Celebrating 150 years of advancing medical research, education, and patient care to help people live longer, healthier lives

UNIVERSITY OF IOWA HOLDEN COMPREHENSIVE CANCER CENTER
University of Iowa Health Care

GI Oncology Update: Colon & Rectal Cancers

Saima Sharif, MD MS

August 25, 2023

CHANGING MEDICINE.
CHANGING LIVES.®

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Disclosure

- I have permission to use slides from Annual Meeting 2023
- Saima Sharif, MD MS reports:
  - Grant/research support - GSK
  - Is a consultant for - none
  - Other - none

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Learning Objectives

- Review of results and updates from select trials and future trials in Colon and Rectal Cancers presented at ASCO Annual meeting 2023
- Discuss their relevance to clinical practice

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Outline of Presentation

- Updates in Colon Cancer, early stage
  - LBA # 3503 – NEOCOL
  - Abstract # 3521 – GALAXY study in CIRCULATE JAPAN
  - Ongoing Trials to personalize therapy utilizing ctDNA
    - Stage II – COBRA, CIRCULATE PRODIGE-70, SU2C ACT3
    - Stage III – DYNAMIC III and CIRCULATE-US
- Updates in Colon Cancer, metastatic
  - Abstract # 3500 - AtezoTRIBE
  - Abstract # 3501 - DESTINY CRC 02
  - Abstract # 3508 – PARADIGM
  - Abstract # 3513 – Codebreak 101
- Updates in Rectal Cancer, early stage
  - LBA # 02 - PROSPECT trial
  - LBA # 3504 - PROGIGE 23 trial
  - Abstract # 3520 – Long term results of OPRA trial

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Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer

The Scandinavian **NeoCol** trial

Lars Henrik Jensen MD PhD

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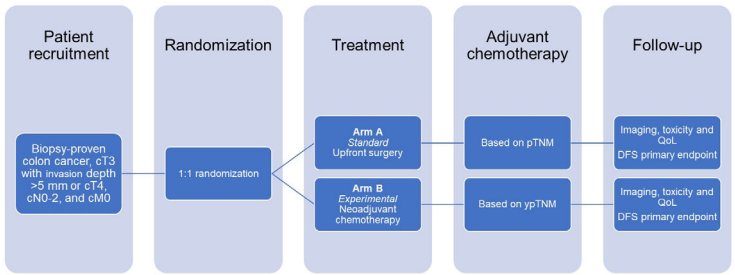
Study design



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Treatment

- Arm A standard upfront surgery
- Arm B neoadjuvant chemotherapy before surgery
  - 3 cycles of CAPOX (3-week cycle, oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 twice daily for 14 days, *or*
  - 4 cycles of FOLFOX (2-week cycle, oxaliplatin 85 mg/m^2, 5FU 400 mg/m^2 bolus and 2400 mg/m^2 over 46 hours)
- Adjuvant chemotherapy in both arms was chosen based on the pathological stage of the cancer according to guidelines

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Adjuvant chemotherapy indication

	Upfront surgery (standard)	Neoadj. Treatment (intervention)	p
Criteria for adjuvant chemotherapy fulfilled, N (%yes)	87 (73%)	72 (59%)	0.05

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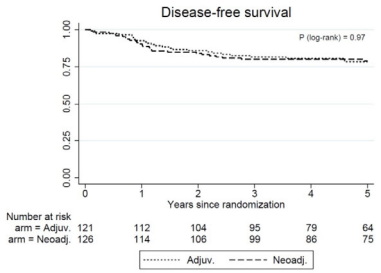
Efficacy outcomes - Disease-free survival (DFS)



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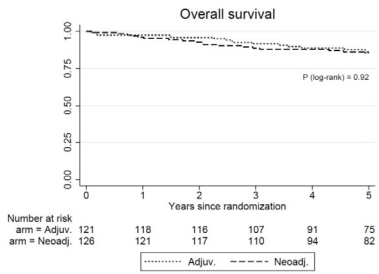
Efficacy outcomes - Overall survival (OS)



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Pathology

		Upfront surgery (standard)	Neoadj. treatment (intervention)	All
Involvement of resection margin, N (%)	R1	10 (9%)	9 (7%)	19 (8%)
	R0	109 (90%)	114 (93%)	223 (91%)
	Unknown	1 (1%)	-	1 (1%)
p/ypT-category at surgery*, N (%)	0		[update]	
	1		[update]	
	2		[update]	
	3	64 (63%)	[update]	[update]
	4	37 (37%)	[update]	[update]
p/ypN-category at surgery, N (%)	0	57 (48%)	72 (59%)	129 (54%)
	1	42 (35%)	31 (25%)	73 (30%)
	2	20 (17%)	19 (16%)	39 (16%)
Perineural invasion, N (%yes)		21 (18%)	19 (15%)	40 (17%)
Vascular invasion, N (%yes)		47 (39%)	30 (25%)	77 (32%)
Perforation, N (%yes)		2 (2%)	3 (2%)	5 (2%)

*: Numbers may vary due to missing data

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Is there a place for neoadjuvant chemotherapy in limited stage colon cancer

- At this time, this remains *unknown*
  - High risk patients (Obstructive presentation, bulky disease)
  - Downstaging
- Lack of optimal staging modalities limits the ability to identify patients who may benefit from neoadjuvant CT
- *Many* still received adjuvant chemotherapy, so perioperative CT *not* TNT

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Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? No
- Impact on value/cost of care, long-/short-term side effects, etc.?
  - Upfront surgery *remains* gold standard

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2023 ASCO ANNUAL MEETING

Circulating tumor DNA dynamics as an early predictor of recurrence in patients with radically resected colorectal cancer: Updated results from GALAXY study in the CIRCULATE-Japan

Eiji Oki[1], Daisuke Kotani[2], Yoshiaki Nakamura[2], Saori Mishima[2], Hideaki Bando[2], Hiroki Yukami[3], Koji Ando[4], Masaaki Miyo[5], Jun Watanabe[6], Keiji Hirata[7], Naoya Akazawa[8], Kun-Huei Yeh[9], George Laliotis[10], Shruti Sharma[10], Minetta C. Liu[10], Hiroya Taniguchi[11], Ichiro Takemasa[5], Takeshi Kato[12], Masaki Mori[13], Takayuki Yoshino[2]

[1]Department of Surgery And Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3]Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, Osaka, Japan; [4]Department of Colorectal Surgery, National Cancer Center Hospital East Kashiwa, Japan, [5]Department of Surgery, Surgical Oncology and Science, Sapporo Medical University, Sapporo, Japan; [6]Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Japan; [7]Department of Surgery, University of Occupational And Environmental Health, Japan; [8]Department of Gastroenterological Surgery, Sendai Open Hospital, Japan; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Natera, Inc., Austin, Texas, USA; [11]Department of Clinical Oncology, Aichi Cancer Center Hospital, Japan; [12]Department of Colorectal Surgery, National Hospital Organization Osaka National Hospital, Japan [13]Tokai University Hospital, Tokai University School of Medicine, Japan

Presented by Eiji Oki MD, PhD, FACS

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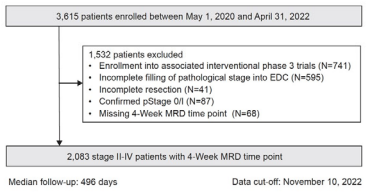
Background and Consort diagram

- Postoperative circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) is reported to be associated with a high risk of recurrence (Kotani D et al. Nature Med 2023)
- Here, we present an updated analysis and the lead time interval (LTI) of ctDNA positivity to radiographic recurrence in patients (pts) with radically resected colorectal cancer (CRC), stage II-IV in the observational GALAXY study (UMIN000039205).



Characteristic	N = 2,083[1]
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Male	1,125 (54%)
Female	958 (46%)
Age	69 (25 - 95)
Tumor Location	
Left	1,447 (70%)
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MSI Status	
MSS	1,775 (85%)
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Follow up (months)	16.3 (0.8 - 30)
Lead Time (months)	4.7 (0 - 17.3)

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BRAF Status	
BRAF wt	1,830 (88%)
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ctDNA status MRD time point	
ctDNA negative	1,797 (86%)
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ctDNA clearance from 4 to 12 weeks	
Clearance	112 (47%)
No Clearance	124 (53%)

[1]n (%); Median (Range)

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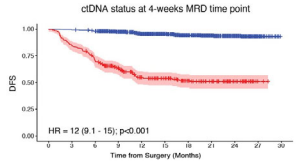
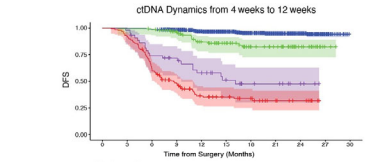
ctDNA dynamics between weeks 4 and 12 post surgery is prognostic of DFS



Dynamics	ctDNA Negative	ctDNA Positive
Events (n)	96/1797 (5.3%)	130/286 (45.5%)
18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001



Dynamics	Persistently Negative	Converted Negative	Converted Positive	Persistently Positive
Events (n)	69/1529 (4.5%)	16/112 (14.3%)	20/43 (46.5%)	78/124 (62.9%)
18M - DFS	94.9 (93.5 - 96)	82.2 (72.3 - 88.9)	47.4 (30.4 - 62.7)	33.8 (25 - 42.8)
HR	Reference	3.5	14.5	25.4
95% CI	Not applicable	1.9 - 5.8	8.8 - 23.8	18.3 - 35.3
P	Not applicable	<0.001	<0.001	<0.001

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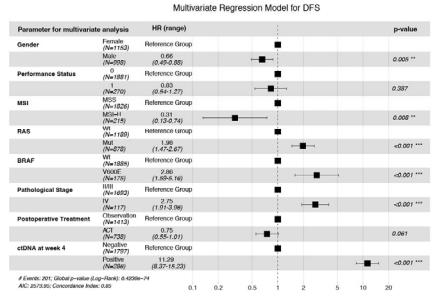
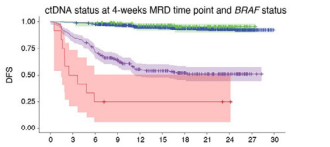
ctDNA status at 4-weeks MRD time point combined with BRAF status is prognostic of DFS





Dynamics	ctDNA Negative *BRAF*^{wt}	ctDNA Negative *BRAF*$^{mut/wt}$	ctDNA Positive *BRAF*^{wt}	ctDNA Positive *BRAF*$^{mut/wt}$
Events (n)	88/1561 (5.6%)	6/157 (3.8%)	121/269 (45%)	9/12 (75%)
18M - DFS	93.7 (92.2 - 94.9)	95.5 (90.1 - 98)	52 (45.4 - 58.2)	25 (6 - 50.5)
HR	Reference	0.65	11	35.1
95% CI	Not applicable	0.3 - 1.5	8.3 - 14.5	17.6 - 70
P	Not applicable	0.306	<0.001	<0.001

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Conclusion

- Our study builds on the existing evidence from the recently published, prospective GALAXY study, demonstrating the prognostic value of ctDNA analyzed in >2000 patients.
- ctDNA-positivity at MRD time point postsurgery was found to be prognostic of patient outcomes and was worse in *BRAF* V600E mutated patients compared to wildtype patients in this population.
- ctDNA positivity predicted radiologic recurrence by a median of 4.7 months ahead of clinical recurrence.
- Patients with positive postoperative ctDNA should be monitored carefully due to a high risk of recurrence.
- ctDNA-guided adjuvant strategy will further be established by ongoing randomized VEGA and ALTAIR clinical trials that are part of the CIRCULATE-Japan study.

