Metastatic Colon Cancer

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Disclosures

Speakers Bureau:
Bristol Myers Squibb
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Key Studies in Metastatic Colorectal Cancer ASCO 2024

- Checkmate 8HW Abstract 3503: Nivolumab plus Ipilimumab vs chemotherapy as first-line treatment for MSI-H/MMR deficient metastatic colorectal cancer: expanded efficacy analysis

- TransMet Abstract 3500: Liver Transplantation and Chemotherapy versus Chemotherapy alone in patients with definitively unresectable colorectal liver metastases: results from a prospective, multicentre randomized trial

- COLLISION Trial LBA 3501: Colorectal liver metastases surgery versus thermal ablation: final results of the international phase 3 randomized controlled COLLISION trial

- Codebreak 300 LBA 3510: Overall survival(OS) of phase 3 CodeBreak 300 study of sotorasib plus panitumumab versus investigator's choice of therapy for KRAS G12C-mutated metastatic colorectal cancer

- MOUNTAINEER Abstract 3509: Phase 2 study of Tucatinib and Trastuzumab for Her2-positive metastatic CRC

- ARC 9: Randomized Ph II trial with Etrumadenant based therapy in previously treated metastatic CRC

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2024 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded efficacy analysis from CheckMate 8HW

Heinz-Josef Lenz,[1] Sara Lonardi,[2] Elena Elez Fernandez,[3] Eric Van Cutsem,[4] Lars Henrik Jensen,[5] Jaafar Bennouna,[6] Guillermo Ariel Mendez,[7] Michael Schenker,[8] Christelle de la Fouchardiere,[9] Maria Luisa Limon Miron,[10] Takayuki Yoshino,[11] Jin Li,[12] José Luis Manzano Mozo,[13] Giampaolo Tortora,[14] Rocio Garcia-Carbonero,[15] Rohit Joshi,[16] Elvis Cela,[17] Tian Chen,[17] Lixian Jin,[17] Thierry Andre[18]

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Abstract number 3503

Why is this study important ?

- MSI-H/dMMR mCRC has poor outcomes compared with standard chemotherapy
- NCCN guidelines recommend Pembrolizumab(KN 177) and Ipilimumab and Nivolumab for MSI-H/MMR def mCRC in the first-line setting
- KEYNOTE-177 study 48% progression free and alive at 2 yrs with1LPembrolizumab
- An unmet need still exists
- Less benefit seen with single agent immunotherapy in KRAS or NRAS gene mutation population
- Real-world evidence studies have shown that single agent immunotherapy has less benefit in patients with liver metastases
- Prespecified interim analysis of CheckMate 8HW showed improved PFS with 1L Ipi/Nivo over chemotherapy with no new safety signals

NCCN guidelines Andre T, et al. *N Engl J Med* 2020;383:2207-2218. Saberzadeh-Ardestani B, et al. *Eur J Cancer* 2024;196:113433. 5 Overman M, et al. *Lancet Oncol* 2017; 18:1182-1191. Overman M, et al. *J Clin Oncol* 2018;36:773-779. Andre T, et al. *Ann Oncol* 2022;33:1052-1060. Andre T, et al. *J Clin Oncol* 2024;42(suppl 3; abstract LBA768).

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

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)

R 2:2:1

1L setting: n = 202

1L setting: n = 101

NIVO 240 mg Q2W for 6 doses, followed by NIVO 480 mg Q4W[b]

NIVO 240 mg + IPI 1 mg/kg Q3W for 4 doses, followed by NIVO 480 mg Q4W[b]

Investigator's choice chemo[c] (mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab)

Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
- Safety
- OS; PFS2 by investigator[e]; ORR by BICR[e]; PROs

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

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[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.

Characteristic (1L all randomized patients)	Category	NIVO + IPI (n = 202)	Chemo (n = 101)
Age	Median (range), years	62 (21–86)	65 (26–87)
	< 65 years	117 (58)	46 (46)
Sex	Male	95 (47)	45 (45)
Region	US/Canada/Europe	133 (66)	71 (70)
	Asia	19 (9)	11 (11)
	Rest of world	50 (25)	19 (19)
ECOG PS	0	111 (55)	52 (51)
Disease stage at initial diagnosis[a]	Stage IV	85 (42)	49 (49)
Tumor sidedness	Right	138 (68)	68 (67)
Sites of metastases[b,c,d]	Liver	76 (38)	42 (42)
	Lung	44 (22)	25 (25)
	Peritoneum	84 (42)	43 (43)
Centrally confirmed MSI-H/dMMR status	Yes	171 (85)	84 (83)
	No	31 (15)	17 (17)
Tumor cell PD-L1 expression[e,f]	< 1%	145 (72)	80 (79)
	≥ 1%	43 (21)	12 (12)
***BRAF, KRAS, NRAS* mutation status**[f,g]	*BRAF*/*KRAS*/*NRAS* wild-type	47 (23)	23 (23)
	BRAF mutant	52 (26)	24 (24)
	KRAS or *NRAS* mutant	43 (21)	21 (21)
	Unknown	55 (27)	31 (31)
Clinical history of Lynch syndrome[f,h]	Yes	22 (11)	17 (17)
	No	135 (67)	49 (49)
	Reported as unknown	44 (22)	30 (30)

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Data are shown as n (%) unless otherwise noted. [a]All patients had stage IV disease at study entry. [b]Per BICR. [c]Metastases not reported in 3 patients in the NIVO + IPI arm. [d]Listed categories are not mutually exclusive as patients may have had multiple sites of metastases. [e]Tumor cell PD-L1 expression indeterminate, not evaluable, or not available: NIVO + IPI, n = 14; chemo, n = 9. [f]Percentages may not add up to 100% due to rounding. [g]*BRAF* and *KRAS*/*NRAS* mutant: NIVO + IPI, n = 5; chemo, n = 2. [h]Patients with Lynch syndrome not reported: NIVO + IPI, n = 1; chemo, n = 5.

Disposition	NIVO + IPI	Chemo
All randomized patients, n	202	101
All treated patients, n	200	88
Ongoing treatment,[a] n (%)	42 (21)	6 (7)
Completed treatment,[a] n (%)	62 (31)	0
Discontinued treatment,[a] n (%)	96 (48)	82 (93)
Disease progression	38 (19)	61 (69)
AE related to treatment	36 (18)	4 (5)
AE not related to treatment	12 (6)	5 (6)
Other[b]	10 (5)	12 (14)
Median duration of treatment (range), mo	13.5 (0–32.3)[c]	4.0 (0.1–27.5)
Death,[a] n (%)	44 (22)	37 (42)
Disease progression	28 (14)	24 (27)
Other[d]	16 (8)	12 (15)

- Among patients treated with NIVO + IPI, 159 patients (80%) received all 4 doses of IPI
- Among patients treated with chemo, 66 patients (75%) received a biologic agent (bevacizumab, n = 56; cetuximab, n = 10)

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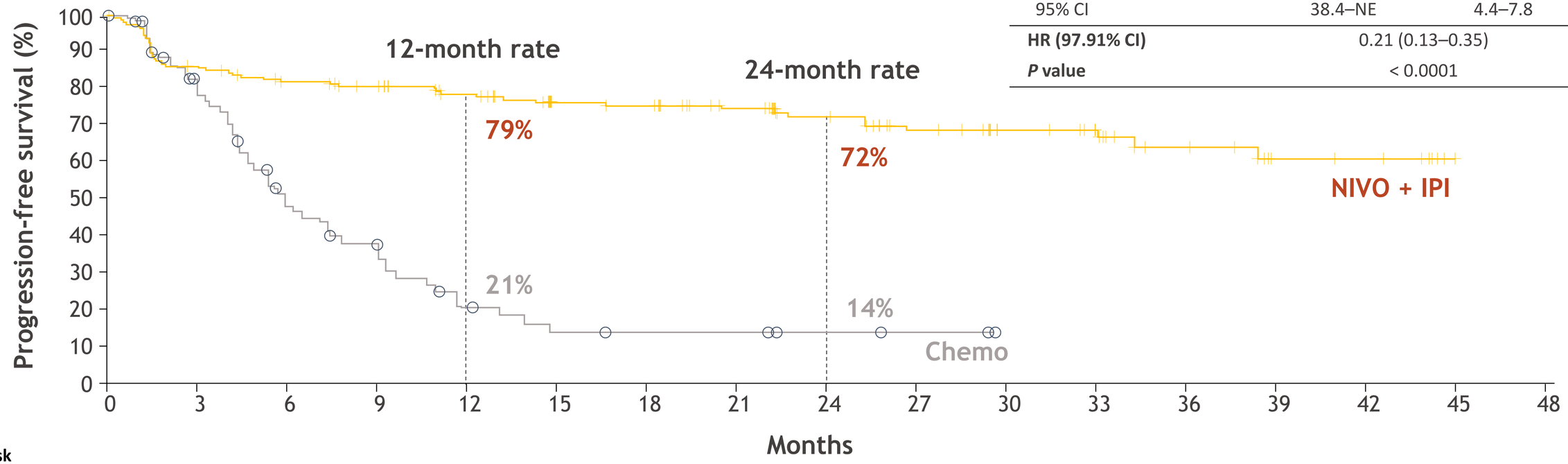
[a]Percentages shown are based on all treated patients. [b]Other reasons for discontinuation included death (n = 2), withdrawal of consent (n = 1), pregnancy (n = 1), patient no longer met study criteria (n = 1), maximum clinical benefit (n = 8), and other reasons (n = 9). [c]Median duration of treatment was 13.5 months (range, 0–32.3) for NIVO and 2.0 months (range, 0–3.7) for IPI. [d]Other reasons for death included study drug-related toxicity (n = 2, both in the NIVO + IPI arm), other reasons (n = 17), and unknown (n = 9).

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)

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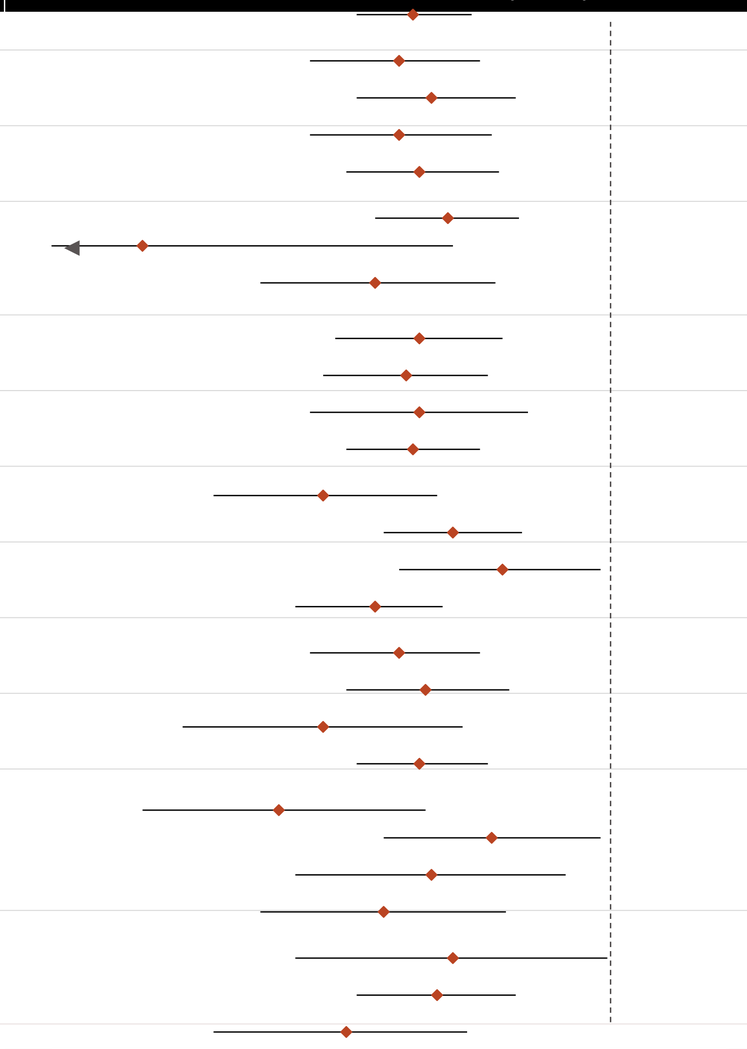
[a]Per BICR. [b]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR	Unstratified HR (95% CI)
		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 (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.

