Baptist Health

Miami Cancer Institute

Updates in Colorectal Cancer

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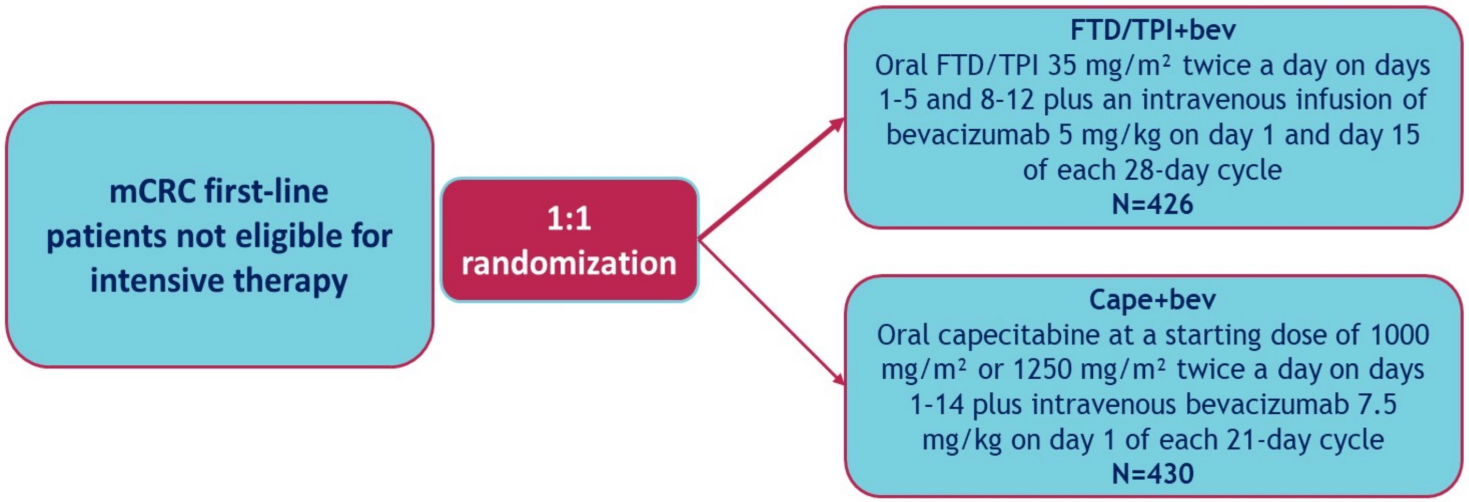
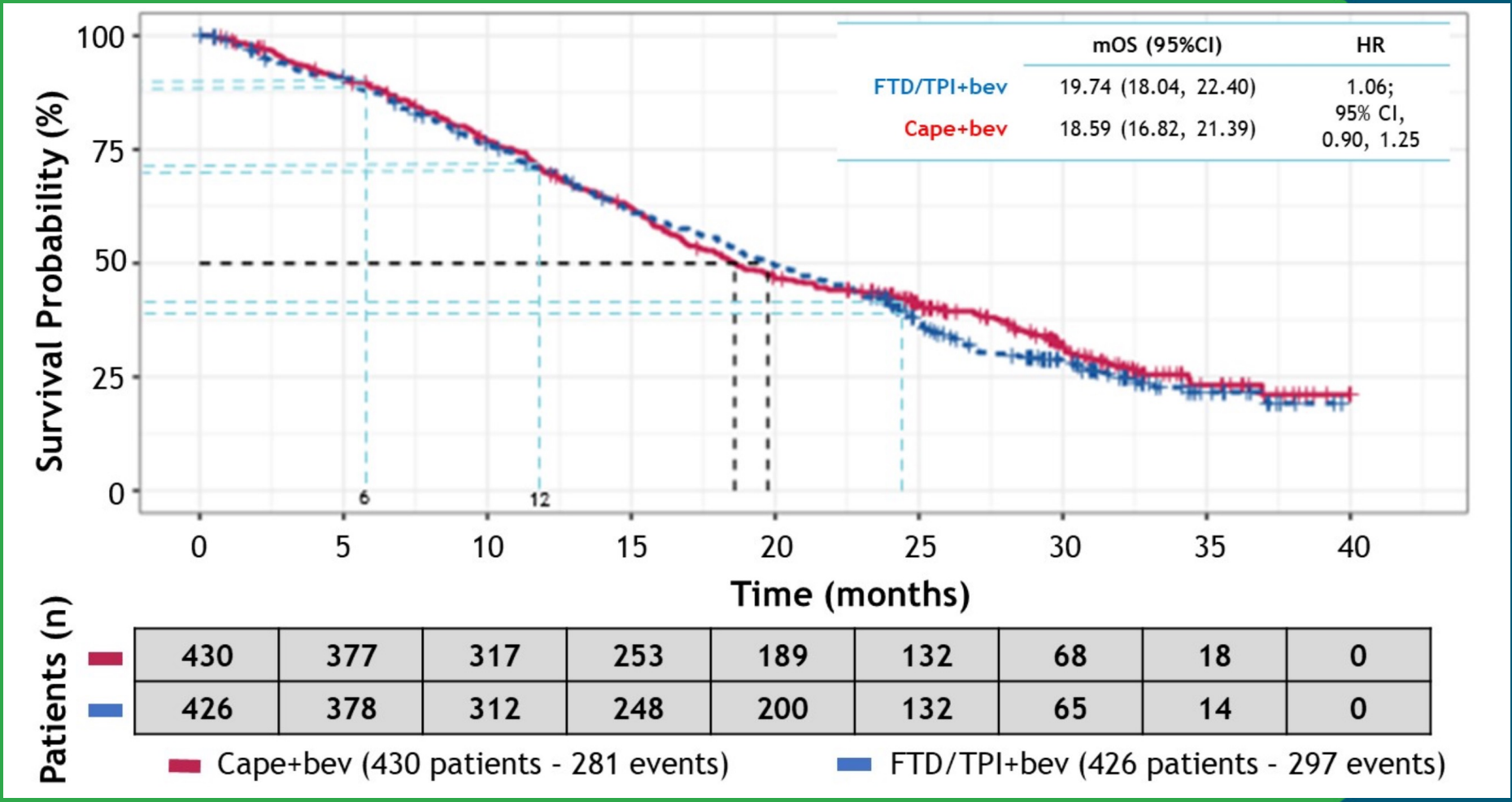
Phase III SOLSTICE Trial



- Stratification factors were:
  - Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1 versus 2)
  - Reason for non-eligibility for intensive therapy (clinical condition versus non-clinical condition)
  - Tumor localization (right versus left)
- Primary endpoint was PFS
- Key secondary endpoint was OS

Thierry, Andre et al. ASCO Annual Meeting 2023. Abstract 3512.

Phase III SOLSTICE Trial



Thierry, Andre et al. ASCO Annual Meeting 2023. Abstract 3512.

Phase III SOLSTICE Trial

Factors significantly associated with prolonged OS in the whole population

Factor	Levels	P-Value	Interaction P-Value	Missing value (n)
Treatment	FTD/TPI+bev (versus cape+bev)	0.3461	n/a	0
Age	<70 Years (versus ≥70 years)	0.0507	0.6037	0
Location of primary disease	Left (versus Right)	0.0477	0.3991	0
Surgical resection	Yes (versus No)	<000.1	0.5130	0
No of metastatic sites	1-2 (versus ≥3)	0.0078	0.2333	1
Presence of liver metastasis	No (versus Yes)	0.0005	0.4878	1
Neutrophils lymphocyte ratio	Nlr <3 (versus Nlr ≥3)	<000.1	0.6607	7
Charlson score	0 (versus 1-2) 1-2 (versus ≥3)	<000.1 0.3619	0.0210 0.7651	4 4
ECOG performance status	0 (versus 1) 1 (versus 2)	0.7652 0.0079	0.6294 0.0145	0 0

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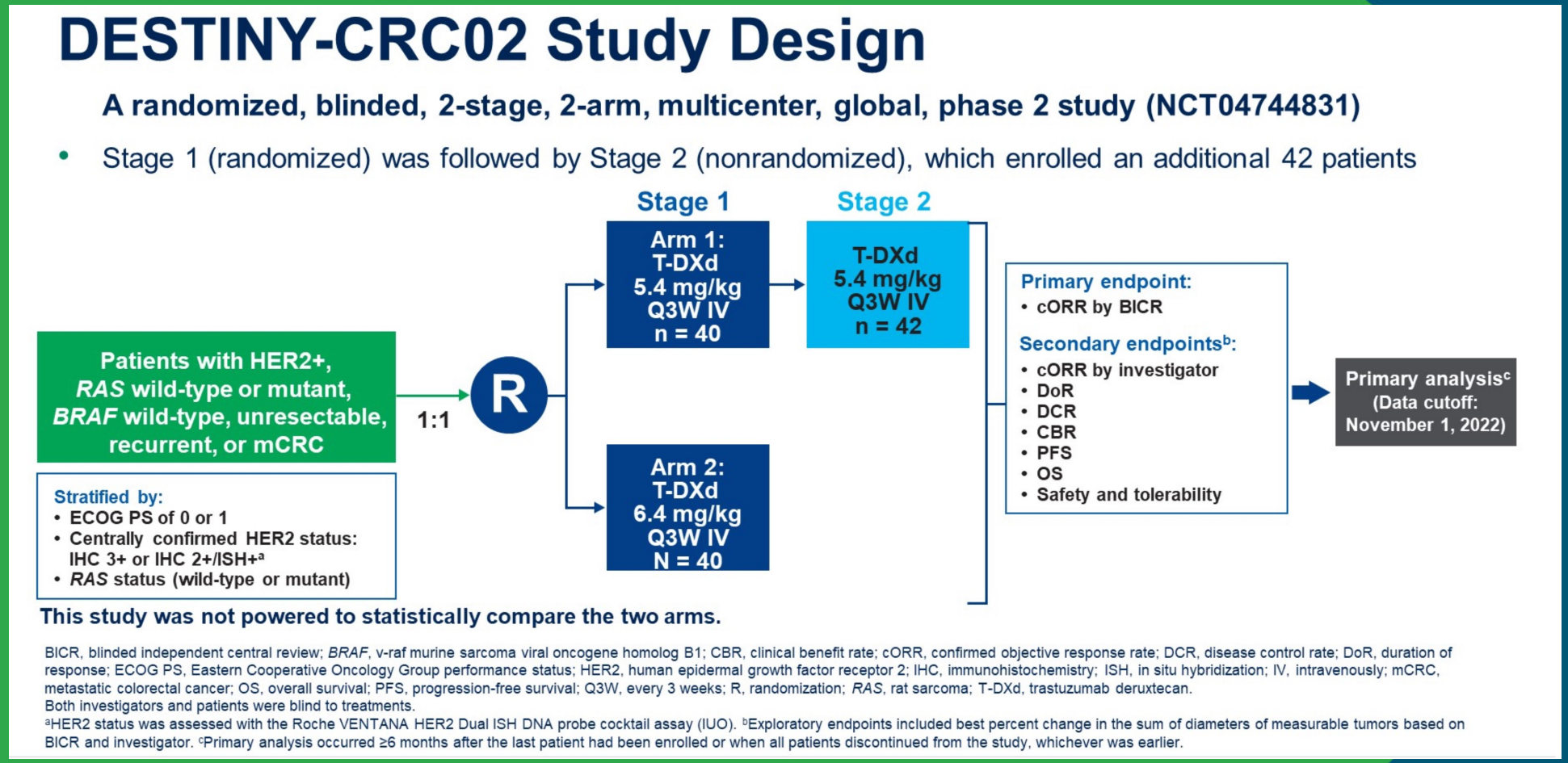
Phase III SOLSTICE Trial Conclusions

- Largest phase 3 study comparing 2 regimens in a population ineligible for intensive therapy.
- FTD/TPI+Bev was not superior to Cape/Bev as first line treatment in terms of PFS and OS in first line treatment.
- Risk of death similar in both arms
- No new safety signals
- FTD/TPI+Bev, with its different and manageable safety profile, represents a feasible alternative in this patient population to Cape/Bev

Thierry, Andre et al. ASCO Annual Meeting 2023. Abstract 3512.

