XXIII JORNADA DE REVISIÓN DEL

CONGRESO AMERICANO DE ONCOLOGÍA

DIGESTIVO COLORRECTAL

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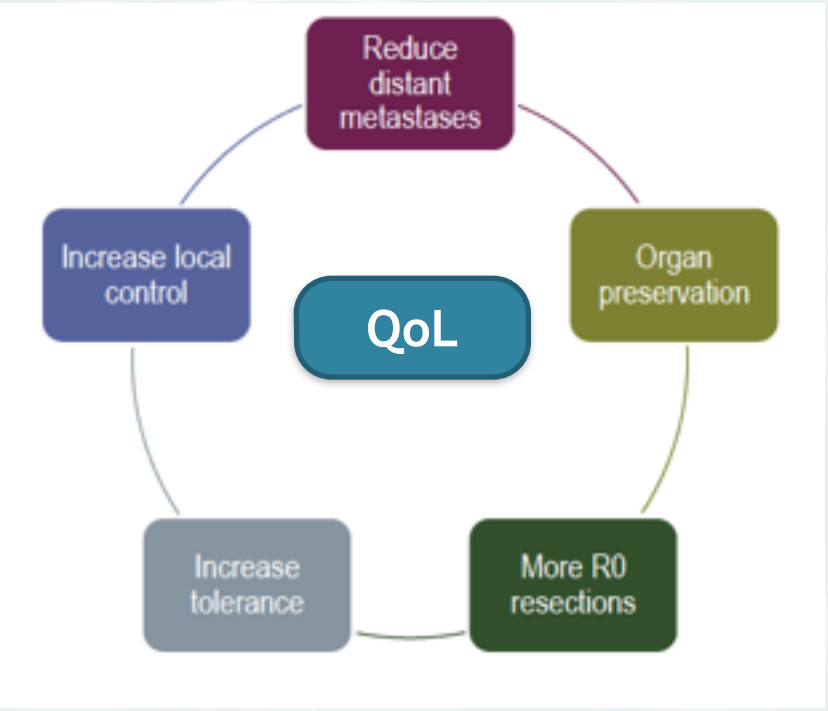
23 de junio de 2023

ENFERMEDAD LOCALIZADA

Evolution of management of LARC

- Surgery
- Surgery → LC CRT
- LC CRT → TME → +- chemo
- LC CRT or SC RT +- chemo → TME



- "TNT"
  - Induction
  - Consolidation

- QT
  - Double?
  - Triplet?

- RT
  - Short?
  - Long?
  - Omitted?
  - Boost?

- Rectal Preservation
  - Watch and wait
  - Local excision

2023 ASCO ANNUAL MEETING

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

The PROSPECT Trial (Alliance N1048)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Treatment of Locally Advanced Rectal Cancer

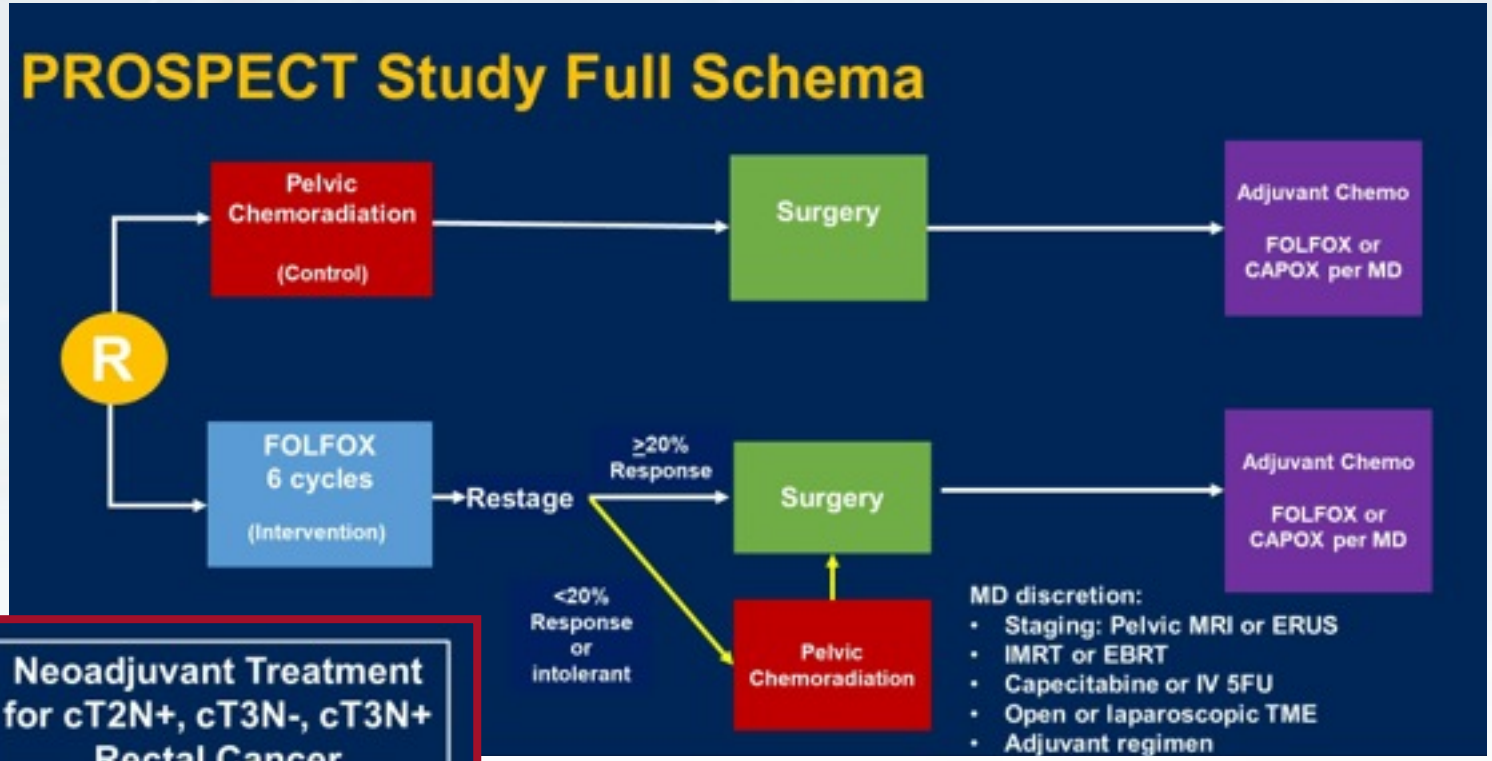
PROSPECT Study Motivation

- Long term toxicity from pelvic chemoradiation:
  - Impaired bowel, bladder, and sexual function[1]
  - Increased risk of pelvic fracture and second malignancy[2]
  - Impaired marrow reserve[3]
  - Infertility and premature menopause[4]
  - Increasing diagnosis of rectal cancer before age 50[5]

PROSPECT Trial Hypothesis

- 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

PROSPECT Study Full Schema



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

D. Schrag. ASCO 2023- LBA2. DOI: 10.1056/NEJMoa2303269

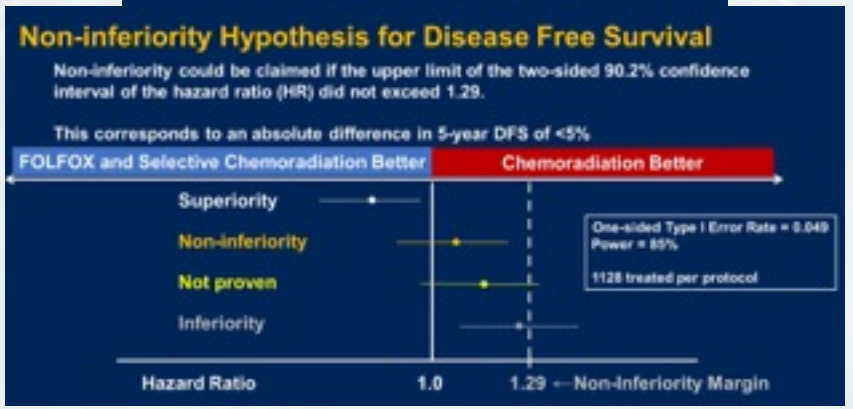
Inclusion:

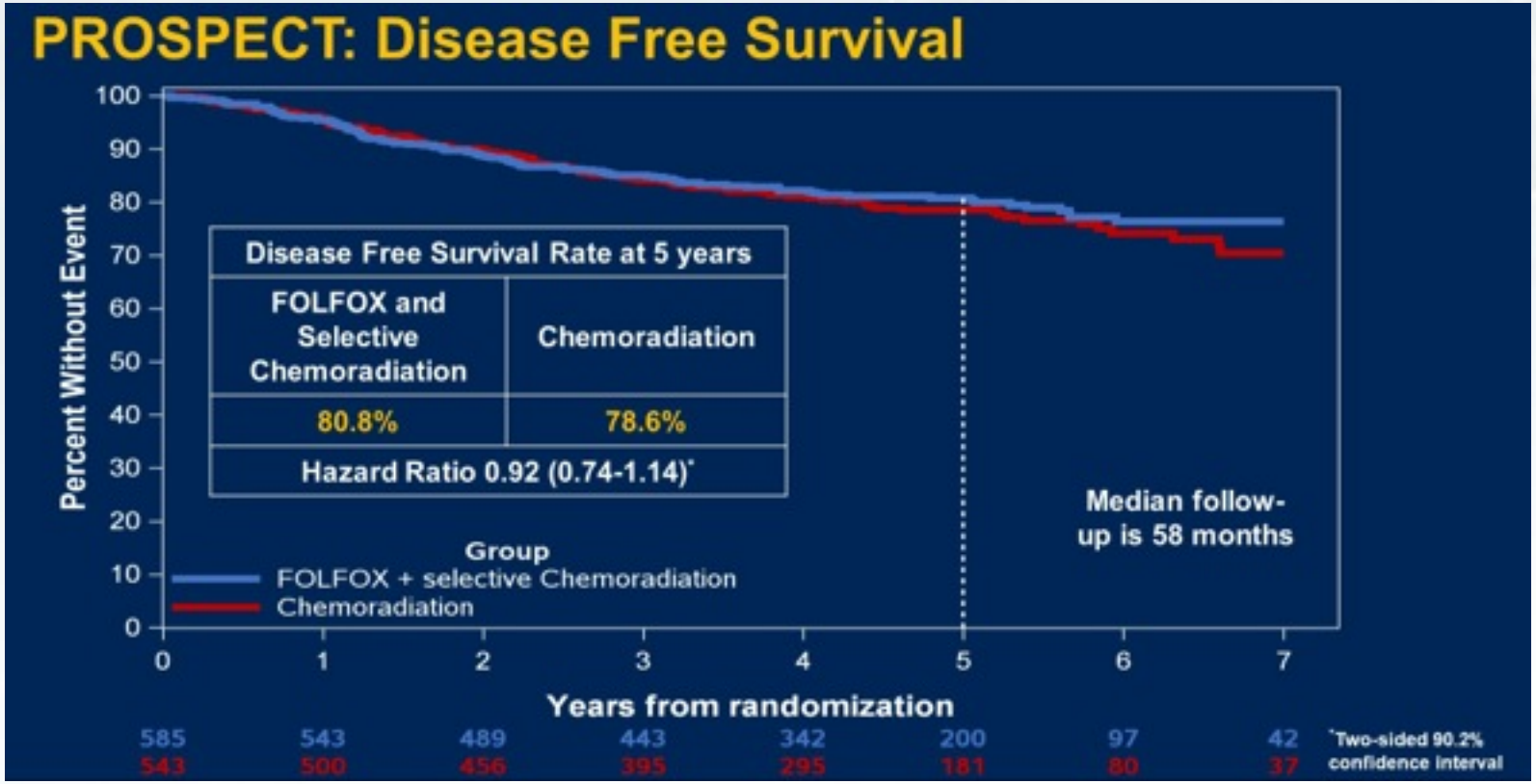
- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

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

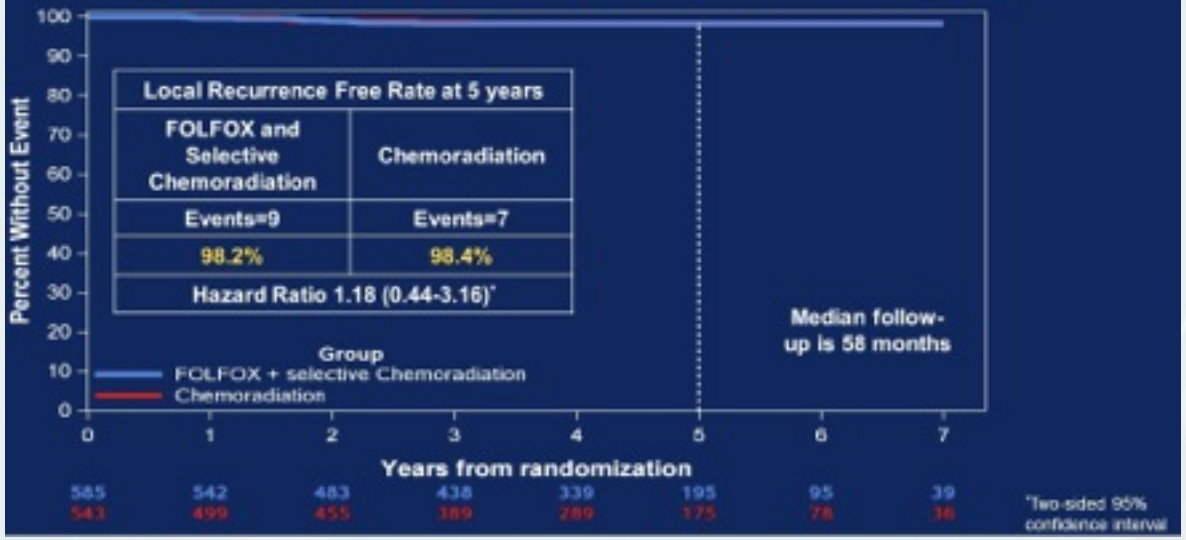
- **Primary Endpoint:**
  - **Disease Free Survival**



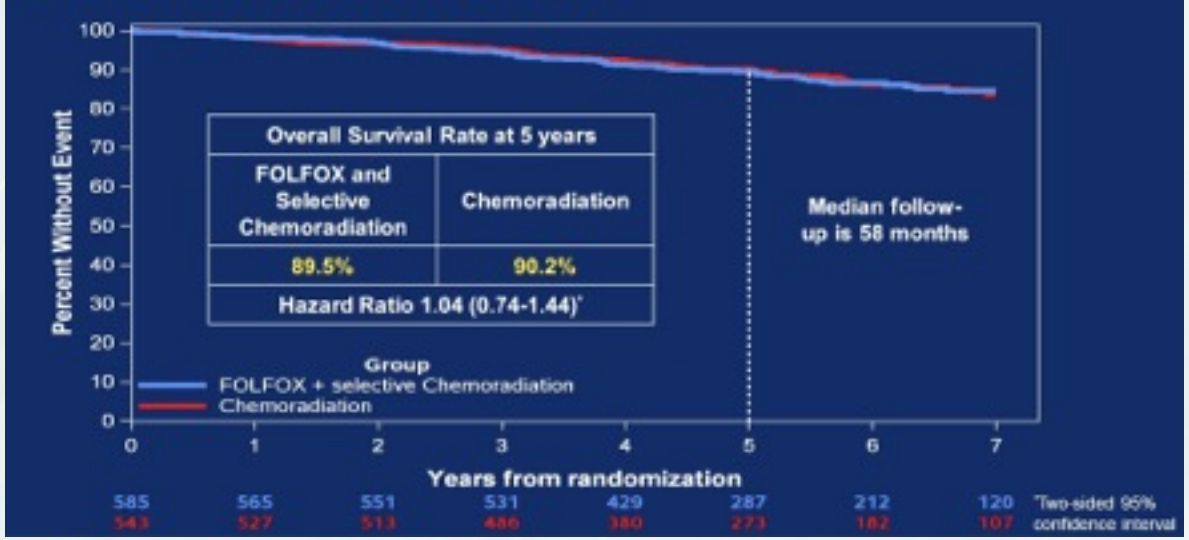


D. Schrag. ASCO 2023 # LBA2

PROSPECT: Freedom from Local Recurrence



PROSPECT: Overall Survival



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%

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)

D. Schrag. ASCO 2023 # LBA2

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

PROSPECT: Clinician-Reported Toxicity

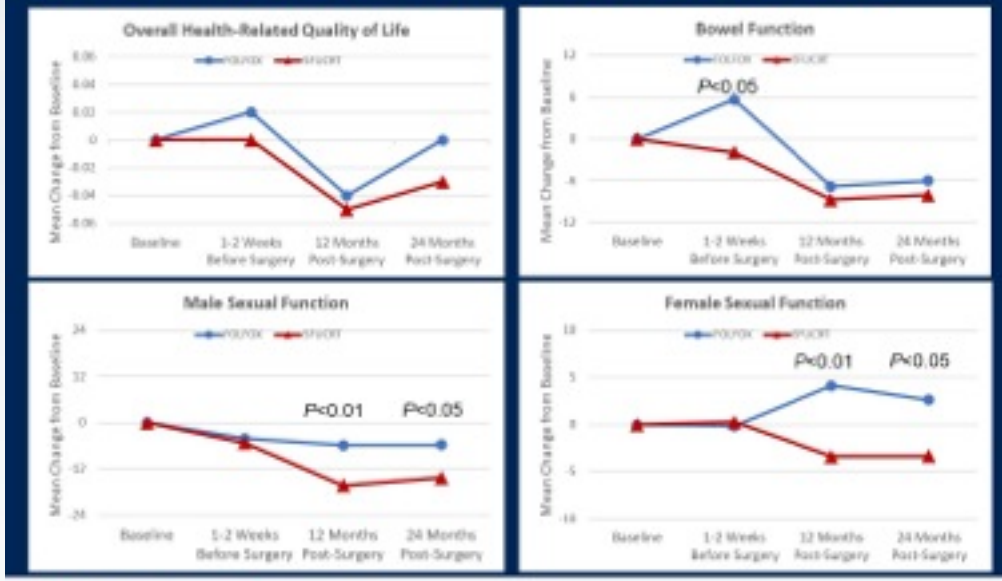
Most severe toxicity during observation period based on CTCAE v. 4.0	FOLFOX and Selective Chemoradiation 12 weeks* 535 patients	Chemoradiation 6 weeks 510 patients
Neoadjuvant grade ≥3 adverse events	41%	23%
Adjuvant grade ≥3 adverse events	25%	39%

*22 weeks if also treated with chemoradiation

During Neoadjuvant treatment:
- More diarrhea in the RT group
- More neuropathy in the FOLFOX group

During Adjuvant treatment:
- More diarrhea in the RT group
- More neuropathy in the RT group

PROSPECT: Quality of Life Evaluation



Quality of Life: Trend, but no significant difference between groups

Bowel function and sexual function favor FOLFOX group

N-373

Positive values represent improvement compared to baseline

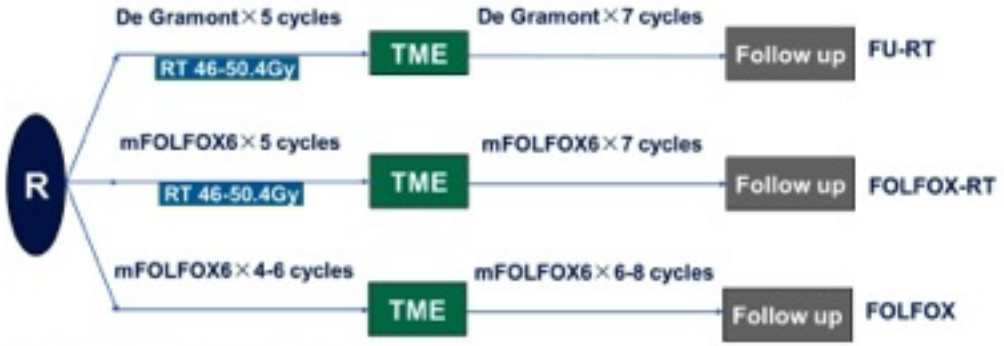
Neoadjuvant FOLFOX, with only selective use of pelvic chemoradiation, is a safe and effective treatment option for patients with cT2N+, cT3N-, or cT3N+ rectal cancer

D. Schrag. ASCO 2023 # LBA2

Long-term Outcome of Neoadjuvant mFOLFOX6 with or without Radiation versus Fluorouracil plus Radiation for Locally Advanced Rectal Cancer(FOWARC): A Multicenter, Randomized Phase III Trial

Study design

15 centers
NCT01211210



Study endpoints

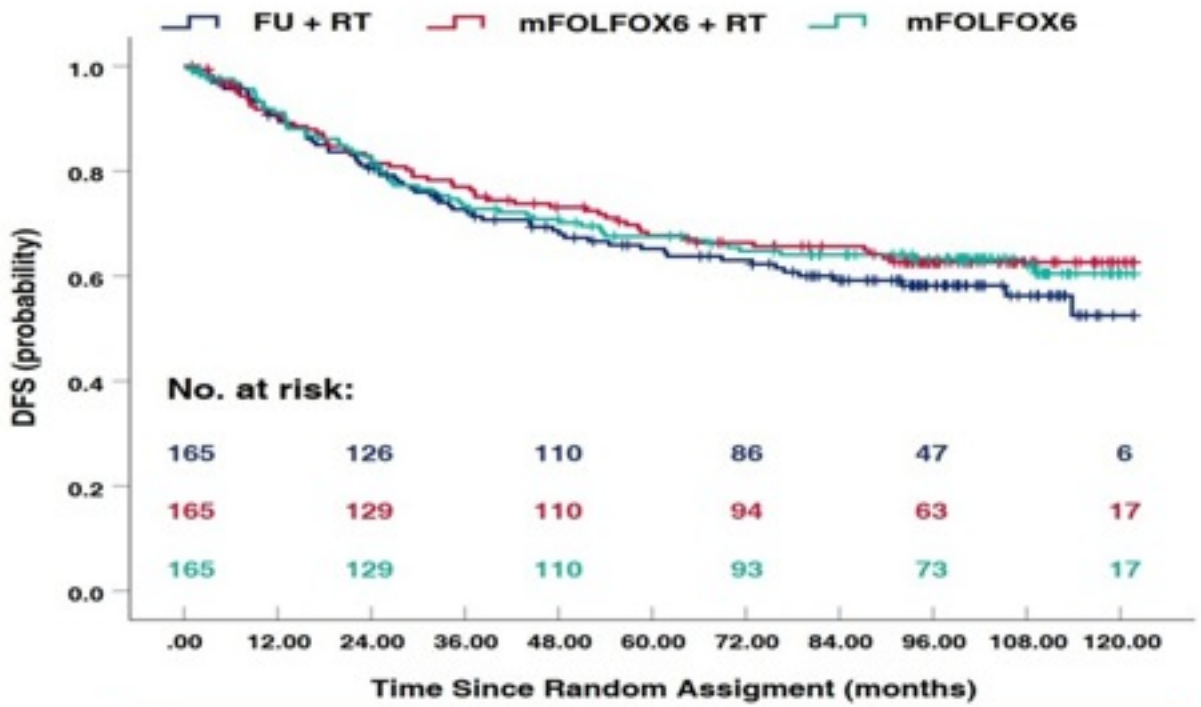
- Primary endpoint:
  3-year disease free survival (3y-DFS)
- Secondary endpoints:
  pCR, OS, morbility, QOL ect

