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with

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LESSONS LEARNED FROM THE RE-ARRANGE TRIAL

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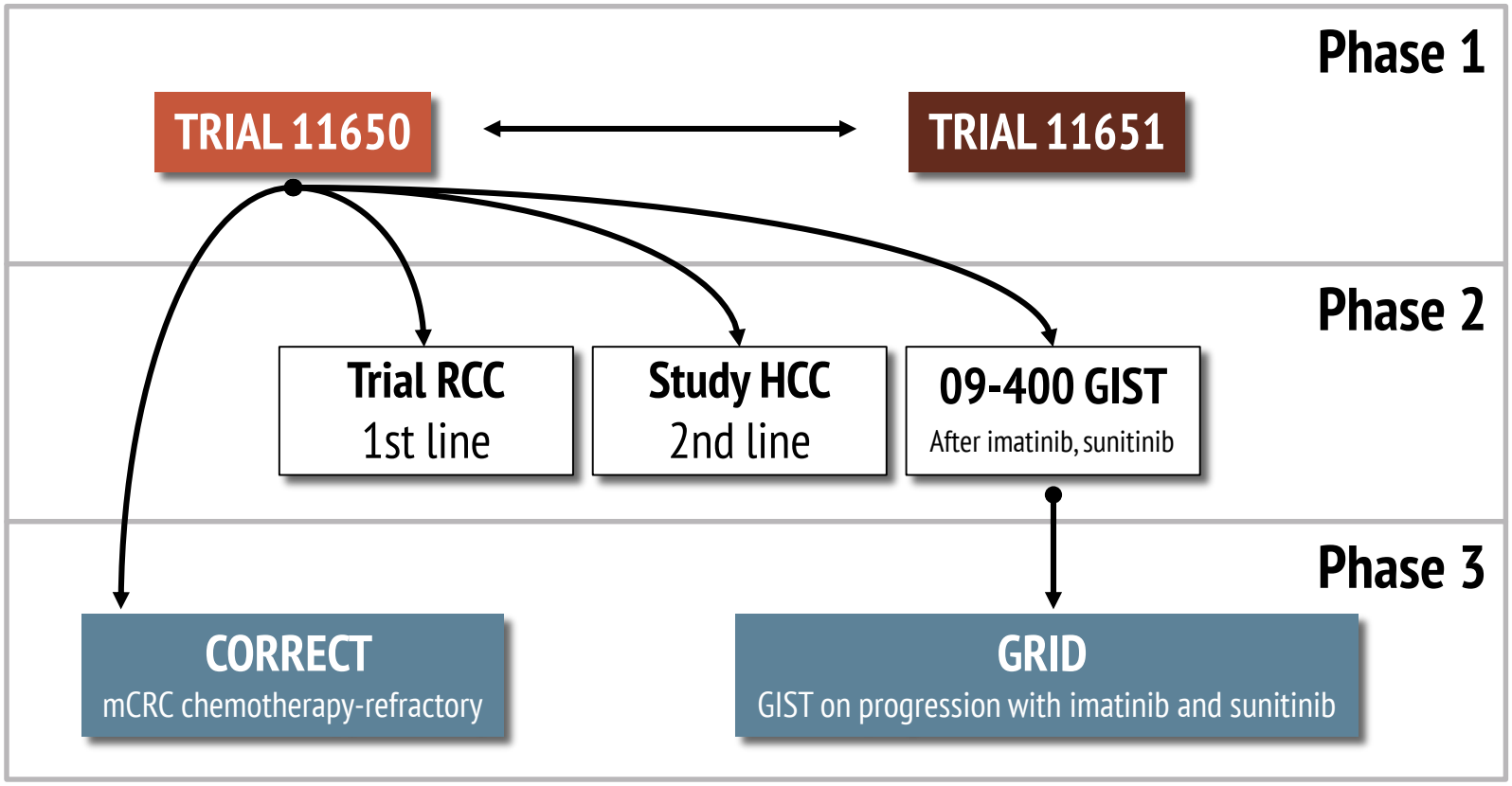
REGORAFENIB EARLY DEVELOPMENT PATHWAY



www.clinicaltrials.gov.

GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; mCRC, metastatic colorectal cancer; RCC, renal cell carcinoma

REGORAFENIB SIGNIFICANTLY IMPROVED OS IN PHASE 3 RCTs

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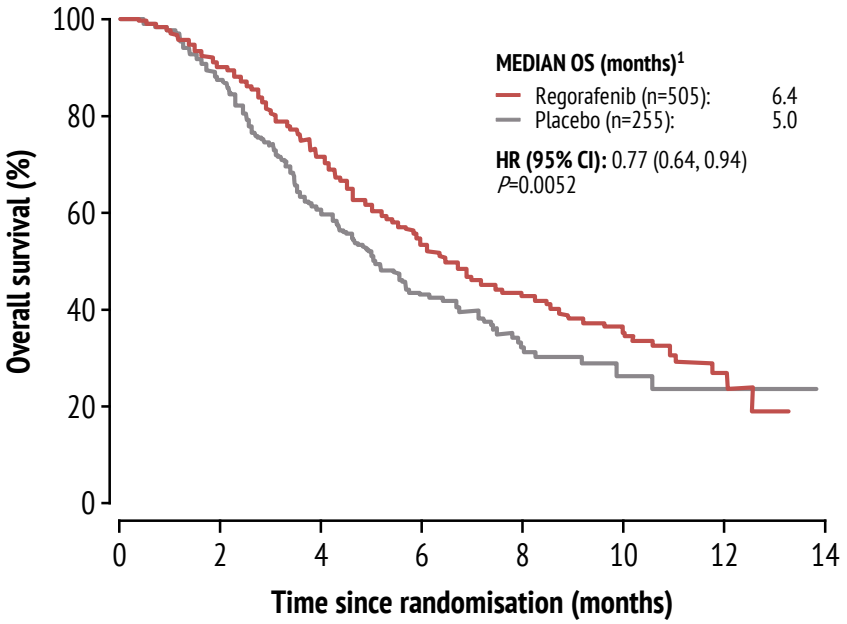
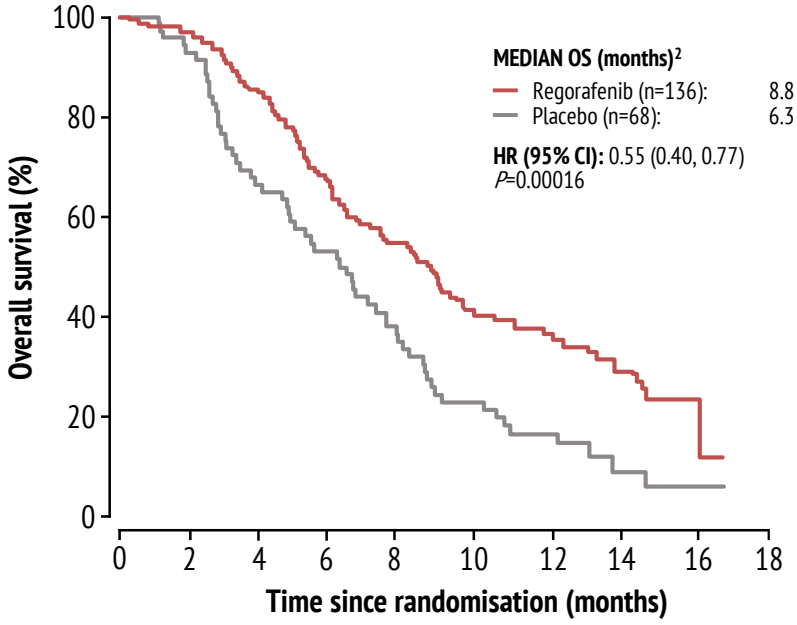
CORRECT[1]



Number at risk						
Regorafenib	452	352	187	93	33	7
Placebo	221	150	75	32	9	3

CONCUR[2]



Number at risk										
Regorafenib	136	131	113	88	72	52	42	24	4	-
Placebo	68	63	45	35	23	15	11	4	1	-

CI, confidence interval; HR, hazard ratio; OS, overall survival; RCT, randomised clinical trial

1. Grothey A, et al. Lancet. 2013;381:303-12; 2. Li J, et al. Lancet Oncol. 2015;16:619-29

COMMON AEs REPORTED BY PATIENTS ON REGORAFENIB

Drug-related AEs, %	CORRECT[1]				CONCUR[2]			
	Regorafenib (n=500)		Placebo (n=253)		Regorafenib (n=136)		Placebo (n=68)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
HFSR	47	17	8	<1	74	16	4	0
Fatigue	47	10	28	5	17	3	7	1
Hypertension	28	7	6	1	23	11	4	3
Diarrhoea	34	7	8	1	18	1	3	1
Rash/desquamation[a]	26	6	4	0	9	4	1	0
Anorexia	30	3	15	3	7	1	4	0
Mucositis, oral	27	3	4	0	NR	NR	NR	NR
Hyperbilirubinemia	9	2	2	1	37	7	7	1
ALT increased	NR	NR	NR	NR	24	7	7	0
AST increased	NR	NR	NR	NR	24	6	9	0
Thrombocytopenia	13	3	2	<1	10	3	1	0
Fever	10	1	3	0	NR	NR	NR	NR
Nausea	14	<1	11	0	NR	NR	NR	NR
Voice changes[b]	29	<1	6	0	21	1	0	0
Weight loss	14	0	2	0	NR	NR	NR	NR

[a]Maculopapular rash in CONCUR; [b]Hoarseness in CONCUR. Adverse events were graded using the NCI-CTCAE version 3.0 (CORRECT) and version 4.0 (CONCUR).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFSR, hand-foot skin reaction; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NR, not reported

1. Grothey A, et al. Lancet. 2013;381:303-12; 2. Li J, et al. Lancet Oncol. 2015;16:619-29

AE MANAGEMENT EXPERIENCE MATTERS: REGORAFENIB AEs FREQUENTLY OCCUR EARLY IN TREATMENT AND ARE NONCUMULATIVE[1,2]

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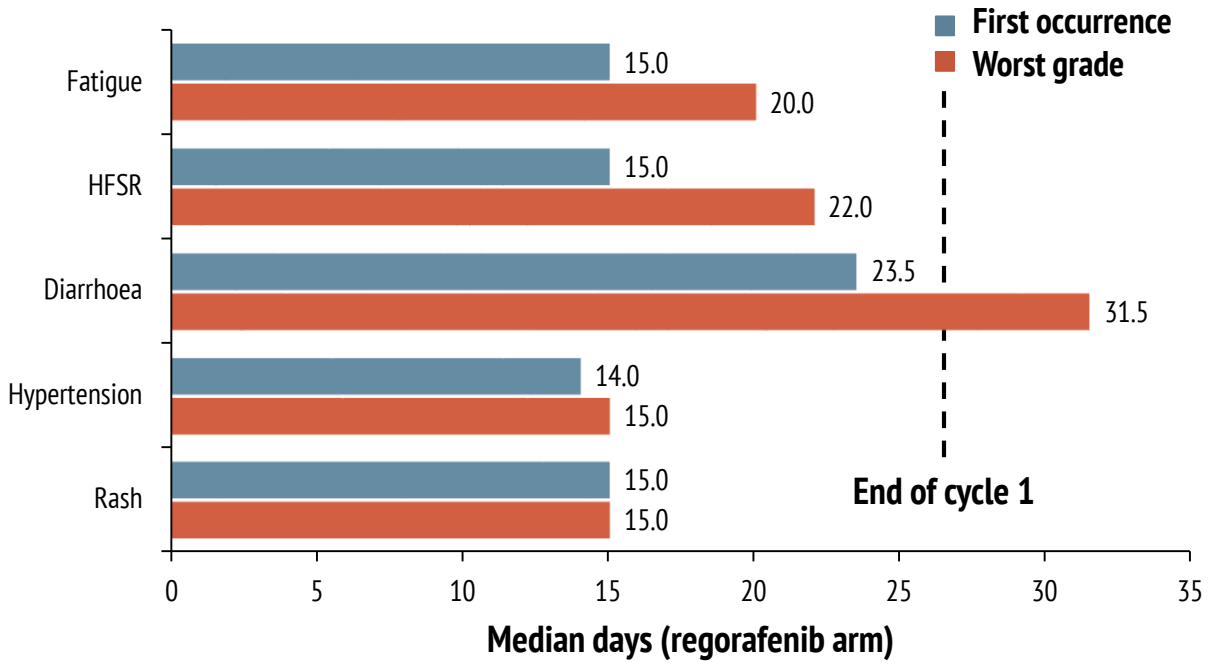
- The incidence and severity of HFSR, hypertension, liver abnormalities, fatigue, diarrhoea, and oral mucositis did not increase over time[2]

Median time to first occurrence and worst grade of select common AEs in regorafenib-treated patients (n=500)[2]



AE, adverse event; HFSR, hand-foot skin reaction

1. Grothey A, et al. Oncologist. 2014;19(6):669-80; 2. Grothey A, et al. ASCO 2013: Poster 3637

AE MANAGEMENT EXPERIENCE MATTERS: REGORAFENIB AEs CAN BE MANAGED WITH DOSE MODIFICATIONS, WITH A LOW RATE OF TREATMENT DISCONTINUATION DUE TO AEs[1–4]

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Patients with an AE, %	CORRECT[1]		CONCUR[4]	
	Regorafenib (n=500)	Placebo (n=253)	Regorafenib (n=136)	Placebo (n=68)
Leading to dose modification	67	23	71	16
Leading to dose reduction	38	3	40	0
Leading to dose interruption	61	22	63	16
Leading to treatment discontinuation	17	12	14	6

AE, adverse event

1. Grothey A, et al. Lancet. 2013;381:303-12; 2. Grothey A, et al. ASCO 2013: Poster 467; 3. Grothey A, et al. ASCO 2013: Poster 3637; 4. Li J, et al. Lancet Oncol. 2015;16:619-29

AE MANAGEMENT EXPERIENCE MATTERS: REAL-WORLD EVIDENCE SUPPORTS AN EXTENSIVE AND CONSISTENT REGORAFENIB SAFETY PROFILE IN mCRC[1–7]

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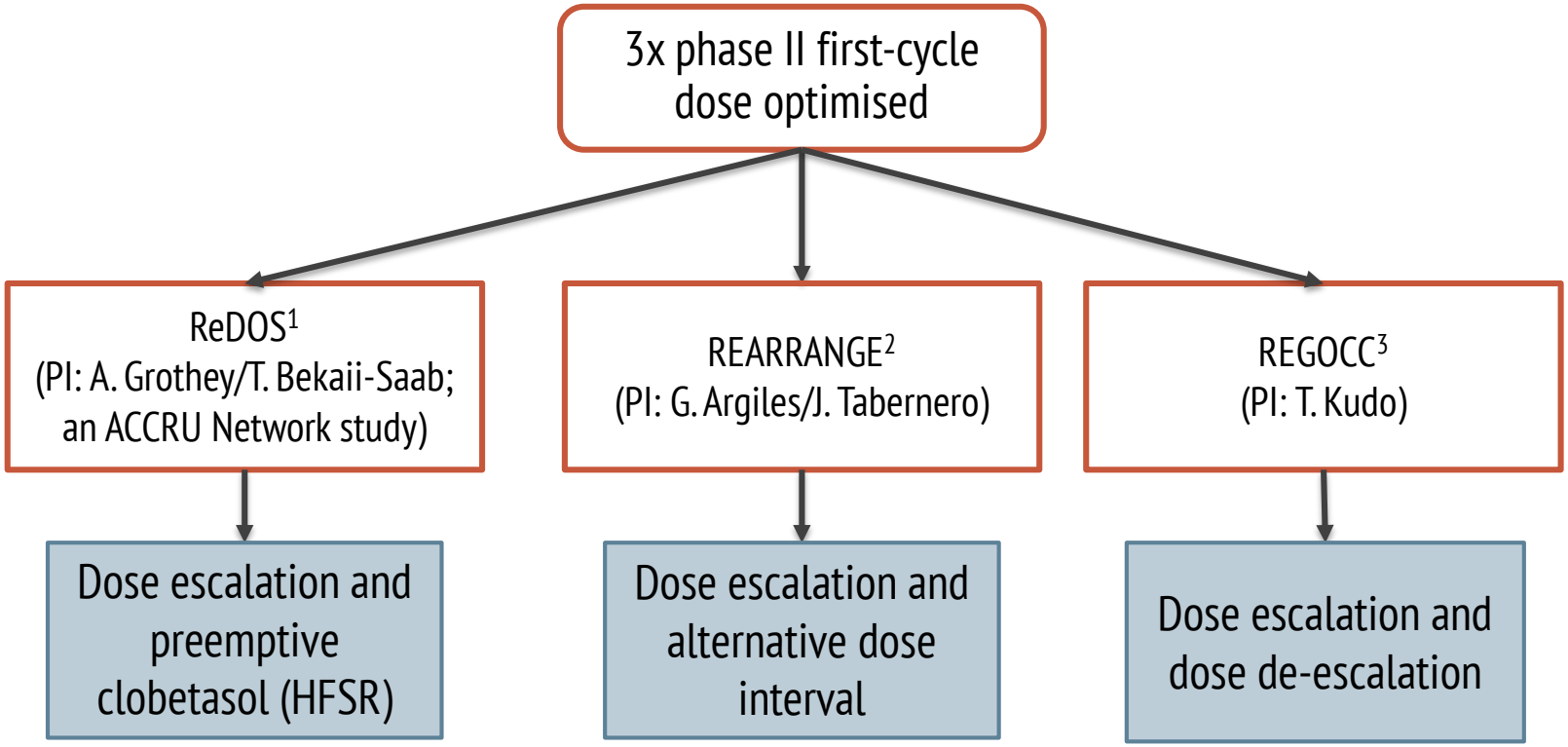
Most common drug-related adverse events, %	Randomised controlled phase III trials						Open-label real-world studies									
	CORRECT[1]		CONCUR[2]		IMblaze370[3]		REBECCA[4]		CONSIGN[5]		Japanese PM[6]		CORRELATE[7]		CORECT[8]	
	Regorafenib (N = 500)		Regorafenib (N = 136)		Regorafenib (N = 80)		Regorafenib (N = 654)		Regorafenib (N = 2864)		Regorafenib (N = 1227)		Regorafenib (N = 1037)		Regorafenib (N = 148)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Gkrade ≥3	All grades	Grade ≥3
HFSR	47	17	74	16			29	9	42	14	58	19	26	7		
Fatigue	47	10	17	3	46	9	41	15	46	13	15	2	41	9	2.0	
Hypertension	28	7	23	11	31	13	11	5	30	15	29	16	14	6		0.7
Diarrhoea	34	7	18	1	40	6	19	4	25	5			19	3		0.7
Rash/desquamation/skin toxicity[¶]	26	6	9	4	24	3	4	1	10	3						0.7
Anorexia	30	3	7	1			15	3	24	2			13	2		0.7
Mucositis, oral	27	3	NR	NR			11	1	25	2			15	2		
Hyperbilirubinemia	9	2	37	7	4	1	1	0	15*	4*						
ALT increased	5†	2†	24	7							31‡	11‡				
AST increased	7†	2†	24	6					7*	2*						
Thrombocytopenia	13	3	10	3			3	<1			15	5				
Fever	10	1	NR	NR					7	<1	12	1	3	<1		
Nausea	14	<1	NR	NR	14	0			11	1						
Voice changes	29	<1							12	<1	10	0				
Weight loss	14	0	NR	NR	21	0	5	<1	13	1						

*In CONSIGN, hyperbilirubinemia, AST and ALT were reported as treatment-emergent laboratory toxicities.
†Not reported as drug-related AEs. ‡Reported as "liver dysfunction." ¶Reported as "maculopapular rash" in CONCUR and CONSIGN

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFSR, hand-foot skin reaction; mCRC, metastatic colorectal cancer; NR, not reported

