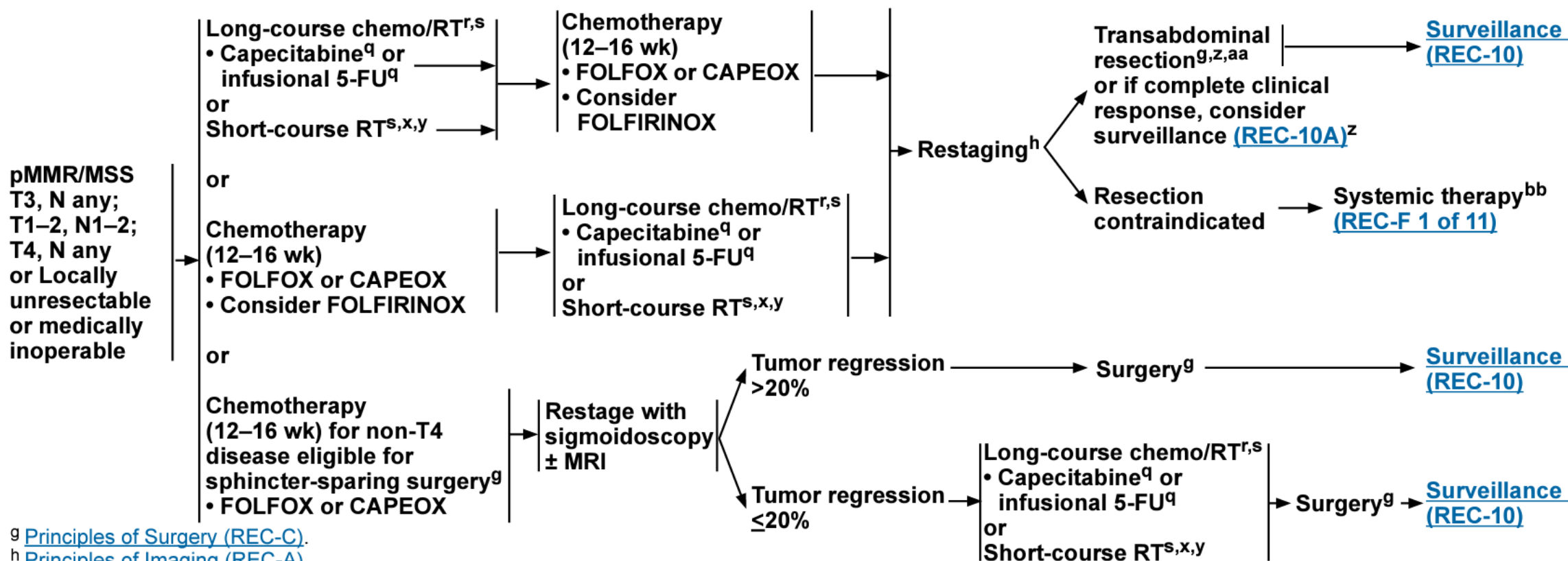
NCCN Guidelines Version 3.2024

pMMR/MSS Rectal Cancer

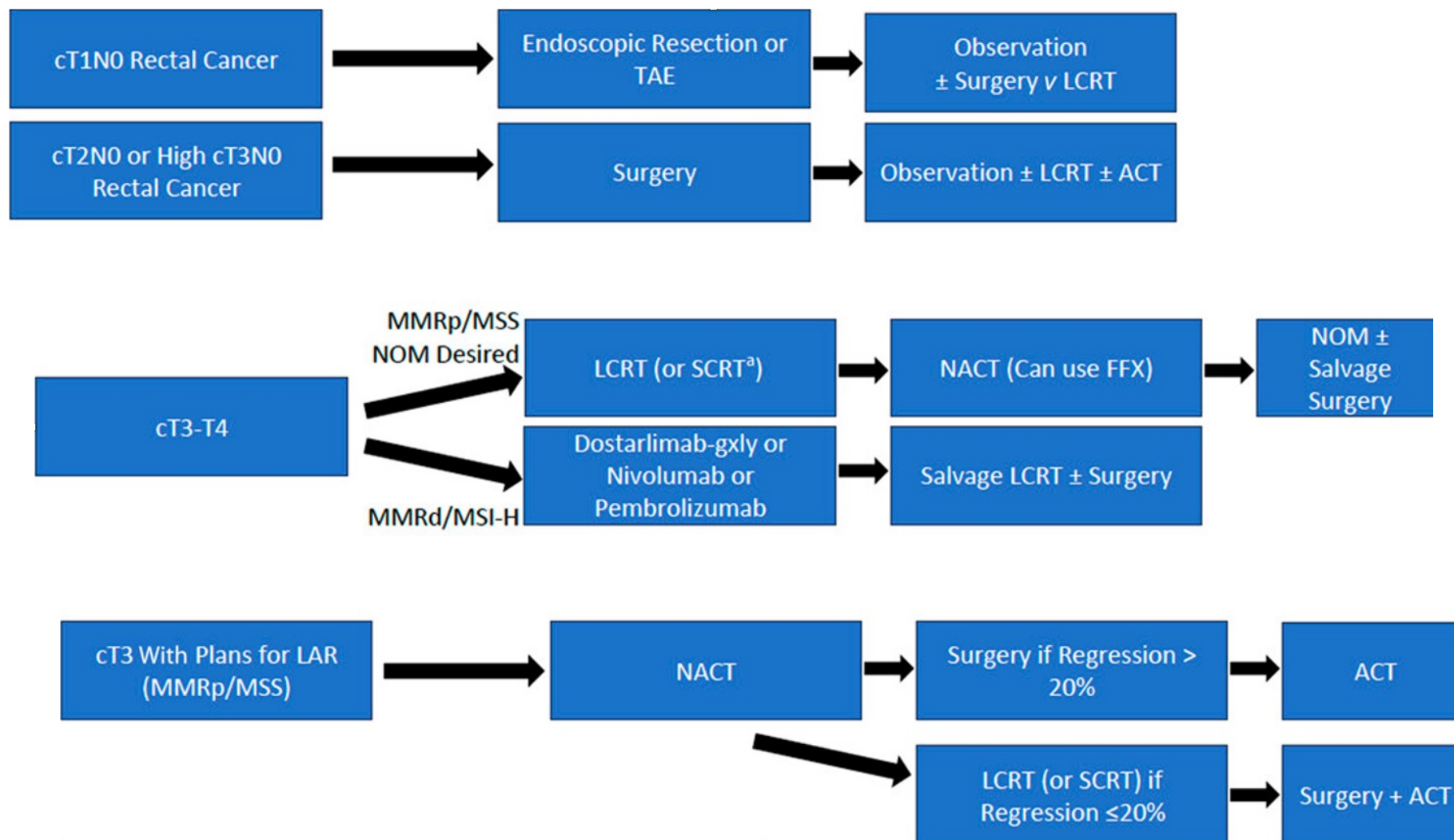