Clinical characteristics (ITT)

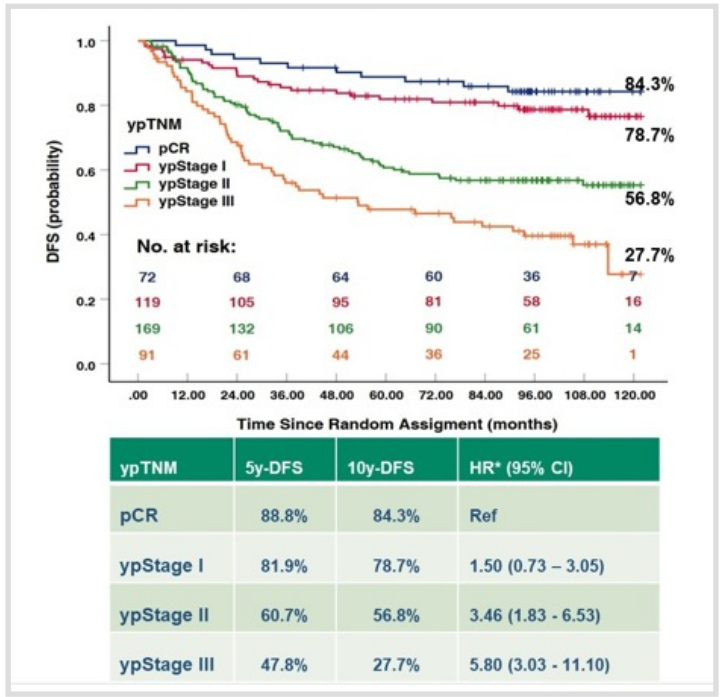
Items	FU-RT N=165	FOLFOX-RT N=165	FOLFOX N=165
Age median,yrs (mean±SD)	53.99±11.91	52.16±11.81	54.10±12.13
Gender, Male (%)	103 (62.4)	114 (69.1)	108 (65.5)
cT4 (%)	57 (34.5)	56 (33.9)	50 (30.3)
cN1 (%)	84 (50.9)	88 (53.3)	76 (46.1)
cN2 (%)	44 (26.7)	47 (28.5)	43 (26.1)
MRF positive (%)	32 (31.5)	38 (37.0)	33 (25.9)
Distance from anal verge ≤5cm	90 (54.5)	83 (50.3)	70 (42.4)

Jianwei Zhang. ASCO 2023 # 3505

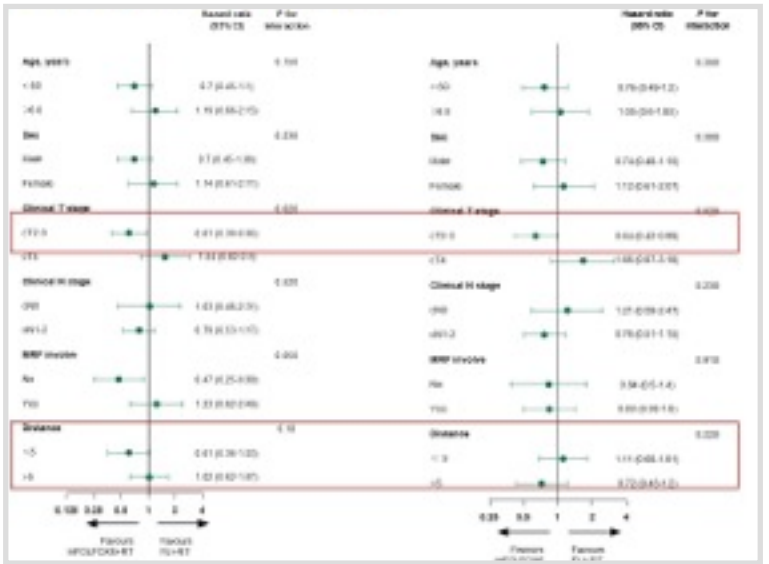
Long term Disease-Free Survival (DFS)



Treatment	5y-DFS	10y-DFS	HR (95% CI)
FU-RT	65.2%	52.5%	Ref
FOLFOX-RT	67.7%	62.6%	0.83 (0.58-1.19)
FOLFOX	67.5%	60.5%	0.86 (0.60-1.23)

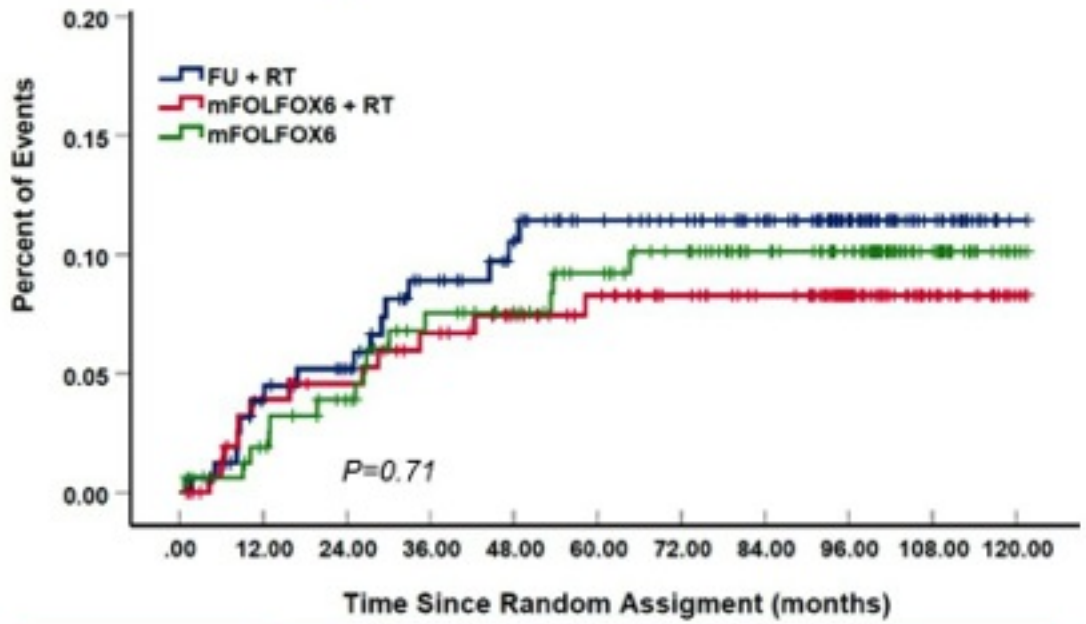


ypTNM	5y-DFS	10y-DFS	HR* (95% CI)
pCR	88.8%	84.3%	Ref
ypStage I	81.9%	78.7%	1.50 (0.73 – 3.05)
ypStage II	60.7%	56.8%	3.46 (1.83 - 6.53)
ypStage III	47.8%	27.7%	5.80 (3.03 - 11.10)



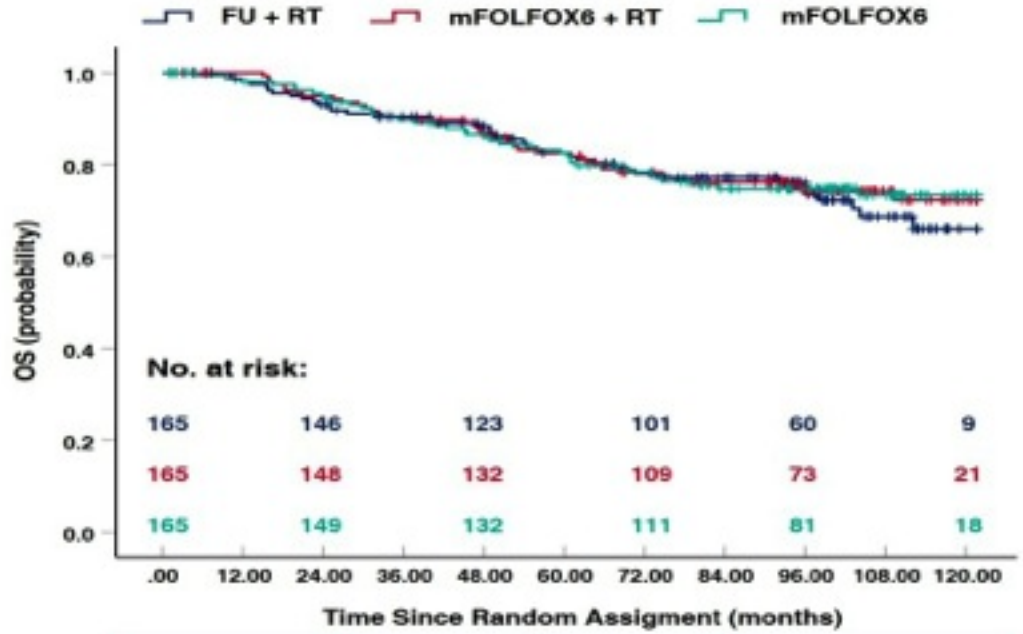
Jianwei Zhang. ASCO 2023 # 3505

Locoregional recurrence (LR)



Treatment	5y-LR(%)	10y-LR (%)	HR (95% CI)
FU-RT	10.8	10.8	Ref
FOLFOX-RT	8.0	8.0	0.825 (0.38-1.81)
FOLFOX	8.8	9.6	0.800 (0.37-1.75)

Overall survival



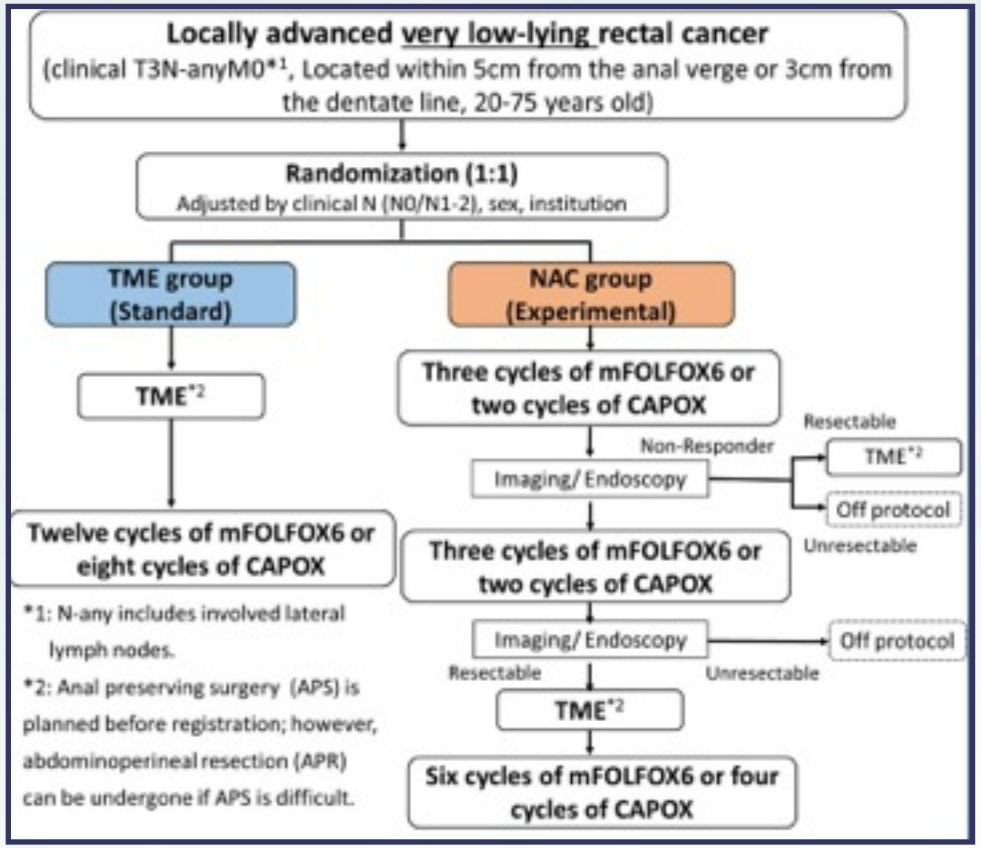
Treatment	5y-OS	10y-OS	HR (95% CI)
FU-RT	82.5%	65.9%	Ref
FOLFOX-RT	81.8%	72.3%	0.91 (0.58-1.41)
FOLFOX	81.8%	73.4%	0.91 (0.58-1.41)

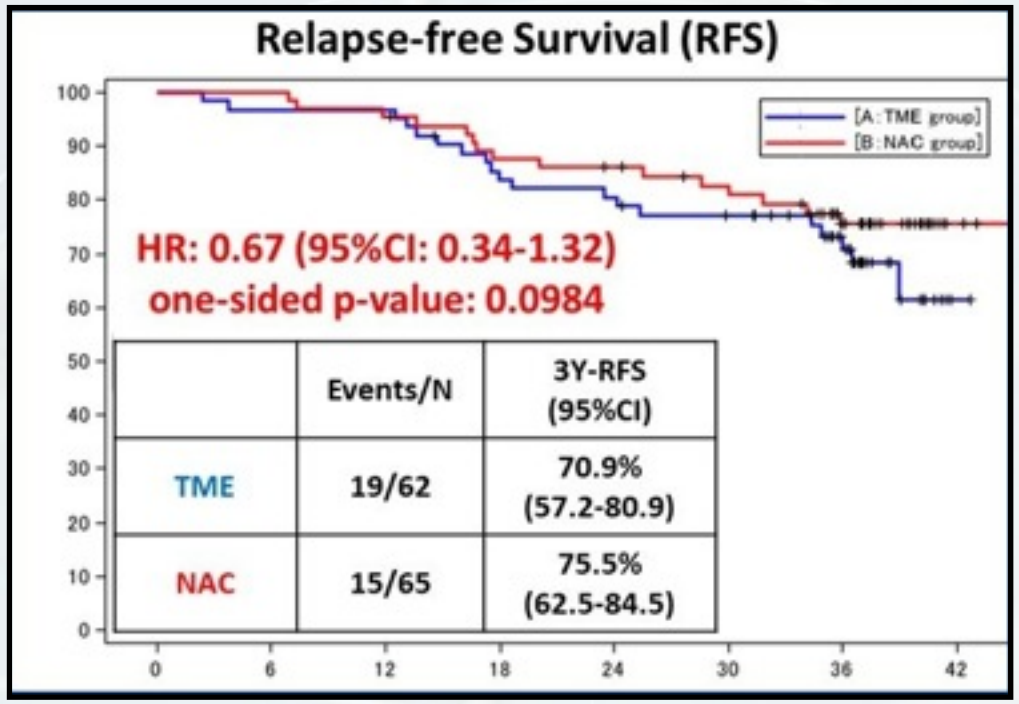
Jianwei Zhang. ASCO 2023 # 3505

Neoadjuvant chemotherapy (NAC) followed by total mesorectal excision and adjuvant chemotherapy versus TME followed by adjuvant chemotherapy in very low-lying cT3 rectal cancer (NAIR): a multicenter, randomized, open-label, phase 2/3 trial

Primary Endpoint:

- Recurrence-free survival (3yrs)





	Events/N	3Y-RFS (95%CI)
TME	19/62	70.9% (57.2-80.9)
NAC	15/65	75.5% (62.5-84.5)

➢ Median Wexner incontinence score

Pre: Preoperatively, M: month(s)

	Pre	3M	6M	12M	24M	36M
TME group	1.0	14.0	12.0	10.0	9.0	10.0
NAC group	1.0	15.0	13.5	12.0	11.0	11.0

At 3 years after randomization, 61 pts in the NAC group (93.8%) and 52 pts in the TME group (83.9%) could defecate via their anuses (P=0.092).

➢ Grade 3 or higher post-operative complications

	TME (N=62)	NAC (N=65)	p value
Any grade 3 or higher complications	13 (21.0%)	13 (20.0%)	1.000
Anastomotic leakage	2 (3.2%)	2 (3.1%)	
Pelvic abscess	5 (8.1%)	6 (9.2%)	
Bowel obstruction	1 (1.6%)	0	

No treatment-related deaths occurred in either of the groups.

Yuichiro Tsukada, ASCO 2023 # 3519

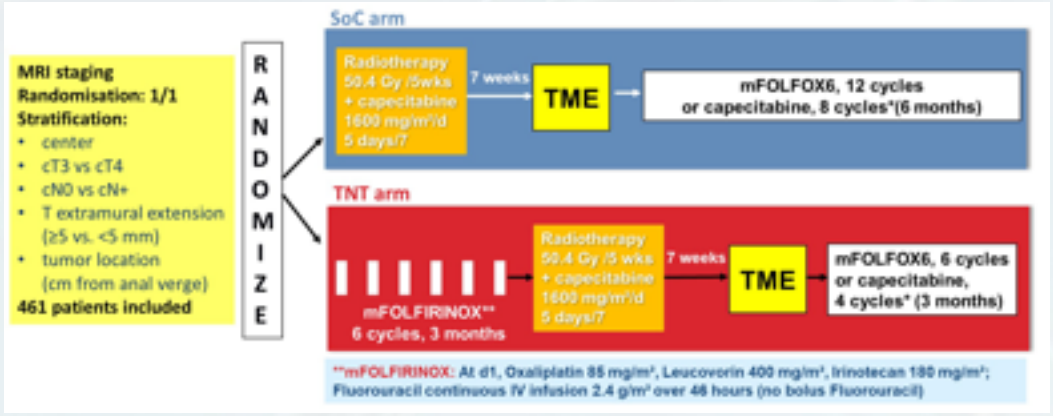
TNT trial results

Outcomes	RAPIDO		STELLAR		PRODIGE-23	
	TNT-SCRT	LCRT	TNT-SCRT	LCRT	TNT-LCRT	LCRT
pCR	28%	14%	21.8% (incl cCR)	12.3%	28%	12%
R0	90%	90%	91.5%	87.8%	95%	94%
3-yr DrTF	23.7%	30.4%	-	-	-	-
3-yr DFS	-	-	64.5%	62.3%	76%	69%
3-yr LR	8.3%	6.0%	8.4%	11.0%	LR: 4.3%	5.7%
3-yr DM	20.0%	26.8%	23.9%	24.7%	21%	28%
3-yr OS	89%	89%	86.5%	75.1%	91%	88%

Bahadoer RR et al. Lancet Oncol 2020; Conroy T et al. Lancet Oncol 2021, Jin J et al. JCO 2022

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.

- Primary: Disease-Free Survival (DFS)

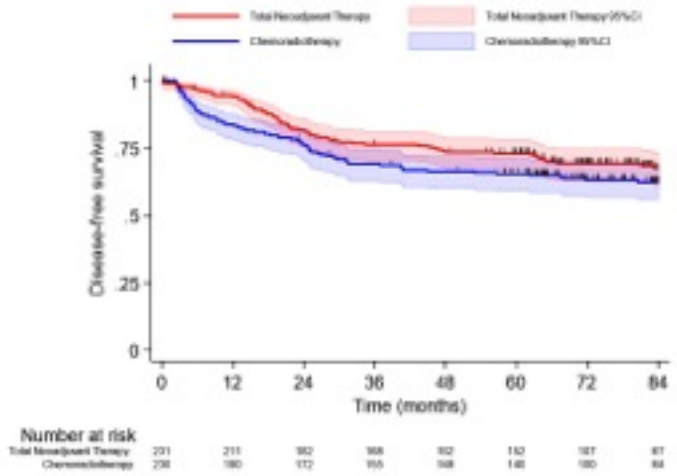


Cumulative incidence of rectal cancer recurrences

Results	TNT	SoC
Local		
At 5 years	4.7% [95%CI: 2.5-8.5]	6.4% [95%CI: 3.8-10.8]
At 7 years	5.3% [95%CI: 2.9-9.3]	8.1% [95%CI: 4.9-13.3]
Metastatic*		
At 5 years	18.4% [95%CI: 13.8-24.2]	26.6% [95%CI: 21.2-33.0]
At 7 years	20.7% [95%CI: 15.6-27.0]	27.7% [95%CI: 22.2-34.2]
Alive with metastases	19/44 (43%)	21/60 (35%)

T Conroy. ASCO 2023 #3504

Disease-Free Survival



155 events

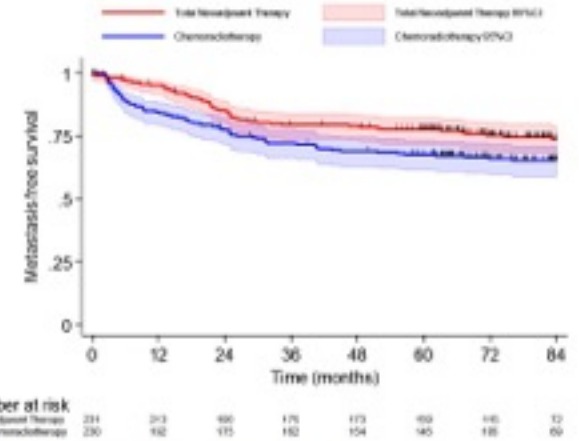
7-yr DFS rate:
- 67.6% [95%CI: 60.7-73.6] TNT arm
- 62.5% [95%CI: 55.6-68.6] SoC arm

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

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.



