Colorectal Cancer Updates in 2024

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Discussion Points

- Epidemiology
- Molecular subsets:
  - Checkmate 8HW
  - MSKCC
  - Mountaineer
  - CODEBREAK 300
- All comers:
  - Transmet
  - Orchestra
  - Collision
  - Fruquintinib maintenance + capecitabine
  - Fruquintinib + TAS-102
  - Fruquintinib sequencing

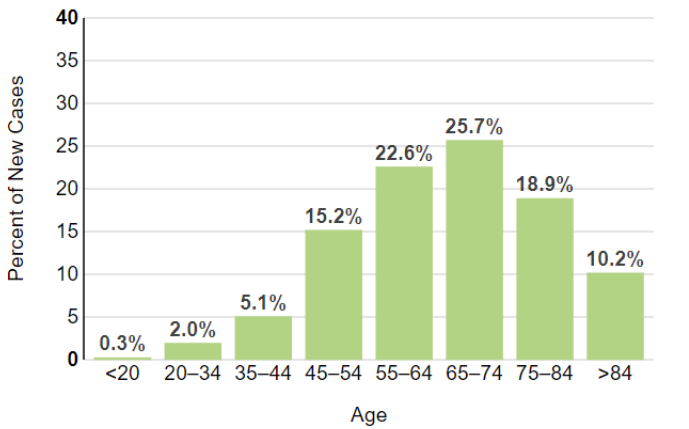
Incidence and Mortality of Colorectal CA in the US and Globally (GloboCan)

At a Glance

Estimated New Cases in 2024	152,810
% of All New Cancer Cases	7.6%

Estimated Deaths in 2024	53,010
% of All Cancer Deaths	8.7%

Percent of New Cases by Age Group: Colorectal Cancer



Colorectal cancer is most frequently diagnosed among people aged 65–74.

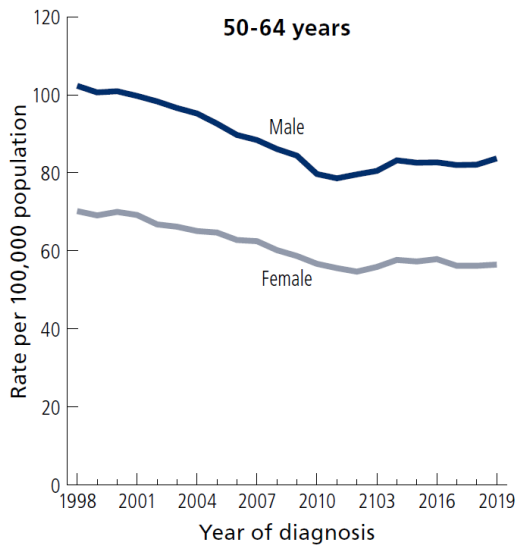
Median Age At Diagnosis
66

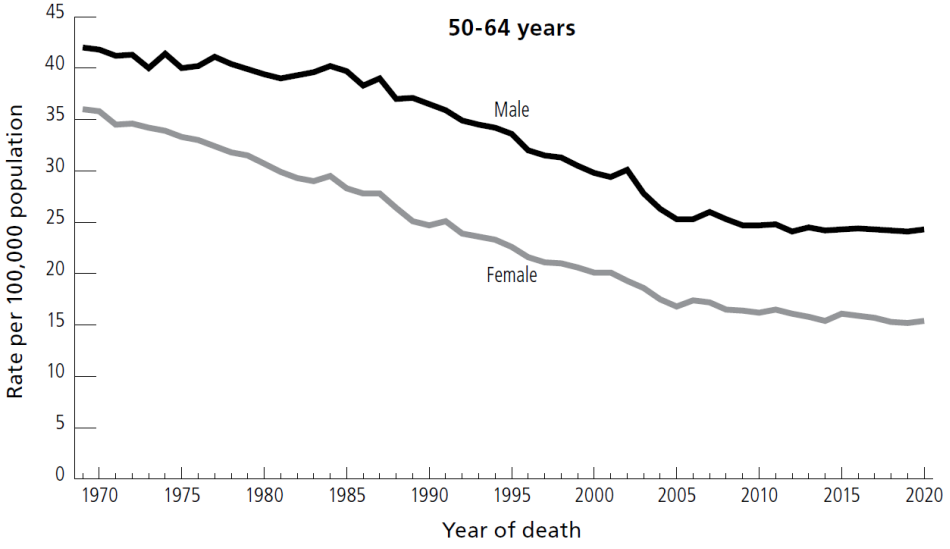
Estimated number of new cases from 2020 to 2040.

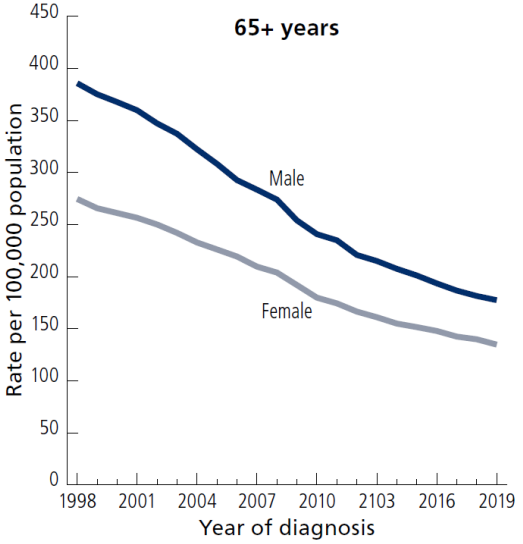
Cancer sites	2020		2040
Colon	1,148,515	↑ 67%	1,916,781
Rectum	732,210	↑ 58%	1,160,296

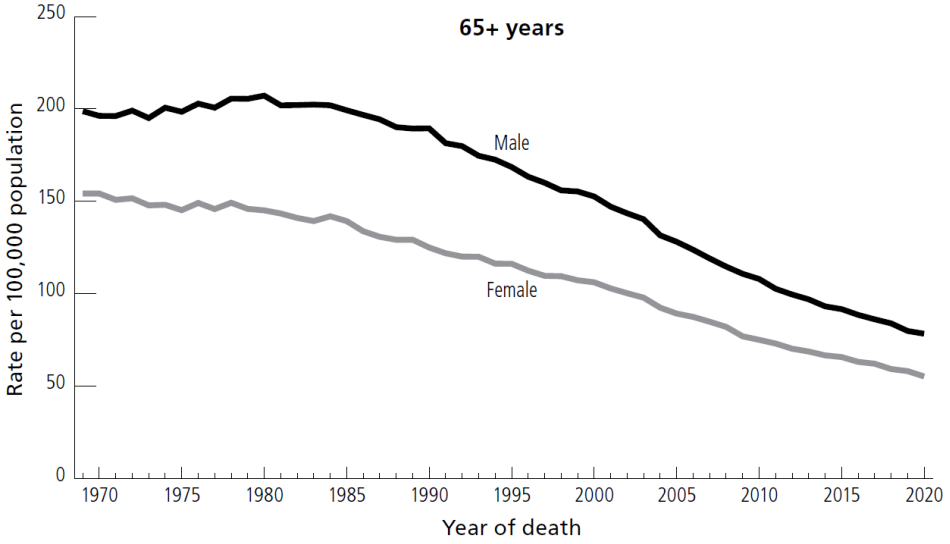
www.seer.cancer.gov; Morgan et al: Gut, 2023

Overall the incidence of CRC is decreasing



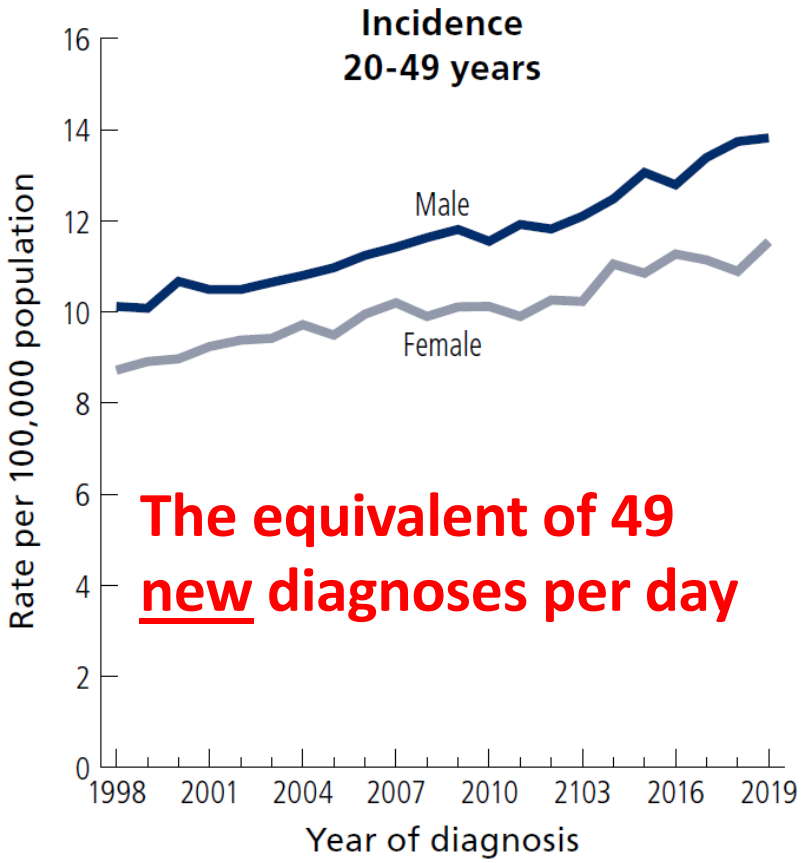




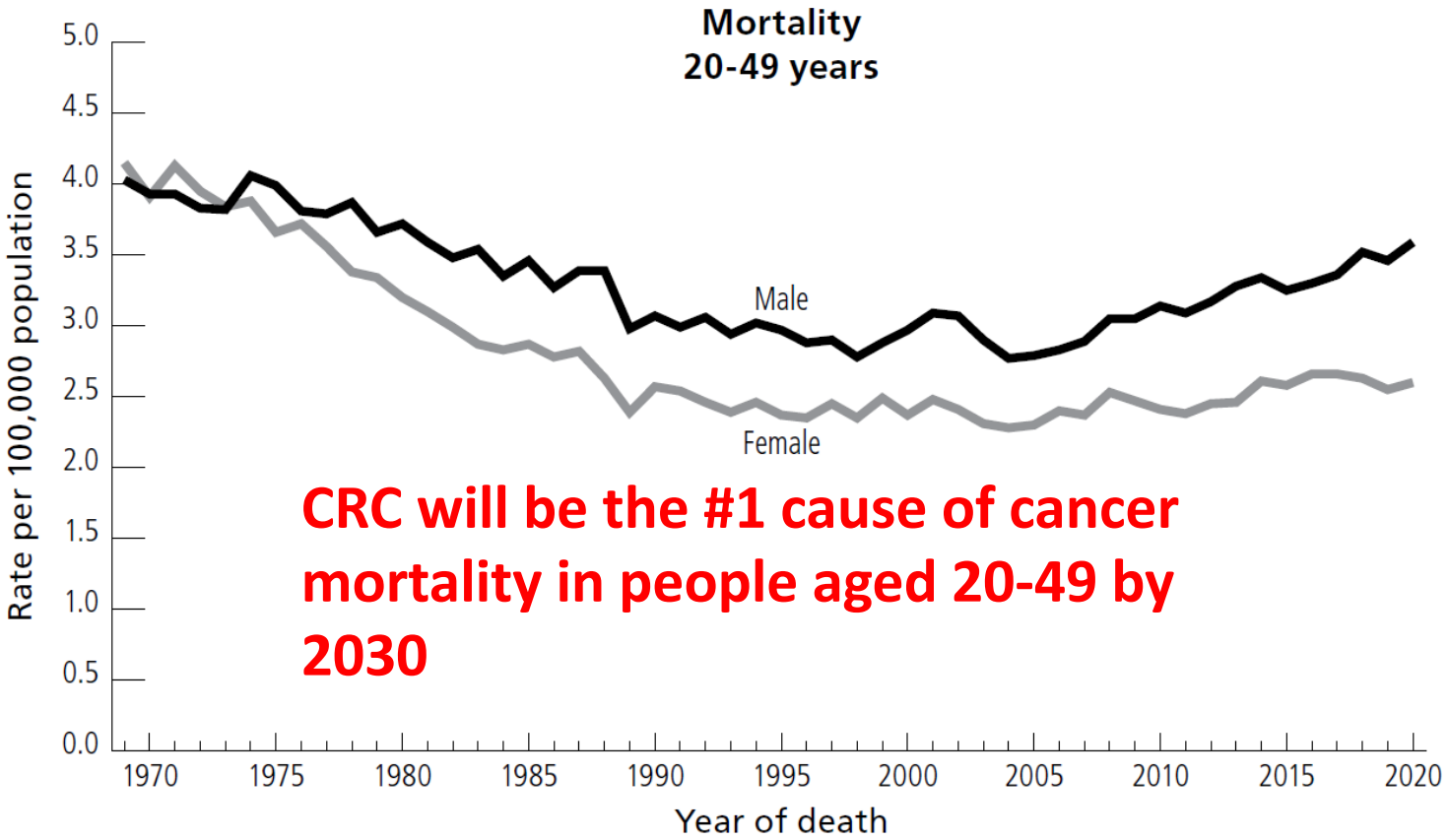


American Cancer Society. Colorectal Cancer Facts & Figures 2023-2025. Atlanta: American Cancer Society; 2023.

But INCREASING in EOCRC Patients



The equivalent of 49 <u>new</u> diagnoses per day



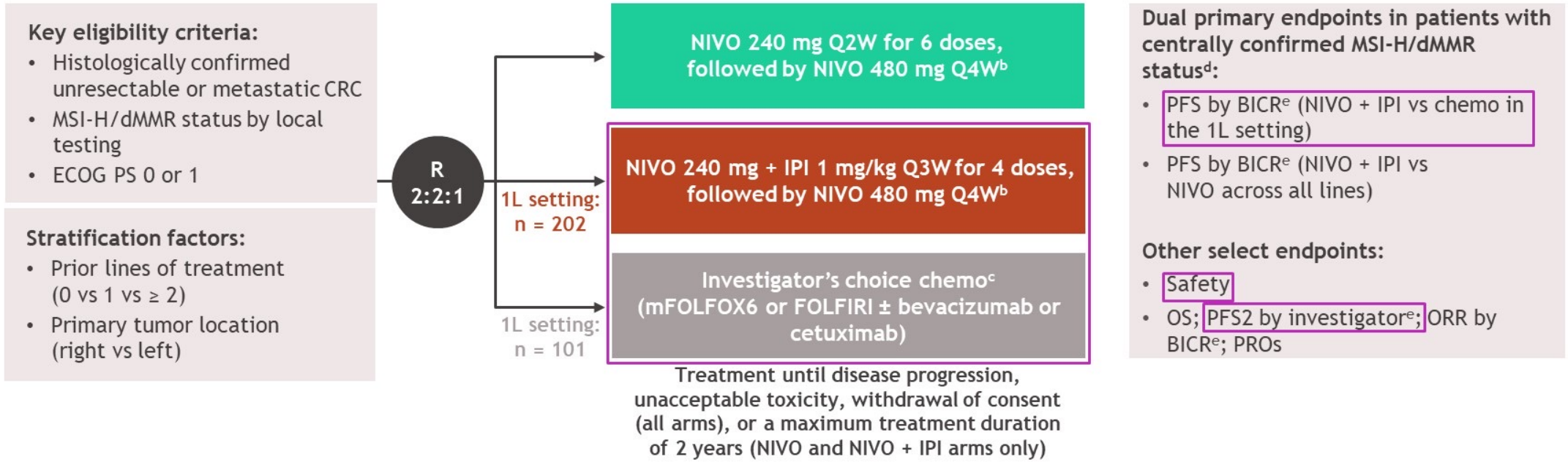
CRC will be the #1 cause of cancer mortality in people aged 20-49 by 2030

American Cancer Society. Colorectal Cancer Facts & Figures 2023-2025. Atlanta: American Cancer Society; 2023.