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2023 ASCO ANNUAL MEETING

Early Predictors of Recurrence in the Curative Setting in Colorectal Cancer: Are We Getting Closer?

Gastrointestinal Cancer—Colorectal and Anal
Poster Discussion

Clara Montagut
Hospital del Mar, Barcelona

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The dilemma in adjuvant treatment: Benefit vs toxicity

CRC: Localized / Ressected metastatic

Curative intent surgery	Risk of Relapse?	Individualize adjuvant chemotherapy (ACT)?	Surveillance
Last decades	TNM Stage Clinicopathological features MSI Gene expression signatures	No (minor) individualization	Imaging CEA
2022	ctDNA	1st positive randomized clinical trial: non-inferiority in ct-DNA guided ACT vs SOC in stage II: (DYNAMIC, Tie NEJM)	ctDNA?

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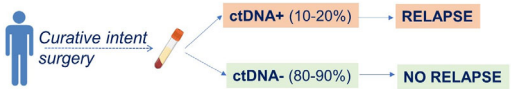
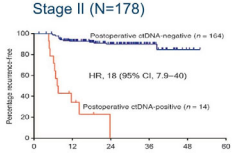
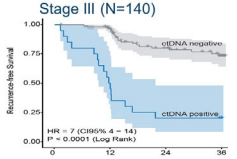
ctDNA defines molecular persistance of disease and is a reliable and powerful predictor of relapse



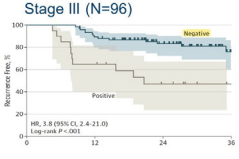
Stage II (N=178)



Stage III (N=140)



Stage III (N=96)



Tie, Sci Transl Med 2016; Tie, JAMA Oncol 2019; Henriksen, CCR 2021; Kotani, Nat Med 2023

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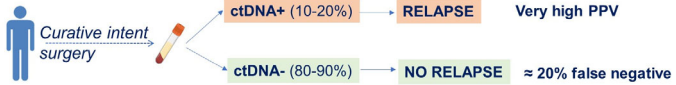

- Incremental improvements in **technology**: Important to use specific assays designed for MRD application (tissue-informed or tissue-agnostic)

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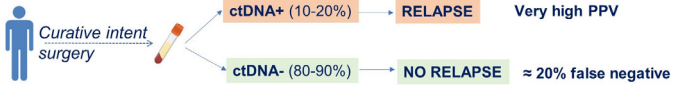

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- Need to improve **biological** understanding. Specific genomic alterations? Beyond ctDNA: tumor microenvironment ?
- Need to show **clinical utility** to adjuvant-chemotherapy decision making / surveillane. Ongoing randomized ctDNA-based clinical trials

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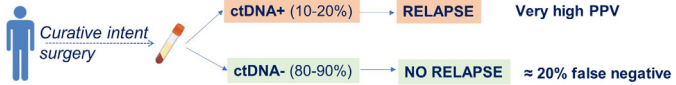

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2023 ASCO ANNUAL MEETING

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Presented by Clara Montagut, MD, PhD

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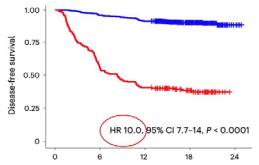
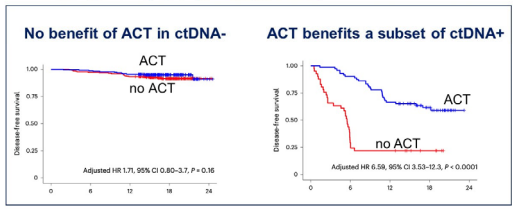
Abstract #3521. Background. **GALAXY**

- observational arm of the CIRCULATE-Japan
- published with **1039 pts stage I-IV**; median follow up of 16mo (Kotani, Nat Med 2023)
- uses a **tissue-informed test for ctDNA detection** (Signatera)

(1) Can ctDNA predict relapse? YES



(2) Can ctDNA help in adjuvant chemotherapy decision-making? YES, but non randomized



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Abstract #3521. Results

Update on GALAXY

very large cohort

6% stage IV (N=114 !)

limitation: short follow-up

Characteristic	N = 2,083[1]
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Male	1,125 (54%)
Female	958 (46%)
Age	69 (25 - 95)
Tumor Location	
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ctDNA clearance from 4 to 12 weeks	
Clearance	112 (47%)
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[1]n (%); Median (Range)

14% ctDNA+ : similar to previous studies

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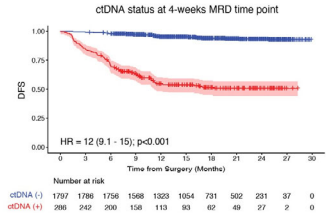
Abstract #3521. Results



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18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001

- Confirm strong prognostic value of ctDNA (HR 12)

- Few events, probably needs longer follow-up (more recurrences):

  Only 5% of false negative results (ctDNA- that recur). Will longer follow-up increase false negative rate?

  Only 45% of ctDNA+ recur: Will longer follow-up increase PPV?

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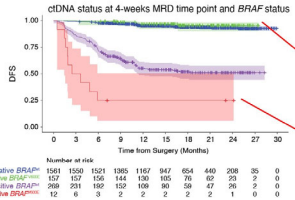
Abstract #3521. Results



ctDNA status at 4-weeks MRD time point combined with BRAF status is prognostic of DFS:

most BRAFV600E tumors are ctDNA- only 3.8% relapse

few **BRAFV600E** tumors are **ctDNA+ 75% relapse**

(short follow-up)

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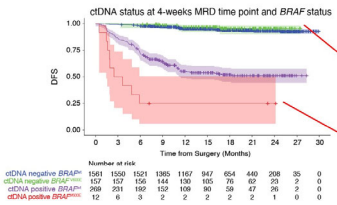

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few **BRAFV600E** tumors are **ctDNA+ 75% relapse**

(short follow-up)

SURVEILLANCE: Follow-up with longitudinal blood extractions (3, 6, 9, 12, 18, and 24 months after surgery) shows **median 4.7 months lead time**

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TAKE AWAY **Update GALAXY Japan**

Large and well-designed trial (needs longer follow-up)

1. Can ctDNA be used **for risk-stratification in clinical practice?** YES

- Confirms results from previous studies (stage II-IV)
- Defines very high-risk population: ctDNA+ and BRAFV600E mutant tumors (exploratory)
- Teaches **practical tips for MRD testing clinical application**:
  - Blood extraction for ctDNA MRD at week 4, to avoid ctDNA dilution
  - Use specific highly sensitive technology for MRD testing: tissue-informed (Signatera)

2. Can ctDNA help in **adjuvant chemotherapy (ACT) decision-making?** Probably

- Results from **randomized clinical trials** very soon to show clinical utility
- In ctDNA negative: consistent data on lack of benefit from ACT (GALAXY, MD Anderson)

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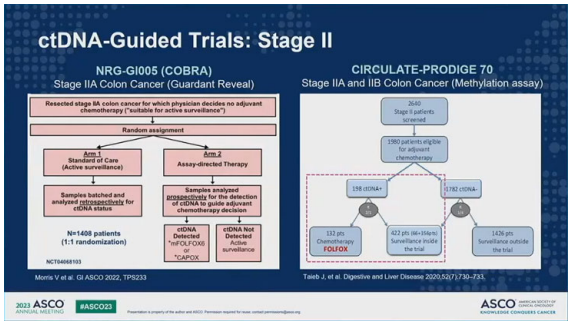
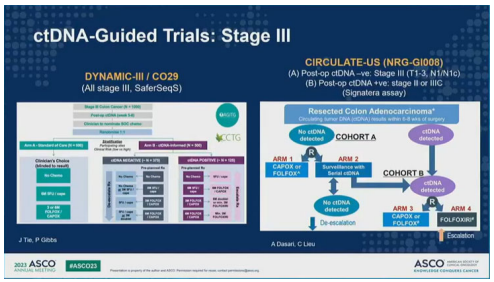
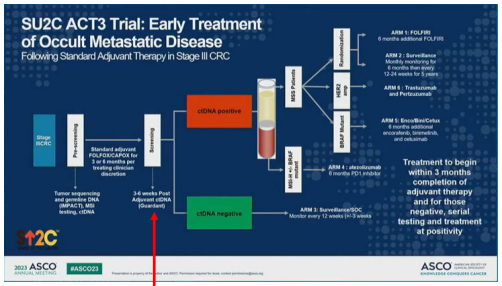
Stage II – Currently enrolling



Stage III – Currently enrolling



Stage III – Currently enrolling (contd.)