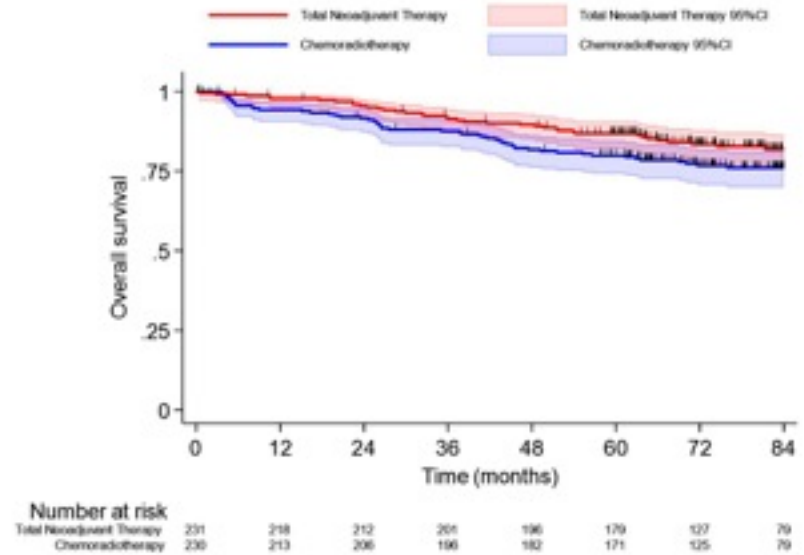
138 events

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

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

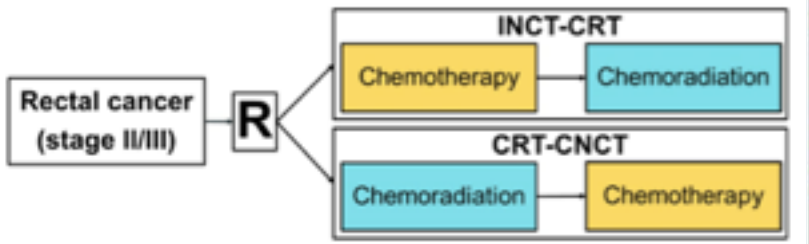
5-yr OS:
- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

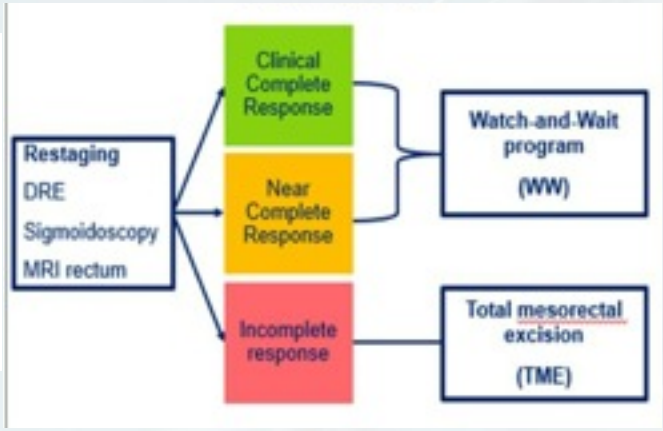
RMST (7-yr), months:
4.37 [0.35-8.38] benefit for TNT arm
p=0.033

T Conroy. ASCO 2023 #3504

Sustained organ preservation in rectal cancer patients treated with total neoadjuvant therapy: Long-term results of the OPRA trial

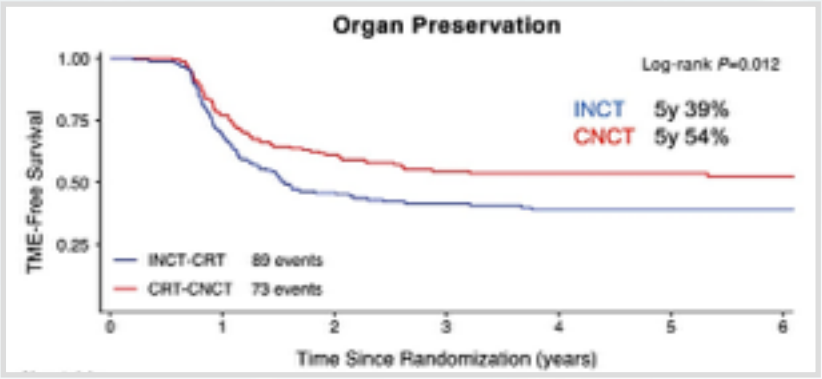
- Randomized phase II trial.

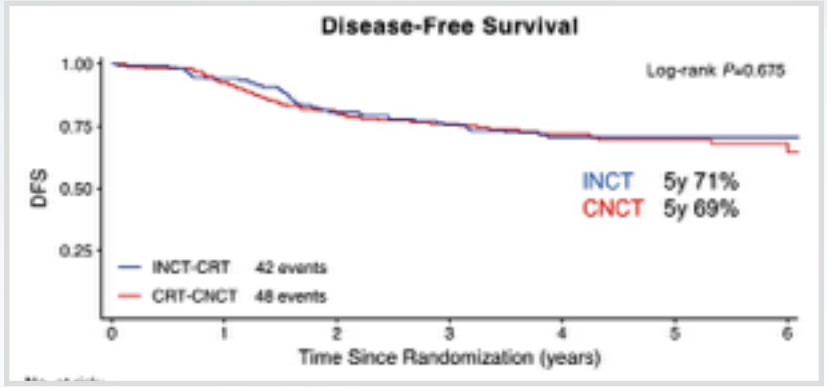


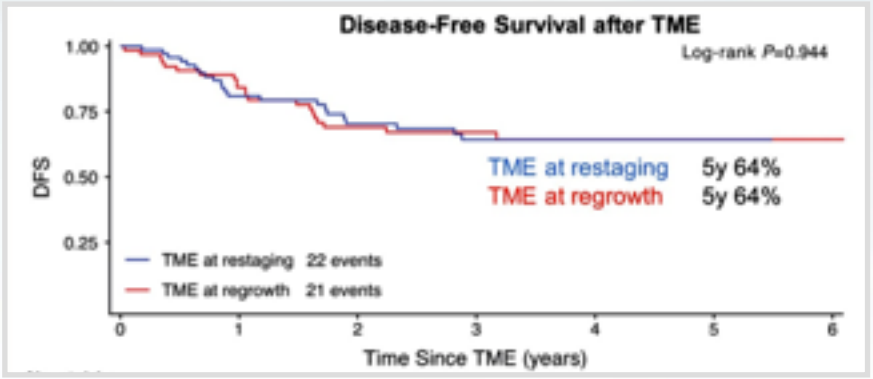


3- and 5-year rates with 95% CI.

	Induction		Consolidation		
	3-year, %	5-year, %	3-year, %	5-year, %	P
DFS	77 (70-84)	72 (65-80)	76 (70-83)	71 (63-78)	0.60
TME-free survival	41 (34-50)	39 (32-48)	55 (48-63)	54 (47-63)	0.01
LRFS	95 (91-99)	94 (90-98)	94 (90-98)	90 (85-95)	0.27
DMFS	83 (78-90)	82 (75-89)	83 (77-89)	79 (72-86)	0.66
OS	95 (92-99)	88 (82-94)	94 (91-98)	88 (82-94)	0.73







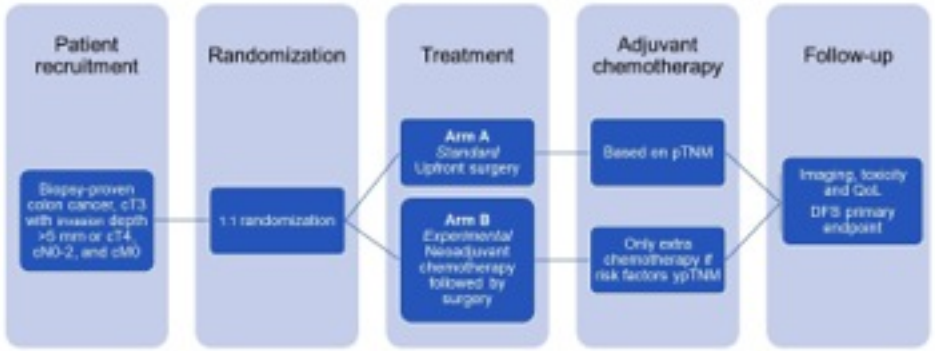
36% patients who started WW developed a regrowth
94% occurred within 2 years and 99% occurred within 3 years

Floris S Verheij. ASCO 2023 # 3520

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

Study design



- Primary endpoint was Disease free survival (DFS)
- Secondary endpoints
  - Rate of patients fulfilling the criteria for adjuvant chemotherapy
  - Overall survival (OS)
  - Toxicity
  - Quality of life

Patients

	Upfront surgery (standard)	Neoadj. treatment (experimental)	All
N	122	126	248
Age (median, min;max)	69.4 (30.3;81.8)	63.8 (23.8;84.3)	66.3 (23.8;84.3)
Sex, N (%female)	45 (37%)	66 (52%)	111 (45%)
Localization of tumor, N (%)			
Right	52 (43%)	59 (47%)	111 (45%)
Left	70 (57%)	66 (52%)	136 (54%)
Right or left not specified	-	1 (1%)	1 (1%)
T-category at baseline CT scan, N (%)			
T3	89 (74%)	91 (72%)	180 (73%)
Median extramural invasion (mm)	7 mm	8 mm	7 mm
T4	31 (25%)	33 (26%)	65 (26%)
T3 or T4 not specified	1 (1%)	2 (2%)	3 (1%)
Performance status, N (%)			
0	107 (88%)	115 (91%)	222 (90%)
1	13 (10%)	8 (6%)	21 (8%)
2	-	1 (1%)	1 (1%)
0, 1 or 2 not specified	2 (2%)	2 (2%)	4 (2%)

L H Jensen ASCO 2023 # 3503

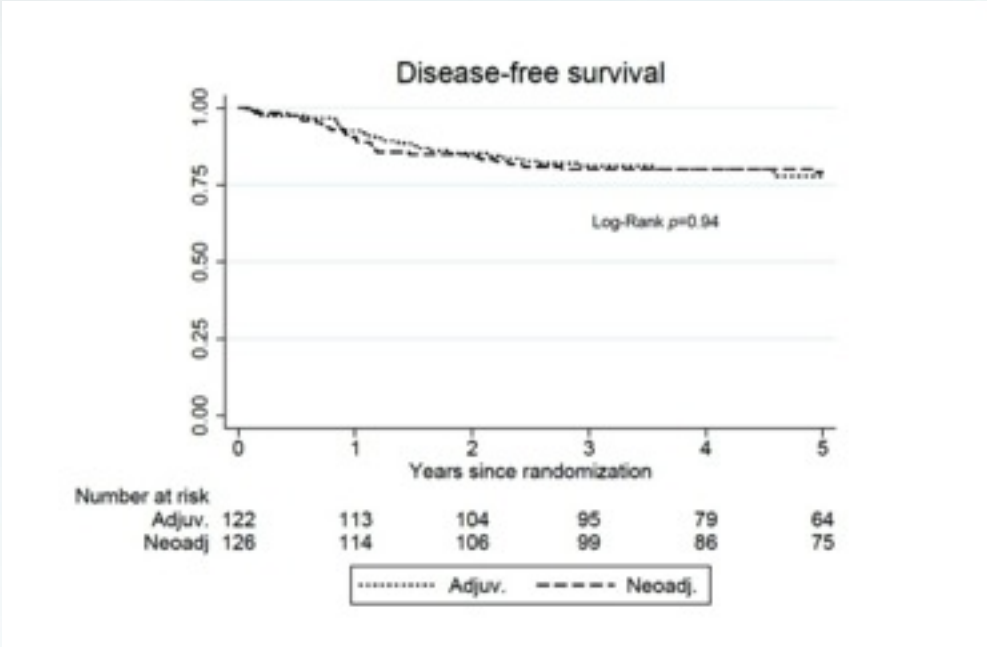
Pathology

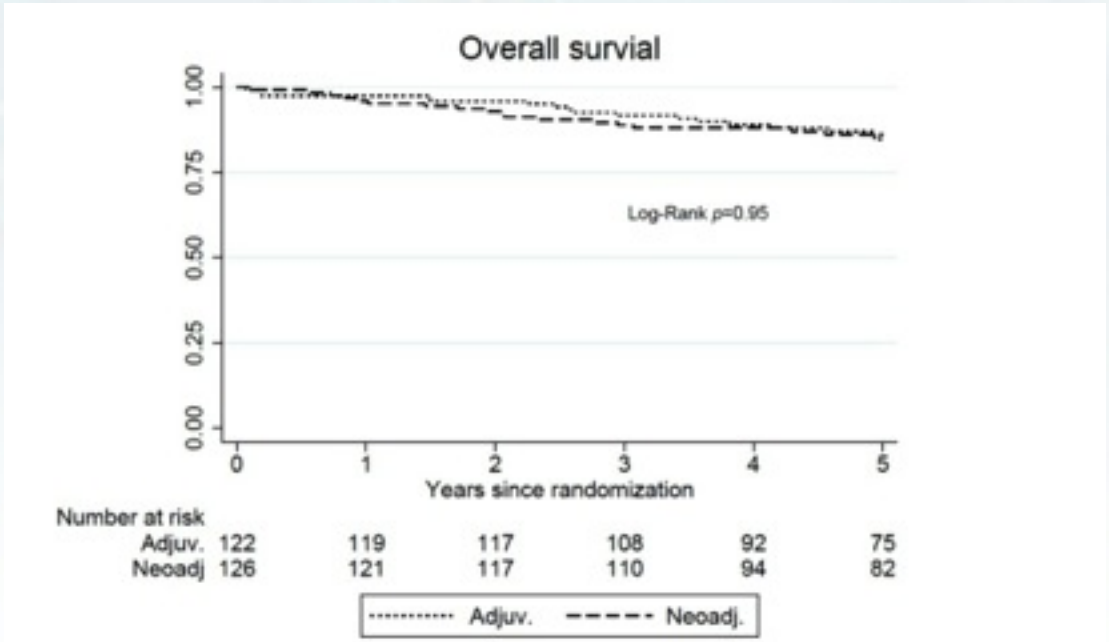
		Upfront surgery (standard)	Neoadj. treatment (experimental)	All
Involvement of resection margin, N (%)	R1	10 (9%)	9 (7%)	19 (8%)
	R0	109 (90%)	114 (93%)	223 (91%)
	Unknown	2 (1%)	-	1 (1%)
p/ypT-category at surgery*, N (%)	0	-	4 (3%)	4 (2%)
	1	2 (2%)	1 (1%)	3 (1%)
	2	3 (2%)	7 (6%)	10 (4%)
	3	75 (62%)	76 (62%)	151 (62%)
	4	39 (32%)	35 (28%)	73 (30%)
p/ypN-category at surgery, N (%)	0	57 (48%)	72 (59%)	129 (54%)
	1	43 (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)		48 (39%)	30 (25%)	77 (32%)
Perforation, N (%yes)		2 (2%)	3 (2%)	5 (2%)

Adjuvant chemotherapy indication

	Upfront surgery (standard)	Neoadj. Treatment (experimental)	p
Criteria for adjuvant chemotherapy fulfilled*, N (%yes)	88 (73%)	72 (59%)	0.03

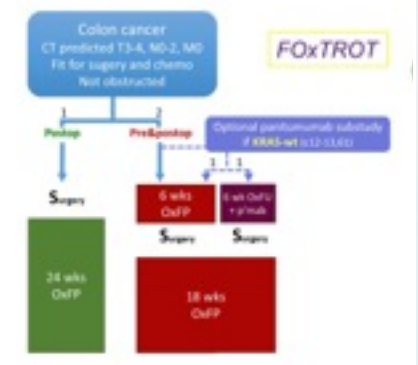
**according to national guidelines applied to p/ypTNM, investigator*

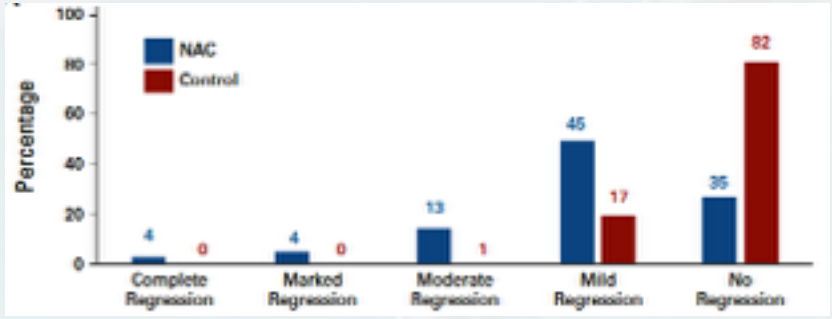


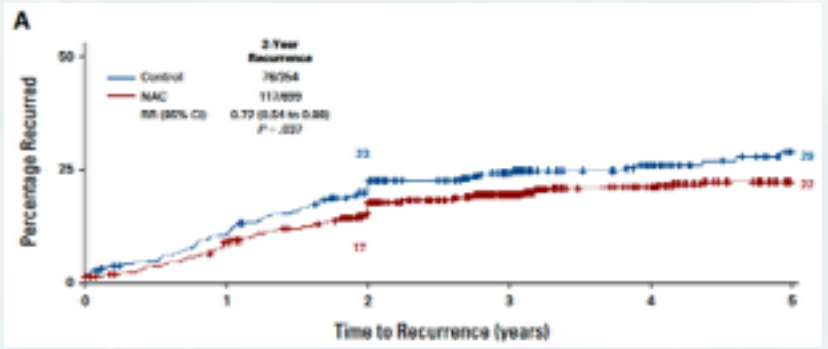


L H Jensen ASCO 2023 # 3503

Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial

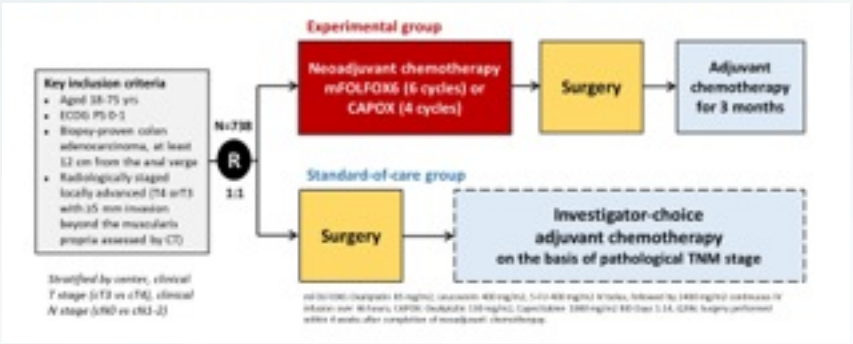


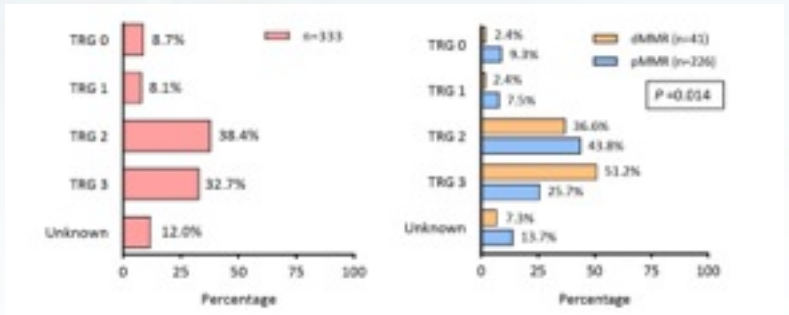




Dion Morton. JCO 2023; 41:1541-1552

Perioperative Chemotherapy With mFOLFOX6 or CAPOX for Patients With Locally Advanced Colon Cancer (OPTICAL): A Multicenter, Randomized, Phase III Trial