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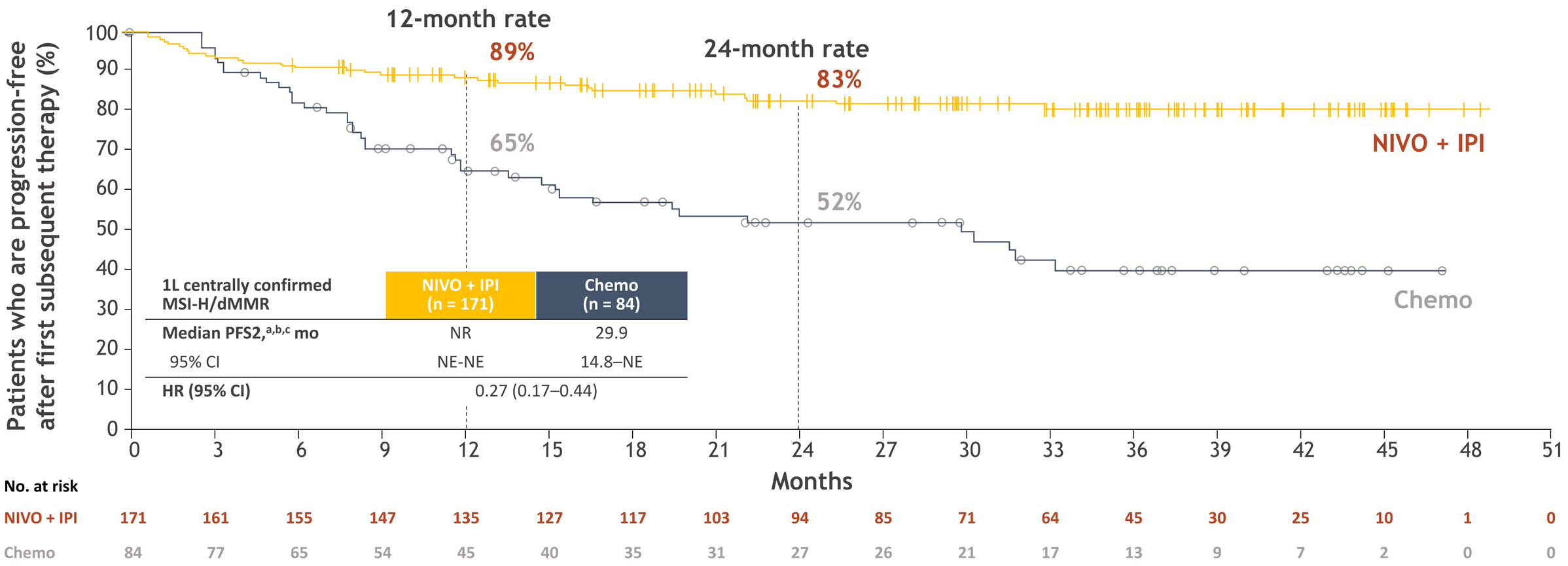

No. at risk

NIVO + IPI	171	161	155	147	135	127	117	103	94	85	71	64	45	30	25	10	1	0
Chemo	84	77	65	54	45	40	35	31	27	26	21	17	13	9	7	2	0	0

- PFS2[a] favored NIVO + IPI vs chemo with a 73% reduction in the risk of death or disease progression after first subsequent therapy

[a]Defined as time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death. [b]Per investigator. [c]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

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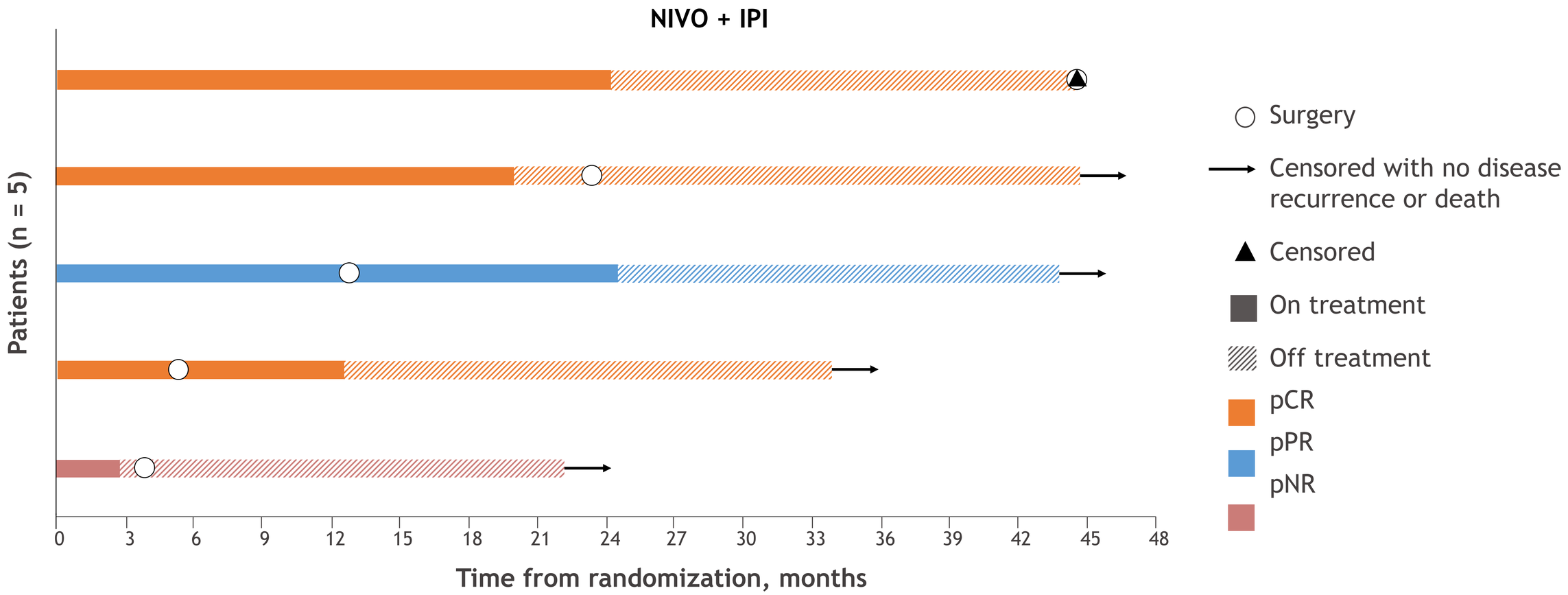

- Among the 5 patients who received subsequent surgery in the NIVO + IPI arm, 3 achieved pathologic complete response[a]

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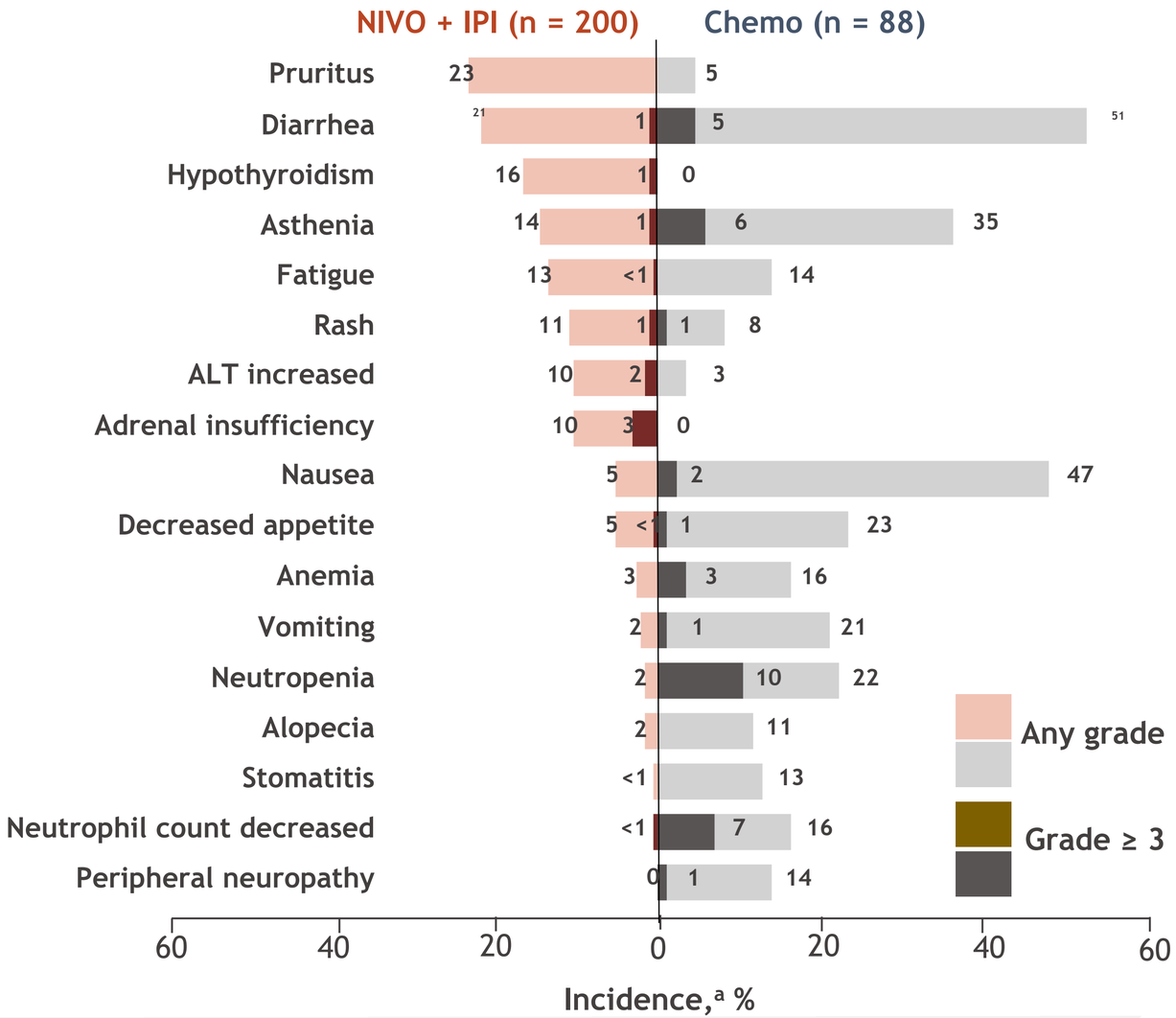
[a]Per investigator

TRAEs occurring in ≥ 10% of patients



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	

- Any-grade and grade 3/4 TRAEs were less frequent in the NIVO + IPI arm than in chemo arm
- The most common any-grade TRAEs occurring in ≥ 10% of patients were:
  - NIVO + IPI: pruritis (23%), diarrhea (21%), and hypothyroidism (16%)
  - Chemo: diarrhea (51%), nausea (47%), and asthenia (35%)

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment.

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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**

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Pembrolizumab or Ipilimumab & Nivolumab ?

Outcome	Keynote 177 Pembro vs Chemo	Checkmate 8HW Nivo/Ipi vs Chemo
PFS	24 mth: 49 vs 21% 36m: 42 vs 11% 16.5 vs 8.2m HR 0.59	24m: 72 vs 14% NR vs 5.9m HR 0.21
OS/HR	0.74 (p=0.0359) NR vs 36.7m	NR
ORR	45.1 vs 33.1%	NR
CR	13.1 vs 3.9%	NR
PFS2	24 mth: 67 vs 50% 36m: 60 vs 39% 54 vs 24.9m HR 0.61	24m: 83 vs 52% NR vs 29.9m HR 0.27

Andre T et al Journal of Clinical Oncology Vol 42, Number 16 suppl 3503
Diaz Jr,LA et al The Lancet Oncology Vol 23, issue 5, 659-670, May 2022

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

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What do we know about colorectal liver metastases (CLM)?

- Liver resection is the best treatment that offers long term survival
- Only 20% are initially resectable
- Conversion chemotherapy may allow secondary resection after downsizing with a survival benefit
- For definitively unresectable CLM, chemotherapy with biologic agents is the standard of care and has shown to improve survival to an average of about 2 years
- Can long term survival be achieved with liver transplantation?

1) Tomlinson JS et al, J Clin Oncol 2007 (2) Adam R et al , Ann Surg 2004 (3) Heinemann V, Lancet Oncol 2014

What do we know about liver transplantation in unresectable CLM ?

Trial	SECA-I	TOSO et al	SECA-II	SECA-II Arm D
No. of pts	21	12	15	10
Median no. liver mets	8	9	12	20
OS: 3yr(%)	68	62	40	NR
OS: 5yr(%)	60	50	13	NR
Time to recurrence (mths)	8	11.8	13.7	4

Hagness M Ann Surg. 2013;**257**:800–6, Toso C *Liver Transpl.* 2017;**23**:1073–6, Dueland S *Ann Surg.* 2020;**271**:212–8, Smedman TM *BJS Open.* 2020;**4**:467–77, Table adapted from Br J Cancer. 2023 May 11; 128(10): 1797–1806

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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: Study Design

Patient Selection by each Center Tumor Board

↓

Validation by an independent multidisciplinary expert committee

↓

Randomisation

LT+C arm

↓

Transplant Waiting list

↓

Prioritisation → LT ≤ 2 Months after last Chemo

C alone arm

↓

Continuation of chemotherapy

20 centers: France, Belgium Italy

Adam et al, eClinical Medicine 2024

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TransMet Trial: Endpoints

Primary Endpoint:

- Overall Survival (OS) at 5 years

Secondary Endpoint:

- OS at 3 years
- Progression –free survival (PFS) at 3 and 5 years
- Recurrence rate at 3 and 5 years

