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EXPERTS KNOWLEDGE SHARE

with

Dr. Lenz,

Dr. Cremolini and Dr. Prager

Munich, Germany

Saturday October 20th

20:00-22:00

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THE ARGUMENT AGAINST TREATMENT SEQUENCING AND FOR FLEXIBLE DOSING IN LATER-LINE MANAGEMENT OF COLORECTAL CANCER

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DISCLAIMER

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Please note:

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion

Disclosures:

Dr. Chiara Cremolini has no financial disclosures to declare

DOES THE CONCEPT OF SEQUENCING APPLY TO LATER LINES OF THERAPY?

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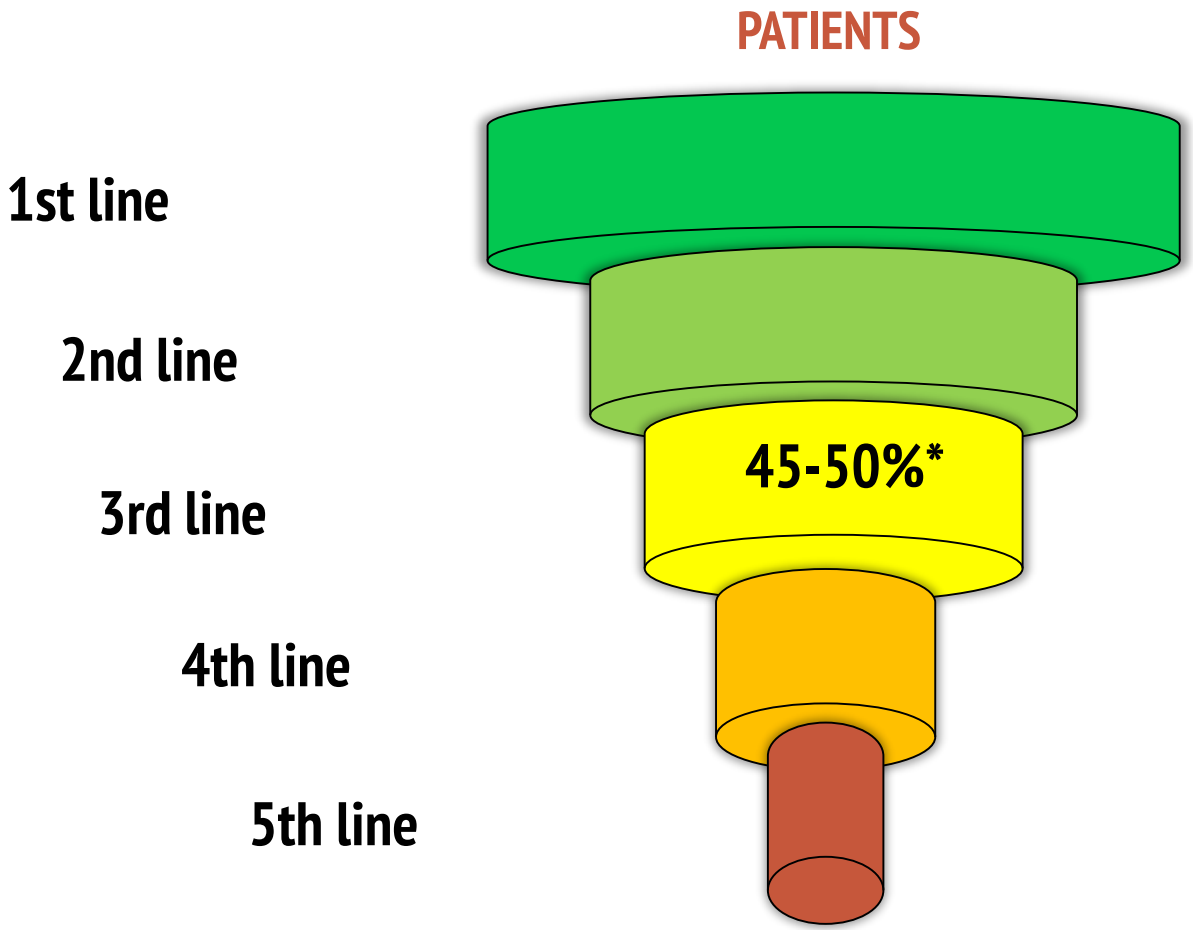

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*based on TRIBE and FIRE-3 trial data

Modest et al. J Clin Oncol 2015
Cremolini et al. Lancet Oncol 2015

WHICH IS THE BEST OPTION NOW?

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PHASE III OPTIONS

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REGORAFENIB VS TFD/TPI: ACTIVITY AND EFFICACY IN PIVOTAL TRIALS

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	CORRECT (N=760)			RECOURSE (N=800)		
	Rego (n=505)	Placebo (n=255)		TFD/TPI (n=534)	Placebo (n=266)	
ORR	1.0%	0.4%	*P* = .19	1.6%	0.4%	*P* = .29
DCR	41%	15%	*P* <.001	44%	16%	*P* <.001
PFS	1.9	1.7	HR = 0.49 *P* <.001	2.0	1.7	HR = 0.48 *P* <.001
OS	6.4	5.0	HR = 0.77 *P* = .0052	7.1	5.3	HR = 0.68 *P* <.001

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Grothey et al. Lancet 2013; Mayer et al. N Engl J Med 2015

DCR, disease control rate; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Rego, regorafenib; TFD/TPI, trifluridine/tipiracil

REGORAFENIB VS TFD/TPI: ACTIVITY AND EFFICACY IN ASIAN POPULATION

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	CONCUR (N=204)			TERRA (N=542)		
	Rego (n=136)	Placebo (n=68)		TFD/TPI (n=271)	Placebo (n=271)	
ORR	4.0%	0%	*P* = .045	1.1%	0	*P* = .55
DCR	51%	7%	*P* <.001	44.1%	14.6%	*P* <.001
PFS	3.2	1.7	HR = 0.31 *P* <.001	2.0	1.8	HR = 0.43 *P* <.001
OS	8.8	6.3	HR = 0.55 *P* < .001	7.8	7.1	HR = 0.79 *P* = .035

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Li et al. Lancet Oncol 2015; Xu et al. J Clin Oncol 2018
DCR, disease control rate; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Rego, regorafenib; TFD/TPI, trifluridine/tipiracil

REGORAFENIB VS TFD/TPI IN THE REAL-LIFE SETTING

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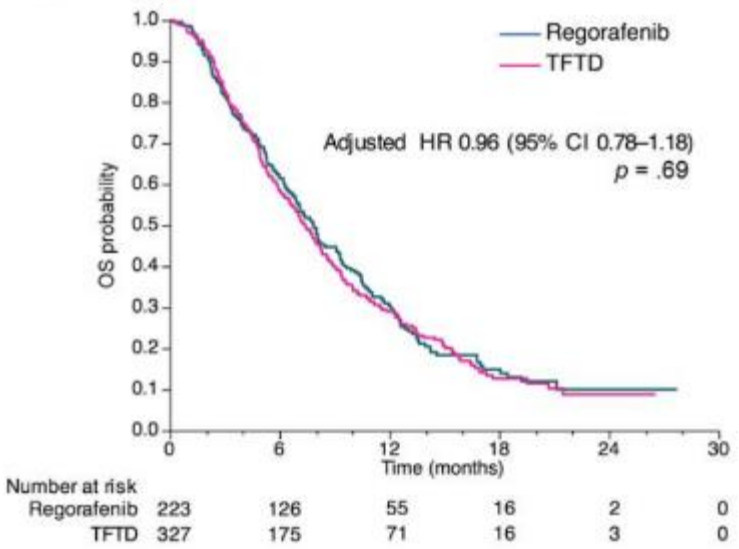
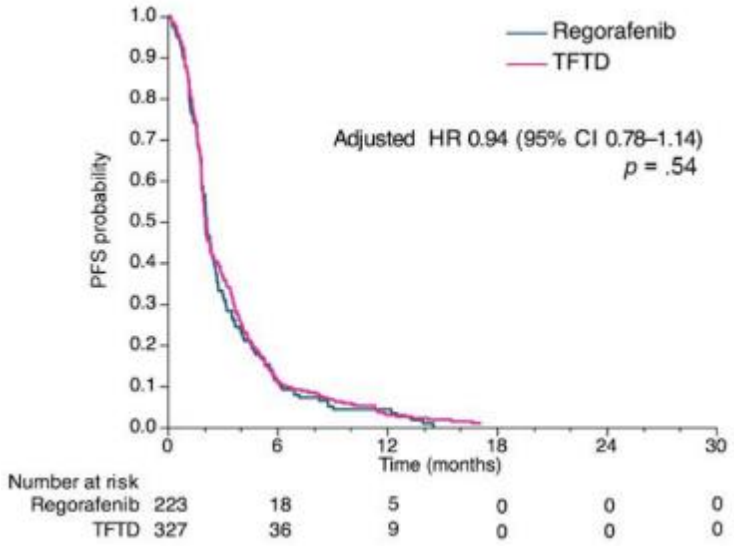
OVERALL SURVIVAL



Subgroup analysis:
Rego showed favorable OS in pts <65 ys, whereas TFD/TPI was favored in pts aged ⩾65 ys

Propensity score-based analysis
N=550

PROGRESSION-FREE SURVIVAL



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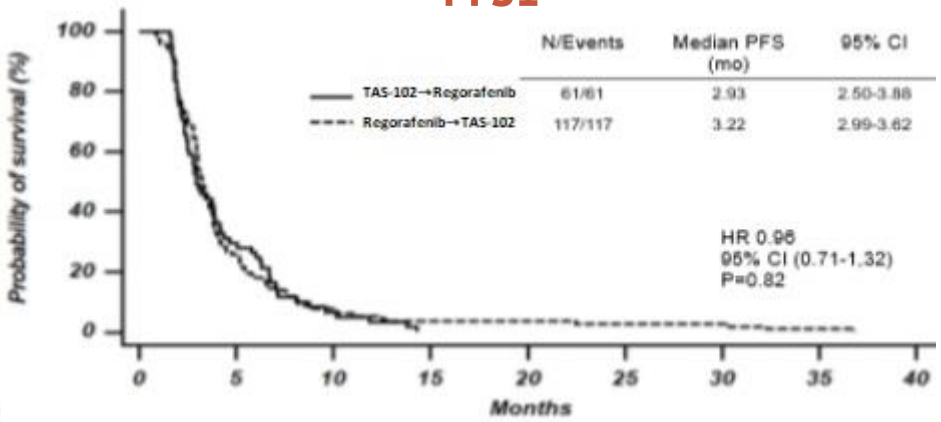
Moriwaki et al. Oncologist 2018
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; pts, patients; Rego, regorafenib; TFD/TPI, trifluridine/tipiracil; TFTD, trifluridine/tipiracil

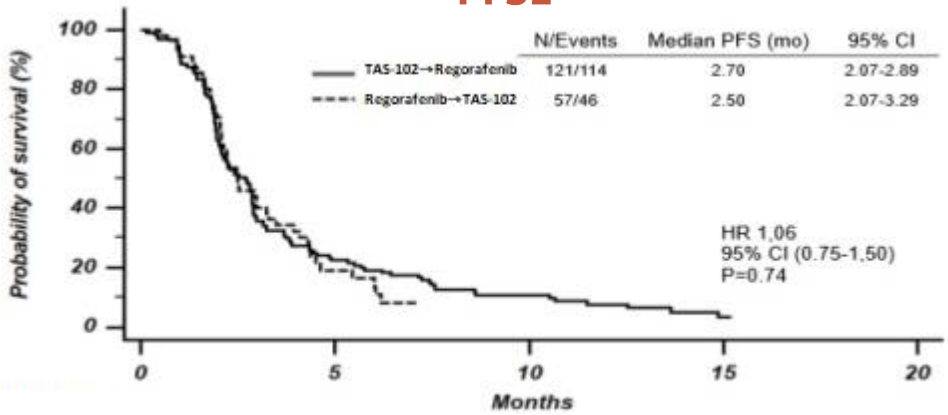
SEQUENCING IN THE REAL-LIFE SETTING

Subgroup of patients who had received both Rego and TFD/TPI N=182

PFS1



PFS2



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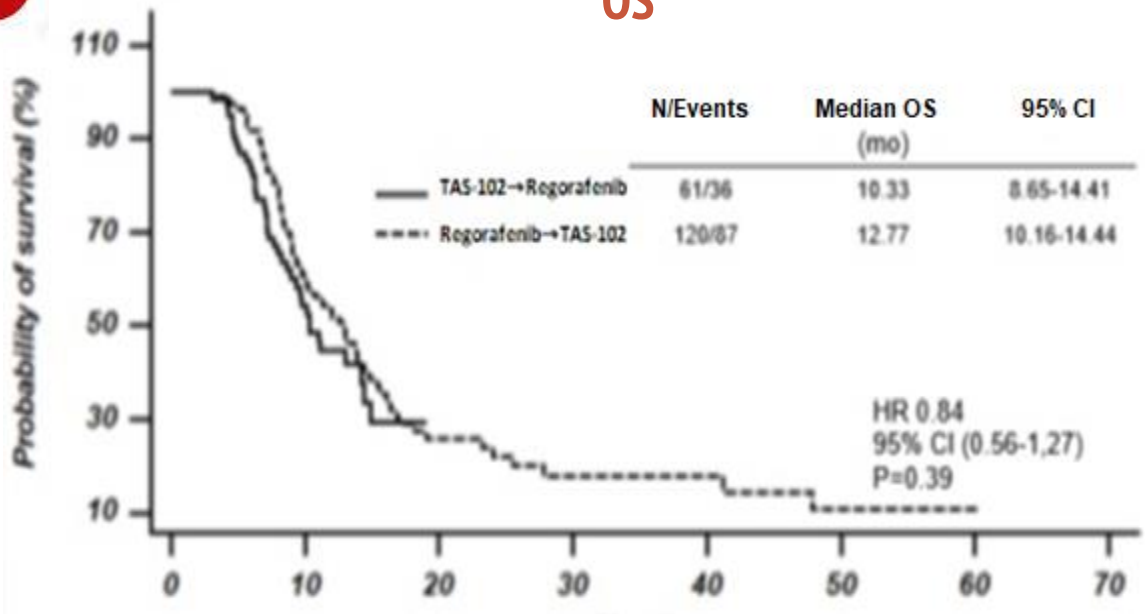
Cremolini et al. Oncologist 2018

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PFS 1, first PFS; PFS 2, second PFS; Rego, regorafenib; TFD/TPI, trifluridine/tipiracil

SEQUENCING IN THE REAL-LIFE SETTING

Subgroup of patients
who had received both Rego and TFD/TPI
N=182

OS



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Cremolini et al. Oncologist 2018
CI, confidence interval; HR, hazard ratio; OS, overall survival; Rego, regorafenib; TFD/TPI, trifluridine/tipiracil

REGORAFENIB VS TFD/TPI: TOXICITY PROFILE

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	REGORAFENIB		TFD/TPI	
G≥3 Adverse events, %	CORRECT (N=500)	CONCUR (N=136)	RECOURSE (N=533)	TERRA (N=271)
Neutropenia	0.6	2	38	33
Leukopenia	NR	2	21	21
Febrile Neutropenia	NR	NR	4	0
Anemia	2.8	2	18	18
Thrombocytopenia	2.8	3	5	3
Bilirubin increase	13	11	9	1
AST/ALT increase	NR	7	3	4
Diarrhea	7	1	3	1
Hypertension	7	11	NR	NR
Fatigue	10	3	4	2
Hand-Foot Skin Reaction	17	16	0	–

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Grothey et al. Lancet 2013; Mayer et al. N Engl J Med 2015; Li et al. Lancet Oncol 2015; Xu et al. J Clin Oncol 2018
AST/ALT, aspartate aminotransferase/alanine aminotransferase; G, grade; NR, not reported; TFD/TPI, trifluridine/tipiracil

REGORAFENIB VS TFD/TPI: TOXICITY PROFILE

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	REGORAFENIB		TFD/TPI
G≥3 Adverse events, %	CONSIGN (N=2864)	CORRELATE (N=1037)	PRECONNECT (N=462)
Neutropenia	1	NR	38
Leukopenia	NR	NR	NR
Febrile Neutropenia	NR	NR	2
Anemia	4	NR	**7**
Thrombocytopenia	2	NR	1
Bilirubin increase	13	NR	NR
AST/ALT increase	7	NR	<1%
Diarrhea	5	3	4
Hypertension	15	8	NR
Fatigue	13	10	2
Hand-Foot Skin Reaction	14	7	NR

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Van Cutsem et al. WCGIC 2015, Oncologist 2018; Ducreux et al. WCGIC 2018; Falcone et al. WCGIC 2018
AST/ALT, aspartate aminotransferase/alanine aminotransferase; G, grade; NR, not reported; TFD/TPI, trifluridine/tipiracil