CLINICAL STAGE

TOTAL NEOADJUVANT THERAPY^w

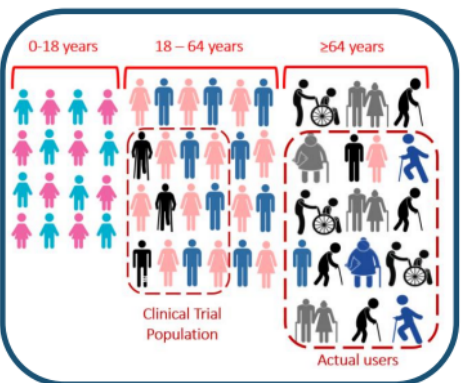
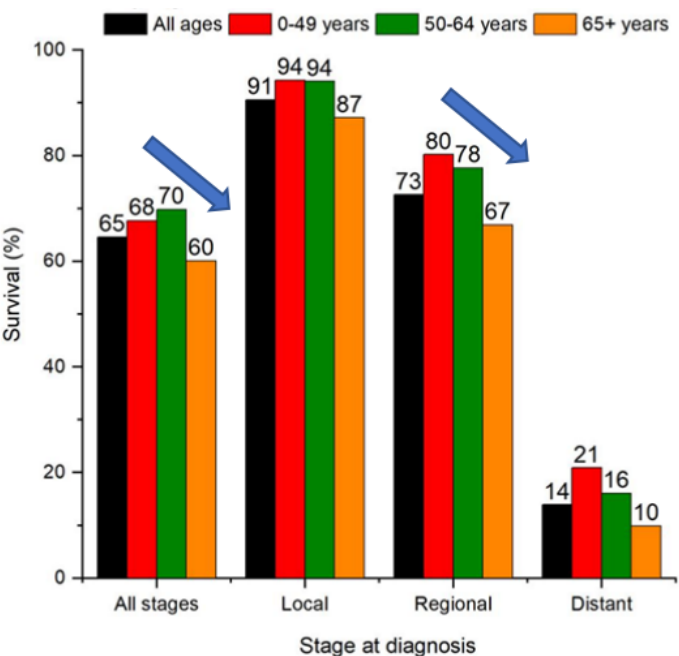
PRIMARY TREATMENT