Progression: Recurrence in the LT+C group/progression in the C group

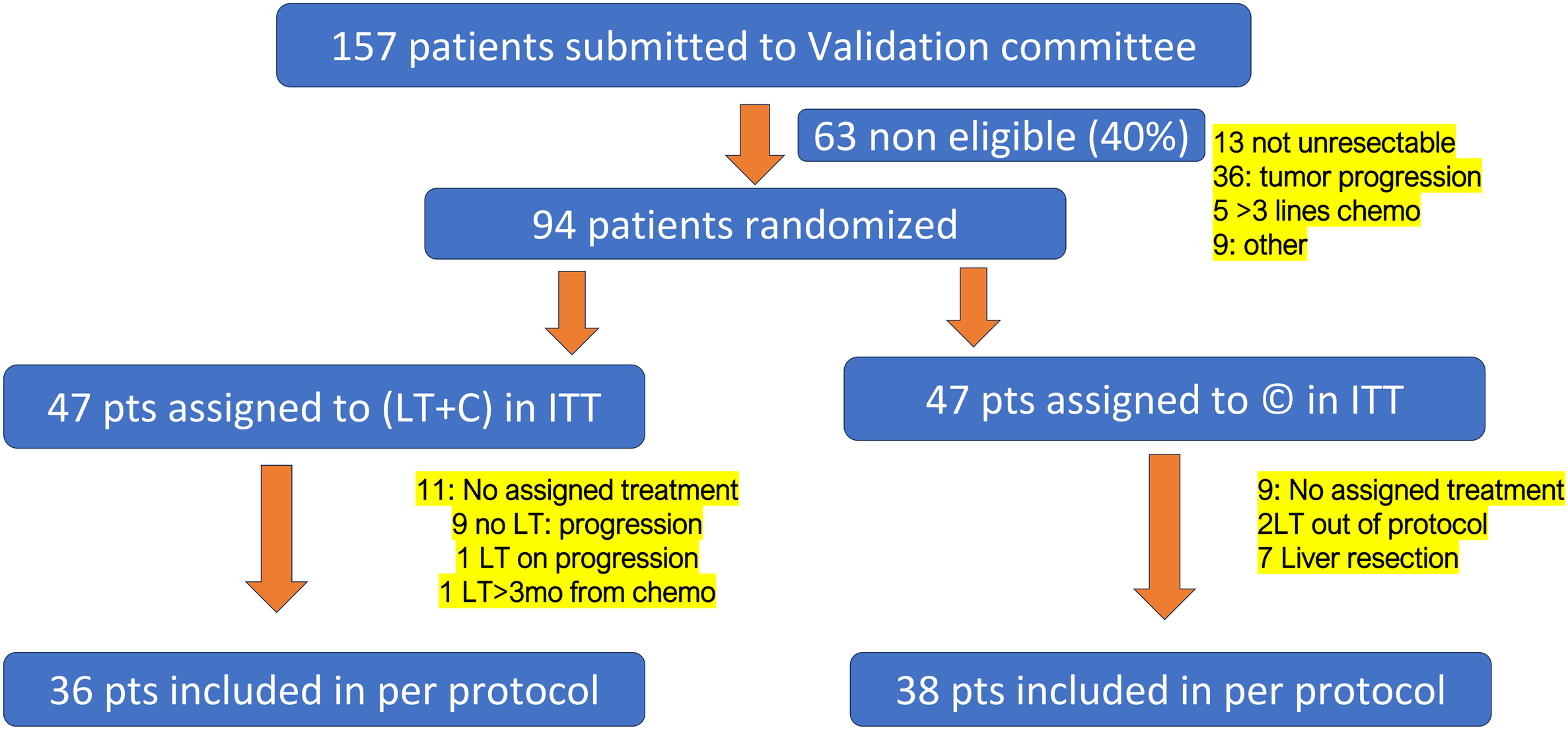
TransMet Trial: Statistical Design

Hypothesis

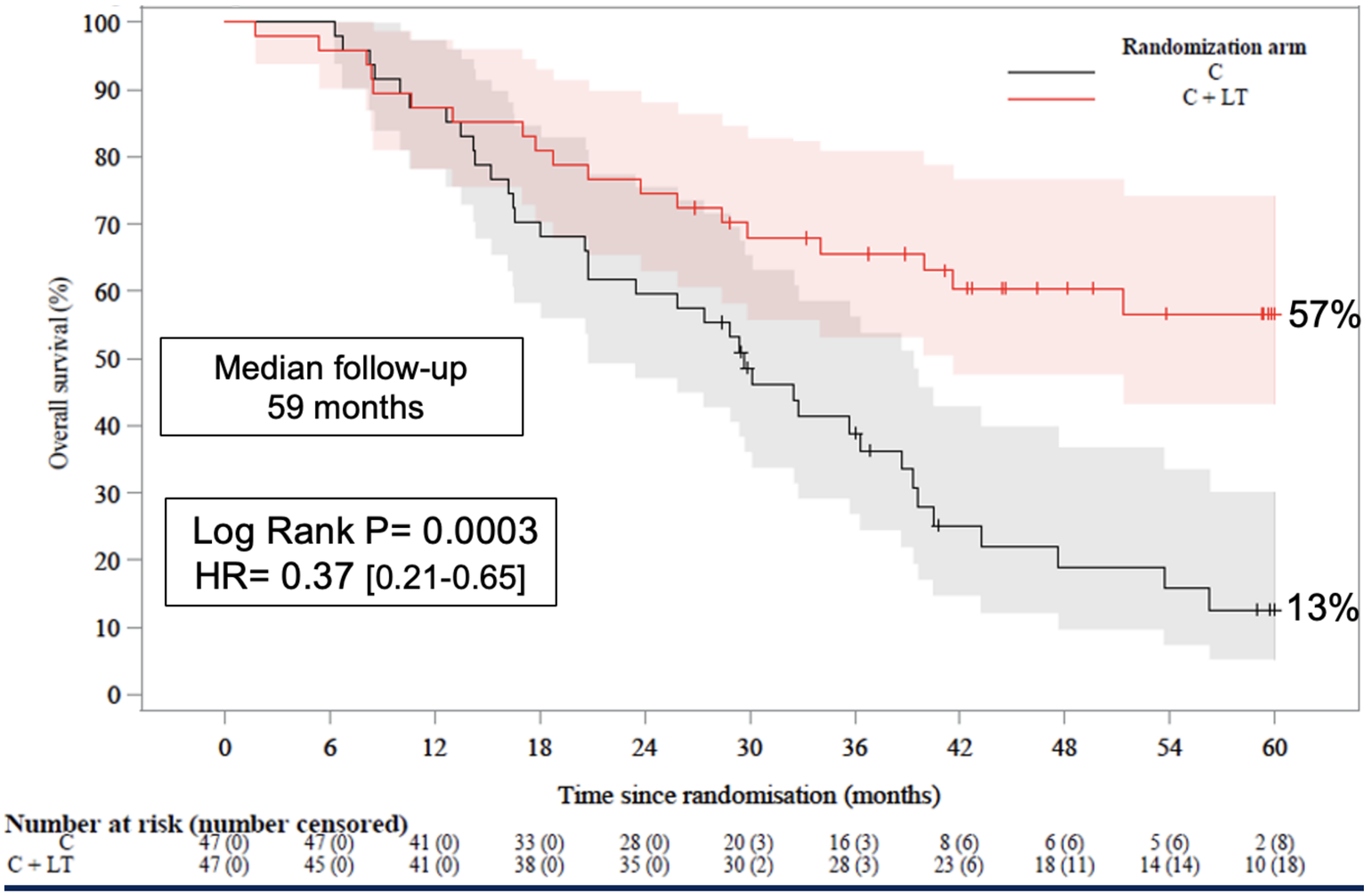
40% difference in 5 yr OS between LT+C (expected 50%)
vs C alone (expected 10%)

Design

50 deaths requires
Power of 90%, Two-sided alpha level of 0.05


157 patients submitted to Validation committee
63 non eligible (40%)
13 not unresectable
36: tumor progression
5 >3 lines chemo
9: other
94 patients randomized
47 pts assigned to (LT+C) in ITT
47 pts assigned to © in ITT
11: No assigned treatment
9 no LT: progression
1 LT on progression
1 LT>3mo from chemo
9: No assigned treatment
2LT out of protocol
7 Liver resection
36 pts included in per protocol
38 pts included in per protocol

TransMet Trial: Primary endpoint 5 yr OS ITT



Presented by: Prof. Rene Adam

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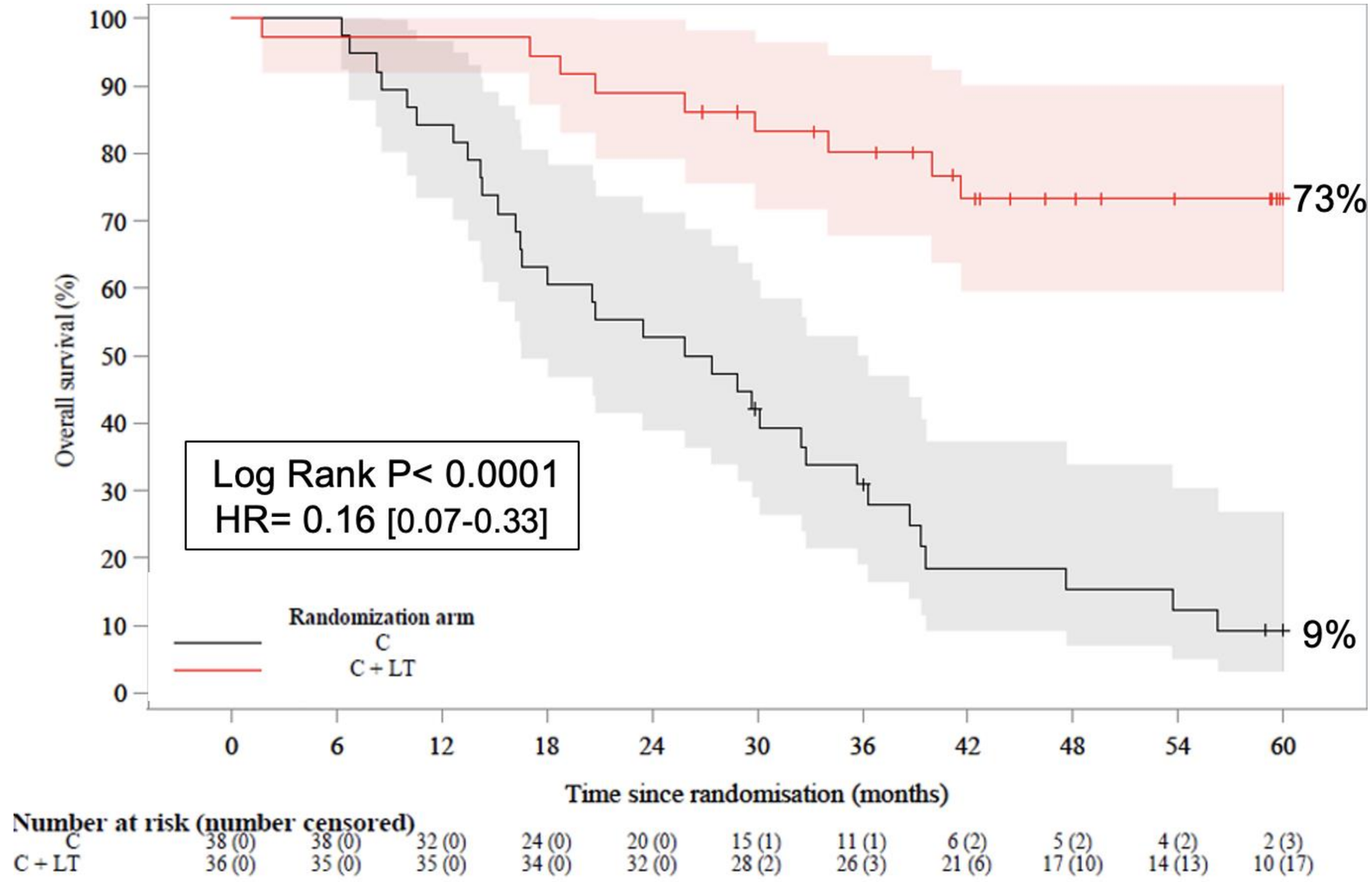
TransMet Trial: Primary endpoint 5 yr OS Per Protocol



Presented by: Prof. Rene Adam

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

Per Protocol Population

36 patients(LT+C)

26 Recurrence (72%)

Liver	Lungs	Lymph N	Other	Multiple
1	14	3	5	3

Surgery or Ablation:12/26(46%)

15 patients NED(42%)

Median FU
50 mo

38 patients (C)

37 progression(97%)

New Regimen Chemotherapy

1 patient NED(3%)

Adapted from presentation by: Prof. Rene Adam

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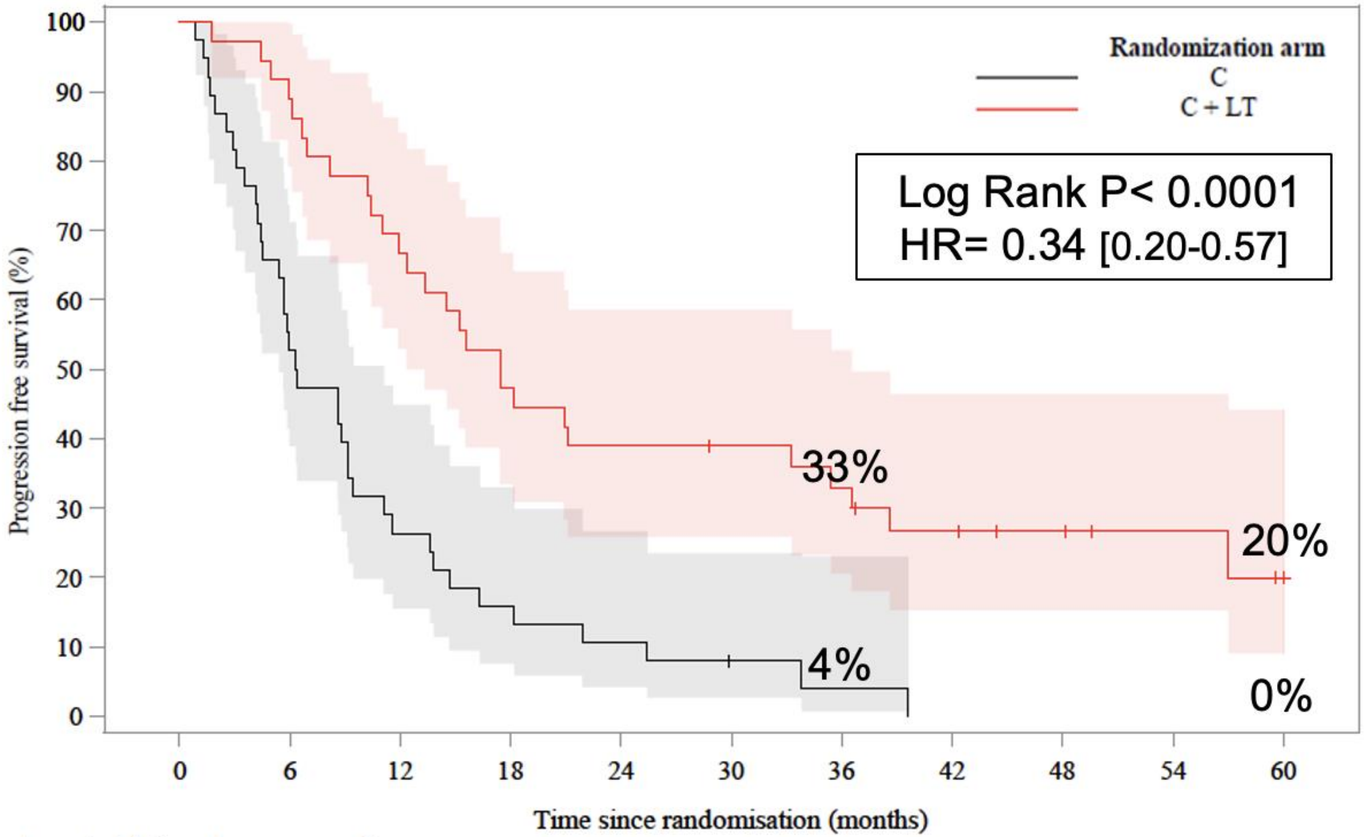
TransMet Trial: 3-5 yr PFS in per protocol pop