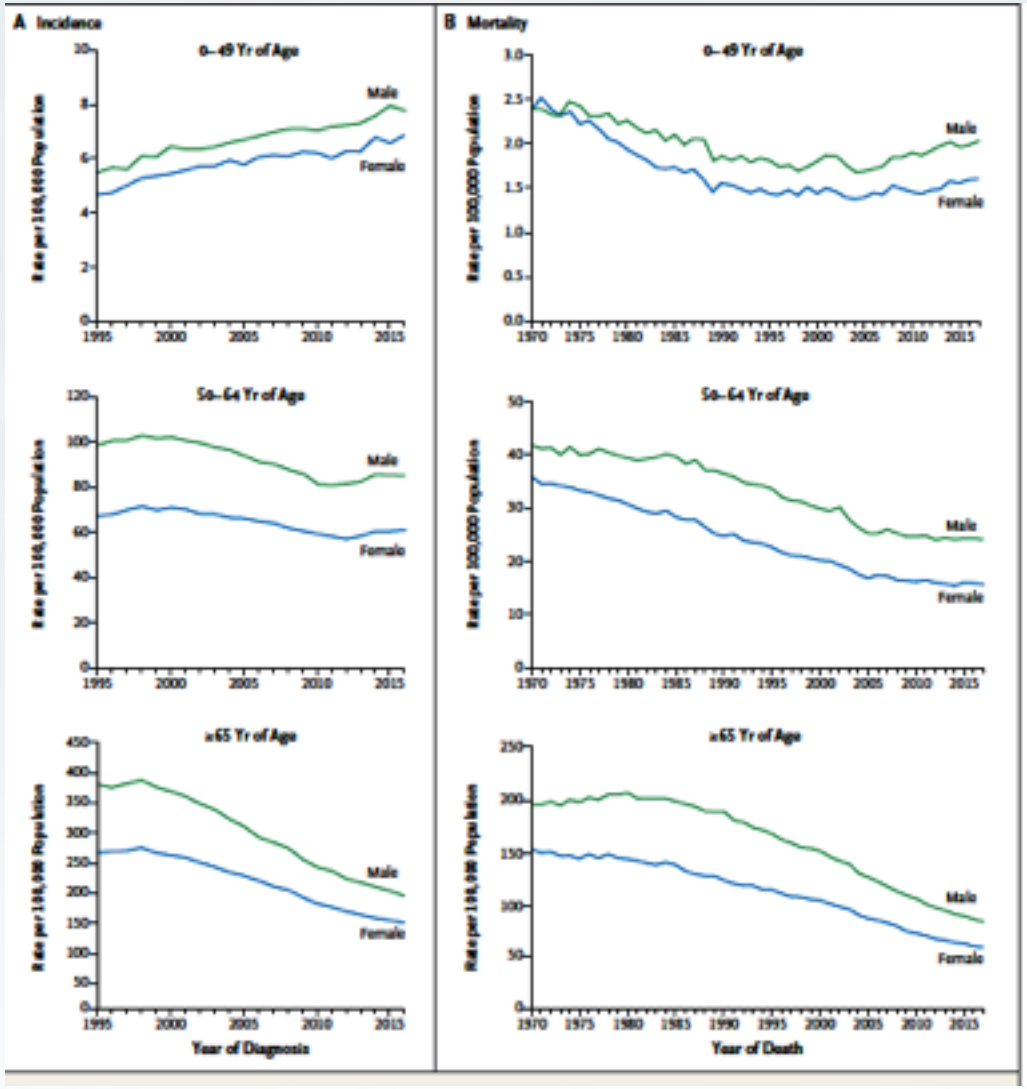
Huabin Hu.. ASCO 2022

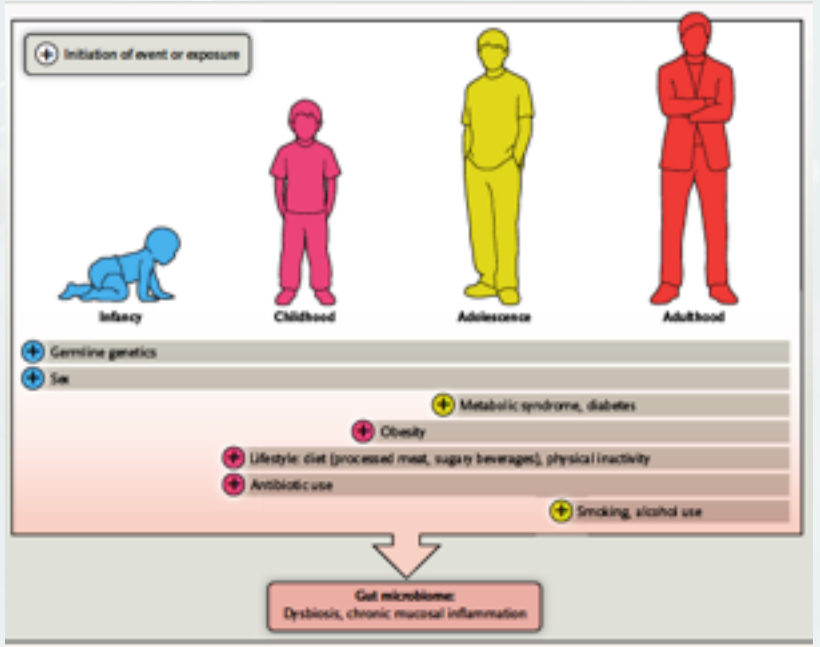
The NEW ENGLAND JOURNAL of MEDICINE

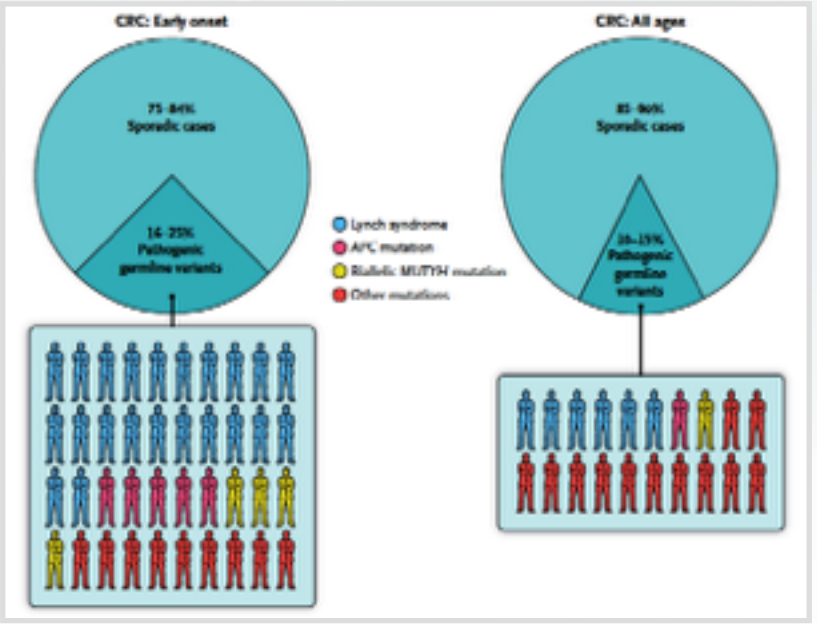
REVIEW ARTICLE

Dan L. Longo, M.D., Editor

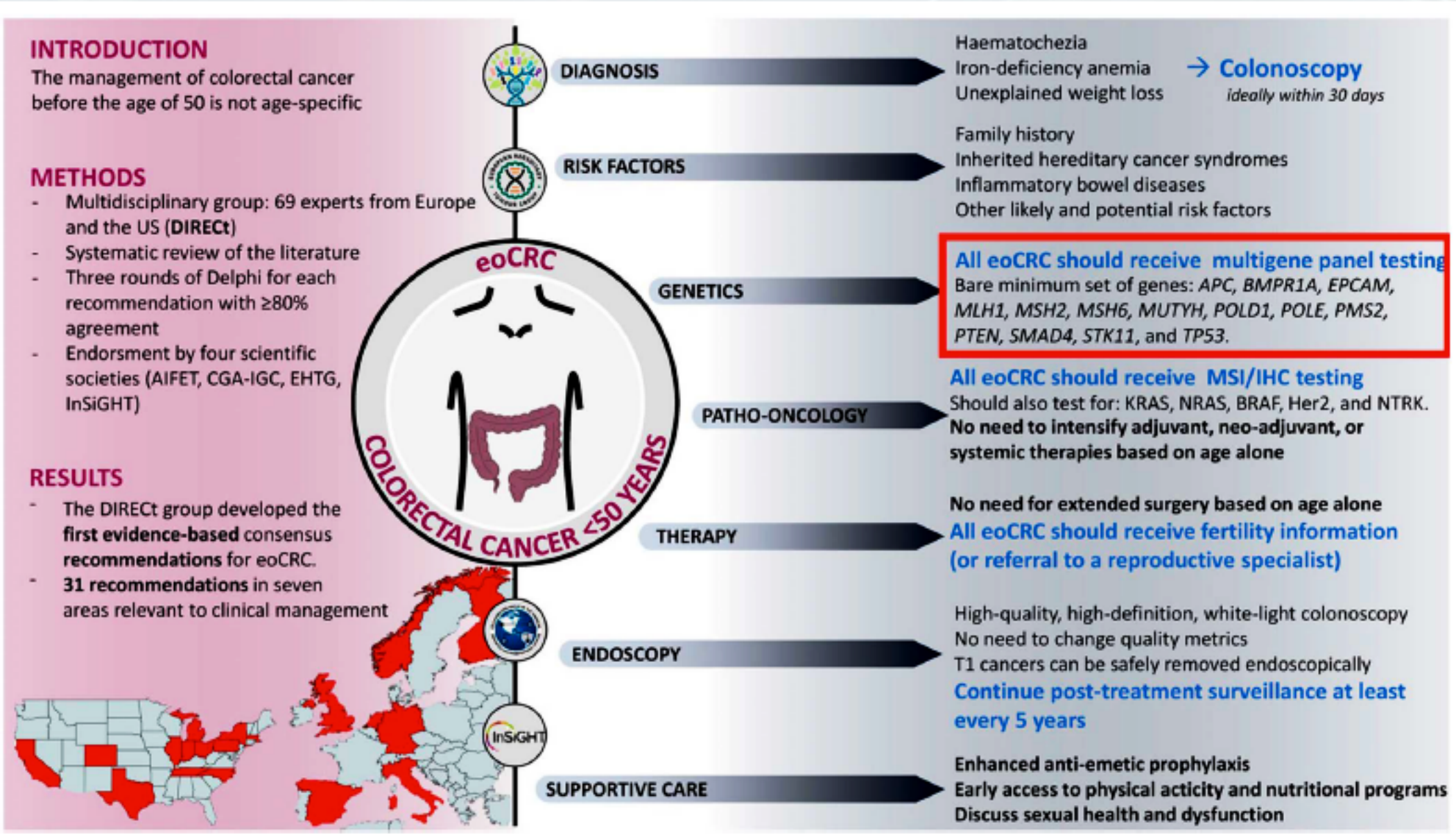
Increasing Incidence of Early-Onset Colorectal Cancer





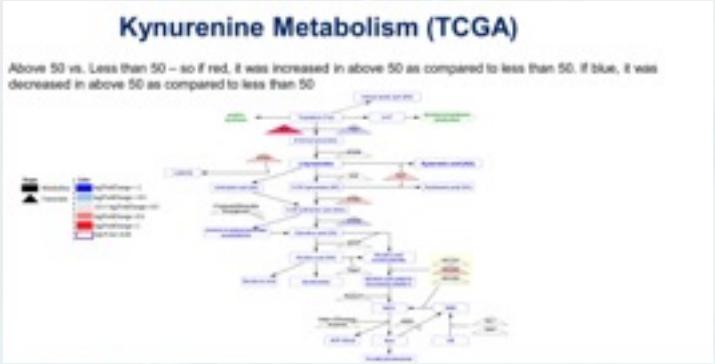


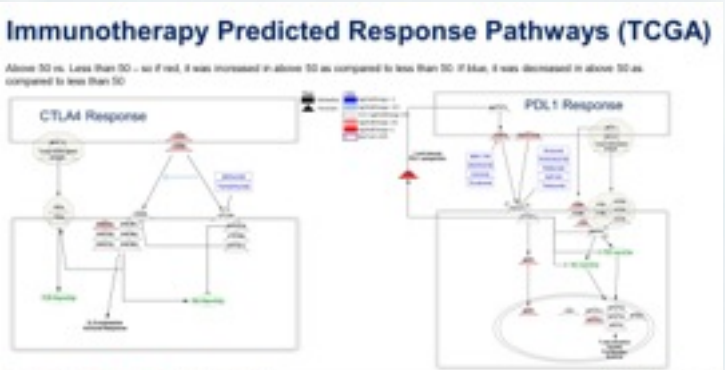
Frank A. Sinicrope. N Engl J Med 2022;386:1547-58.



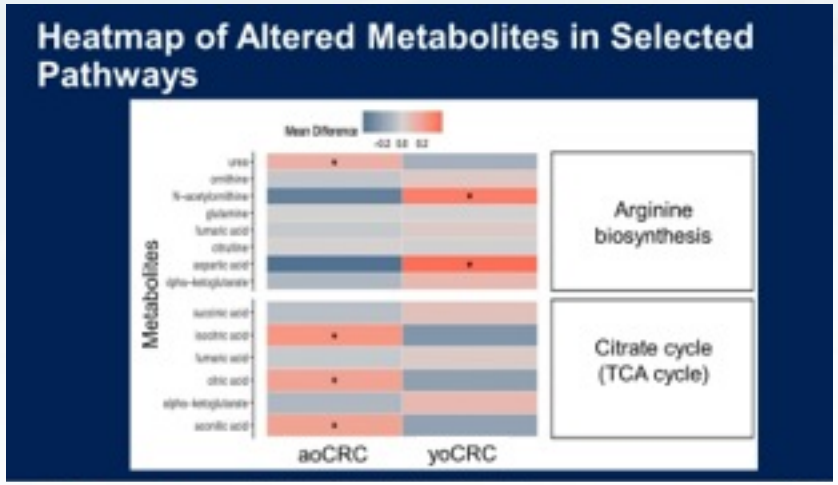
Emily Harrold. 2023 ASCO EDUCATIONAL BOOK

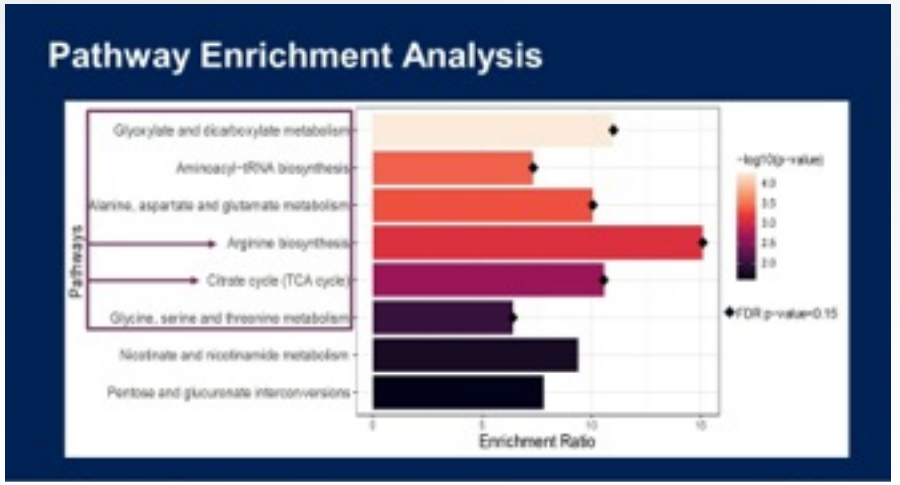
Abstract 3509: Transcriptional metabolic profiling in young onset colorectal cancer (YOCRC) patients





Metabolomic Differences in Young-onset versus Average-onset Colorectal Adenocarcinoma



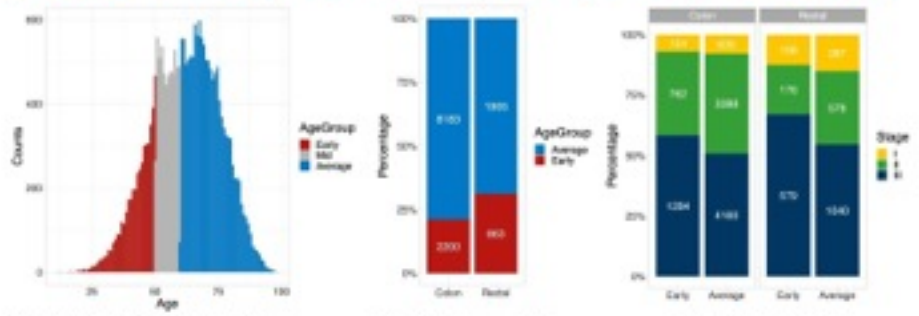


D Vadehras. ASCO 2023 # 3509

Theus Jayakrishnan. ASCO 2023 # 3510

Evaluation of genomic alterations in early-onset versus average-onset colorectal cancer

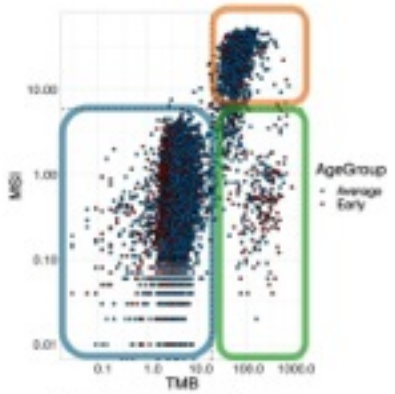
EOCRC was more frequently rectal primary and stage III compared to AOCRC.



- Early (N=3084; 16.4%); median age=44.1 years
- Mid (N=5631; 29.8%); median age=56.9 years
- Average (N=10150; 53.8%); median age=70.5 years

21% of colon cases were EO
31% of rectal cases were EO

EO presented with stage III disease more often than AO

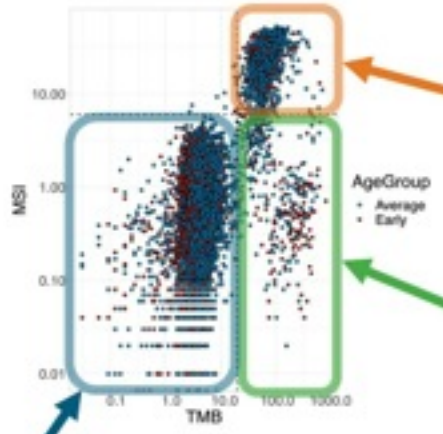


TMB-High is ≥ 20 Mut/Mb

EOCRC was 3.2 times more likely to be MSS/TMB-High compared to AOCRC (p<0.001)

Key genomic differences between EO and AO

(significance: adjusted p-value < 0.05)



MSI-H/TMB-High: EO compared to AO has:

- More *KRAS* mutations (46% vs 15%)
- More *PIK3CA* mutations (47% vs 28%)
- More *ERBB2/3* mutations (16% and 13% vs 7% and 5%)
- Fewer *BRAF* mutations (8% vs 65%)
- Fewer *RNF43* mutations (25% vs 59%)

MSS/TMB-High: EO compared to AO has:

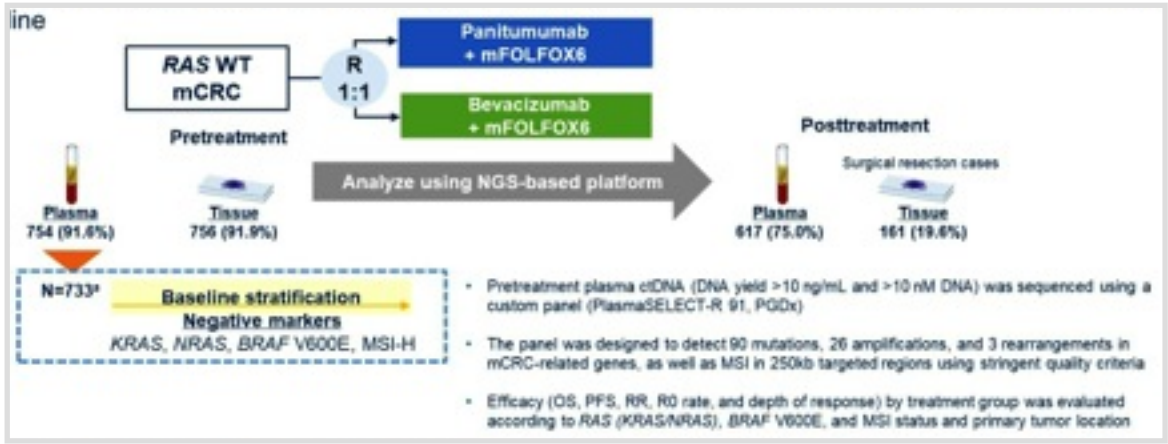
- More *POLE* mutations (65% vs 35%)
- Fewer *ACVR2A* mutations (32% vs 51%)

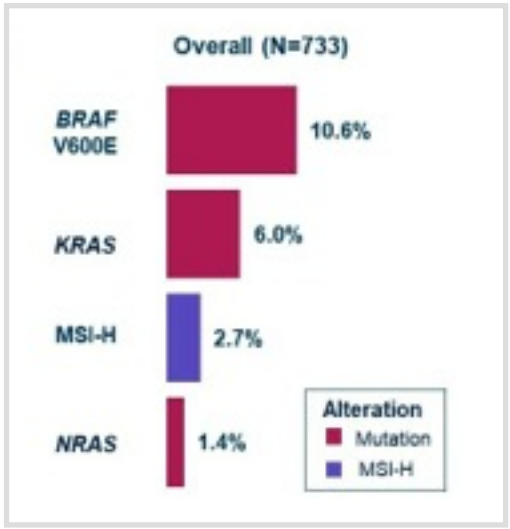
MSS/TMB-Low: No relevant differences

Eric M Lane+der. ASCO 2023 # 3511

ENFERMEDAD AVANZADA

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





Co-occurring gene alterations by tumor sidedness

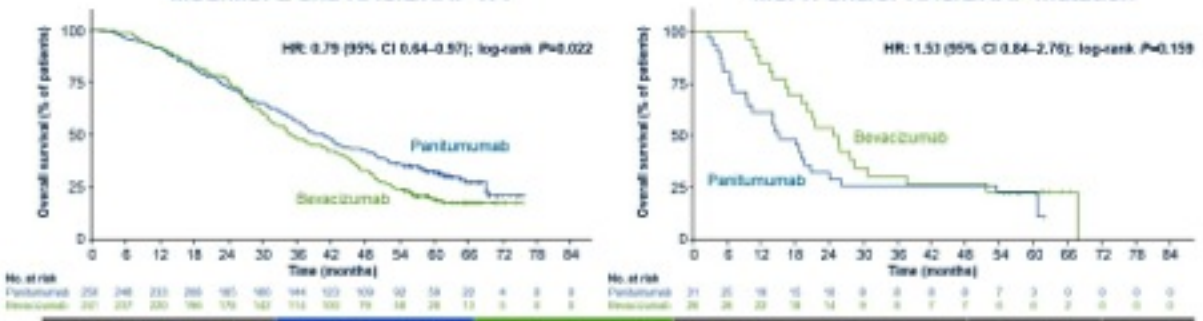
Gene alteration status, n (%)	Left-sided mCRC (n=554)	Right-sided mCRC (n=169)	Other[a] (n=10)	Overall (n=733)
MSI-H or *RAS*/*BRAF* mutation	57 (10.3)	73 (43.2)	5 (50%)	135 (18.4)
MSS/MSI-L and *RAS*/*BRAF* WT	497 (89.7)	96 (56.8)	5 (50%)	598 (81.6)

Incidence of gene alterations in baseline ctDNA

Gene alteration, n (%)	Left-sided mCRC (n=554)		Right-sided mCRC (n=169)		Overall population (N=733)	
	Panitumumab + mFOLFOX6 (n=287)	Bevacizumab + mFOLFOX6 (n=267)	Panitumumab + mFOLFOX6 (n=78)	Bevacizumab + mFOLFOX6 (n=91)	Panitumumab + mFOLFOX6 (n=368)	Bevacizumab + mFOLFOX6 (n=365)
BRAF V600E	16 (5.6)	8 (3.0)	26 (33.3)	27 (29.7)	42 (11.4)	36 (9.9)
KRAS	11 (3.8)	15 (5.6)	9 (11.5)	6 (6.6)	21 (5.7)	23 (6.3)
NRAS	6 (2.1)	2 (0.7)	1 (1.3)	0	7 (1.9)	3 (0.8)
MSI-H	1 (0.3)	2 (0.7)	8 (10.3)	8 (8.8)	9 (2.4)	11 (3.0)