1. Grothey A, et al. Lancet. 2013;381:303-12; 2. Li J, et al. Lancet Oncol. 2015;16:619-29; 3. Eng C, et al. Lancet Oncol. 2019;20:849-61; 4. Adenis A, et al. BMC Cancer. 2016;16:412; 5. Van Cutsem E, et al. Oncologist. 2019;24:185-92; 6. Yamaguchi K, et al. Oncologist. 2019;24:e450-57; 7. Ducreux M, et al. WCGI 2018: Abstract O-012; 8. Kopeckova K, et al. Target Oncol. 2017;12:89-95

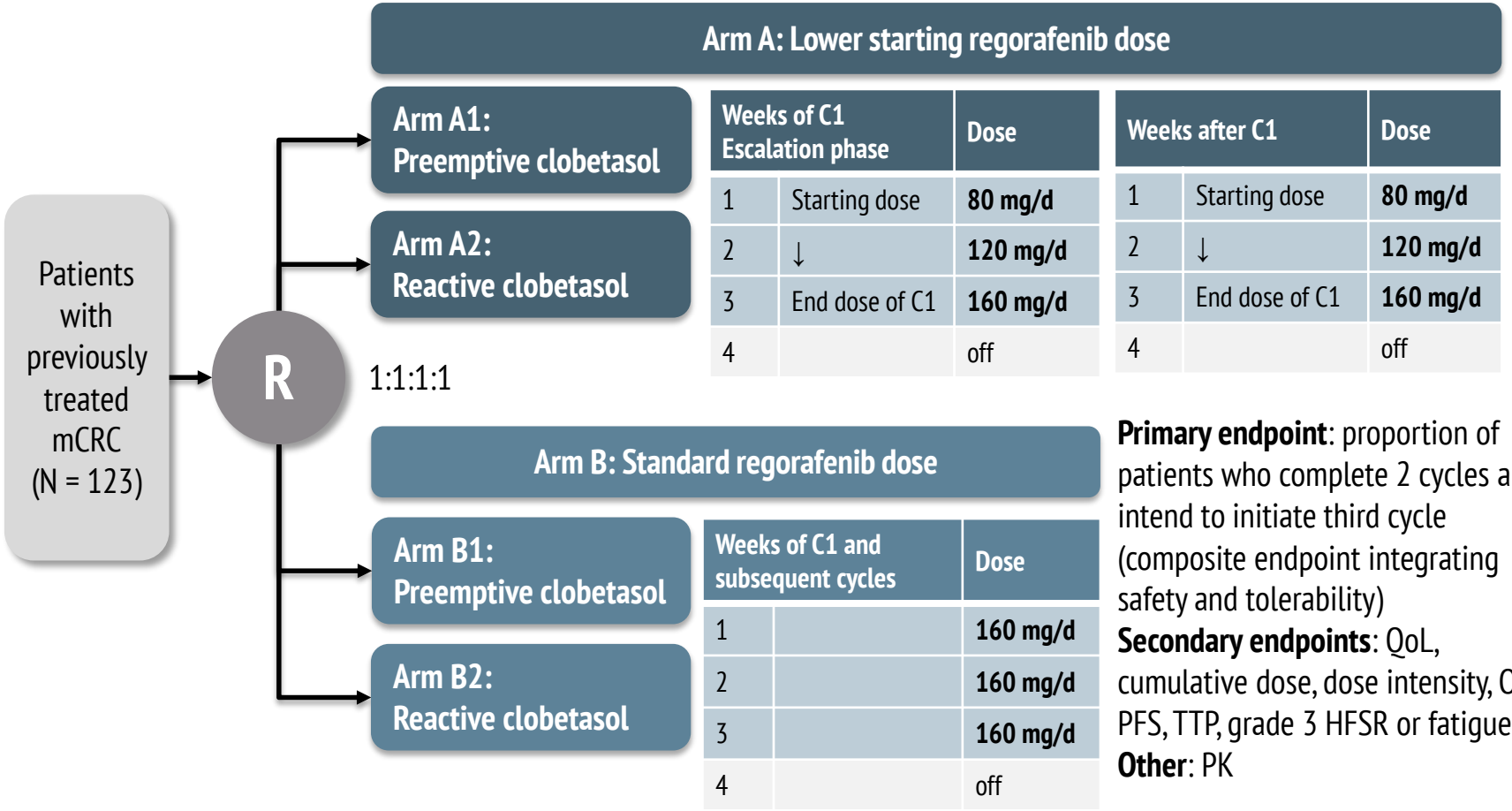
CAN TOLERABILITY WITH REGORAFENIB BE IMPROVED WITH FLEXIBLE FIRST-CYCLE DOSE-OPTIMISATION STRATEGIES?



HFSR, hand-foot skin reaction; PI, principal investigator

1. Bekaii-Saab T, et al. Lancet Oncol. 2019;20:1070-82; 2. Argiles G, et al. WCGI 2019: Abstract O-026; 3. Kudo T, et al. ASCO 2018: Poster 821

ReDOS: REGORAFENIB DOSE-OPTIMIZATION STUDY COMPARING FIRST-CYCLE DOSE OPTIMISATION WITH STANDARD DOSE IN PATIENTS WITH REFRACTORY mCRC – A RANDOMISED PHASE II TRIAL[1]



Weeks of C1 Escalation phase		Dose
1	Starting dose	**80 mg/d**
2	↓	**120 mg/d**
3	End dose of C1	**160 mg/d**
4		off

Weeks after C1		Dose
1	Starting dose	**80 mg/d**
2	↓	**120 mg/d**
3	End dose of C1	**160 mg/d**
4		off

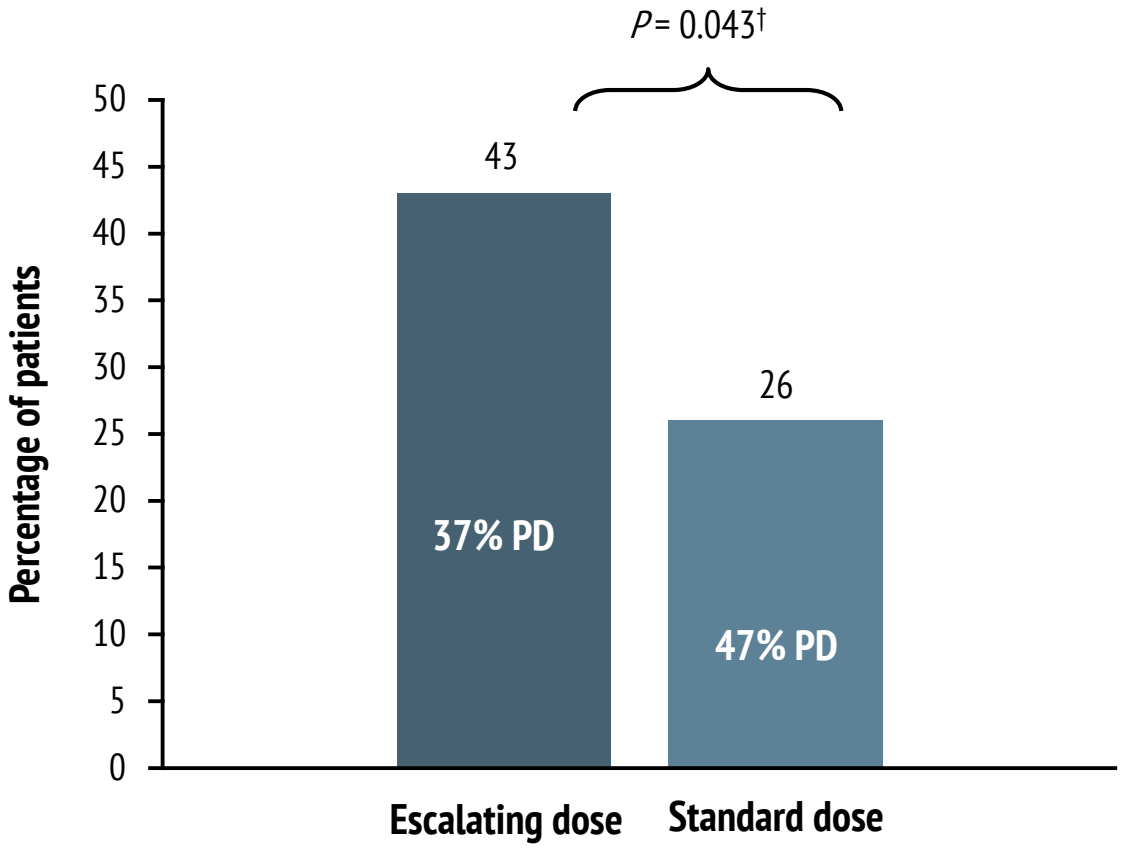
Weeks of C1 and subsequent cycles		Dose
1		**160 mg/d**
2		**160 mg/d**
3		**160 mg/d**
4		off

Primary endpoint: proportion of patients who complete 2 cycles and intend to initiate third cycle (composite endpoint integrating safety and tolerability)
Secondary endpoints: QoL, cumulative dose, dose intensity, OS, PFS, TTP, grade 3 HFSR or fatigue
Other: PK

Clobetasol is a steroid cream used to treat skin conditions and may help prevent HFSR in patients receiving regorafenib. C1, cycle 1; HFSR, hand-foot skin reaction; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; QoL, quality of life; R, randomisation; TTP, time to progression

1. Bekaii-Saab T, et al. Lancet Oncol. 2019;20:1070-82

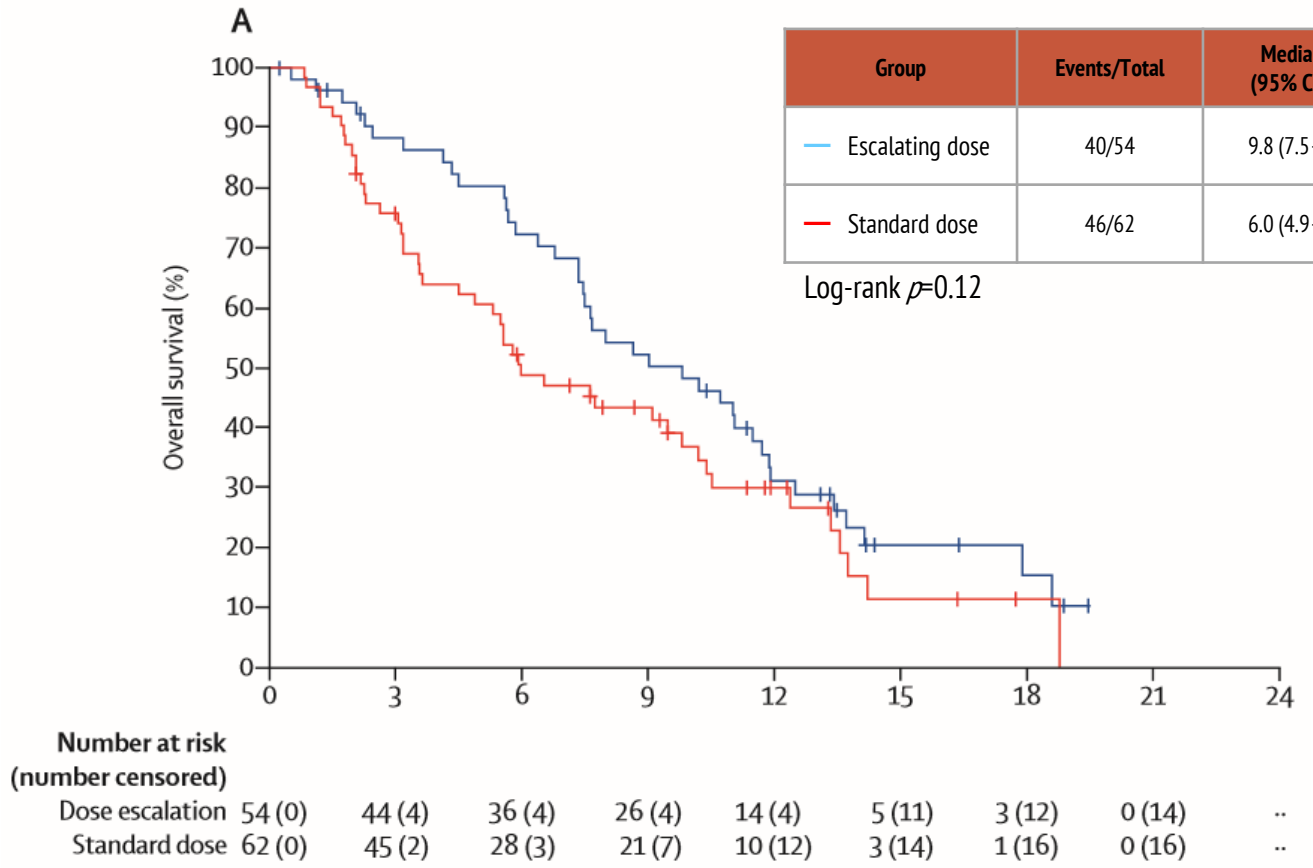
ReDOS: 43% OF PATIENTS ON THE FIRST-CYCLE DOSE OPTIMISATION ARM STARTED CYCLE 3 OF THERAPY, VS 26% OF PATIENTS ON STANDARD DOSE[1]



The primary endpoint is a composite endpoint integrating efficacy (patients needed to have at least stable disease at the planned disease evaluation) and safety (patients needed to tolerate the drug with no unacceptable toxicity issues); †Fisher's exact test (1-sided). PD, progressive disease

1. Bekaii-Saab T, et al. Lancet Oncol. 2019;20:1070-82

ReDOS OS CONFIRMS SURVIVAL SEEN IN OTHER TRIALS WITH REGORAFENIB[1]



Group	Events/Total	Median OS (95% CI), mo	HR (95% CI)
Escalating dose	40/54	9.8 (7.5–11.9)	0.72 (0.47–1.10)
Standard dose	46/62	6.0 (4.9–10.2)	

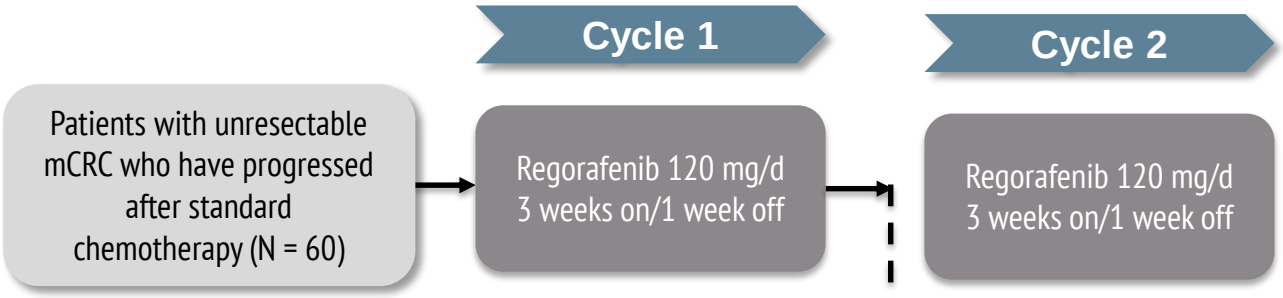
Log-rank p=0.12

+Censored

CI, confidence interval; HR, hazard ratio; Mo, month; OS, overall survival

1. Bekaii-Saab T, et al. Lancet Oncol. 2019;20:1070-82

REGOCC: PHASE II DOSE-TITRATION STUDY OF REGORAFENIB IN JAPANESE PATIENTS WITH UNRESECTABLE METASTATIC COLORECTAL CANCER WHO PROGRESSED AFTER STANDARD CHEMOTHERAPY[1]



Primary endpoint: DCR

Secondary endpoints: OS, PFS, response rate, safety, and drug adherence

Dose modification

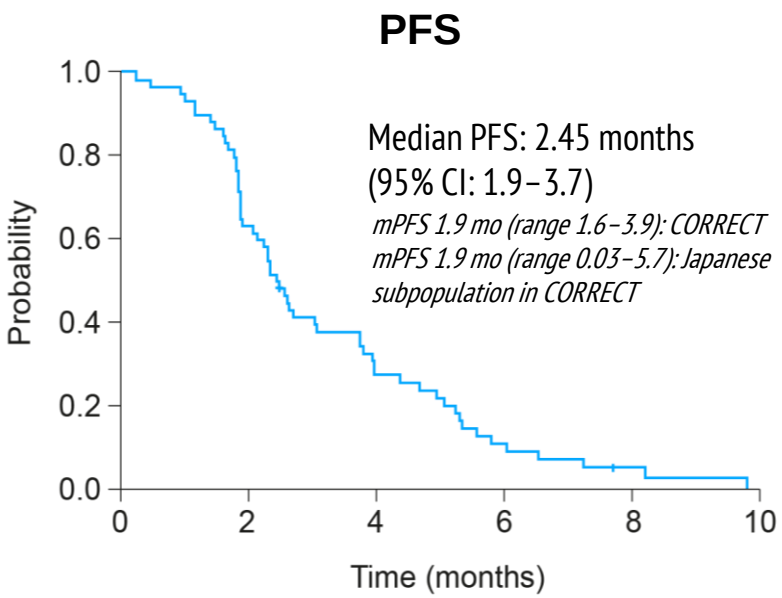
Dose Level	Dose of Regorafenib
0 (starting dose)	120 mg once daily
+1	160 mg once daily
-1	80 mg once daily
-2	40 mg once daily
-3	Discontinued

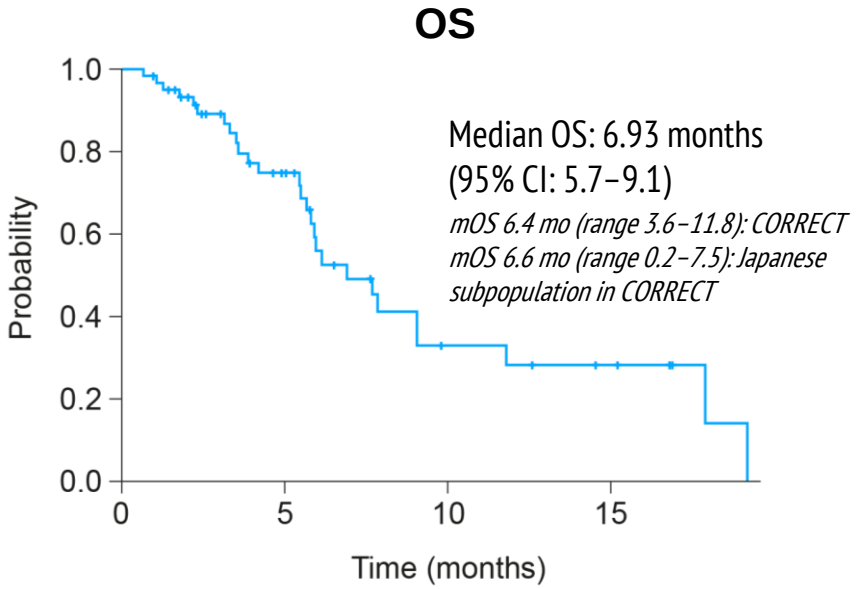
*When grade ≥2 AEs are not observed in cycle 1, an increase to 160 mg/day in cycle 2 and later is allowed. However, for liver dysfunction (ALT, AST, or bilirubin increased), even if the observed AE is grade 1, increase in dose of the drug is not allowed.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCR, disease control rate; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival. 1. Kudo T, et al. ASCO 2018: Poster 821

REGOCC DCR OF 38.3% SUGGESTS AN ALTERNATIVE DOSE SCHEDULE FOR PATIENTS IN JAPAN[1]

- DCR was 38.3% (90% CI: 28.0–48.7)
- The lower limit of the DCR exceeded the pre-specified threshold of 27%





CI, confidence interval; DCR, disease control rate; m, median; Mo, month; OS, overall survival; PFS, progression-free survival

1. Kudo T, et al. ASCO 2018: Poster 821

RESULTS OF REARRANGE TRIAL: A RANDOMIZED PHASE 2 STUDY COMPARING DIFFERENT DOSING APPROACHES FOR REGORAFENIB DURING THE FIRST CYCLE OF TREATMENT IN PATIENTS WITH METASTATIC COLORECTAL CANCER

G. Argilés[1], N. Mulet[1], M. Valladares-ayerbes[2], J. Mª. Viéitez[3], C. Grávalos[4], P. García-alfonso[5], C. Santos[6], M. Tobeña[7], J. Sastre[8], M. Benavides[9], M.T. Cano[10], F. Loupakis[11], M. Rodríguez Garrote[12], F. Rivera[13], R.M. Goldberg[14], A. Falcone[15], J. Bennouna[16], F. Ciardiello[17], J. Tabernero[1], E. Aranda[10] On Behalf Of The Spanish Cooperative Group For The Treatment Of Digestive Tumors And UNICANCER GI.