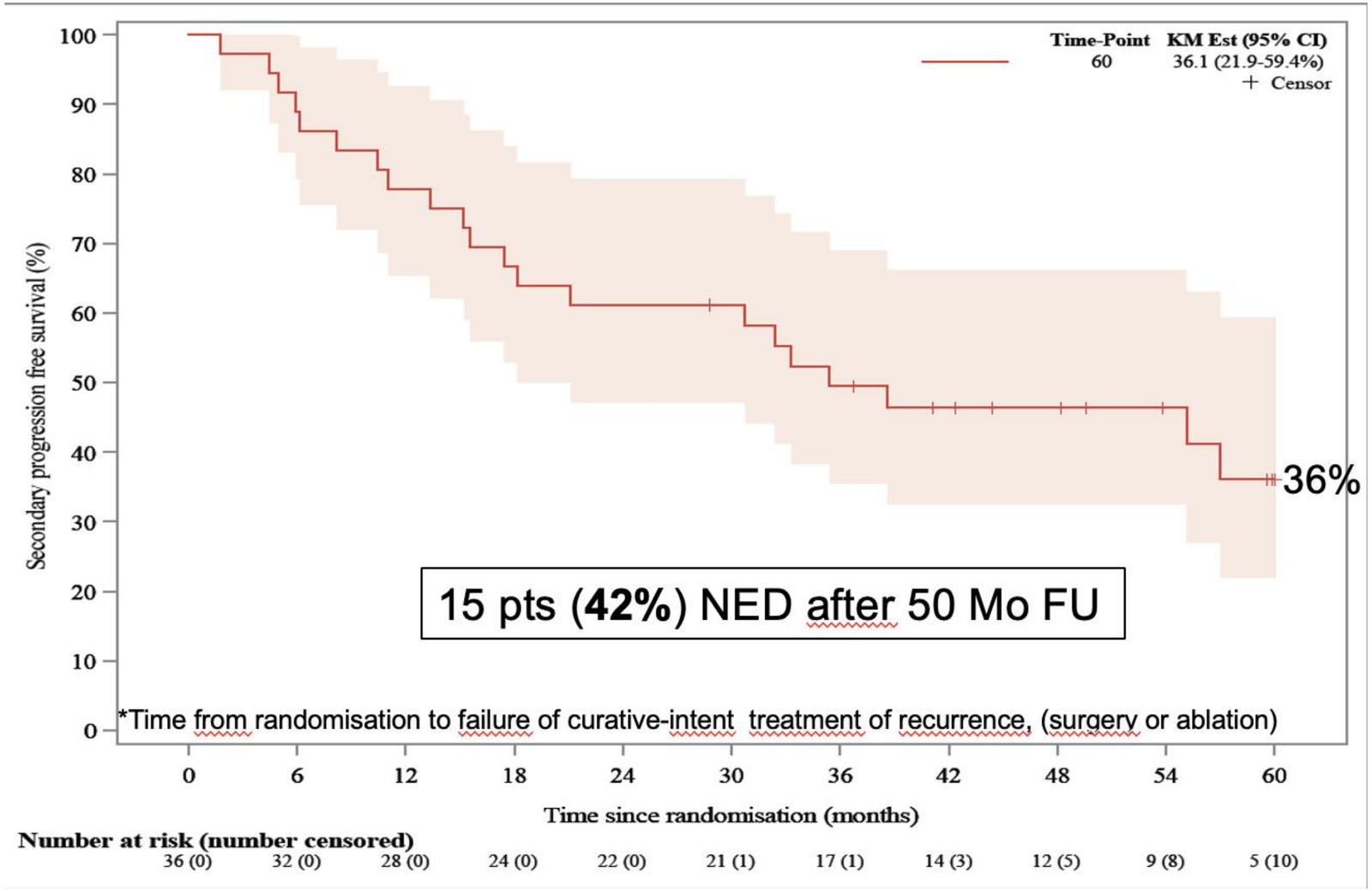


Number at risk (number censored)

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 by rescue surgery in LT+C arm



Presented by: Prof. Rene Adam

Iowa Oncology Society

TransMet Trial Author Conclusions

- Liver Transplantation + chemotherapy significantly improves OS and PFS in ***selected*** patients with unresectable colorectal liver metastasis compared to chemotherapy alone
- ***Rigorous patient selection*** and prioritization for organ allocation
- Transplanted patients for CLM have similar survival(73% at 5 yrs) as those transplanted for established LT indications
- LT+C offers a potential of cure to cancer patients with otherwise poor long term outcome

Summary

- Multidisciplinary discussion for unresectable CLM
- Invite the Liver Transplant Surgeons to your colorectal tumor board
- Highly selective patient population
- Potential for cure
- Close FU since 45-50% can be resected at relapse

COLLISION TRIAL LBA 3501

Colorectal liver metastases: surgery versus thermal ablation (COLLISION) – a phase III single-blind prospective randomized controlled trial

Robbert S. Puijk[1*], Alette H. Ruarus[1], Laurien G. P. H. Vroomen[1], Aukje A. J. M. van Tilborg[1], Hester J. Scheffer[1], Karin Nielsen[2], Marcus C. de Jong[1], Jan J. J. de Vries[1], Babs M. Zonderhuis[2], Hasan H. Eker[2], Geert Kazemier[2], Henk Verheul[3], Bram B. van der Meijs[1], Laura van Dam[1], Natasha Sorgedrager[1], Veerle M. H. Coupé[4], Petrousjka M. P. van den Tol[2], Martijn R. Meijerink[1] and COLLISION Trial Group

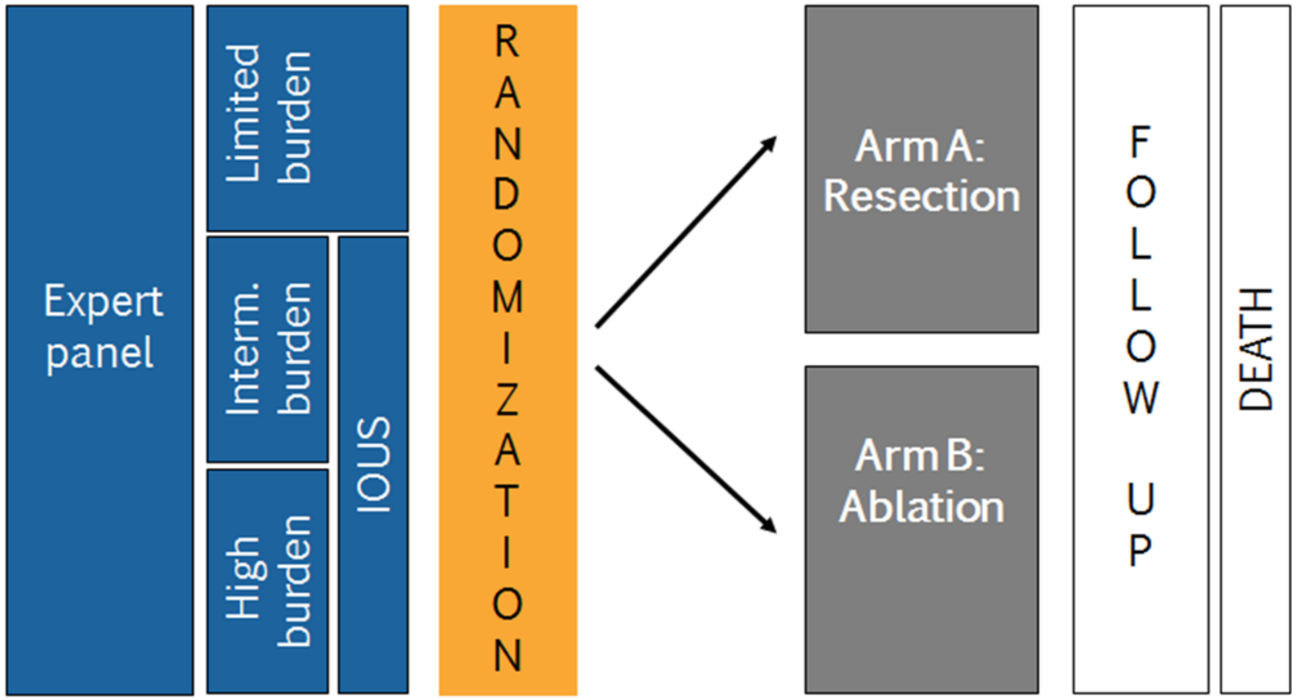
Phase III international multicenter randomized controlled trial to prove / disprove hypothesis of non-inferiority of thermal ablation compared to surgical resection for small-size colorectal liver metastases (CRLM)

COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation

Patients with Resectable Colorectal Liver Metastases (CRLM)

- No extrahepatic mets
- Total number of CRLM ≤ 10
- ≥1 resectable & ablatable CRLM ≤ 3cm
- Additional resection(s) >3cm allowed
- Additional ablations for unresectable CRLM allowed

n = 599



Phase III multicenter partially single-blind randomized controlled trial to prove/disprove non-inferiority of thermal ablation compared to partial hepatectomy for small resectable colorectal liver metastases

- 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)

Meijerink MR et al, Journal of Clinical Oncology, Vol 42, No. 17, suppl LBA 3501

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DESIGN

COLLISION
Colorectal Liver Metastases: surgery vs thermal ablation

PREDEFINED HALFTIME STOPPING RULES (n = 300 / 599)

STOPPING RULES FOR FUTILITY

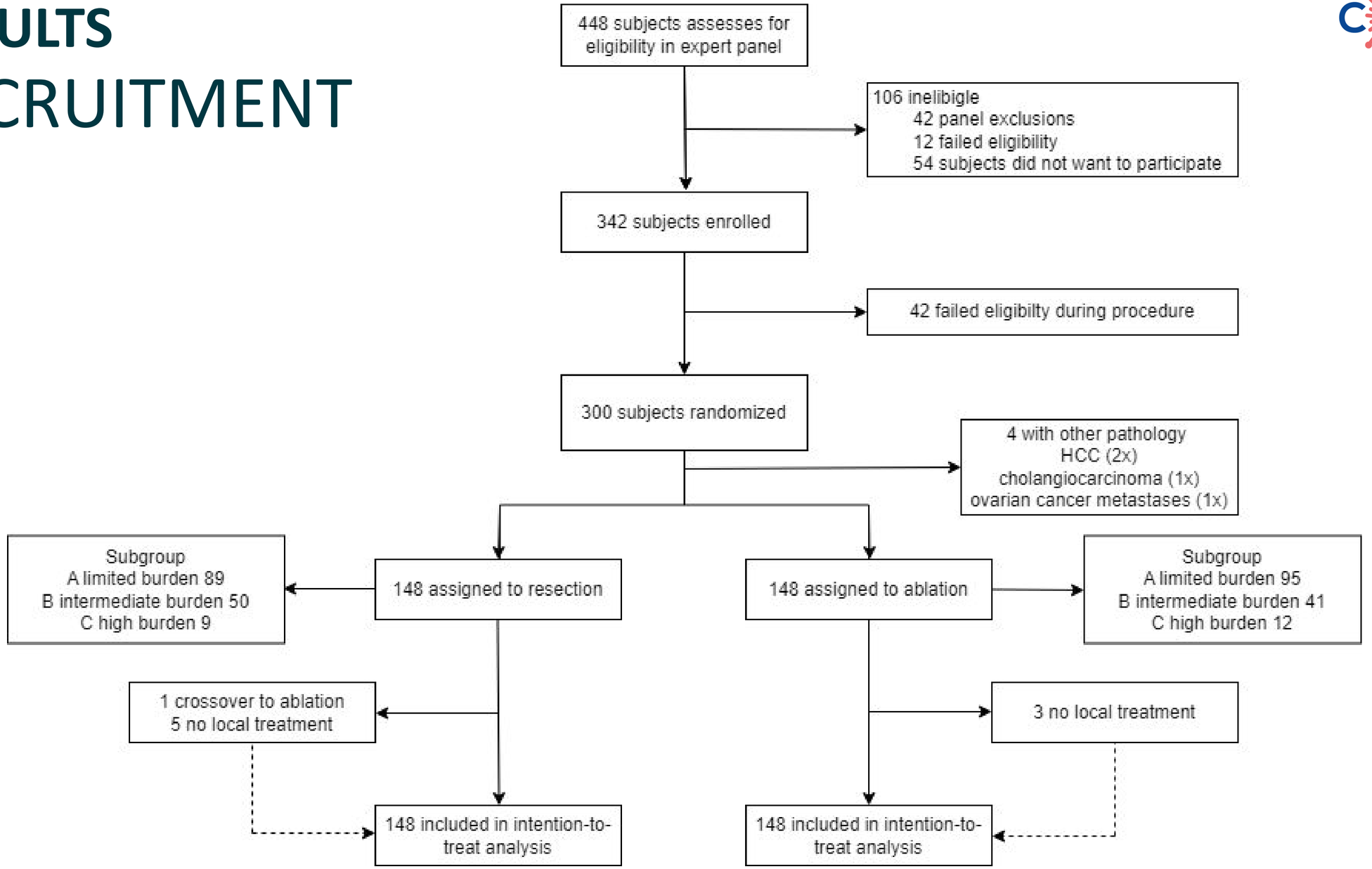
- higher number of **adverse events** (CTCAE) in the experimental arm (ablation)
- **conditional probability** to prove non-inferiority of the experimental arm (ablation) <20%