Currently being amended to allow q3mo serial longitudinal ctDNA testing for 3 years

Outline of Presentation

- Updates in Colon Cancer, early stage
  - LBA # 3503 – NEOCOL
  - Abstract # 3521 – GALAXY study in CIRCULATE JAPAN
  - Ongoing Trials to personalize therapy utilizing ctDNA
    - Stage II – COBRA, CIRCULATE PRODIGE-70, SU2C ACT3
    - Stage III – DYNAMIC III and CIRCULATE-US
- Updates in Colon Cancer, metastatic
  - Abstract # 3500 - AtezoTRIBE
  - Abstract # 3501 - DESTINY CRC 02
  - Abstract # 3508 – PARADIGM
  - Abstract # 3513 – Codebreak 101
- Updates in Rectal Cancer, early stage
  - LBA # 02 - PROSPECT trial
  - LBA # 3504 - PROGIGE 23 trial
  - Abstract # 3520 – Long term results of OPRA trial

2023 ASCO ANNUAL MEETING

FOLFOXIRI plus bevacizumab and atezolizumab as upfront treatment of unresectable mCRC patients: updated and overall survival results of the phase II randomized AtezoTRIBE study

Carlotta Antoniotti, Daniele Rossini, Filippo Pietrantonio, Lisa Salvatore, Federica Marmorino, Margherita Ambrosini, Sara Lonardi, Maria Bensi, Roberto Moretto, Stefano Tamberi, Ilaria Toma, Alessandro Passardi, Maria Caterina De Grandis, Veronica Conca, Federica Palermo, Alessandro Cappetta, Aurelie Catteau, Luca Boni, Jérôme Galon, Chiara Cremolini

On behalf of GONO Foundation investigators

Carlotta Antoniotti, MD PhD

University Hospital of Pisa, Italy

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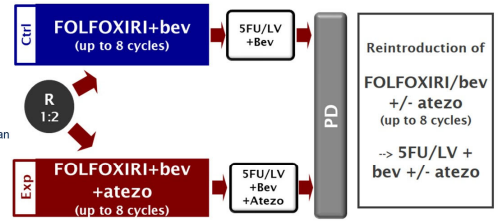
AtezoTRIBE – study design

Key eligibility criteria

- Previously untreated, unresectable and RECIST v1.1-measurable mCRC
- Age 18-75 years
- ECOG PS ≤ 2 (ECOG PS= 0 if age= 71-75 years)
- Adjuvant oxaliplatin-containing chemotherapy not allowed
- Adjuvant fluoropyrimidine monotherapy allowed if more than 6 months elapsed between the end of adjuvant and first relapse
- Adequate bone marrow, liver and renal functions
- No contraindications to ICI



Stratification factors: center; ECOG PS (0 *vs* 1-2); primary tumour location (right *vs* left or rectum); previous adj chemotherapy (yes *vs* no)
Participating centers: 22 Italian sites

Primary endpoint: Progression-Free Survival
Sample size: Assuming a median PFS of 12 months in the control arm, 201 pts (129 PFS events) would provide 85% power to detect a difference in PFS in favour of the experimental arm with a HR of 0.66 at a one-sided α of 0.10.

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Why is MSS (pMMR) mCRC resistant to ICIs?

- Presence of immunosuppressive factors and cells (TAMS, MDSCs ..)in local tumor microenvironment – (Liver worst)
- Loss of tumor antigen expression
- Activation of immunosuppressive oncologic pathways (MAPK, PIK3CA etc..)
- Others including unknown
- Most have low TMB , but even with TMB > 10 mut/MB → no benefit (NEJM 2021)

Pecci F et al . Curr Treatment options in Oncology. 2021

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Patients' characteristics – ITT population

Characteristic, % patients	N= 218 FOLFOXIRI/Bev N = 73	 FOLFOXIRI/Bev/Atezo N = 145
Gender (M / F)	58 / 42	57 / 43
Median Age (range)	61 (20 – 74)	60 (35 – 75)
ECOG PS (0 / 1-2)	**84** / 16	**85** / 15
Synchronous Metastases (Y / N)	**89** / 11	**86** / 14
Prior Adjuvant CT (Y / N)	5 / 95	3 / 97
Primary Tumor Side (right / left)	44 / 56	45 / 55
Number Metastatic Sites (1 / >1)	40 / 60	43 / 57
Liver Only Disease (Y / N)	27 / 73	27 / 73
Resected Primary (Y / N)	44 / 56	41 / 59
RAS/BRAF (*RAS* mut / *BRAF* mut / wt / NE)	71 / 14 / 15 / -	75 / 8 / 15 / 2
Right and/or *RAS* mut (Y / N)	**86** / 14	**90** / 10
MMR status* (pMMR / dMMR / NE)	92 / **7** / 1	92 / **6** / 2

* per local assessment by IHC

Antoniotti et al, Lancet Oncol 2022

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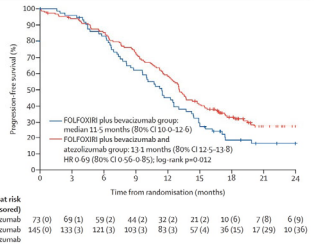
Primary analysis: Main findings

In the ITT population:

- PFS was significantly longer in the experimental arm (median 13.1 vs 11.5, HR:0.69 [80% CI:0.56-0.85], p=0.012) with no difference in response rate (64% vs 59%, p=0.21).
- No unexpected G3/4 or serious adverse events were reported.

Progression-Free Survival



Cut-off date: August 1st, 2021. At median follow-up: 19.9 months (IQR: 17.3-23.9)

Antoniotti et al, Lancet Oncol 2022

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Primary analysis: Main findings

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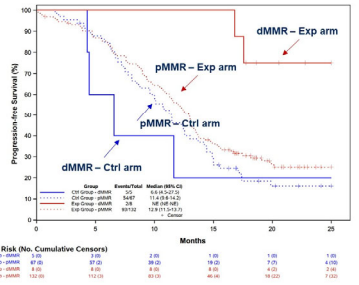
- No unexpected G3/4 or serious adverse events were reported.
- Significant interaction between treatment arm and MMR status was found (p=0.010).
  - pMMR: HR: 0.77 [0.55-1.08]
  - dMMR: HR: 0.10 [0.02-0.42]

Progression-Free Survival



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AtezoTRIBE – translational analyses on tumour specimens

	Biomarker description	Assessable population
TMB[1]	Number of mutations per megabase	**141** (65%)
Immunoscore[2]	Densities of CD8+ and CD3+ cells into the tumour core and at the invasive margin*	**77** (35%)
Immunoscore IC[2]	Densities of CD8+ and PD-L1+ cells and their proximity into the tumour core	**157** (72%)
PD-L1 TPS[2]	Density of PD-L1+ tumour cells	**162** (74%)
Tumour infiltrating lymphocytes[3]	Density of tumour epithelium infiltrating lymphocytes	**181** (83%)
Determa IO gene signature[4]	Immune-related 27-gene targeted panel	**122** (56%)

1: FoundationOne CDx assay, US; 2: Veracyte, US; 3: University of Pisa, Italy; 4: Oncocyte Inc, US. *assessed only on tumour surgical resection (no biopsies).

Antoniotti et al, Lancet Oncol 2022; Moretto et al, J Immunother Cancer 2023; Antoniotti et al, Clin Cancer Res 2023

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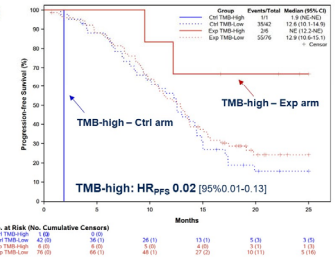
Primary analysis: Main findings from translational analyses

In the pMMR population - PFS:

- Significant interaction between treatment arm and TMB (p=0.012)

pMMR TMB-high*: 6%



*defined as TMB≥10 mut/Mb

Antoniotti et al, Lancet Oncol 2022

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Immunoscore IC [IS IC] – more than TILs evaluation

CD8+ and PD-L1+ cell densities and proximity between them, by means of IHC and digital pathology

High IS-IC: high density of CD8+ and PD-L1+ cells and proximity between them
Low IS-IC: low density of CD8+ and PD-L1+ cells and proximity between them

Concordance between Immunoscore IC and TILs*

	TILs-HIGH	TILs-LOW	*K* of Cohen
Immunoscore IC-HIGH	21 (39%)	24 (25%)	*0.15*
Immunoscore IC-LOW	33 (61%)	73 (75%)	

*assessed by means of optical microscope

Antoniotti et al, Lancet Oncol 2022; Moretto et al, J Immunother Cancer 2023

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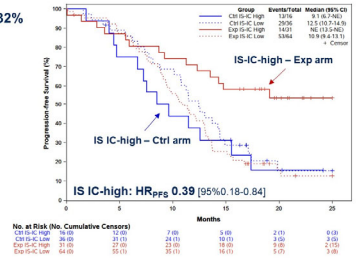
Primary analysis: Main findings from translational analyses

In the pMMR population - PFS:

- Significant interaction between treatment arm and Immunoscore IC [IS-IC] (p=0.006)

pMMR IS IC-high: 32%



Antoniotti et al, Lancet Oncol 2022

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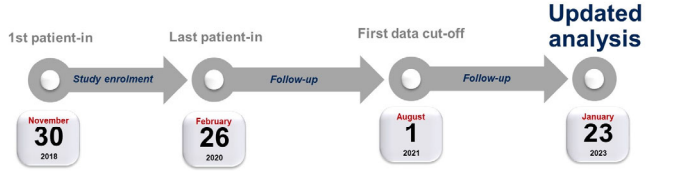
Study timeline



PFS events: 159 (73%)
median follow-up: 19.9 months

PFS events: 175 (80%)
OS events: 118 (54%)
median follow-up: 37.0 months

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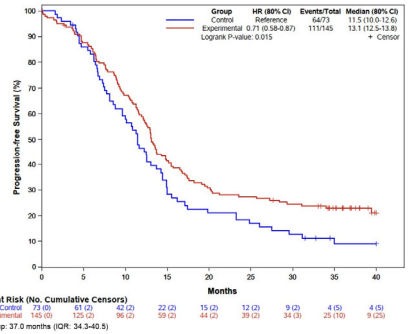
Updated PFS – ITT population



Cut-off date: January 23rd, 2023. At median follow-up: 37.0 months (IQR: 34.3-40.5)

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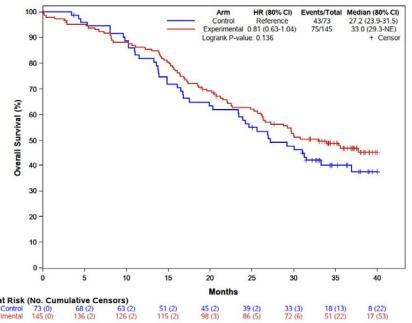
Overall Survival – ITT population



Cut-off date: January 23rd, 2023. At median follow-up: 37.0 months (IQR: 34.3-40.5)