1. Vall D'hebron University Hospital And Institute Of Oncology (VHIO), CIBERONC, TTD Group, Barcelona; 2. Virgen Del Rocío University Hospital And Institute Of Biomedicine (IBIS). Sevilla; 3. Universitario Central De Asturias Hospital (Oviedo); 4. 12 De Octubre Hospital (Madrid); 5. Gregorio Marañón Hospital (Madrid); 6. Ico. Duran I Reynals Hospital (Barcelona); 7. Santa Creu I Sant Pau Hospital (Barcelona); 8. Clínico San Carlos Hospital. Instituto De Investigación Hospital Clinico San Carlos (Idissc), Madrid / Spain. Ciberonc, 9. Regional Universitario Hospital (Málaga); 10. IMIBIC, Reina Sofía Hospital, University Of Córdoba, CIBERONC, Instituto De Salud Carlos III; 11. Istituto Oncologico Veneto, Italy; 12. IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón Y Cajal, Madrid; 13. Marqués De Valdecilla Hospital (Santander); 14. West Virgina University Cancer Institute (Morgantown); 15. S. Università Degli Studi Di Napoli, Italy;
16. University Hospital Of Nantes, Digestive Oncology, Nantes, France; 17. Università Della Campania L. Vanvitelli, Italy.

REARRANGE STUDY DESIGN[1]

- mCRC pts
- Progressed on standard of care
- ECOG ⩽ 1
- Measurable disease following RECIST 1.1

N = 299 patients

R 1:1:1

ARM A: Control Arm (labeled regimen)
160 mg/d 3w on/1w off

ON ON ON off ON ON ON off

ARM B: Experimental Arm 1
120 mg/d 3w on/1w off 1st cycle;
160 mg/d 3w on/1w off 2nd cycle on

on on on off ON ON ON off

ARM C: Experimental Arm 2
160 mg/d 1w on/1w off 1st cycle;
160 mg/d 3w on/1w off 2nd cycle on

ON off ON off ON ON ON off

PD

Primary endpoint:
- **Safety**: % of patients having G3/G4 treatment-related AEs during the entire course of the treatment

Secondary endpoints:
- OS
- PFS
- % of patients starting C3 in each arm
- Dose intensity
- DCR

DOSE ESCALATION CONDITIONS FOR ARM B AND C:
1. If no G3/4 drug-related AE happened
2. Any G2 AE of especial relevance happened:
   a. G2 diarrhoea lasting more than 3 days despite optimal treatment (guidelines for diarrhoea management according to local practice.)
   b. G2 vomiting (not nausea) lasting more than 3 days despite optimal treatment (guidelines for vomiting management according to local practice.)
   c. G2 HFSR lasting more than 7 days despite optimal treatment (guidelines for HFSR management according to local practice.)

AE, adverse event; DCR, disease control rate; C3, cycle 3; ECOG, Eastern Cooperative Oncology Group; G, grade; HFSR, hand-foot skin reaction; mCRC, metastatic colorectal cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria In Solid Tumors. 1. Argiles G, et al. WCGI 2019: Abstract O-026

PATIENTS CHARACTERISTICS[1]

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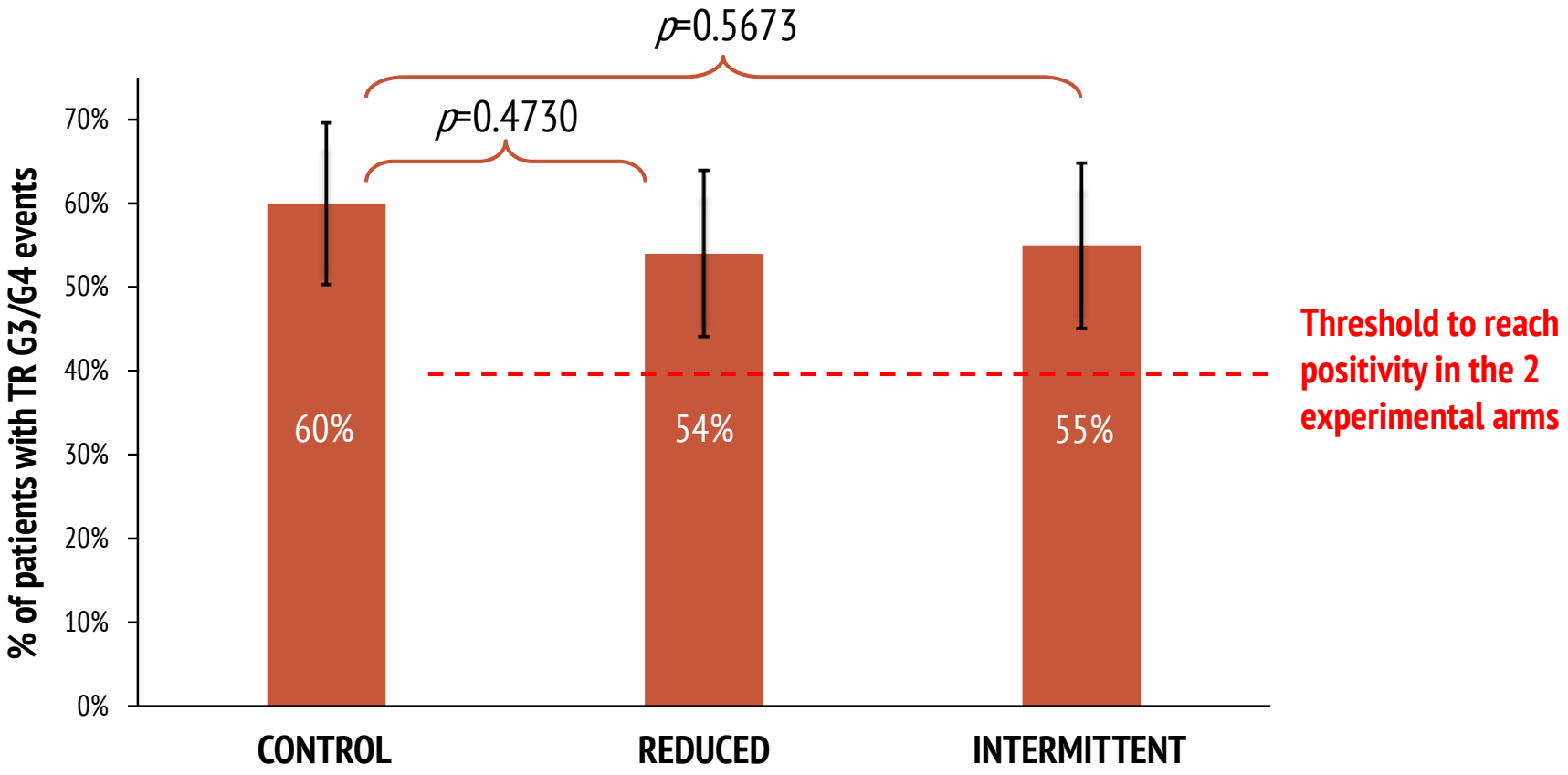
		CONTROL ARM (n=101)	REDUCED ARM (n=99)	INTERMITTENT ARM (n=99)	P Value
Age	**Median [Q1-Q3]**	65.0 [56.0, 70.0]	63.0 [56.0, 70.0]	63.0 [56.0, 69.0]	0.8791
	> 70 years n (%)	21 (21)	18 (18)	19 (19)	0.8950
Gender	**Male n (%)**	59 (58)	53 (54)	52 (53)	0.6691
ECOG PS	**0 n (%)**	36 (36)	33 (33)	35 (35)	0.9329
Number of metastatic sites	**1**	23 (23)	15 (15)	14 (14)	0.4465
	2	35 (35)	35 (35)	33 (33)	
	3+	43 (43)	49 (49)	52 (53)	
Liver mets	**Yes n (%)**	79 (78)	73 (74)	75 (76)	0.7592
Tumour location	**Left-sided n (%)**	69 (68)	78 (79)	79 (80)	0.1038
	Right-sided n (%)	31 (31)	19 (19)	20 (20)	
Primary tumour resection		83 (82)	81 (82)	79 (80)	0.8980
Time from diagnosis of metastases	**< 18 months**	29 (29)	19 (19)	35 (35)	0.0385
	≥ 18 months	72 (71)	80 (81)	64 (65)	
Prior treat. lines	**Mean (SD)**	4.1 (1.8)	4.2 (1.7)	3.9 (1.6)	0.2992
RAS	**Mutant n (%)**	72 (71)	59 (60)	60 (61)	0.1613
BRAF	**Mutant n (%)**	2 (2)	3 (3)	3 (3)	0.9977

ECOG PS, Eastern Cooperative Oncology Group Performance Status; mets, metastases; Q, quartile; SD, standard deviation

1. Argiles G, et al. WCGI 2019: Abstract O-026

PRIMARY ENDPOINT: PATIENTS WITH G3/G4 AEs DURING TREATMENT COURSE[1]



AE, adverse event; G, grade; TR, treatment-related

1. Argiles G, et al. WCGI 2019: Abstract O-026

TOLERABILITY PROFILE DURING THE WHOLE STUDY[1]

G3/4 AEs in > 4% of pts (%)	CONTROL	REDUCED	INTERMITTENT
Total G3–G5	61%	57%	55%
Asthenia + Fatigue	20%	14%	15%
Hypertension	19%	12%	20%
Hypokalaemia	11%	7%	10%
HFSR	8%	7%	3%
GGT increased	2%	7%	2%
Proteinuria	6%	3%	1%
Rash	1%	4%	2%
AST increased	1%	4%	1%
Decreased appetite	2%	4%	2%

AE, adverse event; AST, aspartate aminotransferase; G, grade; GGT, gamma-glutamyl transferase; HFSR, hand-foot skin reaction; pts, patients

1. Argiles G, et al. WCGI 2019: Abstract O-026

TOLERABILITY CYCLE 1+2 VS. CYCLE 3+[1]

G3/4 AEs in > 4% of pts (%)	CONTROL		REDUCED		INTERMITTENT	
	Cycle 1+2	Cycle 3+	Cycle 1+2	Cycle 3+	Cycle 1+2	Cycle 3+
Total G3–G5	55%	15%	55%	8%	45%	14%
Asthenia + Fatigue	16%	4%	14%	1%	11%	4%
Hypertension	17%	4%	12%	0%	18%	2%
Hypokalaemia	10%	4%	7%	1%	7%	6%
HFSR	6%	2%	4%	3%	3%	0%
GGT increased	2%	0%	7%	0%	2%	0%
Proteinuria	6%	0%	3%	0%	1%	0%
Rash	1%	0%	3%	1%	2%	0%
AST increased	0%	1%	4%	0%	1%	0%
Decreased appetite	2%	0%	4%	0%	2%	0%

AE, adverse event; AST, aspartate aminotransferase; G, grade; GGT, gamma-glutamyl transferase; HFSR, hand-foot skin reaction; pts, patients

1. Argiles G, et al. WCGI 2019: Abstract O-026

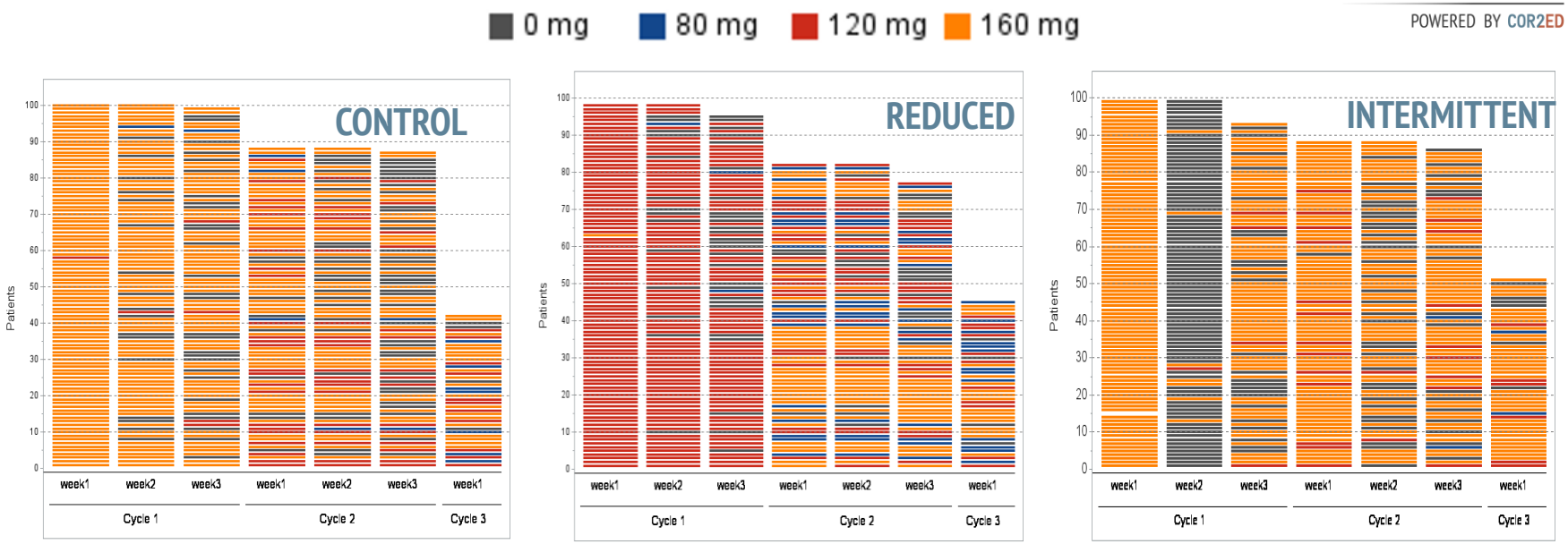
TOLERABILITY CYCLE 1+2 VS. CYCLE 3+[1]

G3/4 AEs in > 4% of pts (%)	CONTROL		REDUCED		INTERMITTENT	
	Cycle 1+2	Cycle 3+	Cycle 1+2	Cycle 3+	Cycle 1+2	Cycle 3+
Total G3–G5	55%	15%	55%	8%	45%	14%
Asthenia + Fatigue	16%	4%	14%	1%	11%	4%
Hypertension	17%	4%	12%	0%	18%	2%
Hypokalaemia	10%	4%	7%	1%	7%	6%
HFSR	6%	2%	4%	3%	3%	0%
GGT increased	2%	0%	7%	0%	2%	0%
Proteinuria	6%	0%	3%	0%	1%	0%
Rash	1%	0%	3%	1%	2%	0%
AST increased	0%	1%	4%	0%	1%	0%
Decreased appetite	2%	0%	4%	0%	2%	0%

AE, adverse event; AST, aspartate aminotransferase; G, grade; GGT, gamma-glutamyl transferase; HFSR, hand-foot skin reaction; pts, patients

1. Argiles G, et al. WCGI 2019: Abstract O-026

HEATMAP[1]

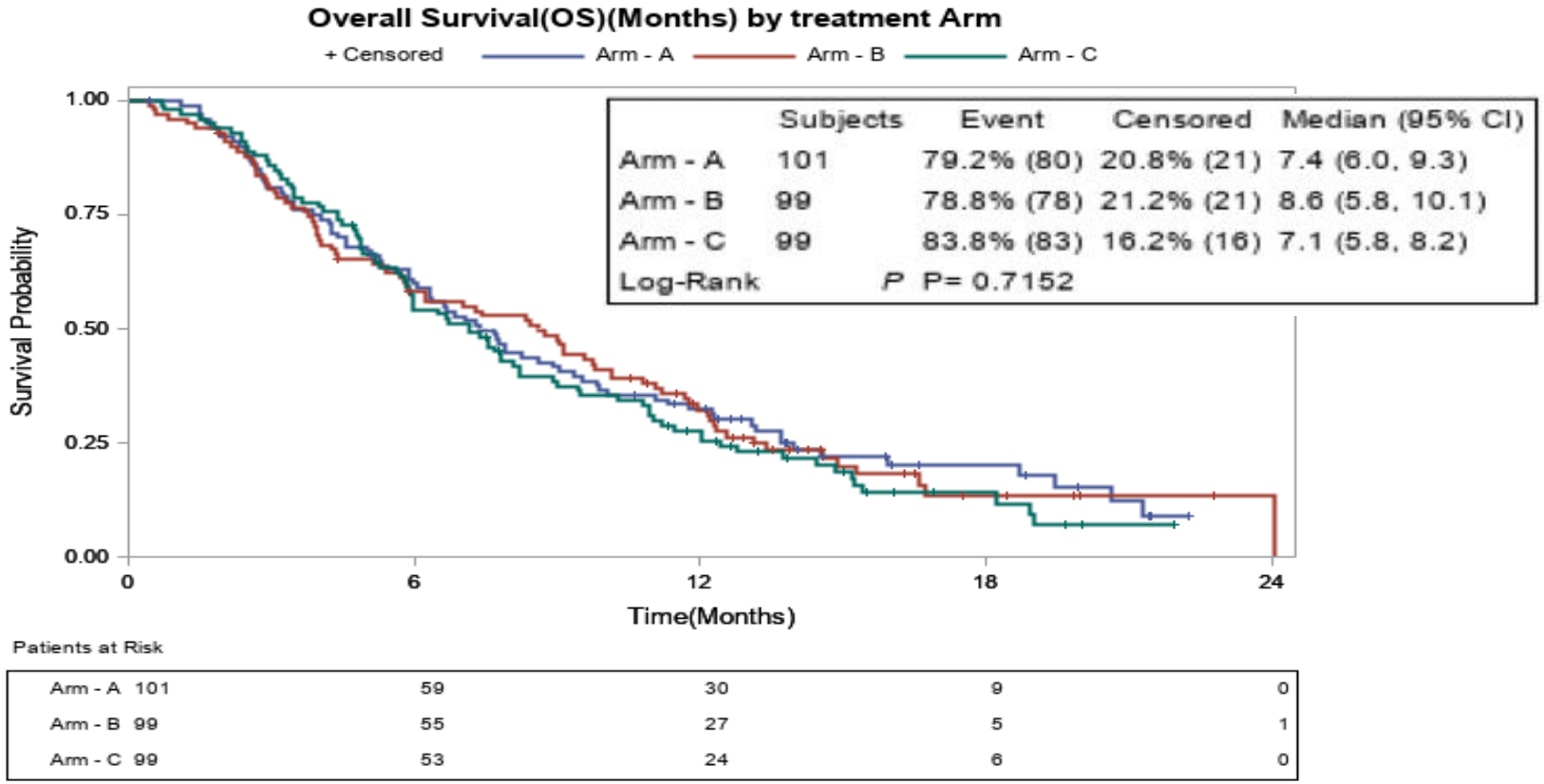


		CONTROL	REDUCED	INTERMITTENT
Treatment exposure	Mean (SD)	3.0 (2.3)	3.7 (3.4)	3.8 (3.3)
	Median [Q1-Q3]	2.2 [1.8, 3.7]	2.3 [1.8, 4.6]	2.5 [1.8, 4.6]
At least one dose delay (%)		35%	34%	29%
At least one dose reduction (%)		39%	39%	25%
At least one dose interruption (%)		81%	79%	70%
Dose escalation (%)		0	45%	64%