Current Developments in Colorectal Cancer

CheckMate 8HW study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

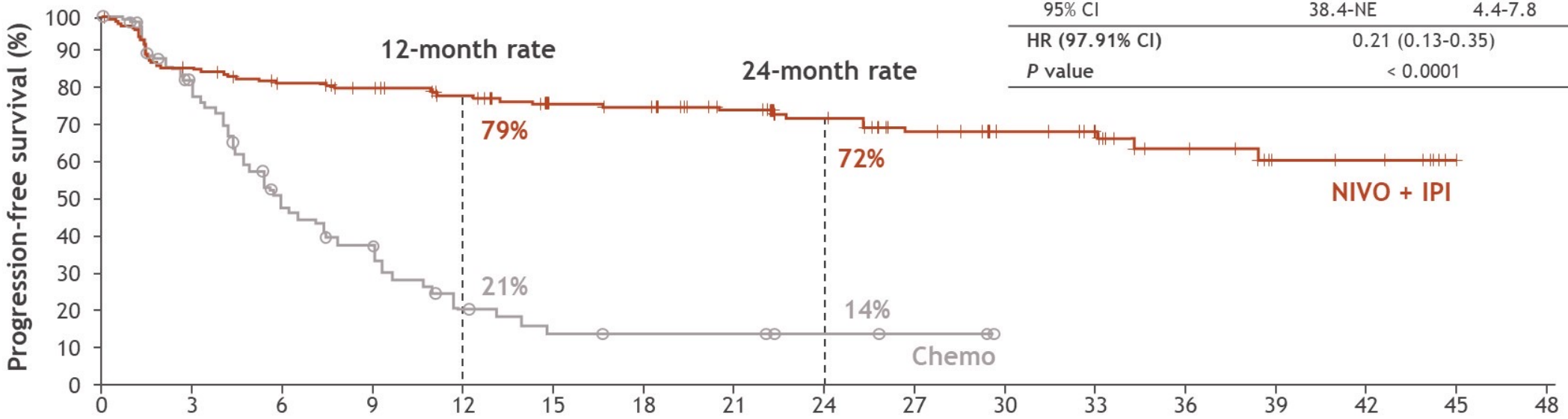


- At data cutoff (October 12, 2023), the median follow-up[f] was 31.5 months (range, 6.1-48.4)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and data cutoff.

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



No. at risk

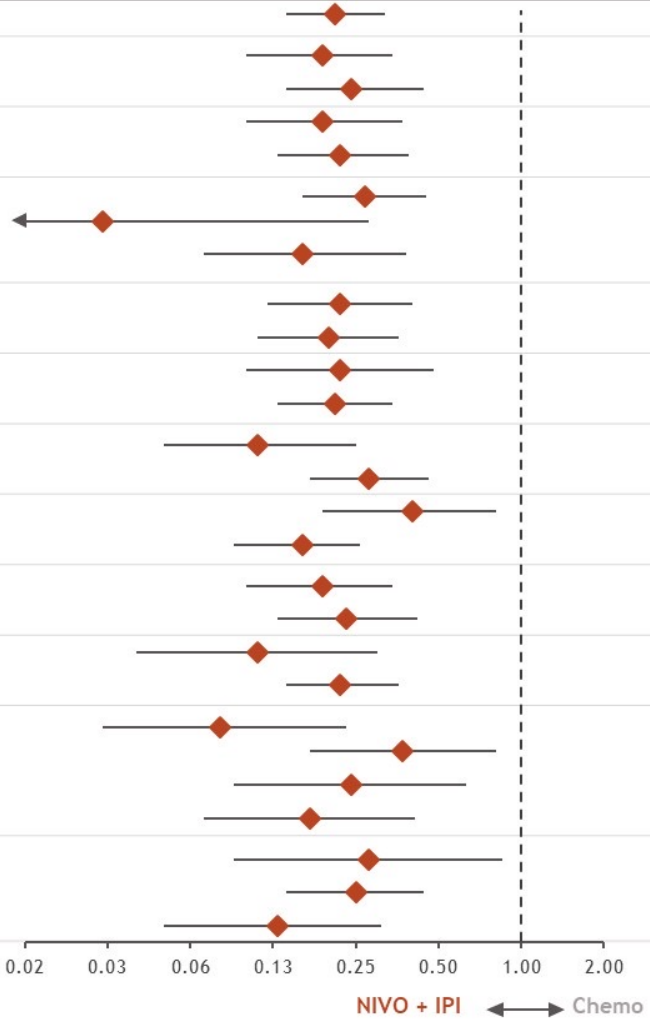
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity and supportive analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23–0.46)

[a]Per BICR. [b]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

Progression-free survival subgroup analysis

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13



[a]Per BICR.

Subsequent therapy

Subsequent therapy (1L centrally confirmed MSI-H/dMMR),[a-c] n (%)	NIVO + IPI (n = 171)	Chemo (n = 84)
Any subsequent therapy	26 (15)	58 (69)
Radiotherapy	1 (< 1)	1 (1)
Surgery	5 (3)	4 (5)
Systemic therapy	20 (12)	57 (68)
Immunotherapy	7 (4)	56 (67)
On-study crossover to NIVO + IPI	0	39 (46)
Non-study immunotherapy	7 (4)	17 (20)
EGFR inhibitors	5 (3)	1 (1)
Platinum compounds	8 (5)	3 (4)
VEGFR targeted therapy	5 (3)	4 (5)
MEK, *NRAS*, and *BRAF* inhibitors	2 (1)	1 (1)
Other systemic anticancer therapy	12 (7)	5 (6)

- In the chemo arm, 67% of patients received subsequent immunotherapy, including 46% who crossed over to receive on-study NIVO + IPI and 20% who received subsequent non-study immunotherapy

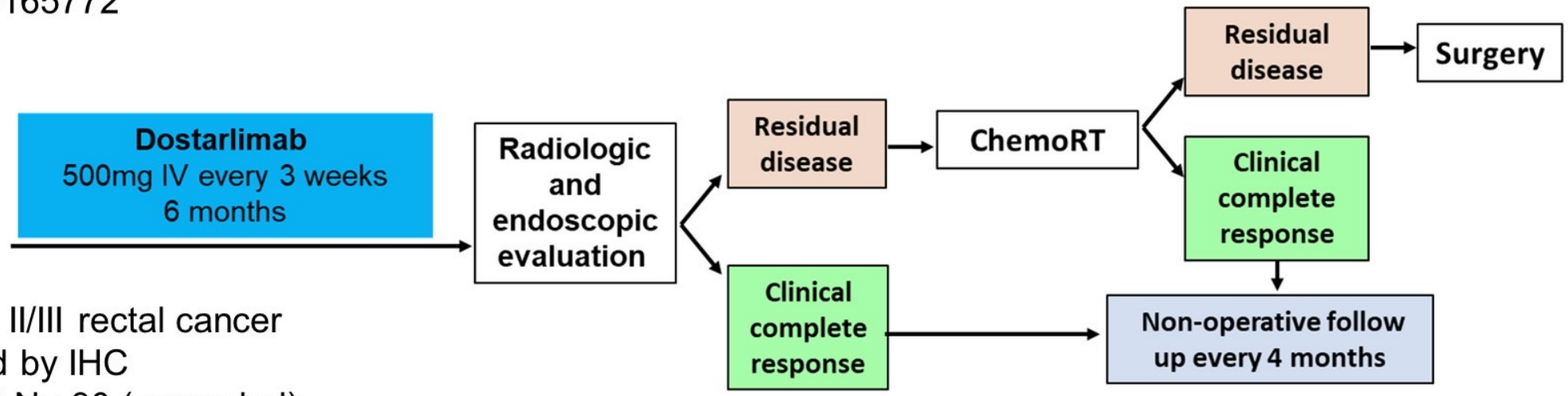
[a]Excludes surgery, radiotherapy, or non-study systemic therapy data collected on or after first crossover dose date. [b]Patients may have received more than 1 type of subsequent therapy. [c]Patients who received crossover treatment in the chemo arm are counted.

Summary

- 1L NIVO + IPI demonstrated superior PFS vs chemo in patients with centrally confirmed MSI-H/dMMR mCRC (HR, 0.21 [97.91% CI, 0.13–0.35]; *P* < 0.0001)
  - 24-month PFS rates for NIVO + IPI vs chemo: 72% vs 14%
  - PFS benefit across all prespecified subgroups, including patients with *BRAF* or *RAS* mutations
- PFS2 favored NIVO + IPI vs chemo (HR, 0.27 [95% CI, 0.17–0.44]) despite a high crossover rate, suggesting clinical benefit is maintained after subsequent therapy
  - 24-month PFS2 rates for NIVO + IPI vs chemo: 83% vs 52%
- The safety profile of NIVO + IPI was different compared with chemo, with fewer grade 3/4 TRAEs despite longer treatment duration
  - Safety of NIVO + IPI was consistent with the known profiles of each individual component, with no new safety signals
- **These results provide further evidence to support NIVO + IPI as a standard-of-care 1L treatment option for patients with MSI-H/dMMR mCRC**

Neoadjuvant PD1 blockade in dMMR locally advanced rectal cancer

NCT04165772



Stage II/III rectal cancer
MMRd by IHC
Target N= 30 (expanded)

Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT

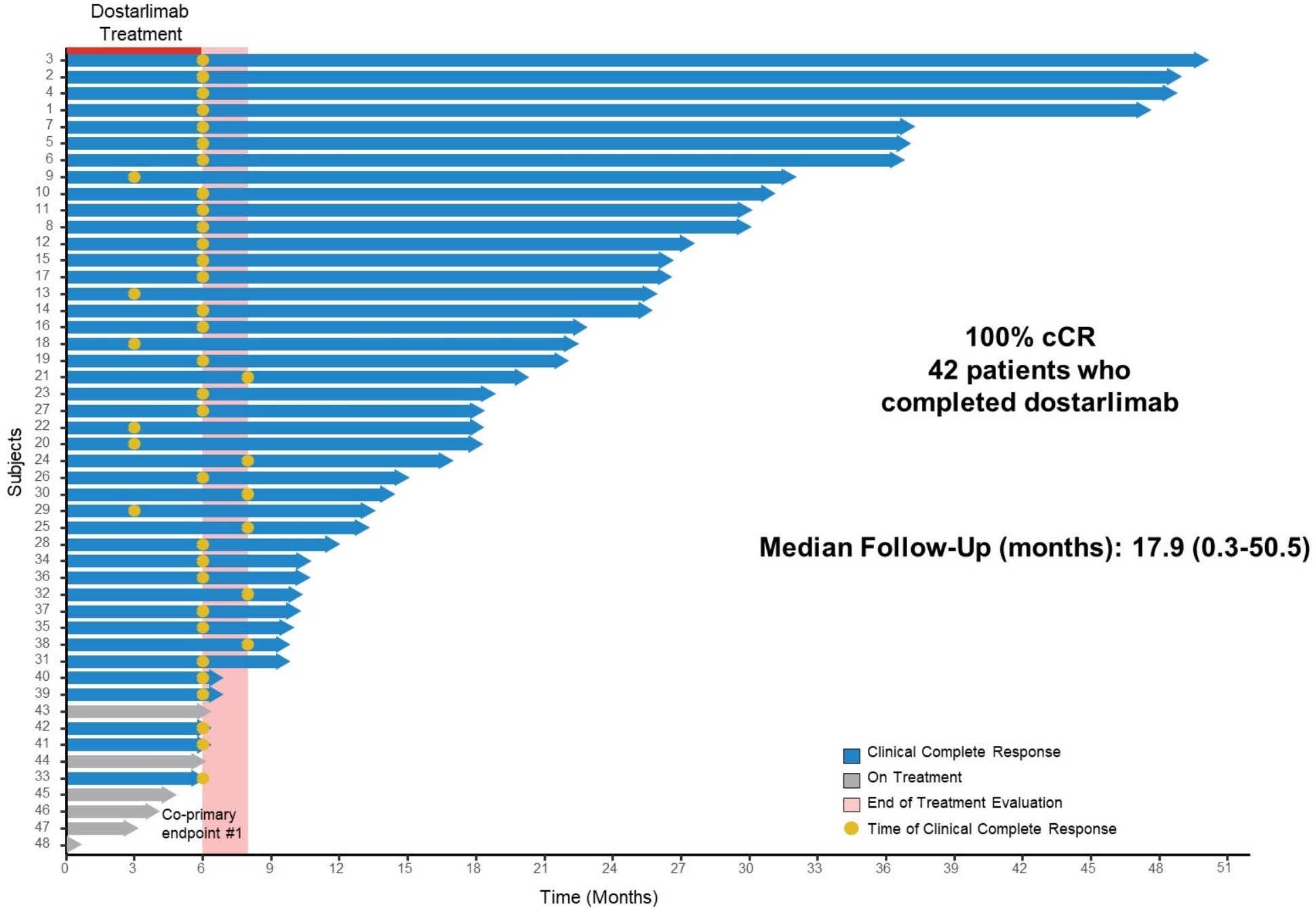
Sample Collection: ctDNA, biopsy, imaging

Baseline, 6 weeks, 3 mo, 6 mo and q4 mo during NOM

Cercek, et al. NEJM 2022

Patient Demographics N= 48	N (%)
Female Sex	**28 (58)**
Median Age (range)	**51 (26,78)**
Race	
White	**37 (77)**
Asian	**5(10)**
Black	**6 (13)**
Non Hispanic/Latino	**42 (85)**
Hispanic/Latino	**6 (13)**
Tumor Stage	
T 0/1/2	**10 (21)**
T 3	**23 (48)**
T 4	**15 (31)**
N +	**41 (85)**
Median Distance from anal verge (cm)	**5.1 (0, 14.8)**

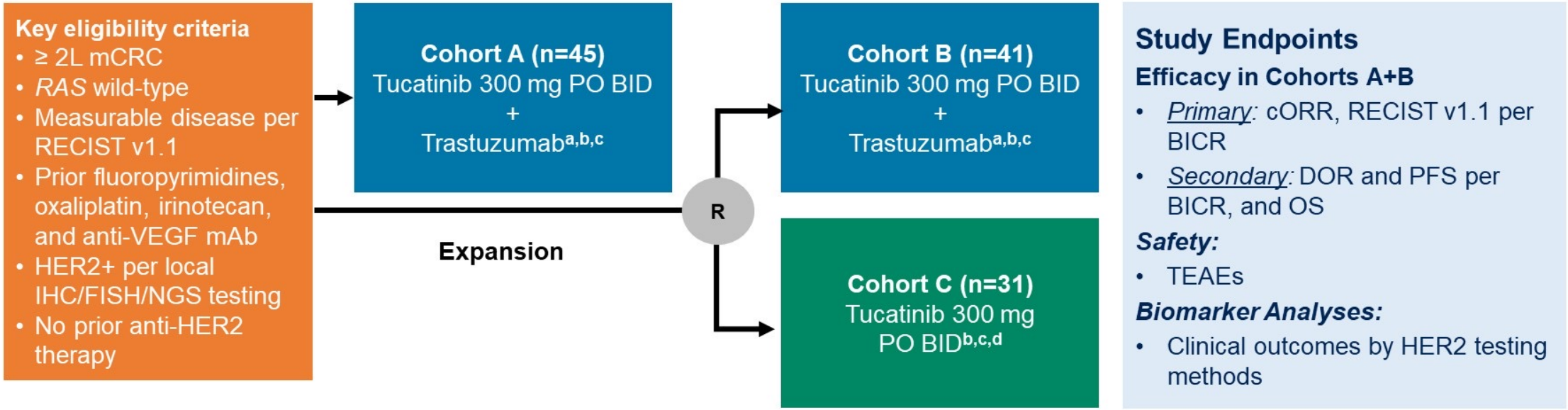
Patient Demographics N= 48		N (%)
ECOG	0	**40 (83)**
	1	**8 (17)**
Pathogenic Germline Mutations Associated with Lynch syndrome (N=41)		**21 (51)**
MSH2		**8 (19)**
MSH6		**4 (10)**
PMS2		**4 (10)**
MLH1		**4 (10)**
Mismatch Repair Deficiency by IHC		
MSH2 alone		**3 (6)**
MSH6 alone		**5 (10)**
PMS2 alone		**5 (10)**
MSH2 and MSH6		**15 (31)**
MLH1 and PMS2		**20 (42)**
Tumor Mutation Burden (range)		**53.6 (27.2-106.3)**
BRAF V600E mutated		**1 (2)**



Conclusions

- 100% clinical complete response in all 42 patients who completed dostarlimab
- Clinical complete responses are durable over 2 years
- No patients have required chemotherapy, radiation or surgery
- AZUR1 Global confirmatory study of dostarlimab in dMMR rectal cancer is ongoing

MOUNTAINEER: Multi-Center, Open-Label, Phase 2 Trial (NCT03043313)



For the final analysis (cutoff date of November 2, 2023), the efficacy and safety endpoints evaluated remained the same. Biomarker analyses, including a long-term responder analysis, were exploratory

[a] 6 mg/kg Q3W (loading dose 8 mg/kg); [b] each treatment cycle is 21 days; [c] Patients remained on therapy until evidence of radiographic or clinical progression or death, unacceptable toxicity, withdrawal of consent, or study closure; [d] Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a partial or complete response by week 12.
≥ 2L, second line and later; BICR, blinded independent central review; BID, twice a day; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; R, randomization; *RAS*: rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE; treatment-emergent adverse event; VEGF, vascular endothelial growth factor.