REGORAFENIB VS TFD/TPI: SUMMARY

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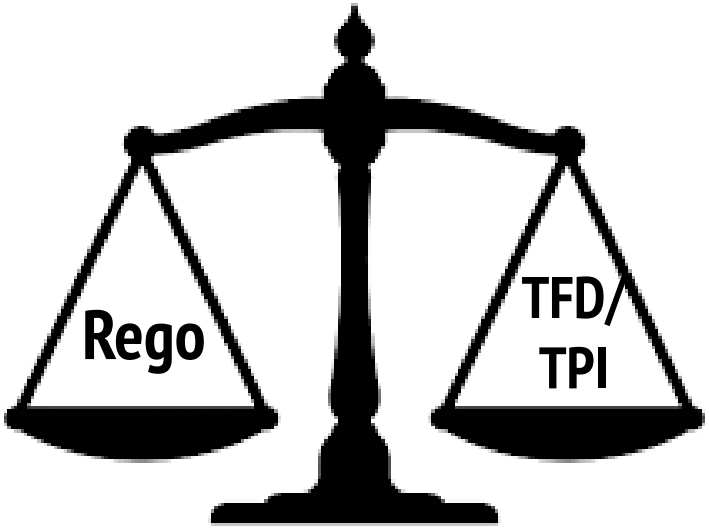
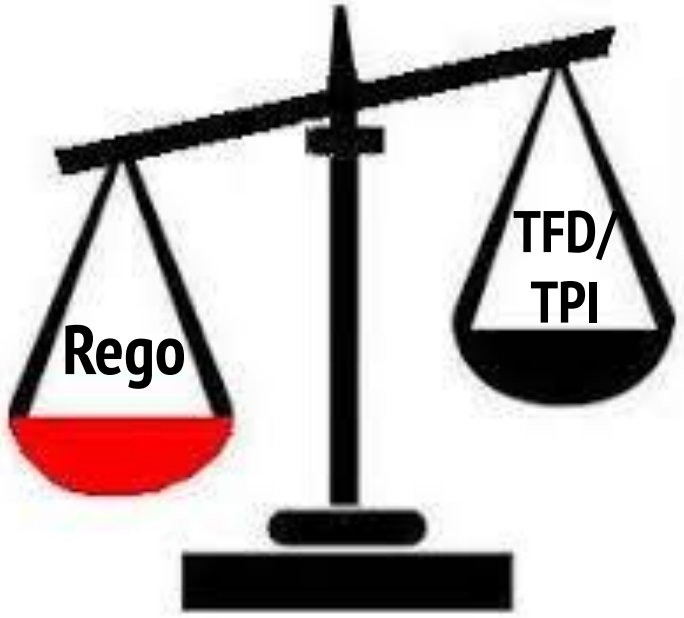
EFFICACY



SUBJECTIVE TOXICITY



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REGORAFENIB VS TFD/TPI: REAL-WORLD TREATMENT COMPLIANCE

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Proportion of Days Covered

Variable	FTD/TPI Patients (n = 1630)	REG Patients (n = 1425)	*P* Value
PDC			
At 3 mo	1524 (93.5)	1333 (93.5)	
PDC	0.71 ± 0.24 (0.81)	0.59 ± 0.25 (0.62)	< .001[a]
PDC ≥ 0.80	774 (50.8)	389 (29.2)	< .001[a]
PDC ≥ 0.90	533 (35.0)	245 (18.4)	< .001[a]
At 6 mo	554 (34.0)	717 (50.3)	
PDC	0.57 ± 0.25 (0.58)	0.45 ± 0.26 (0.43)	< .001[a]
PDC ≥ 0.80	131 (23.6)	90 (12.6)	< .001[a]
PDC ≥ 0.90	67 (12.1)	43 (6.0)	< .001[a]

[a]Statistically significant (*P*< .05)

Patel et al. Clin Col Canc 2018
FTD/TPI, trifluridine/tipiracil; PDC, proportion of days covered; REG, regorafenib; TFD/TPI, trifluridine/tipiracil

HOW TO IMPROVE REGORAFENIB TOLERABILITY AND COMPLIANCE?

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Flexible dosing

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REGORAFENIB TREATMENT MODIFICATIONS IN PROSPECTIVE AND OBSERVATIONAL STUDIES

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	CORRECT Phase III N=505	CONCUR Phase III N=136	CONSIGN Phase IIIb N=2864	REBECCA Observ N=654	CORRELATE# Observ N=500
Initial daily dose 160mg/120mg/80mg/other	100/0/0/0	100/0/0/0	100/0/0/0	80/14/6/<1	53/34/12/1
Any treatment modification§	76%	75%	87%	50%	65%
Any treatment modification§ caused by drug-related AE	67%	71%	60%	–	19%*
Median PFS, months	1.9	3.2	2.7	2.7	2.5
Median OS, months	6.4	8.8	–	5.6	6.5

#data from interim analysis; §modifications include reductions, interruptions/delays, and re-escalations; *data refers only to dose reduction.

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Grothey et al. Lancet 2013; Li et al. Lancet Oncol 2015; Van Cutsem et al. Oncologist 2018;
Adenis et al. BMC 2016; Ducreux et al. ASCO GI Symposium 2017
AE, adverse event; Obser, observational; OS, overall survival; PFS, progression-free survival

ADDITIONAL OBSERVATIONAL DATA FROM GERMANY: RECORA STUDY

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	CORRECT Phase III N=505	RECORA Observ N=458
Initial daily dose 160mg/120mg/80mg/other	100/0/0/0	54/17/25/4
Any treatment modification[§]	76%	43%
Median duration of treatment	1.7 mos	2.3 mos
Median PFS	1.9 mos	3.1 mos
Median OS	6.4 mos	5.9 mos

[§] modifications include reductions, interruptions/delays, and re-escalations

Schulz et al. ASCO GI Symposium 2018
Obser, observational; OS, overall survival; PFS, progression-free survival

REDOS TRIAL: DESIGN AND ENDPOINTS

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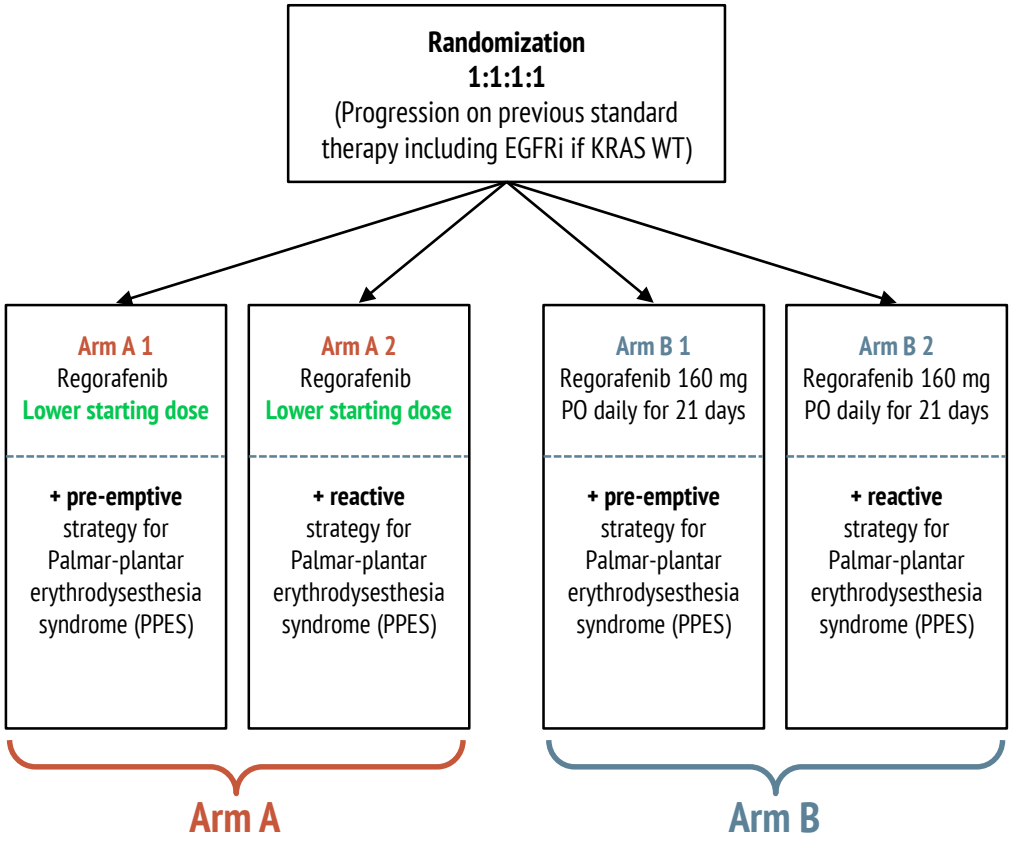
PHASE II RANDOMIZED TRIAL

Week of C1		Daily dose
1	Starting dose C1	80 mg
2	↓	120 mg
3	End dose C1	160 mg
4		off
Week of C2+		**Dose**
1		Dose from C1



1ary endpoint: proportion of pts who completed 2 cycles and initiated cycle 3 in arm A versus B
2ary endpoints included: OS, PFS, TTP

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Bekaii-Saab et al. ASCO GI Symposium 2018
C, cycle; EGFRi, epidermal growth factor receptor inhibitor; KRAS, Kirsten RAS oncogene homolog; OS, overall survival; PFS, progression-free survival; PO, orally; PPES, Palmar-plantar erythrodysesthesia syndrome; TTP, time to progression; WT, wild type

REDOS TRIAL: RESULTS (PRIMARY ENDPOINT)

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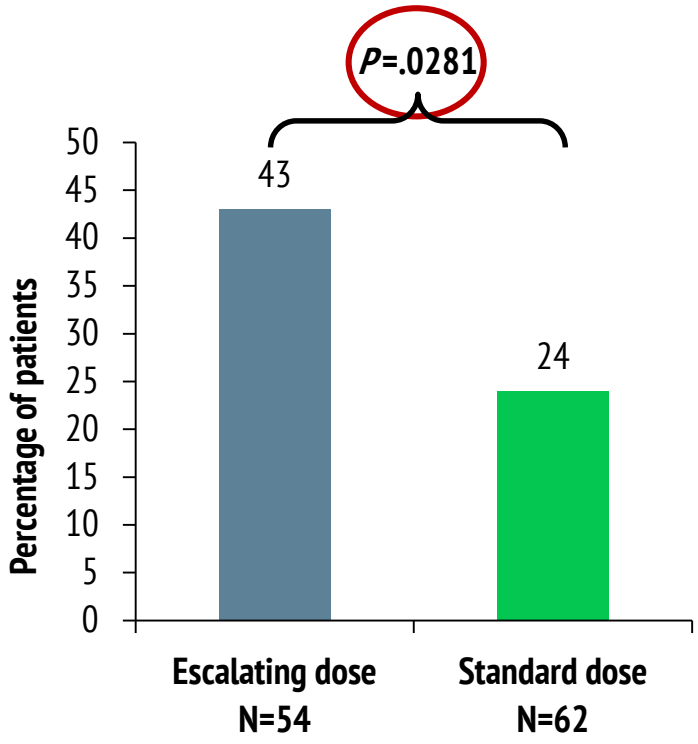
% OF PTS STARTING CYCLE 3



SAFETY

	ESCALATING DOSE N=54	STANDARD DOSE N=62	P value
Grade ≥3 HFSR	15%	16%	n/a
Grade ≥3 HTN	7%	15%	n/a
Grade ≥3 fatigue	13%	18%	n/a

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Bekaii-Saab et al. ASCO GI Symposium 2018
HFSR, hand-food skin reaction; HTN, hypertension; pts, patients

REDOS TRIAL: PFS AND OS RESULTS

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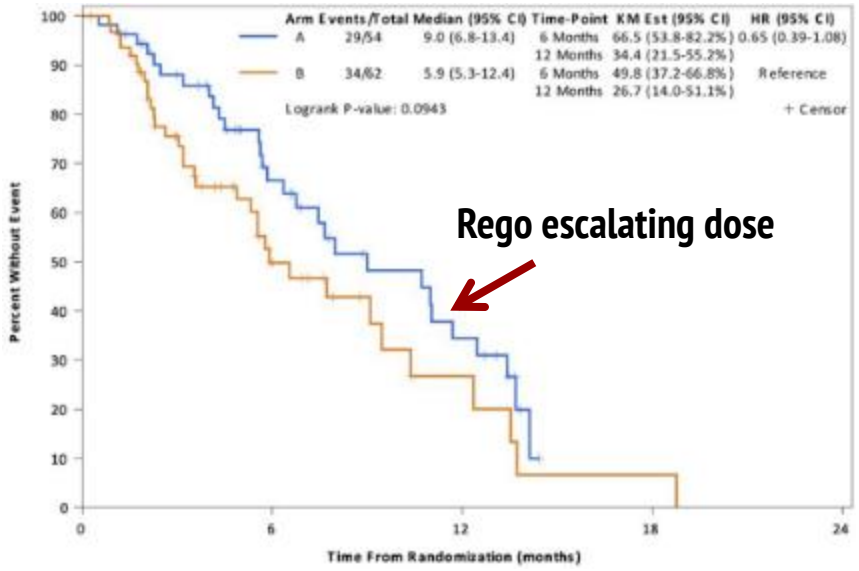
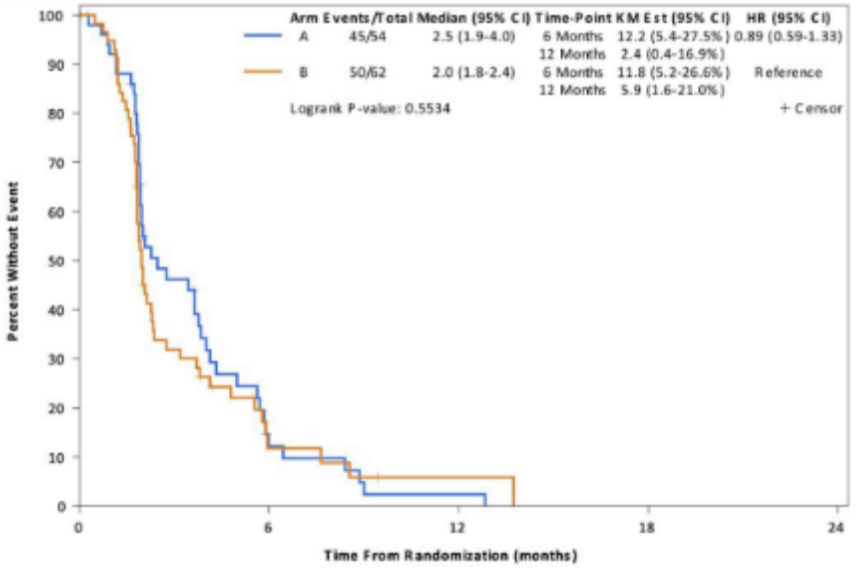
OVERALL SURVIVAL



PROGRESSION-FREE SURVIVAL



	ESCALATING DOSE N=54	STANDARD DOSE N=62	HR (95% CI)	P value
Median OS, months	9.0	5.9	0.65 (0.39-1.08)	0.094
Median PFS, months	2.5	2.0	0.89 (0.59-1.33)	0.553

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Bekaii-Saab et al. ASCO GI Symposium 2018
CI, confidence interval; Est, estimate; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

RE-ARRANGE TRIAL: STUDY DESIGN (ONGOING) (ACCRUAL COMPLETED)

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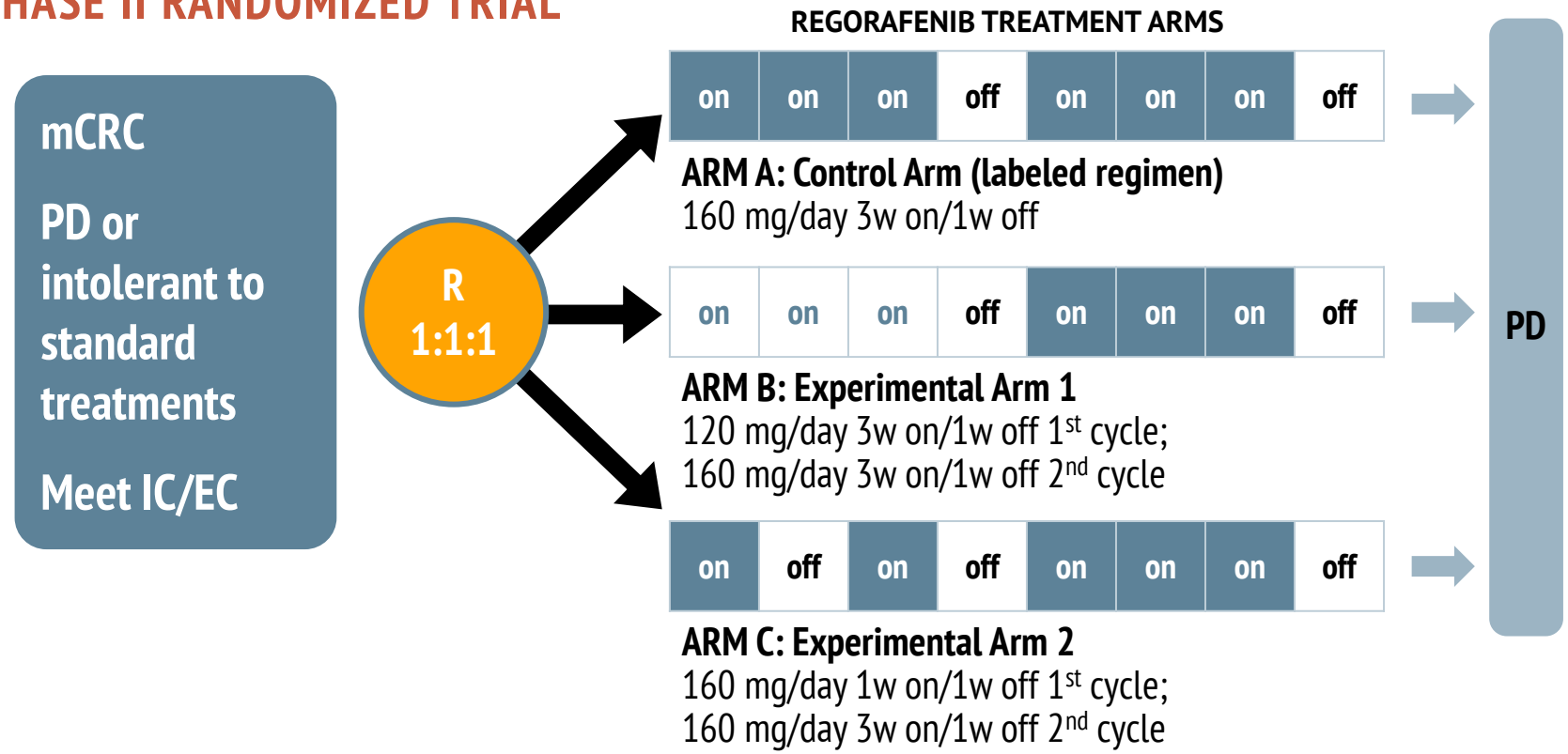
PHASE II RANDOMIZED TRIAL



1ary endpoint: % of pts with G3/4 treatment-related AEs in each arm, according to CTCAE v4.03 criteria.
2ary endpoints: OS, PFS, TTF, DCR, dose intensity and drug administration.