DESTINY-CRC02 Trial



Raghav, Kanwal et al. ASCO Annual Meeting 2023. Abstract 3501.

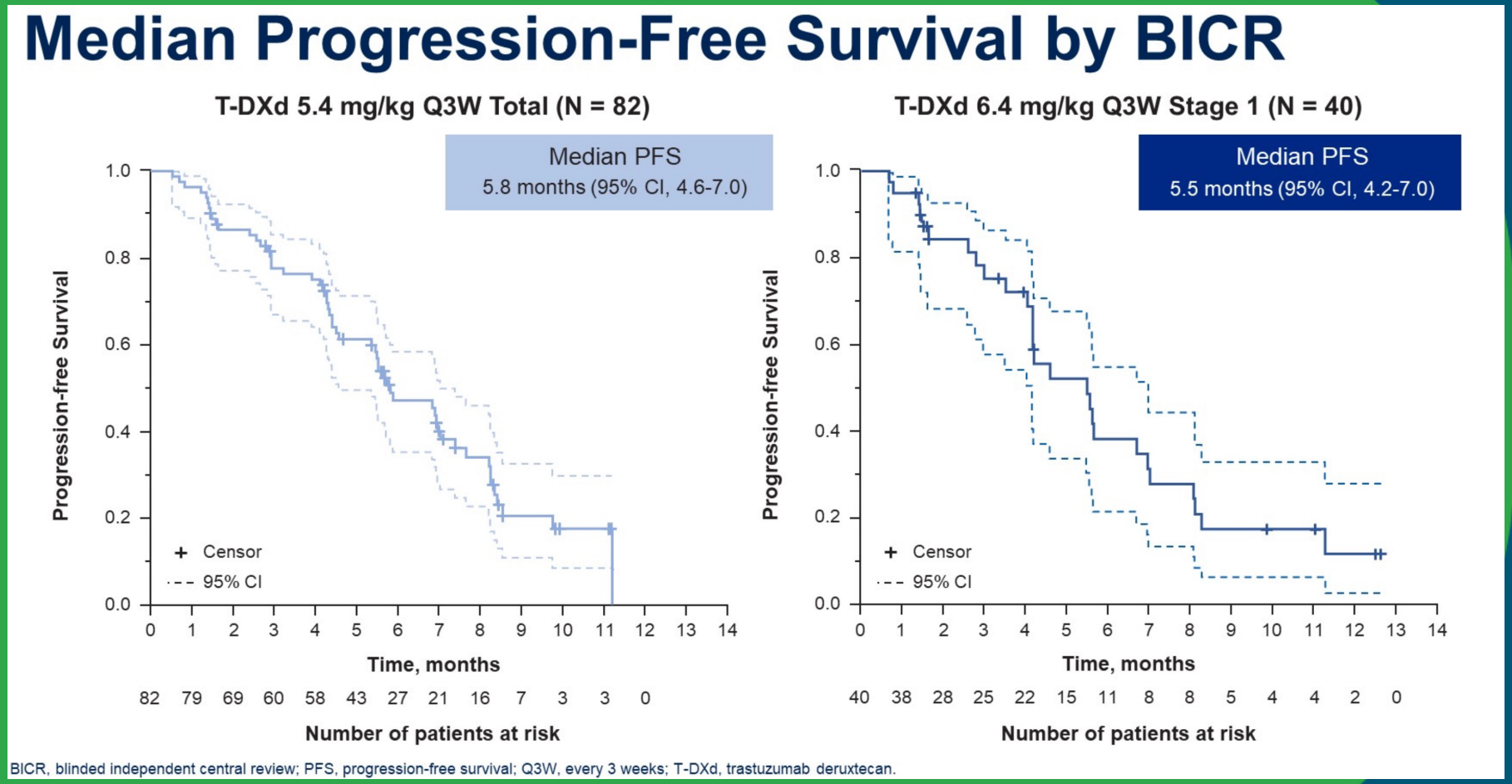
DESTINY-CRC02 Trial

	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.

Raghav, Kanwal et al. ASCO Annual Meeting 2023. Abstract 3501.

DESTINY-CRC02 Trial



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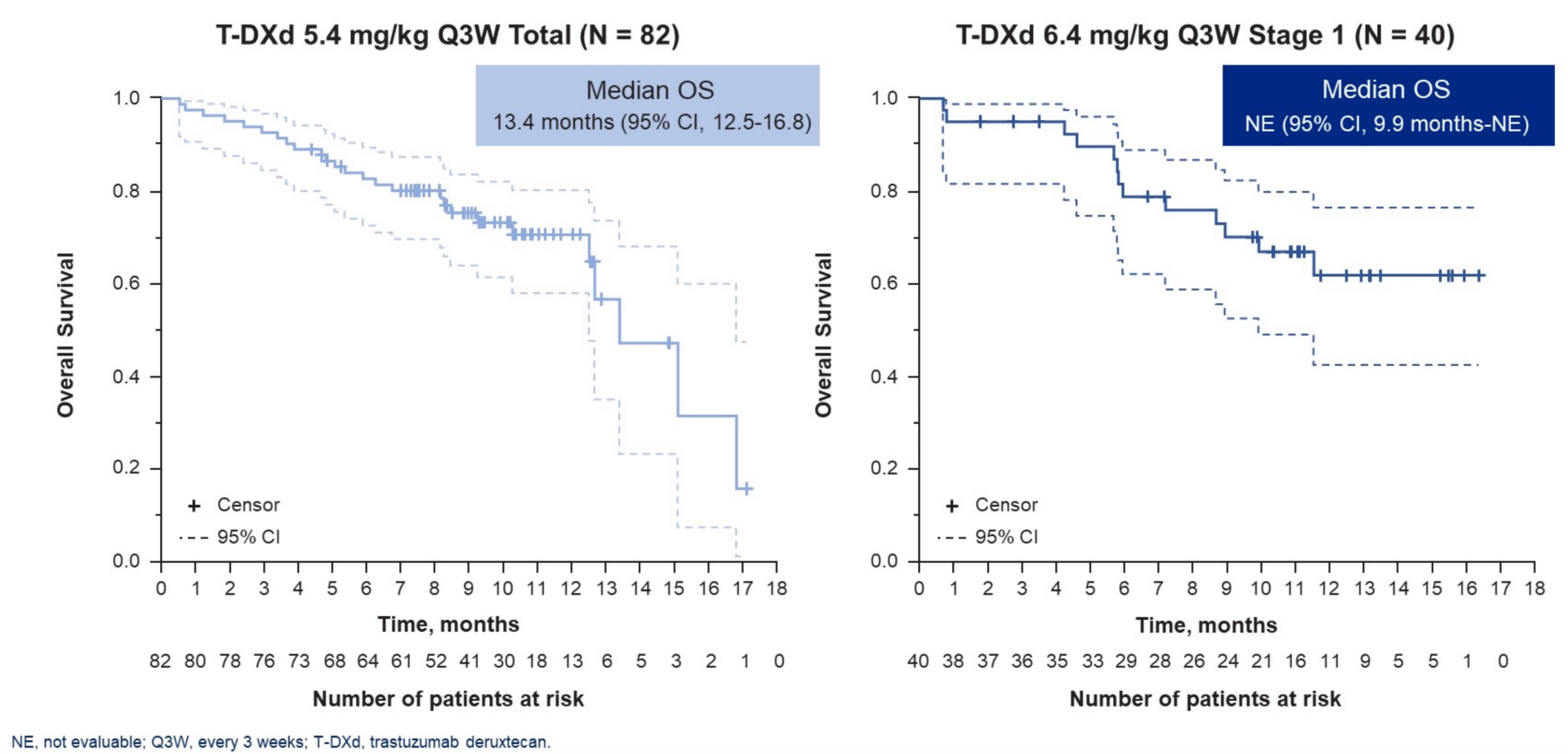
DESTINY-CRC02 Trial



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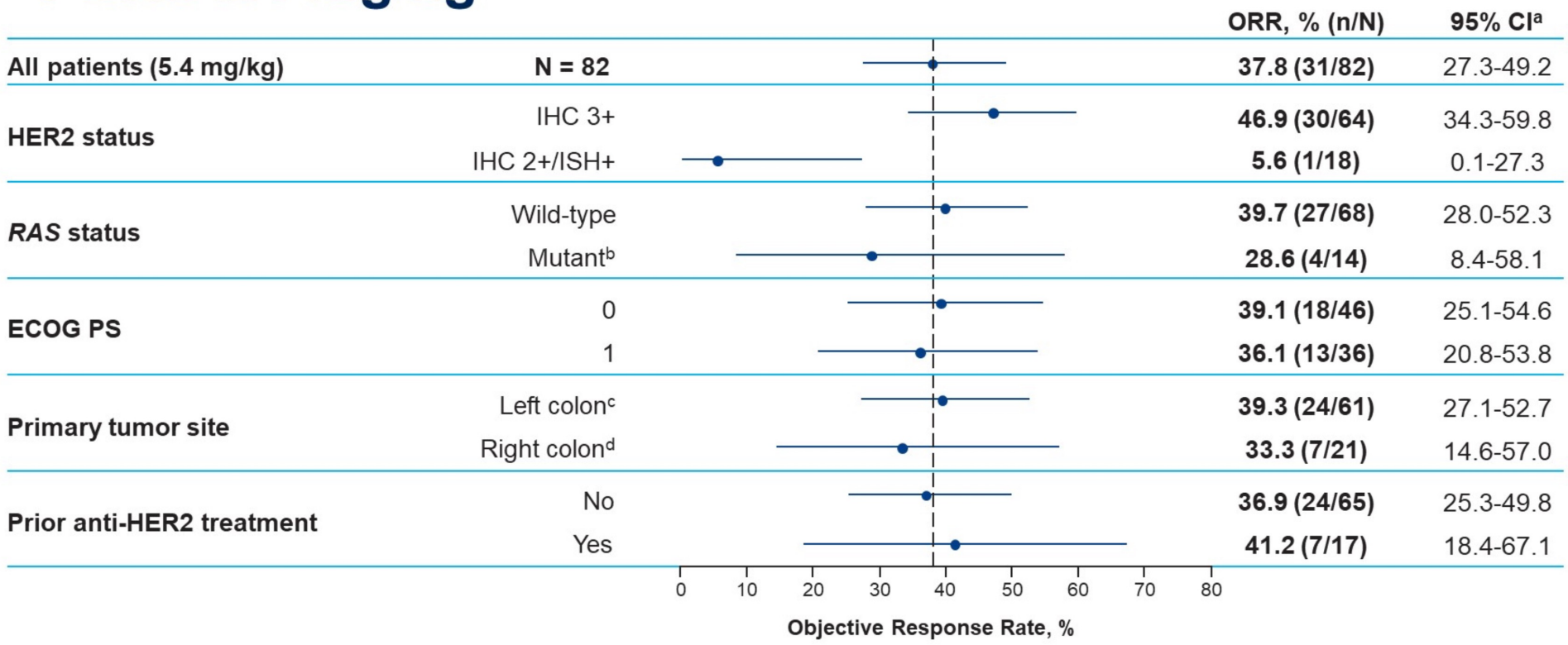
DESTINY-CRC02 Trial

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 Trial Conclusions

- Promising antitumor activity was observed in patients with Her2+ mCRC at both the T-DXd 5.4mg/kg and 6.4 mg/kg doses.
  - Numerically higher cORR at the lower dose (37.8% vs 27.5%)
  - Higher ORR observed in patients with IHC 3+ Her2 status (46.9%) than 2+/+ (5.6%) at the 5.4mg/kg dose.
  - ORR seen in patients with/without RAS mutations (28.6%/39.7%) and in patients previously treated with anti-Her2 therapy (41.2%) at the 5.4 mg/kg dose.