Kentaro Yamazaki. ASCO 2023 # 3508

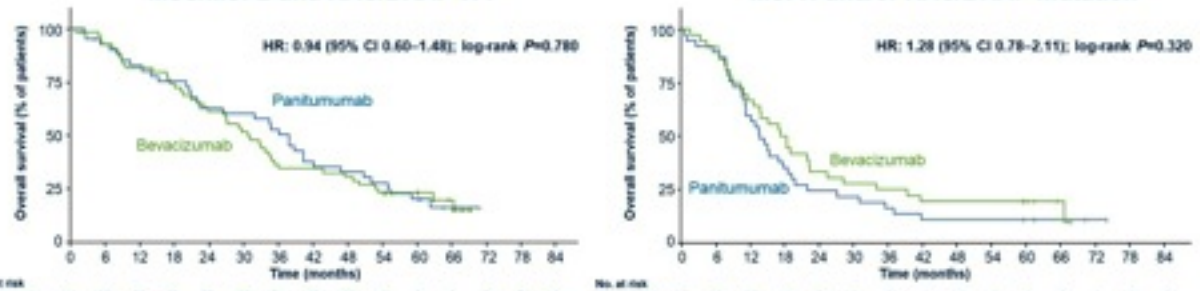
Overall survival by MSS/MSI and *RAS/BRAF* status in left-sided mCRC



	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)	287	34.1 (30.8–38.0)		0.83 (0.69–1.01)	0.089
MSS/MSI-L and *RAS/BRAF* WT	256	43.6 (36.3–44.4)	261	34.8 (31.3–41.2)		0.79 (0.64–0.97)	
MSI-H and/or *RAS/BRAF* mutation	31	15.4 (9.6–28.8)	26	25.2 (17.9–36.0)		1.53 (0.84–2.76)	

0.5 1.0 3.0 5.0
Panitumumab better | Bevacizumab better

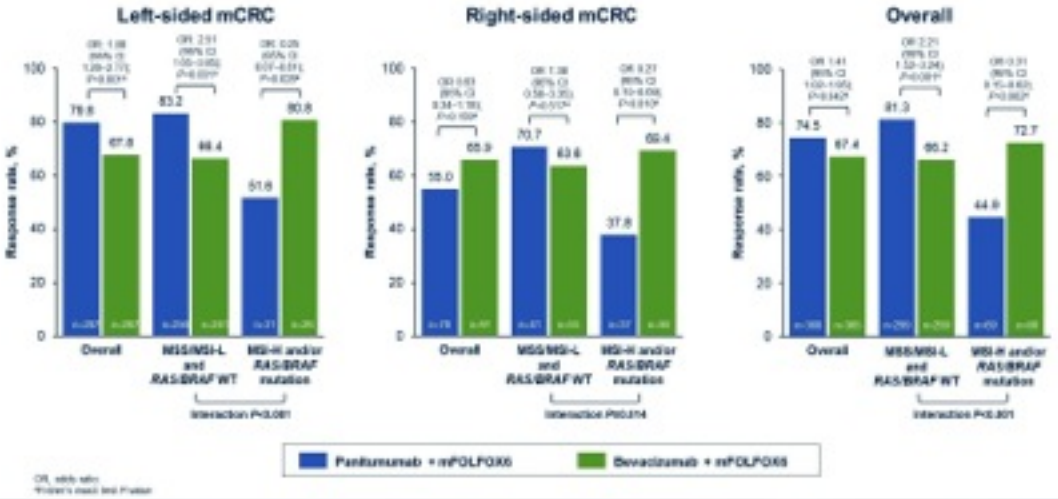
Overall survival by MSS/MSI and *RAS/BRAF* status in right-sided mCRC



	Panitumumab		Bevacizumab				*P*-value for interaction
	n	mOS, months (95% CI)	n	mOS, months (95% CI)		HR (95% CI)	
All	78	20.8 (15.1–32.8)	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)	

0.5 1.0 3.0 5.0
Panitumumab better | Bevacizumab better

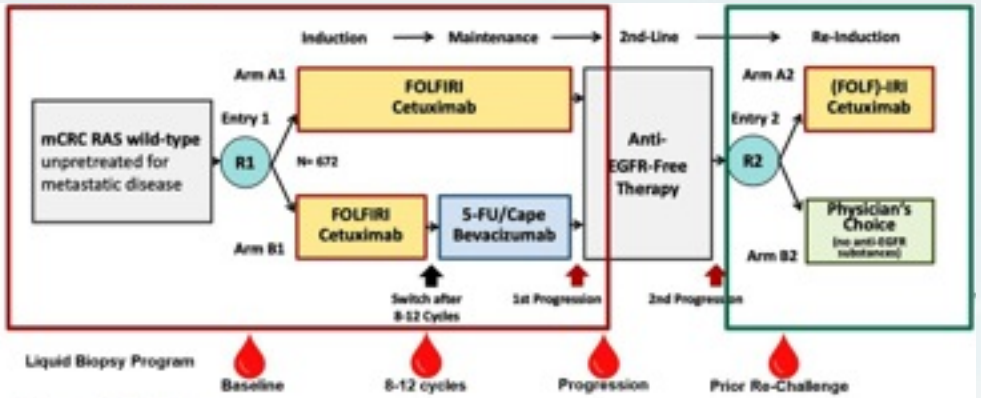
Response rate by MSS/MSI and *RAS/BRAF* status



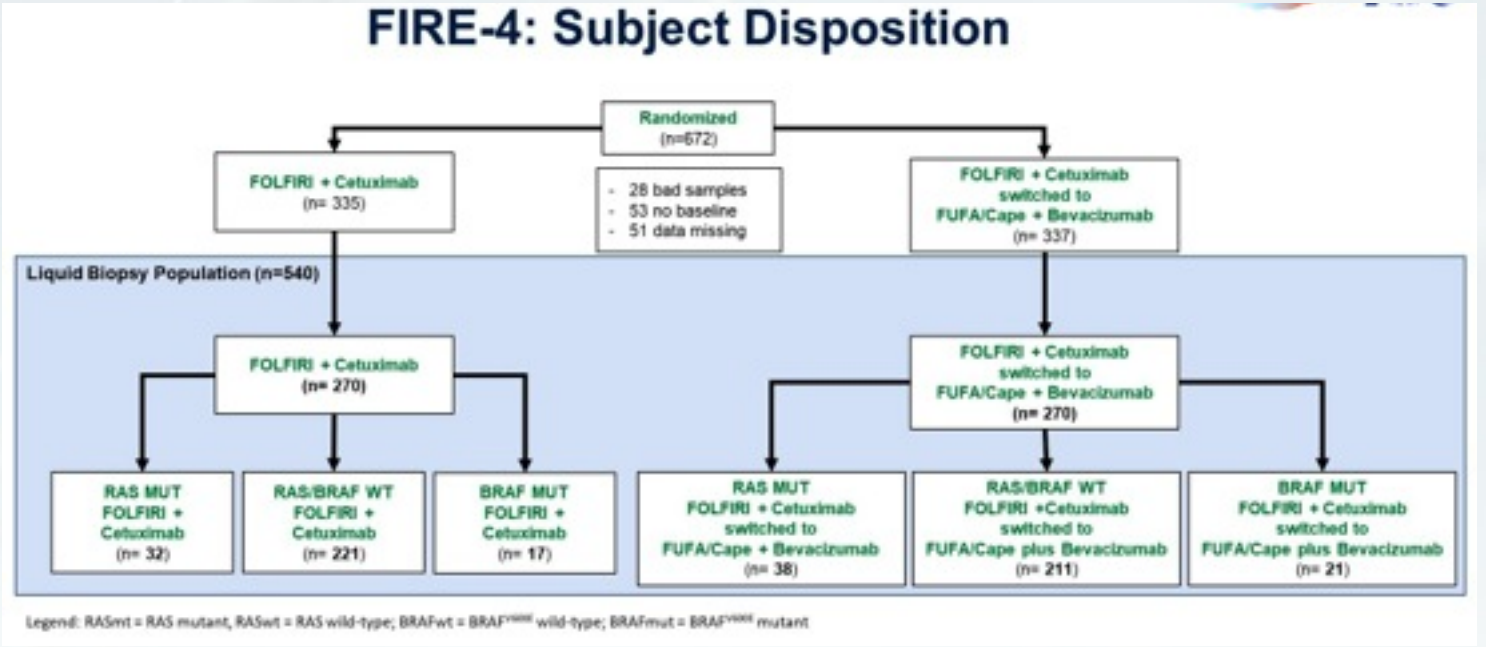
Kentaro Yamazaki. ASCO 2023 # 3508

Influence of baseline liquid biopsy results on first-line treatment efficacy of FOLFIRI plus Cetuximab in patients with tissue RAS-WT mCRC

Data of the phase III FIRE-4 study (AIO KRK-0114):



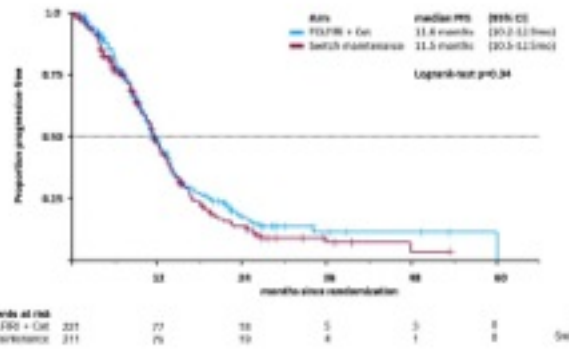
Primary Endpoint:
Overall Survival (OS) after randomisation 2



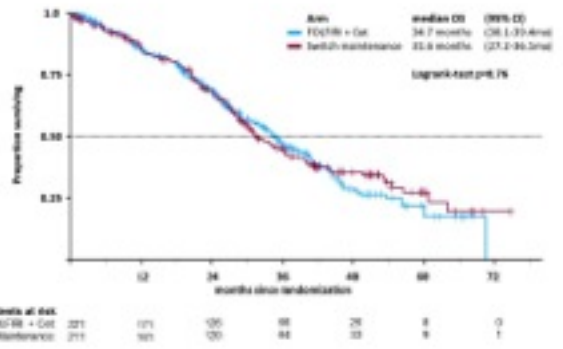
S. Stintzing. ASCO 2023 # 3507

FIRE-4: Effect of treatment arm on survival
RAS/BRAF wild-type population (n=432)

Progression-free survival (PFS)



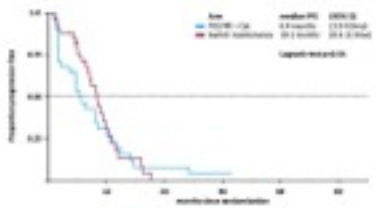
Overall survival (OS)



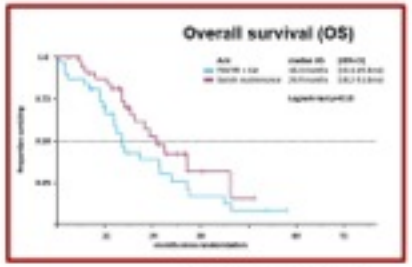
FIRE-4: Effect of treatment arm on survival

RAS mutant population (n= 72)

Progression-free survival (PFS)

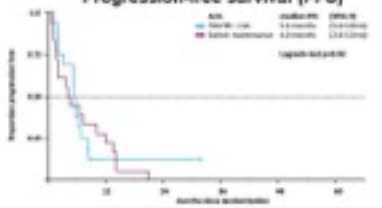


Overall survival (OS)

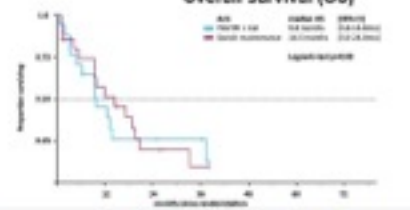


$BRAF^{V600E}$ mutant population (n= 38)

Progression-free survival (PFS)

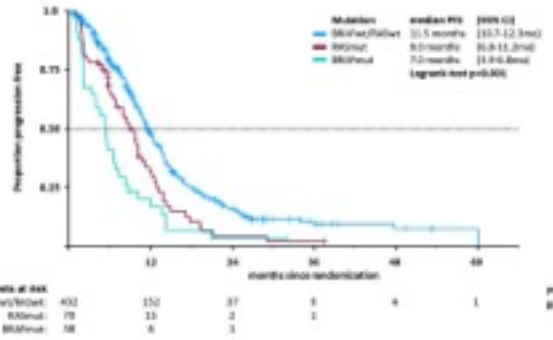


Overall survival (OS)

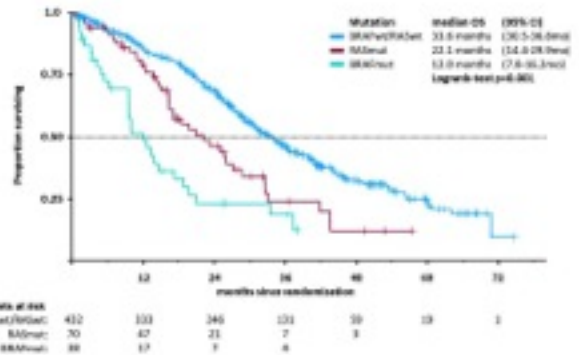


FIRE-4: Effect of baseline liquid biopsy result on survival

Progression-free survival (PFS)



Overall survival (OS)



FIRE-4: Impact of emerging RAS mutations on survival

	Liquid Biopsy Baseline → Follow Up	PFS months (95%CI)	OS months (95%CI)
Arm A	RASwt → RASwt (n=112)	10.4 (8.3 - 11.6)	36.0 (28.7-41.0)
	RASwt→ RAS mutant (n= 27)	15.1 (11.9-19.1)	35.4 (32.5-44.1)
		P*= 0.04	P*=0.73
Arm B	RASwt → RASwt (n= 142)	12.5 (11.2-13.6)	31.1 (28.5-36.4)
	RASwt→ RAS mutant (n= 19)	13.8 (8.5 - 16.8)	28.0 (20.6-39.8)
		P*= 0.47	P*=0.08
All	RASwt→ RASwt (n= 254)	11.4 (10.5-12.5)	32.7 (29.1-36.4)
	RASwt→ RAS mutant (n= 46)	13.9 (11.9-16.6)	33.6 (27.2-40.0)
		P*= 0.31	P*= 0.22

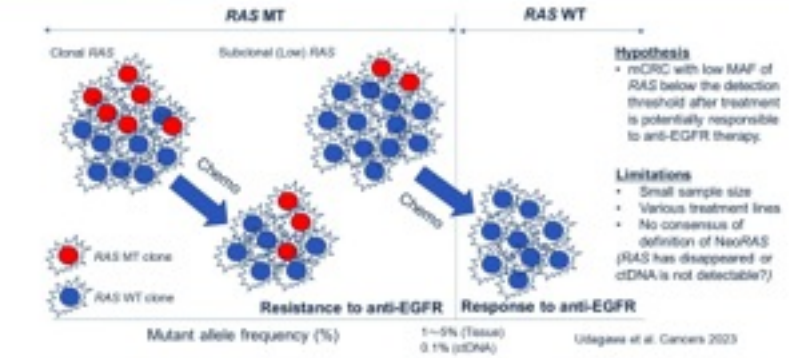
Arm A Continuous Cetuximab administration: **19.4%**
Arm B Switch 5FU Bevacizumab maintenance: **11.8%** **p= 0.049**

- **Emerging RAS mutations**:
  - were associated with a significantly longer median Cetuximab exposure (**27.6** weeks vs. **48.3** weeks (Logrank test **P= 0.001**))
  - were associated with a longer median PFS in the Cetuximab continuation arm (**10.4** months vs. **15.1** months (Logrank test P= **0.04**))
  - did ***not*** impact median OS

S. Stintzing. ASCO 2023 # 3507

Neo*RAS* wild-type metastatic colorectal cancer in the SCRUM-Japan GOZILA study

The concept of Neo*RAS* WT mCRC



Patients and methods

- mCRC patients with tissue *RAS* MT (*KRAS* or *NRAS* exon 2, 3, 4 MT) prior to initiation of 1st line chemotherapy are eligible, regardless of treatment lines (n=647).

The incidence of Neo*RAS* WT mCRC depend on the *RAS* variants

Group A			Site of original *KRAS* MT in tissue (codon)						Site of original *NRAS* MT in tissue (codon)					
			Exon 2		Exon 3		Exon 4		Exon 2		Exon 3		Exon 4	
		All	12	13	59	61	117	146	12	13	59	61	117	146
Plasma *RAS MT*	Not detected	91	64	12	0	5	0	6	3	0	0	1	0	0
	Detected	387	278	66	0	11	4	11	5	3	0	9	0	1
	Neo*RAS* (%)	19.0	18.7	15.4	0	31.3	0	35.3	37.5	0	0	10	0	0

- *KRAS* codon 12/13 (18.1%) vs other *RAS* MTs (25.1%). P = 0.21

Group B			Site of original *KRAS* MT in tissue (codon)						Site of original *NRAS* MT in tissue (codon)					
			Exon 2		Exon 3		Exon 4		Exon 2		Exon 3		Exon 4	
		All	12	13	59	61	117	146	12	13	59	61	117	146
Plasma *RAS MT*	Not detected	42	27	7	0	2	0	4	1	0	0	1	0	0
	Detected	387	278	66	0	11	4	11	5	3	0	9	0	1
	Neo*RAS* (%)	9.8	8.9	9.6	0	15.4	0	26.7	16.7	0	0	10	0	0

- *KRAS* codon 12/13 (9.0%) vs other *RAS* MTs (15.4%). P = 0.14

H. Osumi. ASCO 2023 # 3506

Logistic regression analysis for Neo*RAS* WT : Group A/B

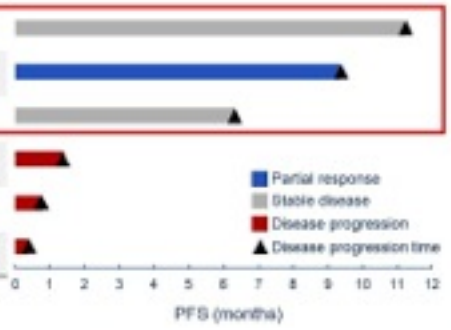
*Ref

GroupA	Odds Ratio	95% CI Lower limit	95% CI Upper limit	P. value
Liver metastasis (Negative* or Positive)	0.17	0.09	0.33	<0.00001
Lung metastasis (Negative* or Positive)	0.75	0.39	1.44	0.39
Lymph node metastasis (Negative* or Positive)	0.45	0.22	0.92	0.028
Peritoneal metastasis (Negative* or Positive)	1.45	0.75	2.83	0.27
Bone metastasis (Negative* or Positive)	0.28	0.06	1.29	0.10
Multiple organ metastases (Negative* or Positive)	0.94	0.49	1.80	0.86
Treatment lines (5th or Later* or 2nd, 3rd and 4th)	1.59	0.77	3.28	0.21
Treatment (Without* or Regorafenib)	0.79	0.19	3.31	0.74
Treatment (Without* or VEGF inhibitors)	1.72	0.85	3.48	0.13
Tissue *RAS* MT (*KRAS* codon 12, 13* or Others)	1.82	0.90	3.70	0.098

GroupB	Odds Ratio	95% CI Lower limit	95% CI Upper limit	P. value
Liver metastasis (Negative* or Positive)	0.37	0.18	0.79	0.0097
Lymph node metastasis (Negative* or Positive)	0.66	0.27	1.59	0.35
Peritoneal metastasis (Negative* or Positive)	1.35	0.63	2.87	0.44
Multiple organ metastases (Negative* or Positive)	0.66	0.30	1.45	0.30
Treatment (Without* or VEGF inhibitors)	2.27	0.96	5.35	0.061
Tissue *RAS* MT (*KRAS* codon 12, 13* or Others)	2.34	1.00	5.49	0.048

Clinical outcomes of anti-EGFR therapy for Neo*RAS* WT mCRC (n=6)

No.	Treatment	Line	Other somatic alteration	MAX MAF (%)	Group	PFS (months)
1	FOLFIRI+Panitumumab	5	None	-	A	11.1
2	Irinotecan+Cetuximab	6	*TP53, ATM*	0.31	A	9.3
3	Irinotecan+Panitumumab	5	*APC*	0.14	B	6.3
4	Irinotecan+Panitumumab	7	*APC*	0.13	B	1.4
5	Panitumumab	4	*TP53, ATM*	0.14	A	0.8
6	Panitumumab	4	*EGFR*	0.18	B	0.4



H. Osumi. ASCO 2023 # 3506

#3567: Reversion of *RAS* mutations in metastatic colorectal cancer in the CCTG CO.26 clinical trial

Authors: Florence T.H. Wu[1], James T. Topham[1], Chris J. O'Callaghan[2], Harriet Feilotter[2], Hagen F. Kennecke[3], Kimberly C. Banks[4], Daniel J. Renouf[1], Derek J. Jonker[5], Dongsheng Tu[2], Eric X. Chen[6], Jonathan M. Loree[1]

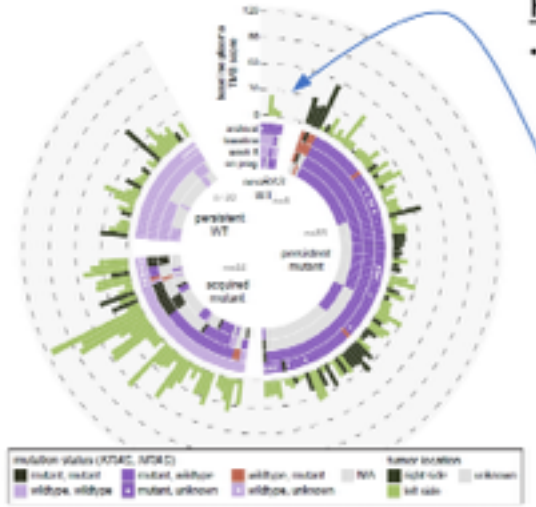
[1]BC Cancer, University of British Columbia, Vancouver, BC, Canada. [2]Canadian Clinical Trials Group, Kingston, ON, Canada. [3]Virginia Mason Cancer Center, Seattle, WA, USA. [4]Guardant Health, Redwood City, CA, USA. [5]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada. [6]Princess Margaret Cancer Centre, Toronto, ON, Canada.