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clinicaltrials.gov/ct2/show/NCT02835924
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; IC/EC, inclusion/eligibility criteria; mCRC, metastatic colorectal cancer; OS, overall survival; PD, progressive disease; TTF, time to treatment failure

REGORAFENIB FLEXIBLE DOSING?

- To improve compliance to the treatment
- To reduce the incidence of adverse events
- To preserve patients' quality of life in a palliative setting

...without impairing treatment efficacy

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WHICH IS THE BEST OPTION NOW?

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PHASE III OPTIONS

NEW OPTIONS ON THE HORIZON...

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TOWARDS POSITIVE PREDICTORS OF BENEFIT: CHECKPOINT INHIBITORS IN MSI-HIGH mCRC

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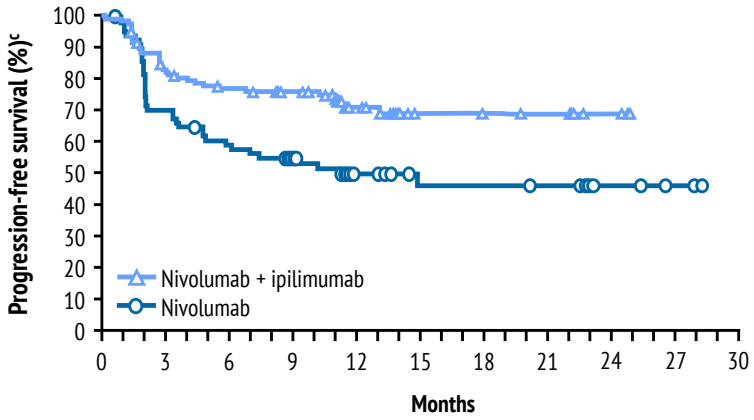
Nivolumab +/- Ipilimumab

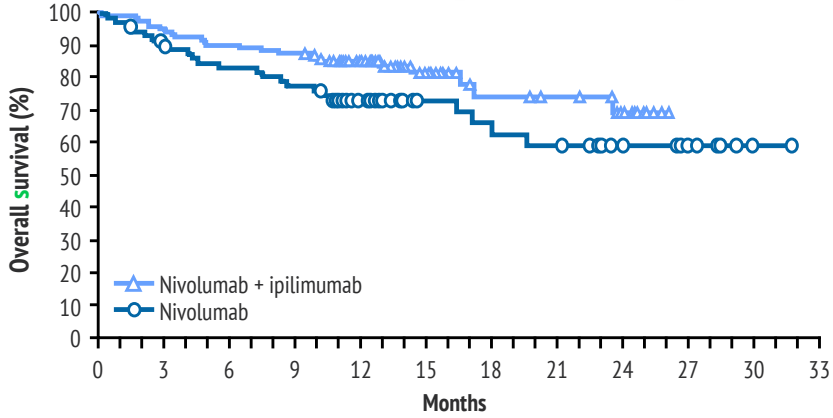
Objective Response Rate:
Nivo: 31%
Nivo + Ipi: 55%

	Nivolumab + ipilimumab	Nivolumab
9-mo rate (95% CI), %	76 (67.0, 82.7)	54 (41.5, 64.5)
12-mo rate (95% CI), %	71 (61.4, 78.7)	50 (38.1, 61.4)



No. at Risk											
Nivolumab + ipilimumab	119	95	86	78	39	12	11	10	3	0	0
Nivolumab	74	48	41	32	17	12	12	11	6	3	0

	Nivolumab + ipilimumab	Nivolumab
9-mo rate (95% CI), %	87 (80.0, 92.2)	78 (66.2, 85.7)
12-mo rate (95% CI), %	85 (77.0, 90.2)	73 (61.5, 82.1)



Nivolumab + ipilimumab	119	113	107	104	78	33	19	17	11	0	0	0
Nivolumab	74	64	59	55	37	21	19	17	11	6	1	0

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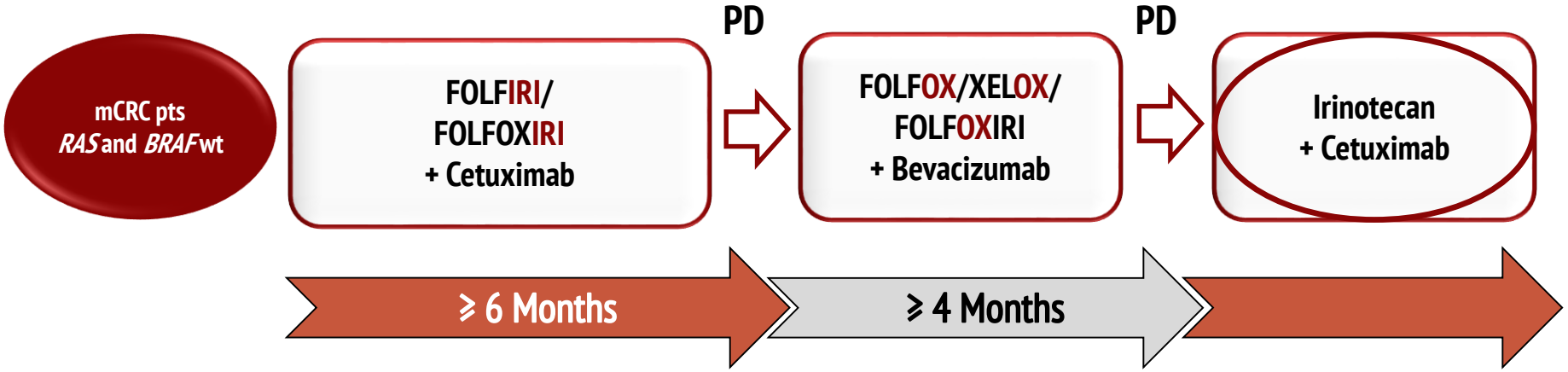
Andre et al. ASCO GI Symposium 2018; Overman et al. ASCO GI Symposium 2018, J Clin Oncol 2018, and Lancet Oncol 2017
CI, confidence interval; Ipi, ipilimumab; MSI-high mCRC, microsatellite instability-high metastatic colorectal cancer; Nivo, nivolumab

RECHALLENGE WITH ANTI-EGFRS THERAPY: CRICKET STUDY

Phase II single-arm study of rechallenge with cetuximab + irinotecan as 3rd-line therapy in *RAS* and *BRAF* wt pts with acquired resistance to 1st-line cetuximab and irinotecan-containing therapy



Statistics: Primary endpoint: Overall Response Rate

H0: RR=5%; H1: RR=20%

Alpha-error: 0.05; Beta-error: 0.20

Sample size: 27 patients

At least 4 responses to deem the rechallenge strategy promising

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Rossini et al. ASCO Annual Meeting 2018

BRAF, rapidly accelerated fibrosarcoma isoform B; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin and irinotecan; H0, null hypothesis; H1, alternative hypothesis; mCRC, metastatic colorectal cancer; pts, patients; RAS, rat sarcoma; RR, rejection rate; XELOX, capecitabine plus oxaliplatin; wt, wild type

CRICKET: PRIMARY ENDPOINT – RESPONSE RATE

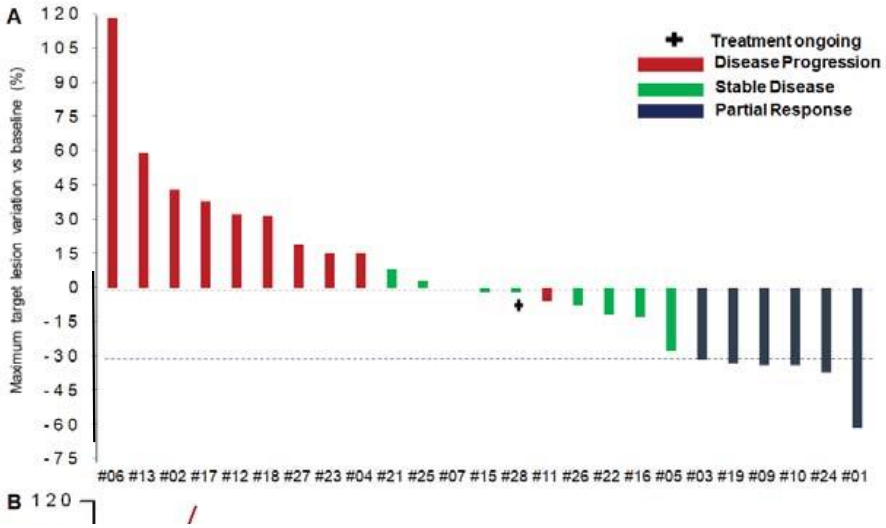
	Study population N=28 No (%) [95% CI]
Partial response	6 (21.5%)
• Confirmed Partial Response	4 (14.3%)
• Unconfirmed Partial Response	2 (7.1%)
Stable disease	9 (32.1%)
Progressive disease	13 (46.4%)
• Radiological PD	10 (35.7%)
• Clinical PD	3 (10.7%)
Response Rate	6 (21.5%) [10-40%]
Disease Control Rate	15 (53.6%) [36-70%]

All reported in patients with *RAS* wt cfDNA at baseline

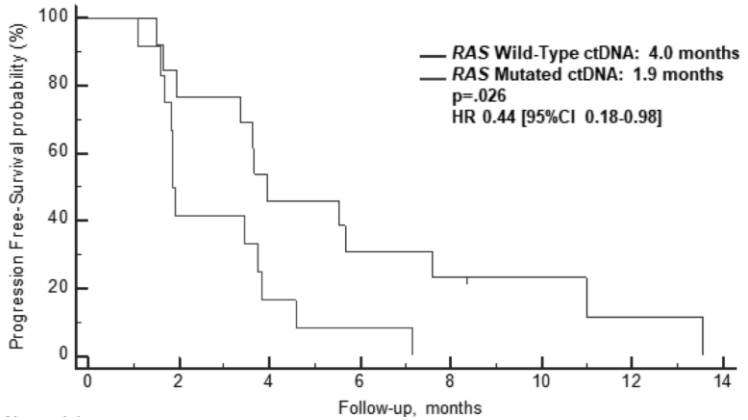
Rossini et al. ASCO Annual Meeting 2018

cfDNA, circulating free DNA; CI, confidence interval; PD, progressive disease; RAS, rat sarcoma; wt, wild type

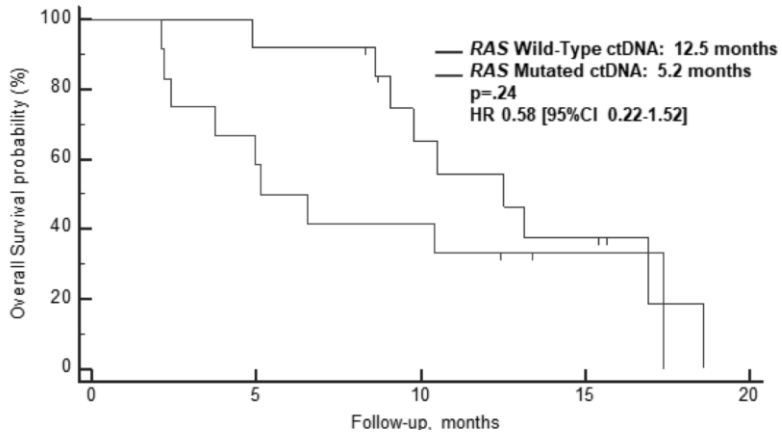
CRICKET: RESULTS ACCORDING TO *RAS* STATUS IN ctDNA



PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



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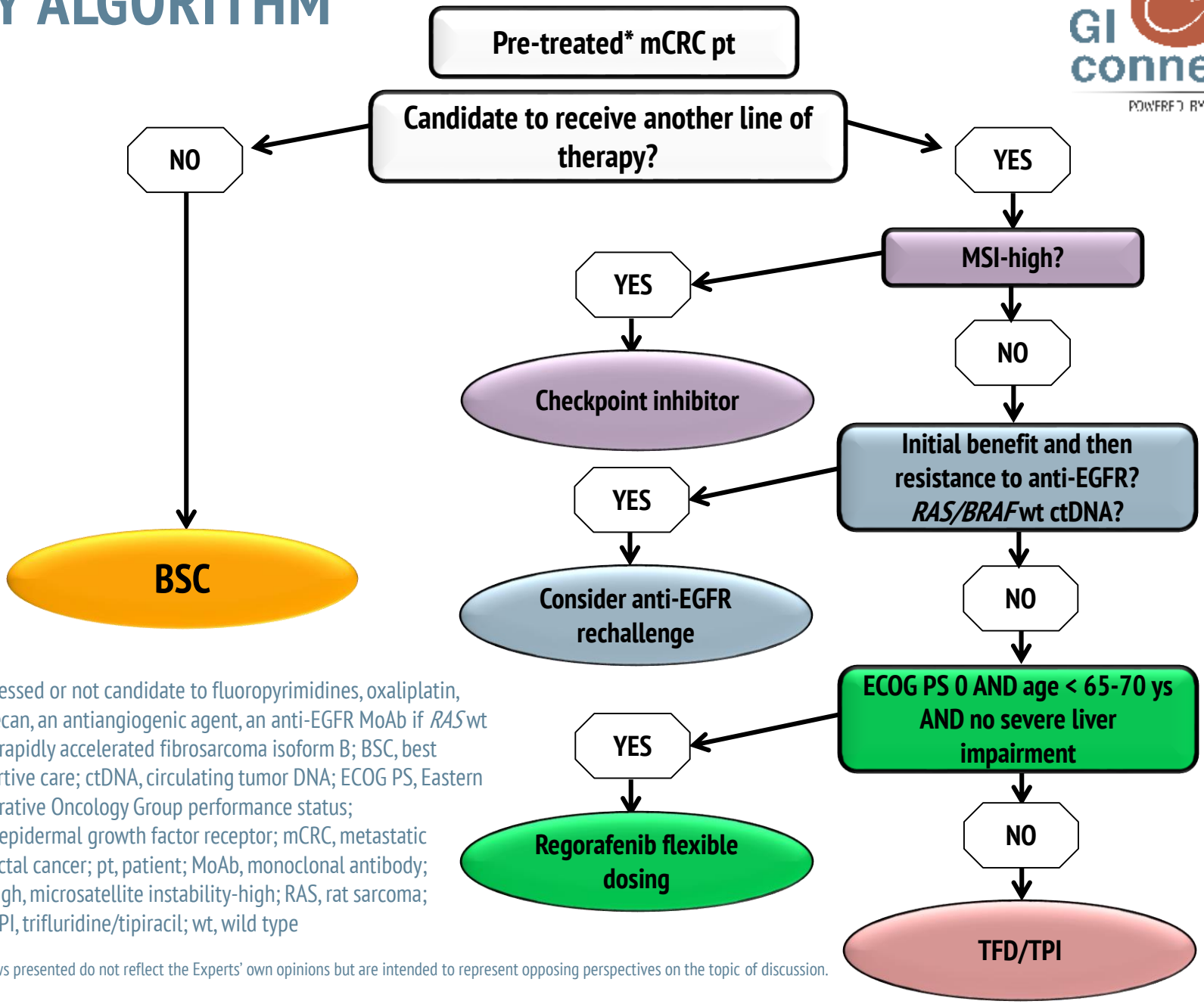
Rossini et al. ASCO Annual Meeting 2018

ctDNA, circulating tumor DNA; CI, confidence interval; HR, hazard ratio; RAS, rat sarcoma; wt, wild type