PRESENTED BY: John H. Strickler

MOUNTAINEER: Key Findings & Conclusions

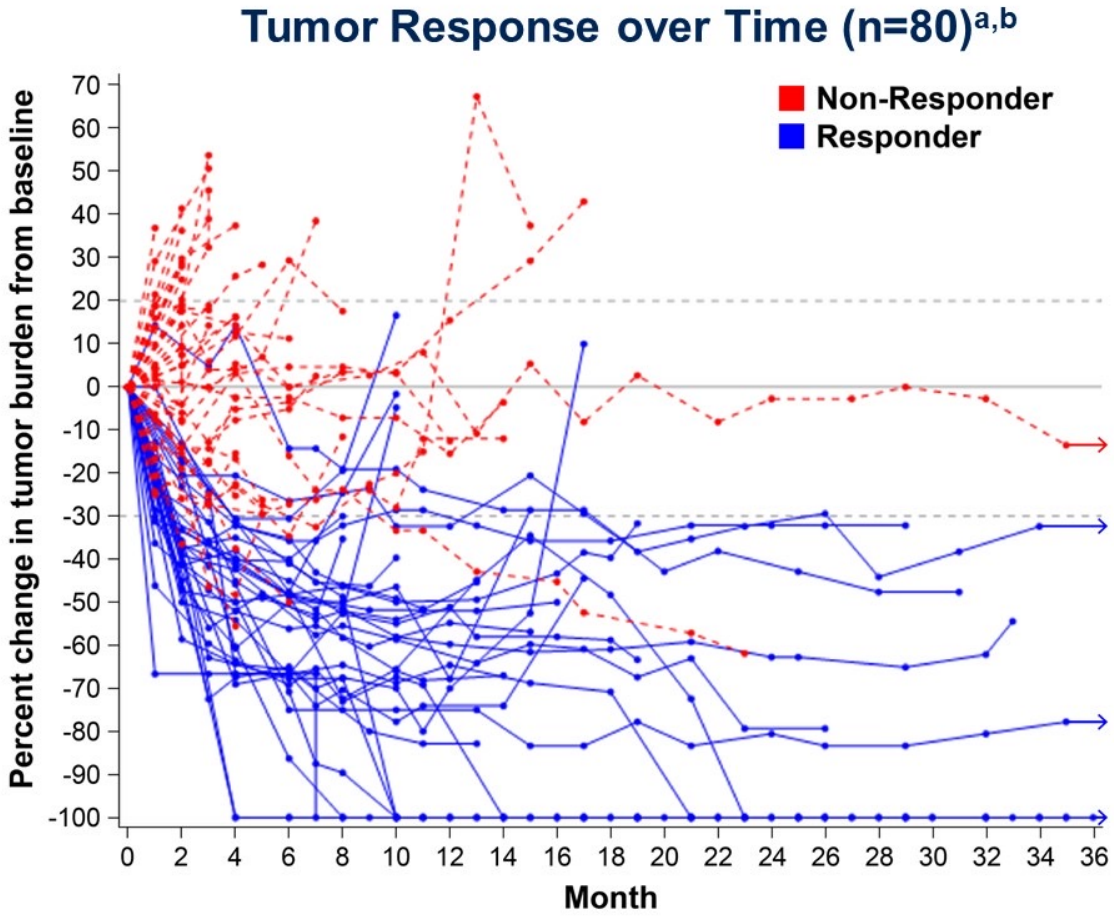
- MOUNTAINEER was a multi-center, open-label, phase 2 trial that evaluated the efficacy and safety of tucatinib + trastuzumab and tucatinib monotherapy in adults with chemotherapy-refractory, HER2+, *RAS* wild-type, unresectable or mCRC
- In this **final analysis**, with a median 32.4-month follow-up, tucatinib + trastuzumab continued to be well tolerated with sustained and clinically meaningful efficacy
  - cORR of 39.3%
  - Median DOR of 15.2 months
  - Median PFS of 8.1 months
  - Median OS of 23.9 months
- Clinical efficacy was similar across HER2 testing methods, supporting the use of a variety of available tests to identify patients who could benefit from tucatinib + trastuzumab
- This final analysis of the MOUNTAINEER trial reaffirms the clinically meaningful anti-tumor activity and favorable tolerability of tucatinib + trastuzumab, a chemotherapy-free treatment option for patients with HER2+ mCRC

cORR, confirmed objective response rate; DOR, duration of response; FDA, US Food and Drug Administration; HER2+, human epidermal growth factor receptor 2-positive; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma virus.

Final Analysis: Efficacy Outcomes

	Cohorts A+B Final analysis (n=84)
cORR, % (95% CI)	**39.3** (28.8–50.5)
Median DOR, mo (95% CI)	**15.2** (8.9–20.5)
Median PFS, mo (95% CI)	**8.1** (4.2–10.2)
Median OS, mo (95% CI)	**23.9** (18.7–28.3)

- Median follow-up: 32.4 months



[a] Data up to 36 months are included; [b] Arrows denote treatment duration beyond 36 months.
CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival.

Long-term Response (LTR) Analysis

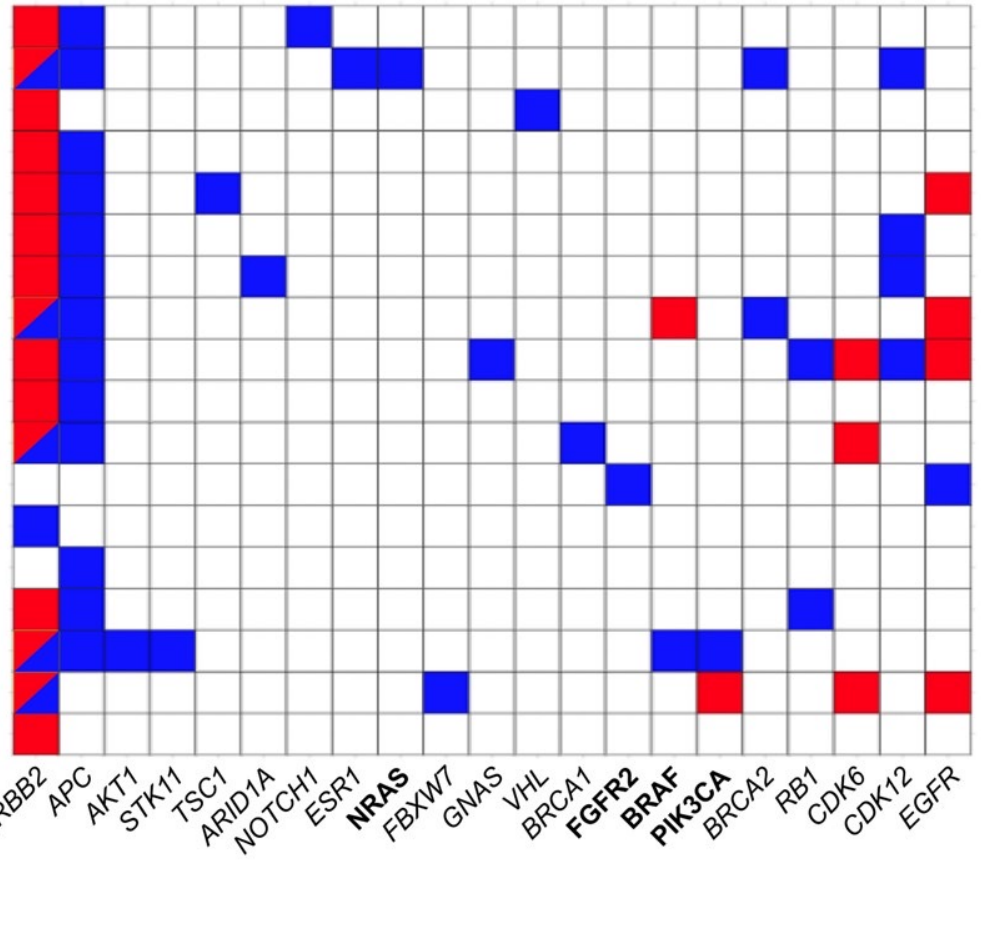
- 23 of 84 (27%) patients[a,b] had LTRs, defined as having >12 months duration of treatment with CR/PR/SD
- LTR status was found among a range of HER2 expression levels
- No evident associations between LTR status and clinicopathologic features, HER2 expression level, or genomic alterations were found

SNV/INDEL | Amplification | SNV/INDEL and amplification

A single blue or red/blue box can represent multiple SNV/INDEL detections in the same gene.

Tumor biomarker alterations by ctDNA analysis and treatment response

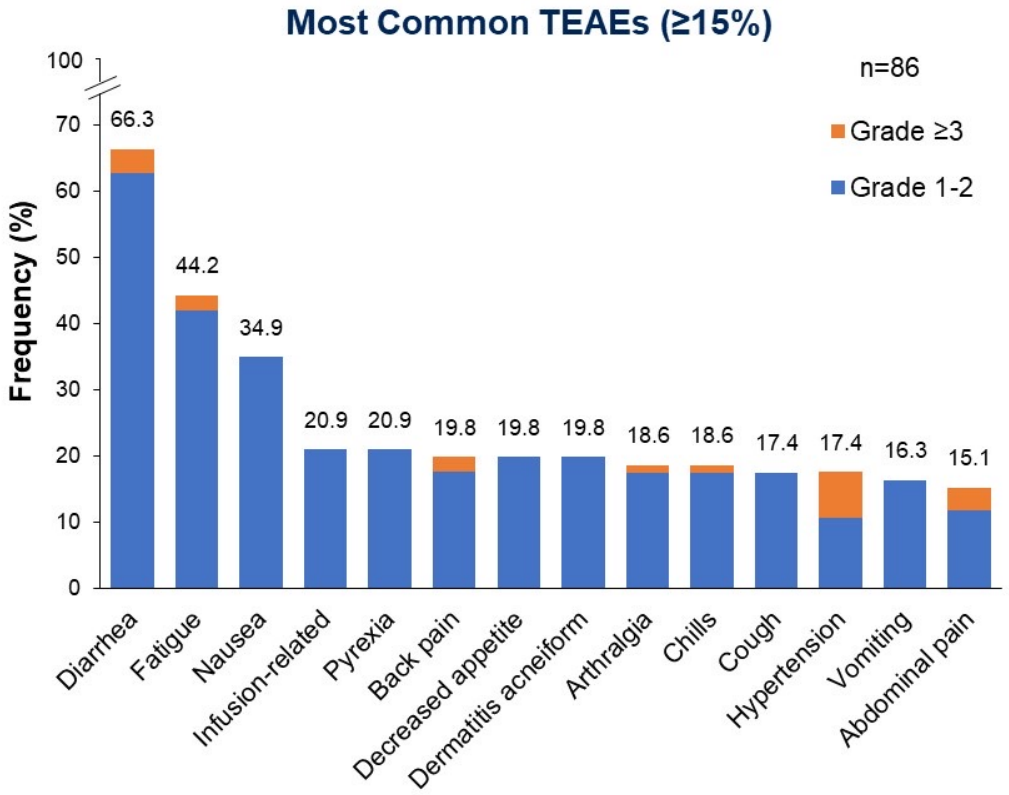
Treatment lines	HER2 IHC	HER2 copies	HER2:CEN17 ratio	Response	PFS
2	2+	17.3	10.8	CR	62.7
2	3+	16.7	7.2	PR	48.4
4	3+	19.2	8.3	SD	45.8
2	3+	19.7	10.4	CR	42.1
2				PR	41.7
1	3+	14.8	5.8	PR	30.6
2	3+	16.4	8	PR	22.8
3				PR	22.2
2	3+	16.5	7.9	PR	20.7
2	3+	20	14.8	CR	20
3	3+	20	9.5	PR	18.5
2	3+	13.2	6	PR	15.5
3	2+	7	2.5	PR	15.2
2	2+	9.9	6.8	SD	14.3
1	3+	20	6.8	PR	13.8
4	3+	20	11.4	PR	13.1
4	3+	18.5	6.8	PR	12.6
2	3+	17.8	12.3	PR	12.5

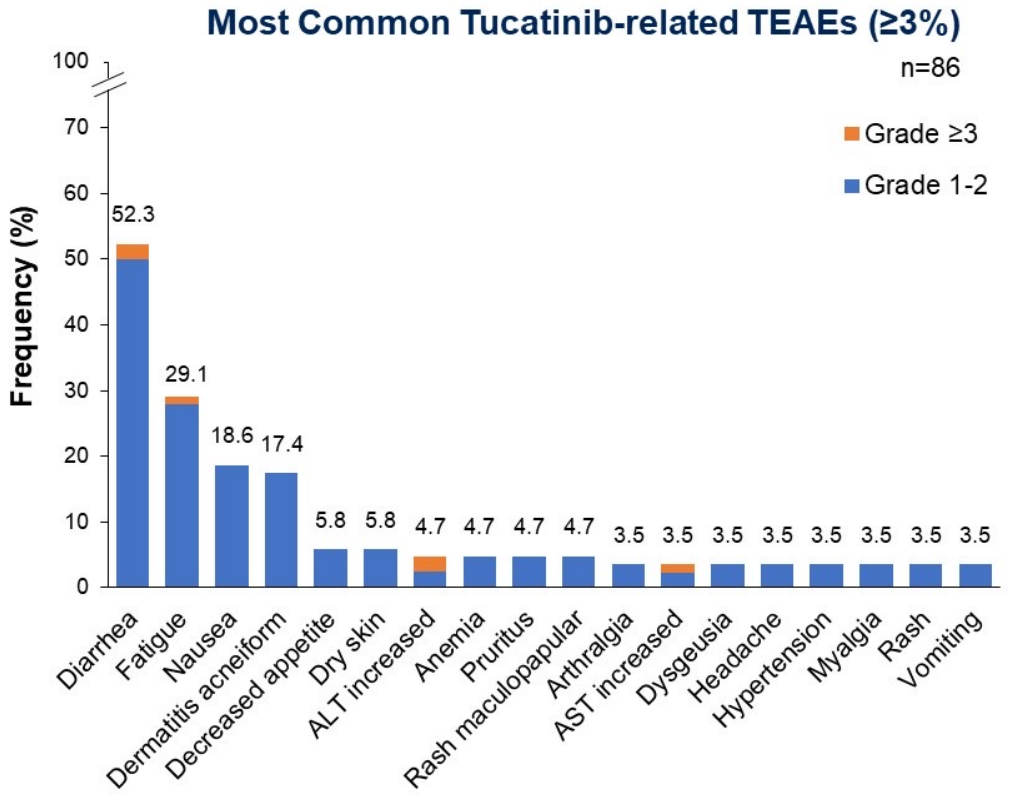


[a] 5/23 (22%) with no co-occurring alterations or no ctDNA results available; [b] 18/23 (78%) with co-occurring alterations.
CEN17, centromere of chromosome 17; ctDNA, circulating tumor DNA; CR, complete response; DOR, duration of response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INDEL, insertions and deletions; PFS, progression-free survival; PR, partial response; SD, stable disease; SNV, single nucleotide variant.

TEAEs in Cohorts A+B

- Majority of TEAEs were low grade, and rates were stable with longer follow-up
- Common TEAEs included diarrhea (66.3%), fatigue (44.2%) and nausea (34.9%)
- Most tucatinib-related TEAEs were of low grade





AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Efficacy by Central HER2 Testing Methods

- Clinical efficacy was similar across all 3 central HER2 testing methods

HER2 results	Tissue IHC/FISH		Tissue NGS (PGDx)		Blood NGS (G360)	
	+ (n=60)	– (n=10)	+ (n=44)	– (n=6)	+ (n=59)	ND (n=16)
cORR, % (95% CI)	41.7 (29.1–55.1)	10.0 (0.3–44.5)	50.0 (34.6–65.4)	0 (0–45.9)	42.4 (29.6–55.9)	25.0 (7.3–52.4)
Median DOR, mo (95% CI)	16.6 (11.4–25.5)	–	16.6 (10.6–18.8)	–	16.6 (8.3–18.8)	15.2 (11.4–NE)
Median PFS, mo (95% CI)	10.1 (4.2–14.5)	2.8 (1.2–6.3)	10.9 (6.8–20.0)	2.1 (1.3–NE)	8.1 (3.1–10.3)	6.3 (2.0–25.5)

Note: To be included in this analysis, a patient had to have a local HER2+ test and ≥1 central HER2+ test from IHC/FISH, tissue-based NGS, and/or blood-based NGS.

CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescent in situ hybridization; G360, Guardant360® CDx test; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mo, months; ND, not detected; NE, not estimable; NGS, next-generation sequencing; PFS, progression-free survival; PGDx, PGDx elio tissue complete.