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

RECRUITMENT



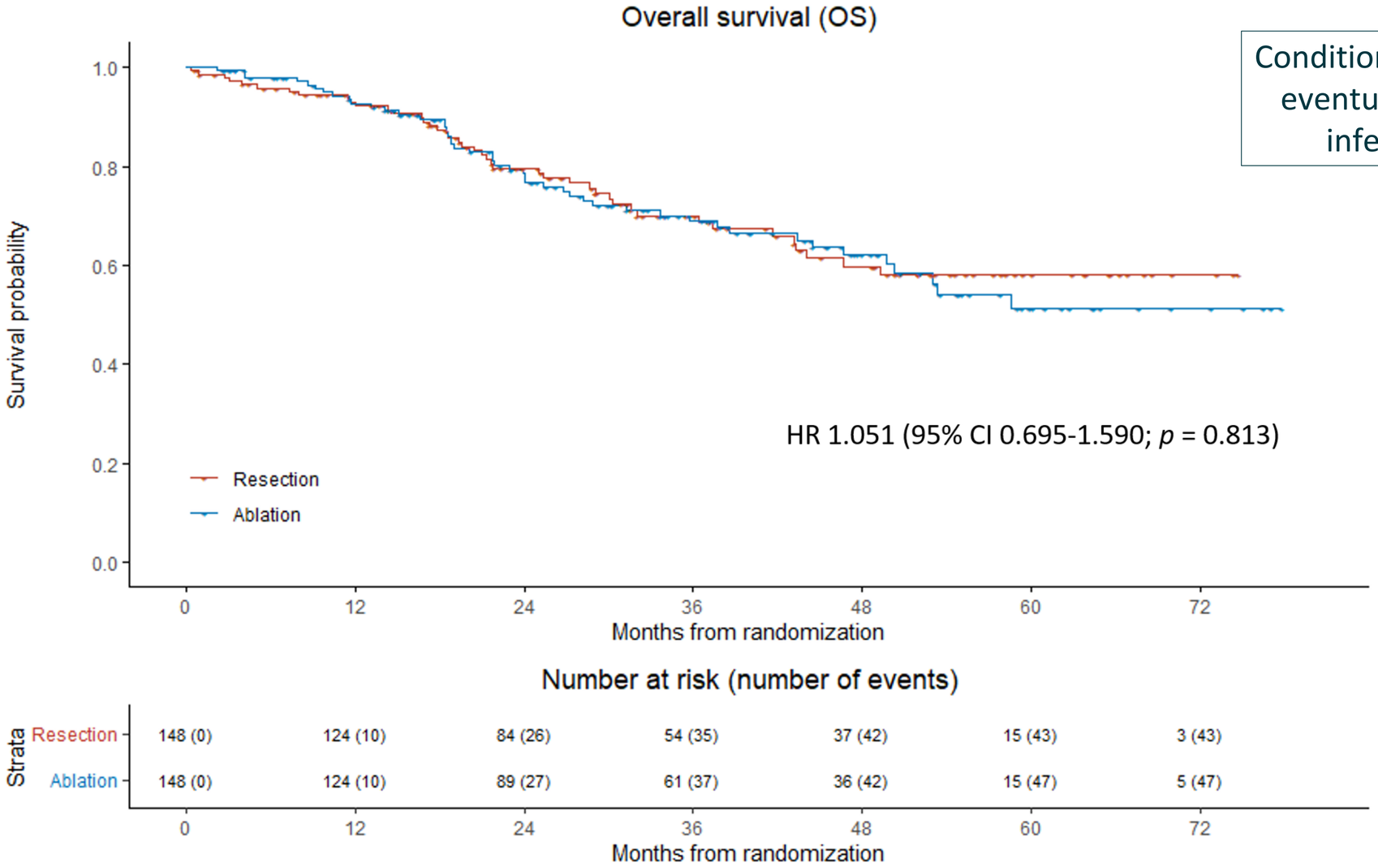
Meijerink MR et al, Journal of Clinical Oncology, Vol 42, No. 17, suppl LBA 3501

the PRIMARY ENDPOINT

- **OVERALL SURVIVAL (OS)**

RESULTS

OVERALL SURVIVAL – PRIMARY ENDPOINT



Conditional probability to eventually prove non-inferiority 91%!

Meijerink MR et al, Journal of Clinical Oncology, Vol 42, No. 17, suppl LBA 3501

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)

Meijerink MR et al, Journal of Clinical Oncology, Vol 42, No. 17, suppl LBA 3501

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2024 ASCO ANNUAL MEETING

MOUNTAINEER: FINAL RESULTS OF A PHASE 2 STUDY OF TUCATINIB AND TRASTUZUMAB FOR HER2-POSITIVE METASTATIC CRC

John H. Strickler, MD; Andrea Cercek, MD; Salvatore Siena, MD; Thierry Andre, MD; Kimmie Ng, MD, MPH; Eric Van Cutsem, MD, PhD; Christina Wu, MD; Andrew Scott Paulson, MD; Joleen M. Hubbard, MD; Andrew L. Coveler, MD; Christos Fountzilas, MD, FACP; Adel Kardosh, MD, PhD; Pashtoon Murtaza Kasi, MD, MSc; Heinz-Josef Lenz, MD; Kristen Keon Ciombor, MD, MS; Elena Elez, MD; David L. Bajor, MD; Mina Nayeri, PharmD; Wentao Feng, PhD; Tanios S. Bekaii-Saab, MD

Presenter: **John H. Strickler, MD**

Duke University Medical Center, Durham, NC, USA

CRC molecular alterations

RAS exon 2-4
45-55%

HER2 overexpressed/amplified
2-4%

BRAF V600E Mutation
8%

RAS wild-type
40-45%

Fusions(NTRK)
<1%

KRAS G12C mutation
3%

dMMR(MSI-high
4-5%

HER2+ CRC

- Tend to be left-sided or distal CRC (OR:0.50)
- More frequent lung metastasis(OR:2.04)
- High incidence of brain metastases(approx. 20%)
- HER2 amplification is enriched in RAS/BRAF wild type tumors(6-12% vs 1-2% in RAS mutant)
- Prognostic role is unclear

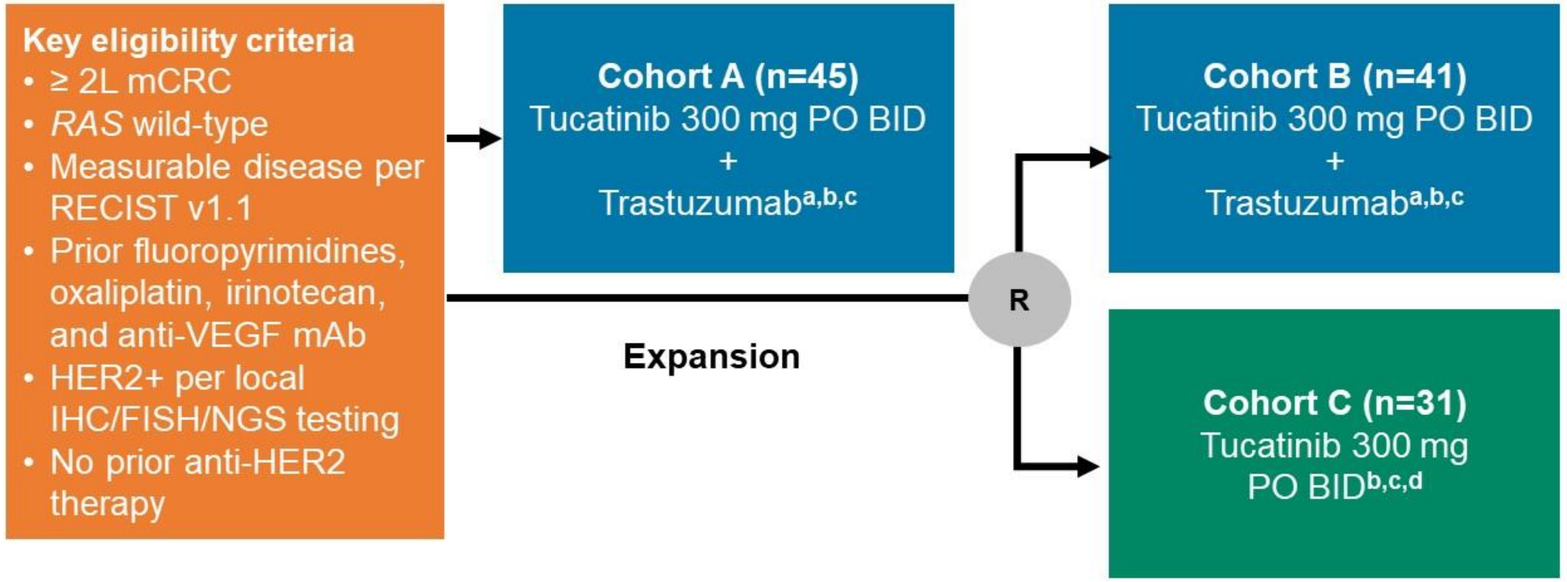
Djaballah ASCO Edu Book.2022;42:219

Guideline recommended biomarker-directed therapy

- HER2-amplified and RAS and BRAF WT
  - Trastuzumab + Pertuzumab
  - Trastuzumab + Lapatinib
  - **Trastuzumab + Tucatinib** 

- HER2-amplified (IHC 3+)
  - Fam-trastuzumab deruxtecan-nkxi

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



Study Endpoints

Efficacy in Cohorts A+B

- *Primary:* cORR, RECIST v1.1 per BICR
- *Secondary:* DOR and PFS per BICR, and OS

Safety:

- TEAEs

Biomarker Analyses:

- Clinical outcomes by HER2 testing methods

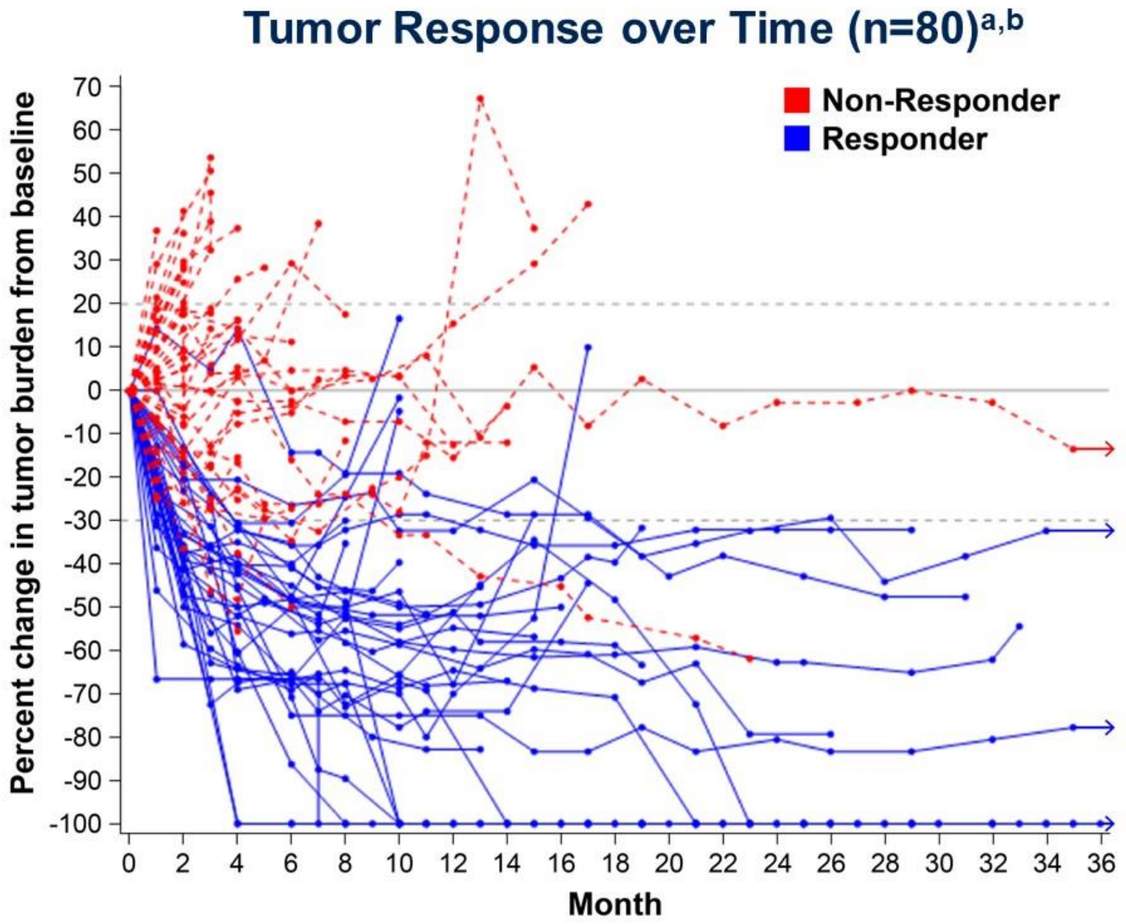
For the final analysis (cutoff date of November 2, 2023), the efficacy and safety endpoints evaluated remained the same. Biomarker analyses, including a long-term responder analysis, were exploratory

[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.