MY ALGORITHM



*Progressed or not candidate to fluoropyrimidines, oxaliplatin, irinotecan, an antiangiogenic agent, an anti-EGFR MoAb if *RAS* wt BRAF, rapidly accelerated fibrosarcoma isoform B; BSC, best supportive care; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; pt, patient; MoAb, monoclonal antibody; MSI-high, microsatellite instability-high; RAS, rat sarcoma; TFD/TPI, trifluridine/tipiracil; wt, wild type

THE ARGUMENT FOR TREATMENT SEQUENCING AND FLEXIBLE DOSING IN LATER-LINE MANAGEMENT OF COLORECTAL CANCER

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DISCLAIMER

Please note:

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion

Disclosures:

- Dr. Gerald Prager has received financial support/sponsorship for research support, consultation or speaker fees from the following companies: Roche, Halozyme, Merck Serono, MSD, Amgen, Bayer, Servier, Taiho, Shire, Celgene, Sanofi, Lilly

3RD LINE SETTING

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The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

3RD LINE TREATMENT IN mCRC:

AFTER FAILURE OF FLUOROPYRIMIDINE, OXALIPLATIN, IRINOTECAN, ANTI-VEGF AND ANTI-EGFR THERAPY (IF RAS WT)

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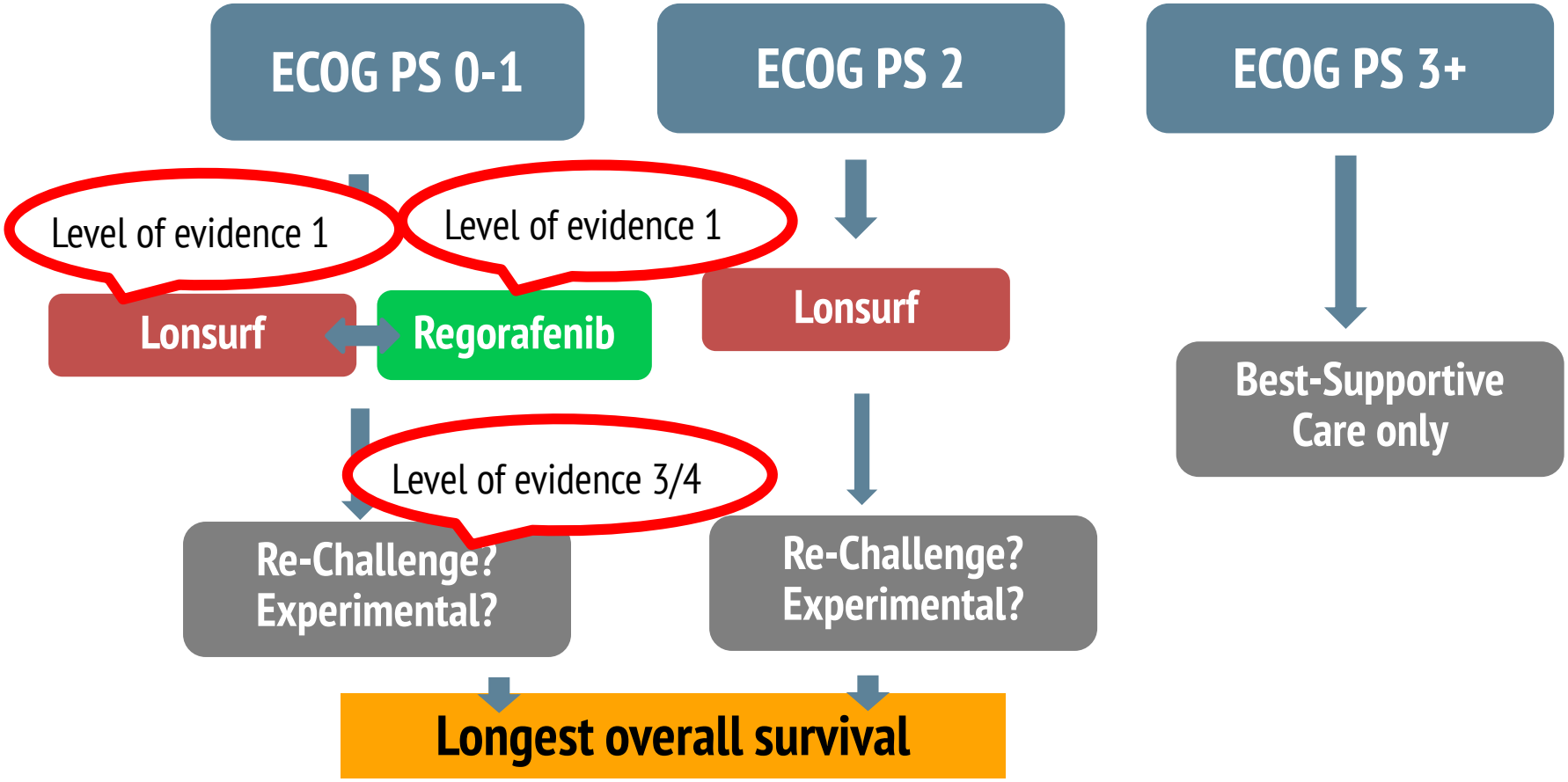

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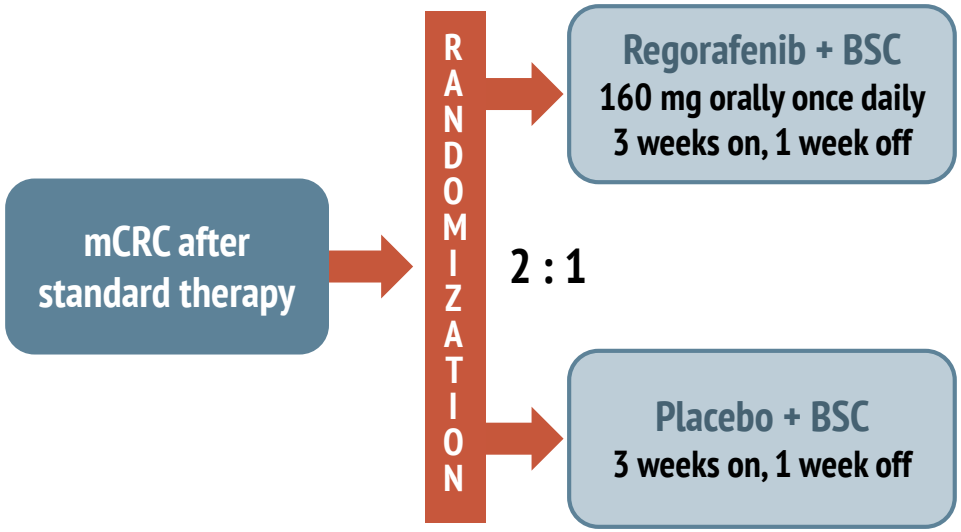
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; RAS, rat sarcoma; VEGF, vascular endothelial growth factor; WT, wild type

REGORAFENIB STUDY DESIGNS

CORRECT[1] and CONCUR[2] Phase III Trials



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - 2:1 randomization
- Trial populations
  - CORRECT
    - Global
    - Japan and China but outside of Asia
  - CONCUR—Asia

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BSC, best supportive care; mCRC, metastatic colorectal cancer

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

REGORAFENIB SIGNIFICANTLY IMPROVED OS VS PLACEBO IN TWO PHASE 3 RCTS

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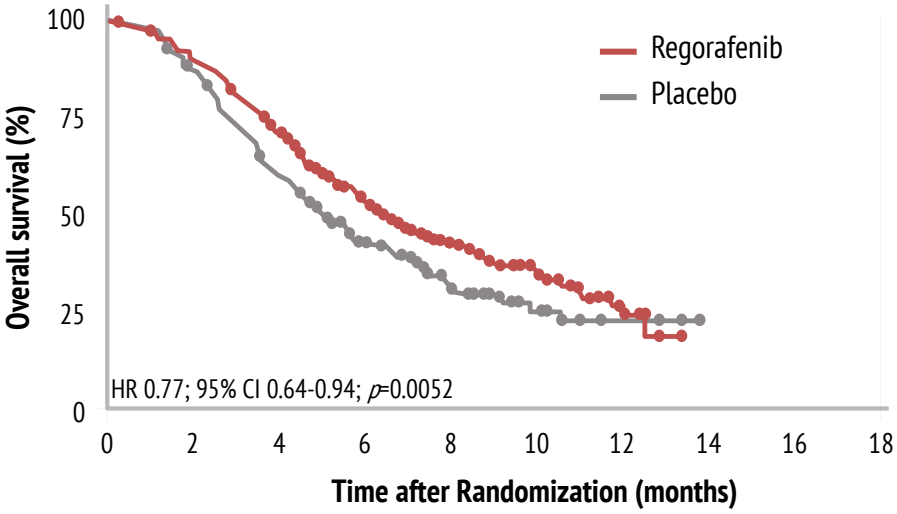
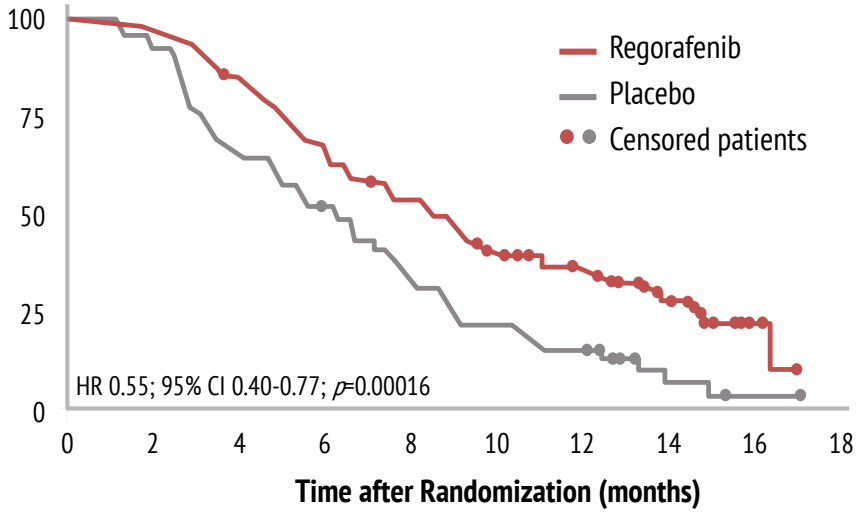
CORRECT[1]



Median OS
Regorafenib: 6.4 months
Placebo: 5.0 months

CONCUR[2]



Median OS
Regorafenib: 8.8 months
Placebo: 6.3 months

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

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

GOOD ECOG PS MAY BE ASSOCIATED WITH INCREASED CLINICAL BENEFIT OF REGORAFENIB: POST-MARKETING SURVEILLANCE IN JAPAN

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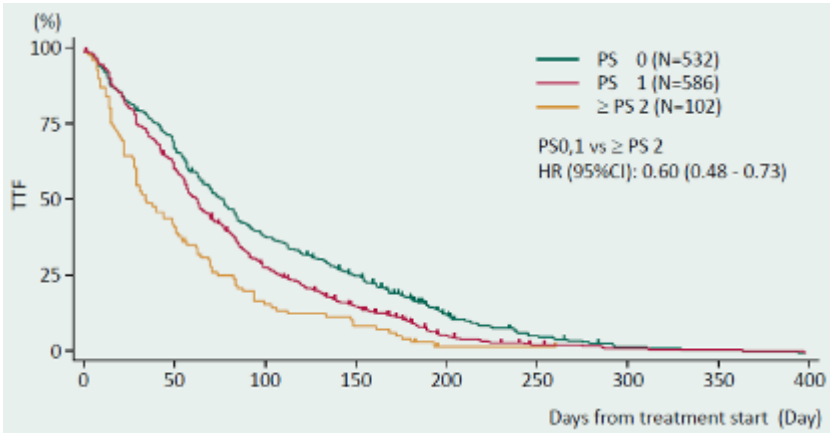
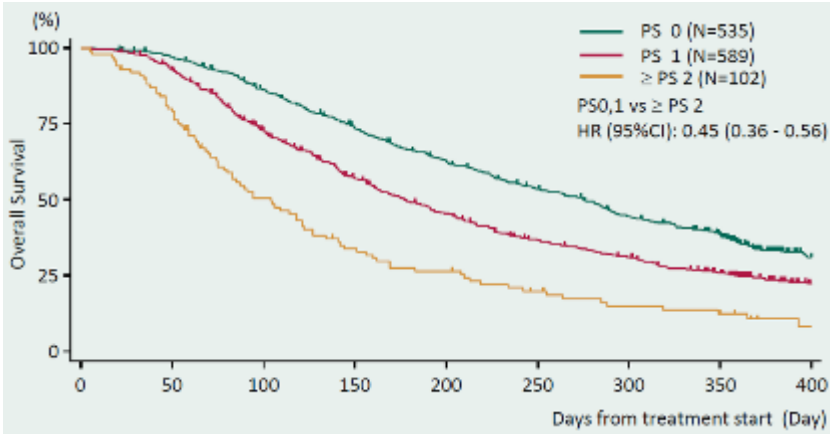
POWERED BY COR2ED

TTF



OS



PS	Median TTF (95% CI), months	Median OS (95% CI), months
0	2.6 (2.3–2.8)	9.1 (8.1–9.6)
1	2.1 (1.9–2.3)	5.8 (5.3–6.5)
⩾2	1.2 (1.0–1.7)	3.4 (2.6–4.0)

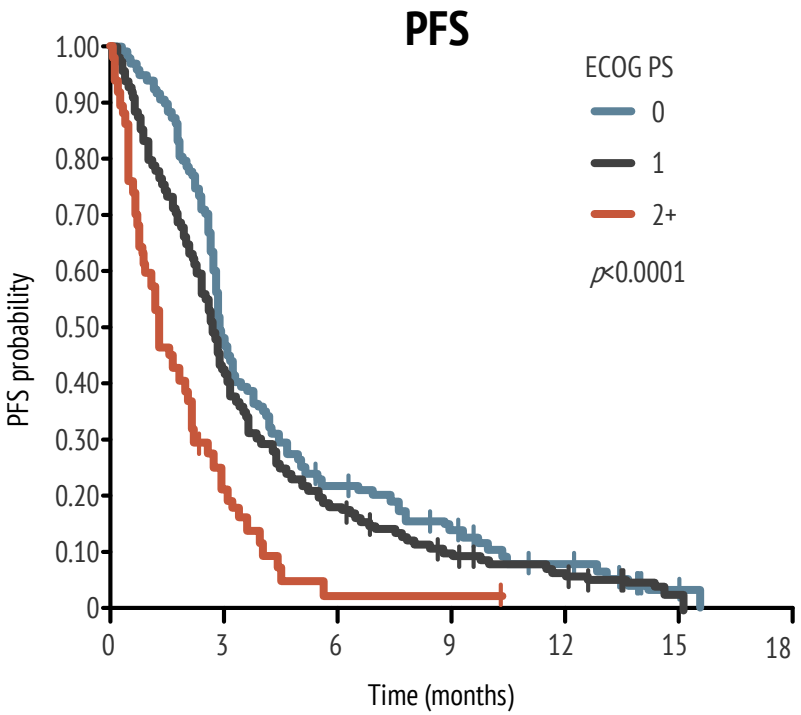
The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

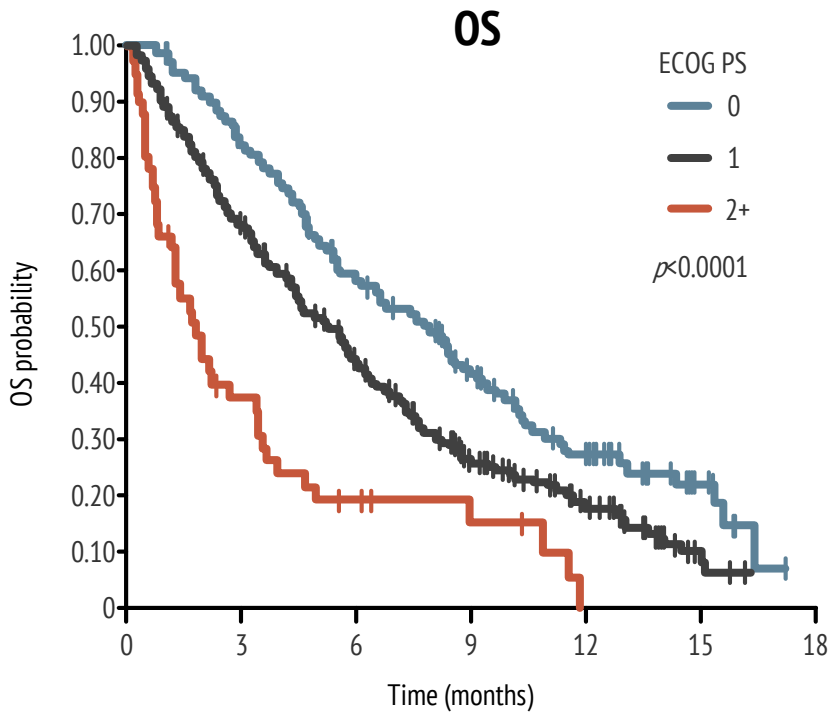
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PS, performance status; TTF, time to treatment failure

Komatsu Y, et al. Presented at ASCO-GI 2017, poster 721

WHO IS THE RIGHT CANDIDATE FOR REGORAFENIB?