CodeBreaK 300 Phase 3 Study Design: OS Update

Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)

Key eligibility criteria

- ≥ 18 years of age
- *KRAS* G12C–mutated mCRC, identified through central molecular testing
- ≥ 1 prior line of therapy for mCRC; progressed on or after fluoropyrimidine, irinotecan, and oxaliplatin*
- ECOG ≤ 2
- Measurable disease per RECIST 1.1
- No prior $KRAS^{G12C}$ inhibitor†

Stratified by: prior anti-angiogenic therapy (yes / no), **time from diagnosis of mCRC** (≥ 18 mo / < 18 mo), **ECOG status** (0 or 1 / 2)

Randomization 1:1:1 (N = 160)

- **Sotorasib 960 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**
- **Sotorasib 240 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**
- **Investigator's choice: Trifluridine/tipiracil or regorafenib (n = 54)**

Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)

Key secondary endpoints: OS, ORR

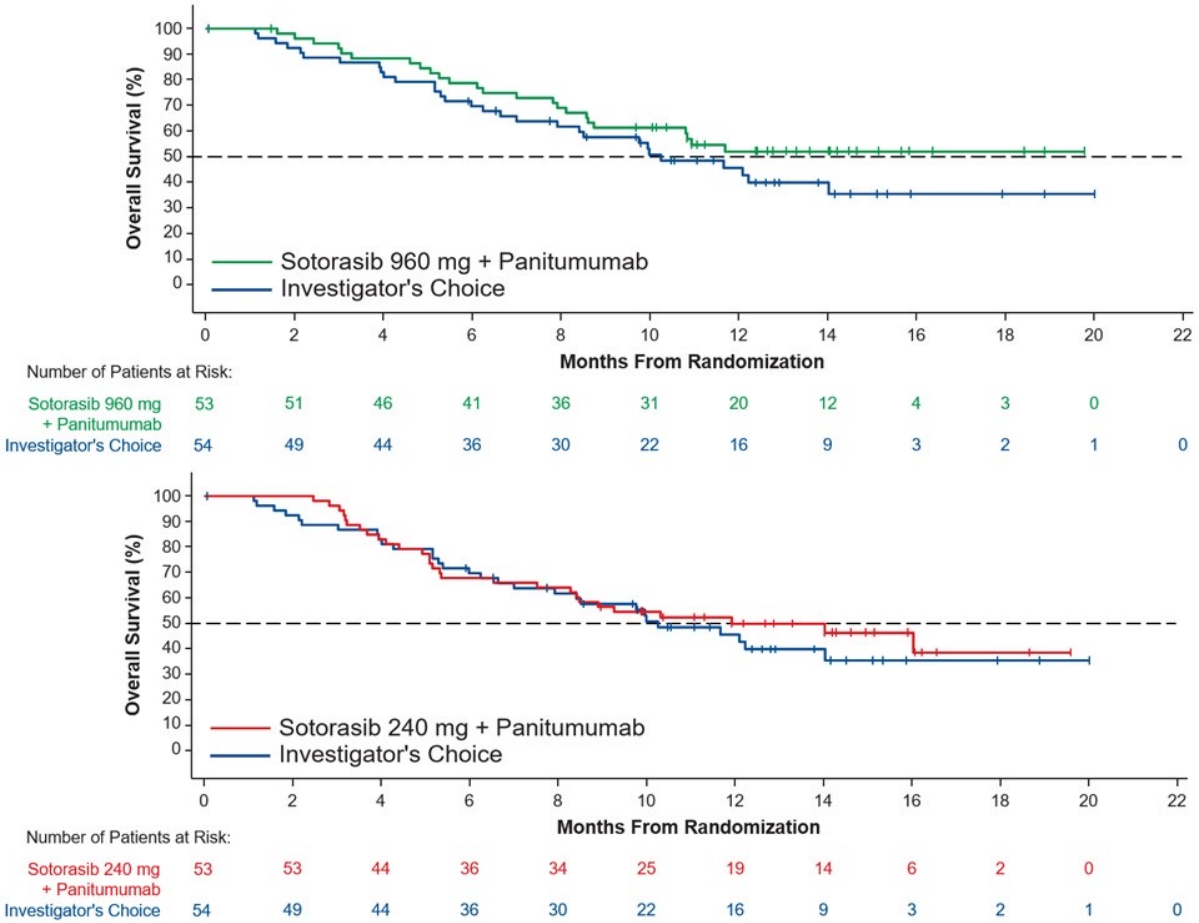
OS analysis was performed at 50% maturity and was not powered for statistical significance

*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †Patients with prior treatment with trifluridine and tipiracil and with regorafenib were excluded, where the investigator's choice would be these agents.

2QW, every 2 weeks; BICR, blinded independent central review; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

PRESENTED BY: Marwan G. Fakih, MD

Secondary Endpoint: Protocol-Specified Final OS in Intent-to-Treat Population



	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median (95% CI) OS, months*	NE (8.6–NE)	11.9 (7.5–NE)	10.3 (7.0–NE)
HR (95% CI)†	0.70 (0.41–1.18)	0.83 (0.49–1.39)	–
P-value (2-sided)‡	0.20	0.50	–
Number of deaths (%)	24 (45)	28 (53)	30 (56)

- **After a median follow-up of 13.6 months, sotorasib (240 mg and 960 mg) + panitumumab showed a trend of improved OS versus investigator's choice, with 30% reduction in risk of death for sotorasib 960 mg + panitumumab**

*Estimated using the Kaplan-Meier method, 95% CIs from log-log transformation. †HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk and a longer OS for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib]. ‡*P*-value from stratified log-rank test. Data cutoff, 18 December 2023. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Conclusions

- While CodeBreaK 300 was not powered to detect a statistically significant difference in OS, the study showed a trend toward improved OS for patients with mCRC randomized to sotorasib 960 mg + panitumumab
  - After a median follow-up of 13.6 months, median OS was not reached with sotorasib 960 mg + panitumumab versus 10.3 months with investigator's choice (HR 0.70, 95%CI 0.41-1.18)
- Updated ORR was 30% (sotorasib 960 mg + panitumumab) versus 2% (investigator's choice)
- Sotorasib 960 mg + panitumumab showed a median DOR of 10.1 months
- **These results support the use of sotorasib 960 mg + panitumumab as a new standard-of-care therapy for patients with chemorefractory *KRAS* G12C–mutated mCRC**

DOR, duration of response; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

2024 ASCO ANNUAL MEETING

Liver Transplantation and Chemotherapy versus Chemotherapy alone in patients with definitively unresectable colorectal liver metastases : results from a prospective, multicentre, randomised trial (TransMet)

R Adam, C Piedvache, L Chiche, E Salamé, O Scatton, V Granger, M Ducreux, U Cillo, F Cauchy, JY Mabrut, C Verslype, L Coubeau, J Hardwigsen, E Boleslawski, F Muscari, J Lerut, L Grimaldi, F Levi, M Lewin, M Gelli

Paris-Saclay – Villejuif – Kremlin Bicêtre (France), Bordeaux (France), Tours (France), Paris (France), Grenoble (France), Villejuif (France), Padova (Italy), Clichy (France), Lyon (France), Leuven (Belgium), Louvain (Belgium), Marseille (France), Lille (France), Toulouse (France), Bruxelles (Belgium)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

PRESENTED BY:

TransMet Trial : Eligibility criteria

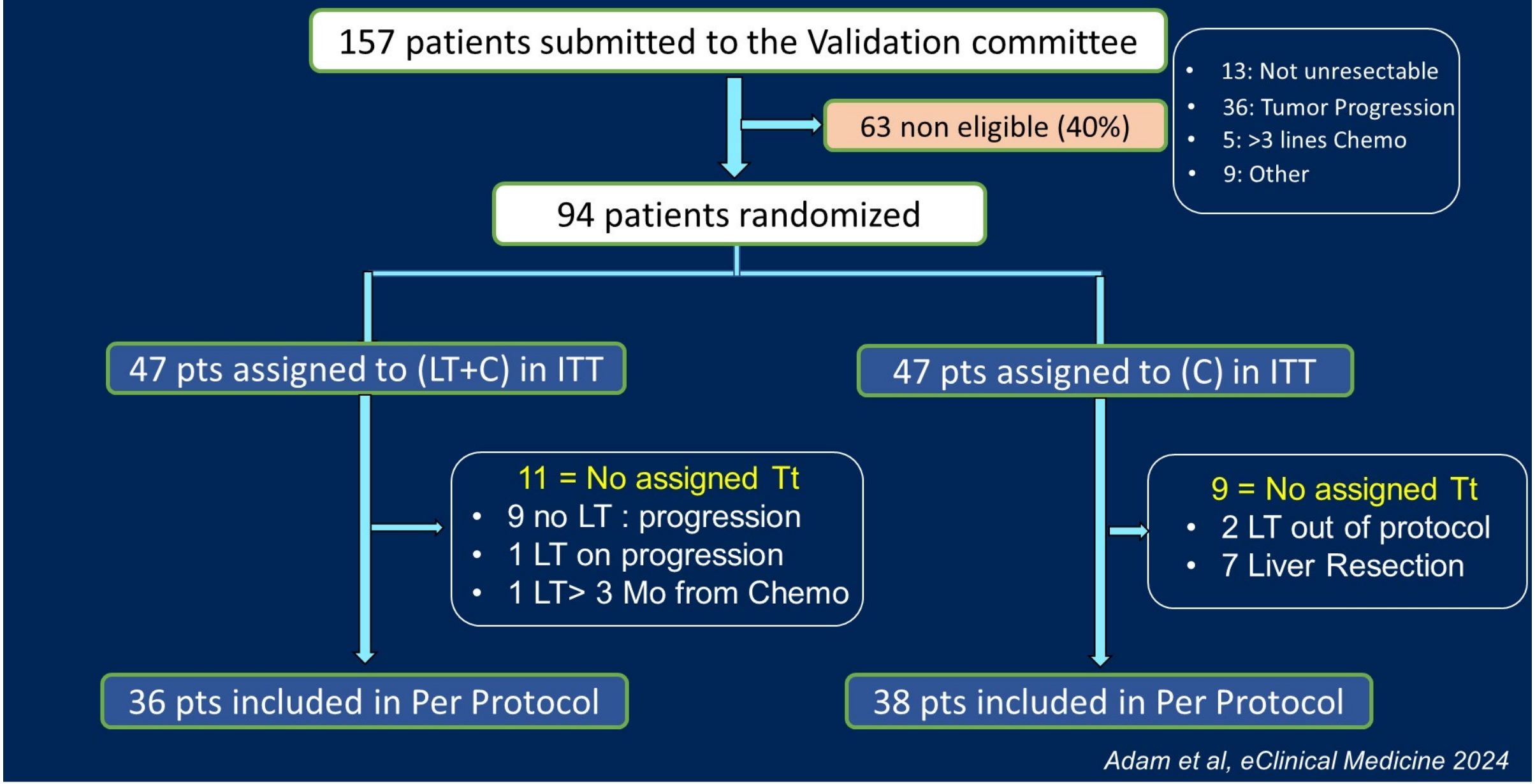
- ≤ 65 years
- Good performance status (ECOG 0 or 1)
- Confirmed unresectability of CLM by expert surgeons
- Gold standard Resection of the primary
- No extrahepatic disease
- Partial Response or Stability with Chemo : ≥ 3 months, ≤ 3 lines
- No BRAF mutation
- CEA < 80 ng/ml or 50% decrease from baseline
- Platelets count > 80.000 and white blood cell count > 2500

TransMet Trial : Patients Demographics at Diagnosis

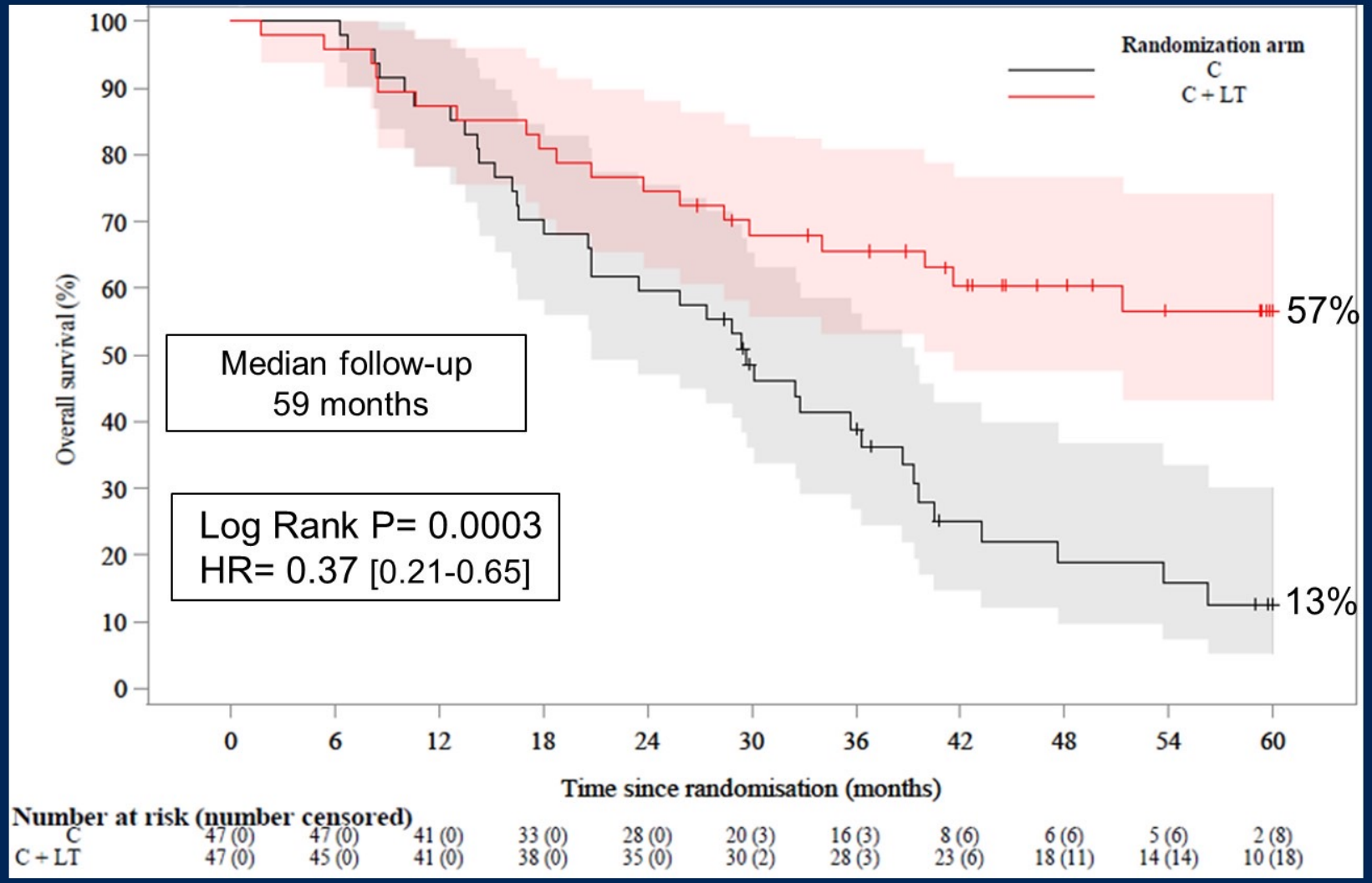
	LT+C group (n=47)	C alone group (n=47)
Age (years)	52·0 (47·0, 59·0)	55·0 (47·0, 59·0)
Gender, n (%)		
Male	27 (57%)	28 (60%)
Female	20 (43%)	19 (40%)
Right sided primary tumour, n (%)	**7 (15%)**	**7 (15%)**
RAS mutation, n (%)	11 (23%)	12 (26%)
No of nodules at diagnosis (Median IQR)	**20·0** (14·0, 25·0)	**20·0** (12·0, 25·0)
< 10	5 (11%)	7 (15%)
Between 10 and 20	19 (40%)	18 (38%)
> 20	23 (49%)	22 (47%)
Diameter max (mm) at diagnosis (Median IQR)	**55·0** (43·0, 76·0)	**50·0** (27·0, 83·0)
Synchronous (0-1 Mo)	**47 (100%)**	**45 (96%)**
CEA (ng/mL) at diagnosis	305·0 (32·9, 762·0)	81·0 (20·0, 530·0)
CA 19-9 (U/mL) at diagnosis	96·0 (19·7, 800·0)	193·0 (20·9, 1949·0)
Fong's clinical risk score > 2	**42 (89%)**	**42 (89%)**