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)

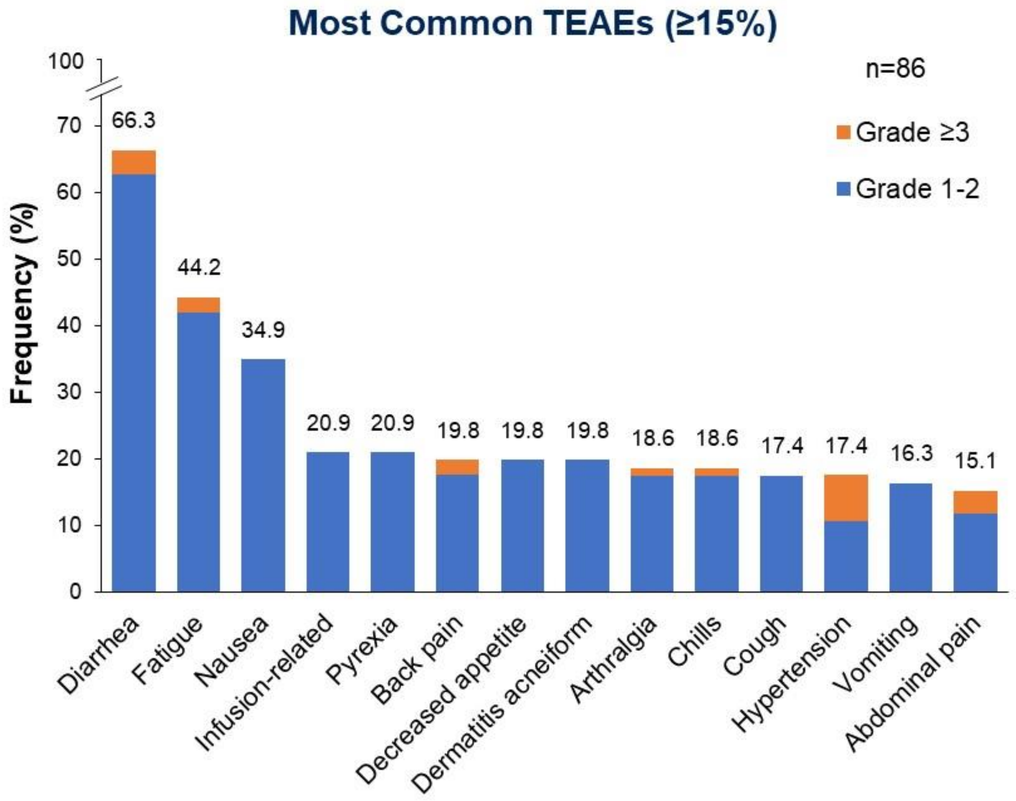
- Median follow-up: 32.4 months

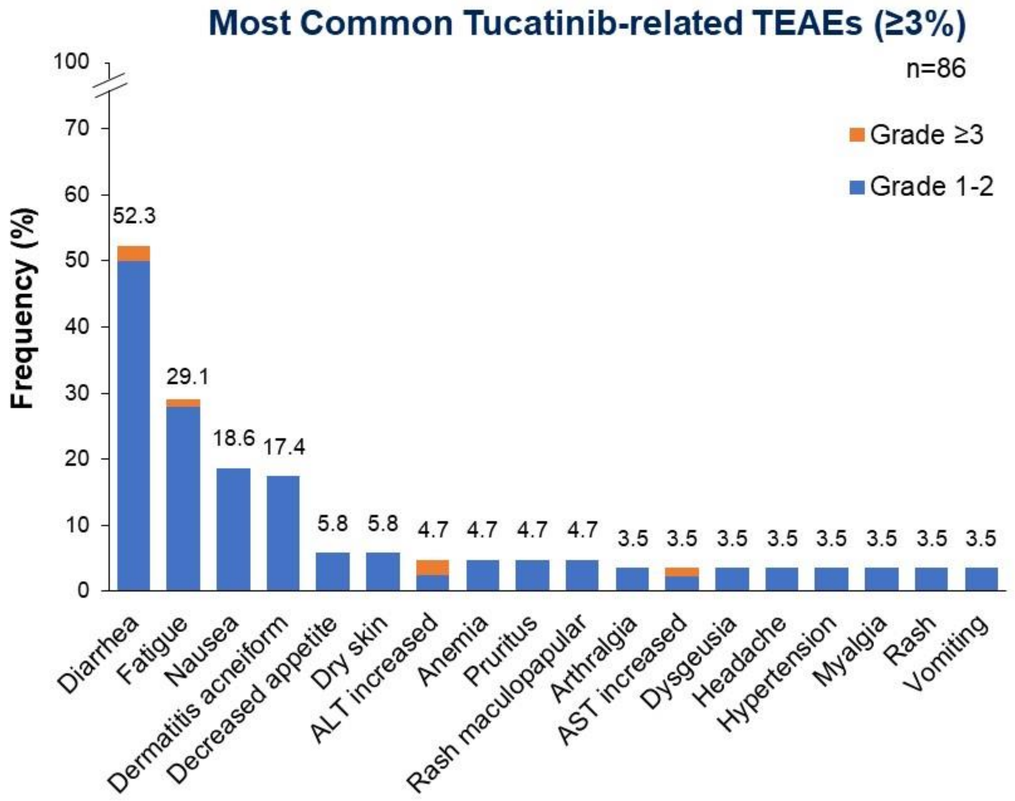


[a] Data up to 36 months are included; [b] Arrows denote treatment duration beyond 36 months.
CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival.

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.

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.

2024 ASCO ANNUAL MEETING

Overall survival (OS) of phase 3 CodeBreaK 300 study of sotorasib plus panitumumab (soto+pani) versus investigator's choice of therapy for *KRAS* G12C-mutated metastatic colorectal cancer (mCRC)

Marwan G. Fakih,[1] Lisa Salvatore,[2,3] Taito Esaki,[4] Dominik Paul Modest,[5] David Paez Lopez-Bravo,[6] Julien Taieb,[7] Michalis V. Karamouzis,[8] Erika Ruiz-Garcia,[9] Tae Won Kim,[10] Yasutoshi Kuboki,[11] Fausto Meriggi,[12] David Cunningham,[13] Kun-Huei Yeh,[14,15] Emily Chan,[16] Joseph Chao,[16] Qui Tran,[16] Chiara Cremolini,[17] Filippo Pietrantonio[18]

[1]Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA; [2]Oncologia Medica, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [4]Department of Gastrointestinal and Medical Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [5]Medicine Department of Hematology, Oncology and Tumor Immunology, Charité - Universitaetsmedizin Berlin, Berlin, Germany; [6]Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [7]Université Paris Cité, SIRIC CARPEM Comprehensive Cancer Center, Department of Gastroenterology and Digestive Oncology, Hopital Européen Georges Pompidou, Paris, France; [8]Department of Biological Chemistry, National and Kapodistrian University of Athens - School of Medicine, Athens, Greece; [9]GI Oncology Department & Translational Medicine Laboratory, INCAN - Instituto Nacional de Cancerologia, Mexico City, Mexico; [10]Oncology Department, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [11]Experimental Therapeutics and GI Oncology Department, National Cancer Center Hospital East, Kashiwa, Japan; [12]Oncology Department, Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy; [13]Medicine Department, The Royal Marsden Hospital, London and Sutton, UK; [14]Department of Oncology, National Taiwan University Hospital, Taipei City, Taiwan; [15]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan; [16]Amgen Inc., Thousand Oaks, CA, USA; [17]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [18]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

The NEW ENGLAND JOURNAL of MEDICINE

Sotorasib plus Panitumumab in Refractory Colorectal Cancer with Mutated KRAS G12C

Authors: Marwan G. Fakih, M.D., Lisa Salvatore, M.D., Taito Esaki, M.D., Dominik P. Modest, M.D., David P. Lopez-Bravo, M.D., Julien Taieb, M.D., Michalis V. Karamouzis, M.D., +11, and Filippo Pietrantonio, M.D. Author Info & Affiliations

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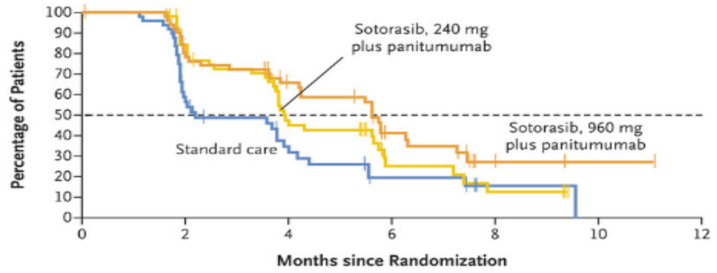
VOL. 389 NO. 23

A Progression-free Survival (Intention-to-Treat Population)

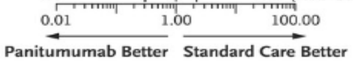


No. at Risk							
Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.49 (0.30–0.80)	0.006
Sotorasib, 240 mg plus Panitumumab	3.91	0.58 (0.36–0.93)	0.03
Standard Care	2.20		

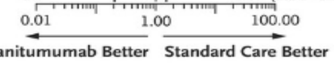
B Subgroup Analysis for Progression-free Survival — Sotorasib, 960 mg plus Panitumumab

Subgroup	Sotorasib, 960 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.49 (0.30–0.80)
Age			
<65 yr	32	27	0.52 (0.26–1.04)
≥65 yr	21	27	0.43 (0.20–0.92)
Sex			
Male	29	24	0.59 (0.30–1.15)
Female	24	30	0.35 (0.17–0.73)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.42 (0.20–0.84)
<18 mo	24	23	0.51 (0.24–1.07)
Location of tumor			
Right side	24	16	0.41 (0.19–0.90)
Left side	28	37	0.62 (0.32–1.20)
Body site at initial diagnosis			
Colon	37	37	0.45 (0.25–0.80)
Rectum	16	17	0.57 (0.24–1.31)
No. of lines of previous therapy for metastatic disease			
1 or 2	37	28	0.39 (0.21–0.72)
≥3	16	26	0.58 (0.22–1.47)
Liver metastasis			
Yes	38	38	0.35 (0.20–0.61)
No	15	16	0.82 (0.30–2.21)



C Subgroup Analysis for Progression-free Survival — Sotorasib, 240 mg plus Panitumumab

Subgroup	Sotorasib, 240 mg plus Panitumumab	Standard Care	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	53	54	0.58 (0.36–0.92)
Age			
<65 yr	39	27	0.63 (0.32–1.23)
≥65 yr	14	27	0.36 (0.14–0.91)
Sex			
Male	26	24	0.71 (0.37–1.37)
Female	27	30	0.63 (0.31–1.27)
Time from initial diagnosis of metastatic disease to randomization			
≥18 mo	29	31	0.49 (0.25–0.97)
<18 mo	22	23	0.78 (0.40–1.52)
Location of tumor			
Right side	17	16	0.59 (0.27–1.32)
Left side	36	37	0.58 (0.33–1.03)
Body site at initial diagnosis			
Colon	32	37	0.53 (0.30–0.95)
Rectum	21	17	0.47 (0.21–1.02)
No. of lines of previous therapy for metastatic disease			
1 or 2	29	28	0.56 (0.31–1.02)
≥3	24	26	0.58 (0.27–1.26)
Liver metastasis			
Yes	36	38	0.47 (0.28–0.80)
No	17	16	0.56 (0.20–1.51)



Investigator's choice:
Trifluridine-tipiracil or Regorafenib

Primary Endpoint:
PFS by BICR

Secondary Endpoint:
OS and ORR

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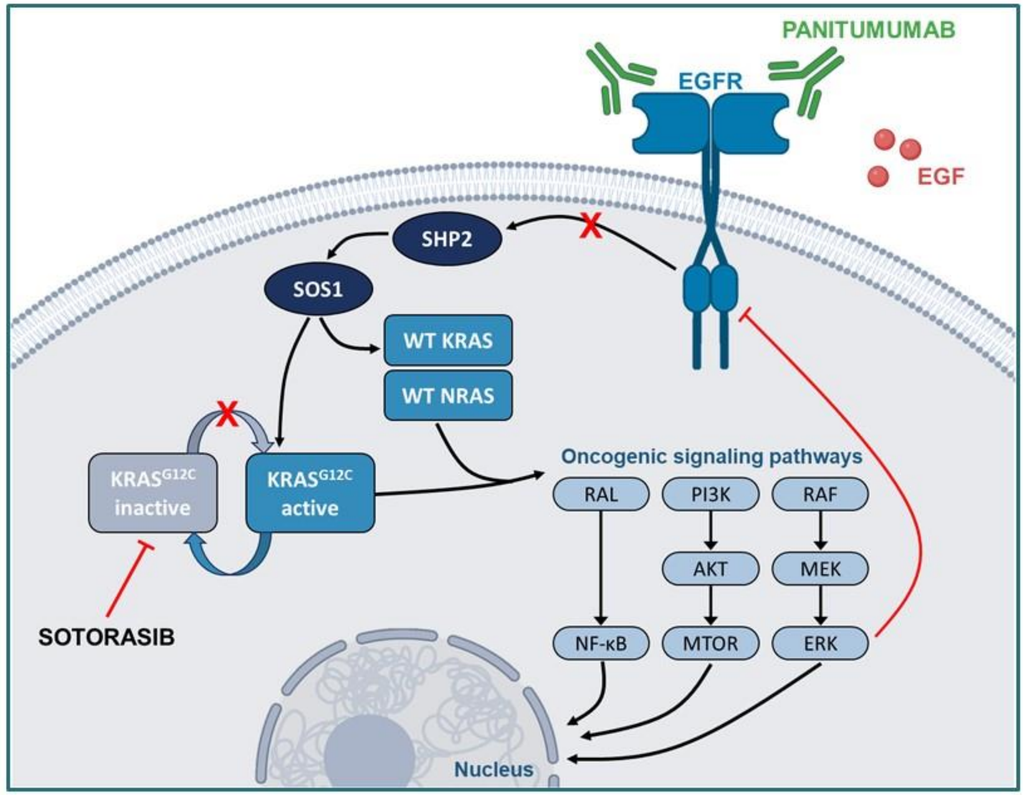
Background

- The oncogenic *KRAS* G12C mutation is present in ~3% of patients with colorectal cancer (CRC) and may be associated with poor prognosis[1–7]
- There is a biological rationale to combine anti-EGFR therapy with a KRAS^{G12C} inhibitor in this molecular subgroup of patients[8–10]
- In CodeBreaK 300, sotorasib + panitumumab was superior to investigator's choice at the primary analysis of progression-free survival (PFS) in patients with *KRAS* G12C–mutated metastatic CRC (mCRC)[11]
- Here we present the protocol-specified final analysis of overall survival



AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated extracellular signal-regulated kinase; MTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; NRAS, neuroblastoma Ras viral oncogene homolog; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-related protein; SHP2, Src homology region 2-containing protein tyrosine phosphatase 2; SOS1, son of sevenless homolog 1; WT, wild type.

1. Neumann J, et al. *Pathol Res Pract*. 2009;205:858-862. 2. Thein KZ, et al. *JCO Precis Oncol*. 2022;6:e2100547. 3. Fakih M, et al. *Oncologist*. 2022;27:663-74. 4. Henry JT, et al. *JCO Precis Oncol*. 2021;5. 5. Lee JK, et al. *npj Precision Oncol*. 2022;6:91. 6. Modest DP, et al. *Ann Oncol*. 2016;27:1746-53. 7. Taieb J, et al. *Ann Oncol*. 2023 Aug 22 [online ahead of print]. 8. Fakih M, et al. *Lancet Oncol*. 2022;23:115-24. 9. Amodio V, et al. *Cancer Discov*. 2020;10:1129-1139. 10. Ryan MB, et al. *Cell Rep*. 2022;39:110993. 11. Fakih, M, et al. New Engl J Med 2023; 389:2125-39.