Q, quartile; SD, standard deviation

1. Argiles G, et al. WCGI 2019: Abstract O-026

SECONDARY ENDPOINT: OS[1]

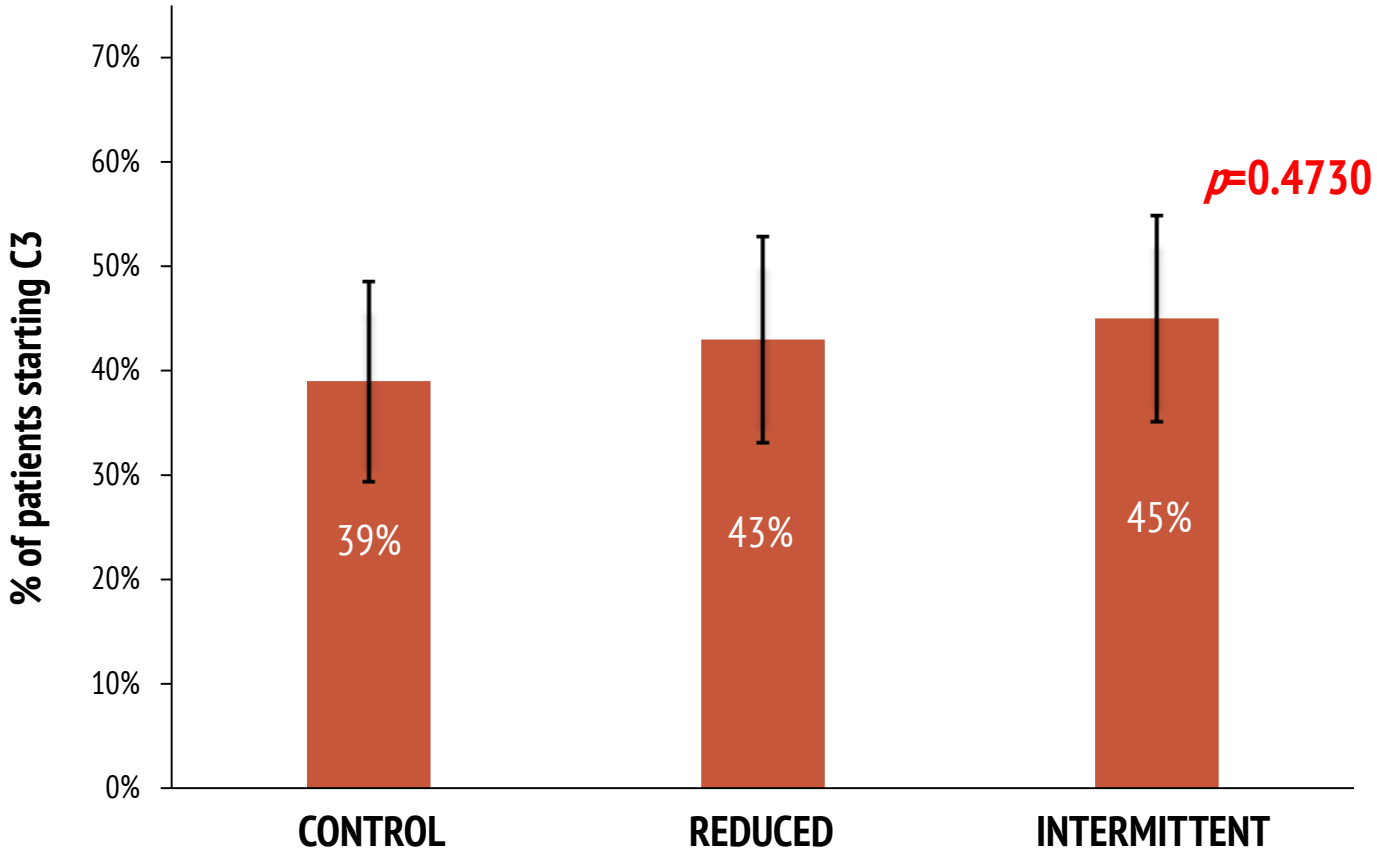


OS rate	CONTROL	REDUCED	INTERMITTENT
12 mo	32.4%	32.3%	27.8%

CI, confidence interval; Mo, month; OS, overall survival;

1. Argiles G, et al. WCGI 2019: Abstract O-026

SECONDARY ENDPOINT: PERCENTAGE OF PATIENTS STARTING C3[1]



C3, cycle 3

1. Argiles G, et al. WCGI 2019: Abstract O-026

STUDY CONCLUSIONS[1]

- REARRANGE did not show a statistically significant improvement of regorafenib tolerability in either the reduced or intermittent dosing arms
- However, experimental arms showed a numerical improvement in relevant AEs, like fatigue and hypertension without jeopardizing efficacy
- These results in the context of other available data, support the use of a initial regorafenib-reduced dosing during the first cycle
- The observed OS data is in line with the most recent reports of regorafenib

AE, adverse event; OS, overall survival

1. Argiles G, et al. WCGI 2019: Abstract O-026

HOW WILL TRIBE-2 DATA IMPACT YOUR SEQUENTIAL CLINICAL PRACTICE IN 2019?

Chiara Cremolini
University of Pisa
Azienda Ospedaliero-Universitaria Pisana
Italy

DO YOU USE FOLFOXIRI/BEV AS 1ST-LINE TX OF mCRC IN YOUR CLINICAL PRACTICE?

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A. Never
B. A few times (5-10% of my patients)
C. Sometimes (10-30% of my patients)
D. Often (>30% of my patients)

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Bev, bevacizumab; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; mCRC, metastatic colorectal cancer; TX, treatment

IF YES, IN WHICH PATIENTS (AMONG THOSE <75 AND IN GOOD GENERAL CONDITION)?

GI connect
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A. *BRAF* mutant

B. *RAS* or *BRAF* mutant, potentially resectable metastases

C. Right sided and/or *RAS* or *BRAF* mutant, potentially resectable metastases

D. Right sided and/or *RAS* or *BRAF* mutant, independently of the tumour burden

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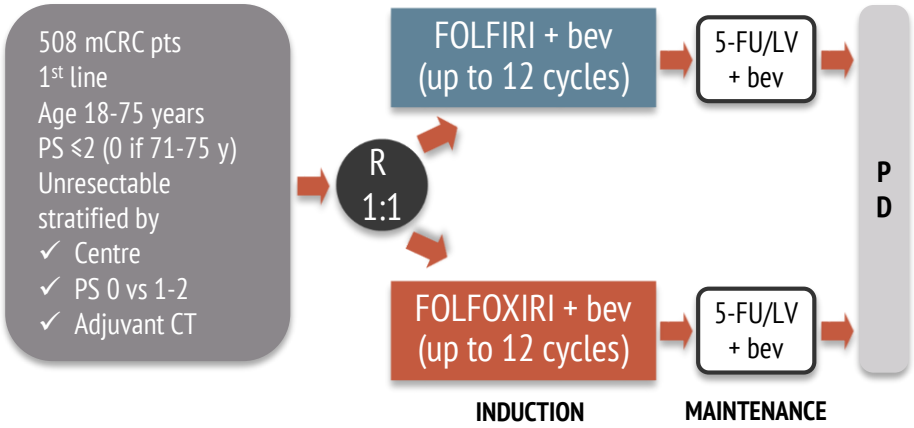
ONE STEP BACK: THE TRIBE STUDY

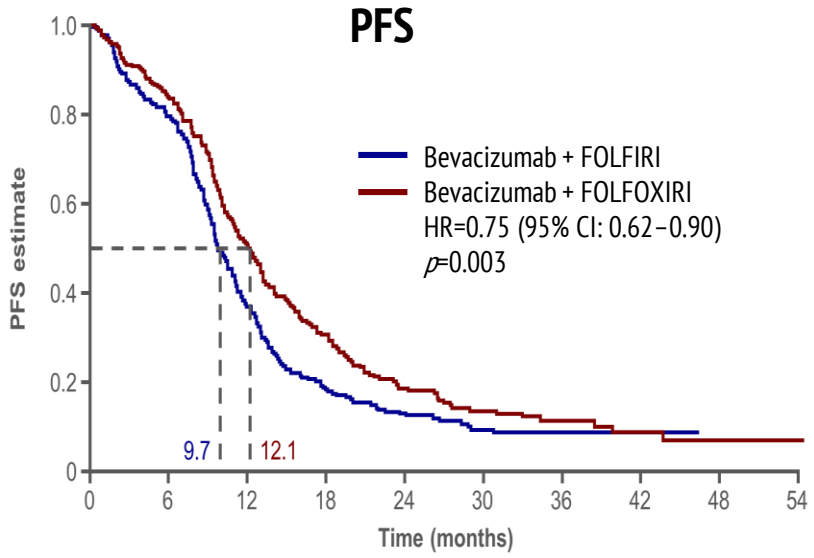


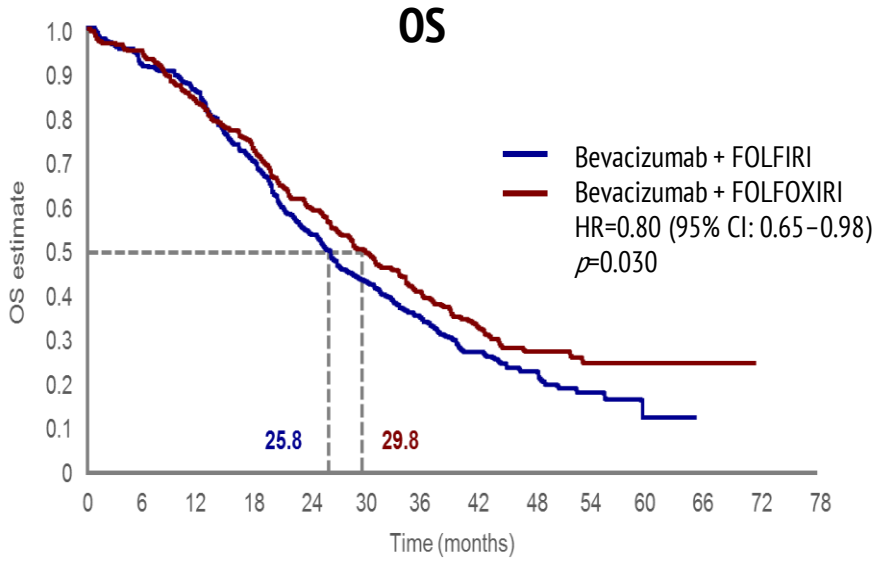
Phase III, randomised, TRIBE study

Jul 2008 – May 2011

Primary endpoint: PFS

ORR: 53% vs 65%; *p*=0.006





5-FU/LV, fluorouracil and leucovorin; bev, bevacizumab; CI, confidence interval; CT, chemotherapy; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; R, randomised

Cremolini C, et al. Lancet Oncol. 2015;16:1306-15; Loupakis F, et al. N Engl J Med. 2014;371:1609-18

FAQS ABOUT FOLFOXIRI/BEV

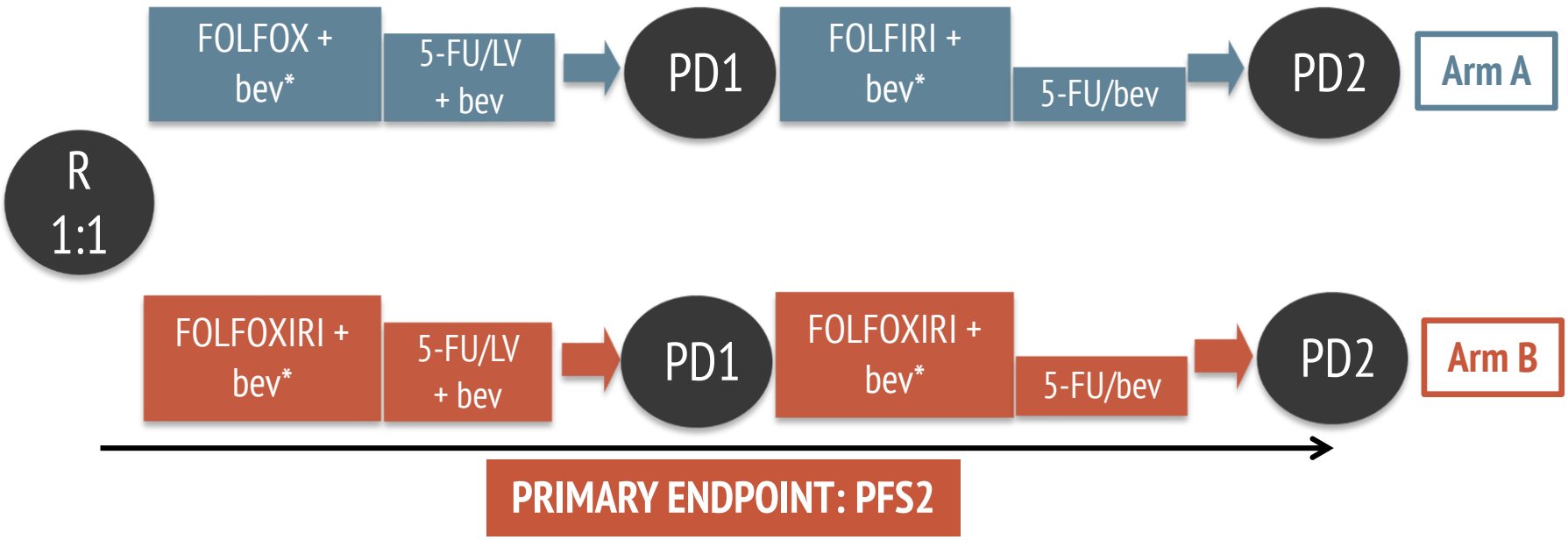
Is FOLFOXIRI/bev better than the pre-planned sequential exposure to the same agents (FOLFOX→FOLFIRI)?

Are treatments after progression feasible and efficacious?

Due to the higher toxicity, is it feasible in every oncology unit?

Bev, bevacizumab; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan

TRIBE2: STUDY DESIGN



679 pts in 58 Italian sites

* Up to 8 cycles.

5-FU, fluorouracil; bev, bevacizumab; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; PD, progressive disease; PFS2, progression-free survival 2; R, randomised

Cremolini C, et al. WCGIC 2019: Abstract LBA-007 and ASCO 2019: Abstract 3508

TRIBE2: KEY ELIGIBILITY CRITERIA

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- Histologically proven adenocarcinoma
- Unresectable (locally assessed) mCRC, not pretreated for metastases
- Measurable disease according to RECIST v1.1 criteria
- Age 18-75
- ECOG PS ⩽2 (ECOG PS 0 if age = 71-75 years)
- Previous adjuvant oxaliplatin-containing chemotherapy NOT allowed
- Adjuvant fluoropyrimidine monotherapy allowed if >6 months elapsed between the end of adjuvant therapy and first relapse
- Adequate bone marrow, liver and renal functions

ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCRC, metastatic colorectal cancer; RECIST, Response Evaluation Criteria In Solid Tumors

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PATIENTS CHARACTERISTICS – ITT POPULATION

	N=679	
Characteristic, % patients	**Arm A N=340**	**Arm B N=339**
Sex (M / F)	61 / 39	54 / 46
Median Age (range)	61 (30–75)	60 (33–75)
ECOG PS (0 / 1 or 2)	85 / 15	86 / 14
Synchronous Metastases (Y / N)	89 / 11	89 / 11
Prior Adjuvant CT (Y / N)	2 / 98	2 / 98
Number Metastatic Sites (1 / >1)	38 / 62	45 / 55
Liver-Only Disease (Y / N)	29 / 71	32 / 68
Primary Tumour Side (right / left)	38 / 62	38 / 62
***RAS/BRAF* Mutation Status** (*RAS* mutant / *BRAF* mutant / wt / NE)	65 / 10 / 20 / 5	63 / 10 / 22 / 5
Right AND/OR *RAS/BRAF* mutant / Left AND *RAS/BRAF* wt / NE	**79** / 16 / 5	**78** / 17 / 5

CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; NA, not available; NE, not evaluable; wt, wild type

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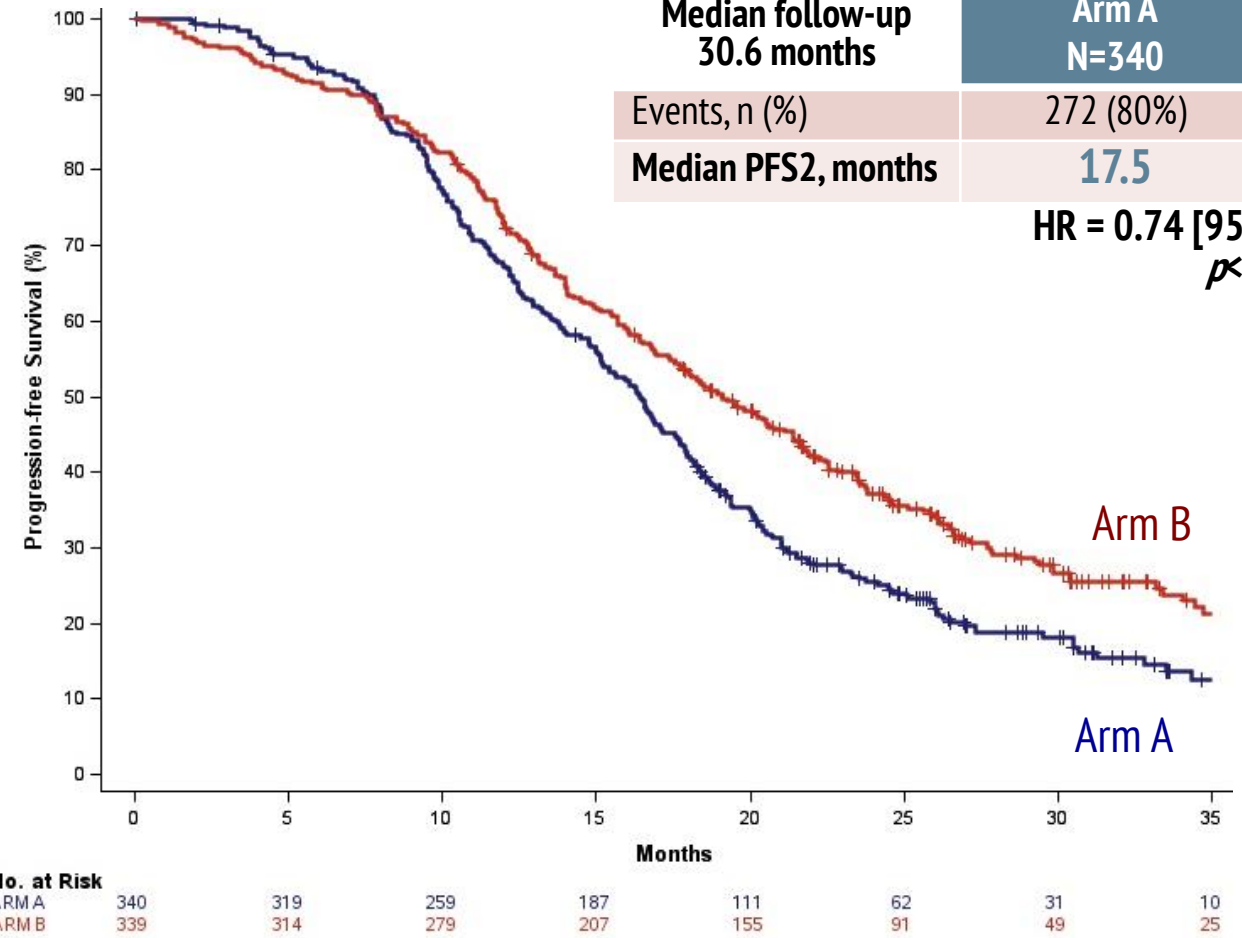
PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL 2