REBECCA COHORT STUDY: GOOD ECOG PS IS ASSOCIATED WITH INCREASED CLINICAL BENEFIT OF REGORAFENIB





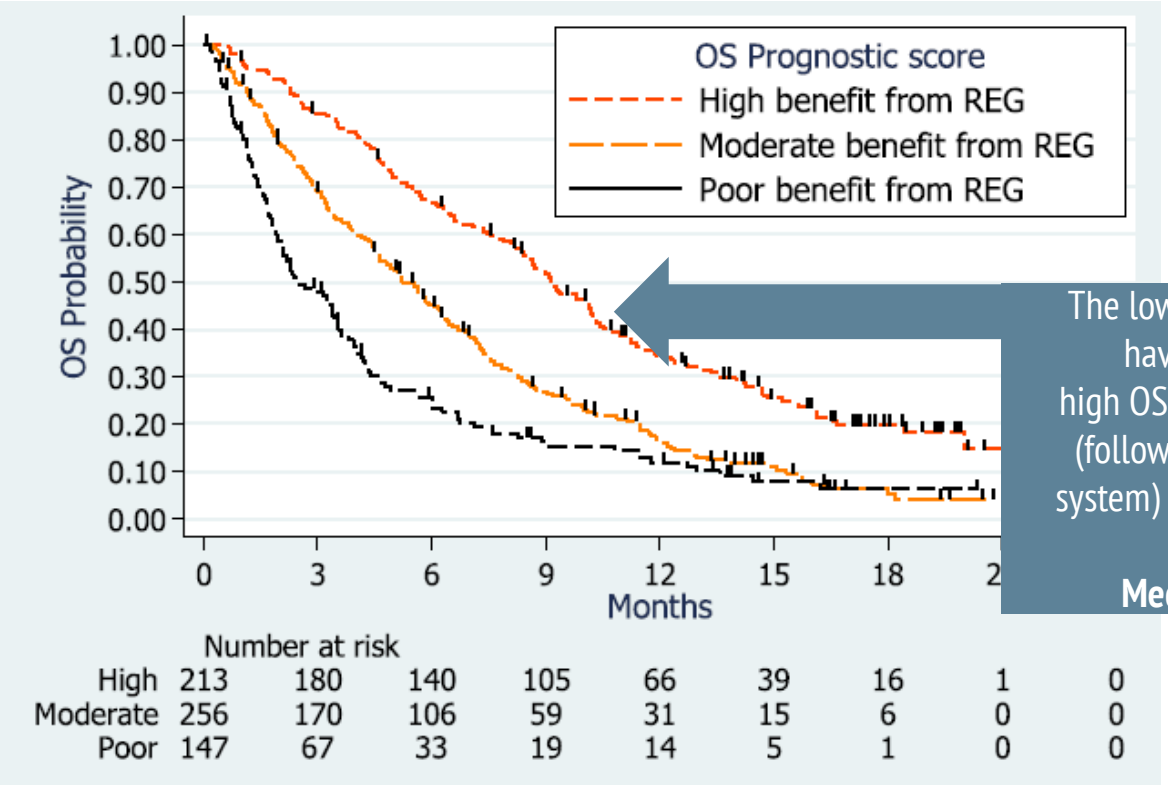
Patients with ECOG PS ⩾2 had a worse prognosis than those with ECOG PS 0–1

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival

Tougeron D, et al. Presented at ESMO 2014, poster 6220

REBECCA: PATIENTS WITH LOW RISK OF DEATH AT THE BEGINNING OF THERAPY EXPERIENCED THE BEST CLINICAL OUTCOMES



The low-risk group identified as having the potential for high OS benefit from regorafenib (following a prognostic scoring system) achieved the best clinical results:
Median OS: 9.2 months

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OS, overall survival; REG, regorafenib
Adenis A, et al. BMC Cancer 2016;16:412

CORRECT: KEY CHARACTERISTICS ARE LINKED WITH LONG-TERM PFS

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	All Patients (N=505; 100%)	Long PFS* (n=98; 19.4%)
Median age, years (range)	61 (54-67)	61 (34–82)
ECOG PS, %		
0	52	63
1	48	37
Primary tumour, %		
Colon	64	52
Rectum	30	37
Tumour metastatic sites, %		
1	19	30
2	36	38
3	27	16
KRAS status, %		
Mutant	54	47
Wild type	41	44
Time from diagnosis of metastatic disease, %		
<18 months	18	11
≥18 months	82	89
Mean treatment duration, months	2.8±2.3†	6.3±2.0
Mean planned dose, % ± SD	78.9±19.9	81.4±16.3
Mean daily dose, mg ± SD	147.1±18.6	138.7±22.0
Treatment modifications, % patients	76	91

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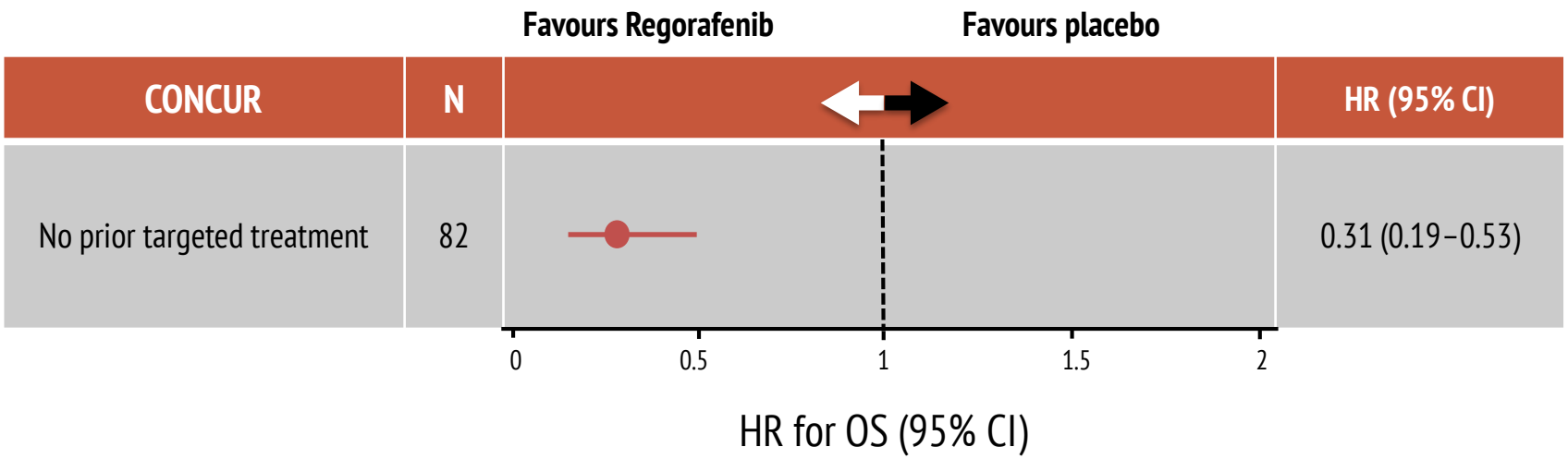
ECOG PS, Eastern Cooperative Oncology Group performance status; KRAS, Kirsten RAS oncogene homolog; PFS, progression-free survival; SD, standard deviation
*Long-PFS: >4 months; median of 6 cycles regorafenib, 92% ≥5 cycles, and 20% >8 cycles; †Treated patients (n=500).
Grothey A, et al. Presented at ASCO-GI 2015, poster 710; Grothey A, et al. Lancet 2013;381:303–312

EARLY USE OF REGORAFENIB IN THE TREATMENT SEQUENCE MAY IMPROVE CLINICAL BENEFIT



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CI, confidence interval; HR, hazard ratio; OS, overall survival
Li J, et al. Lancet Oncol 2015;16:619–29

EARLY USE OF REGORAFENIB IN THE TREATMENT SEQUENCE MAY IMPROVE CLINICAL BENEFIT

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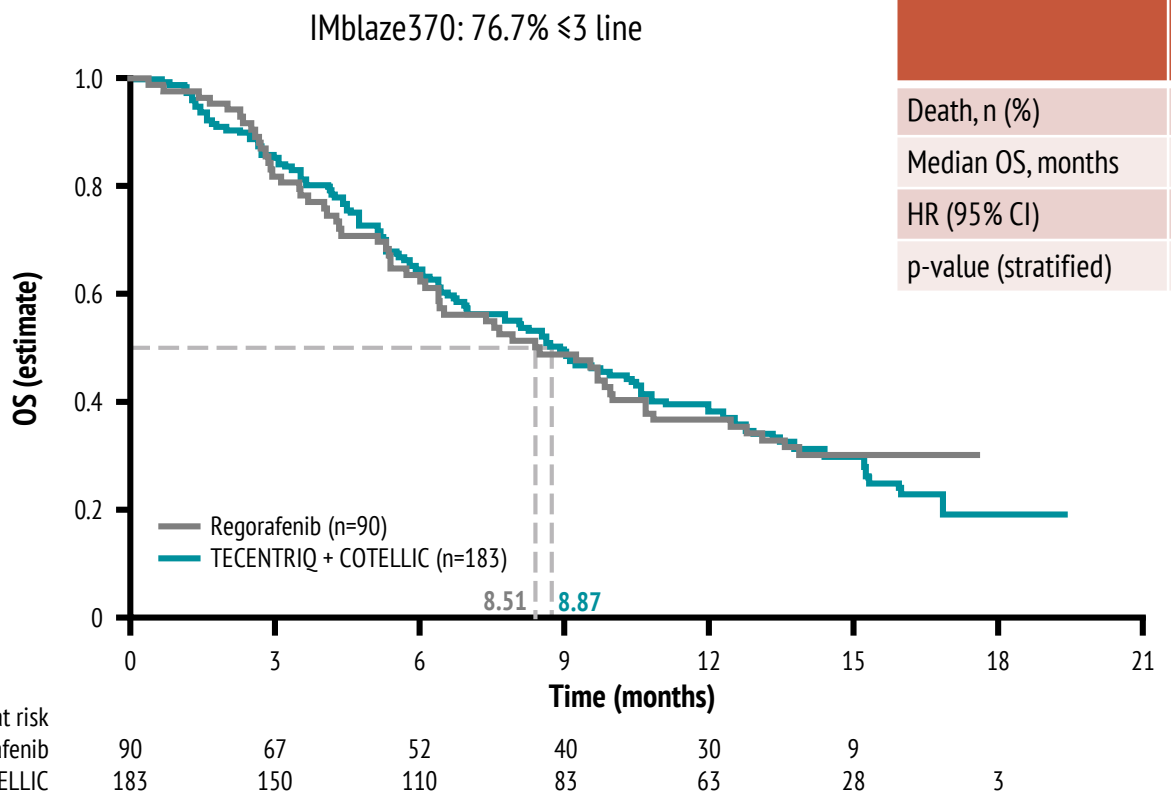
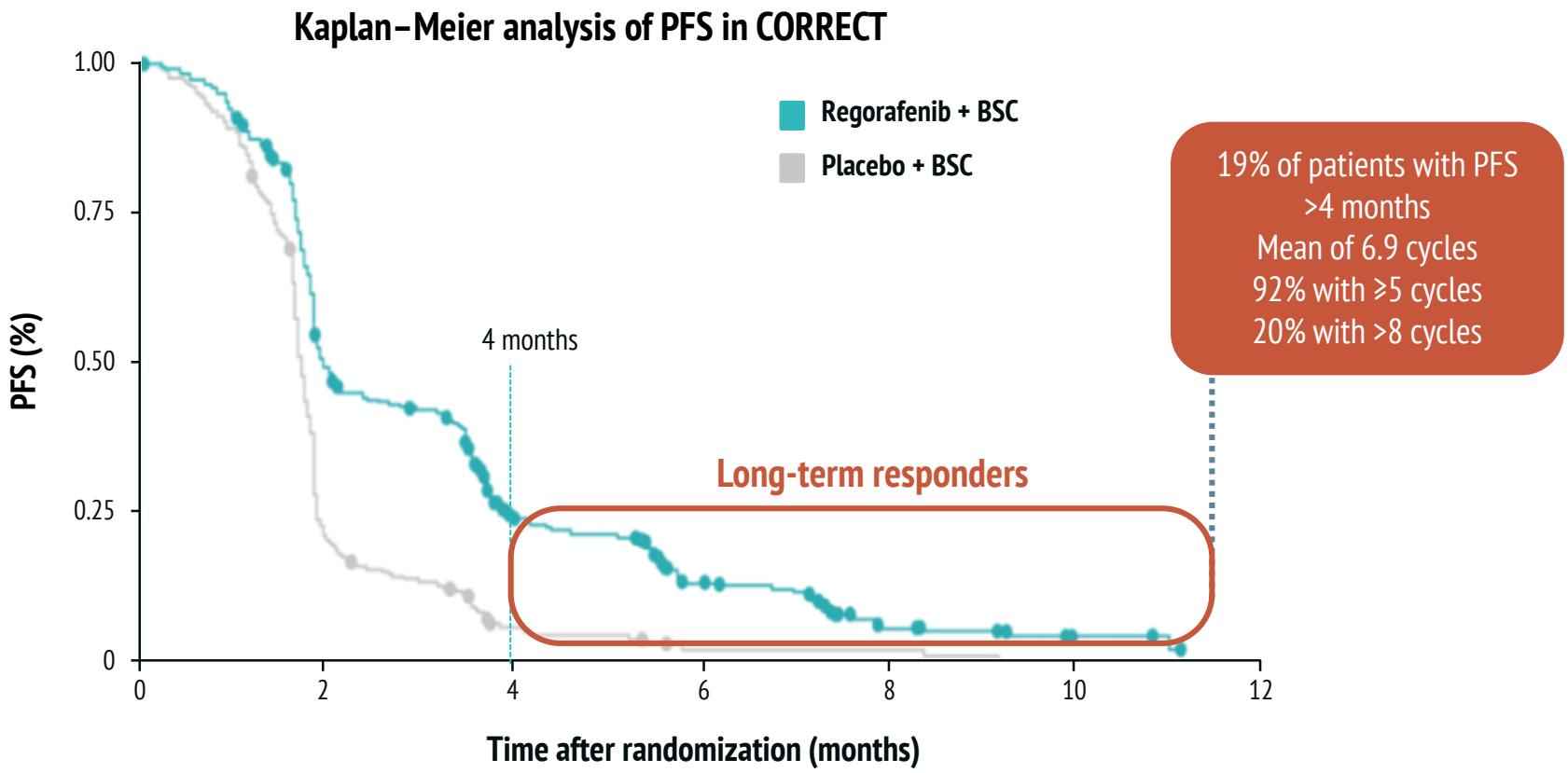


	Regorafenib (n=90)	TECENTRIQ + COTELLIC (n=183)
Death, n (%)	57 (63.33)	125 (68.31)
Median OS, months	8.51	8.87
HR (95% CI)	1.00 (0.73–1.38)	
p-value (stratified)	0.9871	

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

Bendell J, et al. Efficacy and safety results from IMblaze370, Annals of Oncology 2018; Volume 29, Issue suppl_5.