Background:

- ***KRAS/NRAS* mutations** in metastatic colorectal cancer (mCRC) drive **resistance to anti-EGFR antibodies**.
- **It is unclear if *RAS* mutations are ever clonally lost, potentially uncovering a new therapeutic option for patients over time.**

Methods:

- **CCTG CO.26** was a phase II clinical trial that assessed durvalumab + tremelimumab in patients with heavily pretreated mCRC.
- For 169 patients enrolled on CO.26, **initial tissue based *KRAS* and *NRAS* mutation status** (wildtype vs. mutated) was determined by whole exome sequencing (WES) of archival tumor tissue or standard of care clinical assays.
- Patients were then divided into four categories (Fig. 1) based on the **temporal evolution** of their mCRC *RAS* mutation status, as determined by Guardant OMNI panel next-generation sequencing of circulating tumor DNA (ctDNA) from plasma collected at trial baseline, week 8, and on progression.



Results:

- Of the 95 cases that were RAS^{mut} at the time of cancer diagnosis, **6 cases (6.3%)** became RAS^{wt} by ctDNA analysis at 'baseline' or 'week 8' of the CO.26 trial. This is comparable with the 1.6% to 8.8% rates of **'neo-*RAS*-wildtype reversions'** previously reported [1].

Figure 1. Participants grouped by stability of *RAS* mutations over time.

Conclusions

- Serial ctDNA sampling is useful for detecting and delineating the duration of *RAS* mutation reversions in mCRC.
- In CO.26, mCRC *RAS* mutation reversions were rare (6.3%) and mostly transient (4.2%), likely reflecting clonal dynamics in action.

Future Directions:

- Is there a *RAS*-mutant MAF threshold below which the bulk of tumor burden can still reliably yield response to anti-EGFR therapy?
- Future studies should incorporate contemporaneous re-biopsy of tumor tissue to confirm ctDNA-detected *RAS* reversions.
- There are at least four Phase II trials underway (MoLiMoR, KAIROS, ConVertix, and CETIDYL) testing anti-EGFR therapy after detection of 'neo-*RAS*-wildtype' reversions [2].

References [1] Henry et al., Kopetz. ASCO GI, abstract #180. *Journal of Clinical Oncology* 38, no. 4_suppl (February 01, 2020) 180-180. [2] Osumi et al. Eur J Cancer. 2021;153:86–95.

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

CCTG CO.26
NCT02870920

Corresponding author:
jonathan.loree@bccancer.bc.ca

Results:

- **Reversions were often transient.** Fig. 2A,B,E,F re-acquired tumour *RAS*-mutant status by 55 to 293 (median 162.5) days after baseline.
- Four cases showed continued strong **presence of other clonal somatic mutations** when 'neo-*RAS*-wildtype' reversion occurred (Fig. 2A,B,C,E), making these less likely to be false negatives from low-volume or non-secreting tumor burden.

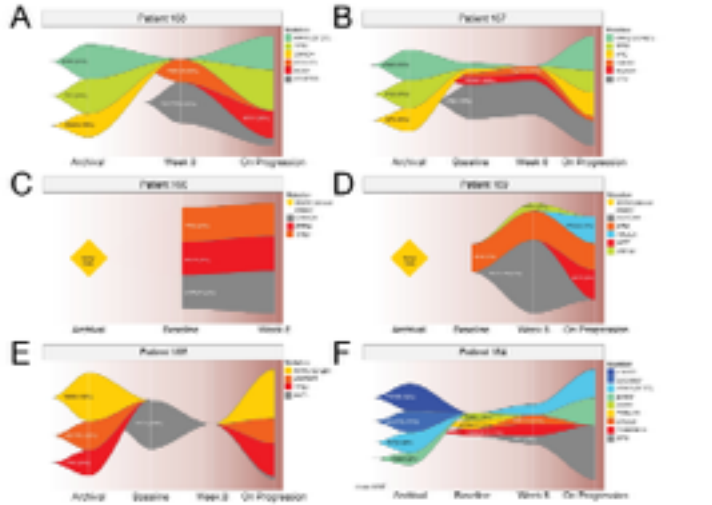


Figure 2. Clonal variant dynamics during neo-*RAS*-wildtype reversions.

- 'Neo-*RAS*-wildtype' group had lower rates of synchronous metastases, but **overall survival (OS) was not significantly different** from overall population once they reach stage IV.

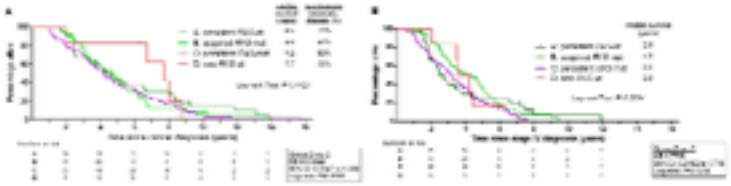


Figure 3. Kaplan-Meier analyses of OS.

Optimizing anti-EGFR therapy for metastatic colorectal cancer

1) Can ctDNA **predict outcomes** with 1st line chemotherapy + anti-EGFR?

2) Can a patient with a tissue *RAS* mutation lose that *RAS* mutation and **benefit from anti-EGFR therapy**?

3) ctDNA vs tissue NGS: What is the **optimal approach**?

Potential explanations for plasma-tissue assay discordance

- Spatial heterogeneity of *RAS/BRAF* mutations in tumor tissue

- Temporal heterogeneity: *RAS/BRAF* mutations emerged in metastatic lesions after surgical resection of the primary

- Assay sensitivity

- What is the optimal absolute/ relative allele frequency for a subclonal *RAS/BRAF* alteration to predict resistance to anti-EGFR therapy?

"NeoRAS" = Loss of driver RAS mutations

- RAS WT (non-mutated)
- RAS Mutated

Acquired resistance to anti-EGFR therapy

Sensitive to anti-EGFR → Emerging resistance → Resistant to anti-EGFR

NeoRAS: Acquired sensitivity to anti-EGFR therapy

Resistant to anti-EGFR → Emerging sensitivity → Sensitive to anti-EGFR

Potential explanations for NeoRAS WT phenomenon

- **False negatives**
  - Low ctDNA shedding
  - Other technical factors
- **Spatial heterogeneity** of *RAS* mutations in tumor tissue
- **Temporal heterogeneity** *RAS* wild-type disease has a fitness advantage(?)

Modified from Pawletz et al., JCO Precis Oncol. 2019 Dec;3:1-3.

- How to distinguish between NeoRAS WT vs "*RAS* mutation not detected" in plasma?
- Anti-EGFR therapy vs SOC?
  - Trial participation is encouraged
  - Outside of trial, consider a tissue biopsy to confirm loss of the *RAS* mutation before treating with anti-EGFR

Clinical trials evaluating anti-EGFR therapy for NeoRAS WT metastatic colorectal cancer

Study	Location	ctDNA Assay	Treatment line	Study design (N)	Description
MoLiMoR (NCT04554836)	Germany	ddPCR	1L	Randomized phase II (N= 144)	Active, not recruiting
CONVERTIX	Spain	BEAMing	2L	Single-arm phase II (N=40)	Closed: No patients met eligibility
CETIDYL (NCT04189055)	France	Real-time PCR	≥ 3L	Single-arm phase II (N=72)	Recruiting
KAIROS	Italy	Real-time PCR	2L	Single-arm phase II (N=112)	Recruiting
C-PROWESS (jRCT031210565)	Japan	ddPCR	≥ 3L	Single-arm phase II (N=112)	Recruiting

Liquid vs tissue biopsy:

- Tissue NGS and ctDNA are complementary
- Both approaches have strengths/ limitations
- Adding ctDNA to tissue testing may capture clinically relevant heterogeneity
- Choice of assay should be tailored to clinical circumstances

John Strickler. ASCO 2023

Abstract ID 3540

Does serial circulating tumor DNA (ctDNA) monitoring identify additional acquired actionable alterations in metastatic colorectal cancer (mCRC)

Jonathan M Loree[1], Adrian Bubie[2], John H Strickler[3], Michael J Overman[4], Ryan B Corcoran[5], Leylah Drusbosky[2], Scott Kopetz[4], Kanwal Raghav[4]

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Introduction

Traditionally, biomarker ascertainment occurred once for patients with mCRC. Assessment of biomarkers by liquid biopsy enables serial monitoring of disease progression and acquired resistance for patients with mCRC without repeated tissue biopsy.

Here we explore the changes in genomic profiles as detected by serial liquid biopsies to identify actionable alterations and their clonal architecture.

Methods

Detected variants from serial Guardant360 ctDNA assays for 3350 patients with mCRC with ≥1 detected somatic alterations were used to assess variant gain or loss across timepoints.

Variant changes were normalized by patient-specific limits of detection (LoD), established by the 0.1% MAF threshold of the serial assay with the lowest max somatic mutant allele frequency (MAF) per patient to control for changes in total ctDNA concentrations at each time point[1].

Relative MAF (rMAF) was defined as the variant MAF divided by the max detected MAF in that sample. Variants were defined as clonal if detected at somatic rMAF ≥ 10%.

MSI scores and status ("MSI High", "MSI Low") was evaluable for 3,030 patients with mCRC across multiple assays. Blood TMB (bTMB) score was evaluable for 1,387 patients across assays. Patients were selected for "MSI-low" and "bTMB Low" status at their initial Guardant360 assay and "MSI High" and "bTMB High" at subsequent assays.

We also assessed whether the presence of DNA damage repair pathway mutations at an initial timepoint pre-disposed patients to having greater changes in MSI score and bTMB score compared to mutation negative patients. Variants evaluated as DNA damage repair pathway mutations included: *BRCA1/2, ATM, CHEK2, MLH1, RAD51D*.

Results

Serial monitoring reveals emergence of anti-EGFR resistance and secondary therapeutic mutations for initially MAPK mutation negative mCRC patients

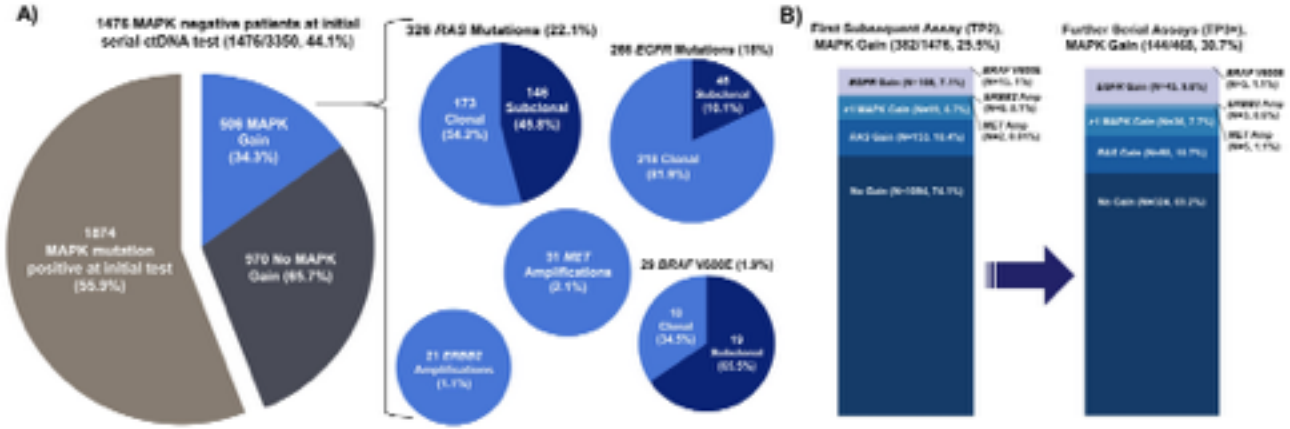
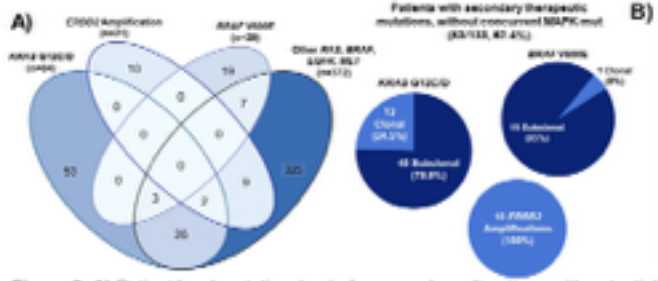


Figure 1. Patient level mutation gain across serial liquid biopsy testing time points. **A)** Of 3350 screened patients, 1476 were negative for MAPK clonal and subclonal mutations at initial assay. Mutations developed in 506 (26.5%) patients, with 382 gains (75.5%) occurring at the first subsequent test. MAPK gains across genes were more often clonal (including amplifications) than subclonal (453:213; 68%:32%). **B)** Subsequent assays demonstrate similar rate of MAPK mutation development beyond the first serial test.



	Median time between assays w/ No Gain (quartiles)	Median time to clonal gain (quartiles) [wilcox test, clonal v. none; p-value]	Median time to subclonal gain (quartiles) [wilcox test, clonal v. none; p-value]
KRAS G12C/D	213 days (112, 400)	417 days (222, 573.5) [W=15799, p<0.0001]	345 days (210, 552) [W=137742, p<0.0001]
BRAF V600E	219 days (114, 408)	308 days (150, 422) [W=43102, p=0.61]	186 days (127, 303) [W=40408, p=0.90]
ERBB2 Amplification	217 days (113, 406)	224 days (187, 414) [W=43741, p=0.08]	N/A

Figure 2. A) Patient level mutational gain for secondary alterations with potential therapeutic relevance (*BRAF* V600E, *KRAS* G12C/D, *ERBB2* amp) in initially MAPK negative patients. 83/133 alterations detected emerged without concurrent MAPK mutation. Subclonal gains (59/83, 71.1%) were more common than clonal gains (24/83, 28.9%). **B)** Time to variant emergence between initial assay and subsequent serial test. Therapeutic mutations emerged a median of 372 days after initial liquid biopsy, with *KRAS* G12C/D clonal and subclonal mutations detected in assays significantly longer than assays with no gains.

Impact of DNA repair pathway alterations (*BRCA1/2, ATM, CHEK2, MLH1, RAD51D*) on acquisition of MSI and blood TMB (bTMB) ≥20M/Mb at a future time point for patients without these alterations at baseline.

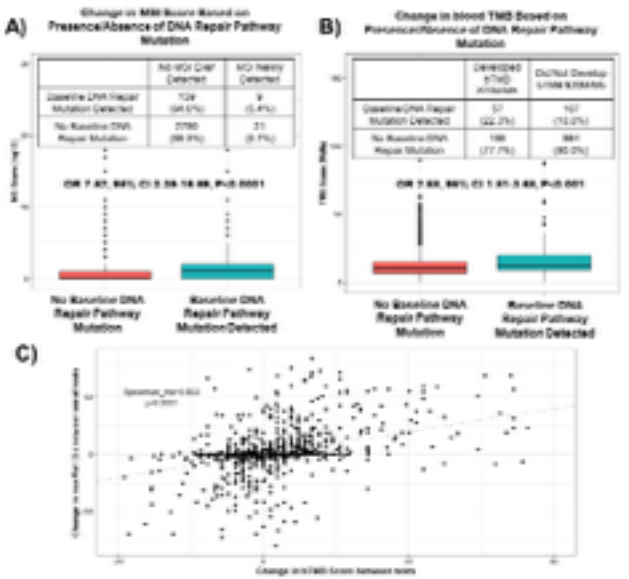


Figure 3. Changes in **A)** MSI scores and **B)** bTMB were more common for patients with DNA repair pathway mutations on their initial assay. We also noted that **C)** increase in bTMB is significantly correlated with increasing max somatic MAF (ρ=0.504, p<0.0001).

Conclusions

- In this large cohort, serial ctDNA appears feasible to identify acquired alterations. Many of these alterations have therapeutic implications and further work is needed to understand if and how to target acquired alterations.

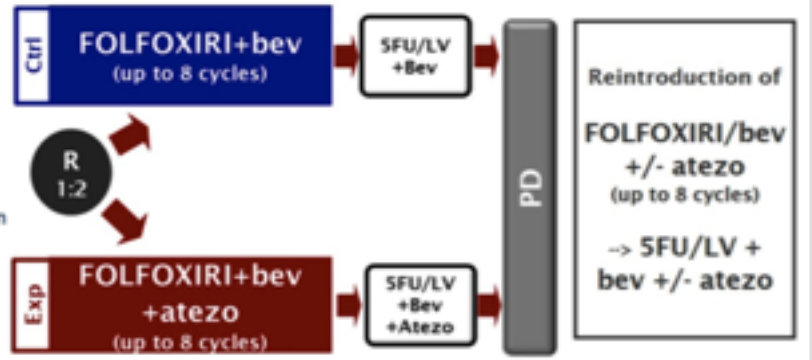
References: 1. Lanman RB, Mortimer SA, Zill OA, et al. Analytical and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA. PLoS One. 2015; 10(10): 1-22.

Corresponding Author Email: jonathan.loree@bccancer.bc.ca

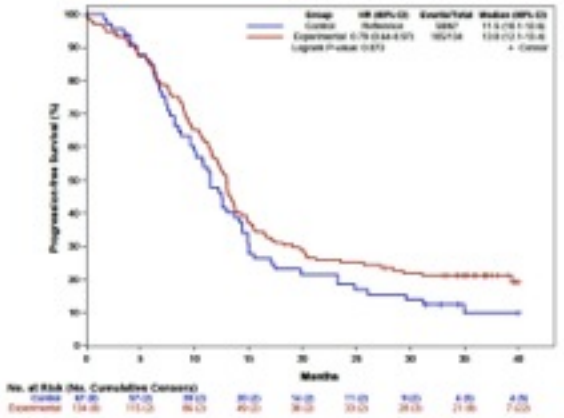
FOLFOXIRI plus bevacizumab and atezolizumab as upfront treatment of unresectable mCRC patients: updated and overall survival results of the phase II randomized AtezoTRIBE study

Key eligibility criteria

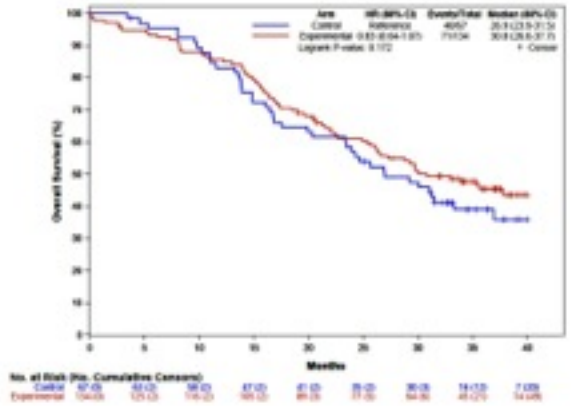
- Previously untreated, unresectable and RECIST v1.1-measurable mCRC
- Age 18-75 years
- ECOG PS ≤ 2 (ECOG PS= 0 if age= 71-75 years)
- Adjuvant oxaliplatin-containing chemotherapy not allowed
- Adjuvant fluoropyrimidine monotherapy allowed if more than 6 months elapsed between the end of adjuvant and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



Updated PFS – pMMR cohort



Overall Survival – pMMR cohort

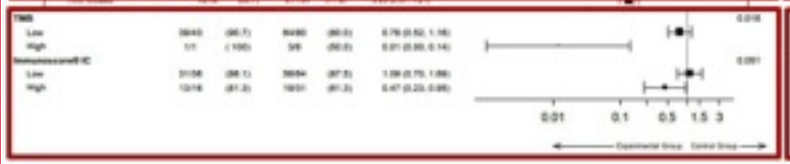


Subgroup analyses for PFS and OS – pMMR cohort

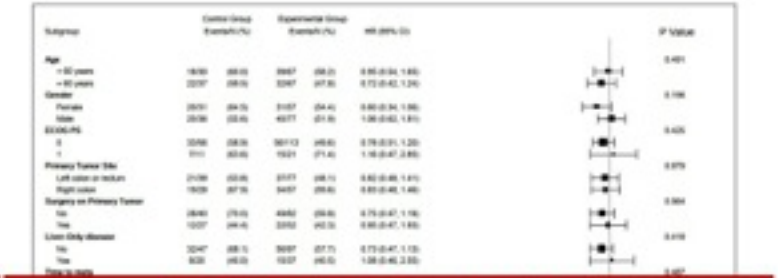
Progression-Free Survival

Multivariate Cox proportional hazard regression model

- TMB: *P* value= 0.014
- Immunoscore IC: *P* value= 0.060

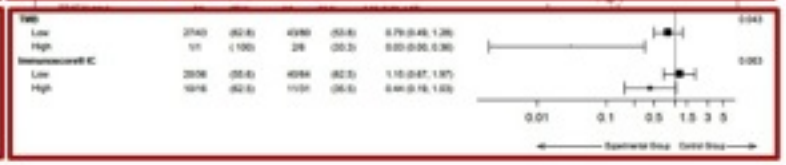


Overall Survival



Multivariate Cox proportional hazard regression model

- TMB: *P* value= 0.033
- Immunoscore IC: *P* value= 0.022



Carlotta Antoniotti. ASCO 2023 # 3500

Gut microbiome composition as predictor of the efficacy of adding atezolizumab to first-line FOLFOXIRI plus bevacizumab in metastatic colorectal cancer: a translational analysis of the AtezoTRIBE study.