Median follow-up 30.6 months	Arm A N=340	Arm B N=339
Events, n (%)	272 (80%)	242 (71%)
Median PFS2, months	**17.5**	**19.1**

HR = 0.74 [95% CI: 0.62–0.88]
***p*<0.001**



CI, confidence interval; HR, hazard ratio; PFS2, progression-free survival 2
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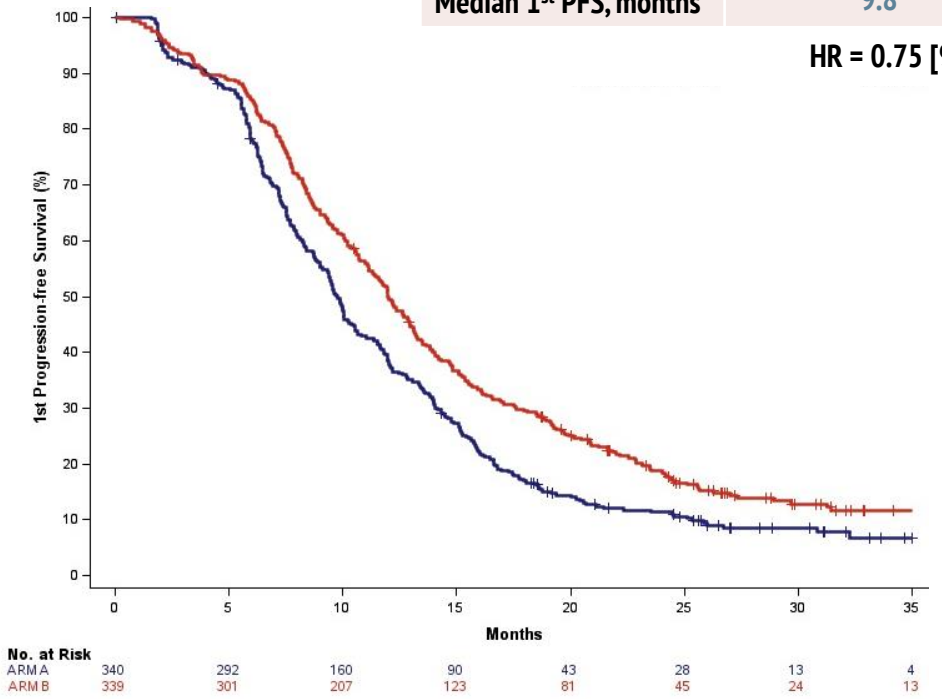
1ST-LINE FOLFOXIRI/BEV VS FOLFOX/BEV

Median follow-up 30.6 months	FOLFOX + bev N=340	FOLFOXIRI + bev N=339
Events, n (%)	303 (89%)	291 (86%)
Median 1st PFS, months	9.8	12.0

HR = 0.75 [95% CI: 0.63–0.88]; p<0.001



	FOLFOX + bev N=340	FOLFOXIRI + bev N=339	p
Response Rate	50%	62%	p=0.002
R0 Resection Rate	12%	17%	p=0.047

Bev, bevacizumab; CI, confidence interval; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; PFS, progression-free survival

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2ND-LINE THERAPY

	Arm A N=340	Arm B N=339
PD events	291 (86%)	272 (80%)
Death before PD	12 (4%)	19 (6%)
Any 2nd-line therapy	**86%** (251/291)	**81%** (219/272)

PD, progressive disease

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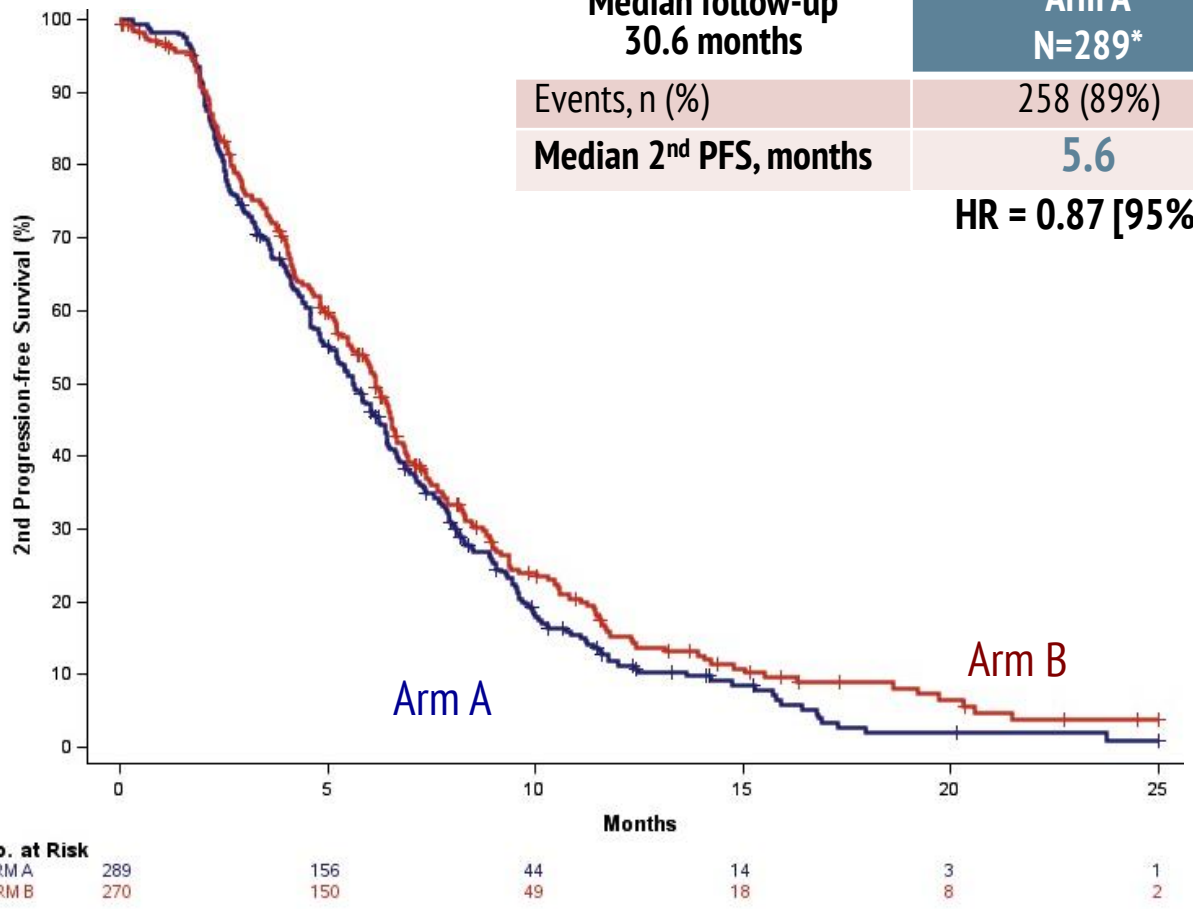
2ND-LINE – PROGRESSION-FREE SURVIVAL (PATIENTS ALIVE AT THE TIME OF PD1)



Median follow-up 30.6 months	Arm A N=289*	Arm B N=270*
Events, n (%)	258 (89%)	221 (82%)
Median 2nd PFS, months	5.6	6.2

HR = 0.87 [95% CI: 0.73–1.04]; p=0.122

* 2 patients in arm A and 2 patients in arm B died on the same day of PD1 and were not included in the 2nd PFS analysis.

CI, confidence interval; HR, hazard ratio; PD, progressive disease; PFS, progression-free survival

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2ND-LINE THERAPY

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	Arm A N=340	Arm B N=339
PFS events	291 (86%)	272 (80%)
Death before PD	12 (4%)	19 (6%)
Any 2nd-line therapy	**86%** (251/291)	**81%** (219/272)
2nd-line therapy	**N=251**	**N=219**
FOLFIRI + bev, %	**195 (78%)**	**16 (7%)**
FOLFIRI, %	**26 (10%)**	**6 (3%)**
FOLFOXIRI + bev, %	**1 (0%)**	**129 (59%)**
FOLFOXIRI, %	**0 (0%)**	**20 (9%)**
FOLFOX +/- bev, %	**6 (2%)**	**16 (7%)**
Anti-EGFR +/- chemotherapy, %	**4 (2%)**	**9 (4%)**
Other, %	**19 (8%)**	**23 (11%)**

Bev, bevacizumab; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; PD, progressive disease; PFS, progression-free survival

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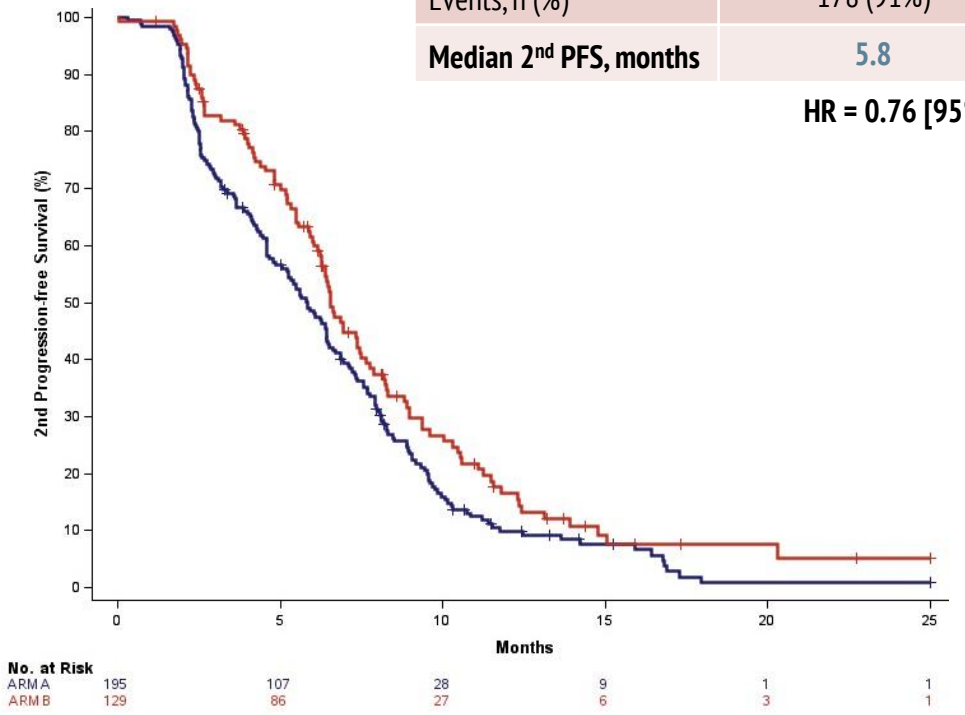
PER-PROTOCOL 2ND-LINE – PROGRESSION FREE SURVIVAL

Median follow-up 30.6 months	FOLFIRI + bev N=195	FOLFOXIRI + bev N=129
Events, n (%)	178 (91%)	104 (81%)
Median 2nd PFS, months	5.8	6.5

HR = 0.76 [95% CI: 0.60–0.97]; *p*=0.025



	FOLFIRI + bev N=195	FOLFOXIRI + bev N=129	*p*
Response Rate	12%	19%	*p*=0.057
Disease Control Rate	64%	77%	*p*=0.037

Bev, bevacizumab; CI, confidence interval; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; PFS, progression-free survival

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SAFETY PROFILES

	1st line		
G3/4 adverse events, % patients	FOLFOX + bev N=336	FOLFOXIRI + bev N=336	*p*
Nausea	3	6	0.140
Vomiting	2	3	0.419
Diarrhoea	5	17	<0.001
Stomatitis	3	5	0.299
Neutropenia	21	50	<0.001
Febrile neutropenia	3	7	0.050
Neurotoxicity	1	2	0.505
Asthenia	6	7	0.633
Hypertension	10	7	0.223
Venous thromboembolism	6	4	0.204

Bev, bevacizumab; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; G, grade

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SAFETY PROFILES

	1st line			2nd line		
G3/4 adverse events, % patients	FOLFOX + bev N=336	FOLFOXIRI + bev N=336	*p*	FOLFIRI + bev N=195	FOLFOXIRI + bev N=129	
Nausea	3	6	0.140	3	6	.263
Vomiting	2	3	0.419	2	3	0.718
Diarrhoea	5	17	<0.001	6		0.269
Stomatitis	3	5	0.299	3		0.356
Neutropenia	21	50	<0.001	24	24	1.000
Febrile neutropenia	3	7	0.050		2	0.686
Neurotoxicity	1	2	0.505		5	0.004
Asthenia	6	7	0.63	6	8	0.654
Hypertension	10	7		2	3	0.443
Venous thromboembolism	6	4	0.204	1	1	1.000

Proper patient selection and management

Bev, bevacizumab; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; G, grade

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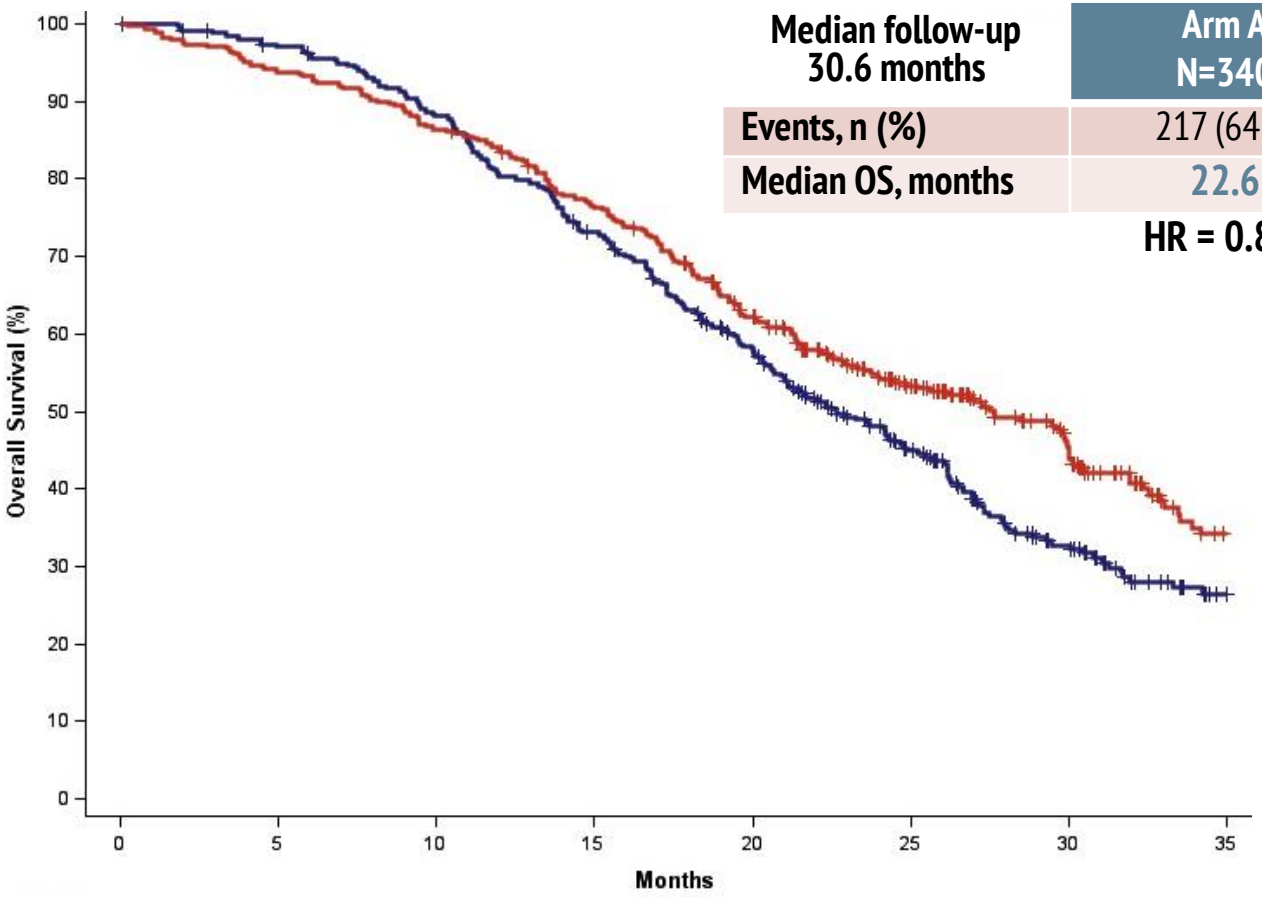
OVERALL SURVIVAL – PRELIMINARY RESULTS



Median follow-up 30.6 months	Arm A N=340	Arm B N=339
Events, n (%)	217 (64%)	191 (56%)
Median OS, months	22.6	27.6

HR = 0.81 [95% CI: 0.67–0.98]
***p*=0.033**

CI, confidence interval; HR, hazard ratio; OS, overall survival

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THE IDEAL PROFILE

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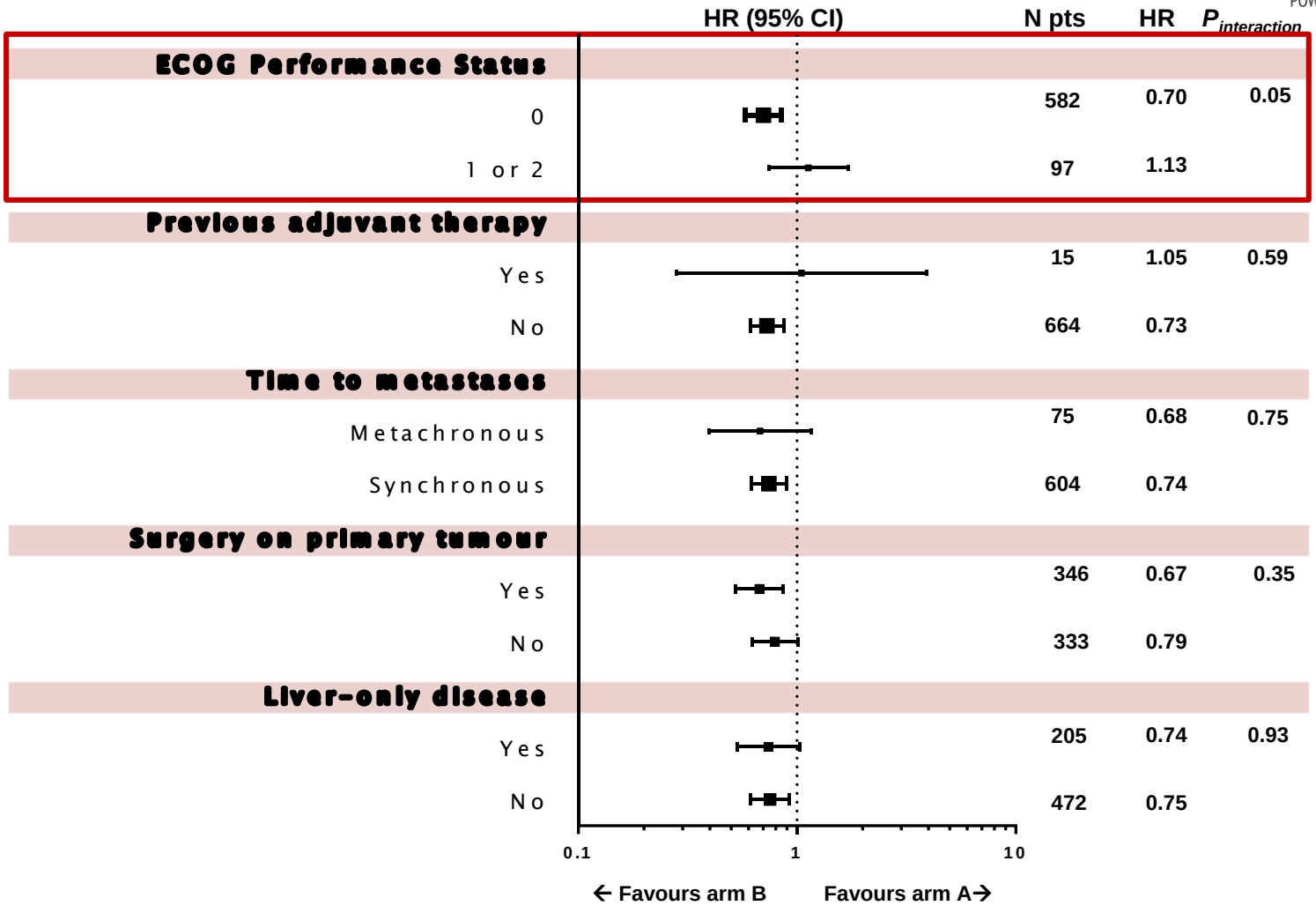
SUBGROUP ANALYSES: PFS2 ACCORDING TO CLINICAL CHARACTERISTICS