- Safety consistent with known safety profile and favored the 5.4 mg/kg dose.

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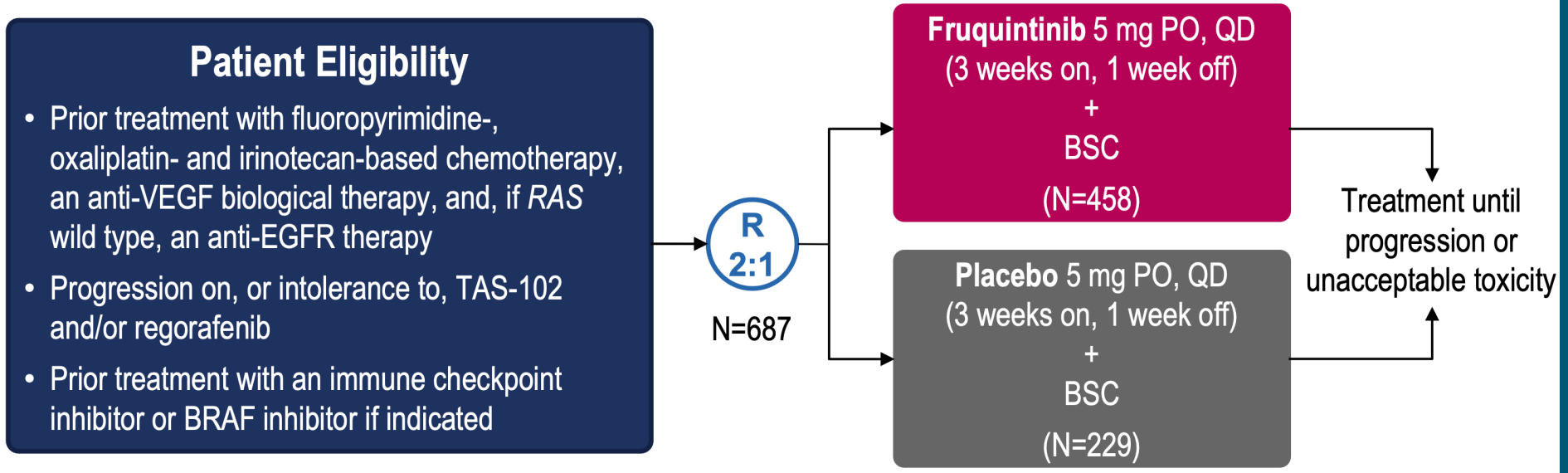
FRESCO-2 Trial

FRESCO-2 Study Design



Stratification Factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

Note: To ensure the patient population is reflective of clinical practice, the number of patients treated with prior regorafenib was limited to 344 patients (50%)

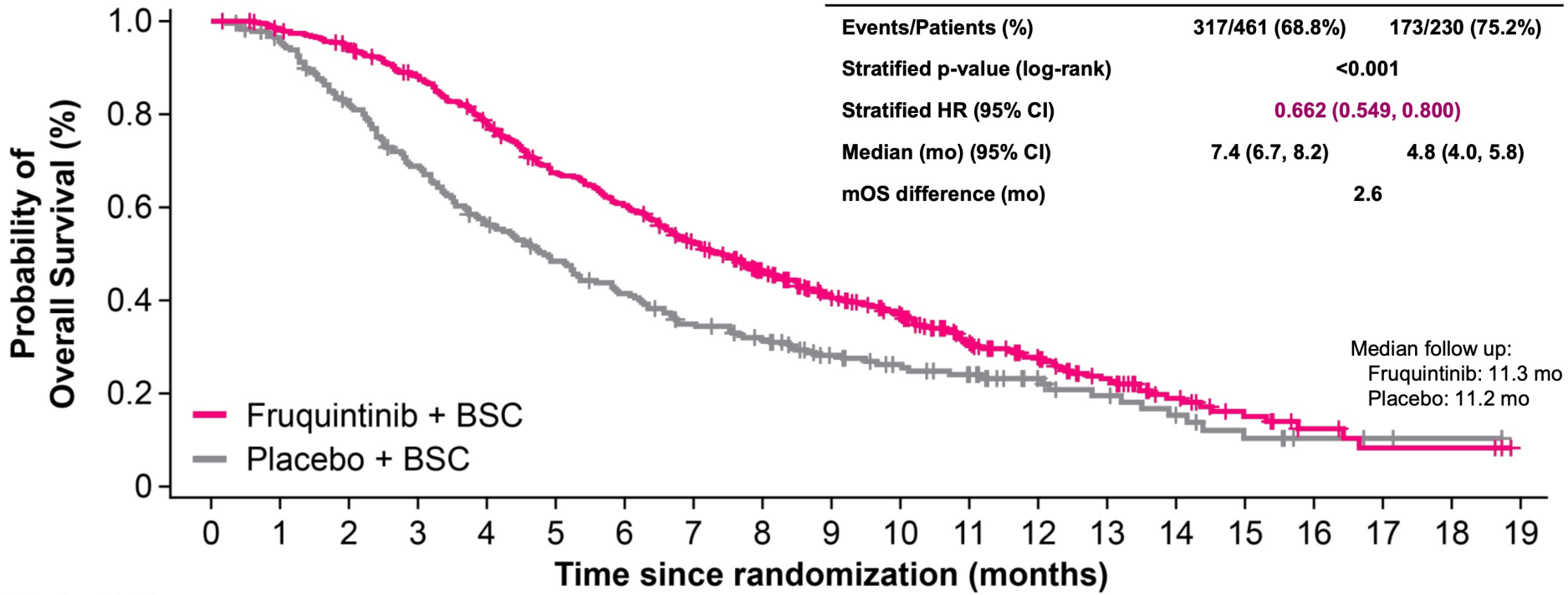
BSC, best supportive care.
NCT04322539.

Dasari, Arvind et al. ESMO Annual Meeting 2022. Abstract LBA25.

FRESCO-2 Trial

Primary Endpoint: Overall Survival

ITT Population



	Fruquintinib	Placebo
Events/Patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.662 (0.549, 0.800)	
Median (mo) (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
mOS difference (mo)	2.6	

Patients at Risk

Fruquintinib	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

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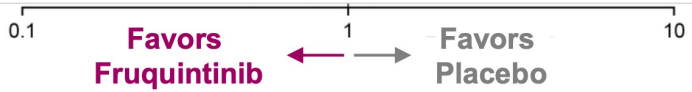
FRESCO-2 Trial

OS Subgroup Analysis

ITT Population

Subgroup		Fruquintinib n/N	Placebo n/N	HR (95% CI)
ITT population		317/461	173/230	0.662 (0.549, 0.800)
Age	< 65	171/247	89/119	0.694 (0.534, 0.903)
	≥ 65	146/214	84/111	0.648 (0.494, 0.851)
Sex	Female	149/216	61/90	0.828 (0.609, 1.125)
	Male	168/245	112/140	0.584 (0.456, 0.749)
ECOG PS	0	121/196	67/102	0.775 (0.573, 1.050)
	1	196/265	106/128	0.571 (0.499, 0.728)
Race	Caucasian	260/367	145/192	0.696 (0.567, 0.854)
	Asian	24/43	14/18	0.377 (0.171, 0.833)
	African American	7/13	5/7	0.550 (0.135, 2.231)
	Other	26/38	9/13	1.199 (0.478, 3.008)
Region	North America	50/82	29/42	0.620 (0.387, 0.995)
	Europe	237/329	130/166	0.688 (0.554, 0.855)
	Asia Pacific	30/50	14/22	0.631 (0.321, 1.241)
Duration of metastatic disease	≤ 18 mo	30/37	8/13	0.605 (0.260, 1.406)
	> 18 mo	287/424	165/217	0.642 (0.529, 0.779)
Primary tumor site at 1st diagnosis	Colon	195/279	109/137	0.672 (0.528, 0.855)
	Rectum	99/143	49/70	0.633 (0.446, 0.900)
	Colon and Rectum	23/39	15/23	0.686 (0.339, 1.388)
RAS status	WT	119/170	62/85	0.667 (0.489, 0.909)
	Mutant	198/291	111/145	0.683 (0.539, 0.865)
# of prior treatment lines in metastatic disease	≤ 3	80/125	45/64	0.714 (0.488, 1.043)
	>3	237/336	128/166	0.645 (0.519, 0.802)
Prior VEGFi	Yes	306/445	167/221	0.683 (0.565, 0.827)
	No	11/16	6/9	0.193 (0.024, 1.557)
Prior EGFRi	Yes	127/180	64/88	0.689 (0.507, 0.936)
	No	190/281	109/142	0.666 (0.524, 0.846)
Prior TAS-102 and Regorafenib	TAS-102	165/240	88/121	0.723 (0.557, 0.938)
	Regorafenib	25/40	12/18	0.772 (0.379, 1.573)
	Both	127/181	73/91	0.600 (0.447, 0.805)
Liver metastases	Yes	255/339	132/156	0.576 (0.465, 0.713)
	No	62/122	41/74	0.771 (0.513, 1.158)



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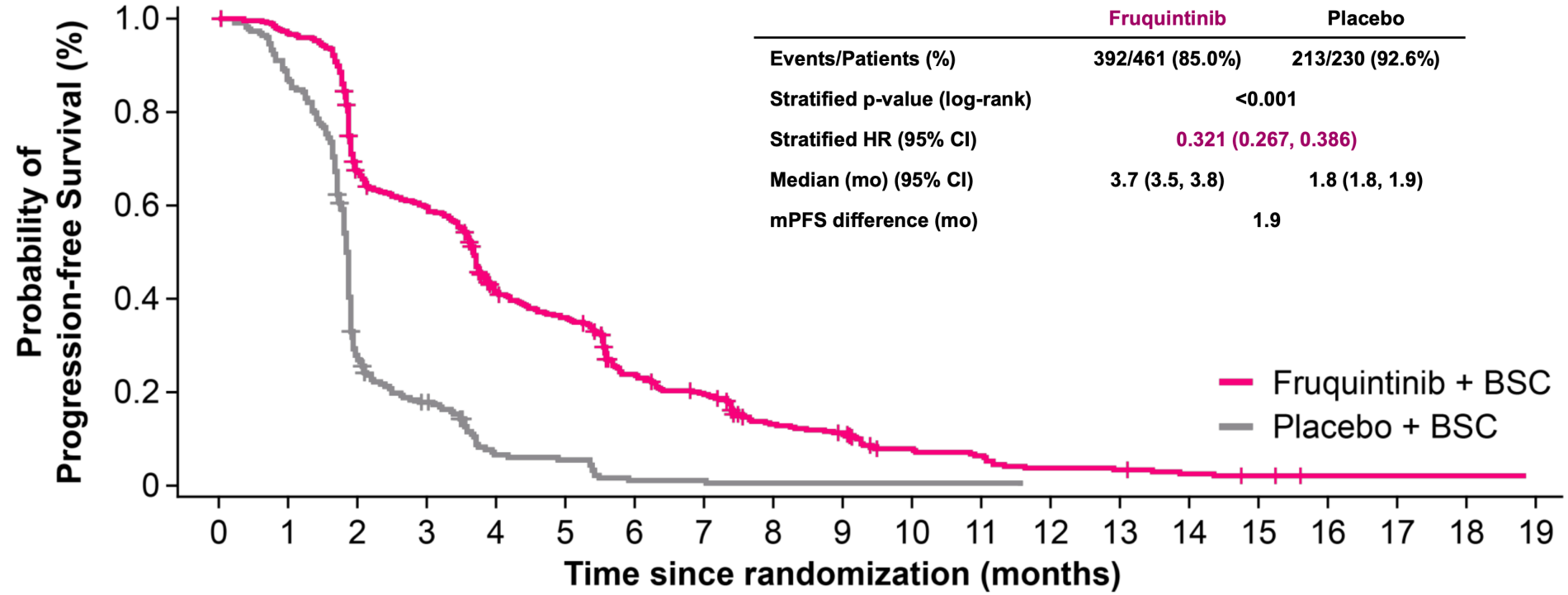
FRESCO-2 Trial