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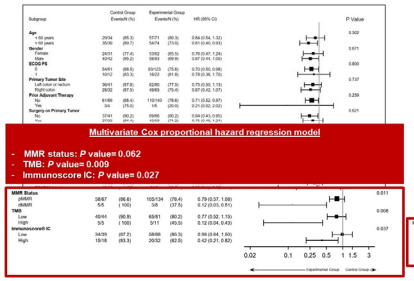
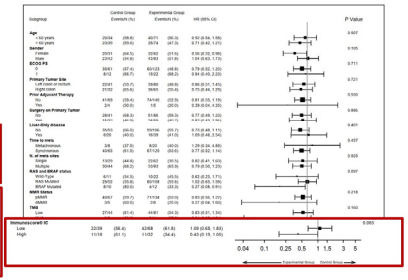
Subgroup analyses for PFS and OS – ITT population

Progression-Free Survival



Multivariate Cox proportional hazard regression model
- MMR status: *P* value= 0.062
- TMB: *P* value= 0.009
- Immunoscore IC: *P* value= 0.027

Overall Survival



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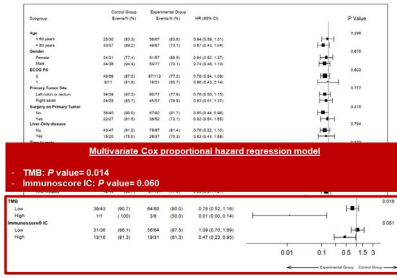
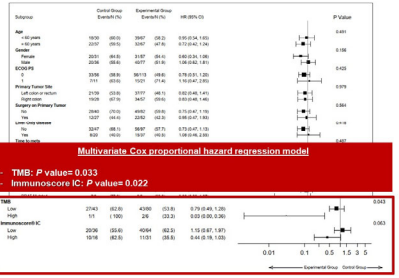
Subgroup analyses for PFS and OS – pMMR cohort

Progression-Free Survival



Multivariate Cox proportional hazard regression model
- TMB: *P* value= 0.014
- Immunoscore IC: *P* value= 0.060

Overall Survival



Multivariate Cox proportional hazard regression model
- TMB: *P* value= 0.033
- Immunoscore IC: *P* value= 0.022

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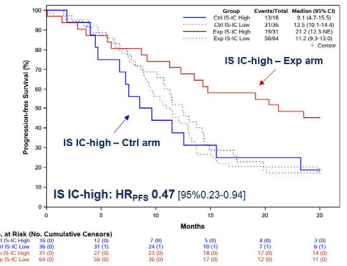
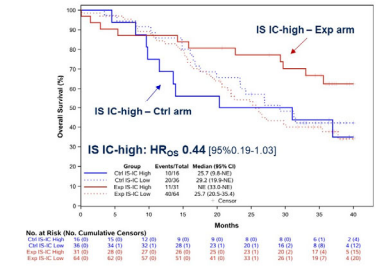
Outcomes according to Immunoscore IC and arm – pMMR cohort

Progression-Free Survival



Overall Survival



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Summary and Conclusions

- At a median follow-up of 37.0 mos, the addition of atezolizumab to FOLFOXIRI plus bevacizumab as initial therapy is confirmed to prolong PFS in molecularly unselected mCRC patients (HR: 0.71, p=0.015).
- At the preliminary OS analysis (54% of events), a trend towards longer OS is observed (HR: 0.81, p=0.136).
- Adding atezolizumab to FOLFOXIRI plus bevacizumab is related to better outcome in terms of both PFS (HR: 0.79, p=0.073) and OS (HR: 0.83, p=0.172) also in the cohort of patients with pMMR tumours.
- In the pMMR cohort, the magnitude of the PFS and OS benefit is heterogeneous according to TMB (P_{int}: 0.016 and 0.043, respectively) and Immunoscore IC (P_{int}: 0.051 and 0.063, respectively), being substantially higher among patients with Immunoscore IC-high and/or TMB-high mCRC.
- The independent predictive impact of both Immunoscore IC and TMB is confirmed in the multivariable models in the pMMR cohort, by supporting the relevance of these markers as a measure of tumour immunogenicity.
- A phase III trial will be launched by GONO Foundation to investigate the added value of the addition of atezolizumab to upfront FOLFOXIRI plus bevacizumab in patients with pMMR and Immunoscore IC-high tumours.

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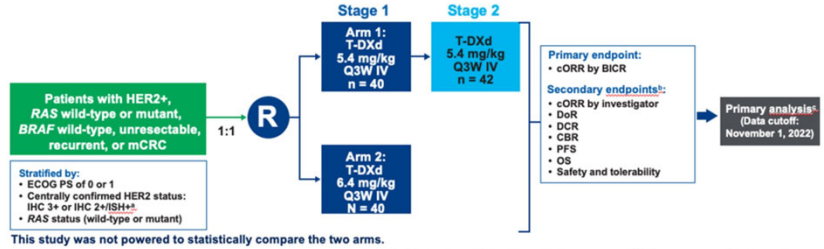
DESTINY-CRC02

DESTINY-CRC02 Study Design

A randomized, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



This study was not powered to statistically compare the two arms.

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

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DESTINY-CRC02

Prior Treatment

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	40 (100)
Fluoropyrimidines[a]	40 (100)	42 (100)	82 (100)	40 (100)
Oxaliplatin	40 (100)	41 (97.6)	81 (98.8)	40 (100)
Anti-EGFR, n (%)	29 (72.5)	28 (66.7)	57 (69.5)	31 (77.5)
Anti-HER2, n (%)	**11 (27.5)**	**6 (14.3)**	**17 (20.7)**	**10 (25.0)**
HER2 TKI[b]	6 (15.0)	4 (9.5)	10 (12.2)	7 (17.5)
Anti-HER2 antibodies[c]	10 (25.0)	6 (14.3)	16 (19.5)	10 (25.0)
Anti-VEGF, n (%)	36 (90.0)	38 (90.5)	74 (90.2)	38 (95.0)
Regorafenib and tipiracil/trifluridine, n (%)	20 (50.0)	14 (33.3)	34 (41.5)	13 (32.5)
Other systemic therapy, n (%)	5 (12.5)	6 (14.3)	11 (13.4)	10 (25.0)

5FU, fluorouracil; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
[a]Includes 5FU, capecitabine, S1, or tegafur. [b]Includes tucatinib and lapatinib. [c]Includes trastuzumab, trastuzumab duocarmazine, trastuzumab emtansine, pertuzumab, and zanidatamab (ZW25).

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DESTINY-CRC02

Efficacy Results

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

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DESTINY-CRC02

TEAEs in ≥20% of Patients[a]

n (%)	T-DXd 5.4 mg/kg Q3W Total N = 83[b]		T-DXd 6.4 mg/kg Q3W Stage 1 N = 39	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Any TEAEs	82 (98.8)	41 (49.4)	39 (100)	23 (59.0)
Nausea	48 (57.8)	7 (8.4)	22 (56.4)	0
Fatigue[c]	38 (45.8)	8 (9.6)	18 (46.2)	2 (5.1)
Neutropenia[d]	25 (30.1)	14 (16.9)	18 (46.2)	11 (28.2)
Decreased appetite	25 (30.1)	2 (2.4)	6 (15.4)	0
Anemia[e]	22 (26.5)	8 (9.6)	16 (41.0)	9 (23.1)
Thrombocytopenia[f]	21 (25.3)	5 (6.0)	14 (35.9)	5 (12.8)
Alopecia	20 (24.1)	0	11 (28.2)	0
Constipation	20 (24.1)	0	5 (12.8)	0
Diarrhea	19 (22.9)	2 (2.4)	11 (28.2)	0
Vomiting	17 (20.5)	4 (4.8)	3 (7.7)	0

Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
Febrile neutropenia occurred in 1 patient in both Stage 1 (grade 3) and Stage 2 (grade 1) treated with T-DXd 5.4 mg/kg and 1 patient treated with T-DXd 6.4 mg/kg (grade 4)
[a]Based on the total population treated with T-DXd 5.4 mg/kg. [b]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [c]Fatigue includes the preferred terms asthenia, fatigue, malaise and lethargy. [d]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [e]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [f]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia.

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DESTINY-CRC02

Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)[b]

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

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T-DXd @ Lower Dose = Winner !

	T-DXd 5.4 mg/kg Q3W	T-DXd 6.4 mg/kg Q3W
	Total N = 82	Total N = 40
cORR, n (%) [95% CI]	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
Confirmed DCR, n (%) [95% CI]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median PFS, mo [95% CI]	5.8 (4.6-7.0)	5.5 (4.2-7.0)
Median OS, mo [95% CI]	13.4 (12.5-16.8)	NE (9.9-NE)
G3/4/5 Toxicities (%)	49	59
ILD/Pneumonitis (%) / G5 (%)	8.4 (0)	12.8 (2.6)

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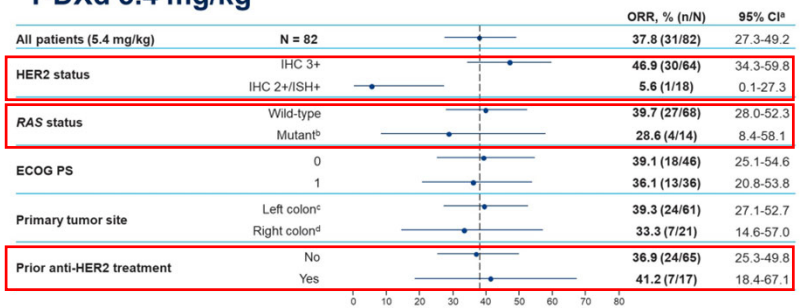
DESTINY-CRC02

Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All *RAS*m responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

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Knowledge Before ASCO #2023 → Data of HER2-targeted therapies in patients with advanced or metastatic colorectal cancer

Regimen	Trial (n) – year	ORR	PFS	OS	Most common Grade 3+ AEs
Trastuzumab + lapatinib	HERACLES-A (n=32) – 2016	28%	4.7m	10m	Fatigue 16% Decreased LVEF 6%
Trastuzumab + pertuzumab	MyPathway (n=84; 57 evaluable) – 2019	32%	2.9m	11.5m	Hypokalemia 5% Abdominal pain 5%
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab deruxtecan	**DESTINY-CRC01 (N=78; 53 HER2+) – 2021**	**45.3%**	**6.9m**	**15.5m**	**Neutropenia 15% Anemia 13%**
Tucatinib + trastuzumab	FDA Approval Jan 19 2023	**38.1%**	**8.2m**	**24.1m**	**Hypertension 7% Diarrhea 3.5%**

Tosi F, Sartore-Bianchi A, et al. Clin Colorectal Cancer. 2020 Dec;19(4):256-262.e2. doi: 10.1016/j.clcc.2020.06.009. Epub 2020 Jun 27.
Meric-Bernstam F, et al. Lancet Oncol. 2019 Apr;20(4):518-530. doi: 10.1016/S1470-2045(18)30904-5. Epub 2019 Mar 8.
Sartore-Bianchi A, et al. ESMO Open. 2020 Sep;5(5):e000911.
Siena S, et al; Lancet Oncol. 2021 Jun;22(6):779-789. doi: 10.1016/S1470-2045(21)00086-3. Epub 2021 May 4.
Strickler J et al ; *Lancet Oncology* , 2023.