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS2, progression-free survival 2

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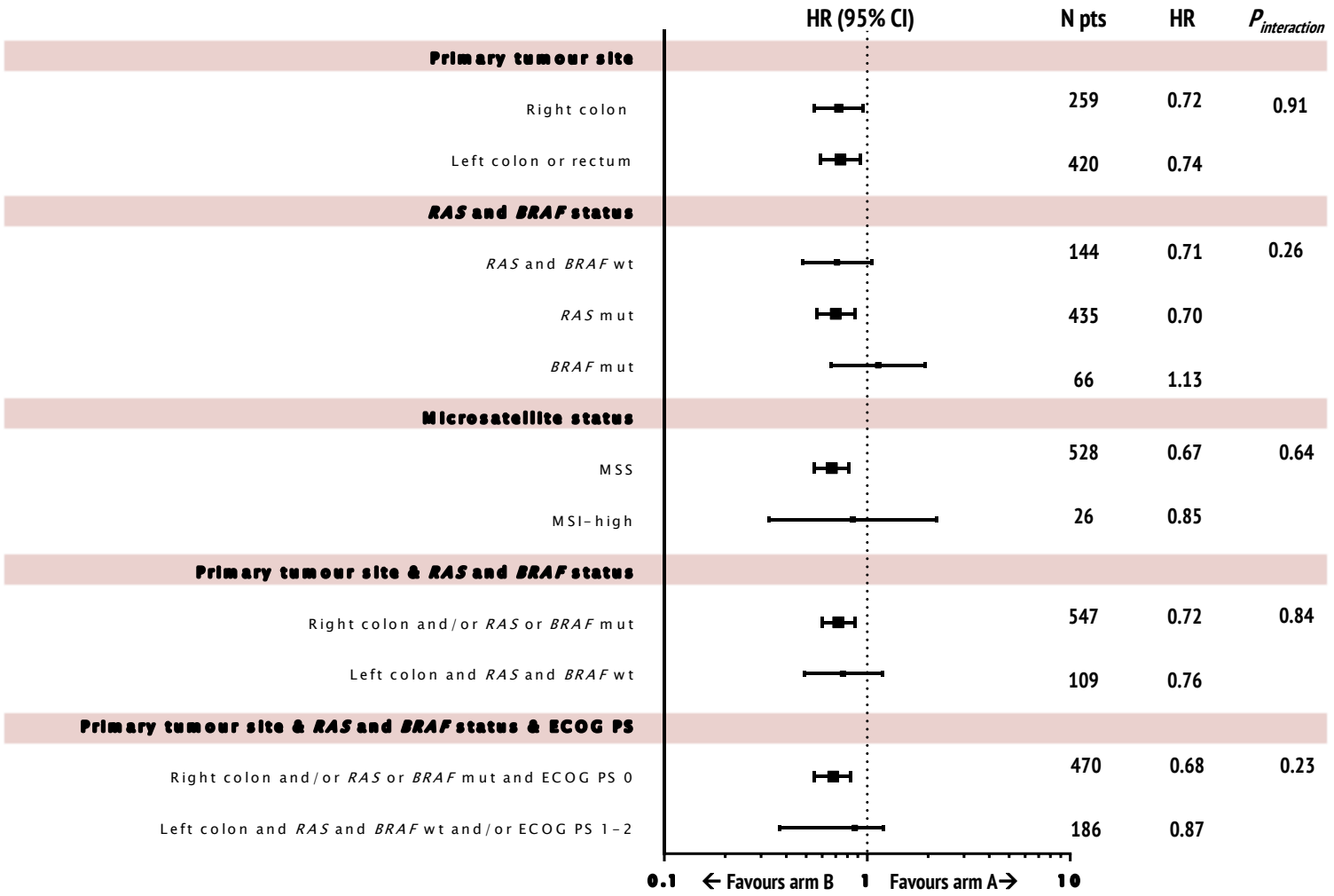
PFS2 ACCORDING TO TUMOUR SIDEDNESS AND MOLECULAR CHARACTERISTICS



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; MSI, microsatellite instability; MSS, microsatellite stable; mut, mutant; PFS2, progression-free survival 2; wt, wild type

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CLINICAL SCENARIO 1

- 63-year old male
- ECOG PS 0
- Unresected right-sided primary tumour with multiple synchronous liver and lung metastases
- *RAS* mutant

Which is your preferred 1st-line option?

A. FOLFOX + bev

B. FOLFIRI + bev

C. FOLFOXIRI + bev

D. FOLFOXIRI

E. FOLFOX/FOLFIRI

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Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan

CLINICAL SCENARIO 2

- 73-year old male
- ECOG PS 1
- Resected right-sided primary tumour with synchronous lung and liver metastases
- *RAS/BRAF* wt

Which is your preferred 1st-line option?

A. FOLFOX/FOLFIRI + bev

B. FOLFOXIRI + bev

C. FOLFOXIRI

D. FOLFOX/FOLFIRI + anti-EGFR

Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; wt, wild type

CLINICAL SCENARIO 3

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- 66-year old male
- ECOG PS 0
- Resected rectal tumour with metachronous lung and nodal metastases (after 3 years, no prior oxaliplatin-based adjuvant)
- *RAS/BRAF* wt

Which is your preferred 1st-line option?

A. FOLFOX/FOLFIRI + bev

B. FOLFOXIRI + bev

C. FOLFOXIRI

D. FOLFOX/FOLFIRI + anti-EGFR

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Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; wt, wild type

CLINICAL SCENARIO 4

- 55-year old female
- ECOG PS 0
- Resected right-sided primary tumour with synchronous peritoneal carcinomatosis
- *BRAF* mutant

Which is your preferred 1st-line option?

A. FOLFOX/FOLFIRI + bev

B. FOLFOXIRI + bev

C. FOLFOXIRI

D. FOLFOX/FOLFIRI + anti-EGFR

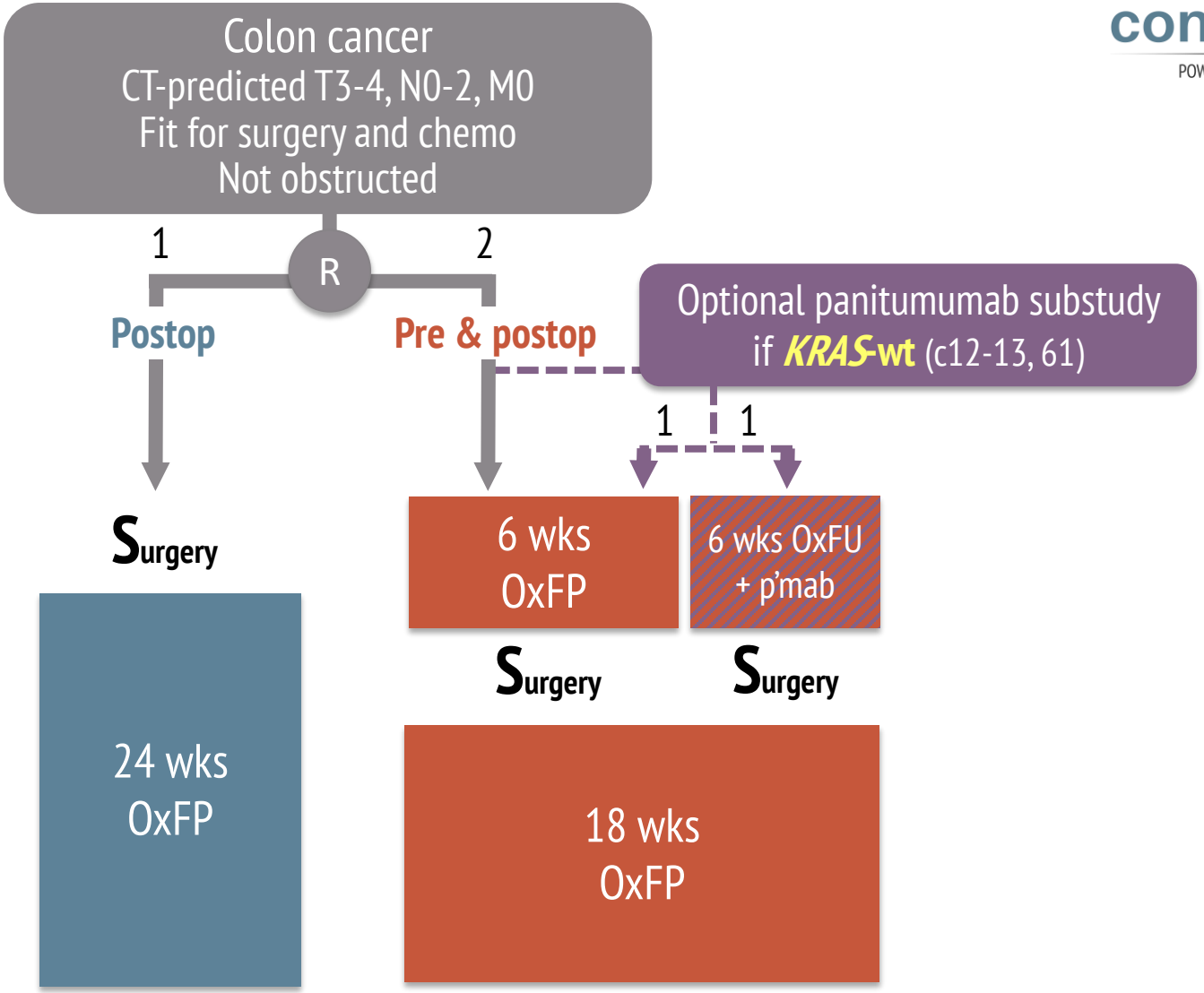
cor2ed.participoll.com

Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan

FoXTROT: AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL IN 1052 PATIENTS EVALUATING NEOADJUVANT CHEMOTHERAPY FOR COLON CANCER

Dr. Jenny Seligmann
University of Leeds, UK

FoXTROT STUDY DESIGN



CT, computed tomography; M, metastasis; N, node; OxFP, oxaliplatin plus fluoropyrimidine; p'mab, panitumumab; postop, postoperative; R, randomised; T, tumour; wt, wild type

Seymour MT, et al. ASCO 2019: Abstract 3504

FOxTROT RESEARCH QUESTIONS

- **Primary question: does NAC increase the cure rate?**
  - Primary outcome: relapse/persistent disease up to 2 years
    - **Target HR=0.75** (e.g 32%→24%)
    - N=1050, for 80% power, 2-tailed $p<0.05$
  - Secondary outcomes: complete resection; perioperative safety; downstaging; tumour regression
- **Does panitumumab increase preoperative efficacy in *KRAS*-wt?**
  - Primary outcome: histological response
    - 90% power to detect 0.38 s.d. effect size at $p<0.01$
    - Prespecified "responder biomarker" subgroups

full analysis late 2019

HR, hazard ratio; NAC, neoadjuvant chemotherapy; s.d., standard deviation; wt, wild type

Seymour MT, et al. ASCO 2019: Abstract 3504

THE PATIENTS

All baseline characteristics were well-balanced between treatment arms

	N=1052
Age	**Median 65 years** (IQR 57-70); **28% ⩾70 years**
Sex M:F	**64:36**
WHO PS 0 : 1 : 2	**76% : 22% : 1%**
Primary location in colon	**49% right : 51% left**
Predicted T-stage from CT scan	**75% rT4/T3$_{\geqslant 5mm}$: 25% rT3$_{<5mm}$**

CT, computed tomography; IQR, interquartile range; r, radiological; T, tumour; WHO PS, World Health Organization Performance Status

Seymour MT, et al. ASCO 2019: Abstract 3504

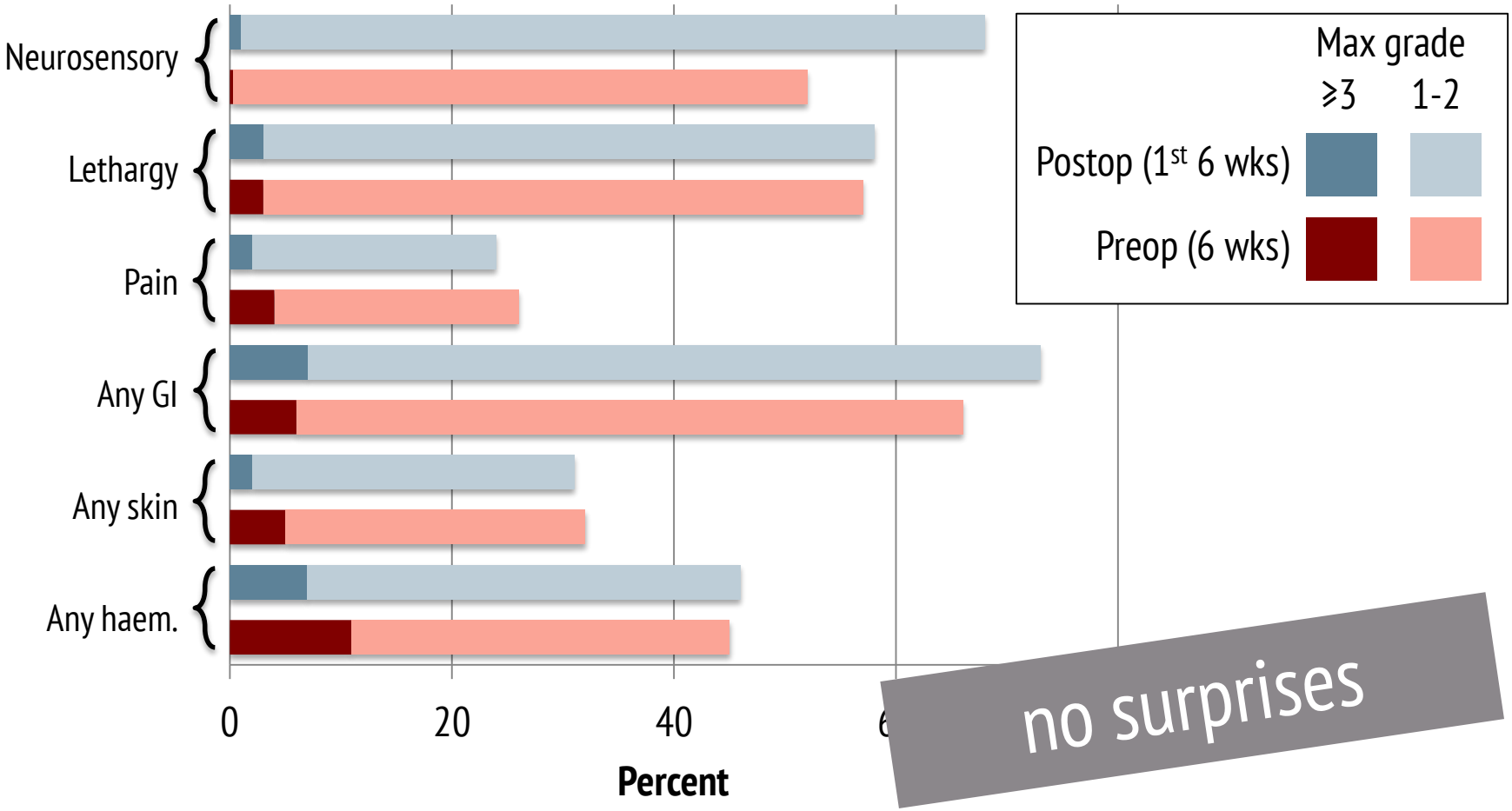
DELIVERING THE TREATMENT PLAN

		Pre & postop n=698	Post n=354	
Attempted curative resection		98.2%	97.7%	*p*=0.54
No attempt at curative resection	Died before surgery	0.4%	0.3%	*p*=0.72
	Inoperable or metastatic disease	1.3%	2.0%	*p*=0.39
Did not receive chemotherapy		4%	27%	*p*<0.0001

11% because patient too unwell or refused chemotherapy
16% because tumour was considered low risk

Postop, postoperative
Seymour MT, et al. ASCO 2019: Abstract 3504

CHEMOTHERAPY TOXICITY



GI, gastrointestinal; haem, haematological; postop, postoperative; preop, preoperative
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PERIOPERATIVE COMPLICATIONS

	Pre & post n=682	Post n=350	
Wound infection	8.5%	8.9%	*p*=0.85
Bronchopneumonia	1.8%	3.1%	*p*=0.16
PE ± DVT	1.6%	0.6%	*p*=0.18
Anastomotic leak or intra-abdo abscess	4.7%	7.4%	*p*=0.07
Complication requiring further surgery	4.3%	7.1%	*p*=0.05
Complication prolonging hospital stay	11.6%	14.3%	*p*=0.22
Death within 30 days	0.6%	0.6%	*p*=0.98

DVT, deep vein thrombosis; intra-abdo, intra-abdominal; PE, pulmonary embolism

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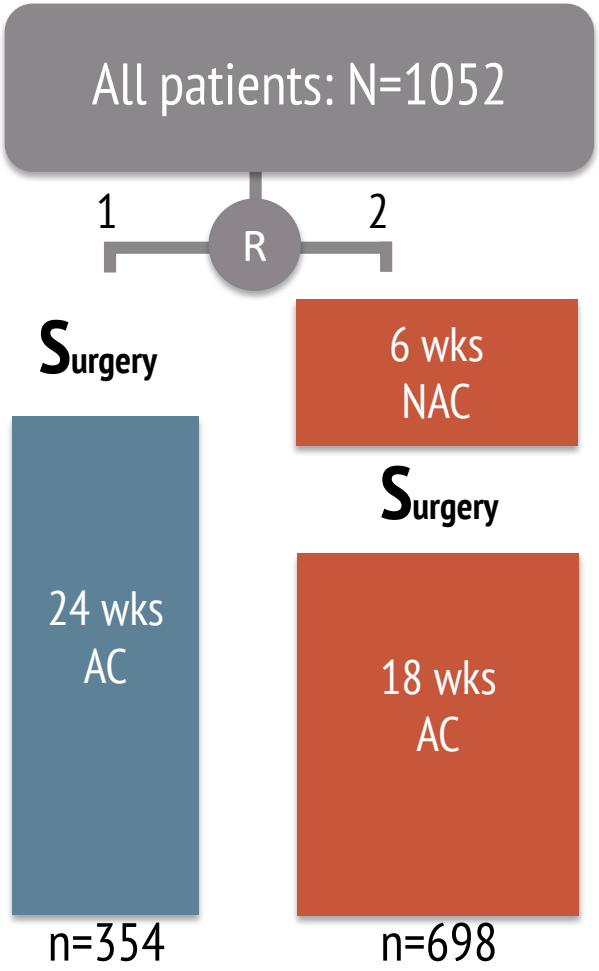
EFFICACY: PRIMARY ANALYSIS



2-year efficacy, ITT

- Recurrence or persistent disease

Short-term efficacy

- Completeness of resection
- Downstaging of tumour
- Histological tumour regression grade