Progression-Free Survival

ITT Population



	Fruquintinib	Placebo
Events/Patients (%)	392/461 (85.0%)	213/230 (92.6%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.321 (0.267, 0.386)	
Median (mo) (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
mPFS difference (mo)	1.9	

Patients at Risk																			
Fruquintinib	461	430	291	256	170	146	89	71	43	36	21	17	10	9	6	4	2	2	2
Placebo	230	194	60	36	12	10	2	2	1	1	1	1	0						

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FRESCO-2 Trial Conclusions

- FRESCO-2 met the primary endpoint of OS
  - mOS improvement of 2.6 months with fruquintinib vs placebo (7.4 m vs 4.8 m; HR=0.66; p<0.001)
  - OS improvement consistent across all pre-specified subgroups.
- FRESCO-2 met the key secondary endpoint of PFS
  - mPFS improvement of 1.9 m with fruquintinib vs placebo (3.7 m vs 1.8 m; HR=0.32; p<0.001)
  - PFS improvement consistent across all pre-specified subgroups
- Well tolerated with a safety profile consistent with previously established monotherapy profile
- Results consistent with FRESCO and support a new global oral treatment option for patients with refractory mCRC.

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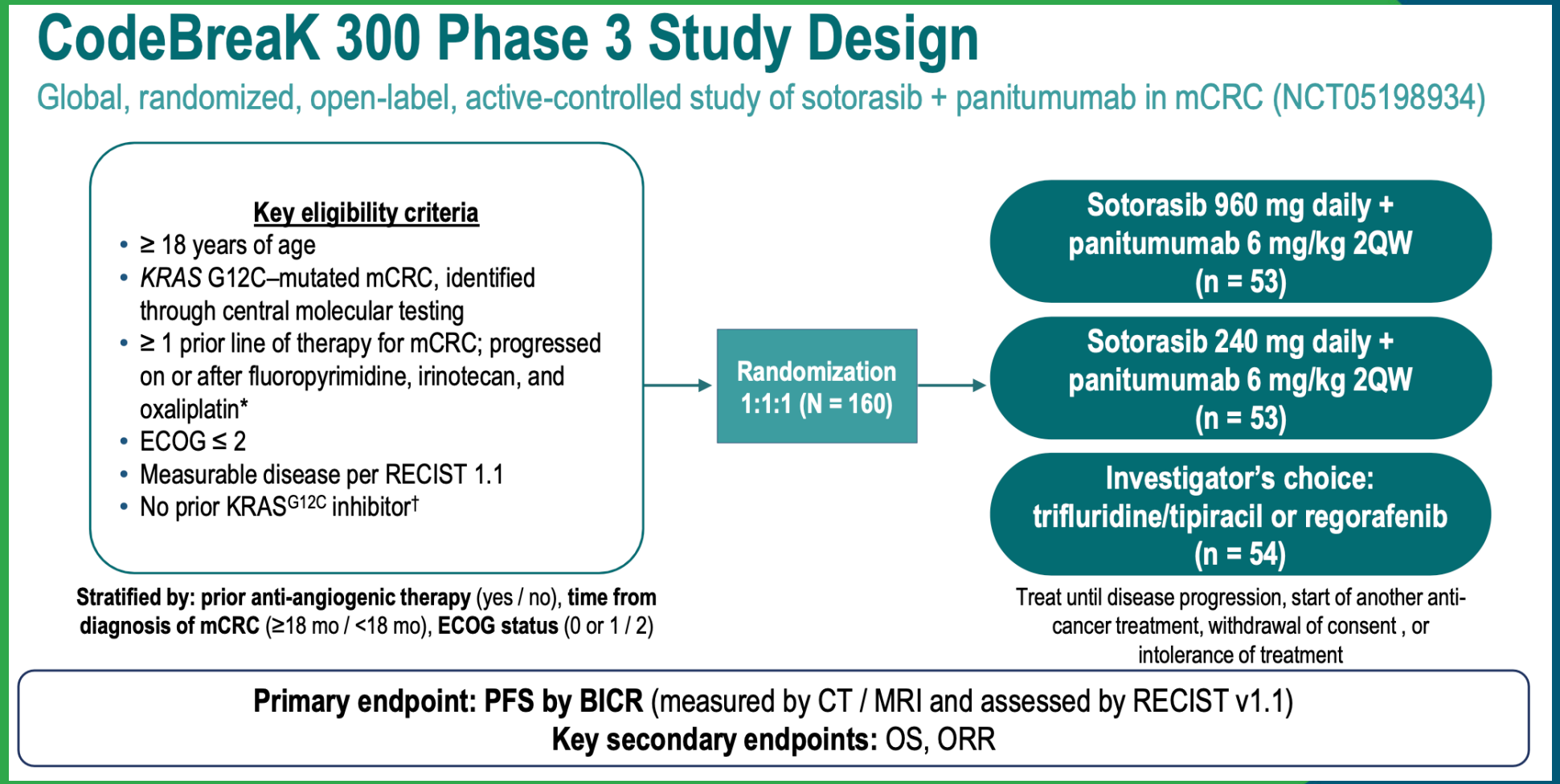
CodeBreaK-300 Trial



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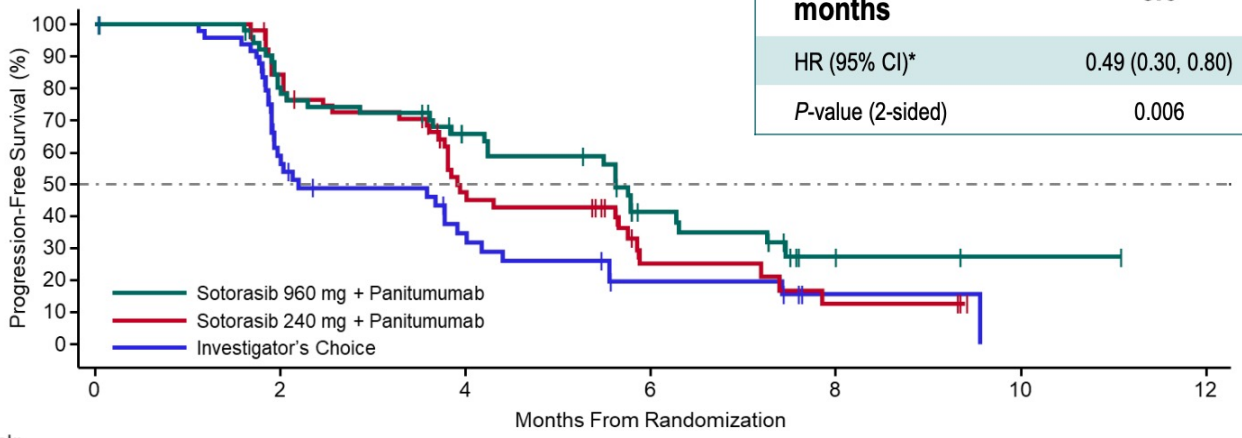
CodeBreaK-300 Trial

Primary Endpoint: PFS in Intent-to-Treat Population

	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median PFS, months	**5.6**	**3.9**	**2.2**
HR (95% CI)*	0.49 (0.30, 0.80)	0.58 (0.36, 0.93)	–
P-value (2-sided)	0.006	0.030	–



Number of Patients at Risk:							
Sotorasib 960 mg + Panitumumab	53	40	28	13	2	1	0
Sotorasib 240 mg + Panitumumab	53	43	20	6	3	0	
Investigator's Choice	54	24	12	5	1	0	

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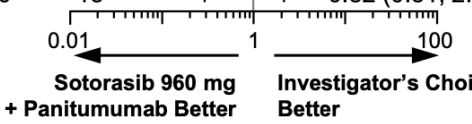
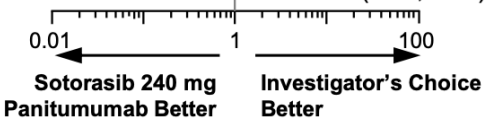
CodeBreaK-300 Trial

PFS Across Subgroups

Subgroup	Investigator's Choice (Number of Patients)	Sotorasib 960 mg + Panitumumab (Number of Patients)	Hazard Ratio for Disease Progression or Death (95% CI)	Investigator's Choice (Number of Patients)	Sotorasib 240 mg + Panitumumab (Number of Patients)	Hazard Ratio for Disease Progression or Death (95% CI)
All randomized patients	54	53	0.49 (0.30, 0.80)	54	53	0.58 (0.36, 0.93)
Age (years)						
< 65	27	32	0.52 (0.26, 1.04)	27	39	0.63 (0.32, 1.23)
≥ 65	27	21	0.43 (0.20, 0.92)	27	14	0.36 (0.14, 0.91)
Sex						
Male	24	29	0.59 (0.30, 1.15)	24	26	0.71 (0.37, 1.37)
Female	30	24	0.35 (0.17, 0.73)	30	27	0.63 (0.31, 1.27)
Time from initial diagnosis of metastatic disease to randomization						
≥ 18 months	31	29	0.42 (0.20, 0.84)	31	29	0.49 (0.25, 0.97)
< 18 months	23	24	0.51 (0.24, 1.07)	23	22	0.78 (0.40, 1.52)
Sidedness						
Right sided	16	24	0.41 (0.19, 0.90)	16	17	0.59 (0.27, 1.32)
Left sided	37	28	0.62 (0.32, 1.20)	37	36	0.58 (0.33, 1.03)
Primary tumor location						
Colon	37	37	0.45 (0.25, 0.80)	37	32	0.53 (0.30, 0.95)
Rectum	17	16	0.57 (0.25, 1.31)	17	21	0.47 (0.21, 1.03)
Number of prior therapy lines for metastatic disease						
1-2	28	37	0.39 (0.21, 0.72)	28	29	0.56 (0.31, 1.02)
≥ 3	26	16	0.58 (0.23, 1.47)	26	24	0.59 (0.27, 1.26)
Liver metastasis						
Yes	38	38	0.35 (0.20, 0.61)	38	36	0.47 (0.28, 0.80)
No	16	15	0.82 (0.31, 2.21)	16	17	0.56 (0.21, 1.51)