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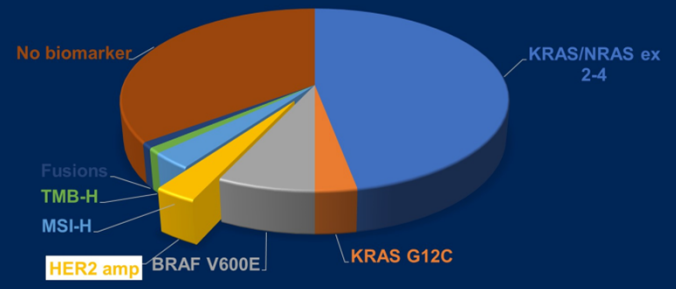
Actionable colorectal cancer targets in 2023



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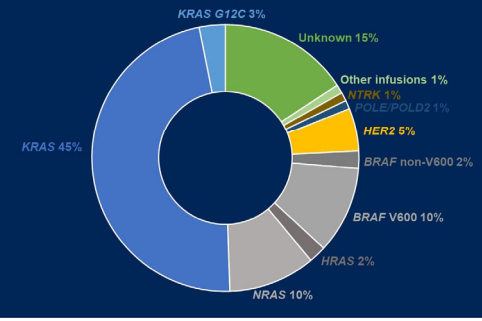
Molecular Alterations With Therapeutic Implications in mCRC



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2023 ASCO ANNUAL MEETING

Efficacy of panitumumab in left-sided patients with MSS/MSI-L and *RAS/BRAF* WT: a biomarker study of the phase III PARADIGM trial

Kentaro Yamazaki,[1] Kei Muro,[2] Jun Watanabe,[3] Kohei Shitara,[4] Hisatsugu Ohori,[5] Manabu Shiozawa,[6] Hirofumi Yasui,[7] Eiji Oki,[8] Takeo Sato,[9] Takeshi Naito,[10] Yoshito Komatsu,[11] Takeshi Kato,[12] Junpei Soeda,[13] Kouji Yamamoto,[14] Riu Yamashita,[15] Kiwamu Akagi,[16] Atsushi Ochiai,[17] Hiroyuki Uetake,[18] Katsuya Tsuchihara,[15] Takayuki Yoshino[19]

[1]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [2]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [3]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; [4]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [5]Division of Medical Oncology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan; [6]Division of Gastrointestinal Surgery, Kanagawa Cancer Center, Kanagawa, Japan; [7]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [8]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [9]Research and Development Center for Medical Education, Department of Clinical Skills Education, Kitasato University School of Medicine, Sagamihara, Japan; [10]Department of Lower Gastrointestinal Surgery, Kitasato University School of Medicine, Sagamihara, Japan; [11]Division of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan; [12]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; [13]Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Ltd., Tokyo, Japan; [14]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; [15]Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; [16]Division of Molecular Diagnosis and Cancer Prevention, Saitama Cancer Center, Saitama, Japan; [17]Research Institute for Biomedical Sciences, Tokyo University of Science, Tokyo, Japan; [18]National Hospital Organization, Disaster Medical Center, Tokyo, Japan; [19]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

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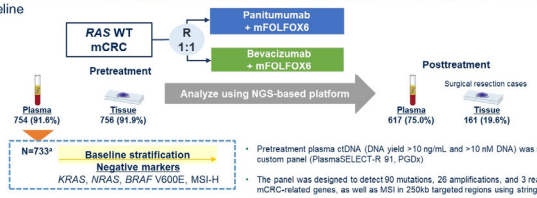
PARADIGM biomarker study

- The PARADIGM biomarker study (NCT02394834) was designed to investigate molecular biomarkers of primary and secondary resistance to each therapy based on testing of tumor tissue and ctDNA
- Based on current guideline recommendations regarding clinically relevant biomarkers for first-line mCRC,[1,2] we report clinical outcomes for patients with MSS or MSI-L and *RAS* (*KRAS*/*NRAS*)/*BRAF* V600E WT in ctDNA at baseline



- Pretreatment plasma ctDNA (DNA yield >10 ng/mL and >10 nM DNA) was sequenced using a custom panel (PlasmaSELECT-R 81, PGDx)
- The panel was designed to detect 90 mutations, 26 amplifications, and 3 rearrangements in mCRC-related genes, as well as MSI in 250kb targeted regions using stringent quality criteria
- Efficacy (OS, PFS, RR, R0 rate, and depth of response) by treatment group was evaluated according to *RAS* (*KRAS/NRAS*), *BRAF* V600E, and MSI status and primary tumor location

ctDNA, circulating tumor DNA; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; NGS, next-generation sequencing
[a]Patients with available ctDNA among those included in efficacy analysis set in the PARADIGM study
1. Morris VK, et al. J Clin Oncol. 2023;41:678–700. 2. Cervantes A, et al. Ann Oncol. 2022;34:10–32.

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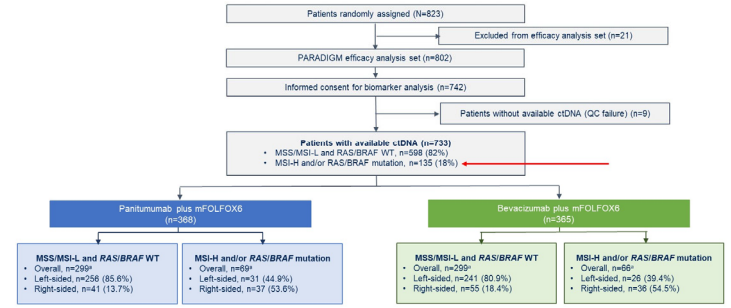
Disposition of ctDNA evaluable population



QC, quality control
[a]Some patients had multiple primary lesions in both the left and right sides

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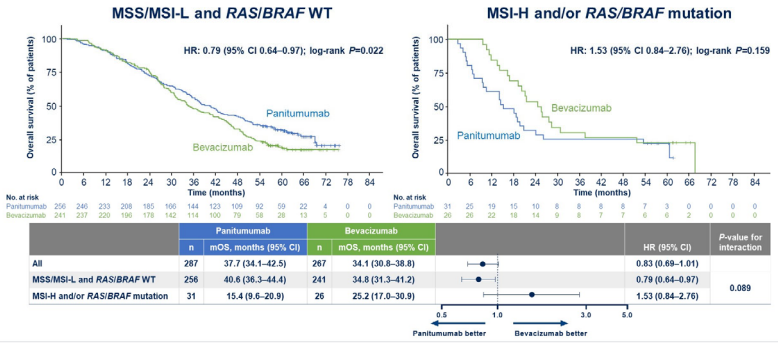
Overall survival by MSS/MSI and *RAS/BRAF* status in left-sided mCRC



	Panitumumab		Bevacizumab			*P*-value for interaction
	n	mOS, months (95% CI)	n	mOS, months (95% CI)	HR (95% CI)	
All	287	37.7 (34.1–42.5)	267	34.1 (30.8–38.8)	0.83 (0.69–1.01)	0.089
MSS/MSI-L and *RAS/BRAF* WT	256	40.6 (36.3–44.4)	241	34.8 (31.3–41.2)	0.79 (0.64–0.97)	
MSI-H and/or *RAS/BRAF* mutation	31	15.4 (9.6–20.9)	26	25.2 (17.0–30.9)	1.53 (0.84–2.76)	

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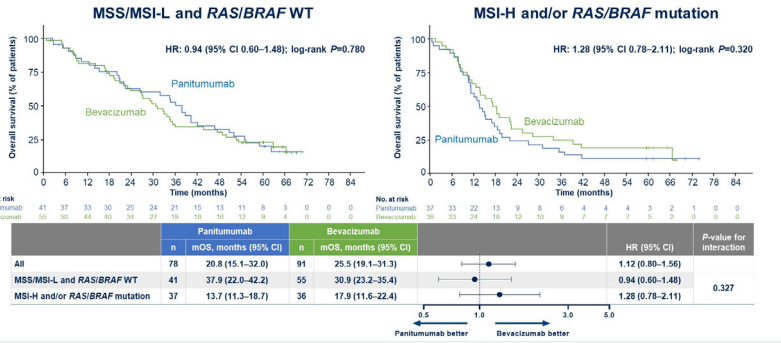
Overall survival by MSS/MSI and *RAS/BRAF* status in right-sided mCRC



	Panitumumab		Bevacizumab			*P*-value for interaction
	n	mOS, months (95% CI)	n	mOS, months (95% CI)	HR (95% CI)	
All	78	20.8 (15.1–32.0)	91	25.5 (19.1–31.3)	1.12 (0.80–1.56)	0.327
MSS/MSI-L and *RAS/BRAF* WT	41	37.9 (22.0–42.2)	55	30.9 (23.2–35.4)	0.94 (0.60–1.48)	
MSI-H and/or *RAS/BRAF* mutation	37	13.7 (11.3–18.7)	36	17.9 (11.6–22.4)	1.28 (0.78–2.11)	

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Does "*side-ness*" matter?

- MSI-H or RAS/RAF mutant 39-45% in left sided disease compared to 53-55% in right sided disease.
- ***Right sided disease is associated with higher incidence RAS/BRAF mutations***

- Blood or tissue?
  - 18% of patients found to have MSI-H or RAS/RAF mutations in blood not observed in tissue.
  - In FIRE-4, 13% of RAS mutations were found in blood but not seen in tissue.
  - ***Blood AND tissue should be tested up front for all patients with mCRC***

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Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? No.
- Key take home points:
  Anti-EGFR mAb should only be considered in the first line with left-sided mCRC.

  Given tumor intra- and inter-tumor genomic heterogeneity, blood *AND* tissue testing should be conducted upfront on all patients.