TransMet Trial : Patients Demographics at Randomisation

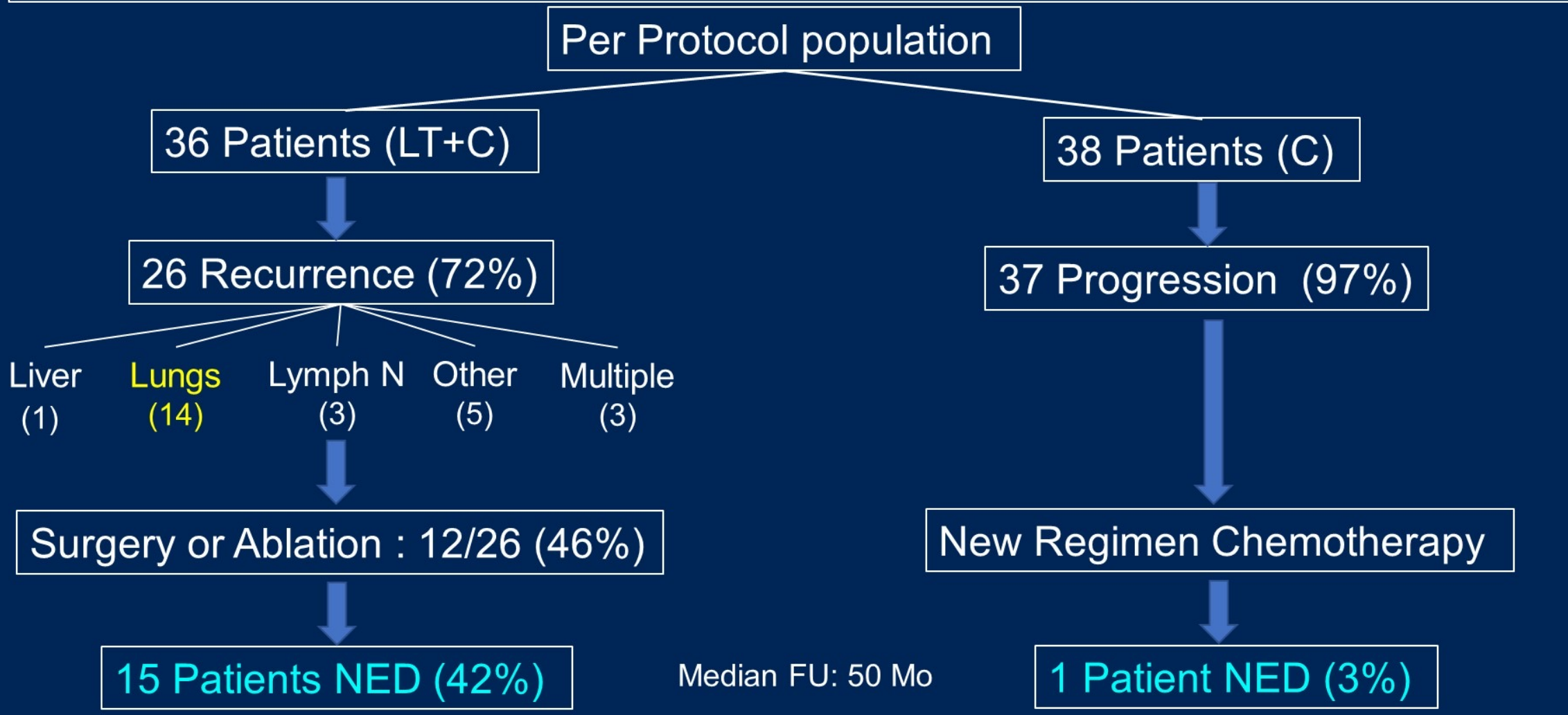
	LT+C group (n=47)	C alone group (n=47)
Type of chemotherapy		
5-FU alone	7 (15%)	1 (2%)
Oxaliplatin-based	12 (26%)	11 (23%)
Irinotecan-based	20 (43%)	27 (57%)
Triplet	8 (17%)	8 (17%)
Targeted therapy agent		
None	2 (4%)	4 (9%)
Anti-VEGF	17 (36%)	16 (34%)
Anti-EGFR	28 (60%)	27 (57%)
Total Number of lines		
1	18 (38%)	23 (49%)
2	21 (45%)	17 (36%)
3	8 (17%)	7 (15%)
Total Number of cycles (Median (IQR)	**21.0** (18.0, 29.0)	**17.0** (12.0, 24.0)
Tumour response		
Partial response	26 (55%)	21 (45%)
Stable disease	21 (45%)	26 (55%)
Delay primary resection – randomisation (Mo)	**16** (12 - 26)	**13·5** (9 - 19)
Delay randomization – LT (days)	51 (30 - 65)	-



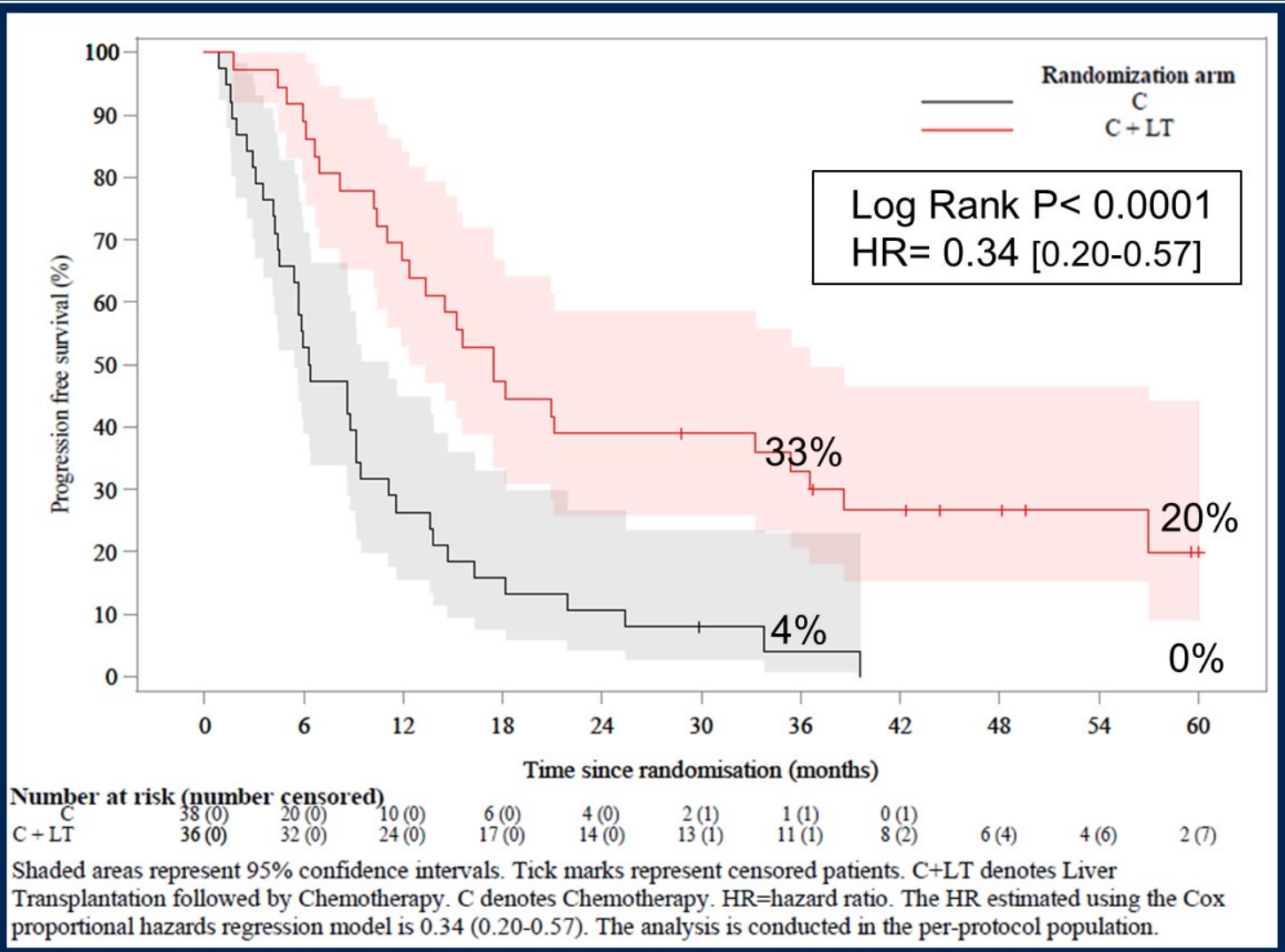
TransMet Trial : Primary Endpoint 5-Yr OS (ITT)



TransMet Trial : Recurrence (LT+C) or Progression (C)



TransMet Trial : Secondary Endpoint 3-5-Yr PFS (Per Protocol)

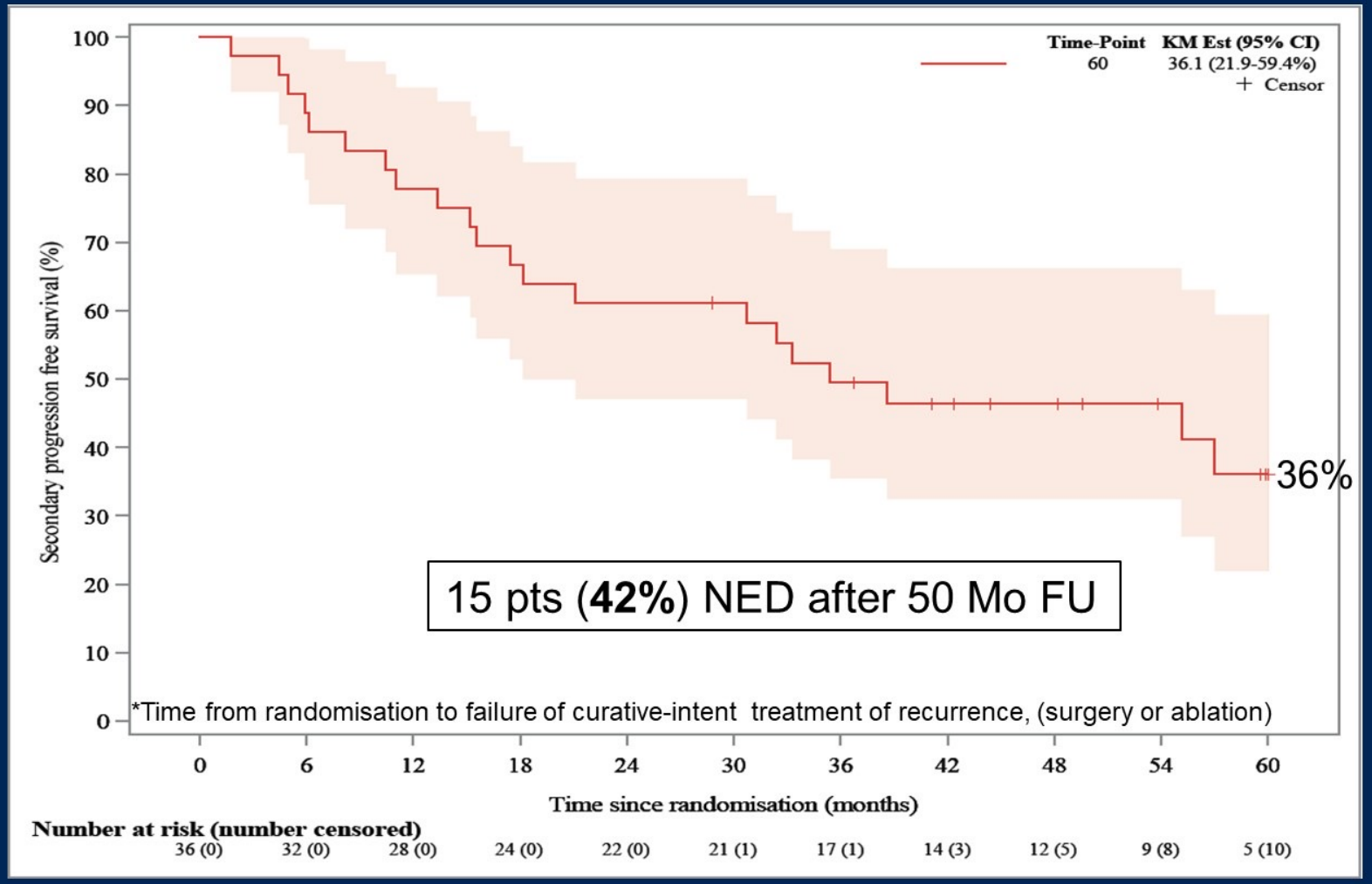


Number at risk (number censored)

C	38 (0)	20 (0)	10 (0)	6 (0)	4 (0)	2 (1)	1 (1)	0 (1)			
C + LT	36 (0)	32 (0)	24 (0)	17 (0)	14 (0)	13 (1)	11 (1)	8 (2)	6 (4)	4 (6)	2 (7)

Shaded areas represent 95% confidence intervals. Tick marks represent censored patients. C+LT denotes Liver Transplantation followed by Chemotherapy. C denotes Chemotherapy. HR=hazard ratio. The HR estimated using the Cox proportional hazards regression model is 0.34 (0.20-0.57). The analysis is conducted in the per-protocol population.

TransMet Trial : 5-Yr PFS* after Rescue Surgery in LT+C group

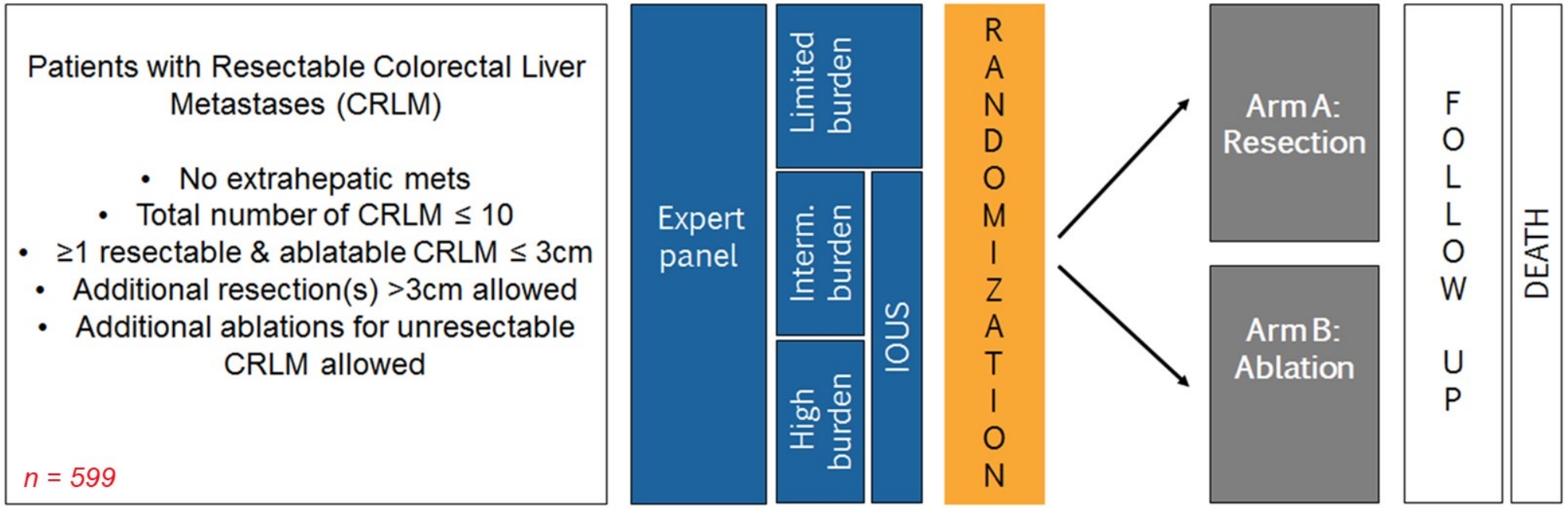


Take Home messages from the TransMet trial

- Liver Transplantation + Chemotherapy significantly improves OS and PFS in selected patients with unresectable colorectal liver metastases compared to C alone
- These results were obtained through a rigorous patient selection and a prioritization for organ allocation
- Transplanted patients for CLM have similar survival (73% at 5 years) as those transplanted for established LT indications
- LT +C offers a potential of cure to cancer patients with otherwise poor long-term outcome

→ These results support LT as a new standard option that could change our practice in treating patients with liver-only, definitively unresectable CLM.

COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation



Phase III international multicenter randomized controlled trial to prove / disprove hypothesis of non-inferiority of thermal ablation compared to surgical resection for small-size colorectal liver metastases (CRLM)

- Approach (percutaneous, laparoscopic or open) according to local expertise
- If limited disease burden (max 3 CRLM ≤ 3cm) consider percutaneous / laparoscopic approach
- If intermediate or high disease burden randomize after eligibility check (after IOUS) during OR (single-blind)

DESIGN

PREDEFINED HALFTIME STOPPING RULES (n = 300 / 599)

COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation

STOPPING RULES FOR FUTILITY

- higher number of **adverse events** (CTCAE) in the experimental arm (ablation)
- **conditional probability** to prove non-inferiority of the experimental arm (ablation) <20%

STOPPING RULES FOR BENEFIT

- lower number of **adverse events** (CTCAE) in the experimental arm (ablation)
- no significant difference or superiority regarding **local control** in the experimental arm (ablation)
- **conditional probability** to prove non-inferiority of the experimental arm (ablation) >90%

RESULTS

BASELINE CHARACTERISTICS

Patient-related characteristics		Resection N = 148	Ablation N = 148
Age in years	Mean (range)	65.1 (31.4 – 87.4)	67.9 (29.2 – 85.7)
Sex	Male	107 (72.3%)	100 (67.6%)
	Female	41 (27.7%)	48 (32.4%)
ASA	2	121 (81.1)	102 (68.90%)
	3	27 (18.2%)	45 (30.4%)
Charlson's comorbidity index	None	74 (50%)	53 (35.8%)
	Minor	70 (47.3%)	69 (46.6%)
	Major	4 (2.7%)	26 (17.6%)
BMI in kg/m²	Mean (range)	26.1 (17.2-45.5)	26.5 (18.6-42.7)
Disease-related characteristics		**N = 148**	**N = 148**
Primary tumor	Right-sided	40 (27.0%)	33 (22.3%)
	Left-sided	50 (33.8%)	57 (38.5%)
	Rectum	58 (39.2%)	58 (39.2%)
T-stage	1	3 (2.0%)	4 (2.7%)
	2	15 (10.1%)	22 (14.9%)
	3	97 (65.5%)	93 (62.8%)
	4	33 (22.3%)	29 (19.6%)
N-stage	0	33 (22.3%)	55 (37.2%)
	1	79 (53.4%)	61 (41.2%)
	2	36 (24.3%)	32 (21.6%)
M-stage (at diagnosis primary tumor)	0	79 (53.4%)	71 (48.0%)
	1	69 (46.6%)	77 (52.0%)
Molecular profile [x]	RASwt / mut	24 / 27	25 /22
	BRAFwt / mut	45 / 6	41 / 5
	MSS / MSI	143 / 1	98 / 0