THERE IS A POPULATION OF LONG-TERM RESPONDERS TO REGORAFENIB



The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

BSC, best supportive care; PFS, progression-free survival

Grothey A, et al. Lancet 2013;381:303–12
Grothey A, et al. Presented at ASCO-GI 2015, poster 710

LONG-TERM RESPONDERS HAVE ALSO BEEN OBSERVED IN OTHER REGORAFENIB CLINICAL TRIALS

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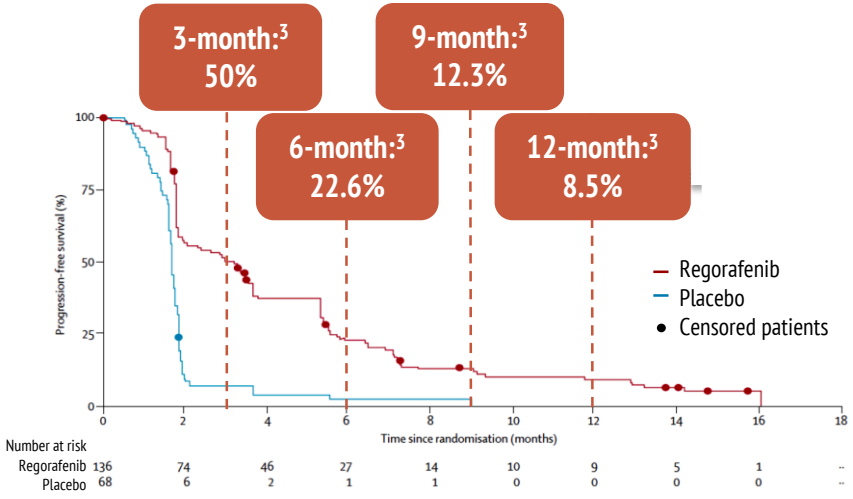
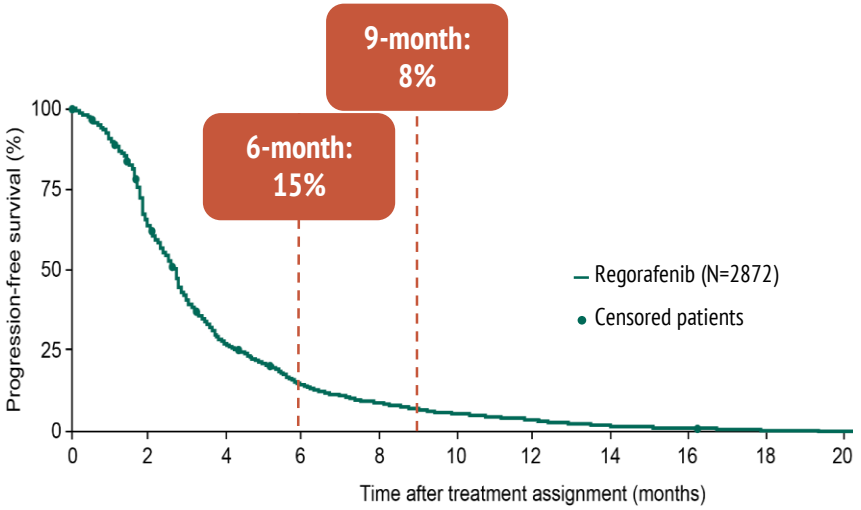
CONCUR: PFS[1]



Median PFS: 3.2 vs 1.7 months
HR 0.31 (95% CI 0.22–0.44)
***p*<0.0001**

CONSIGN: PFS[2]



Median PFS: 2.7 months

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

1. Li J, et al. Lancet Oncol 2015;16:619–29; 2. Van Cutsem E, et al. Presented at ECC 2015, abstract 2139; 3. Data on file

SIMILAR SAFETY PROFILE IN LONG-TERM RESPONDER GROUP VS OVERALL CORRECT COHORT

	PFS >4 months, % (n=98)		Overall CORRECT population, % (n=500)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	100	82	100	78
Diarrhoea	66	17	43	8
HFSR	63	20	47	17
Weight loss	48	2	32	<1
Hypertension	42	17	30	8

Compared with the overall CORRECT cohort, the long-term response group had:

A broadly similar safety profile although some AEs were more common (possibly related to the longer duration of treatment)

Higher incidence of all-grade diarrhoea, HFSR, and weight loss

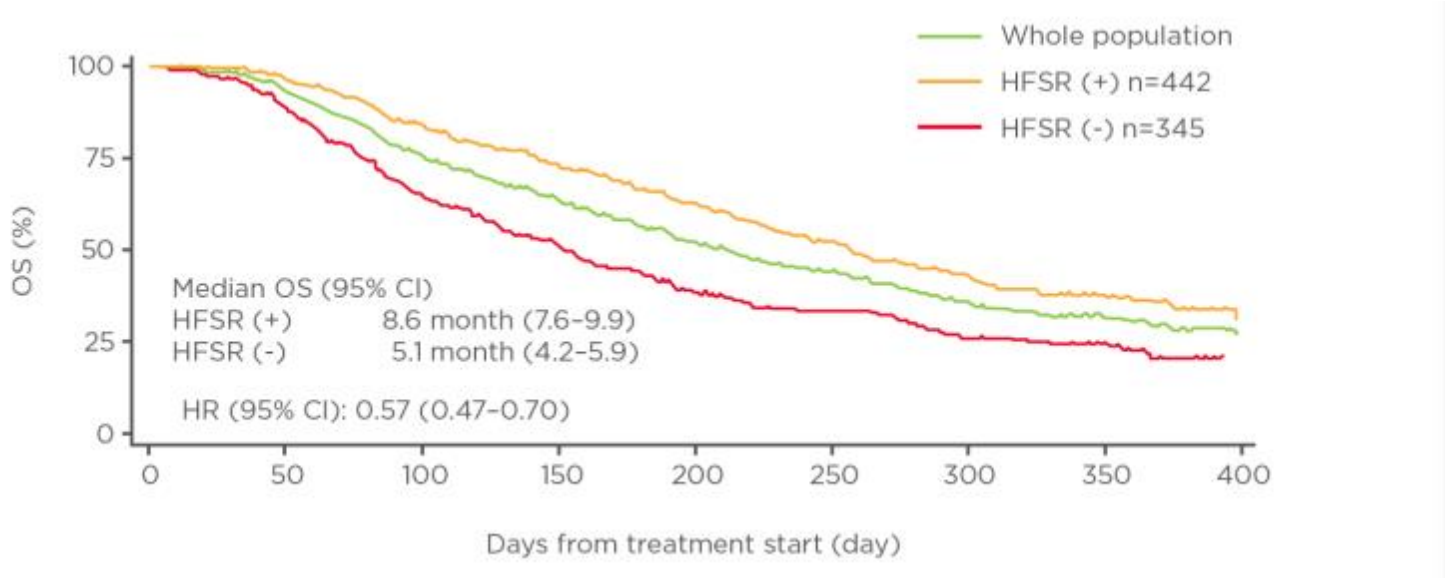
Higher incidence of grade ≥3 diarrhoea and hypertension vs the overall population

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

AE, adverse event; HFSR, hand-foot skin reaction; PFS, progression-free survival.

Grothey A, et al. Presented at ASCO-GI 2015, poster 710

HAND-FOOT SKIN REACTION (HFSR) AND OUTCOMES IN THE USA SUBGROUP OF THE PHASE IIIB CONSIGN STUDY OF REGORAFENIB FOR METASTATIC COLORECTAL CANCER (mCRC)

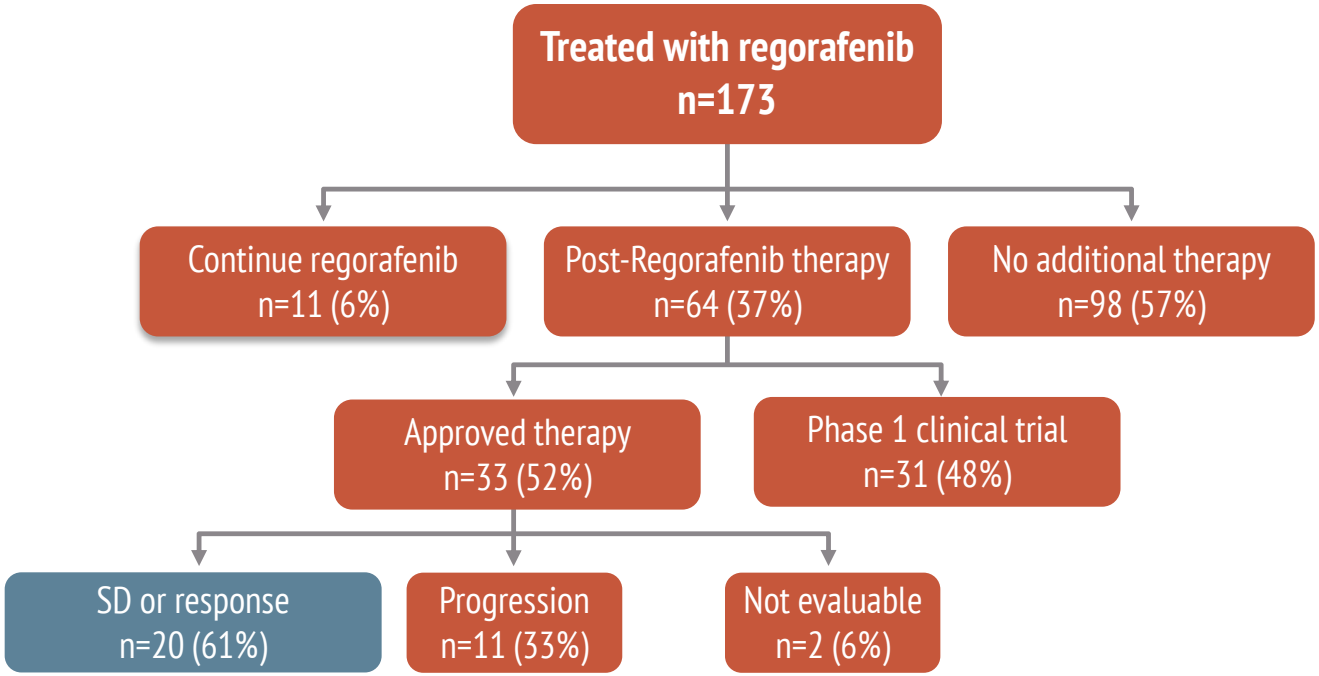


Interim analysis of overall survival stratified by the presence of any grade of HFSR.

CI, confidence interval; HFSR, hand-foot skin reaction; HR, hazard ratio; OS, overall survival

Van Cutsem E, et al. Oncologist 2018 [Epub ahead of print]

RECHALLENGING WITH STANDARD TREATMENT OPTIONS AFTER REGORAFENIB MAY BE BENEFICIAL IN SELECT PATIENTS WITH mCRC



The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

mCRC, metastatic colorectal cancer; SD, stable disease
Response and progression were determined by investigator review.
Kidd MT, et al. Presented at ASCO-GI 2015, abstract 678

STANDARD LINES OF SYSTEMIC TREATMENT

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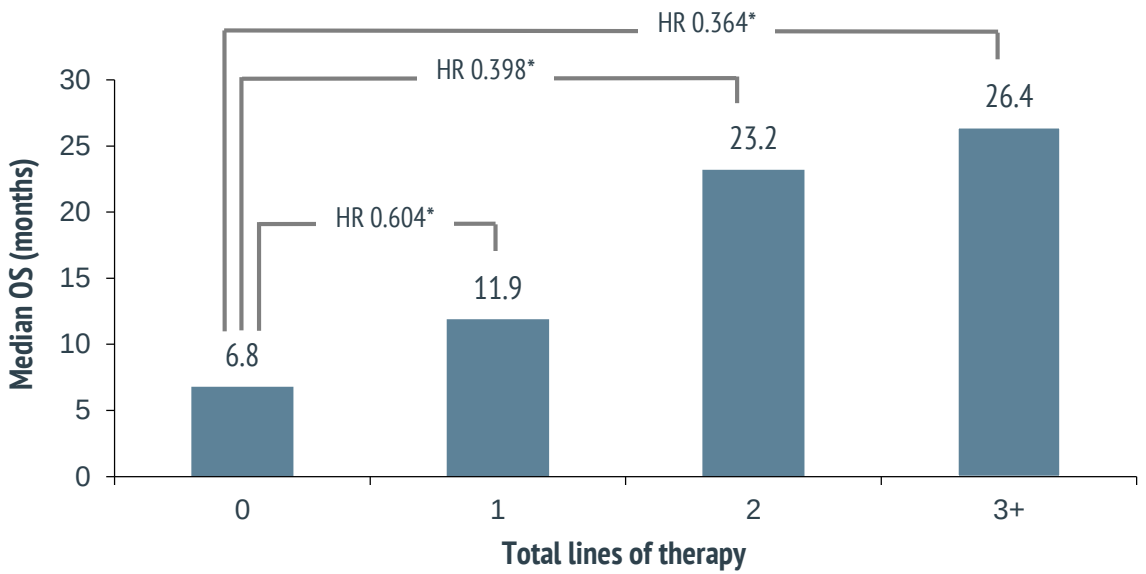
mCRC → 1 → 2 → 3

Different agents are given sequentially and switched because of disease progression, unacceptable toxicity, or patient choice

Evidence from the **SEER database** suggests survival increases in patients who are exposed to multiple treatment options



The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results Program
SEER Medicare Database Analysis for mCRC (2003–2007; N=5129; *p<0.001); Hanna N, et al. J Clin Oncol 2014;32(Suppl 3): abstract 559.

NCCN AND ESMO GUIDELINE RECOMMENDATIONS 3RD-LINE CRC:

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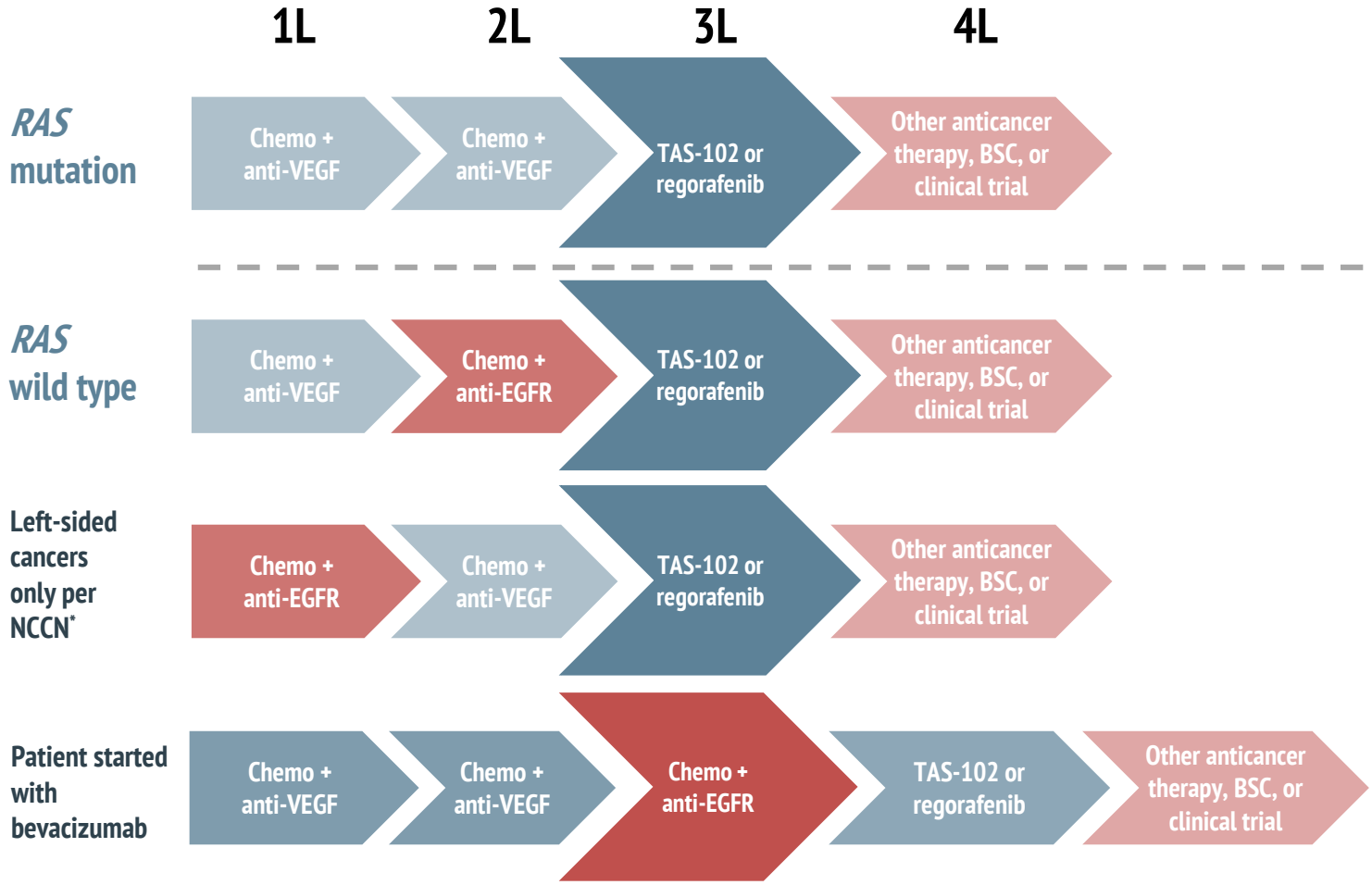

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BSC, best supportive care; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; RAS, rat sarcoma; VEGF, vascular endothelial growth factor

*Only patients whose tumours originated on the left side of the colon should be offered EGFR inhibitors in the first line. Patients with RAS wild-type tumours can be considered for cetuximab or panitumumab in subsequent lines if neither was previously given.