PFS by BICR favored sotorasib + panitumumab across key patient subgroups

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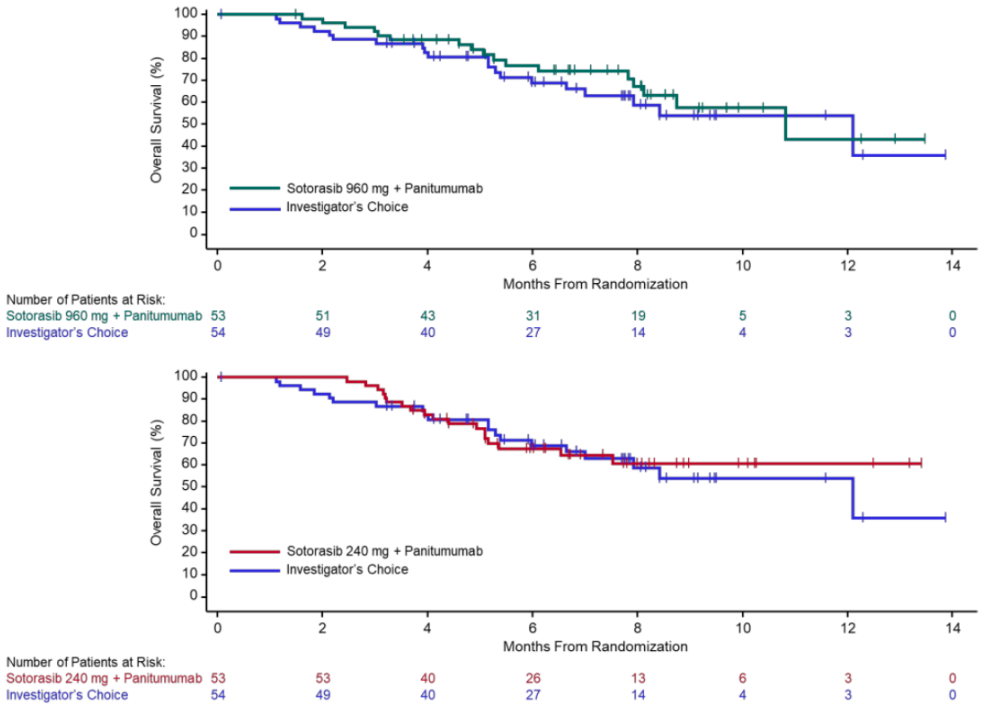
CodeBreaK-300 Trial

Overall Survival



	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
HR (95% CI)*	**0.77 (0.41, 1.45)**	**0.91 (0.48, 1.71)**	**–**
Deaths, n (%)	17 (32)	18 (34)	20 (37)
Median follow-up, months (95% CI)	8.1 (6.7, 8.7)	7.7 (6.2, 8.3)	7.8 (6.5, 8.5)

Overall survival data were not mature at data cutoff, with 55 (34%) deaths observed

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CodeBreak-300 Trial Conclusions

- CodeBreak 300 met its primary endpoint for superior PFS vs investigators choice therapy in mCRC
- Sotorasib (960mg and 240mg) showed statistically significant improvements in PFS, with the 960mg dose demonstrating a more clinically meaningful benefit.
  - mPFS was 5.6 months and 3.9 months (sotorasib + panitumumab) vs 2.2 months (investigators choice)
  - PFS favored sotorasib + panitumumab across subgroups
- Higher ORR and DCR were observed, OS was immature at data cutoff
- No new safety concerns were observed
- Sotorasib 960mg plus panitumumab is a potential new standard of care therapy for patients with chemorefractory KRAS G12C-mutated mCRC

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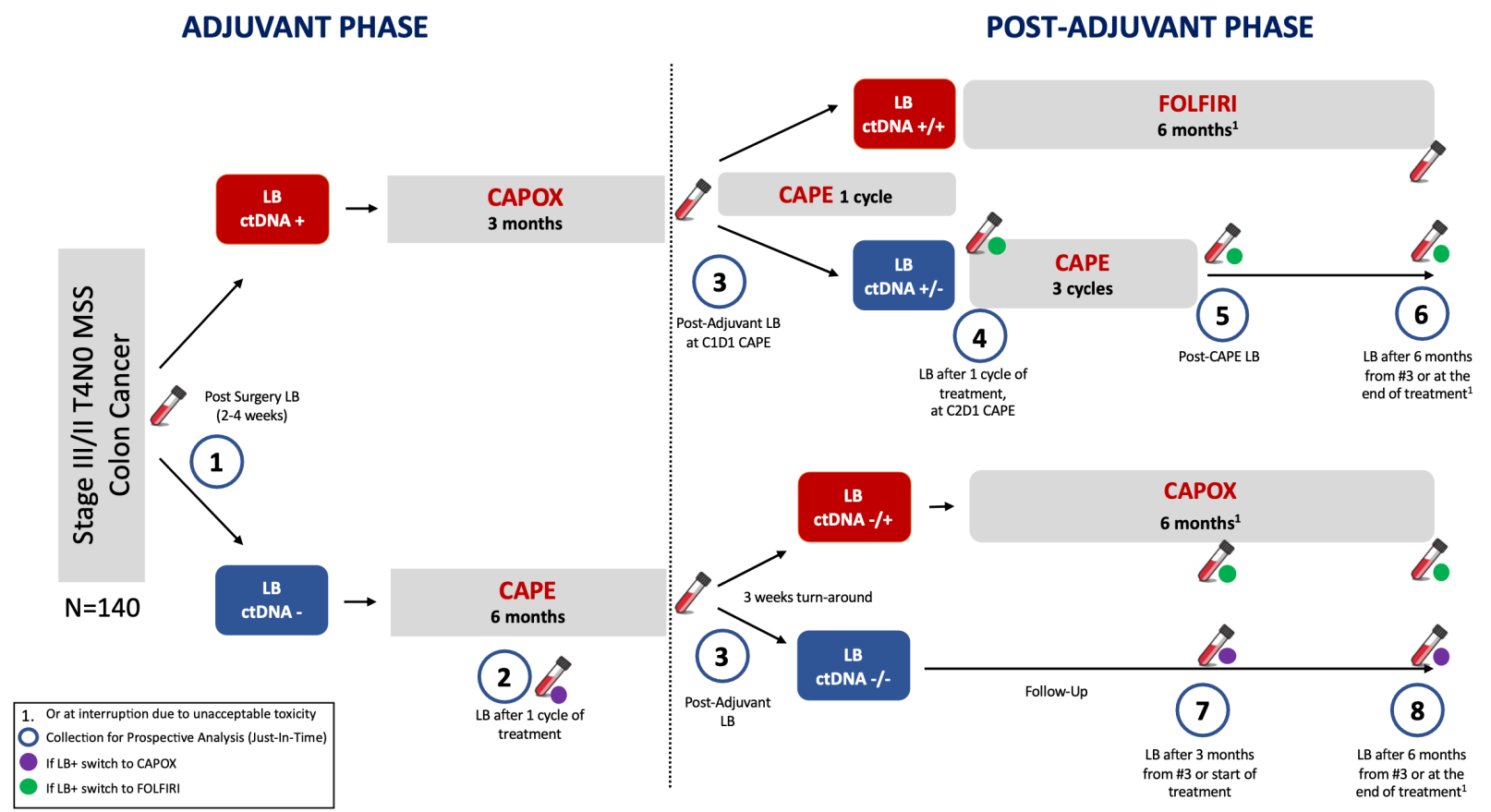
PEGASUS Trial

Study Design



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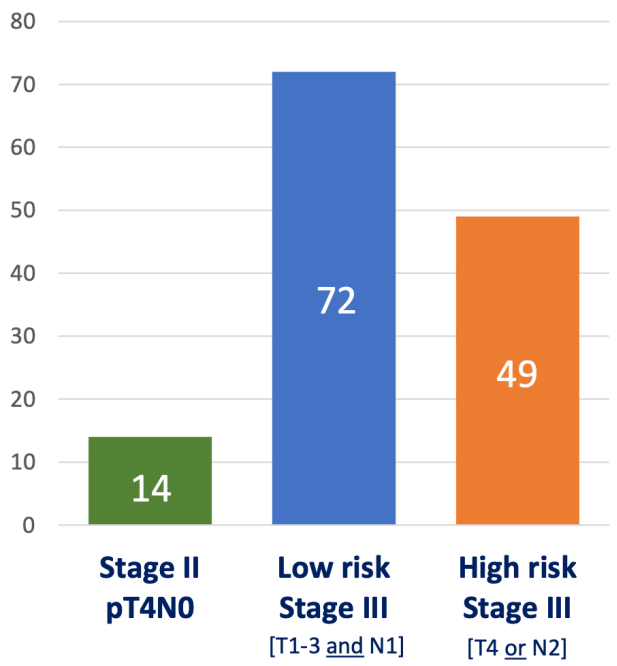
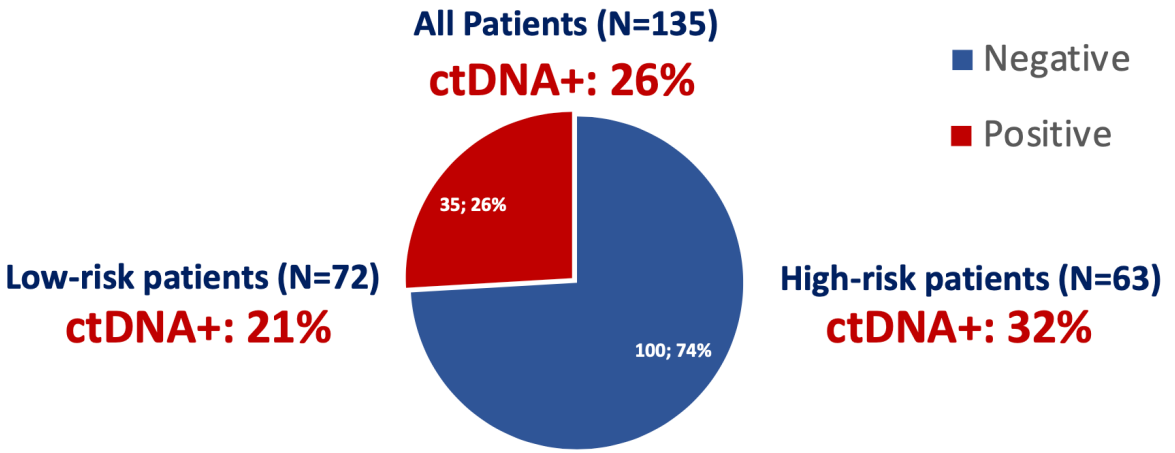
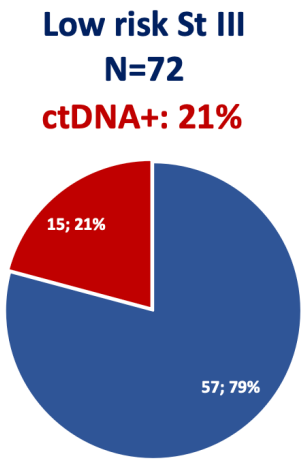
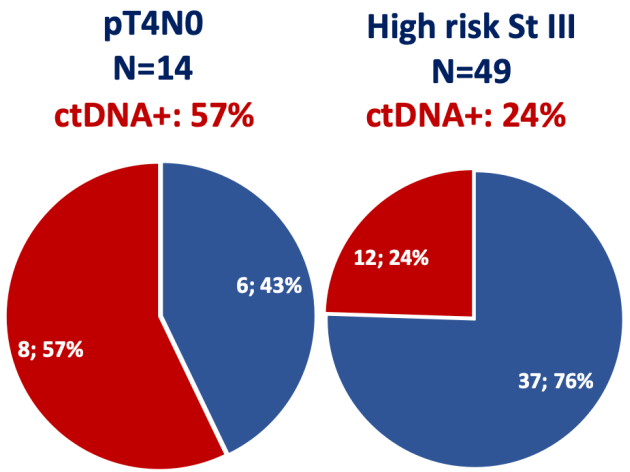
PEGASUS Trial