AC, adjuvant chemotherapy; ITT, intention-to-treat; NAC, neoadjuvant chemotherapy; R, randomized
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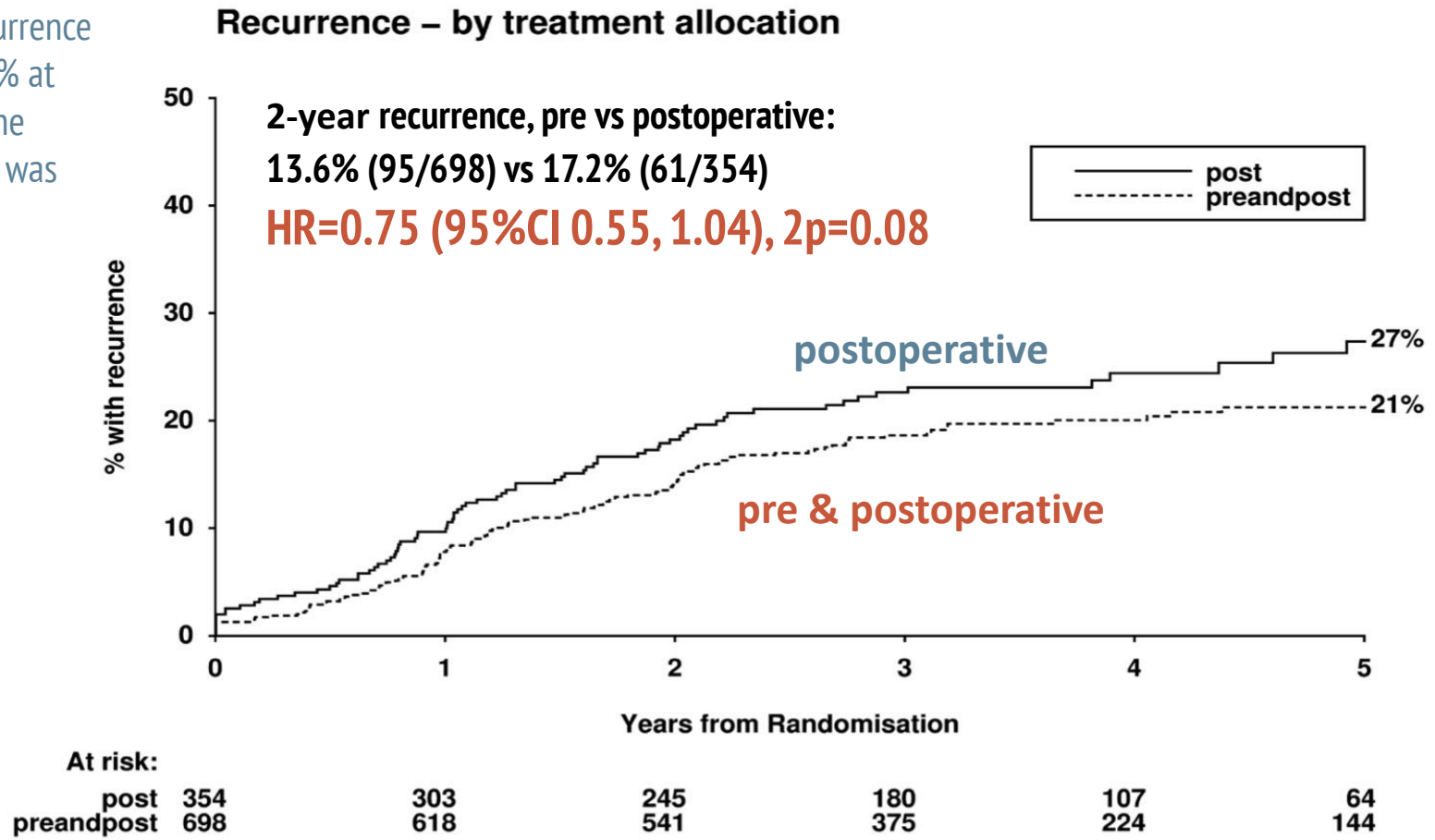
PRIMARY OUTCOME: 2-YEAR EFFICACY

NB: the recurrence rate of 17.2% at 2 years in the control arm was lower than anticipated



2p, 2-tailed p-value; CI, confidence interval; HR, hazard ratio

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COMPLETENESS OF RESECTION

Local pathologist score*	Neoadjuvant chemotherapy n=689	Straight to surgery n=353	
Did not proceed to surgery	0.6%	0.6%	
Surgery but no resection	0.3%	1.1%	*p*=0.001 (MH)
R2 – macroscopically incomplete	0.3%	1.1%	
R1 – microscopically incomplete	4.2%	8.8%	
R0 – microscopically complete	93.1%	88.4%	

MH, Mantel-Haenszel test; R, residual tumour

*Concordance of local vs central assessment of resection margins = 99% (n=904)

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COMPLETENESS OF RESECTION

Local pathologist score*	Neoadjuvant chemotherapy n=689	Straight to surgery n=353	
Did not			
Surgery			
R2 – m			.001 (MH)
R1 – microscopically incomplete	4.2%	8.8%	
R0 – microscopically complete	93.1%	88.4%	

Risk of undergoing surgery without achieving R0:

R1, R2 or no resection: 4.8% vs 11.1%

MH, Mantel-Haenszel test; R, residual tumour

*Concordance of local vs central assessment of resection margins = 99% (n=904)

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TUMOUR STAGE/SIZE AT SURGERY

GI connect
POWERED BY COR2ED

Local pathology	Neoadj. chemo n=682	Straight to surgery n=347	
pT0	4.1%	0%	$p<0.0001$ (MH)
pT1 / pT2	11.7%	5.8%	
pT3	63.7%	64.5%	
pT4	20.5%	29.8%	
Max tumour diameter – median	35mm	50mm	$p<0.0001$
Spread beyond muscularis – median	4mm	5mm	$p=0.005$
Extramural vascular invasion (EMVI+)	32.3%	44.8%	$p<0.0001$

EMVI, extramural vascular invasion; MH, Mantel-Haenszel test; pT, pathological tumour stage
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NODAL STAGE AT SURGERY

GI connect
POWERED BY COR2ED

Local pathology	Neoadjuvant chemotherapy n=682	Straight to surgery n=346	
pN0	59.4%	48.8%	$p<0.0001$ (MH)
pN1 (1-3 nodes)	25.4%	25.1%	
pN2 (≥4 nodes)	15.2%	25.9%	
Apical node positive	3.8%	7.5%	$p=0.013$

MH, Mantel-Haenszel test; pN, pathological nodal stage
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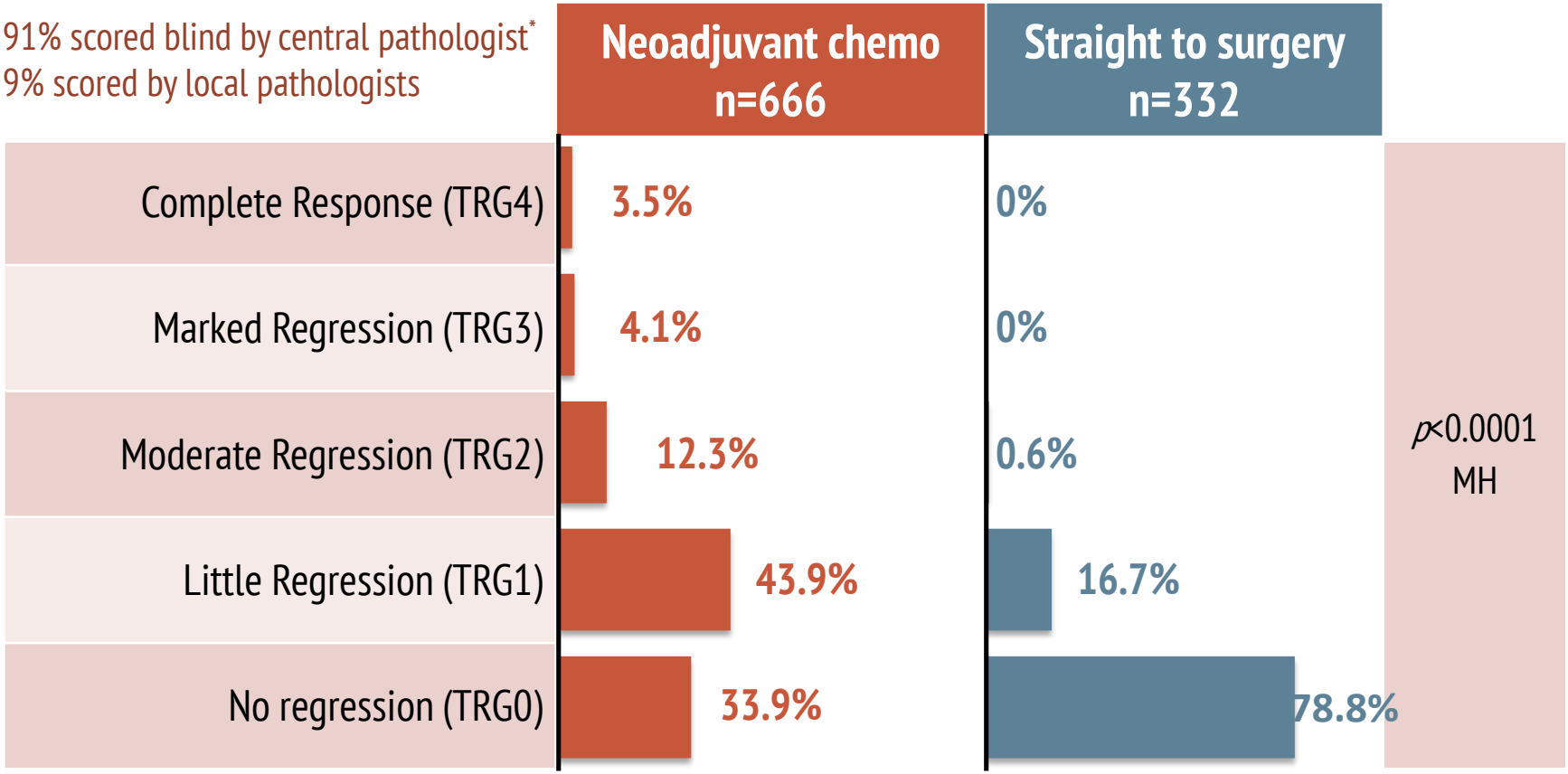
TUMOUR REGRESSION GRADE[1] AT SURGERY

GI connect
POWERED BY COR2ED

91% scored blind by central pathologist*
9% scored by local pathologists

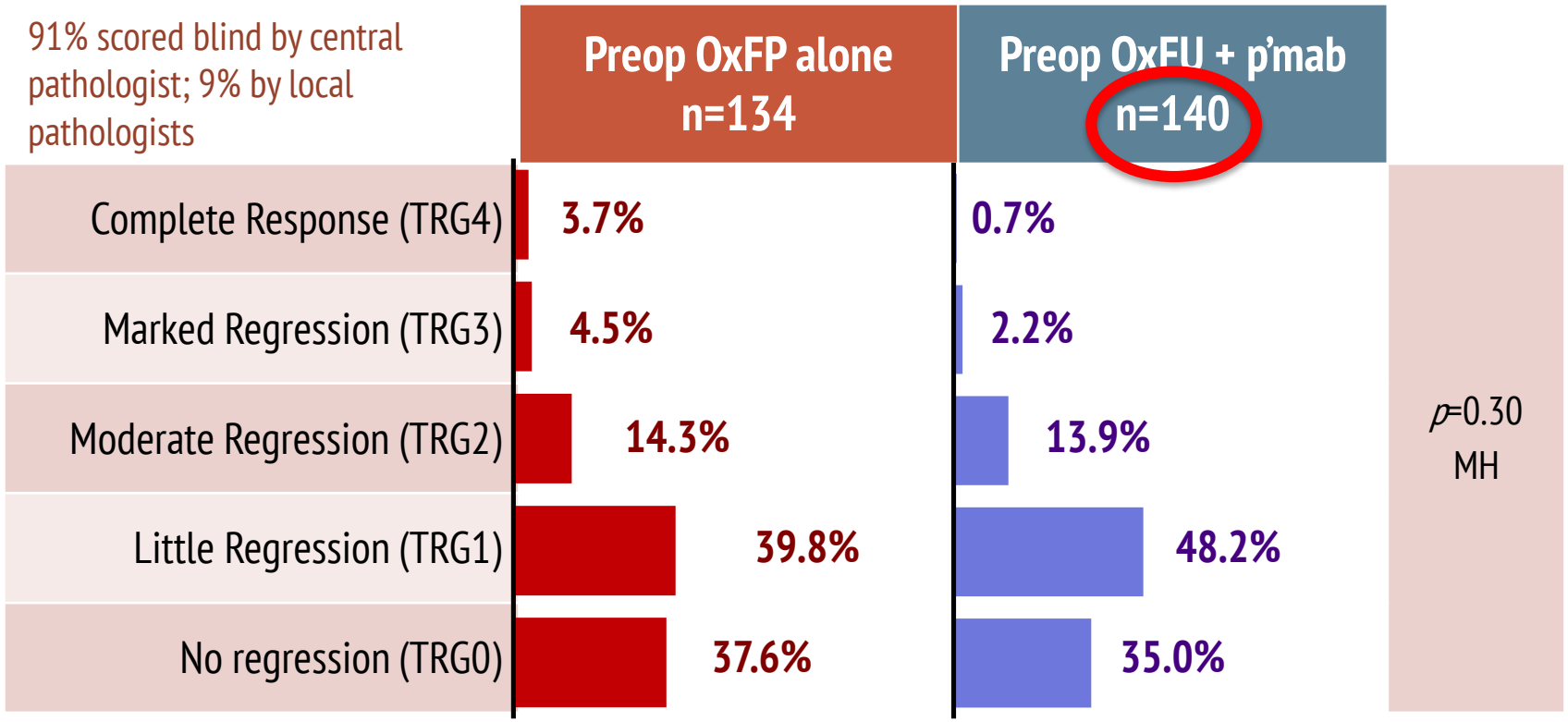


*https://www.virtualpathology.leeds.ac.uk/clinical/colorectal/foxtrot/

MH, Mantel-Haenszel test; TRG, tumour regression grade

1. Dworak O, et al. Intl J Colorectal Dis. 1997;12:19-23

EFFECT OF PANITUMUMAB



MH, Mantel-Haenszel test; OxFU, oxaliplatin plus fluoropyrimidine; p'mab, panitumumab; preop, preoperative; TRG, tumour regression grade

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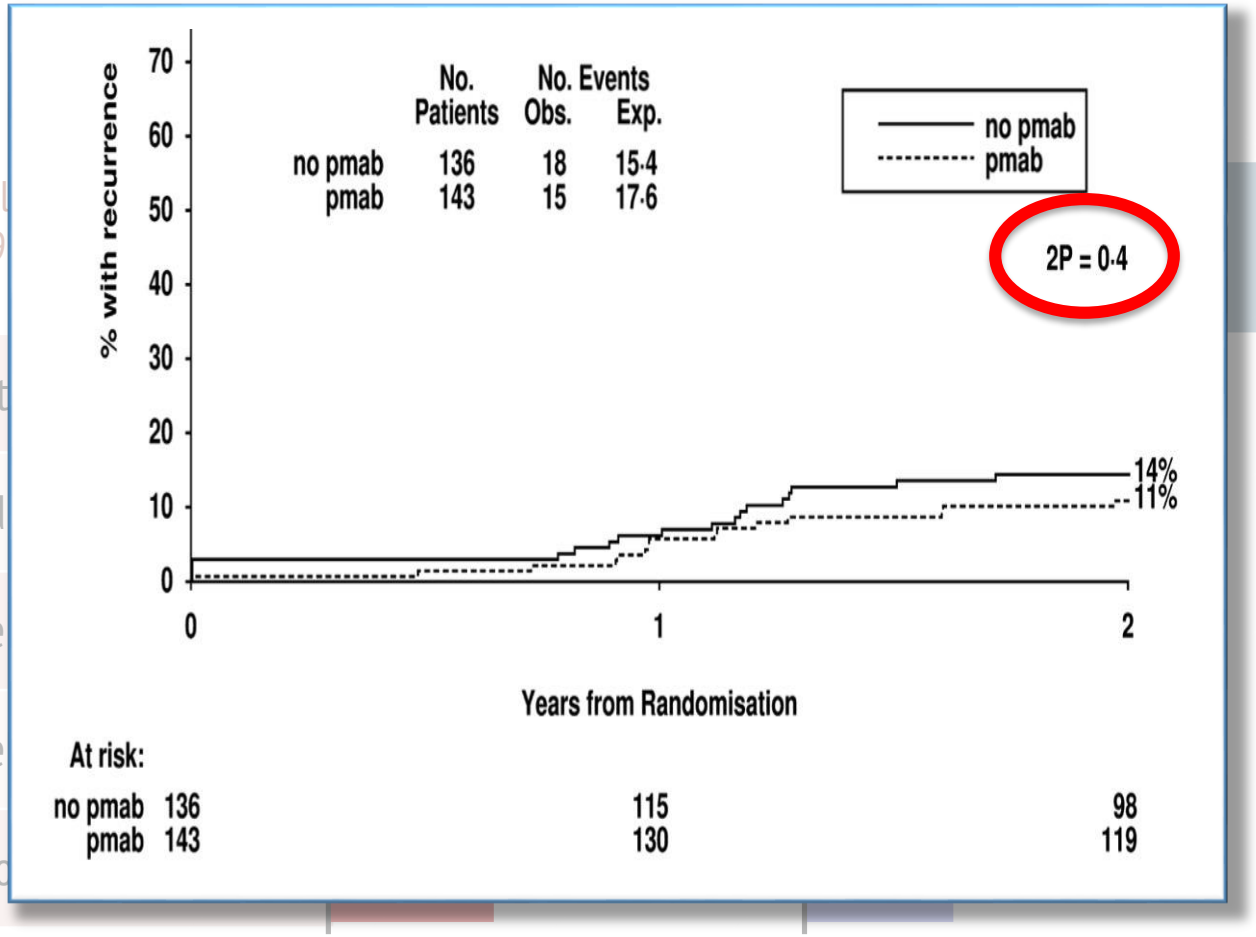
EFFECT OF PANITUMUMAB



91% scored bl
pathologist; 9
pathologists

Complet

Marked

Moderate

Little

No

p=0.30
MH

"P, 2-tailed p value; Exp, events expected; MH, Mantel-Haenszel test; obs, events observed; OxFU, oxaliplatin plus fluoropyrimidine; p'mab, panitumumab; preop, preoperative; TRG, tumour regression grade