Adapted from NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. V4.2018; NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. V3.2018

NCCN GUIDELINES EXCLUDE THE OPTION OF RECHALLENGING WITH ANTI-EGFR ANTIBODIES

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The NCCN guidelines: EGFR inhibitors are only recommended **if they have not been given previously**

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BSC, best supportive care; EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; VEGF, vascular endothelial growth factor
Adapted from NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. V4.2018; NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. V3.2018

REVERCE TRIAL: CETUXI>REGO VS. REGO>CETUXI

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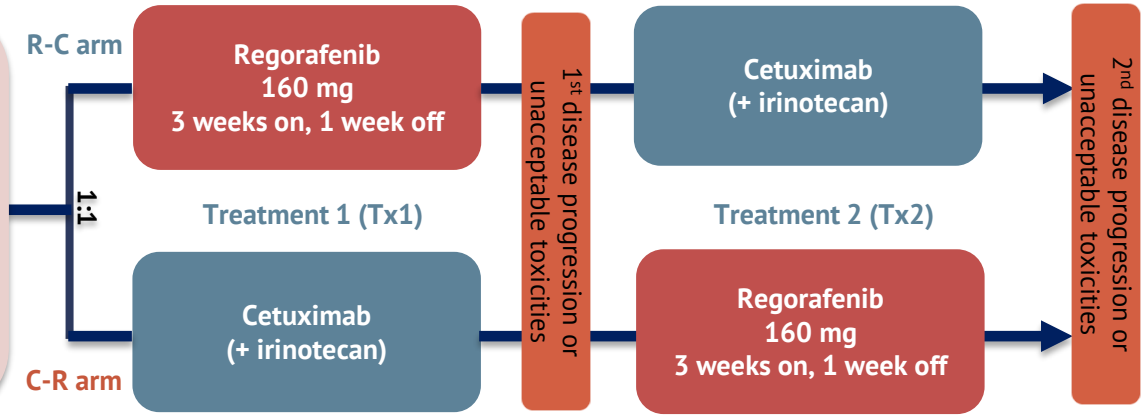
Key patient inclusion criteria
- Metastatic CRC
- Treatment failure with fluoropyrimidine, oxaliplatin, and irinotecan
- Anti-EGFR naive
- *KRAS* exon 2 WT
- Pts with minor *RAS* mutations* are excluded since March 2015

**KRAS* exon 3 (codon 59/61), exon 4 (codon 117/146), *NRAS* exon 2 (codon 12/13), exon 3 (codon 59/61), and exon 4 (codon 117/146)



Stratified by intent to use irinotecan at enrollment, prior history of bevacizumab, and institutions

Cetuximab: 400 mg/m^2 (initial dose), 250 mg/m^2 (subsequent doses) every week with or without irinotecan 150 mg/m^2 (or 120 mg/m^2 at the investigators' discretion) every 2 weeks

Clinical trial identifier UMIN000011294

- Primary endpoint was OS
- Secondary endpoints included PFS1, PFS2, safety, and QOL

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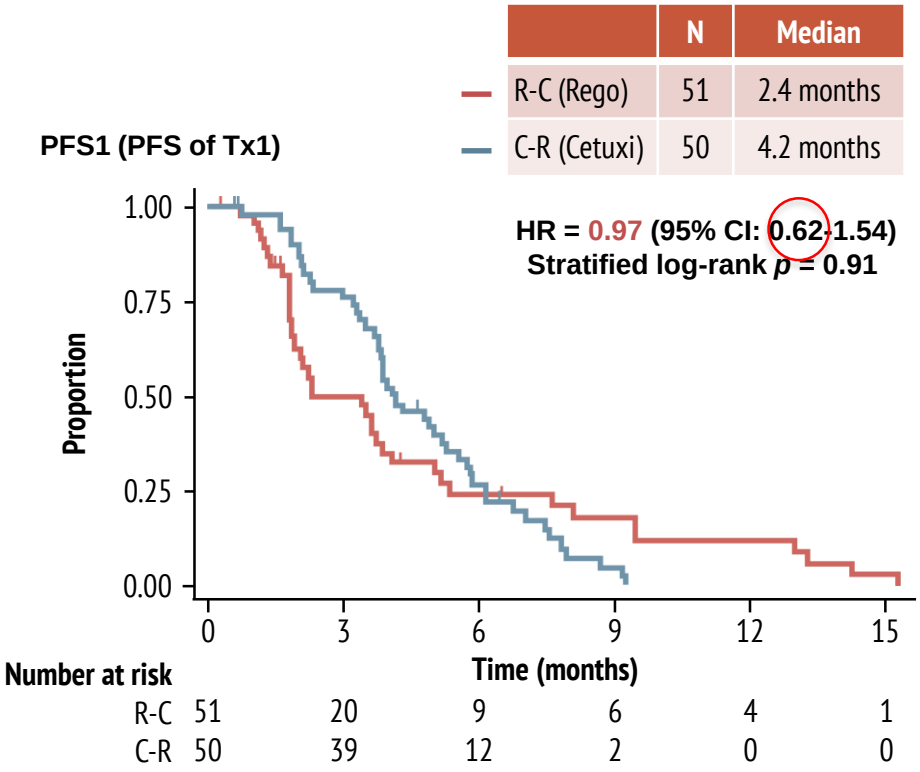
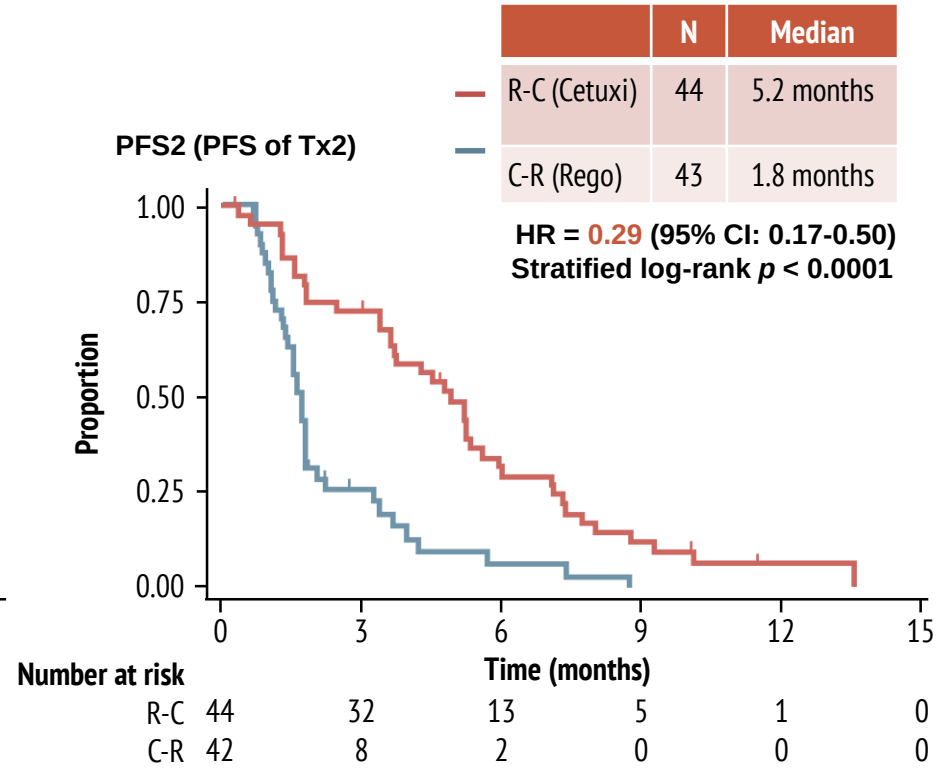
C, cetuximab; CETUXI, cetuximab; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; KRAS, Kirsten RAS oncogene homolog; NRAS, neuroblastoma RAS oncogene homolog; OS, overall survival; PFS, progression-free survival; PFS1, PFS on first treatment; PFS2, PFS on second treatment; Pts, patients; QOL, quality of life; RAS, rat sarcoma; R, regorafenib; REGO, regorafenib; Tx, treatment; WT, wild type

Shitara K, et al. Presented at ASCO 2018, abstract 557; Yoshino T, et al. Presented at WCGIC 2018, poster PD-10

REVERCE TRIAL: CETUXI>REGO VS. REGO>CETUXI

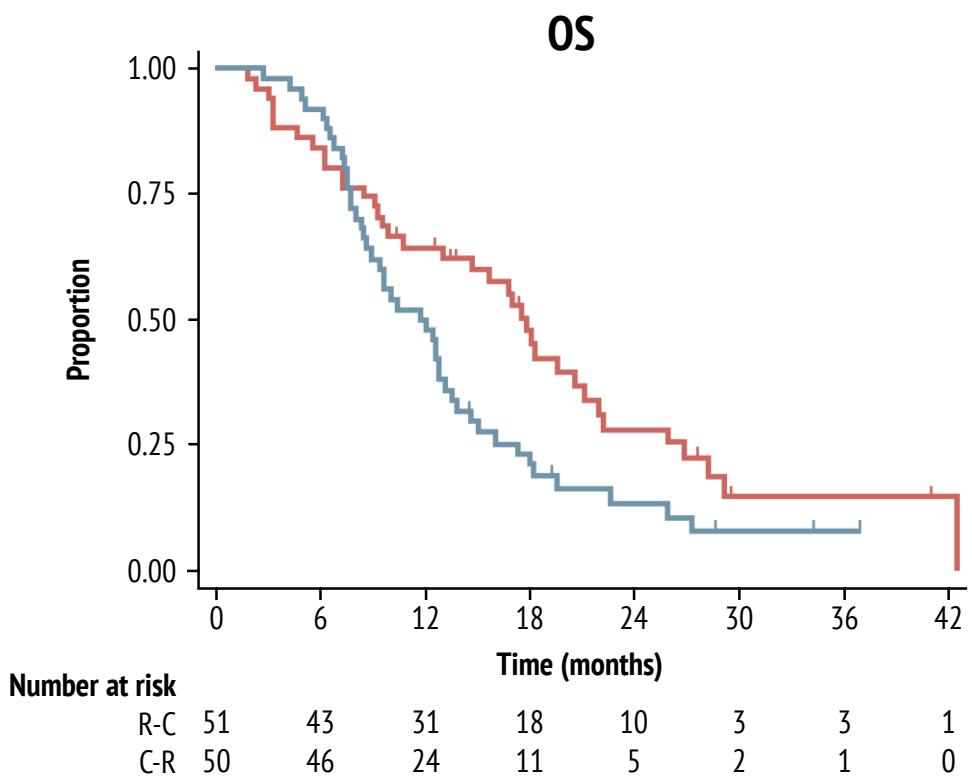




C, cetuximab; Cetuxi, cetuximab; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PFS1, PFS on first treatment; PFS2, PFS on second treatment; R, regorafenib; Rego, regorafenib; Tx, treatment

Shitara K, et al. Presented at ASCO 2018, abstract 557

REVERCE TRIAL: REGO>CETUXI PROVIDED SUPERIOR OS VS. CETUXI>REGO



	N	Median
R-C	51	17.4 months
C-R	50	11.6 months

HR = 0.61 (95%CI: 0.39-0.96)
Stratified log rank *p* = 0.029
Median follow-up: 29.0 months

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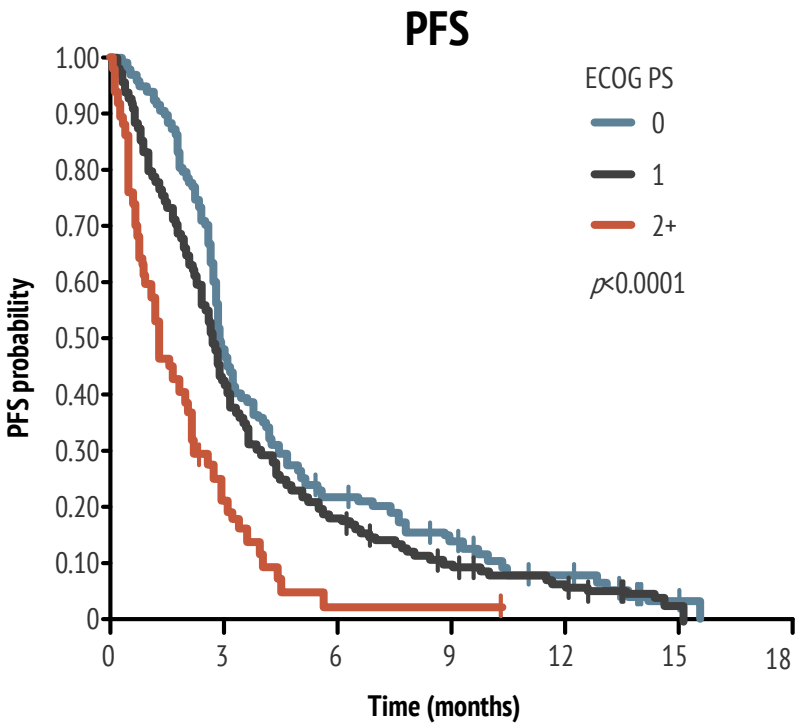
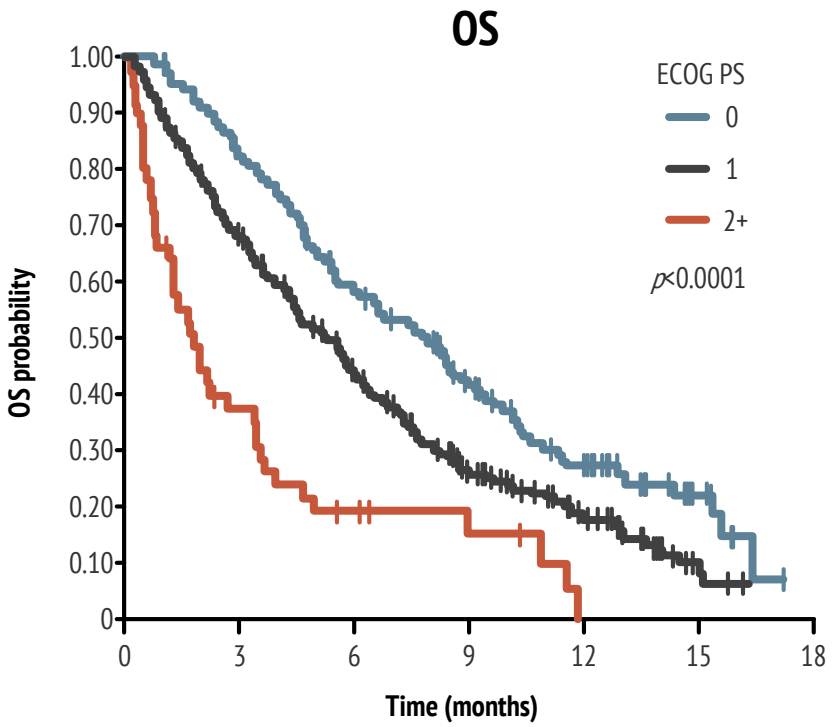
C, cetuximab; CETUXI, cetuximab; CI, confidence interval; HR, hazard ratio; OS, overall survival; R, regorafenib; REGO, regorafenib; Tx, treatment

Shitara K, et al. Presented at ASCO 2018, abstract 557

WHO IS THE RIGHT CANDIDATE FOR REGORAFENIB?

REBECCA COHORT STUDY: GOOD ECOG PS IS ASSOCIATED WITH INCREASED CLINICAL BENEFIT OF REGORAFENIB





Patients with ECOG PS ⩾2 had a worse prognosis than those with ECOG PS 0–1

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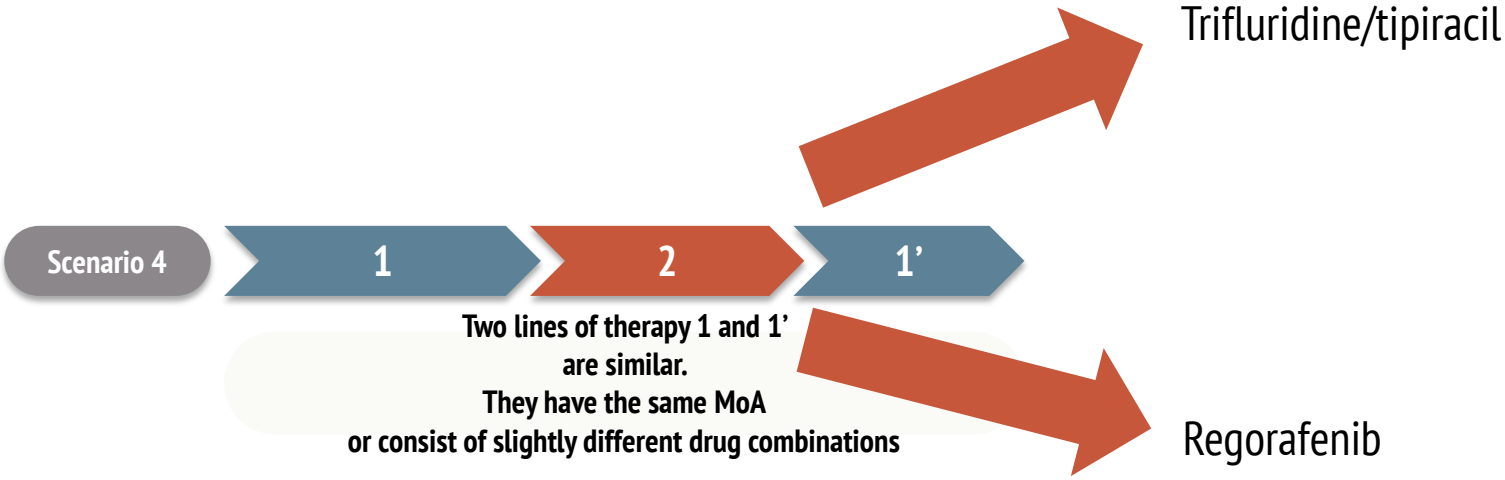
ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival

Tougeron D, et al. Presented at ESMO 2014, poster 6220

WHAT IS THE BEST 3RD-LINE OPTION?