- **pMMR (MSS) in 99.6%!**
- RAS mutation in 50.0%
- BRAF mutation in 11.3%
- Unknown RAS/BRAF in 2/3rds!
- Synchronous CRLM in 49.3%
- Metachronous CRLM in 50.7%

RESULTS

BASELINE CHARACTERISTICS

Procedure-related characteristics		N = 148	N = 148	
Subgroup	A low disease burden	89 (60.1%)	94 (64.2%)	0.469
	B intermediate disease burden	50 (33.8%)	41 (27.7%)	
	C high disease burden	9 (6.1%)	12 (8.1%)	
Preprocedural systemic therapy	No	112 (75.7%)	118 (79.7%)	0.485
	Yes	36 (24.3%)	30 (20.3%)	
	Capecitabine	2 (1.4%)	2 (1.4%)	
	CAPOX	2 (1.4%)	3 (2.0%)	
	CAPOX-B	23 (15.6%)	21 (14.2%)	
	FOLFOX-B	2 (1.4%)	2 (1.4%)	
	FOLFIRI-B	2 (1.4%)	1 (0.7%)	
	FOLFIXIRI-B	4 (2.7%)	1 (0.7%)	
	Missing	1 (0.7%)	0 (0%)	
Procedures	Resection alone	90 (60.8%)	0 (0%)	
	Ablation alone	1 (0.72.0%) *	118 (79.7%)	
	Resection + ablation	52 (35.1%)	27 (18.2%)	
	No local treatment	5 (3.4%)	3 (2.1%)	
Cycles of systemic therapy	Median (range)	5.5 (2 – 10)	6 (3 – 12)	0.420
Approach ◦	Percutaneous	2 (1.4%)	84 (56.8%)	
	Laparoscopic	68 (46.6%)	10 (6.8%)	
	Open	76 (52.1%)	54 (36.5%)	
Anesthesia ◦	General	146 (100%)	111 (75.0%)	
	Propofol	0 (0.0%)	37 (25.0%)	
Number of CRLM	Median number CRLM (range)	2 (1 – 10)	2 (1 – 12)	0.964
Tumor-related characteristics		**N = 446**	**N = 447**	
CRLM ◦	Target	304 (68.2%)	349 (78.1%)	
	Non-target (unresectable / unablatable)	142 (31.8%)	98 (21.9%)	
Size CRLM randomization (mm)	Mean size target CRLM (range)	14 (2 – 34)	13 (3 – 34)	0.457
Size CRLM treatment (mm)	Mean size target CRLM (range)	14 (2 – 40)	14 (2 – 50)	0.459

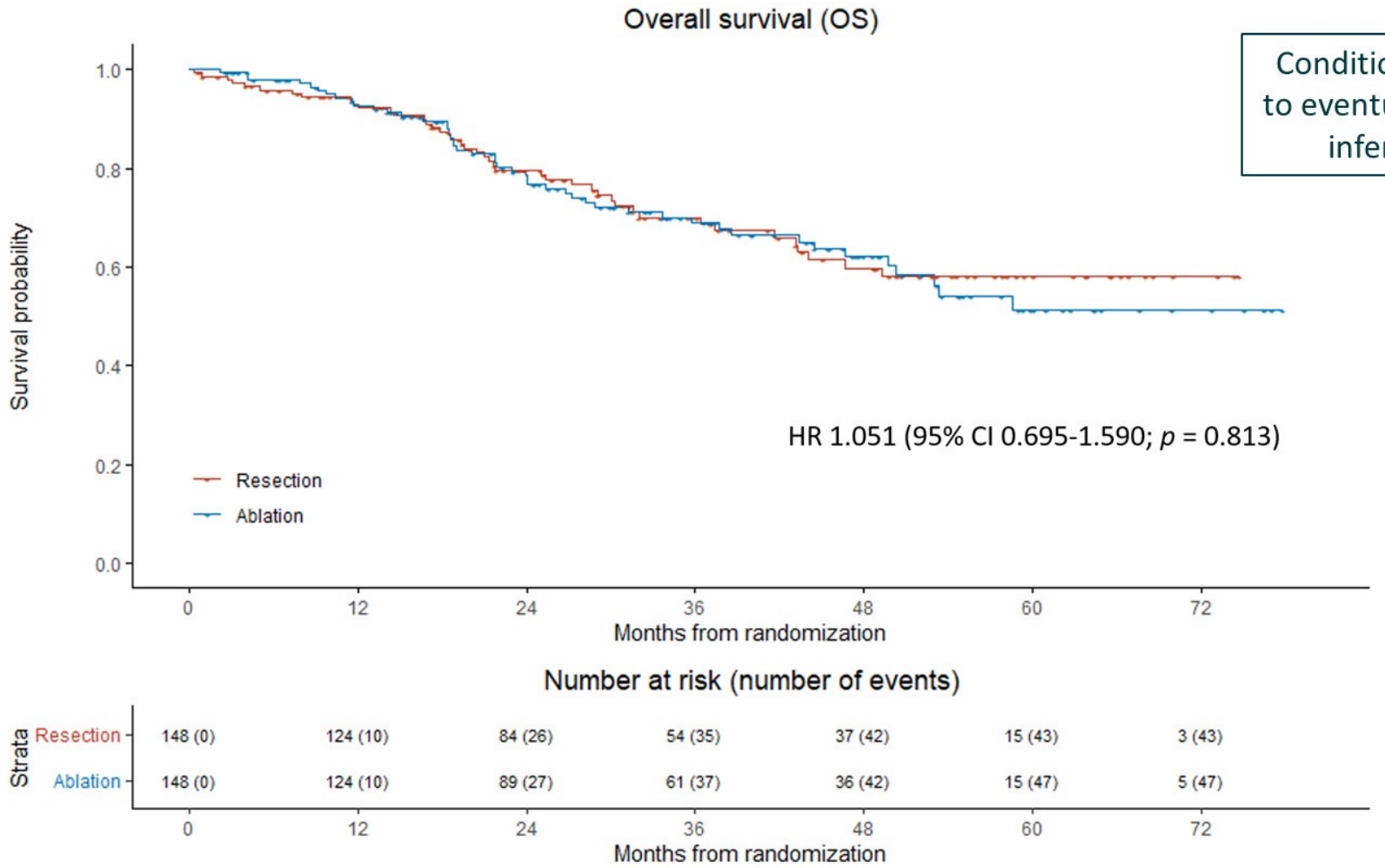
- 62% low disease burden
- **22% chemo first**
- median number CRLM = 2
- mean-size CRLM 14mm

- ***64% of resections in low disease burden group performed using (robot) laparoscopy***

- ***83% of ablations in low disease burden group performed percutaneously***

RESULTS

OVERALL SURVIVAL – PRIMARY ENDPOINT

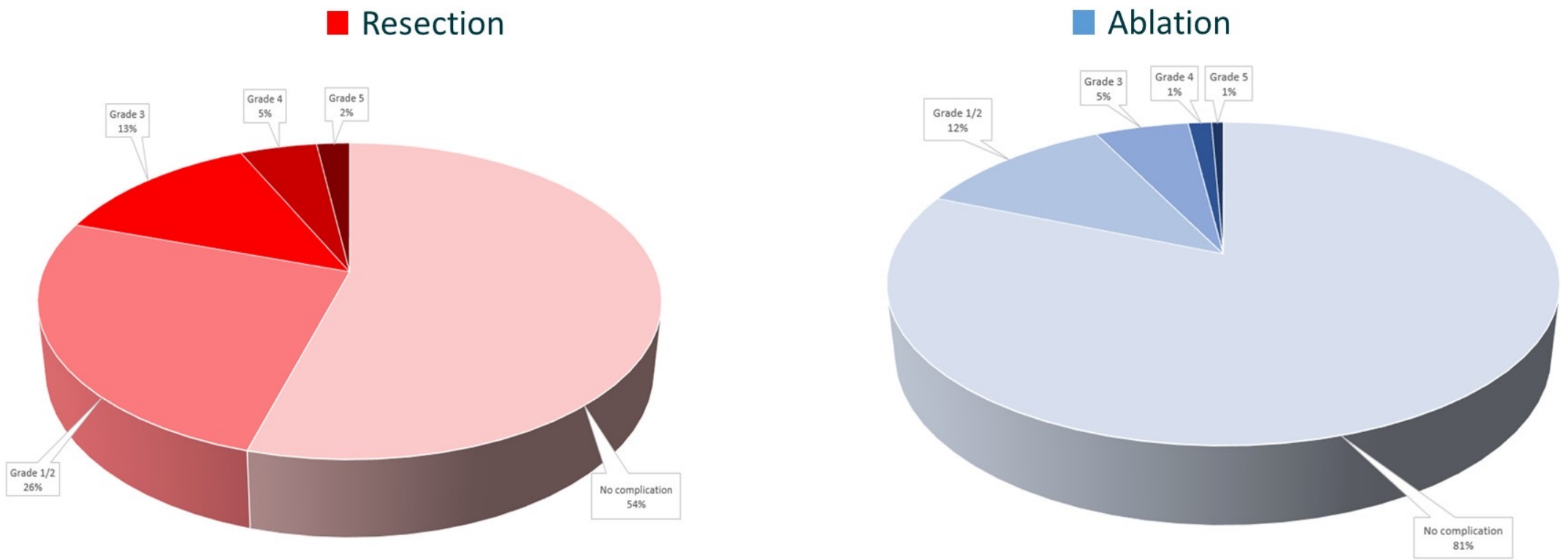


Conditional probability to eventually prove non-inferiority 91%!

RESULTS

ADVERSE EVENTS (CTCAE v5.0)

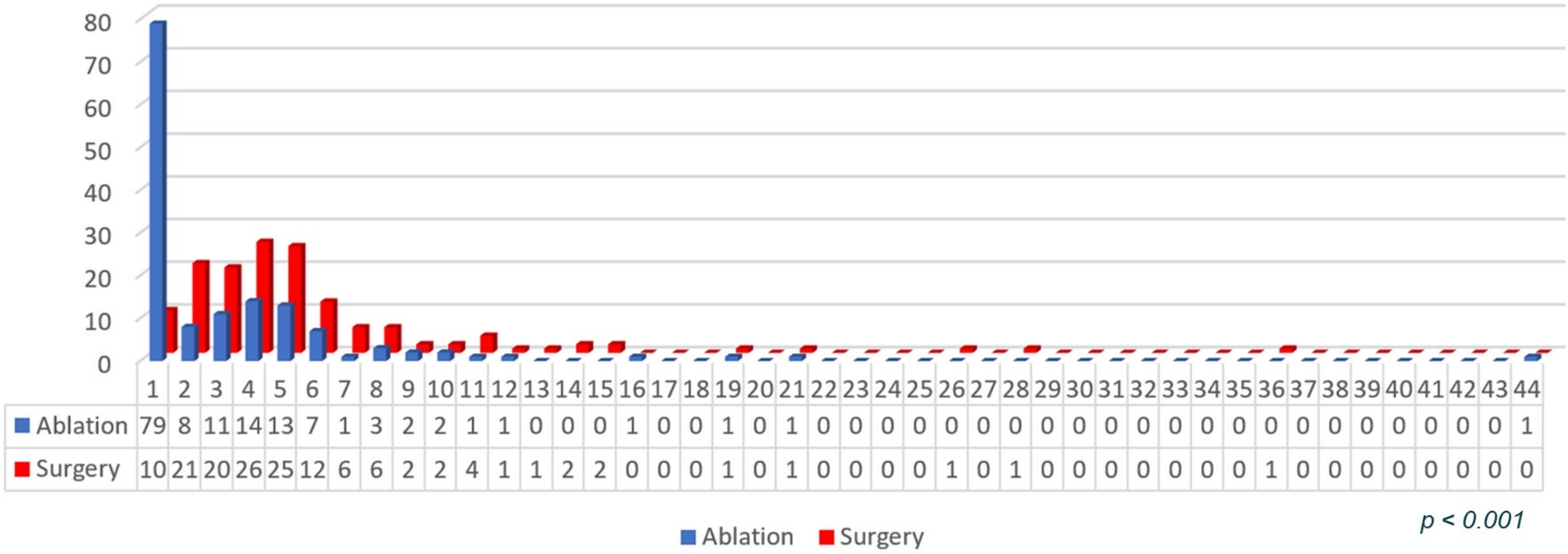
COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation



p < 0.001

RESULTS

LENGTH OF HOSPITAL STAY (DAYS)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ablation	79	8	11	14	13	7	1	3	2	2	1	1	0	0	0	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Surgery	10	21	20	26	25	12	6	6	2	2	4	1	1	2	2	0	0	0	1	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

SUMMARY

COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation

- **COLLISION stopped at halftime based on predefined stopping rules for**
  - Showing benefit of the experimental arm (ablation) over standard-of-care (resection)

- **For patients with small-size colorectal liver metastases, thermal ablation compared to standard-of-care surgical resection**
  - Substantially reduced morbidity and mortality
    - treatment related mortality 2.1% (resection) → 0.0% (ablation)
    - all-cause 90-day mortality 2.1% (resection) → 0.7% (ablation)
    - AEs rate 56% (resection) → 19% (ablation) and SAE rate 20% (resection) → 7% (ablation)
  - Was at least as good as surgical resection in locally controlling CRLM
    - no difference in *per-patient* local control: HR 0.131 (95% CI 0.016-1.064; p = 0.057)
    - superior *per-tumor* local control: HR 0.092 (95% CI 0.011-0.735; p = 0.024)
  - Showed no difference in local & distant tumor progression-free survival
  - Did not compromise overall survival (OS)

ORCHESTRA

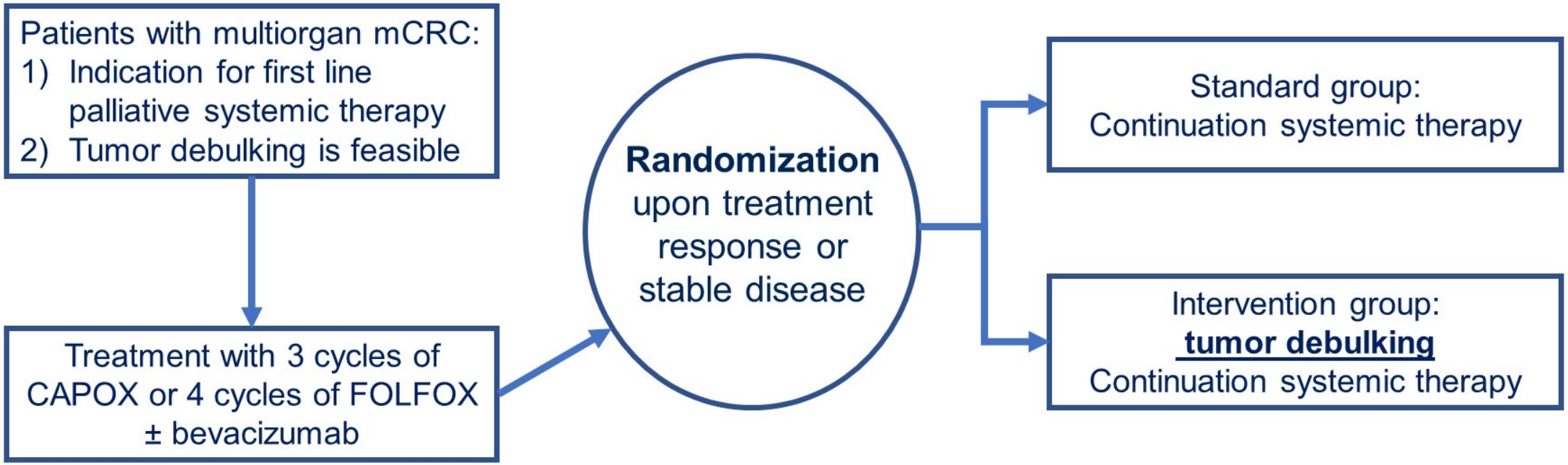
Key findings

In patients with extensive multiorgan metastatic colorectal cancer:

- Tumor debulking ***provides no survival benefit*** in addition to standard palliative combination chemotherapy
- Increasing use of local therapies needs further consideration

PRESENTED BY: Elske Gootjes, MD PhD, medical oncologist, RadboudUMC, The Netherlands

ORCHESTRA Design



Primary endpoint:	overall survival (OS)
Primary aim:	>6 months OS benefit
Patients needed for randomization:	382

PRESENTED BY: Elske Gootjes, MD PhD, medical oncologist, RadboudUMC, The Netherlands

Main eligibility criteria

1) Metastases **in at least two different organs AND**:

    1) >1 extrahepatic metastases

    OR

    2) 1 extrahepatic metastasis if:

        - >5 hepatic metastases not located in one lobe *OR*
        - para-aortal lymph or celiac nodes *OR*
        - adrenal gland metastases *OR*
        - peritoneal/pleural carcinomatosis

2) Prior to start of systemic therapy **maximal tumor debulking is feasible**, defined as at least 80% of metastatic lesions