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2023 ASCO ANNUAL MEETING

T-DXd in Patients With HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results From the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

Kanwal Raghav

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 4, 2023

Additional authors: Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

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DESTINY-CRC02

Prior Treatment

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	40 (100)
Fluoropyrimidines[a]	40 (100)	42 (100)	82 (100)	40 (100)
Oxaliplatin	40 (100)	41 (97.6)	81 (98.8)	40 (100)
Anti-EGFR, n (%)	29 (72.5)	28 (66.7)	57 (69.5)	31 (77.5)
Anti-HER2, n (%)	**11 (27.5)**	**6 (14.3)**	**17 (20.7)**	**10 (25.0)**
HER2 TKI[b]	6 (15.0)	4 (9.5)	10 (12.2)	7 (17.5)
Anti-HER2 antibodies[c]	10 (25.0)	6 (14.3)	16 (19.5)	10 (25.0)
Anti-VEGF, n (%)	36 (90.0)	38 (90.5)	74 (90.2)	38 (95.0)
Regorafenib and tipiracil/trifluridine, n (%)	20 (50.0)	14 (33.3)	34 (41.5)	13 (32.5)
Other systemic therapy, n (%)	5 (12.5)	6 (14.3)	11 (13.4)	10 (25.0)

5FU, fluorouracil; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
[a]Includes 5FU, capecitabine, S1, or tegafur. [b]Includes tucatinib and lapatinib. [c]Includes trastuzumab, trastuzumab duocarmazine, trastuzumab emtansine, pertuzumab, and zanidatamab (ZW25).

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DESTINY-CRC02

Efficacy Results

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; SD, stable disease.

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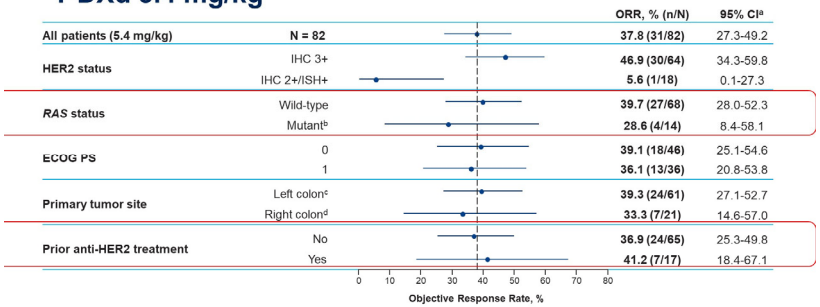
DESTINY-CRC02

Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All *RAS*m responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

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DESTINY-CRC02

Overall Safety Summary

n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
TEAEs	**40 (97.6)**	**42 (100)**	**82 (98.8)**	**39 (100)**
Drug-related	38 (92.7)	38 (90.5)	76 (91.6)	37 (94.9)
TEAEs grade ≥3	**20 (48.8)**	**21 (50.0)**	**41 (49.4)**	**23 (59.0)**
Drug-related	16 (39.0)	18 (42.9)	34 (41.0)	19 (48.7)
Serious TEAEs	**8 (19.5)**	**12 (28.6)**	**20 (24.1)**	**12 (30.8)**
Drug-related	4 (9.8)	7 (16.7)	11 (13.3)	6 (15.4)
TEAEs associated with drug discontinuation	**3 (7.3)**	**5 (11.9)**	**8 (9.6)**	**3 (7.7)**
Drug-related	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
TEAEs associated with dose reduction	**9 (22.0)**	**6 (14.3)**	**15 (18.1)**	**10 (25.6)**
Drug-related	9 (22.0)	6 (14.3)	15 (18.1)	9 (23.1)
TEAEs associated with drug interruption	**19 (46.3)**	**20 (47.6)**	**39 (47.0)**	**19 (48.7)**
Drug-related	13 (31.7)	9 (21.4)	22 (26.5)	10 (25.6)
TEAEs associated with death	**1 (2.4)**	**3 (7.1)**	**4 (4.8)**	**3 (7.7)**
Drug-related	1 (2.4)[b]	0	1 (1.2)[b]	0[c]

Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]Patient experienced grade 5 hepatic failure. [c]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

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DESTINY-CRC02

TEAEs in ≥20% of Patients[a]

n (%)	T-DXd 5.4 mg/kg Q3W Total N = 83[b]		T-DXd 6.4 mg/kg Q3W Stage 1 N = 39	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Any TEAEs	82 (98.8)	41 (49.4)	39 (100)	23 (59.0)
Nausea	48 (57.8)	7 (8.4)	22 (56.4)	0
Fatigue[c]	38 (45.8)	8 (9.6)	18 (46.2)	2 (5.1)
Neutropenia[d]	25 (30.1)	14 (16.9)	18 (46.2)	11 (28.2)
Decreased appetite	25 (30.1)	2 (2.4)	6 (15.4)	0
Anemia[e]	22 (26.5)	8 (9.6)	16 (41.0)	9 (23.1)
Thrombocytopenia[f]	21 (25.3)	5 (6.0)	14 (35.9)	5 (12.8)
Alopecia	20 (24.1)	0	11 (28.2)	0
Constipation	20 (24.1)	0	5 (12.8)	0
Diarrhea	19 (22.9)	2 (2.4)	11 (28.2)	0
Vomiting	17 (20.5)	4 (4.8)	3 (7.7)	0

Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
Febrile neutropenia occurred in 1 patient in both Stage 1 (grade 3) and Stage 2 (grade 1) receiving T-DXd 5.4 mg/kg and 1 patient receiving T-DXd 6.4 mg/kg (grade 4)
[a]Based on the total population treated with T-DXd 5.4 mg/kg. [b]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [c]Fatigue includes the preferred terms asthenia, fatigue, malaise and lethargy. [d]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [e]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [f]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia.

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DESTINY-CRC02

Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set.

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Recent data of HER2-targeted therapies in advanced CRC

Regimen	Trial	ORR	PFS	OS	Most common G3 AE's
Trastuzumab + lapatinib	HERACLES-A (N=32)	28%	4.7m	10m	Fatigue- 16%, Decreased LVEF 6%
Trastuzumab + Pertuzumab	MyPathway (N=57)	32%	2.9m	11.5m	Hypokalemia 5%, Abdominal pain 5%
Pertuzumab + T-DM1	HERACLES-B (N=31)	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab + tucatinib	MOUNTAINEER (N=117)	38.1%	8.2m	24.1m	Hypertension 7%, Diarrhea 3.5%
T-DXd	**DESTINY-CRC02 (N=82)**	**37.8%**	**5.8m**	**13.4m**	**Neutropenia 17%, fatigue and anemia (10%)**

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Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? Yes. Findings confirm another targeted therapy for HER2+ mCRC, with 5.4mg/kg the preferred dose.
- Moving forward:
  Clinical trials (MOUNTANEER-3) will establish the role in early line settings.

  Optimal sequence of HER2 directed therapies?
  1. Tucatinib/trastuzumab (only FDA approved regimen and activity in HER2 2+/3+)
  2. Pertuzumab/trastuzumab
  3. T-DxD (RAS MT/WT and IHC3+, activity in prior HER2+ Rx, toxicities may limit utility)

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CodeBreaK 101 Subprotocol H Study Schema

Phase 1b, multicenter, open-label study*:
Sotorasib + panitumumab + FOLFIRI in previously treated *KRAS* G12C–mutated mCRC

Key eligibility criteria
- *KRAS* G12C–mutated mCRC, identified through local molecular testing
- No dose reduction or intolerance to prior KRAS^{G12C} inhibitor treatment (Part 1 only)
- KRAS^{G12C} inhibitor-naive (Part 2 only)
- ≥ 1 prior treatment for advanced disease
- No dose reduction or delay due to 5-FU or irinotecan toxicity if previously received

→ **Part 1: Cohort B dose exploration† (N = 6)**
Dose Level 1:
Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W

→ **No DLTs were observed, and Dose Level 1 was declared the RP2D‡**

→ **Part 2: Cohort G dose expansion† (N = 40)**
Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W

Primary Endpoint: Safety and tolerability
Secondary Endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) and PK

*NCT04185883.
†Treatment until disease progression, withdrawal of consent, or end of study.
‡No dose adjustment was needed.
5-FU, fluorouracil; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; FOLFIRI, irinotecan, leucovorin plus 5-fluorouracil; KRAS, Kirsten rat sa
mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; Q2W, every 2 we
Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TTR, time to response.

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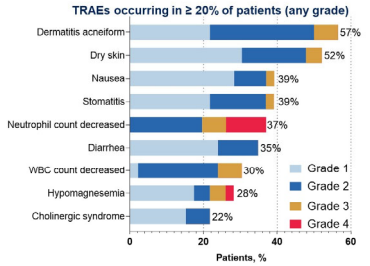
Safety

TRAE	N = 46 n (%)
TRAE, any grade	44 (96)
Grade 3	13 (28)
Grade 4*	7 (15)
Serious	2 (4)
Fatal	0
TRAE leading to ≥ 1 dose interruption/reductions	34 (74)
Attributed to sotorasib	6 (13)
Attributed to panitumumab	20 (43)
Attributed to FOLFIRI (any component)	30 (65)
TRAE leading to discontinuation of ≥ 1 agent	12 (26)
Sotorasib†	1 (2)
Panitumumab	2 (4)
FOLFIRI (any component)‡	11 (24)
TRAE leading to discontinuation of all agents	1 (2)



Data cutoff, April 13, 2023.
*Grade 4 TRAEs were neutrophil count decreased (n = 5, 11%), blood creatine phosphokinase increased (n = 1, 2%), and hypomagnesemia (n = 1, 2%).
†Sotorasib discontinuation was required in 1 patient due to grade 3 alanine aminotransferase increase attributed to all components of treatment.
‡The most common component discontinued due to TRAE was 5-FU, occurring in 11 (24%) patients. Discontinuation of 5-FU bolus while continuing 5-FU continuous as discontinuation of one component.
TRAE, treatment-related adverse event; WBC, white blood cell.