Stage and MRD detection rate









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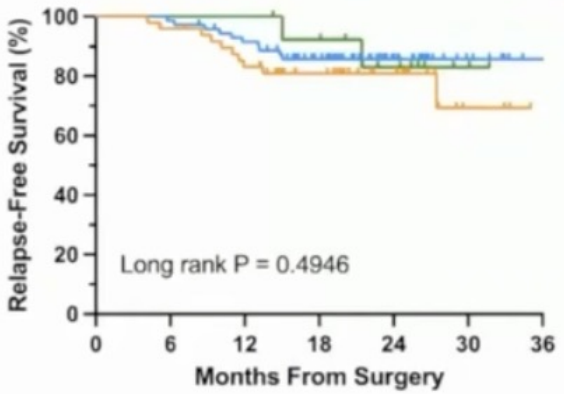
PEGASUS Trial

PEGASUS: ctDNA as Prognostic Biomarker

	Follow up (months)		Relapse
	Median	95%CI range	N events; %
Overall	21.7	19.6 – 23.6	22/135; 16%
ctDNA -	21.2	19.1 – 23.1	10/100; 10%
ctDNA +	24.2	19.8 – 26.4	12/35; 34%

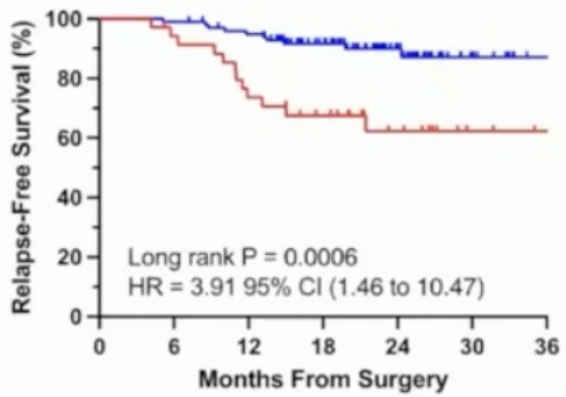
TTR according to Clinical Stage



No at risk:

Stage II - T4N0	14	14	14	12	7	2	0
Stage III - LR	72	71	64	46	23	8	2
Stage III - HR	49	46	39	25	14	3	0

TTR according to ctDNA



No at risk:

ctDNA Positive	35	32	25	20	11	3	1
ctDNA Negative	100	99	92	63	33	10	1

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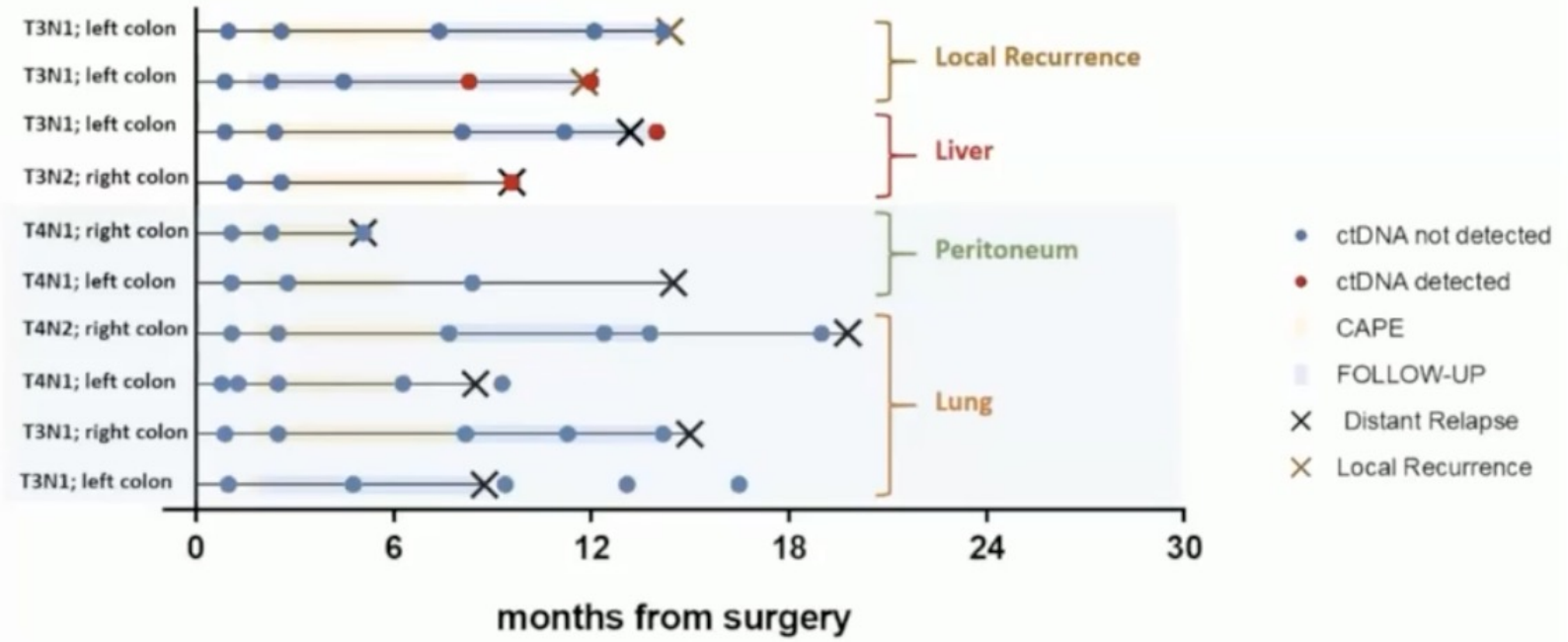
PEGASUS Trial

PEGASUS: ctDNA Negative Patients

At a median follow-up of 21.2 months (95%CI 19.1-23.1) 10 relapses (10%) have been observed:
- 2 local recurrences (both low risk stage III)
- 8 distant relapses (3 low risk stage III, 5 high risk stage III)



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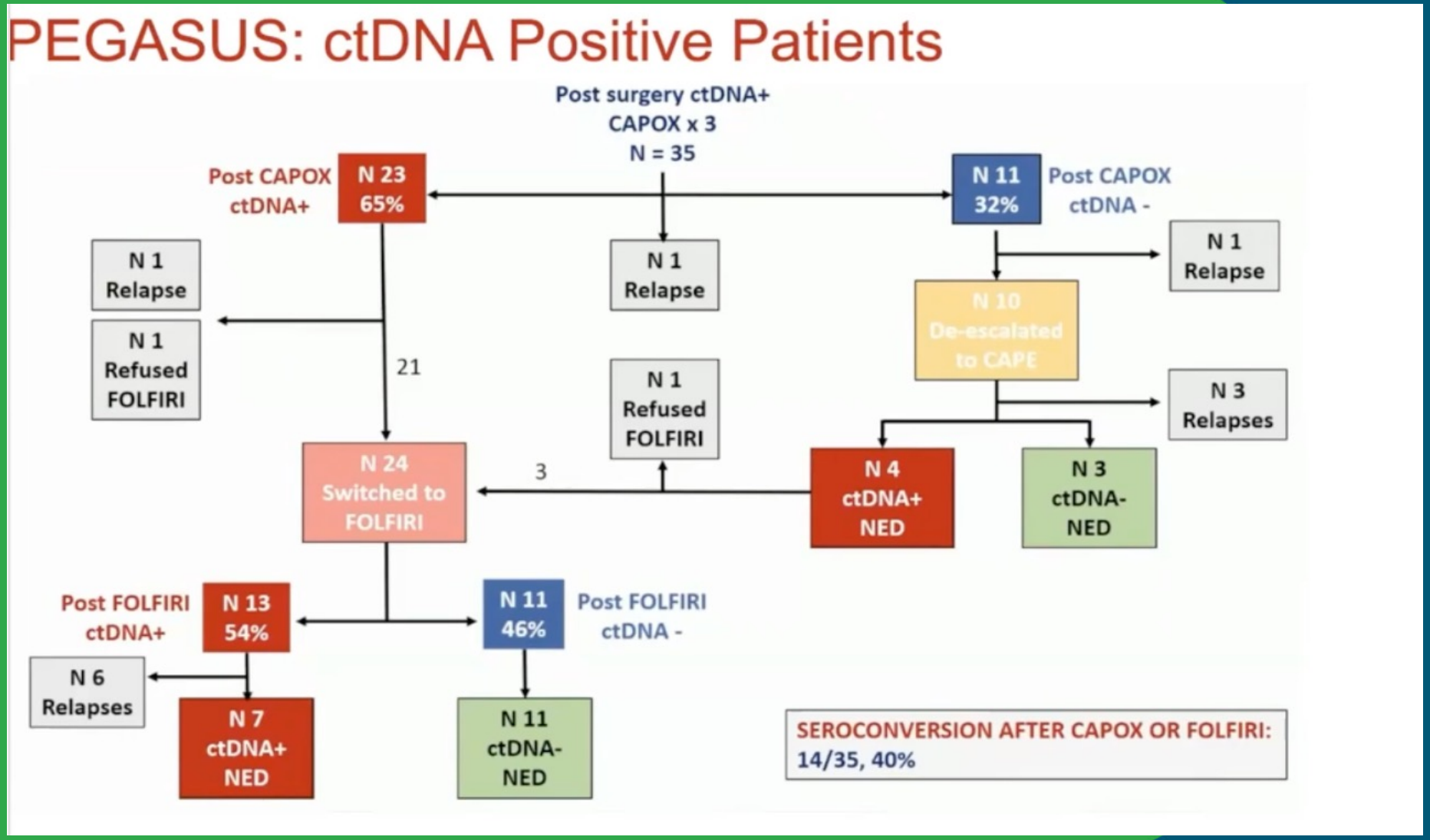
PEGASUS Trial



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Pegasus Conclusions

- ctDNA clearance measured by the Guardant Reveal assay after standard 3-month capecitabine–oxaliplatin therapy did not appear to be indicative of treatment efficacy in eradicating MRD, given the high (73%) rate of subsequent relapse.
- Almost half (11/24) of the patients who remained ctDNA+ after standard 3-month capecitabine–oxaliplatin cleared their ctDNA with 'second-line' adjuvant FOLFIRI and remained recurrence-free at last follow-up.
- There was a low relapse rate (7%) in patients with stage III and high-risk stage II colon cancer, despite only receiving single-agent capecitabine, supporting a de-escalation treatment strategy in low-risk ctDNA– patients.
- Positive methylation status in blood could be a false-positive, and the only option – the current gold standard – is clinical follow-up.