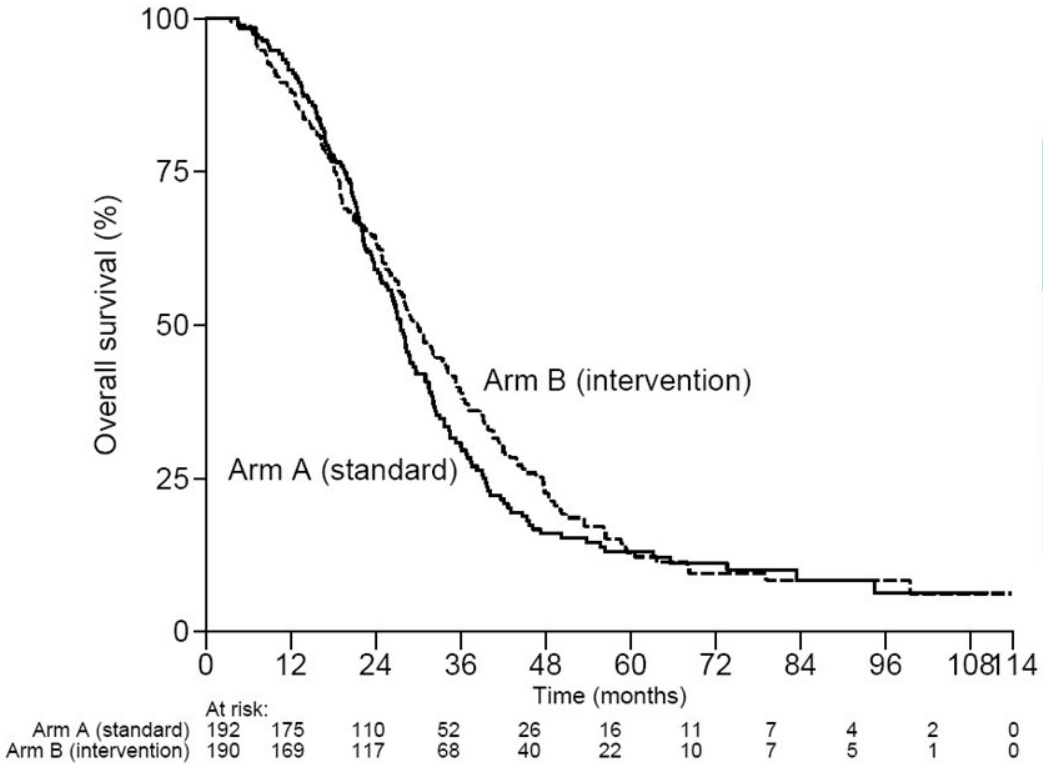
PRESENTED BY: Elske Gootjes, MD PhD, medical oncologist, RadboudUMC, The Netherlands

Metastatic pattern of randomized patients

		Standard N = 192	Intervention N = 190
>2 organs involved		72 (38)	74 (40)
Liver and lung only		81 (42)	86 (45)
Peritoneal disease present		63 (33)	60 (32)
Number of metastases	<5	76 (40)	67 (35)
(peritoneal excluded)	5-10	84 (44)	94 (50)
	>10	32 (17)	29 (15)

PRESENTED BY: Elske Gootjes, MD PhD, medical oncologist, RadboudUMC, The Netherlands

Overall Survival (OS)



	Standard	Intervention
Nº of events	153	155
Median OS (months)	27.5	30.0
Adjusted HR 0.88 [95% CI 0.70-1.10] p=0.23		

Median FU 32.3 months

PRESENTED BY: Elske Gootjes, MD PhD, medical oncologist, RadboudUMC, The Netherlands

In conclusion:

***The ORCHESTRA TRIAL:* A randomized phase III trial of Additional Tumor Debulking to First-Line Palliative Combination Chemotherapy for Patients with Multiorgan Metastatic Colorectal Cancer**

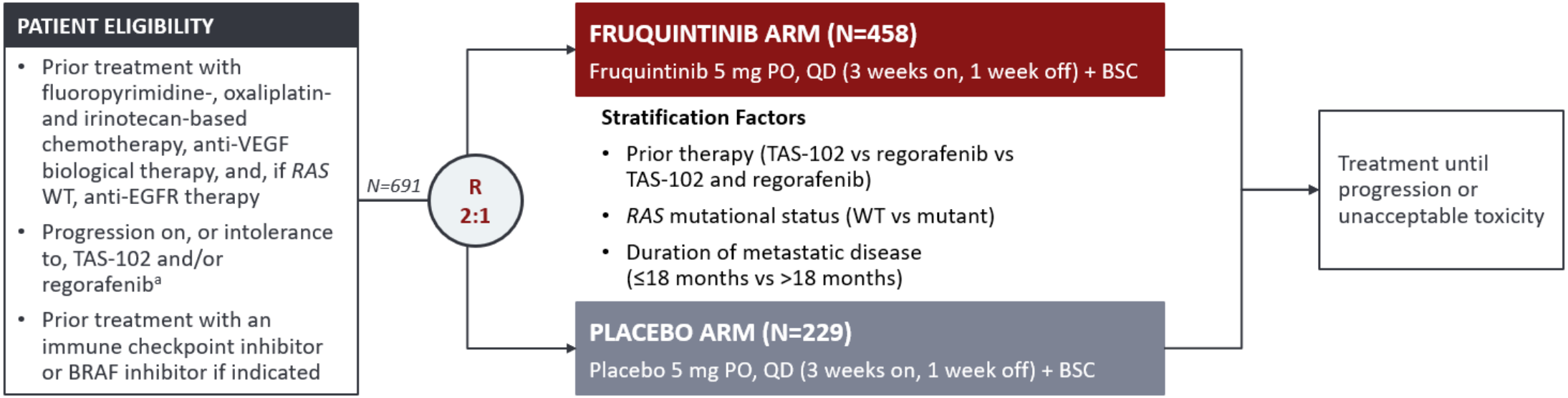
shows that:

1) Tumor debulking in addition to standard palliative combination chemotherapy provides no survival benefit
2) Increasing use of local therapies needs further consideration
3) Randomization is important for evaluating new treatment strategies

PRESENTED BY: Elske Gootjes, MD PhD, medical oncologist, RadboudUMC, The Netherlands

FRESCO-2 (NCT04322539): Study Design

Phase 3, Global Study



Primary endpoint	Secondary endpoints		Statistical assumptions
• Overall survival	**Key** • Progression-free survival	**Other** • ORR • DCR • Safety[b]	**Sample size** • 687 patients (480 OS events) would provide 90% power to detect a difference in OS with a HR of 0.73 at a 2-sided α of 0.05 • Median OS assumption in the placebo arm is 5.0 months and median OS in fruquintinib arm is 6.8 months • Non-binding interim futility analysis at one-third (160) of OS events

Dasari et al: Lancet 2023

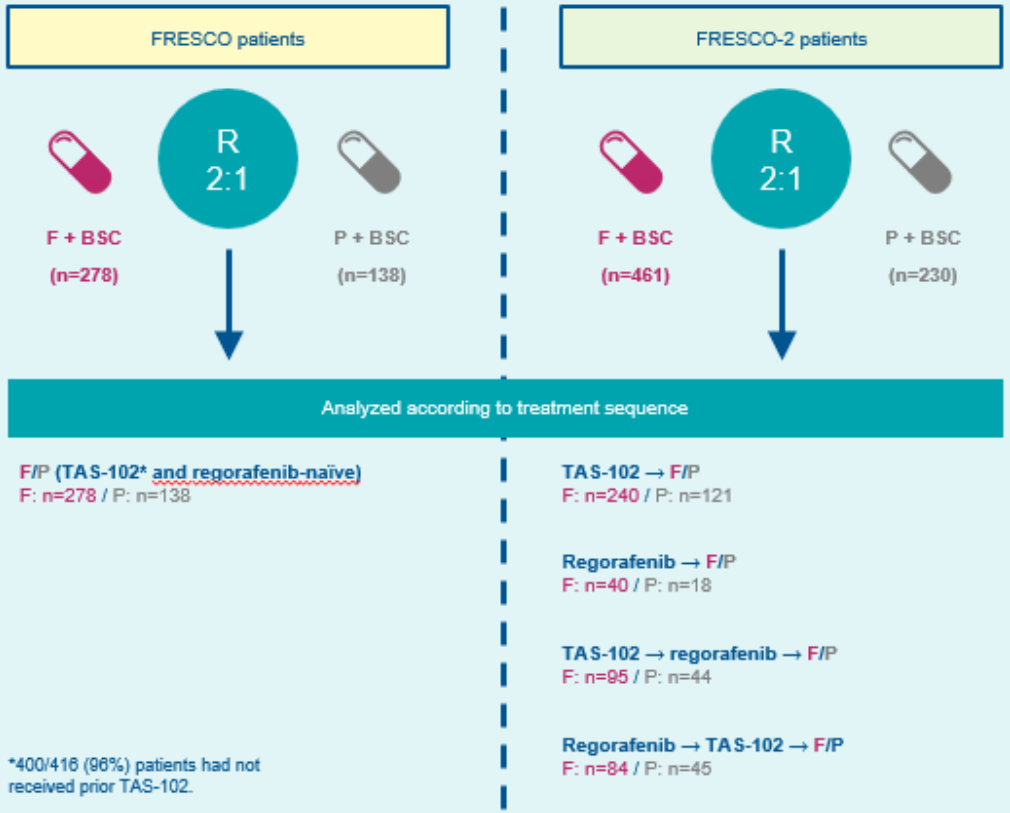
Clinical Utilization: Potential ≥ Grade 3 TAE's:

	CORRECT	SUNLIGHT	FRESCO and FRESCO2
Phase III trial design	Regorafenib vs. Placebo (2:1)	TAS-102 +/- Bevacizumab (1:1)	Fruquintinib vs. Placebo (2:1)
N	760	492	416; 691
Neutropenia	NR	106 (43%)	NR
Hypertension	36 (7%)	NR	59 (21.2%); 62 (14%)
Hand-foot skin reaction	83 (17%)	NR	30 (10.8%); 29 (6%)
Diarrhea	35 (7%)	2 (0.8%)	8 (2.9%); 16 (4%)
Anemia	12 (2%)	15 (6.1%)	NR
Asthenia	NR	10 (4.1%)	NR: 35 (8%)
Fatigue	46 (9%)	3 (1.2%)	3(1.1%);18 (4%)

Grothey et al: Lancet, 2013; Li et al: JAMA Network, 2018; Prager et al: NEJM 2023; Dasari et al: Lancet, 2023

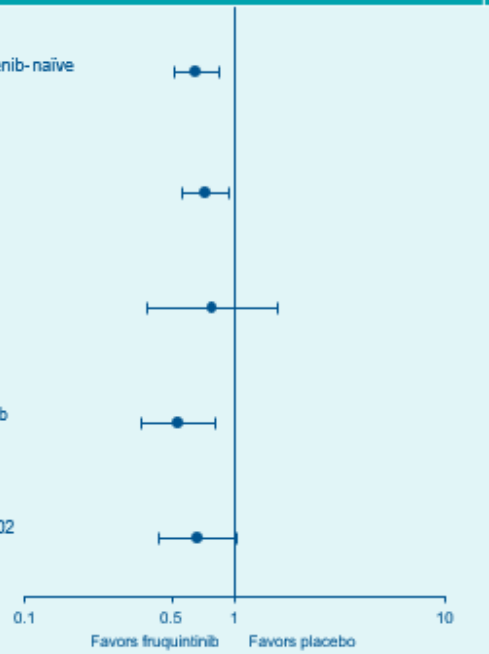
Efficacy and Safety of Fruquintinib according to prior treatment

Study design



Results

Figure 1: Forest plot of OS for patients in FRESCO and FRESCO-2 according to prior treatment status and sequence, if applicable (ITT population)

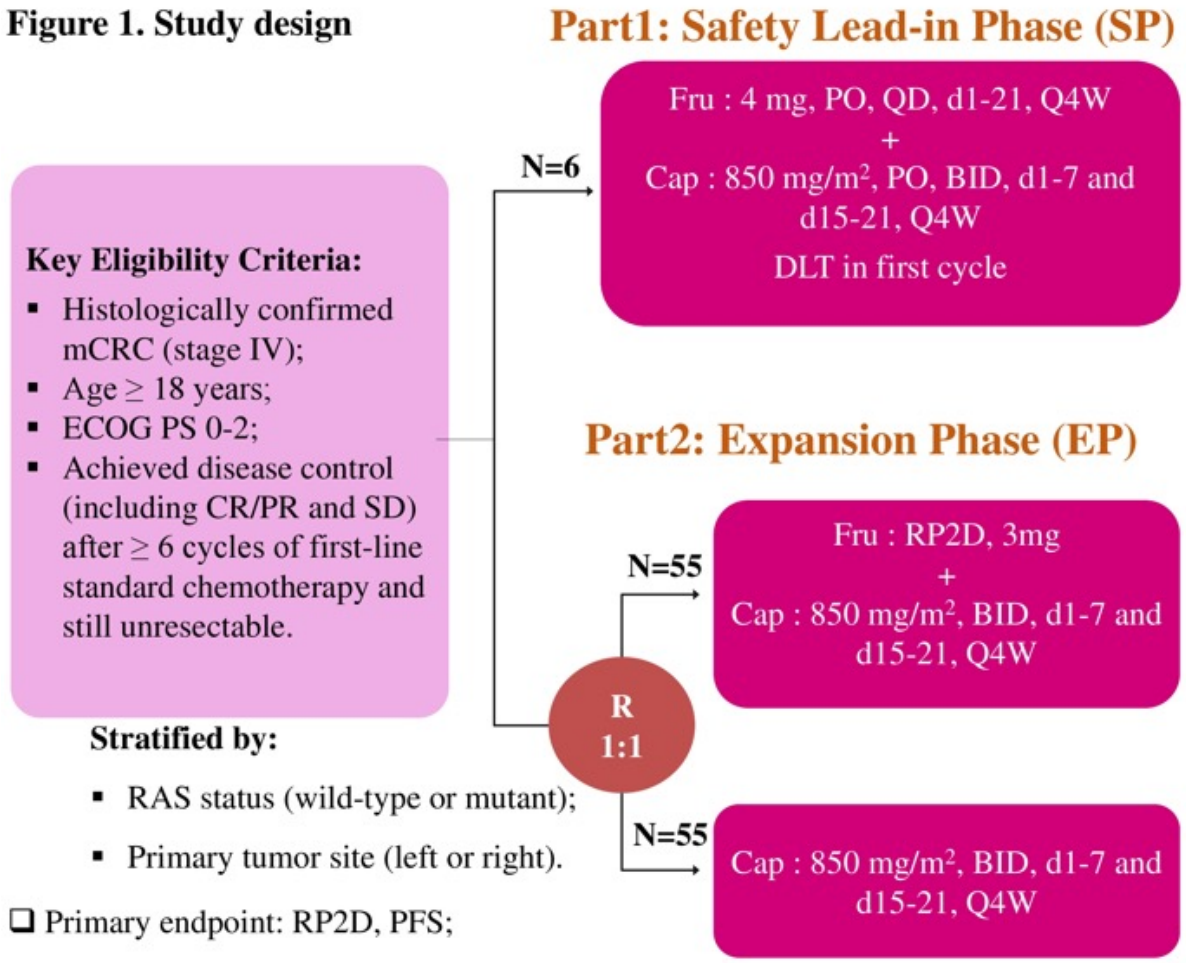


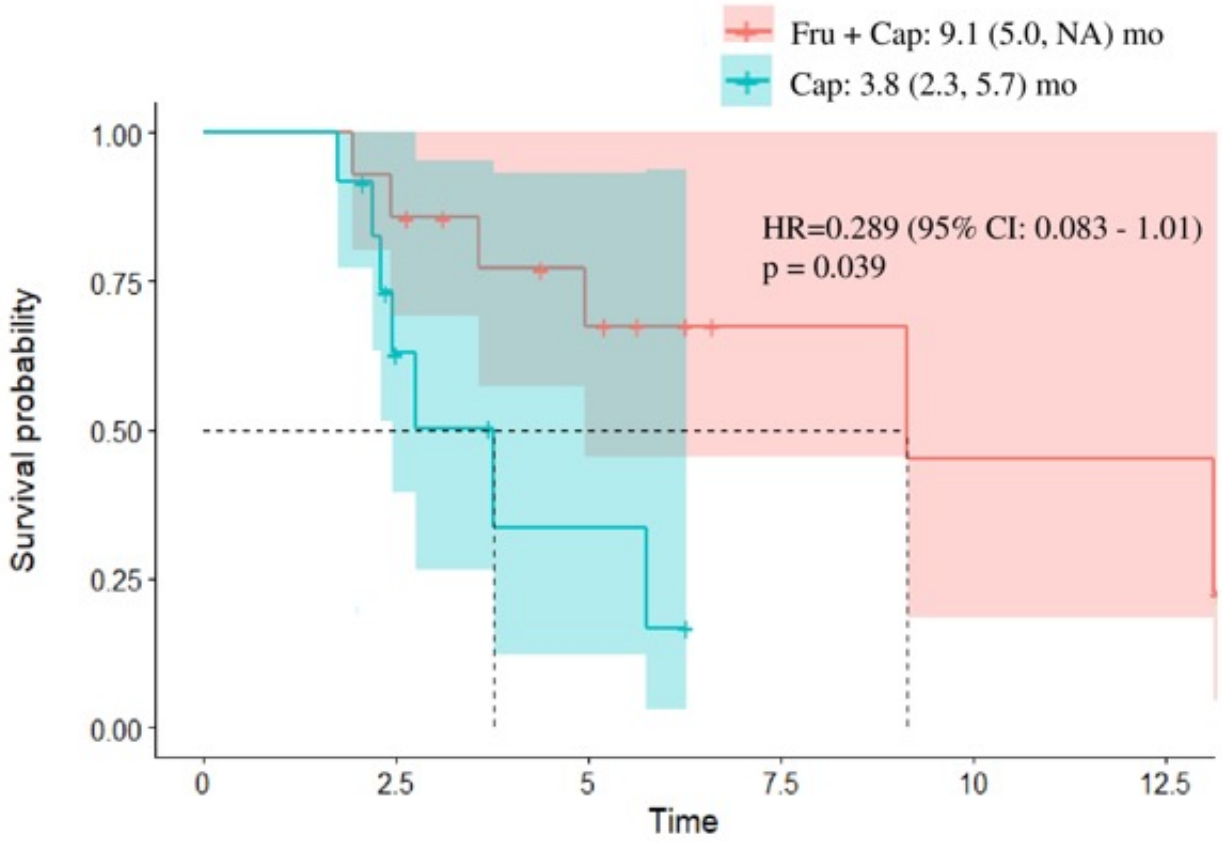
	HR (95% CI)	Events / n		Median OS, months (95% CI)	
		F	P	F	P
TAS-102* and regorafenib-naïve	0.652 (0.512, 0.829)	188/278	109/138	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)
TAS-102 only	0.723 (0.557, 0.938)	165/240	88/121	7.7 (6.7, 8.5)	5.1 (4.0, 6.3)
Regorafenib only	0.772 (0.379, 1.573)	25/40	12/18	10.2 (6.1, 11.6)	8.2 (3.7, 14.4)
TAS-102 → regorafenib	0.532 (0.353, 0.802)	66/95	37/44	6.6 (4.9, 7.8)	3.3 (2.8, 5.4)
Regorafenib → TAS-102	0.666 (0.432, 1.025)	60/84	36/45	8.5 (6.3, 10.5)	4.8 (3.4, 6.7)