CodeBreaK 300 Phase 3 Study Design

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)

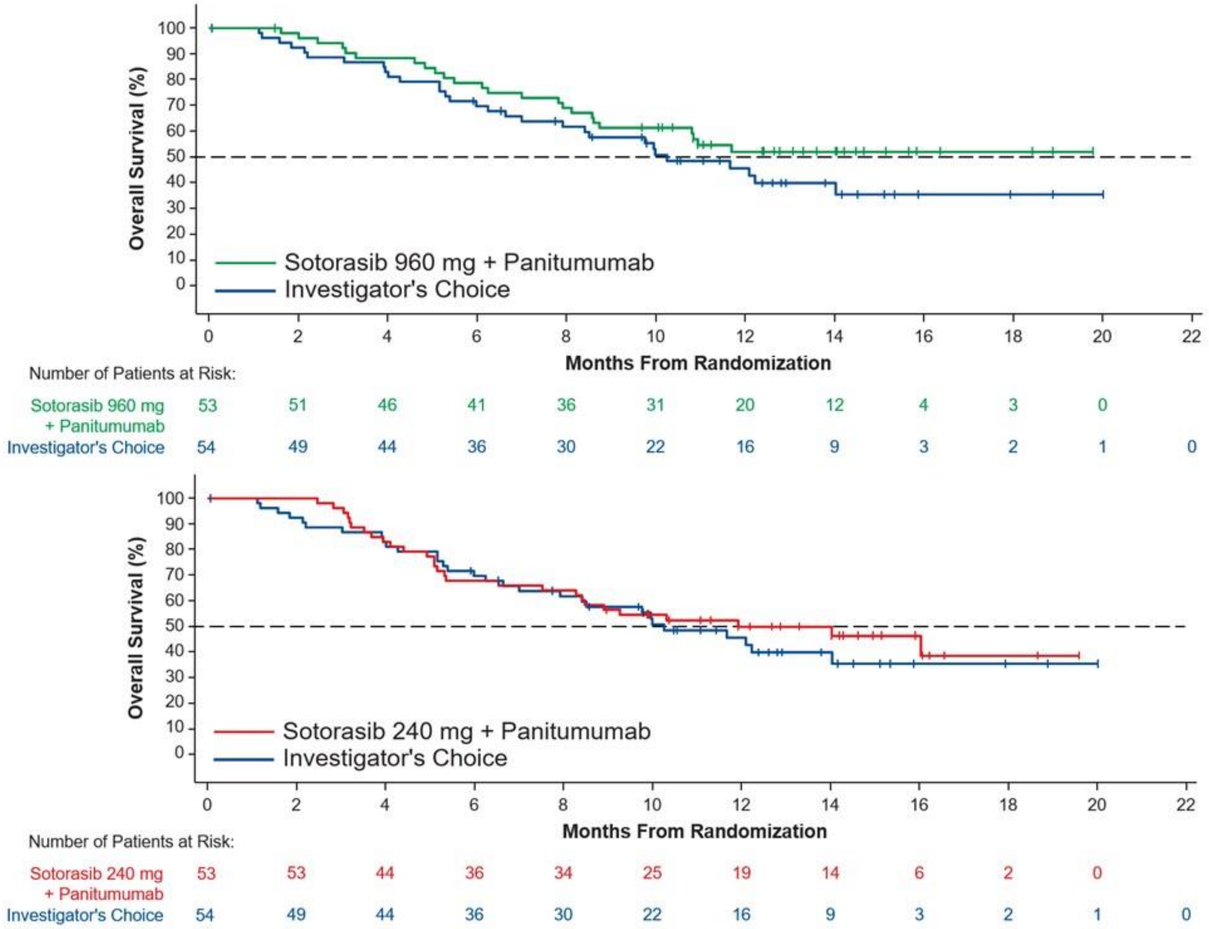
Key secondary endpoints: OS, ORR

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.

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.

Subsequent Anticancer Therapy

Characteristic	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Patients with subsequent anti-cancer therapy, n (%)	**23 (43)**	**27 (51)**	**33 (61)**
$KRAS^{G12C}$ inhibitors			
Any $KRAS^{G12C}$ inhibitor	**1 (2)**	**0**	**17 (31)**
$KRAS^{G12C}$ inhibitor + EGFR antibody	**0**	**0**	**15 (28)**
$KRAS^{G12C}$ inhibitor + other	**0**	**0**	**2 (4)**
$KRAS^{G12C}$ inhibitor monotherapy	**1 (2)**	**0**	**0**
Control arm agents			
Regorafenib or trifluridine / tipiracil	15 (28)	22 (42)	14 (26)
Regorafenib	8 (15)	6 (11)	8 (15)
Trifluridine and tipiracil	12 (23)	19 (36)	6 (11)
Anti-angiogenics			
Bevacizumab	9 (17)	12 (23)	7 (13)
Aflibercept	0	0	0
Ramucirumab	1 (2)	0	0
Chemotherapy agents			
Oxaliplatin	5 (9)	3 (6)	2 (4)
Irinotecan	1 (2)	3 (6)	4 (7)
Fluoropyrimidine	15 (28)	23 (43)	13 (24)
Other	6 (11)	6 (11)	3 (6)

EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma.

Additional Outcomes

Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Objective response rate, % (95% CI)*	30 (18.3–44.3)	8 (2.1–18.2)	2 (0–9.9)
Duration of response, median (range),† months (+, censored)	10.1 (3.1–12.9+)	– (5.6–11.2+)	– (5.2–5.2)
PFS per BICR (ad hoc analysis at final OS DCO)			
Events, n (%)	36 (68)	42 (79)	38 (70)
Median (95% CI),† months	5.8 (4.2–7.5)	4.0 (3.7–5.9)	2.0 (1.9–3.9)
HR (95% CI)‡	0.46 (0.29–0.72)	0.57 (0.37–0.88)	

- No new safety findings were observed

*ORR 95% CI using Clopper-Pearson method. †Kaplan-Meier estimates with 95% CIs from log-log transformation. Evaluation was only done if at least 10 patients. ‡HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib].
Data cutoff, 18 December 2023. BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival.

Summary CodeBreak 300

Sotorasib 960 mg + panitumumab is a new SOC therapy for patients with chemotherapy-refractory KRAS G12C-mutated mCRC

Superior PFS for sotorasib 960 mg + panitumumab compared to investigator's choice

Study was not powered to detect a statistically significant difference in OS, there was a trend toward improved OS for the sotorasib 960 mg + panitumumab

Median FU 13.6 m, median OS was not reached with sotorasib 960 mg + panitumumab vs 10.3 m in the investigator's choice (HR 0.70 95% CI 0.41-1.18)

Updated ORR was 30% (sotorasib 960 mg +panitumumab) vs 2% investigator's choice

Sotorasib 960 mg + panitumumab showed a median duration of response of 10.1 months

Fakih, M, Journal of Clinical Oncology, Vol 42, No.17 suppl LBA3510

2024 ASCO ANNUAL MEETING

ARC-9: A Randomized Study to Evaluate Etrumadenant Based Treatment Combinations in Previously Treated Metastatic Colorectal Cancer

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ARC-9 Cohort B: Etruma + Zim + mFOLFOX-6 + Bev[a] (EZFB) vs Regorafenib (Rego) in 3L mCRC

Sample size of approximately 105 participants was estimated in a 2:1 ratio randomization to detect an improvement of HR of 0.5 in PFS using a log-rank test in order to achieve 80% power at a two-sided significance level of 0.05

Key inclusion criteria	• Histologically confirmed unresectable mCRC
	• Measurable disease per RECIST v1.1
	• ECOG PS of 0 or 1
	• Disease progression **on or after** treatment with oxaliplatin and irinotecan containing chemotherapy in combination with anti-VEGF(R) or anti-EGFR
	  • **≤ 2 prior lines** of treatment in the metastatic setting
	  • Re-introduction of an initially successful induction regimen, per investigator judgement, not counted as one additional line of treatment
	  • **Metastatic setting:** could not have progressed ≤2 months of last dose of oxaliplatin
	  • **Adjuvant setting:** will count as line of treatment if progressed ≤6 months of last dose
	  • Patients treated with FOLFIRINOX meet this eligibility criteria if they did not progress ≤2 months of last dose of oxaliplatin

Key exclusion criteria	• Prior treatment with immune checkpoint blockade therapies • Mutation in the *BRAF* oncogene; patients with unknown *BRAF* status will be required to undergo testing at a local laboratory and provide results at screening

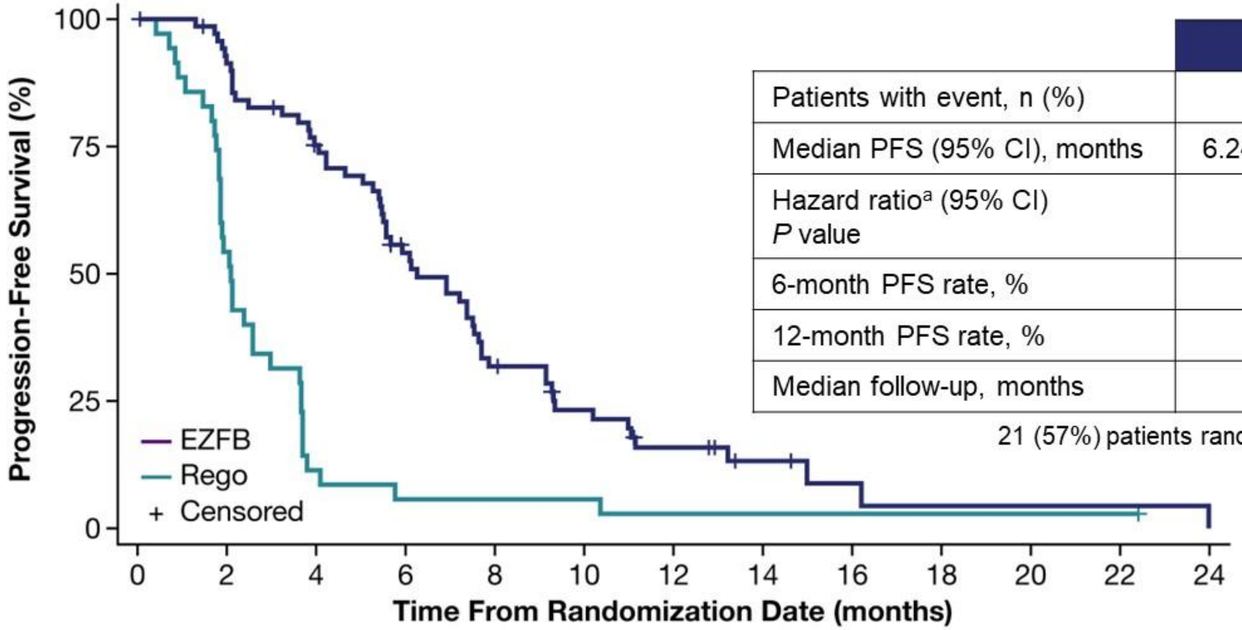
Primary Endpoints
PFS (Investigator assessed)

Key Secondary Endpoints
OS
ORR (Investigator assessed)
Safety

3L, third line; bev, bevacizumab; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; etruma, etrumadenant; mCRC, metastatic CRC; ORR, objective response rate; OS, overall survival; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; zim, zimberelimab.
[a] bev will be included for all patients in whom it is not contraindicated. [b] Patients were randomized 2:1 to EZFB: E (150 mg orally [PO] once daily [QD]) + Z (240 mg intravenous [IV] once every 2 weeks [Q2W]) + mFOLFOX-6 + bev (5 mg/kg IV Q2W), or rego (160 mg PO QD [days 1-21 every 4 weeks]).

Primary Endpoint: Investigator-Assessed Progression-Free Survival (Efficacy Evaluable Population)

- EZFB demonstrated statistically significant improvement in PFS vs rego



	EZFB	Rego
Patients with event, n (%)	58 (77)	34 (92)
Median PFS (95% CI), months	6.24 (5.49, 7.52)	2.07 (1.84, 2.96)
Hazard ratio[a] (95% CI) *P* value	0.27 (0.17, 0.43) <0.001	
6-month PFS rate, %	54	6
12-month PFS rate, %	16	3
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB

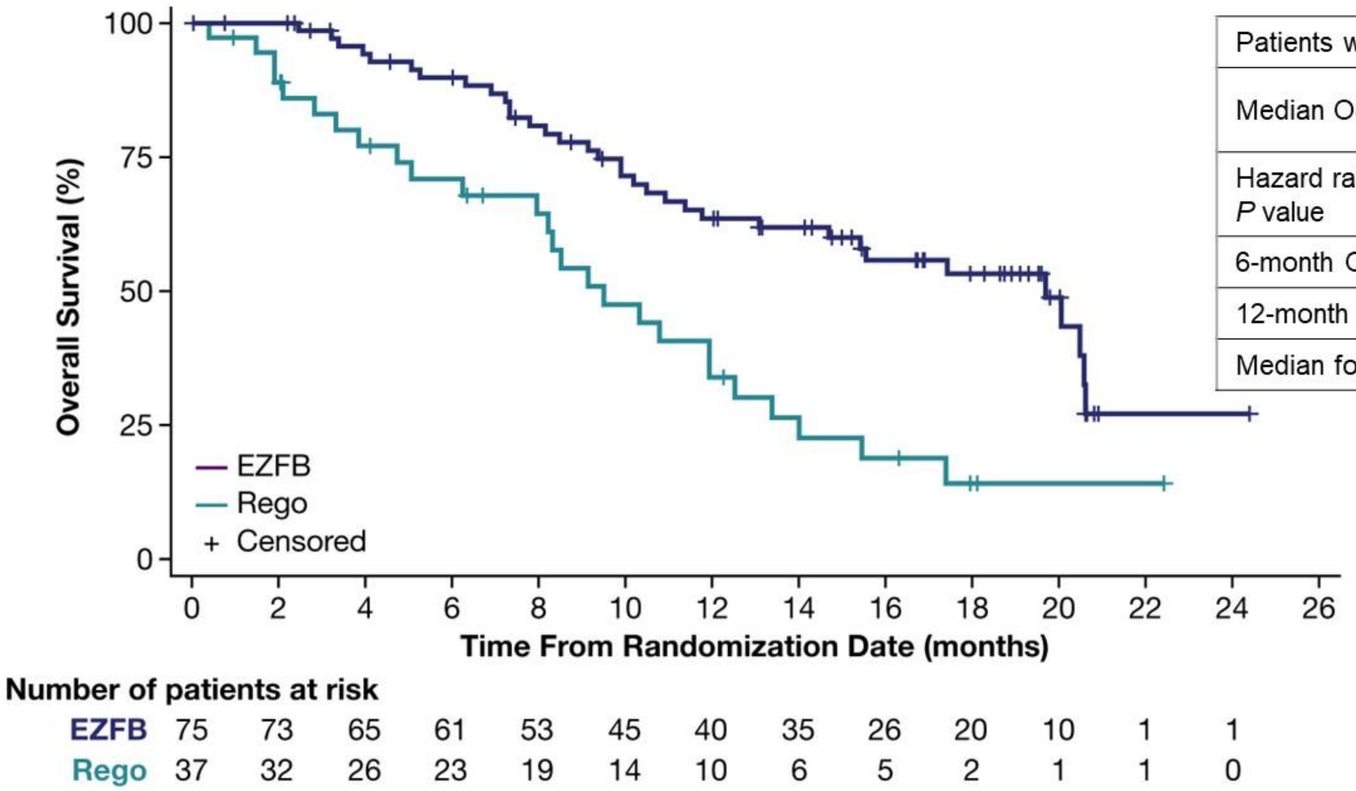
Number of patients at risk

EZFB	75	63	50	34	20	13	8	4	2	1	1	1
Rego	37	19	4	2	2	2	1	1	1	1	1	1

Date cutoff date: November 13, 2023.
PFS is defined as the first occurrence of progressive disease per RECIST v1.1 or death, whichever occurs first. Patients without documented disease progression at the time of analysis were censored on the date of their last adequate tumor assessment. If no tumor assessment was performed after the start of study treatment, PFS will be censored on the date of first dose of study treatment with duration of 1 day.
EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; PFS, progression-free survival; rego, regorafenib.
[a] Hazard ratio and 95% CIs are based on stratified (geographic region) Cox model. Study was not designed as a powered study to control for alpha in multiplicity testing.