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ctDNA Trials

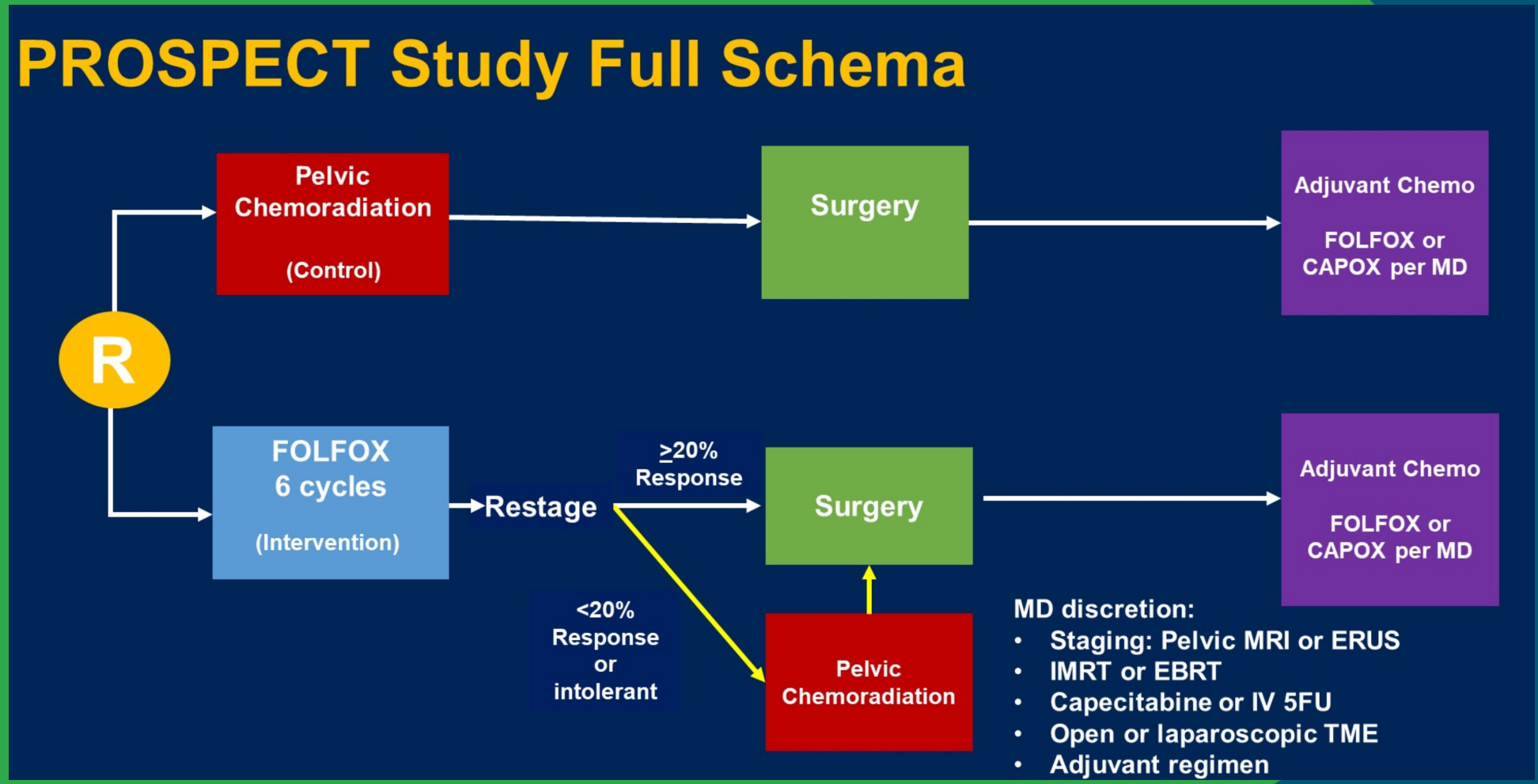
- PRECISION study showed that pre-treatment genomic alterations (detected using the Guardant360 assay) and 4-week post-operative MRD analysis (evaluated using the Guardant Reveal assay) were able to accurately stratify patients into prognostic categories and could be useful for guiding personalised adjuvant chemotherapy for those with resectable metastatic disease.

- GALAXY study update in 2,176 patients with resected CRC confirmed that serial ctDNA status analysed using a commercial tumour-informed assay (Signatera) was the most significant prognostic factor; it was predictive of patient outcomes and could potentially be used to guide adjuvant chemotherapy.

- ASCOLT trial showed that tumour-naïve, serial ctDNA detection using a commercial assay (SafeSEQ) within 1 year of adjuvant chemotherapy was associated with recurrence in patients with resected CRC.

- Other challenges include the limited half-life of ctDNA – in many cases only 50 minutes or less – which impacts the optimal timing of sample collection. Also, different assays have different sensitivities and specificities, which impact the interpretation of results. Ideally, assays should achieve sensitivities and specificities of ≥90%, but for stage I–III CRC, this is difficult to achieve with current assays because of the low quantity of ctDNA in liquid biopsy.

PROSPECT Trial



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PROSPECT Trial

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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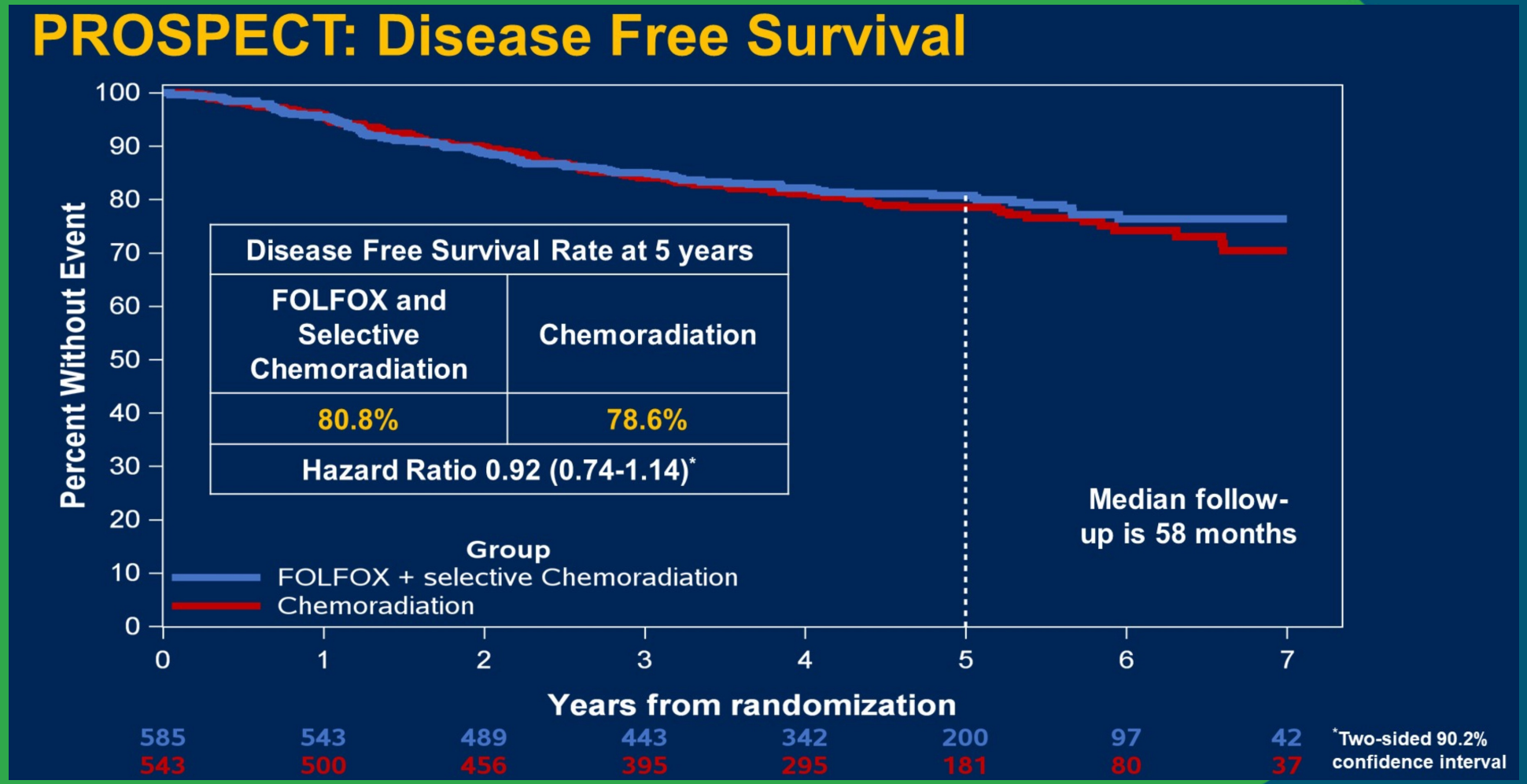
PROSPECT Trial



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PROSPECT Trial Conclusions

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

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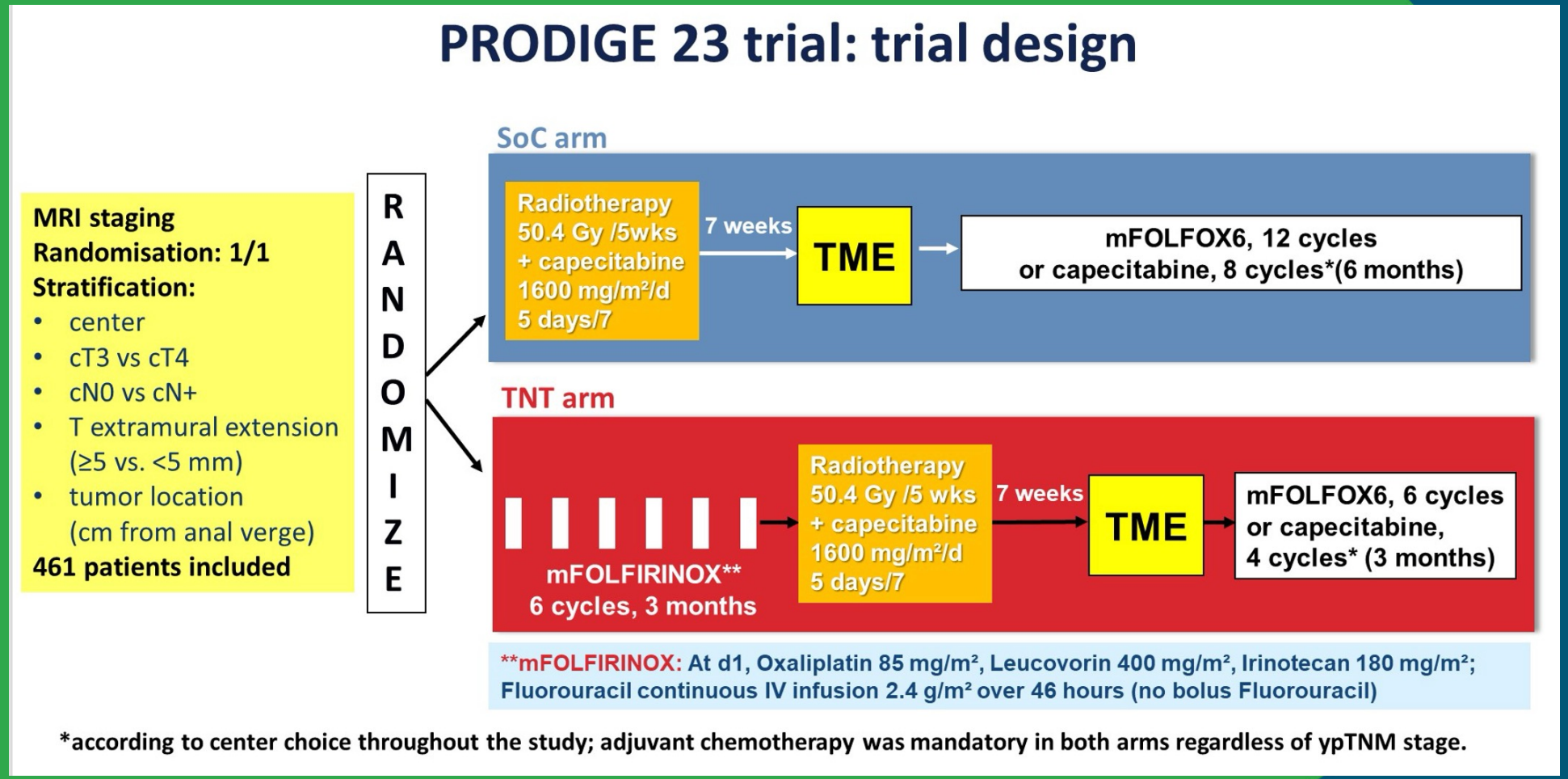
PRODIGE-23 Trial