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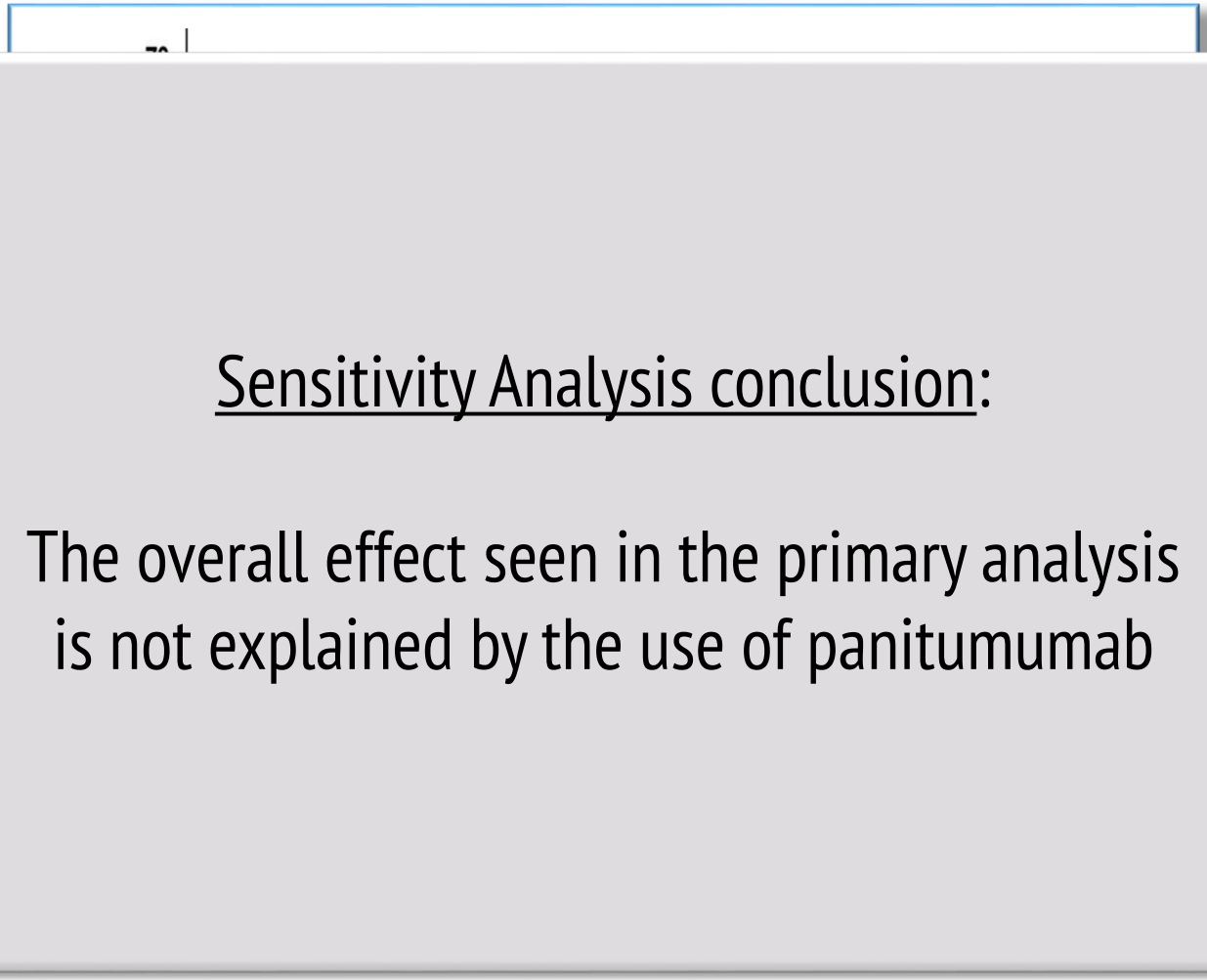
EFFECT OF PANITUMUMAB



Sensitivity Analysis conclusion:

The overall effect seen in the primary analysis is not explained by the use of panitumumab

MH, Mantel-Haenszel test; OxFU, oxaliplatin plus fluoropyrimidine; p'mab, panitumumab; preop, preoperative; TRG, tumour regression grade

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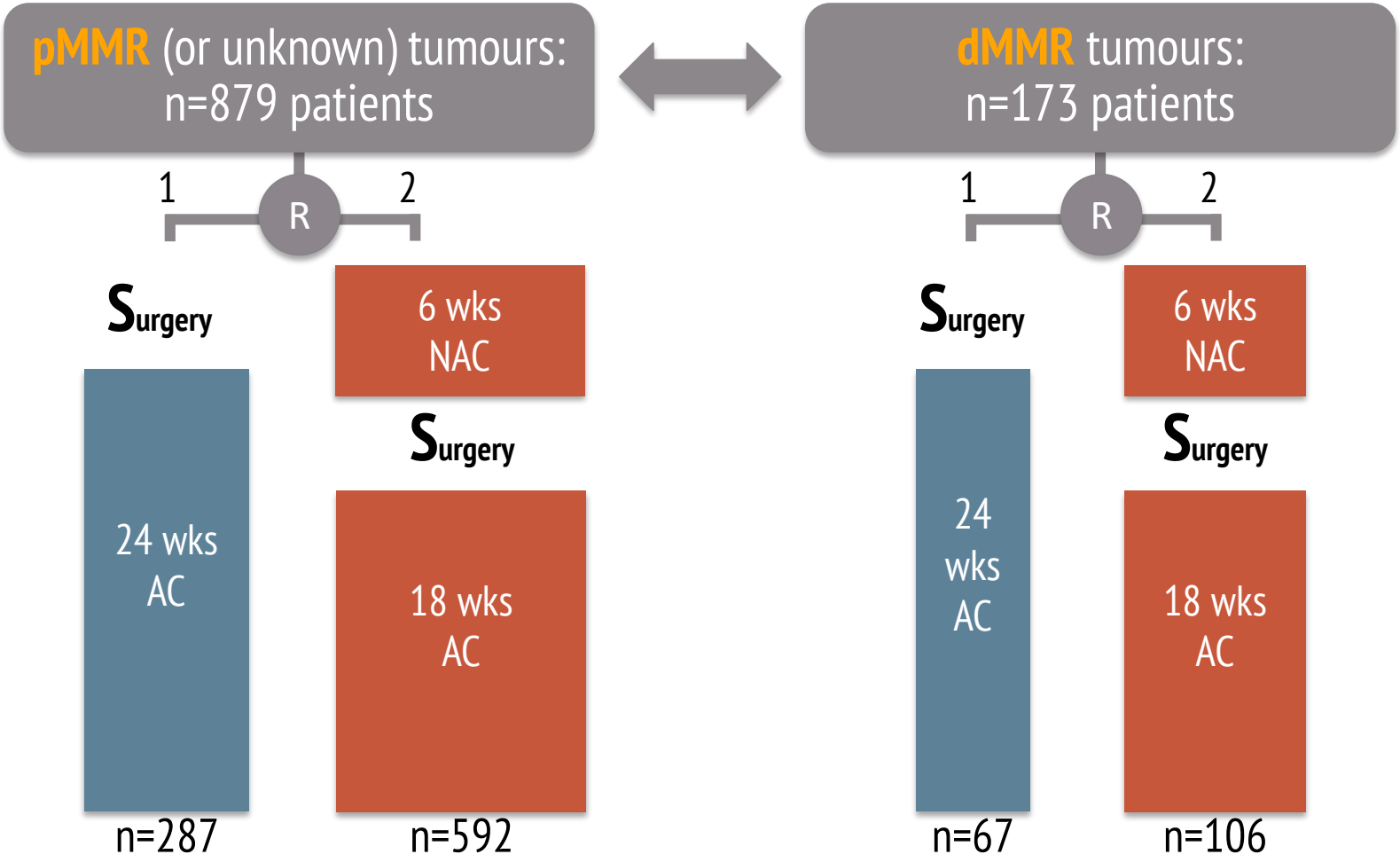
KEY SUBGROUP ANALYSIS: MMR



AC, adjuvant chemotherapy; dMMR, deficient MMR; MMR, mismatch repair; NAC, neoadjuvant chemotherapy; pMMR, proficient MMR; R, randomized

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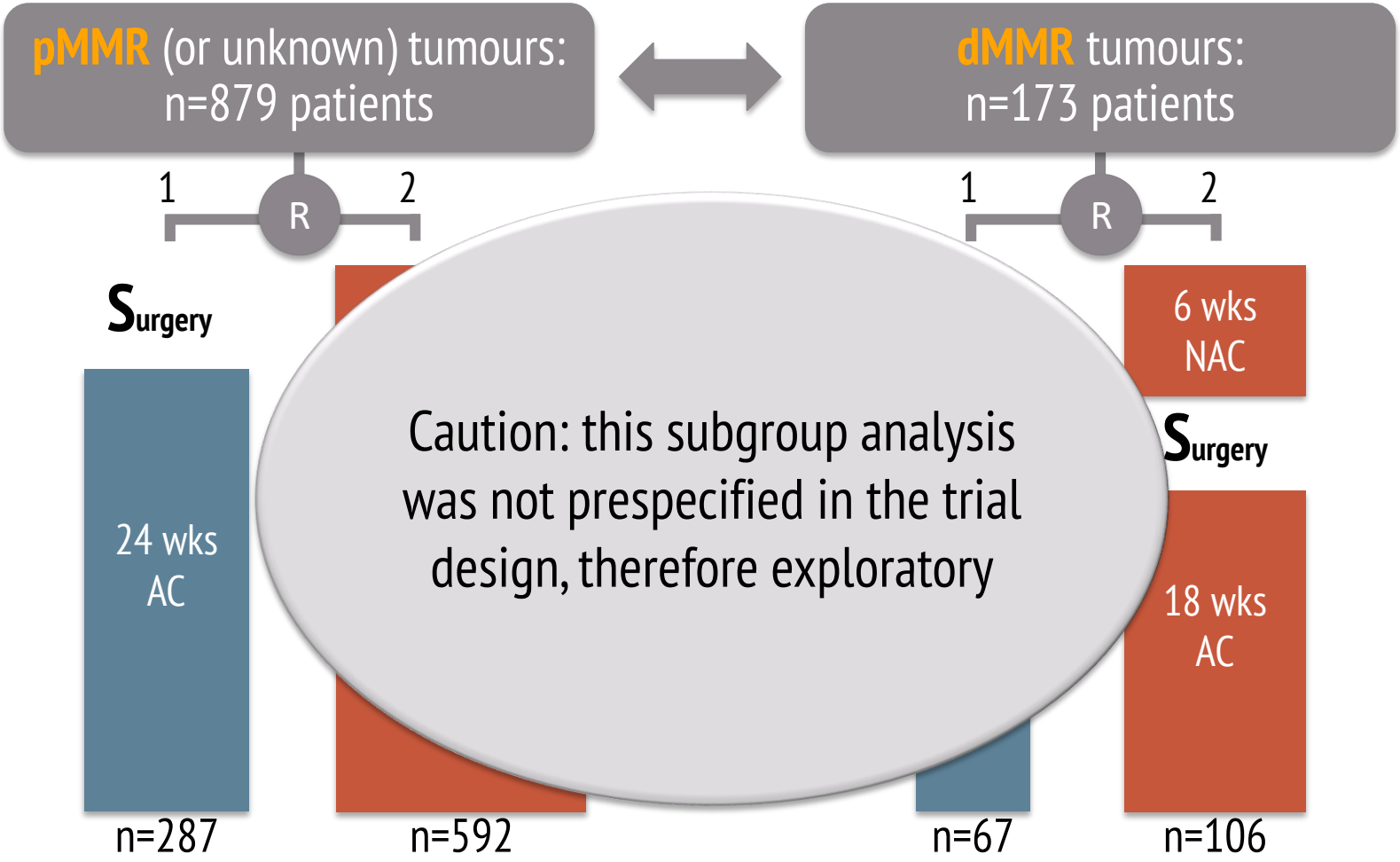
KEY SUBGROUP ANALYSIS: MMR



AC, adjuvant chemotherapy; dMMR, deficient MMR; MMR, mismatch repair; NAC, neoadjuvant chemotherapy; pMMR, proficient MMR; R, randomized

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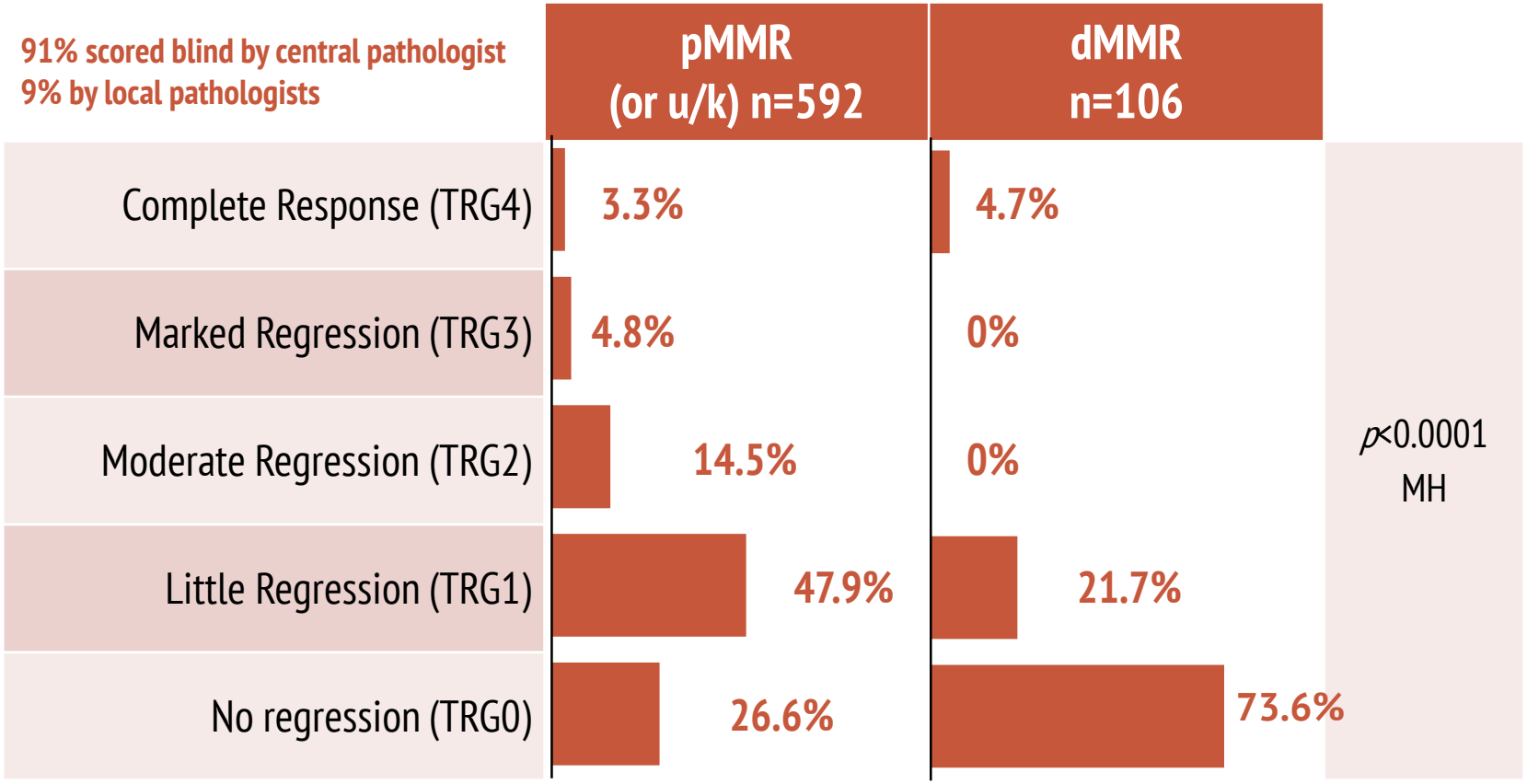
KEY SUBGROUP ANALYSIS: MMR

RATE OF TUMOUR REGRESSION AFTER NAC MARKEDLY REDUCED IN dMMR TUMOURS



dMMR, deficient MMR; MH, Mantel-Haenszel test; MMR, mismatch repair; NAC, neoadjuvant chemotherapy; pMMR, proficient MMR; TRG, tumour regression grade; u/k, unknown

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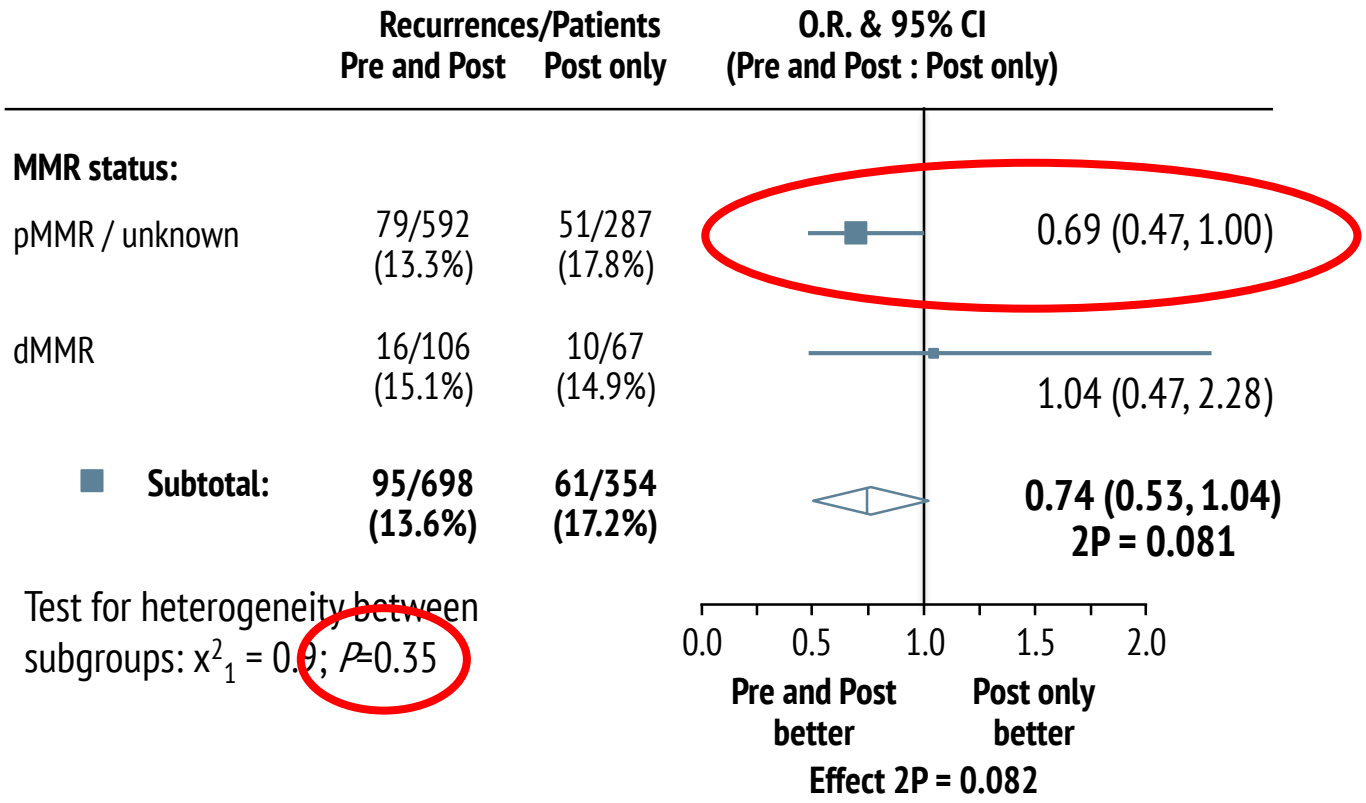
EFFECT OF NAC ON 2-YEAR RELAPSE BY MMR STATUS



2P, 2-tailed p-value; CI, confidence interval; dMMR, deficient MMR; MMR, mismatch repair; NAC, neoadjuvant chemotherapy; O.R., odds ratio; pMMR, proficient MMR

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FoXTROT – MAIN CONCLUSIONS

FOxTROT did not reach target significance for its primary endpoint

But: moving 6 weeks of chemotherapy ahead of surgery,
without major addition to the cost or patient burden of treatment…

- was safe, with less major postoperative morbidity
- significantly downstaged tumours and reduced incomplete resections
- **trended** towards improved 2-year cancer control (HR=0.75; *p*=0.08)

…can be considered a new therapeutic option for locally advanced operable colon cancer

HR, hazard ratio

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FoXTROT – ADDITIONAL FINDINGS

- No response seen in most dMMR cancers
- No benefit from adding panitumumab in unselected *KRAS*-wt
  - **But**: NGS shows extended-*RAS* or *BRAF* mut in >35% patients
  - Full analysis of enriched biomarker population ongoing - results soon
- A superb opportunity to assess tumour biology and develop intelligent postop management

dMMR, deficient mismatch repair; mut, mutant; NGS, next generation sequencing

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