Saab et al: J Clin Oncol 42, 2024 (suppl 16; abstr 3579)

Phase Ib/II: Fruquintinib vs. Capecitabine Maintenance Therapy

Figure 1. Study design





- Li et al: J Clin Oncol 42, 2024 (suppl 3; abstr 119)

Fruquintinib + TAS-102: Single arm, Phase II

Eligibility: Unresectable mCRC
2 prior lines of therapy

↓

Fruquintinib 4 mg Po qD +
TAS-102
(35 mg/m2, BID, Days 1-5, 8-12)

↓

Primary endpoint: PFS

N	50
Median Follow-up	15.5M
ORR	PR: 10.9% (5/46); SD: 63% (29/46)
PFS	6.46M (95%CI: 4.2-8.62M
≥ Grade 3 SAE's	
Neutropenia	80%
Anemia	52%
Loss of appetite	22%
Malaise	14%
Abdominal Pain	12%
Vomiting	10%

- Peng et al: J Clin Oncol 42, 2024 (suppl 16; abstr 3536)

VANDERBILT-INGRAM CANCER CENTER

YOUNG ADULT CANCER PROGRAM

FOR THOSE 45 AND UNDER

For updates on events, services, and more please join our mailing list by scanning the QR Code and signing up today.

We look forward to helping you navigate your cancer journey!

We're here to help you get the support you need on topics you're concerned about:

- Reproductive health, fertility, and sexuality
- Financial/ insurance guidance
- Access to age-specific support groups and individual counseling
- Nutritional and exercise consults
- Educational and vocational resources
- Navigating relationships
- Parenting with cancer
- Music, art, and pet therapy
- Pain management
- And more....

Never Miss a Monday: YA Wellness Series

In collaboration with Survivor Fitness Foundation and Gilda's Club Middle Tennessee, we invite you to join us for **Never Miss A Monday: Young Adult Wellness Series.**

Start off your week on the right track with an all levels/survivor friendly movement class. Come on out and connect with other young adults impacted by cancer, the 2nd Monday of every month.

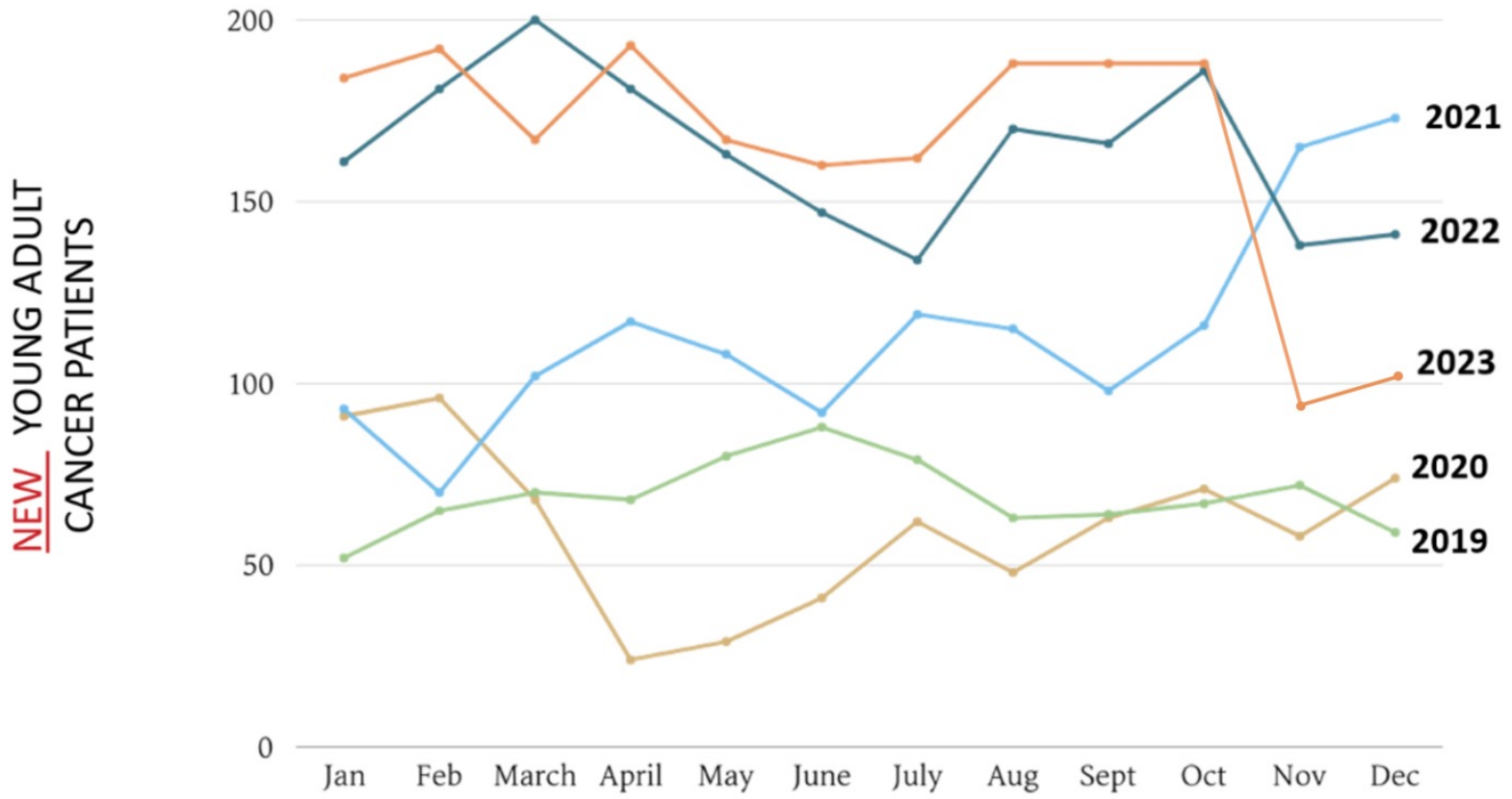
One of the First Young Adult Cancers Program Nationally

Co-Directors:

Elizabeth Davis, MD and Bhagi Dholaria MBBS

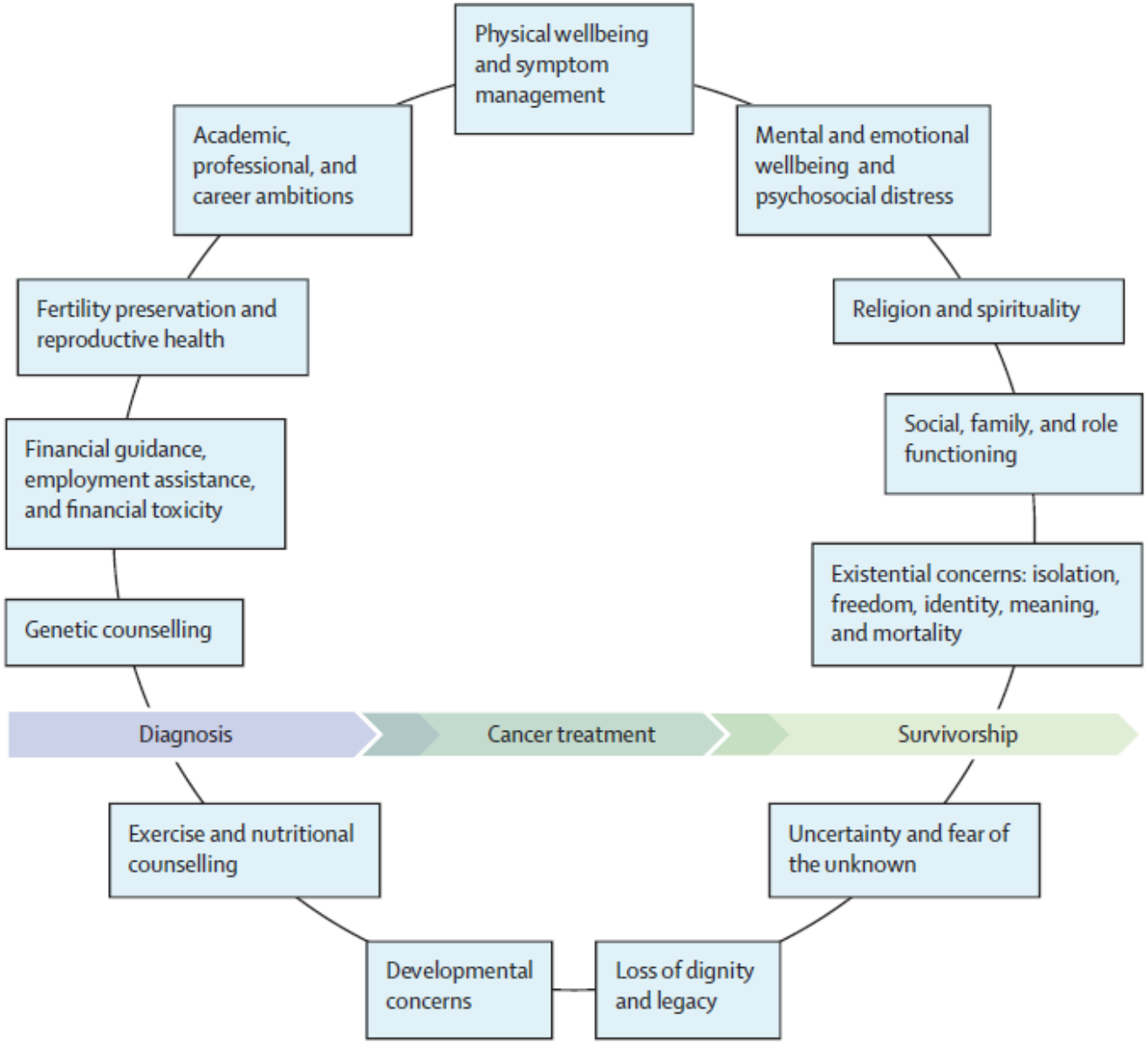
Director: Cathy Eng, MD, FACP, FASCO

Early Age Onset New Patient Referrals to VICC



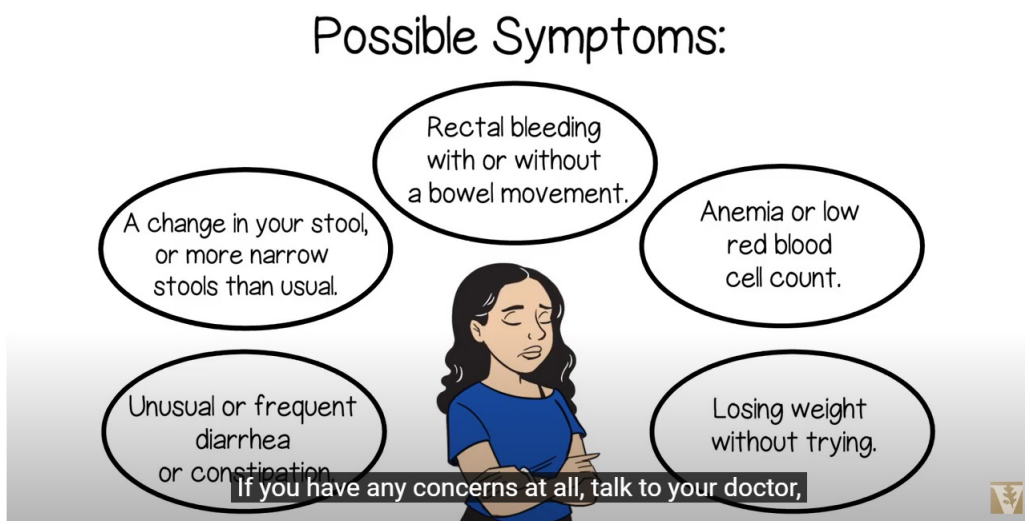
*These number are based on a set of locations and may not represent all of the VICC YAC population due to EMR limitations- number may be higher
**Departments included: TVC 1-3, OHO, Cool Springs, Belle Meade, Spring Hill, Hendersonville, Pleasant View, Oncology and Endocrinology Surgeons

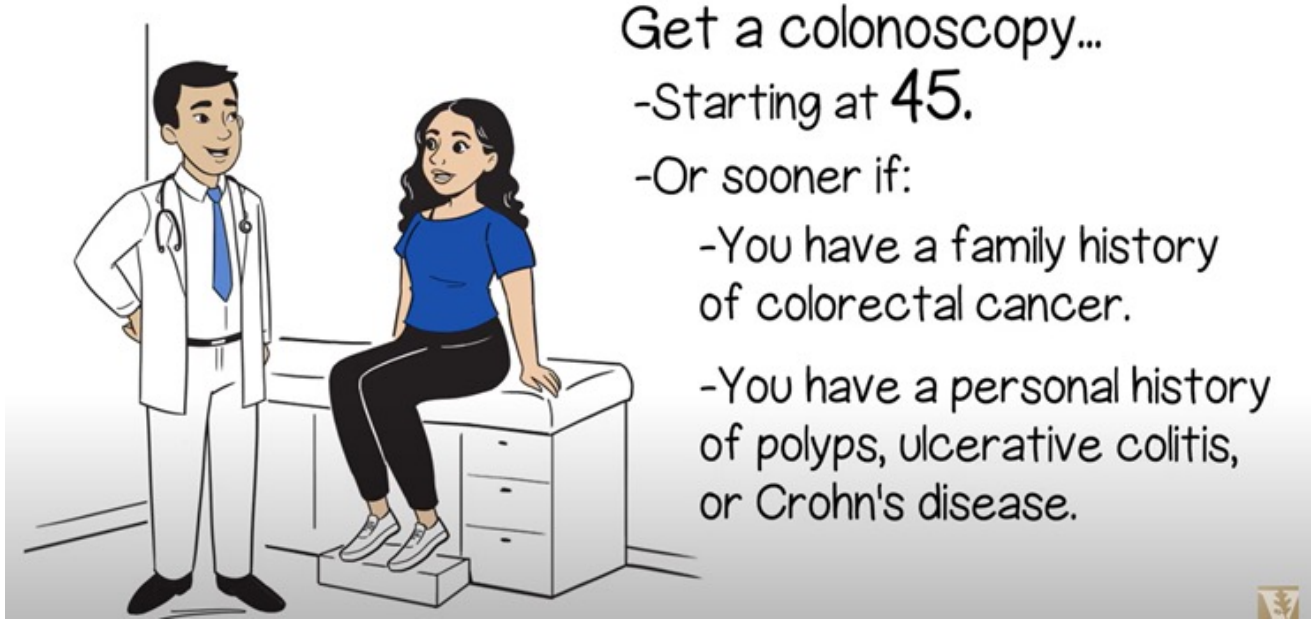
Optimizing the Care of EOCRC Patients



Eng et al: Lancet Onc 2022

Vanderbilt-Ingram Cancer Center: Impact of Education and Awareness on EOCRC





https://www.youtube.com/watch?v=nUh3V9an6So

VANDERBILT-INGRAM CANCER CENTER

Thank you for your attention!

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www.youngadultswithcancer.com

Courtesy of Fight CRC