Overall Survival (Efficacy Evaluable Population)

- EZFB demonstrated significant improvement in OS vs rego



	EZFB	Rego
Patients with event, n (%)	34 (45)	26 (70)
Median OS (95% CI), months	19.68 (14.69, 20.60)	9.49 (7.95, 12.52)
Hazard ratio[a] (95% CI) *P* value	0.37 (0.22, 0.63) <0.001	
6-month OS rate, %	90	71
12-month OS rate, %	64	34
Median follow-up, months	20.4	

21 (57%) patients randomized to rego crossed over to EZFB

Number of patients at risk

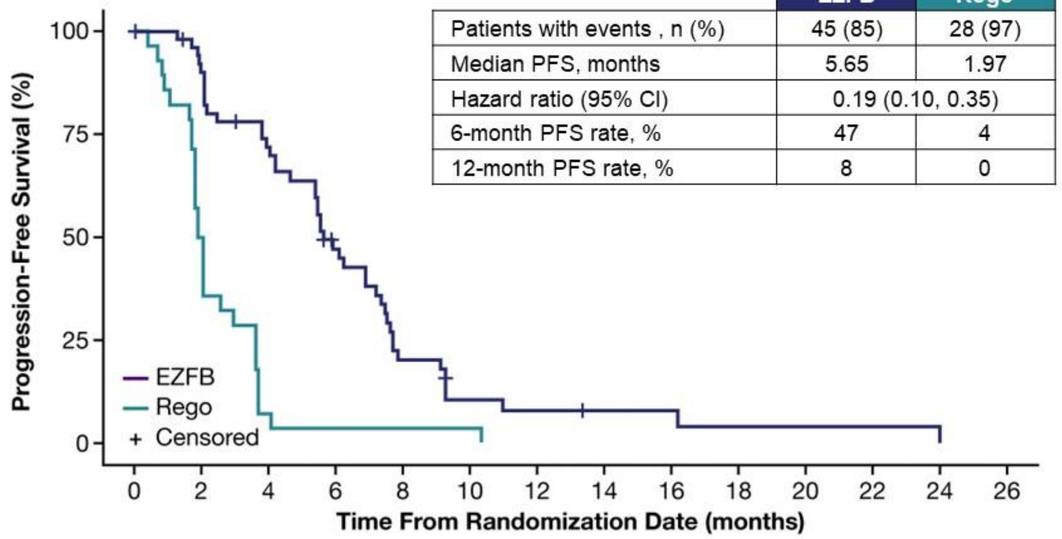
EZFB	75	73	65	61	53	45	40	35	26	20	10	1	1
Rego	37	32	26	23	19	14	10	6	5	2	1	1	0

Date cutoff date: November 13, 2023.
OS is defined as time (months) from randomization until death from any cause. Patients who did not die while on study are censored at the last known date they were alive.
EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; OS, overall survival; rego, regorafenib.
[a] Hazard ratio and 95% CIs are based on stratified (geographic region) Cox model. Study was not designed as a powered study to control for alpha in multiplicity testing.

Progression-Free Survival and Overall Survival in Patients With Baseline Liver Metastasis

- 5.7 month median PFS for EZFB in patients with liver metastasis
- 20 month median OS for EZFB in patients with liver metastasis

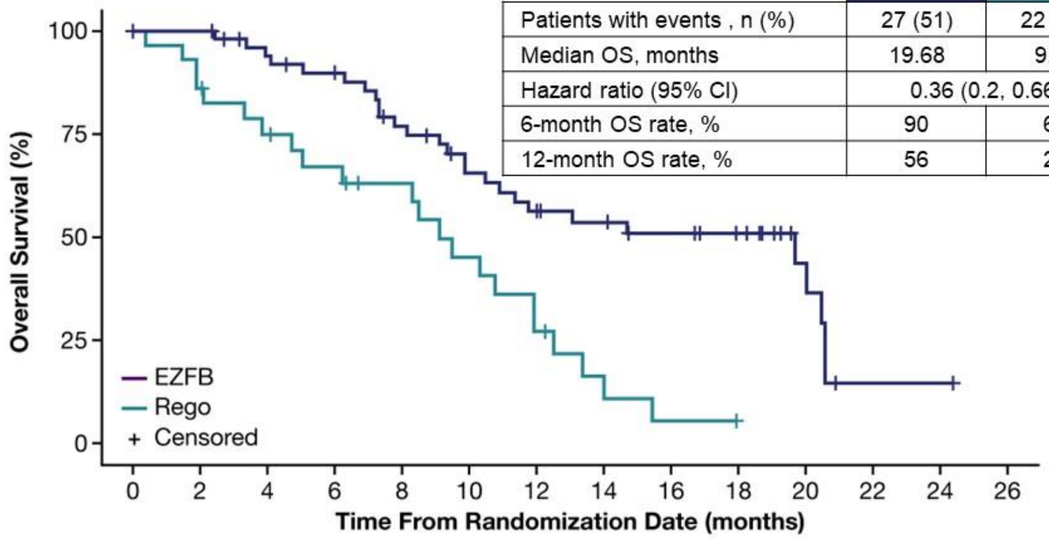
	EZFB	Rego
Patients with events , n (%)	45 (85)	28 (97)
Median PFS, months	5.65	1.97
Hazard ratio (95% CI)	0.19 (0.10, 0.35)	
6-month PFS rate, %	47	4
12-month PFS rate, %	8	0



Number of patients at risk

EZFB	53	45	35	21	9	4	3	2	2	1	1	1	0
Rego	29	14	2	1	1	1	0						

	EZFB	Rego
Patients with events , n (%)	27 (51)	22 (76)
Median OS, months	19.68	9.13
Hazard ratio (95% CI)	0.36 (0.2, 0.66)	
6-month OS rate, %	90	67
12-month OS rate, %	56	27



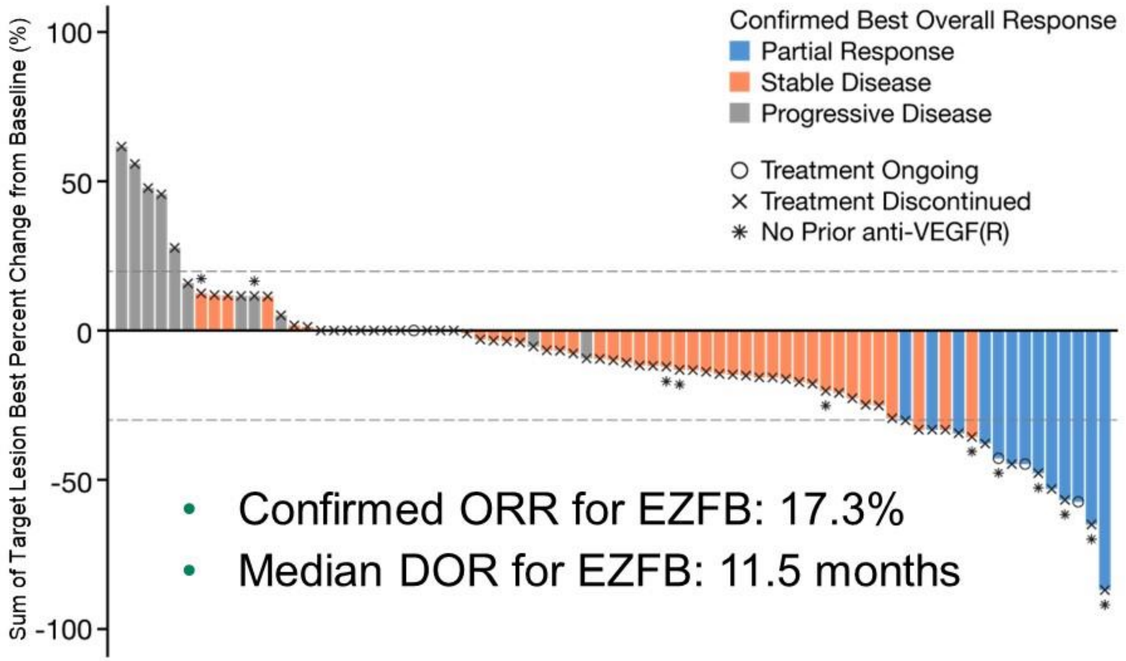
Number of patients at risk

EZFB	53	52	46	43	35	28	24	21	18	13	6	1	1	0
Rego	29	25	20	17	14	10	6	2	1	0				

Date cutoff date: November 13, 2023.
PFS is defined as the first occurrence of progressive disease per RECIST v1.1 or death, whichever occurs first. Patients without documented disease progression at the time of analysis were censored on the date of their last adequate tumor assessment. If no tumor assessment was performed after the start of study treatment, PFS will be censored on the date of first dose of study treatment with duration of 1 day. OS is defined as time (months) from randomization until death from any cause. Patients who did not die while on study are censored at the last known date they were alive.
EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; rego, regorafenib.

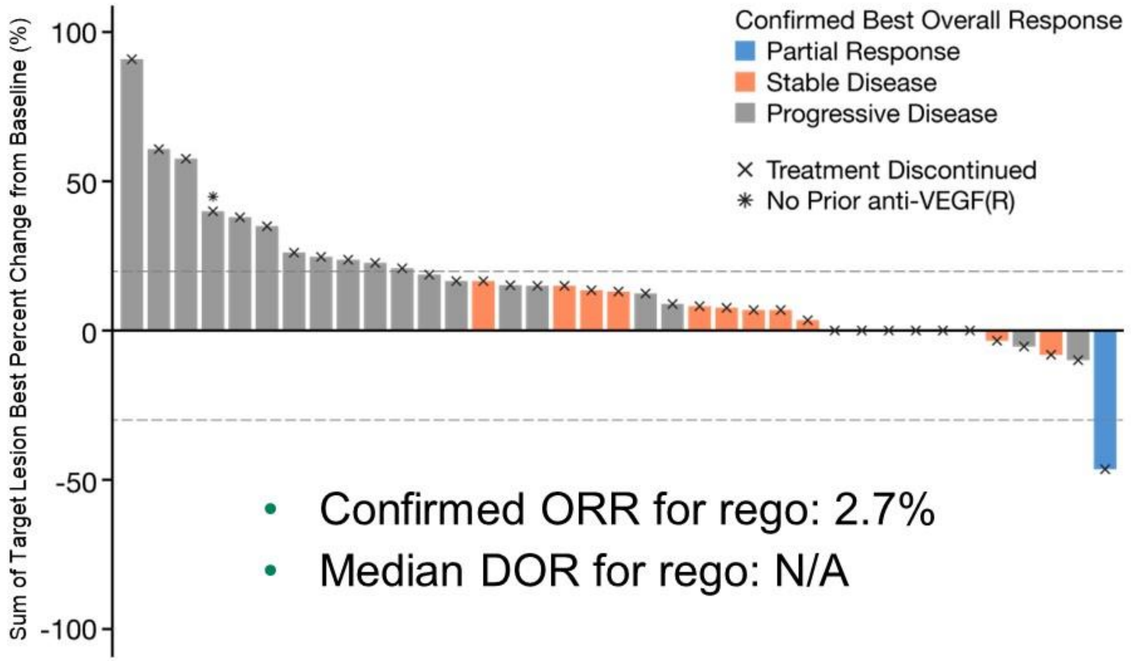
Investigator-Assessed Objective Response Rate (Efficacy Evaluable Population)

EZFB



- Confirmed ORR for EZFB: 17.3%
- Median DOR for EZFB: 11.5 months

REGO



- Confirmed ORR for rego: 2.7%
- Median DOR for rego: N/A

Date cutoff date: November 13, 2023.
DOR was defined as the time from first documentation of confirmed disease response (CR or PR) until first documentation of progressive disease per RECIST v1.1.
DOR, duration of response; EZFB, etrumadenant + zimberelimab + mFOLFOX-6 + bevacizumab; N/A, not applicable; ORR, objective response rate; rego, regorafenib.

Conclusions

- This is the first randomized, phase 2, proof-of-concept study showing EZFB significantly improves PFS and OS compared with standard-of-care in microsatellite-stable 3L mCRC
  - Longest OS reported for a randomized clinical trial in 3L mCRC
  - Meaningful improvement shown across all subgroups, including 20-month median OS in patients with liver metastasis
- Safety was consistent with the individual study drugs and manageable with no treatment related deaths
- These data demonstrate the therapeutic potential of etruma in CRC and supports further development of EZFB as a regimen in CRC