Treatment schema



Elderly patients



Siegel RL et al CA Cancer J Clin. 2023

OPRA
Mean Age 57

PROSPECT Trial
Mean Age 57

RAPIDO
Mean Age 62

PRODIGE 23
Mean Age 62

Watch & Wait Intl DB
Mean Age 65

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)
Age (years)	57 (34-87)	56 (32-84)	56 (21-76)	58 (33-72)
Sex				
Female	23 (38%)	30 (45%)	30 (45%)	24 (37%)
Male	37 (62%)	37 (55%)	37 (55%)	41 (63%)

Characteristic	FOLFOX Group (N=585)	Chemoradiotherapy Group (N=543)
Age — yr		
Mean	57.3±10.9	57.0±11.1
Median (range)	57 (19-91)	57 (25-84)

Age at randomisation, years		
Median (IQR)	62 (55-68)	62 (55-68)
Range	31-83	23-84

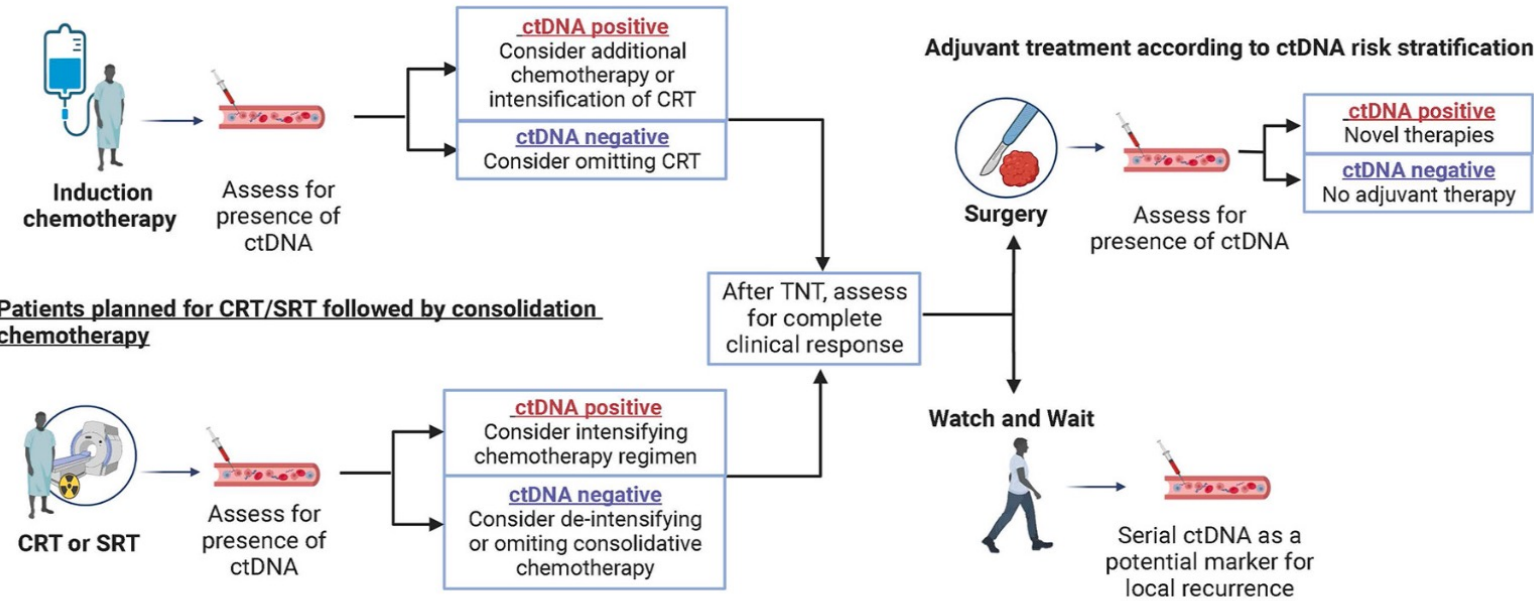
	Neoadjuvant chemotherapy group (n=231)	Standard-of-care group (n=230)
Age at randomisation, years		
Median (IQR)	61 (53-66)	62 (55-66)
Range	34-77	26-75