- **No DLTs were observed in dose exploration, and sotorasib 960 mg daily, panitumumab 6 mg and FOLFIRI IV Q2W was determined as the RP2D**
- **Safety findings were consistent with known profiles of sotorasib, panitumumab, and FOLFI**

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Efficacy

Response by investigator assessment*	Part 1 Sotorasib + Panitumumab + FOLFIRI (n = 6)	Part 2 Sotorasib + Panitumumab + FOLFIRI (n = 36)	Total (N = 42*)
ORR confirmed, n (%) (95% CI)	3 (50) (11.8, 88.2)	20 (56) (38.1, 72.1)	**23 (55)** (38.7, 70.2)
CR	0	0	0
PR	3 (50)	20 (56)†	23 (55)†
SD, n (%)	3 (50)	13 (36)	16 (38)
PD, n (%)	0	2 (6)	2 (5)
Unavailable, n (%)	0	1 (3)	1 (2)
DCR, n (%) (95% CI)	6 (100) (54.1, 100.0)	33 (92) (77.5, 98.3)	**39 (93)** (80.5, 98.5)

Data cutoff, April 13, 2023.
The 2 patients treated with prior sotorasib achieved PR (n = 1) and SD (n = 1).
*42 patients enrolled at least 7 weeks before analysis cutoff were included for response summary.
†2 additional patients had unconfirmed PRs that are awaiting confirmatory scan and not included in these numbers.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

- **Confirmed ORR (all PRs) was 55%, and DCR was 93%, with 2 additional patients w unconfirmed responses awaiting confirmatory scan**
- **Response to sotorasib plus panitumumab and FOLFIRI appeared to be independe lines of therapy or prior progression with irinotecan-based treatments**

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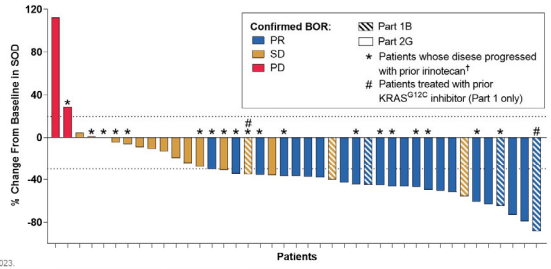
Tumor Response



Data cutoff, April 13, 2023.
†Patients whose disease progressed on prior irinotecan include those with clinical or radiographic progression.
‡42 patients enrolled at least 7 weeks before analysis cutoff were included for response summary; 1 patient with no post-baseline scan is not shown in figure but is includ
BOR, best overall response; SOD, sum of diameters.

Reduction in RECIST target lesions was observed in 86% of patients‡

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Key Findings

- Sotorasib 960 mg PO daily, panitumumab 6 mg/kg IV Q2W, and FOLFIRI IV Q2W was declared the RP2D
  - No DLTs observed in the 6 patients enrolled in dose exploration and was the dose used in dose expansion
- Sotorasib plus panitumumab and FOLFIRI demonstrated a manageable safety profile with AEs consistent with those expected for the therapies under study
- No clinically meaningful sotorasib and irinotecan PK interaction observed
- Confirmed ORR was 55% and DCR was 93%, with responses observed regardless of number of prior lines of therapy and progression on prior irinotecan-based therapy
- The combination of sotorasib plus panitumumab and FOLFIRI demonstrates promising response rates in pre-treated *KRAS* G12C–mutated mCRC pa population, regardless of prior irinotecan and 5-FU exposure

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Outline of Presentation

- Updates in Colon Cancer, early stage
  - LBA # 3503 – NEOCOL
  - Abstract # 3521 – GALAXY study in CIRCULATE JAPAN
  - Ongoing Trials to personalize therapy utilizing ctDNA
    - Stage II – COBRA, CIRCULATE PRODIGE-70, SU2C ACT3
    - Stage III – DYNAMIC III and CIRCULATE-US
- Updates in Colon Cancer, metastatic
  - Abstract # 3500 - AtezoTRIBE
  - Abstract # 3501 - DESTINY CRC 02
  - Abstract # 3508 – PARADIGM
  - Abstract # 3513 – Codebreak 101
- Updates in Rectal Cancer, early stage
  - LBA # 02 - PROSPECT trial
  - LBA # 3504 - PROGIGE 23 trial
  - Abstract # 3520 – Long term results of OPRA trial

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Does it matter?
Sequencing therapies in early stage CRC

Abstract	Disease	Trial
3504	T3-T4 rectal cancer	PRODIGE23
3503	T3-T4 colon cancer	NEOCOL

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PRODIGE PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

unicancer

LA LIGUE CONTRE LE CANCER

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

T. Conroy, P-L. Etienne, E. Rio, L. Evesque, N. Mesgouez-Nebout, V. Vendrely, X. Artignan, O. Bouché, A. Boilève, M. Delaye, D. Gargot, V. Boige, N. Bonichon-Lamichhane, C. Louvet, C. de la Fouchardière, C. Morand, V. Pezzella, E. Rullier, F. Castan, and C. Borg

UCGI unicancer FFCD GERCOR

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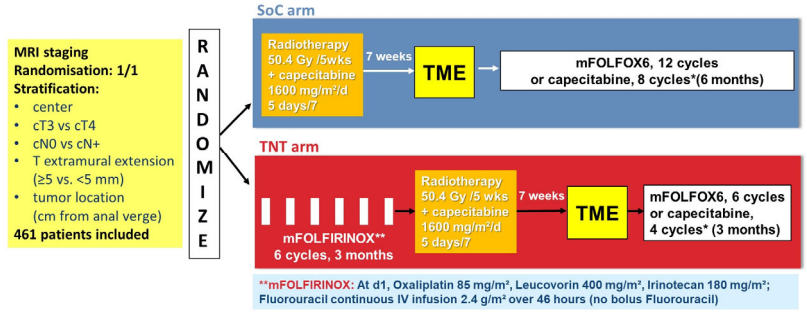
PRODIGE 23 trial: trial design



**mFOLFIRINOX: At d1, Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²; Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours (no bolus Fluorouracil)

*according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.

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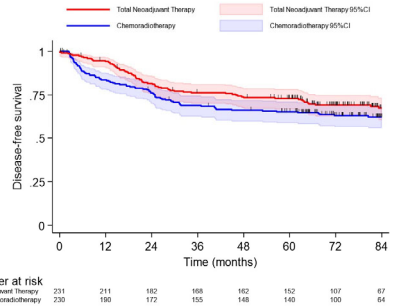
Disease-Free Survival



155 events

7-yr DFS rate:
- 67.6% [95%CI: 60.7-73.6] TNT arm
- 62.5% [95%CI: 55.6-68.6] SoC arm

5-yr DFS rate:
- 73.1% [95%CI: 66.8-78.4] TNT arm
- 65.5% [95%CI: 58.9-71.3] SoC arm

RMST (7-yr), months:
5.73 [0.05-11.41] DFS benefit for TNT arm
p=0.048

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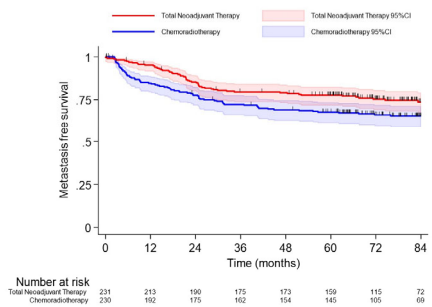
Metastasis-free Survival

At 5 years, the cumulative incidence of developing metastatic recurrences was 18.4% in the TNT arm vs 26.6% in the SoC arm.



138 events

7-yr MFS:
- 73.6% [95%CI: 67.0-79.2] TNT arm
- 65.4% [95%CI: 58.7-71.3] SoC arm

5-yr MFS:
- 77.6% [95%CI: 71.5-82.5] TNT arm
- 67.7% [95%CI: 61.2-73.4] SoC arm

RMST (7-yr), months:
7.1 [1.65-12.63] MFS benefit for TNT arm
p=0.011

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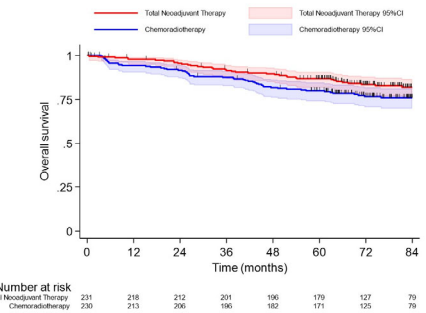
Overall Survival



98 events.

7-yr OS:
- 81.9% [95%CI: 75.8-86.7] TNT arm
- 76.1% [95%CI: 69.8-81.3] SoC arm

5-yr OS:
- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

RMST (7-yr), months:
4.37 [0.35-8.38] benefit for TNT arm
p=0.033

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Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? Yes
- Based on RAPIDO, PROSPECT and PRODIGE, TNT remains *de facto* gold standard for localized rectal cancer. The approach:
  Low risk (PROSPECT) – Chemo +/- XRT
  Low lying tumor (goal for cCR) – XRT -> chemo
  High risk (T4 and/or N2) – Chemo (Triplet if appropriate) + XRT

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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

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network

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PROSPECT Trial Hypothesis (circa 2011):

- Neoadjuvant chemotherapy with FOLFOX and only *selective* use of pelvic chemoradiation will be noninferior to routine use of pelvic chemoradiation for locally advanced rectal cancer

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PROSPECT Study Summary

Recruitment 2012-2018 from 264 practice sites in the USA, Canada and Switzerland

Neoadjuvant Treatment for cT2N+, cT3N-, cT3N+ Rectal Cancer

R

1:1

- **Pelvic Chemoradiation** 5040cGy in 5.5 weeks
- **FOLFOX 6 cycles** Chemoradiation if poor response or FOLFOX not tolerated

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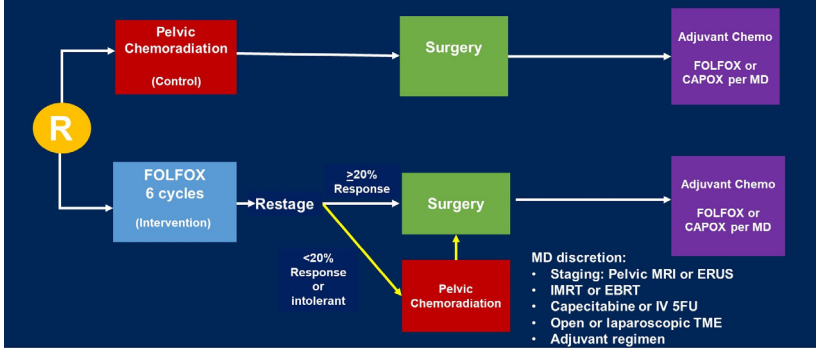
PROSPECT Study Full Schema



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PROSPECT Main Eligibility Criteria

Inclusion:

- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

- Tumor requiring an APR
- cT4 tumor
- ≥ 4 pelvic lymph nodes ≥ 1cm in short axis

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PROSPECT Study Endpoints

- **Primary Endpoint:**
  - Disease Free Survival
- **Secondary Endpoints:**
  - Local recurrence
  - Overall survival
  - Complete (R0) surgical resection
  - Complete pathologic response
  - Toxicity-CTCAE and PRO-CTCAE
  - Quality of Life

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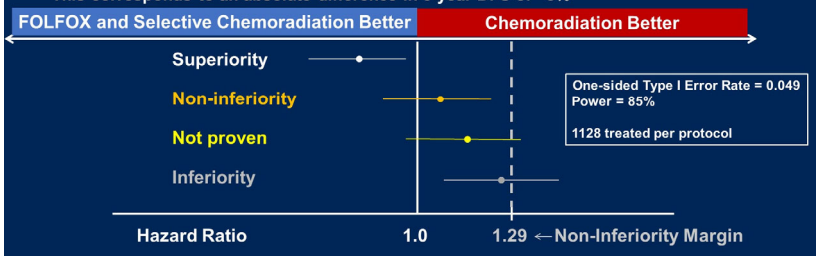
Non-inferiority Hypothesis for Disease Free Survival

Non-inferiority could be claimed if the upper limit of the two-sided 90.2% confidence interval of the hazard ratio (HR) did not exceed 1.29.