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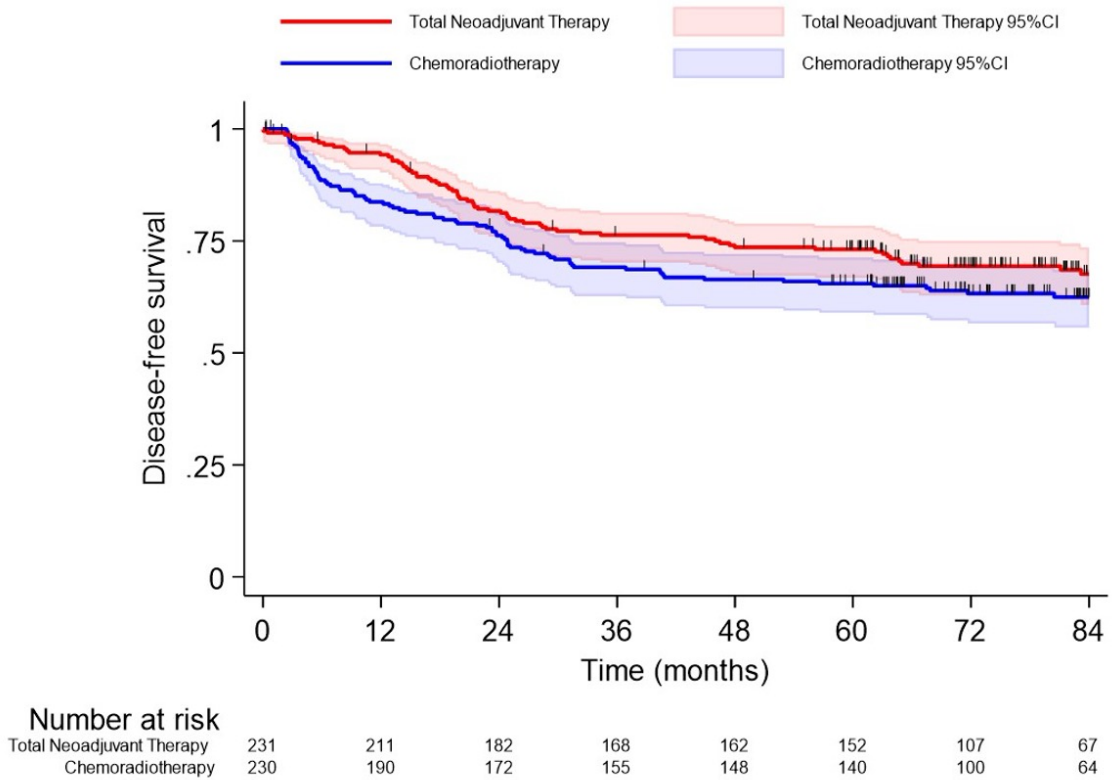
PRODIGE-23 Trial

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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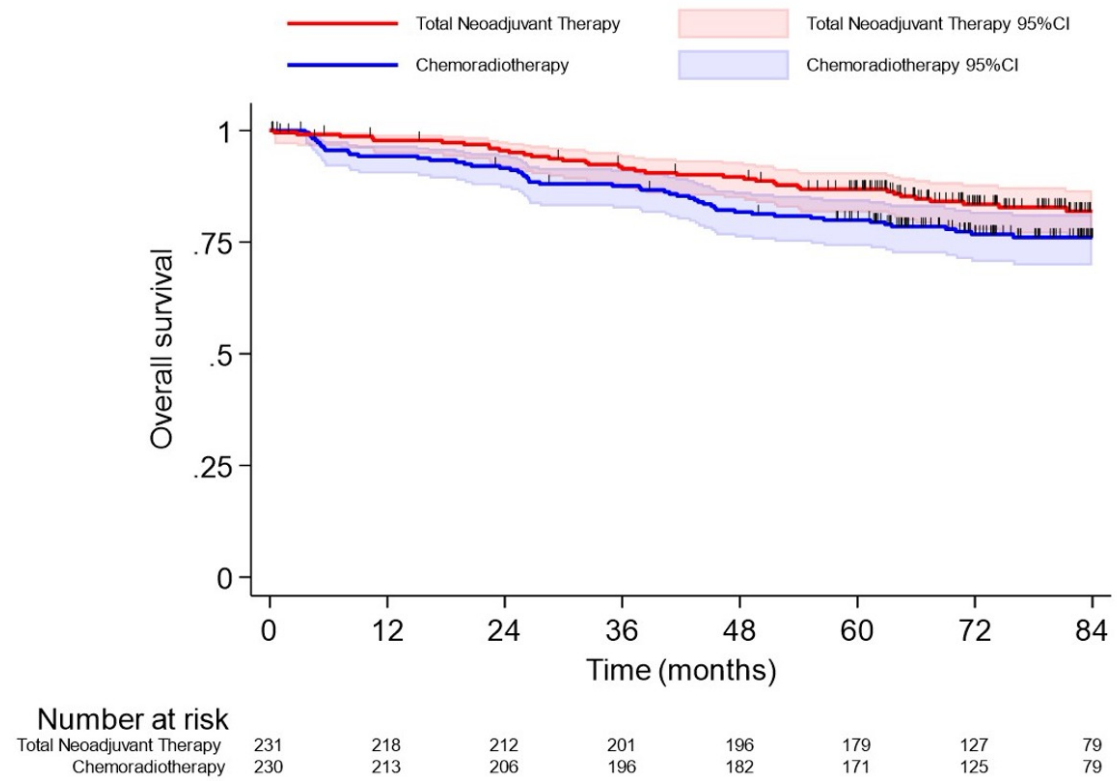
PRODIGE-23 Trial

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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PRODIGE-23 Trial Conclusions

- Induction chemotherapy with mFOLFIRINOX before chemoradiotherapy improves OS of patients with locally advanced rectal cancer
- DFS and MFS are durable
- TNT with mFOLFIRINOX should now be considered as one of the best options of care in patients with locally advanced rectal cancers.

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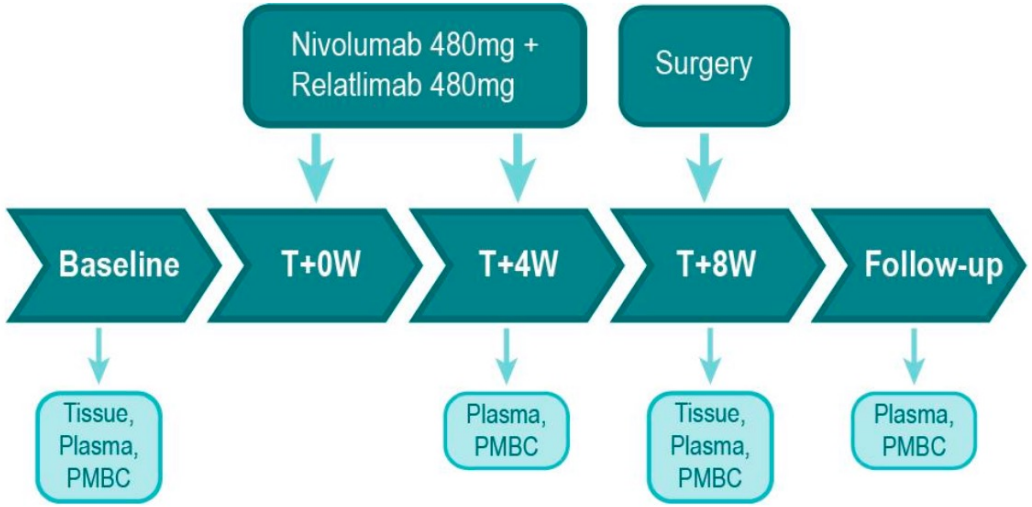
NICHE-3 Trial

Investigator-initiated, non-randomized multicenter study

Key eligibility criteria:

- Resectable, previously untreated dMMR* colon adenocarcinoma
- No distant metastases
- Locally advanced stage (≥ cT3 and/or N+)

** dMMR status was determined by IHC*



Primary endpoint: pathologic response rate

According to a Simon-2-stage design, ≥15/19 responders needed in stage I to continue accrual into stage II with an additional 40 patients

With the assumption that the pathologic response rate exceeds 85%, a minimal pathologic response rate of ≤70% was considered unacceptable. Using a one-sided α of 0.05 and a power of 80%, the study will be considered successful with >46 responders in 59 patients.

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NICHE-3 Trial

Baseline patient characteristics

Characteristic	Number at risk (%) *n* = 19
Age, median (range)	56 (36-85)
Female sex	10 (53%)
WHO performance status	
0	14 (74%)
1	5 (26%)
Radiologic T stage	
T2	1 (5%)
T3	11 (58%)
T4	7 (37%)
Radiologic N stage	
N-	5 (26%)
N+	14 (74%)
Primary tumor location	
Right colon	16 (84%)
Left colon	3 (16%)
Lynch syndrome	5 (26%)

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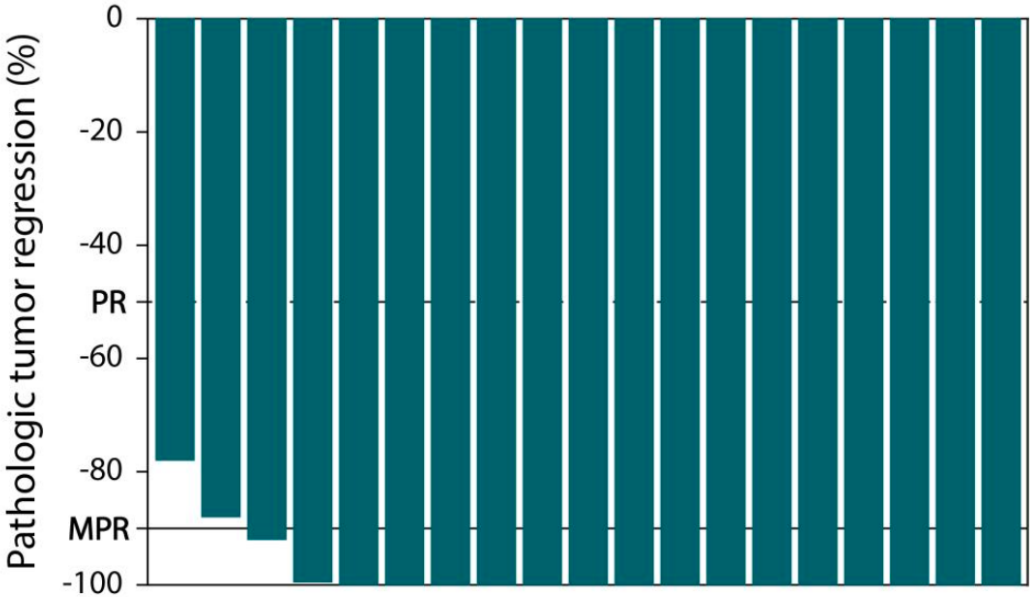
NICHE-3 Trial

Pathologic response in 100% of patients; 79% pCR



Pathologic response (RVT)	Patients *n* = 19
Yes (≤50%)	**19 (100%)**
Major (≤10%)	17 (89%)
Complete (0%)	15 (79%)
Partial (10-50%)	2 (11%)
No (>50%)	**0**

Adjuvant chemotherapy
All patients had ypN0 disease at resection and no patients received adjuvant chemotherapy

The primary endpoint was met in stage I with a pathologic response rate of 100%

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NICHE-3 Trial

Conclusion and next steps

- In the NICHE nivolumab + anti-LAG3 cohort, a 100% pathologic response rate is observed in patients with dMMR locally advanced colon cancers
  - Including 15/19 (79%) pathologic complete responses
- Compared to NICHE-2 with nivolumab+ipilimumab: difference in treatment doses, scheduling and timing of surgery
- No surgical delay and only 5% grade 3 irAE, yet 21% endocrinopathies requiring long-term supplementation
- Accrual in stage II (*n*=40) ongoing; first data full cohort expected in 2024
- Future cohorts: explore organ preservation in dMMR colon cancer patients

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Thank You!

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