	All patients (n=793)
Age, years*	65.0 (56.0-72.0)

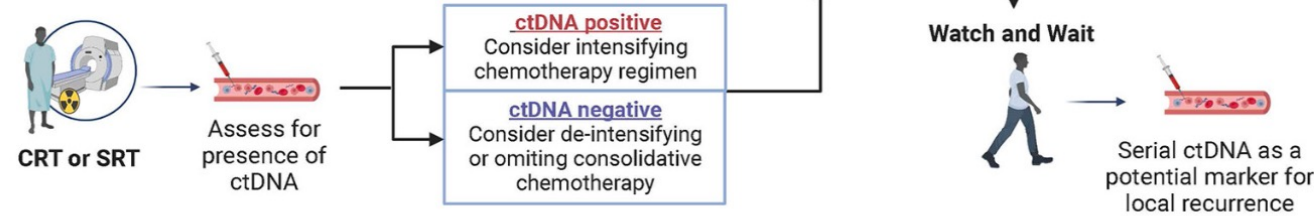


Patients suitable for a total neoadjuvant approach

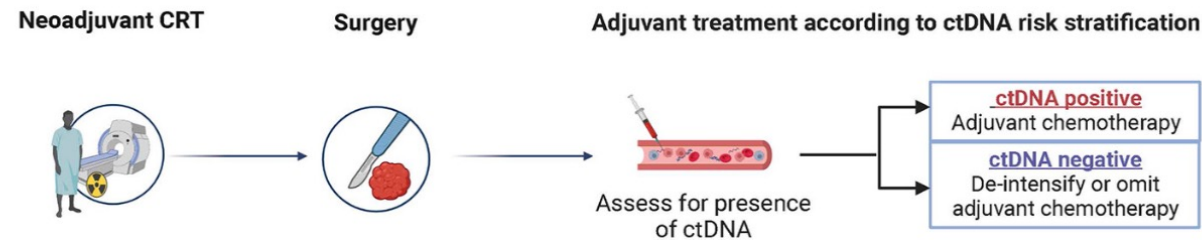
Patients planned for induction chemotherapy followed by CRT or SRT