Abstract Number: 3534

Federica Marmorino, Gianmarco Piccinno, Daniele Rossini, Filippo Ghelardi, Sabina Murgioni , Lisa Salvatore, Vincenzo Nasca, Carlotta Antoniotti, Francesca Daniel, Francesco Schietroma, Veronica Conca, Carolina Alves Costa Silva, Emiliano Tamburini, Stefano Tamberi, Alessandro Passardi, Lorenzo Antonuzzo, Raffaella D'Onofrio, Laurence Zitvogel, Chiara Cremolini and Lisa Derosa

Poster Board #: 234

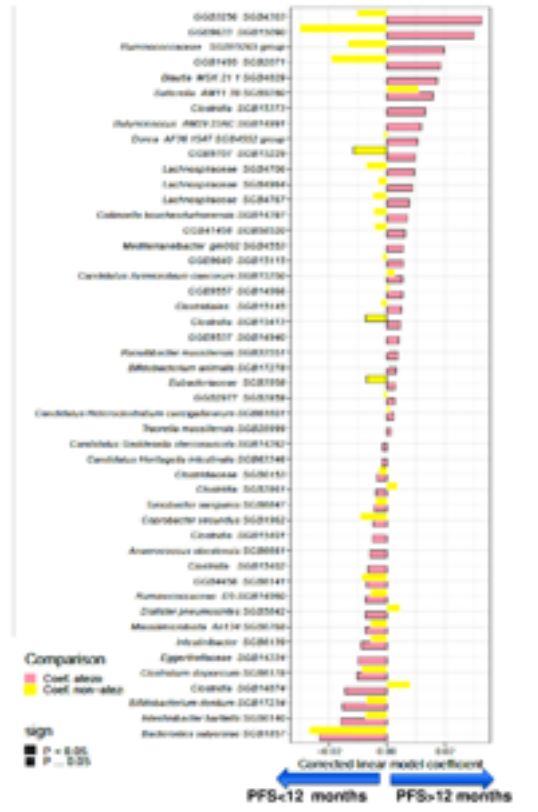
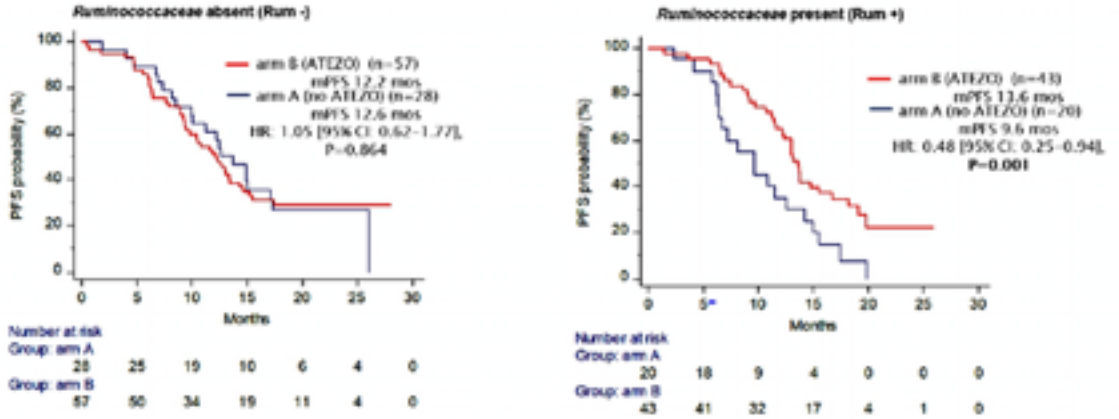
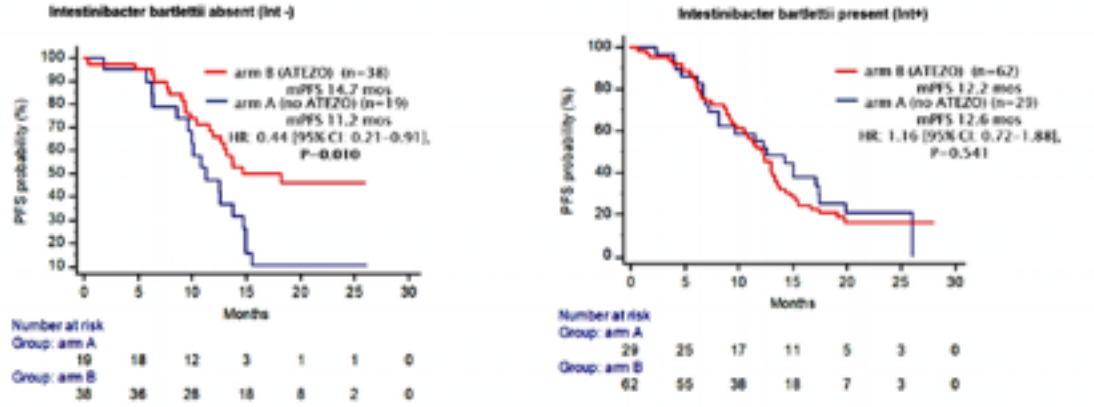


Figure 3. KM for PFS according to treatment arm and *Ruminococcaceae unclass* prevalence



P for interaction= 0.06

Figure 4. KM for PFS according to treatment arm and *Intestinibacter bartlettii* prevalence



P for interaction= 0.009

First-line nivolumab + ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 64-month follow-up from CheckMate 142

Heinz-Josef Lenz | Michael J. Overman | Eric Van Cutsem | Maria Luisa Limon | Ke Yeung Yoon Wong | Hein Hendlisz | Massimo Aglietta | Pilar Garcia-Alfonso | Bart Neyns | Fabio Grizzi

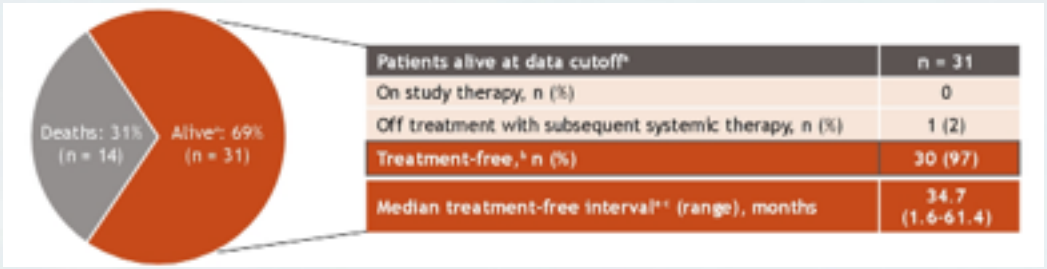
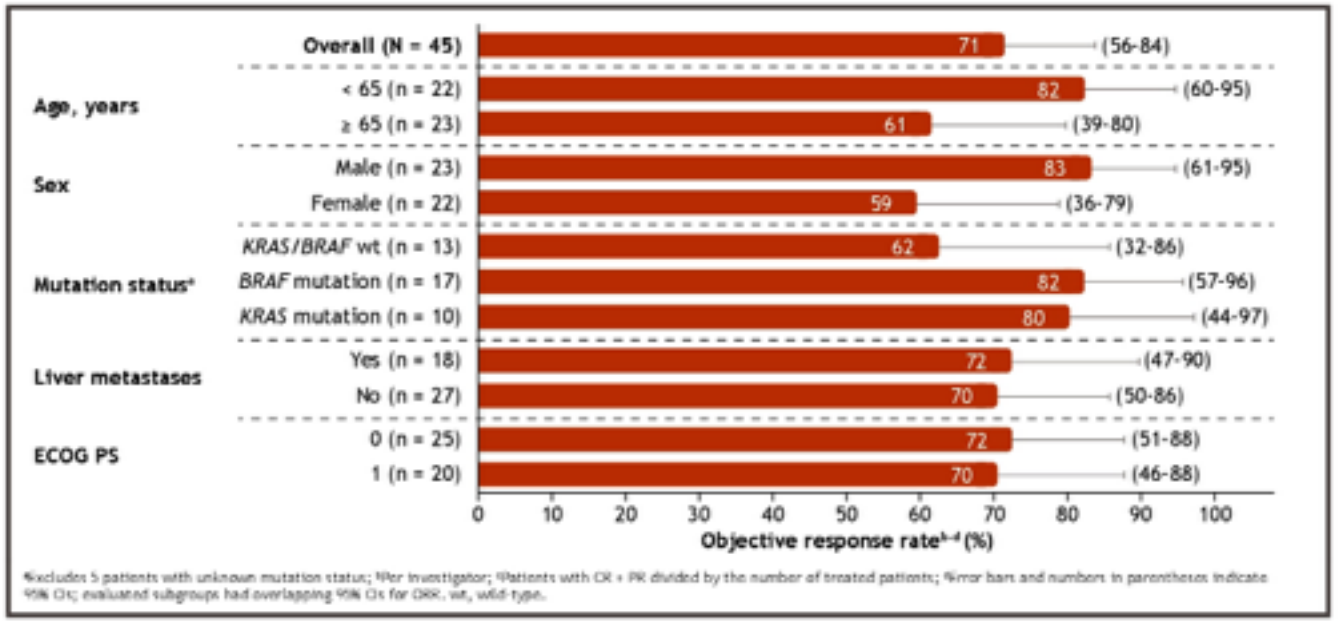


Figure 2. Objective response rate by subgroup



[a]Excludes 5 patients with unknown mutation status; [b]Per investigator; [c]Patients with CR + PR divided by the number of treated patients; [d]Error bars and numbers in parentheses indicate 95% CIs; evaluated subgroups had overlapping 95% CIs for ORR. wt, wild type.

– At 60 months, PFS and OS rates were 55% and 67%, respectively

Exploratory biomarker analysis

- In TMB-evaluable patients (n = 20; **Figure 7**):
  - ORR was 50% in patients with TMB-low tumors and 70% in those with TMB-high tumors
  - Median PFS was 17.4 months in patients with TMB-low tumors and not reached in those with TMB-high tumors
  - Median OS was 28.8 months in patients with TMB-low tumors and not reached in those with TMB-high tumors

H-J Lenz. ASCO 2023 # 3550

Molecular Targets in Colorectal Cancer

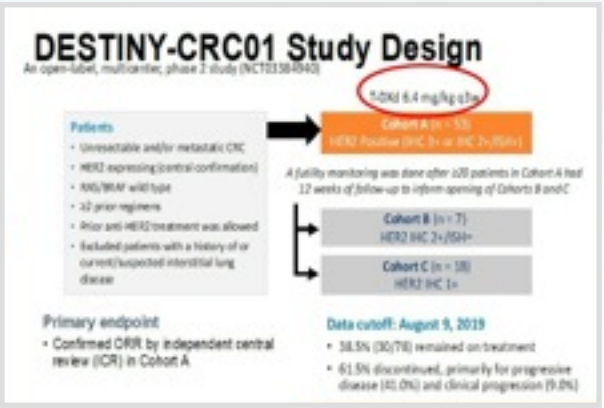
Moving Beyond EGFR, BRAF, and dMMR

- Targets:
  - HER2 amplification
  - KRAS G12C mutation
  - NTRK fusion
  - RET fusion

Anti-HER2 strategies in mCRC

	Treatment	n	Prior Lines of Treatment	Mutational Status	mPFS (m)	ORR (%)
MyPathway	Trastuzumab + pertuzumab	57	≥1	RAS WT	2.9	32
TAPUR	Trastuzumab + pertuzumab	28	≥0	NS	NR	14
TRIUMPH	Trastuzumab + pertuzumab	27 (Tissue)	≥1	RAS WT	4.0	30
		25 (ctDNA)			3.1	25
Monoclonal antibody + TKI						
HERACLES-A	Trastuzumab + lapatinib	35	≥2	KRAS WT	4.7	28
Yuan et al.	Trastuzumab + pyrotinib	11	≥2	RAS WT and mutated	NR	27
MOUNTAINEER	Trastuzumab + tucatinib	23	≥2	RAS WT	8.1	52
ADCs						
HERACLES-B	Pertuzumab + T-DM1	31	≥2	RAS/BRAF WT	4.1	10
DESTINY-CRC01	TD	53 (Cohort A)	≥2	RAS/BRAF WT	6.9	45

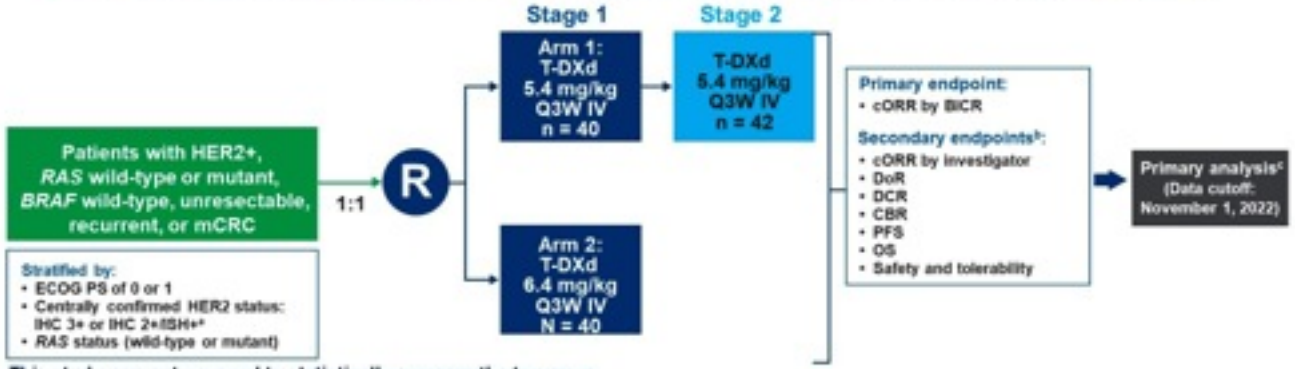
FDA Approval Jan 2023



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

A randomized, blinded, 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.

Baseline Characteristics

	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 age, years (range)	58.2 (26-78)	60.6 (30-84)	59.1 (26-84)	62.3 (35-81)
Sex, n (%)				
Male	21 (52.5)	24 (57.1)	45 (54.9)	19 (47.5)
Region, n (%)				
Asia-Pacific	25 (62.5)	22 (52.4)	47 (57.3)	24 (60.0)
US	5 (12.5)	1 (2.4)	6 (7.3)	2 (5.0)
Europe	10 (25.0)	19 (45.2)	29 (35.4)	14 (35.0)
HER2 status, n (%)				
IHC 3+	32 (80.0)	32 (76.2)	64 (78.0)	34 (85.0)
IHC 2+/ISH+	8 (20.0)	10 (23.8)	18 (22.0)	6 (15.0)
ECOG PS, n (%)				
0	22 (55.0)	24 (57.1)	46 (56.1)	22 (55.0)
1	18 (45.0)	18 (42.9)	36 (43.9)	18 (45.0)
***RAS* status, n (%)**				
Wild-type	34 (85.0)	34 (81.0)	68 (82.9)	34 (85.0)
Mutant	6 (15.0)	8 (19.0)	14 (17.1)	6 (15.0)
HER2/*RAS* status, n (%)				
IHC 2+ ISH+/wild-type	7 (17.5)	5 (11.9)	12 (14.6)	6 (15.0)
IHC 2+ ISH+/mutant	1 (2.5)	5 (11.9)	6 (7.3)	0
IHC 3+/wild-type	27 (67.5)	29 (69.0)	56 (68.3)	28 (70.0)
IHC 3+/mutant	5 (12.5)	3 (7.1)	8 (9.8)	6 (15.0)
Liver metastases at baseline, n (%)	29 (72.5)	30 (71.4)	59 (72.0)	26 (65.0)
CNS metastases at baseline, n (%)	3 (7.5)	0	3 (3.7)	1 (2.5)
Primary tumor site, n (%)				
Left colon[a]	32 (80.0)	29 (69.0)	61 (74.4)	34 (85.0)
Rectum	15 (37.5)	12 (28.6)	27 (32.9)	19 (47.5)
Right colon[b]	8 (20.0)	13 (31.0)	21 (25.6)	6 (15.0)

Prior Treatment

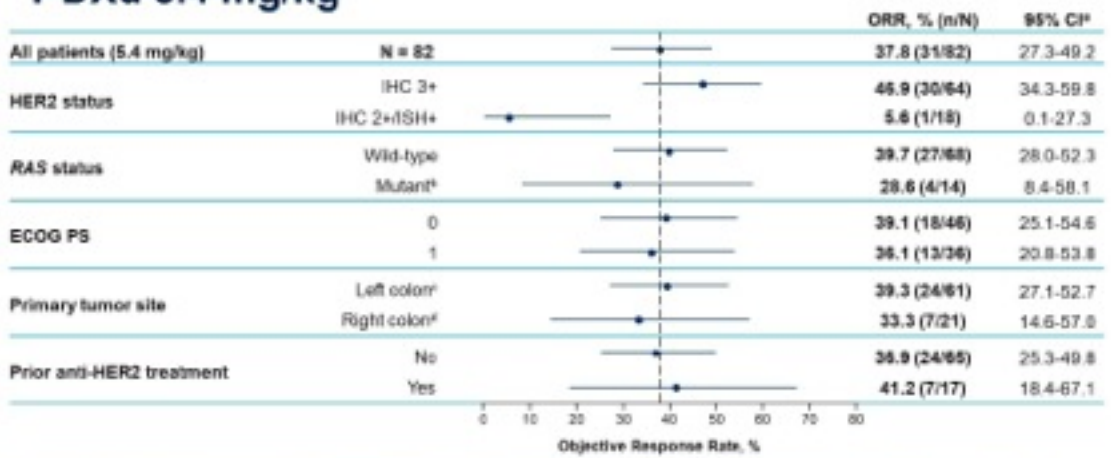
	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	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)

K. Raghav. ASCO 2023 # 3501

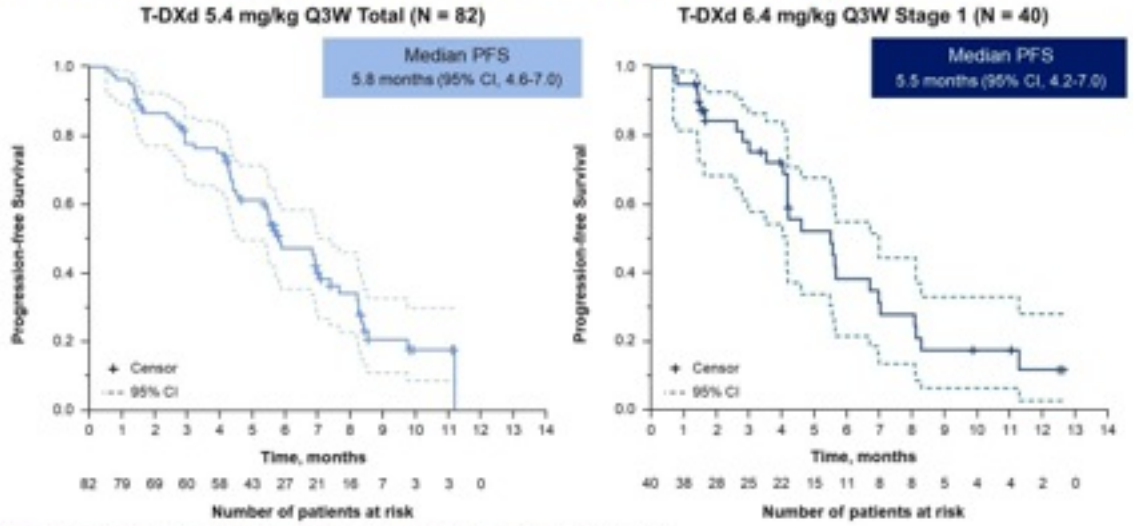
Efficacy Results

	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)

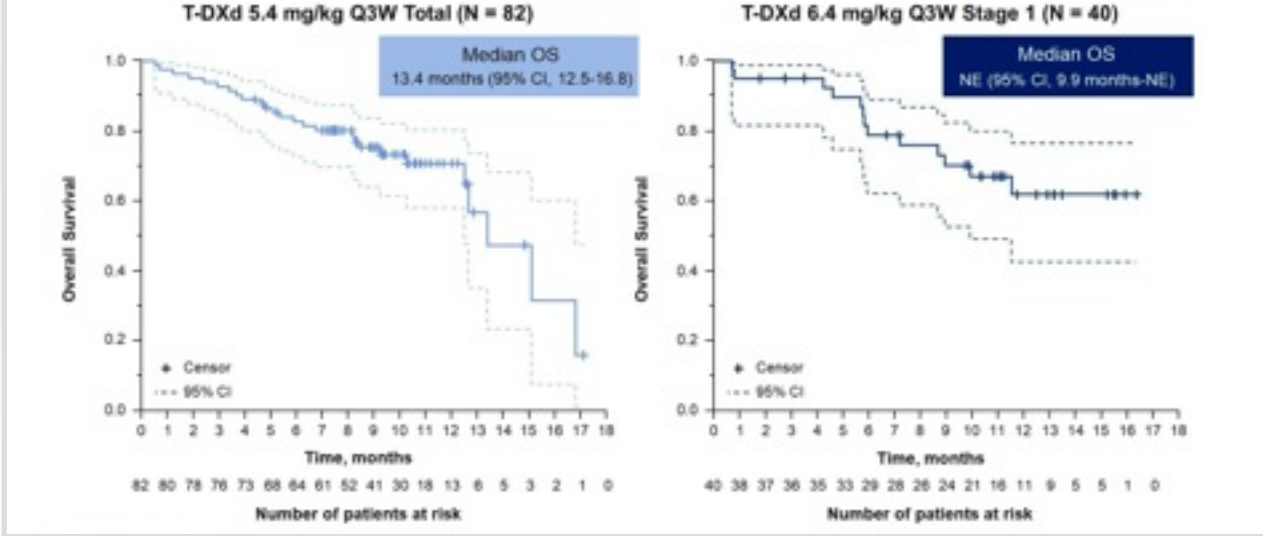
Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg



Median Progression-Free Survival by BICR



Median Overall Survival



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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)

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)

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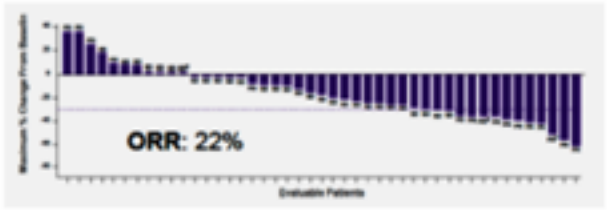
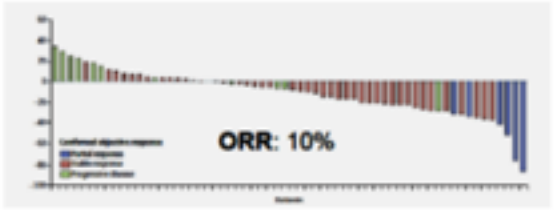
KRAS G12C inhibitors in mCRC