This corresponds to an absolute difference in 5-year DFS of <5%



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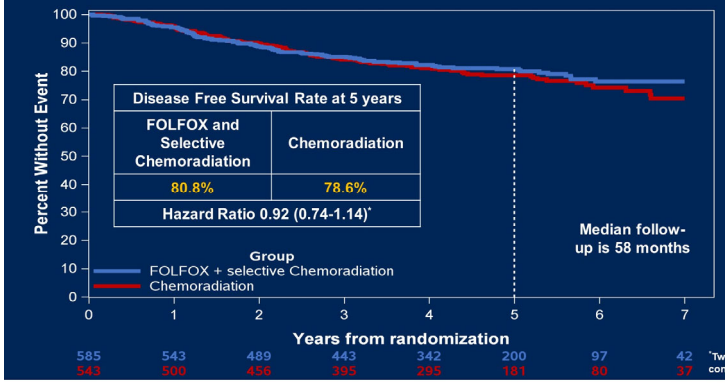
PROSPECT: Disease Free Survival



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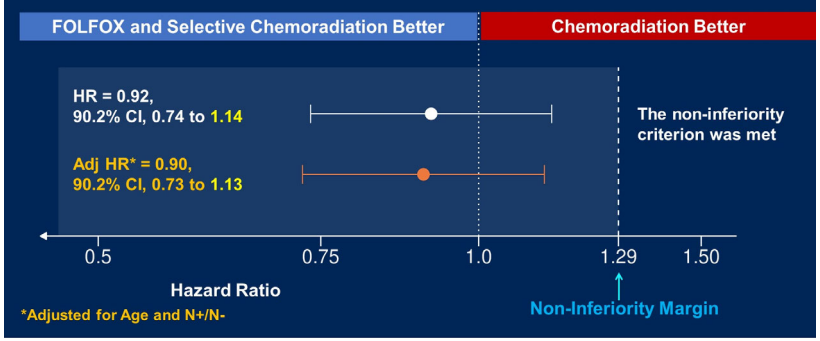
PROSPECT: Disease Free Survival



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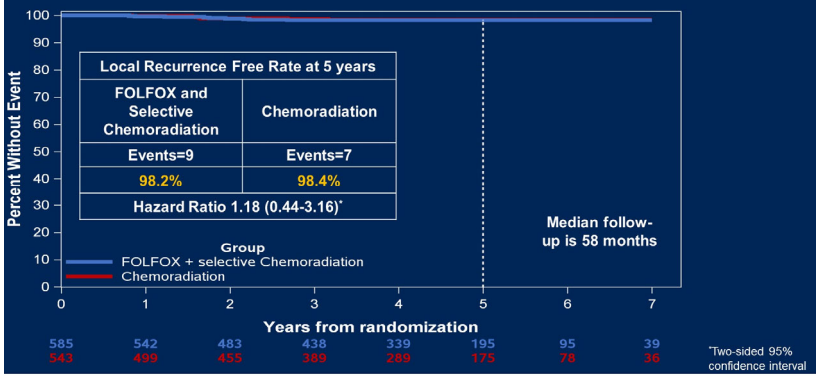
PROSPECT: Freedom from Local Recurrence



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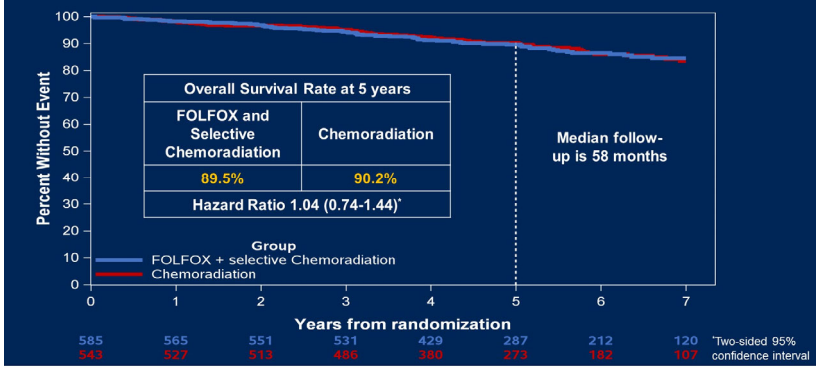
PROSPECT: Overall Survival



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Surgical and Pathologic Endpoints

Secondary endpoints in participants who completed Surgery	FOLFOX and Selective Pelvic Chemoradiation N=535	Pelvic Chemoradiation N=510
Complete (R0) Rectal Resection	99%	97%
Low Anterior Resection Rate	98%	98%
Pathologic Complete Response	22%	24%
Positive Radial margin	1.2%	1.5%

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Adjuvant Treatment and Therapy Duration

Adjuvant treatment in patients who had surgery	FOLFOX and Selective Pelvic Chemoradiation N=535	Pelvic Chemoradiation N=510
Received any adjuvant chemotherapy	82%	83%
Median duration (IQR) from randomization to last dose of postoperative therapy (weeks)	35 (33, 39)	37 (34, 40)

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Use of Pelvic Chemoradiation in patients randomized to FOLFOX

9% (53/585) of participants randomized to FOLFOX received neoadjuvant chemoradiation either because:

Restaging demonstrated clinical response <20% or

They did not tolerate at least 5 cycles of FOLFOX

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Abstract 3520

Sustained organ preservation in rectal cancer patients treated with total neoadjuvant therapy.

Long-Term Results of the OPRA Trial

Floris S Verheij, Dana M Omer, Hannah Williams, James T Buckley, Sabrina T Lin, Li-Xuan Qin, Hannah M Thompson, Jonathan B Yuval, Marc J Gollub, Abraham J Wu, Leonard B Saltz, Julio Garcia-Aguilar, on behalf of the OPRA Consortium.

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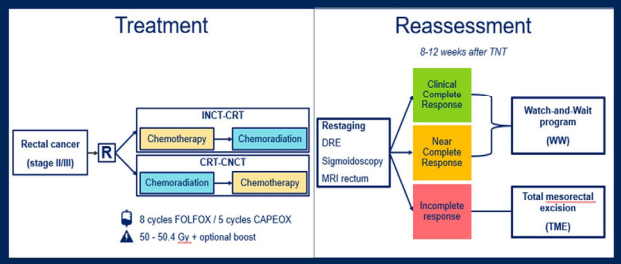
Organ Preservation in Rectal Adenocarcinoma (OPRA) Trial



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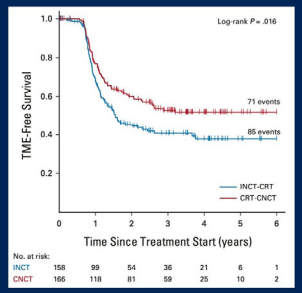
OPRA Trial – Initial Results at 3 Years

- No difference in DFS between treatment strategies.
- Both similar to historical controls.
- **Higher rates of organ preservation in CRT-CNCT.**



Garcia-Aguilar, JCO 2022

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Unanswered Questions from 2022

- **Do patients who develop regrowth and require salvage TME do worse than those treated with upfront TME (i.e., do we miss the window for cure)?**
  - **Compare 5-year DFS between TME after restaging and TME after tumor regrowth.**
- **Updated (5-year) organ preservation (TME-free survival) between INCT-CRT and CRT-CNCT.**
- **What is the timing of Regrowth (i.e., when can we stop surveillance)?**

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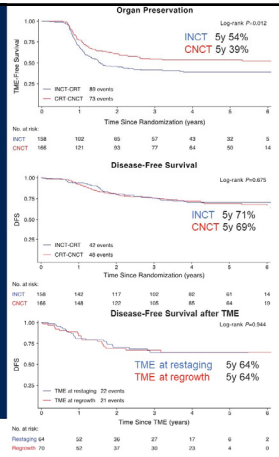
Results

Median follow-up 5.1 years

- 225/304 (74%) were offered WW:
  - 105/146 (72%) of INCT-CRT patients.
  - 120/158 (76%) of CRT-CNCT patients.
- 81 (36%) developed a regrowth:
  - 46/105 (44%) of INCT-CRT patients.
  - 35/120 (29%) of CRT-CNCT patients.
- 76 (94%) of regrowths occurred within 2 years and 80 (99%) occurred within 3 years after restaging.



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Take Home Points

- Nearly **half of rectal cancer patients preserve their rectum at 5 years**, higher rates of organ preservation in patients treated with CRT-CNCT.
- The majority of tumor **regrowths occur in the first 2 years**, suggesting that a close follow-up in this period is critical.
- **Salvage TME for tumor regrowth offers similar outcomes** to immediate TME.

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Is Total Neoadjuvant Therapy the Preferred Approach for Every Patient With Rectal Cancer?

- *Yes**
- *If chemotherapy is planned (most patients with LARC), there is ample evidence to suggest it is safe and effective to give neoadjuvantly as opposed to adjuvantly
  - Increase chance for cCR/ organ preservation
  - Decrease distant metastases
  - Greater proportion of planned chemotherapy delivered
- CRT can potentially be omitted in selected patients with very-low rectal cancers in whom surgery is planned

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Thank you for your attention

Questions?

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