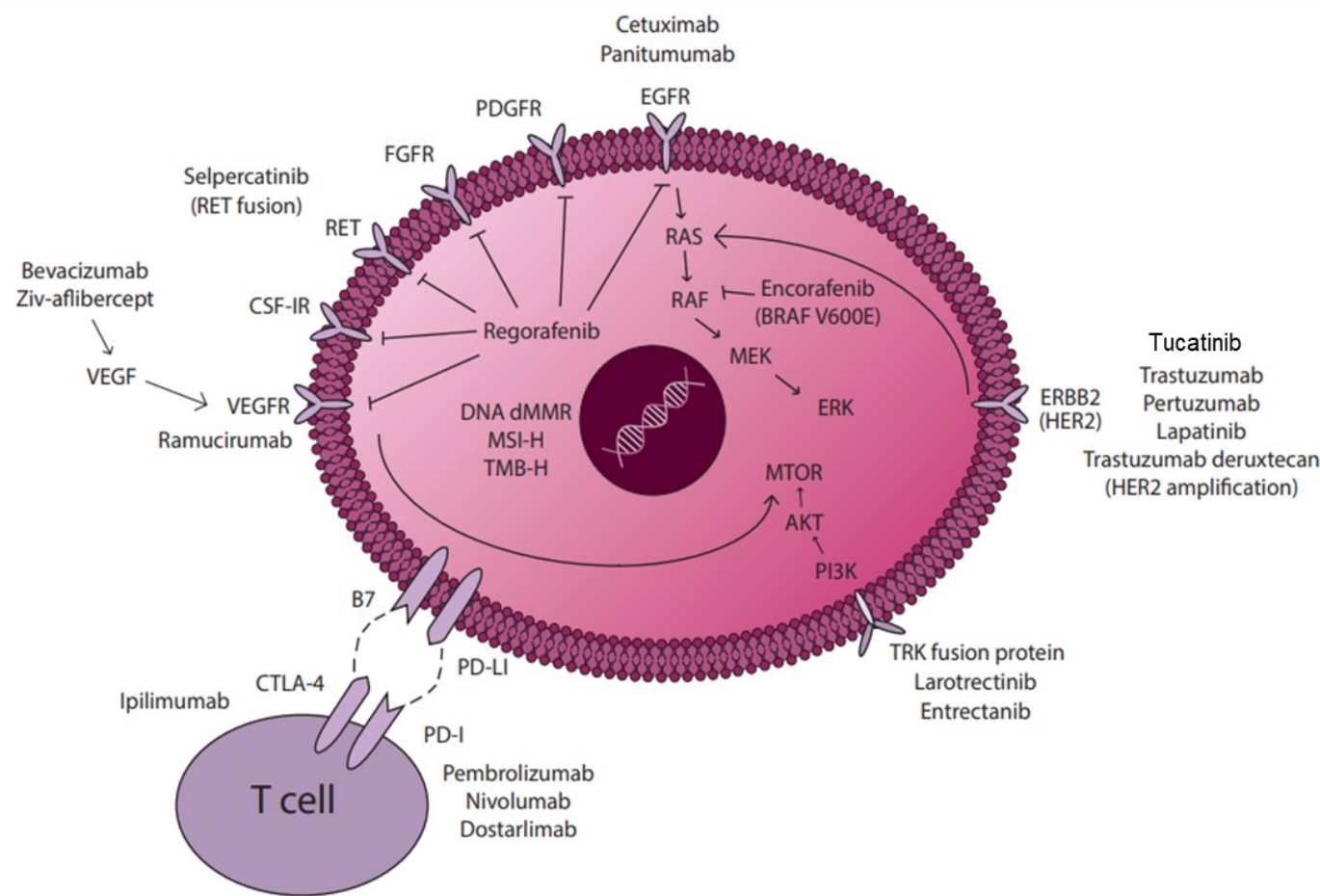
Patients planned for CRT/SRT followed by consolidation chemotherapy



Patients receiving traditional long course chemoradiation followed by surgery



New targets



Targets	Drug
EGFR (RAS/RAF wild-type)	<ul style="list-style-type: none">CetuximabPanitumumab
VEGF	<ul style="list-style-type: none">BevacizumabZiv-afliberceptRamucirumabRegorafenib
PDL-1 (dMMR or MSI-H)	<ul style="list-style-type: none">PembrolizumabNivolumab +/- ipilimumabDostarlimab
BRAF V600E mutation	<ul style="list-style-type: none">Encorafenib + anti-EGFR
ERBB2 (HER2) overexpression (+RAS/RAF wild-type)	<ul style="list-style-type: none">Trastuzumab + TucatinibPertuzumabLapatinibTrastuzumab deruxtecan
TRK fusion	<ul style="list-style-type: none">LarotrectinibEntrectanib
RET fusion	<ul style="list-style-type: none">Selpercatinib

Conclusion

- Recent advances in the perioperative management of early rectal cancers have led to improved outcomes
- Current efforts at personalizing treatments are promising, and could minimize short and long term toxicities
- Additional efforts are needed regarding emerging technologies, such as optimization of ctDNA as a biomarker

Save the date!

Winship Cancer Institute
of Emory University
presents

13th Annual Winship Gastrointestinal Cancer Symposium

SATURDAY, OCTOBER 12th 2024

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3300 Lenox Road NE
Atlanta, GA 30326