Adagrasib



Weiss et al, ESMO 2021

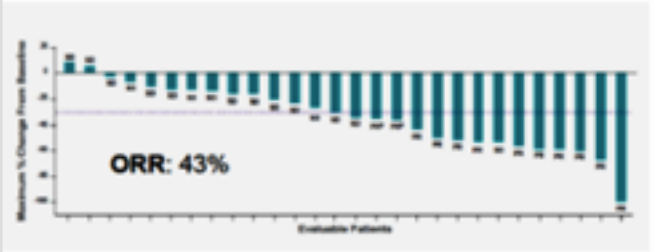
Sotorasib



Fakih et al, Lancet Oncol 2022

KRAS G12C inhibitors + anti-EGFR in mCRC

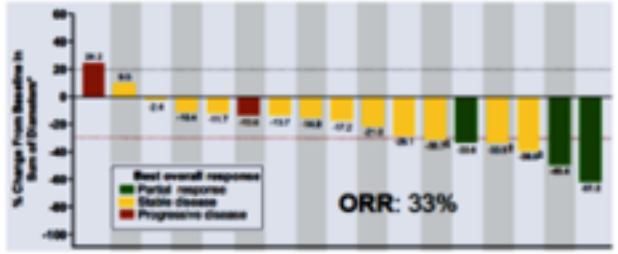
Adagrasib + Cetuximab



Updated **ORR** (n=28): 46%

Weiss et al, ESMO 2021
Klempner et al, ESMO 2022

Sotorasib + Panitumumab

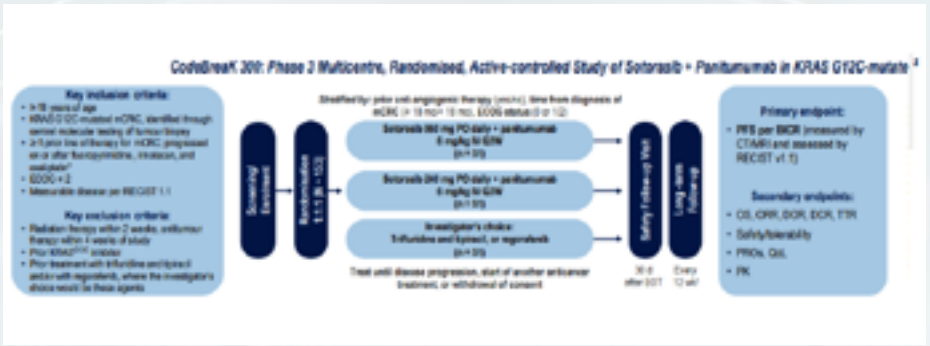


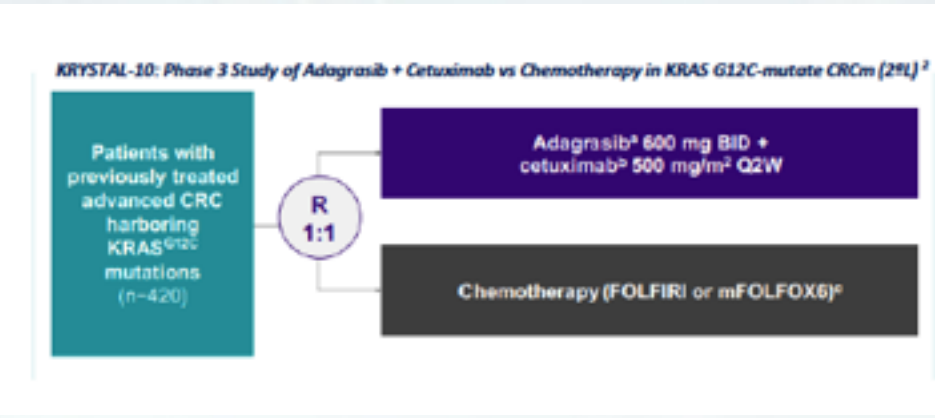
Updated **ORR** (n=40): 30%

Fakih et al, ESMO 2021
Kuboki et al, ESMO 2022

KRYSTAL-1

CodeBreaK 101



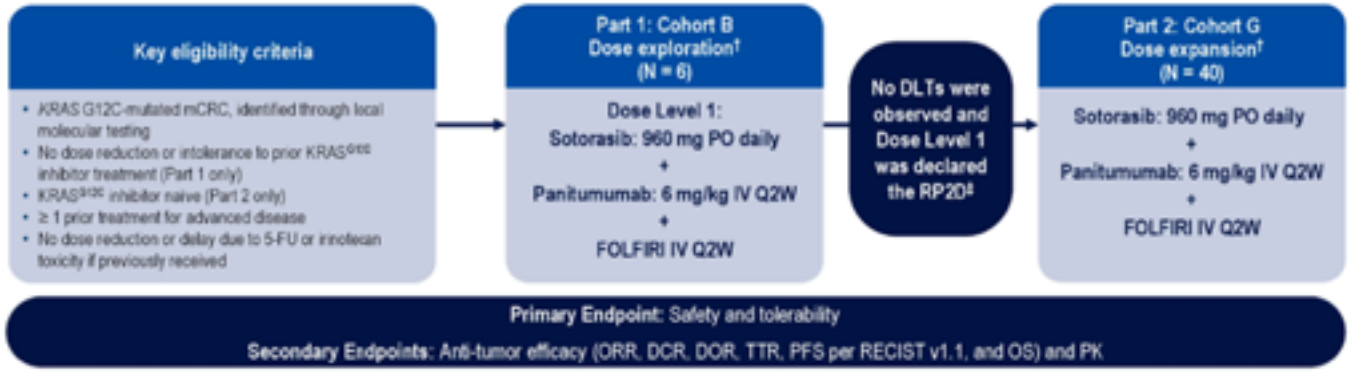


Sotorasib (Soto) Plus Panitumumab (Pmab) and FOLFIRI for Previously Treated *KRAS* G12C-mutated Metastatic Colorectal Cancer (mCRC): CodeBreaK 101 Phase 1b Safety and Efficacy

David S. Hong,[1] Yasutoshi Kuboki,[2] John H. Strickler,[3] Marwan Fakih,[4] Hélène Houssiau,[5] Timothy J. Price,[6] Elena Élez,[7] Salvatore Siena,[8] Emily Chan,[9] Jane Hippenmeyer,[9] Panli Cardona,[9] Qui Tran,[9] Toshiki Masuishi[10]

STUDY SCHEMA

CodeBreaK 101 Subprotocol H phase 1b, multicenter, open-label study: sotorasib + panitumumab + FOLFIRI in previously treated KRAS G12C-mutated mCRC*



- All patients received prior fluoropyrimidine, and 70% of patients received prior irinotecan
- Patients received a median of 2 prior lines of therapy with approximately one-third each receiving the study regimen as second-line, third-line or ≥ fourth-line therapy

- No clinically meaningful PK interaction was observed between sotorasib and irinotecan

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

- Confirmed ORR (all partial responses) was 55% (95% CI: 38.7, 70.2) and DCR was 93% (95%CI: 80.5, 98.5), with 2 additional patients with unconfirmed responses awaiting confirmatory scan

Response by investigator assessment*	Part 1 Sotorasib + Panitumumab + FOLFIRI (n = 6)	Part 2 Sotorasib + Panitumumab + FOLFIRI (n = 36)	Total (N = 42*)
ORR confirmed (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	3 (50)	13 (36)	16 (38)
PD	0	2 (6)	2 (5)
Unavailable	0	1 (3)	1 (2)
DCR (95% CI)	6 (100) (54.1, 100.0)	33 (92) (77.5, 98.3)	**39 (93)** (80.5, 98.5)

Abstract number: 3586

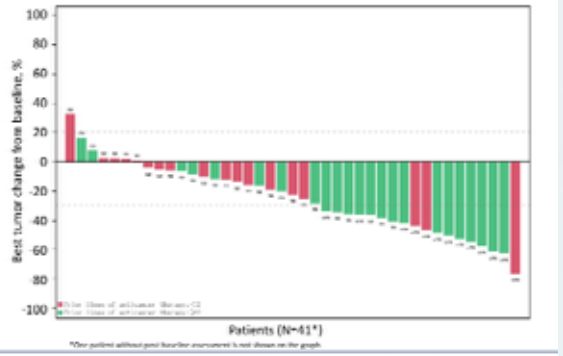
Efficacy and safety of IBI351 (GFH925) monotherapy in metastatic colorectal cancer harboring KRASG12C mutation: preliminary results from a pooled analysis of two phase I studies

Ying Yuan[1], Yanhong Deng[2], Yongdong Jin[3], Yueyin Pan[4], Cunji Wang[5], Zhiwu Wang[6], Zhiye Zhang[7], Xiangjiao Meng[8], Yi Hu[9], Mingfang Zhao[10], Huijuan Wang[11], Nong Yang[12], Dongde Wu[13], Xiaorong Dong[14], Dingzhi Huang[15], Meili Sun[16], Lian Liu[17], Dong Hua[18], Zengqing Guo[19], Kefeng Ding[1]

BACKGROUND

- $KRAS^{G12C}$ oncogenic mutation occurs in 3-4% of colorectal cancer (CRC),[1] and it has shown to be a promising target in $KRAS^{G12C}$ mutant cancers.
- IBI351 (GFH925) is an irreversibly covalent inhibitor of $KRAS^{G12C}$ and has demonstrated promising anti-tumor activity with acceptable safety in advanced solid tumors.[2]
- We present a pooled analysis of two phase I studies to evaluate the efficacy and safety of IBI351 (GFH925) monotherapy for metastatic CRC harboring $KRAS^{G12C}$ mutation.

Figure 1. Tumor change in target lesion size from baseline at 600 mg BID



*One patient without post-baseline assessment is not shown on the graph.

Abstract #3563

Safety and Efficacy of D-1553 in KRAS G12C-mutated Colorectal Cancer: Results from a Phase I/II Study

Dan-yun Ruan[1], Myung Ah Lee[2], Yanhong Deng[3], Keun-Wook Lee[4], Michael Millward[5], Jaspreet Singh Grewal[6], Shirish M. Gadgeel[7], Rachel E. Sanborn[8], Xinfang Hou[9], Shaozhong Wei[10], Seok Jae Huh[11], Fu-rong Liu[1], Xiaoxi Xie[12], Ziyong Xiang[12], Zhe Shi[12], Yaolin Wang[12], Ling Zhang (ling.zhang@inventisbio.com)[12], Gary Richardson[13], Rui-hua Xu[1]

METHODS

Figure 1. Study Design

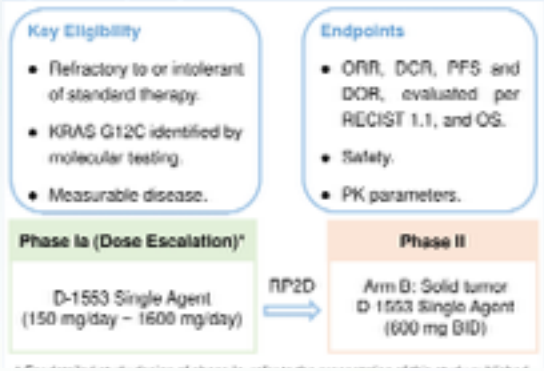
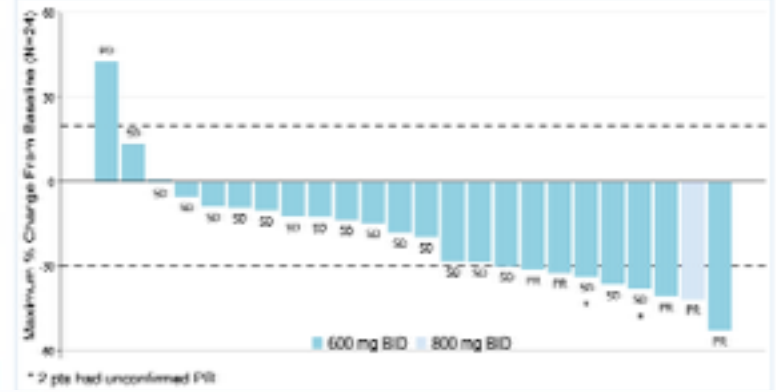
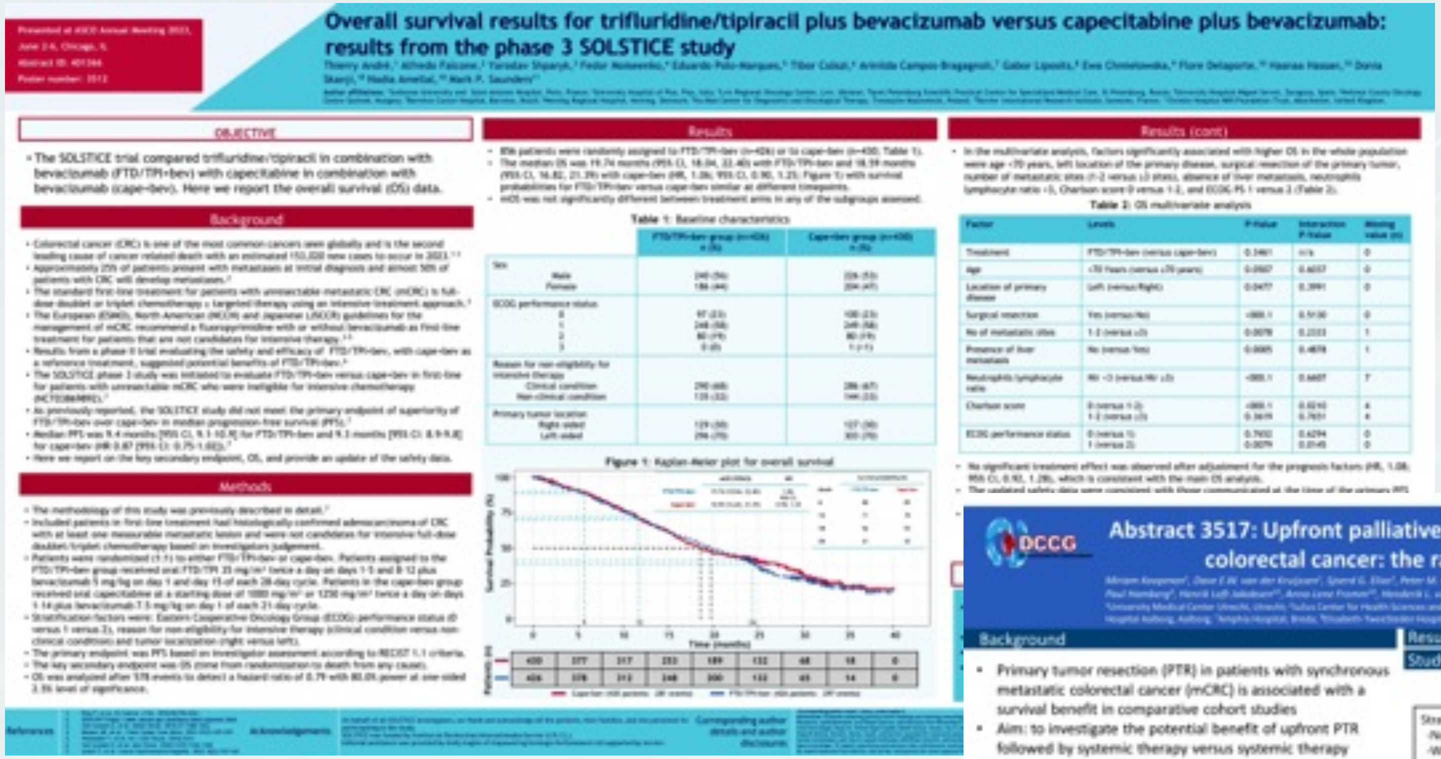


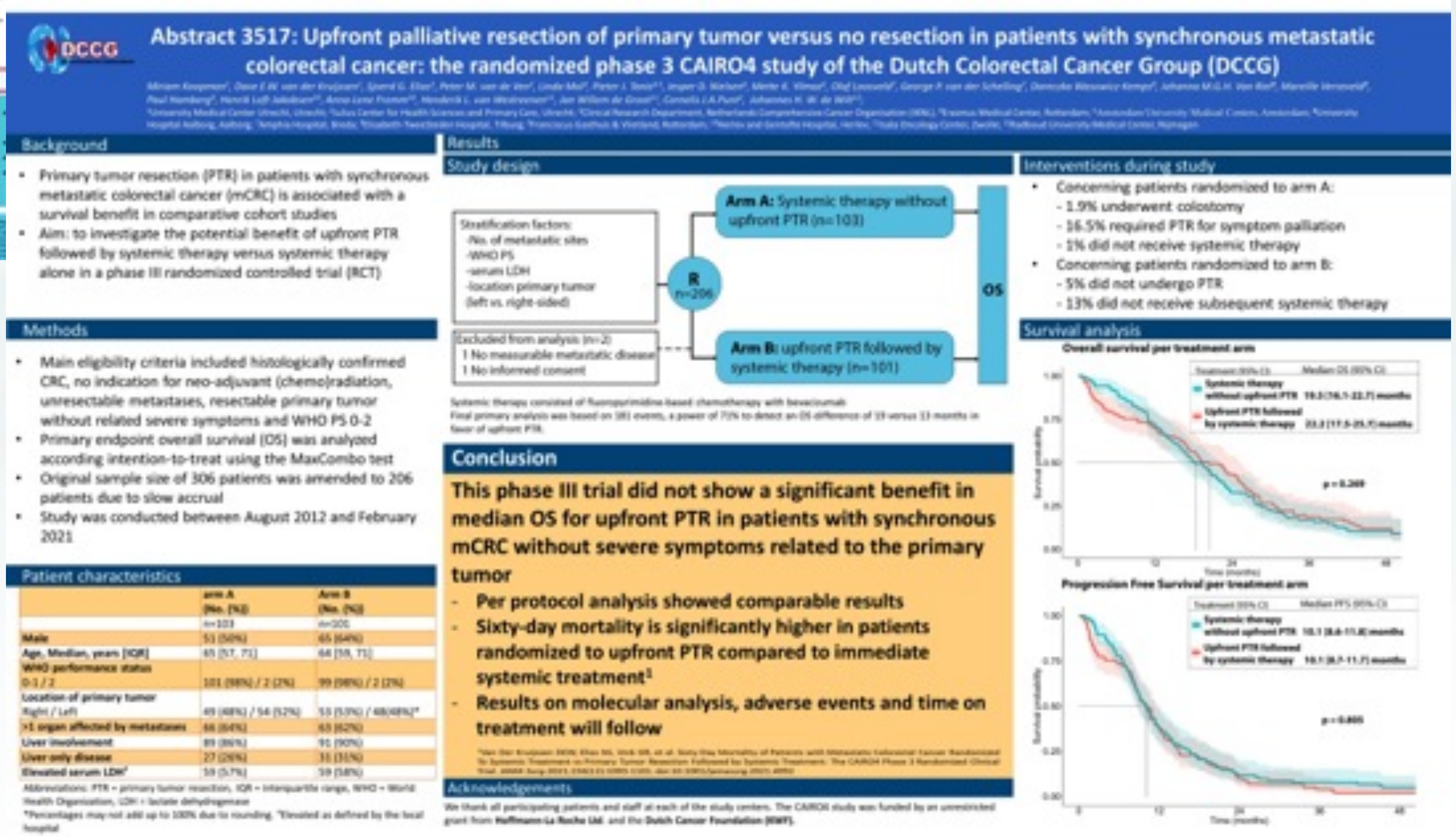
Figure 3. Best Tumor Response and Tumor Burden Change



* 2 pts had unconfirmed PR



Overall survival results for trifluridine/tipiracil plus bevacizumab versus capecitabine plus bevacizumab: results from the phase 3 SOLSTICE study
OBJECTIVE
The SOLSTICE trial compared trifluridine/tipiracil in combination with bevacizumab (FTD/TPI+bev) with capecitabine in combination with bevacizumab (cape-bev). Here we report the overall survival (OS) data.
Background
Methods
Results
Table 1: Baseline characteristics
Figure 1: Kaplan-Meier plot for overall survival
Results (cont)
Table 2: OS multivariate analysis



DCCG
Abstract 3517: Upfront palliative resection of primary tumor versus no resection in patients with synchronous metastatic colorectal cancer: the randomized phase 3 CAIRO4 study of the Dutch Colorectal Cancer Group (DCCG)
Background
Primary tumor resection (PTR) in patients with synchronous metastatic colorectal cancer (mCRC) is associated with a survival benefit in comparative cohort studies
Aim: to investigate the potential benefit of upfront PTR followed by systemic therapy versus systemic therapy alone in a phase III randomized controlled trial (RCT)
Methods
Main eligibility criteria included histologically confirmed CRC, no indication for neo-adjuvant (chemo)radiation, unresectable metastases, resectable primary tumor without related severe symptoms and WHO PS 0-2
Primary endpoint overall survival (OS) was analyzed according intention-to-treat using the MaxCombo test
Original sample size of 306 patients was amended to 206 patients due to slow accrual
Study was conducted between August 2012 and February 2021
Patient characteristics
Results
Study design
Stratification factors:
-No. of metastatic sites
-WHO PS
-serum LDH
-location primary tumor (left vs. right-sided)
R n=206
Arm A: Systemic therapy without upfront PTR (n=103)
Arm B: upfront PTR followed by systemic therapy (n=101)
OS
Excluded from analysis (n=2)
1 No measurable metastatic disease
1 No informed consent
Interventions during study
Concerning patients randomized to arm A:
- 1.9% underwent colostomy
- 16.5% required PTR for symptom palliation
- 1% did not receive systemic therapy
Concerning patients randomized to arm B:
- 5% did not undergo PTR
- 13% did not receive subsequent systemic therapy
Survival analysis
Overall survival per treatment arm
Progression Free Survival per treatment arm
Conclusion
This phase III trial did not show a significant benefit in median OS for upfront PTR in patients with synchronous mCRC without severe symptoms related to the primary tumor
- Per protocol analysis showed comparable results
- Sixty-day mortality is significantly higher in patients randomized to upfront PTR compared to immediate systemic treatment[1]
- Results on molecular analysis, adverse events and time on treatment will follow
Acknowledgements

XXIII JORNADA DE REVISIÓN DEL

CONGRESO AMERICANO DE ONCOLOGÍA

Muchas gracias