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MoA, mechanism of action

Kuczynski EA, et al. Nat Rev Clin Oncol 2013;10:571–87

COMPARISON PHASE III REGORAFENIB, TAS-102

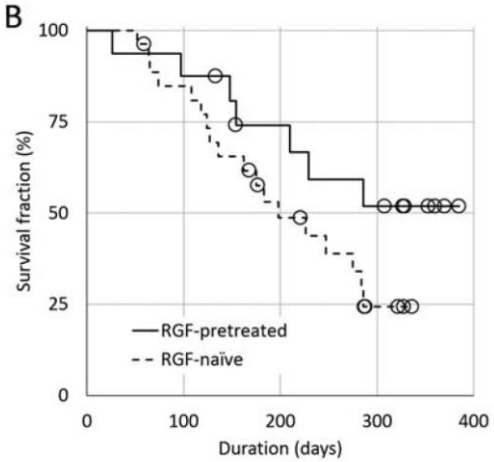
	Regorafenib				TAS-102			
Study	CORRECT		CONCUR		RECOURSE		TERRA	
Prior biologics	100% BEV 100% EGFR mAbs		59%		100% BEV 52% EGFR mAbs		19% BEV 17% EGFR mAbs	
	Rego	**BSC**	**Rego**	**BSC**	**TAS-102**	**BSC**	**TAS-102**	**BSC**
N pts	505	255	136	68	534	266	271	135
Median OS (mos)	6.4	5.0	8.8	6.3	7.1	5.3	7.8	7.1
	HR 0.77 p=0.0052		**HR 0.55** p=0.0002		**HR 0.68** p<0.001		**HR 0.79** P = .035	
Median PFS (mos)	1.9	1.7	3.2	1.7	2.0	1.7	2.0	1.8
	HR 0.49 p<0.0001		HR 0.31 p<0.0001		HR 0.48 p<0.001		HR 0.43 P <.001	
RR (%)	1.0	0.4	4.4	0	1.6	0.4	1.1	0
Main AEs	HFSR Fatigue				Neutropenia Diarrhea			

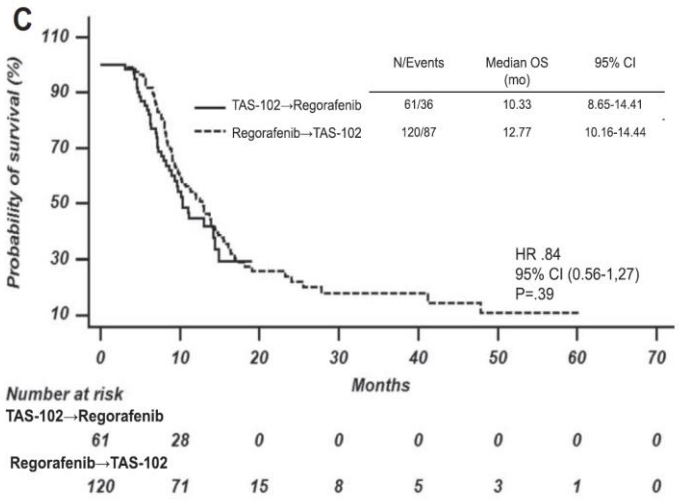
The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

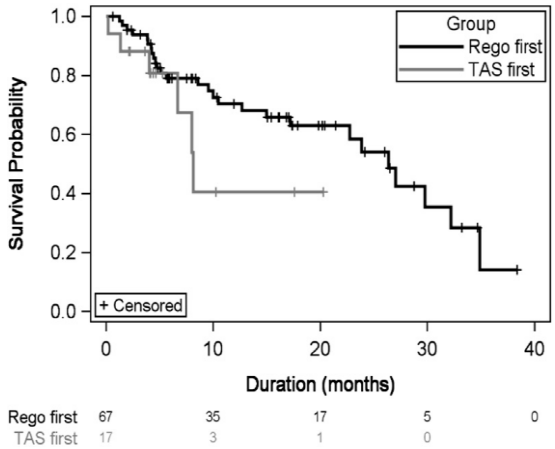
AE; adverse event; BEV, bevacizumab; BSC, best supportive care; CI, confidence interval; EGFR, epidermal growth factor receptor; HFSR, hand-foot skin reaction; HR, hazard ratio; mAb, monoclonal antibody; OS, overall survival; PFS, progression-free survival; Rego, regorafenib; RR, response rate

Grothey A, et al. Lancet 2013;381:303–12; Li J, et al. Lancet Oncol 2015;16:619–29; Mayer RJ, et al. NEJM 2015;372:1909–19; Xu, J et al. J Clin Oncol 2018;36:350–58

IS THERE A PREFERABLE SEQUENCE?







OS after TAS-102 treatment of regorafenib-pretreated and regorafenib-naïve patients (n=43)

OS in patients who received TAS-102 followed by regorafenib or the reverse sequence

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CI, confidence interval; HR, hazard ratio; OS, overall survival; Rego, regorafenib; RGF, regorafenib

Arita S, et al. Anticancer Res 2016;36:1959-1966; Cremolini C, et al. Oncologist 2018;23:1178-1187; Unseld M, et al. Clin Colorectal Cancer 2018 [Epub ahead of print]

RECOURSE: PFS SUBGROUP ANALYSES OF TAS-102

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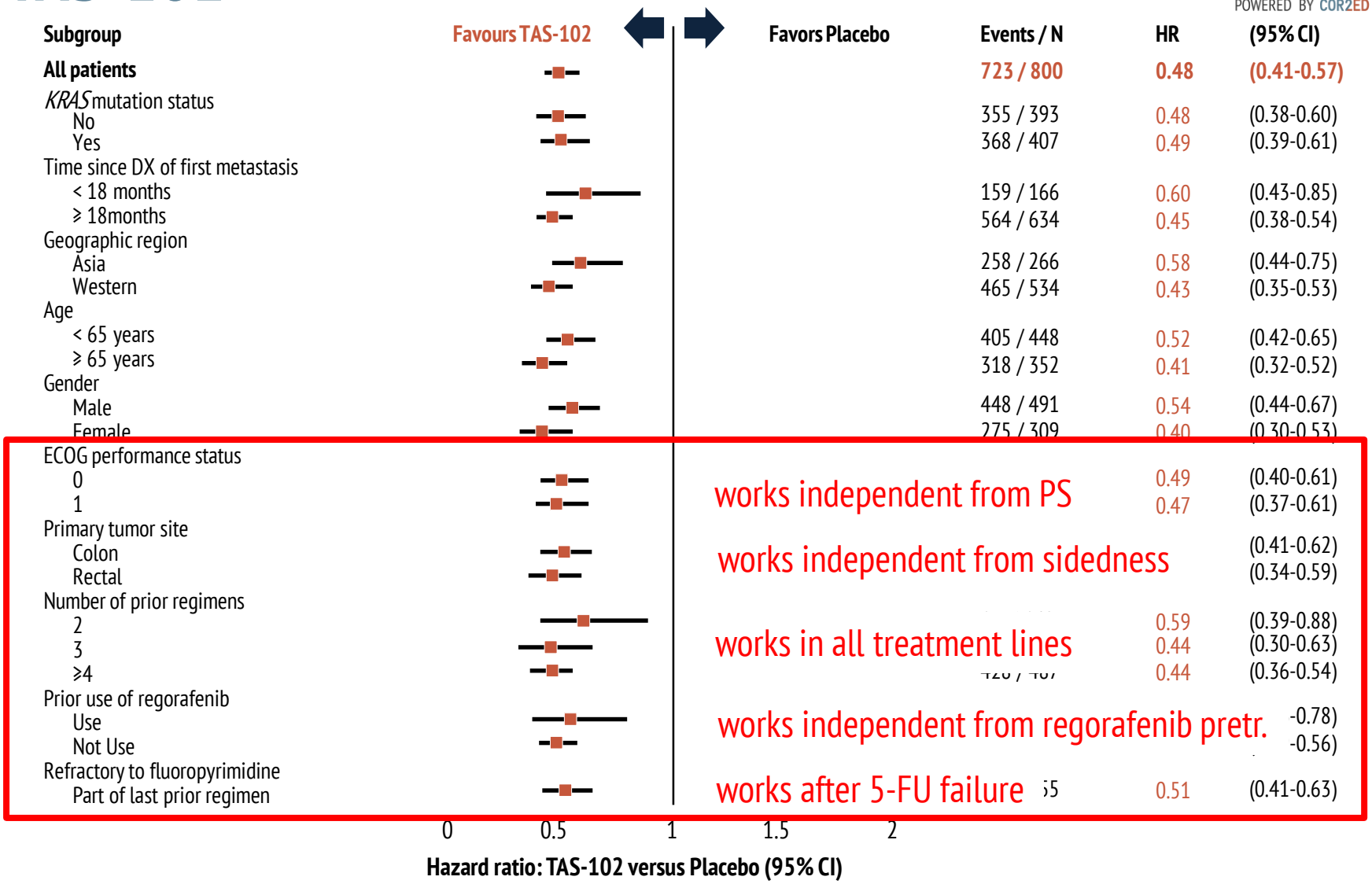
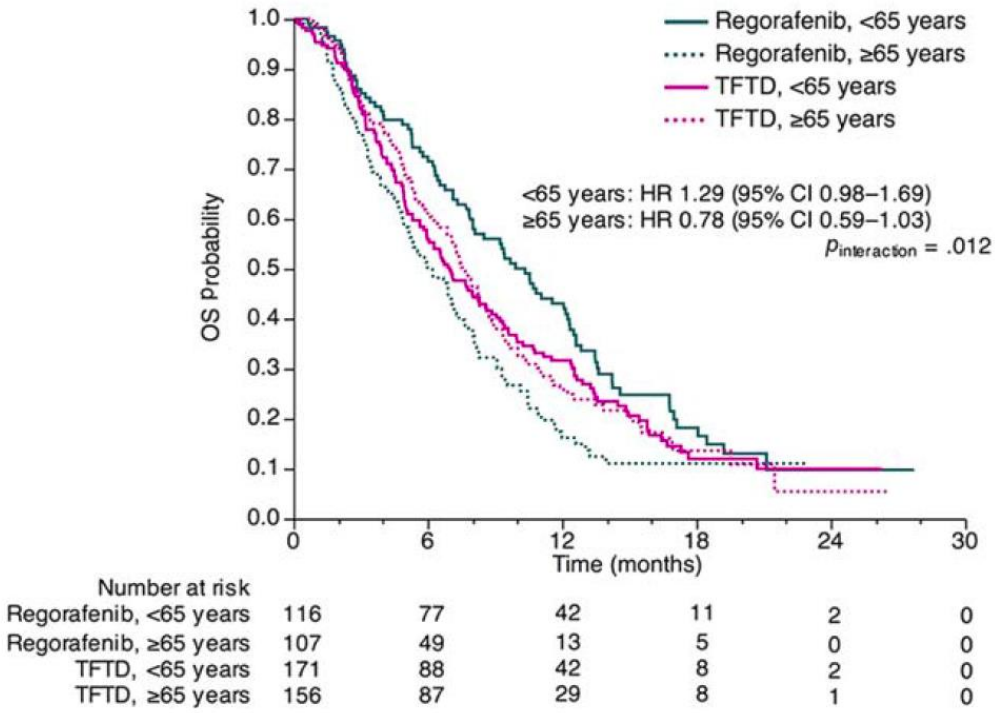


5-FU, fluorouracil; CI, confidence interval; DX, diagnosis; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; KRAS, Kirsten RAS oncogene homolog; PFS, progression-free survival; PS, performance status. Mayer RJ, et al. NEJM 2015;372:1909–19

PROPENSITY SCORE ANALYSIS: REGORAFENIB IS FAVORED IN PATIENTS <65 YEARS, WHILE TFTD IS FAVORED IN PATIENTS ≥65 YEARS



Kaplan-Meier curves for OS according to age <65 years and ≥65 years

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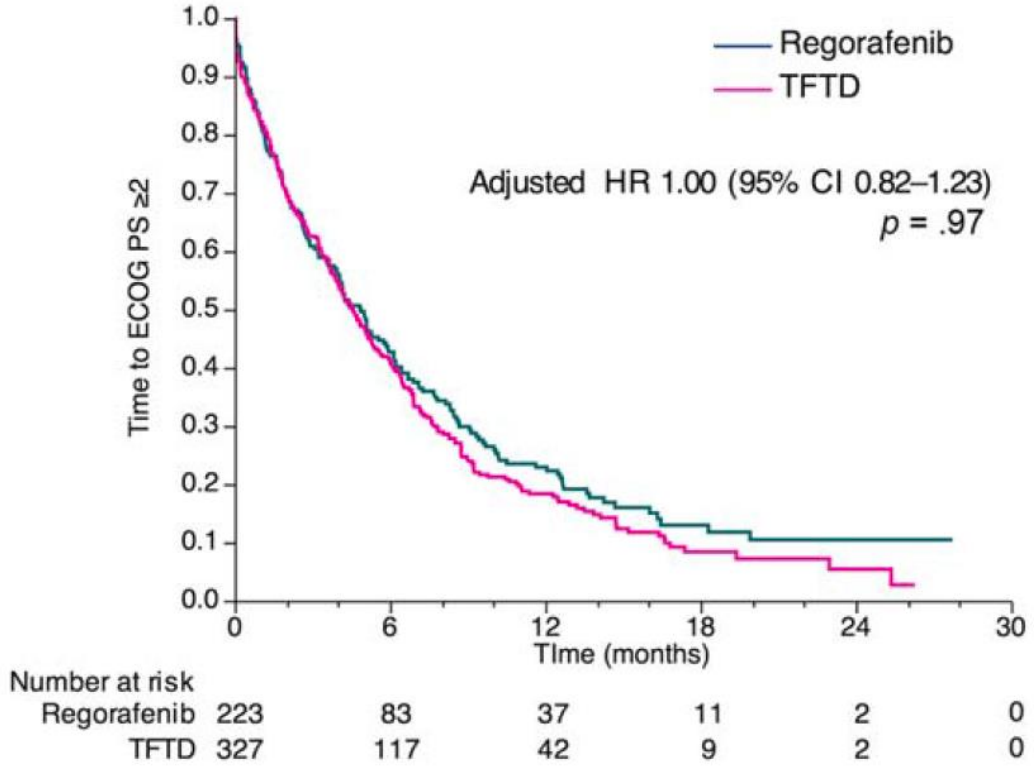
CI, confidence interval; HR, hazard ratio; OS, overall survival; TFTD, trifluridine/tipiracil
Moriwaki T, et al. Oncologist 2018;23:7–15

TIME TO DETERIORATION OF PERFORMANCE STATUS (ECOG PS 2+)

No earlier deterioration of performance status upon different toxicity profiles



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; TFTD, trifluridine/tipiracil

Moriwaki T, et al. Oncologist 2018;23:7–15

SUMMARY TO USE REGORAFENIB IN THE 3RD LINE

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Patients should be exposed to **as many active agents as possible**;[1] delaying treatment with regorafenib risks patient deterioration and missing the opportunity to receive this option

Regorafenib has a **high level of evidence for use in the 3rd line,**[2,3] and is guideline recommended

Regorafenib should be used **before deterioration of performance status**[4]

Patients may still receive **chemotherapy after regorafenib**[5]

Regorafenib appears to provide **most benefit** in patients who have received **less previous treatment lines**[3]

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion.

1. Hanna N, et al. J Clin Oncol 2014;32(Suppl 3): abstract 559; 2. Grothey A, et al. Lancet 2013;381:303–12;
3. Li J, et al. Lancet Oncol 2015;16:619–29; 4. Tougeron D, et al. Presented at ESMO 2014, poster 6220;
5. Kidd MT, et al. Presented at ASCO-GI 2015, abstract 678

3RD LINE TREATMENT IN mCRC:

AFTER FAILURE OF FLUOROPYRIMIDINE, OXALIPLATIN, IRINOTECAN, ANTI-VEGF AND ANTI-EGFR THERAPY (IF RAS WT)

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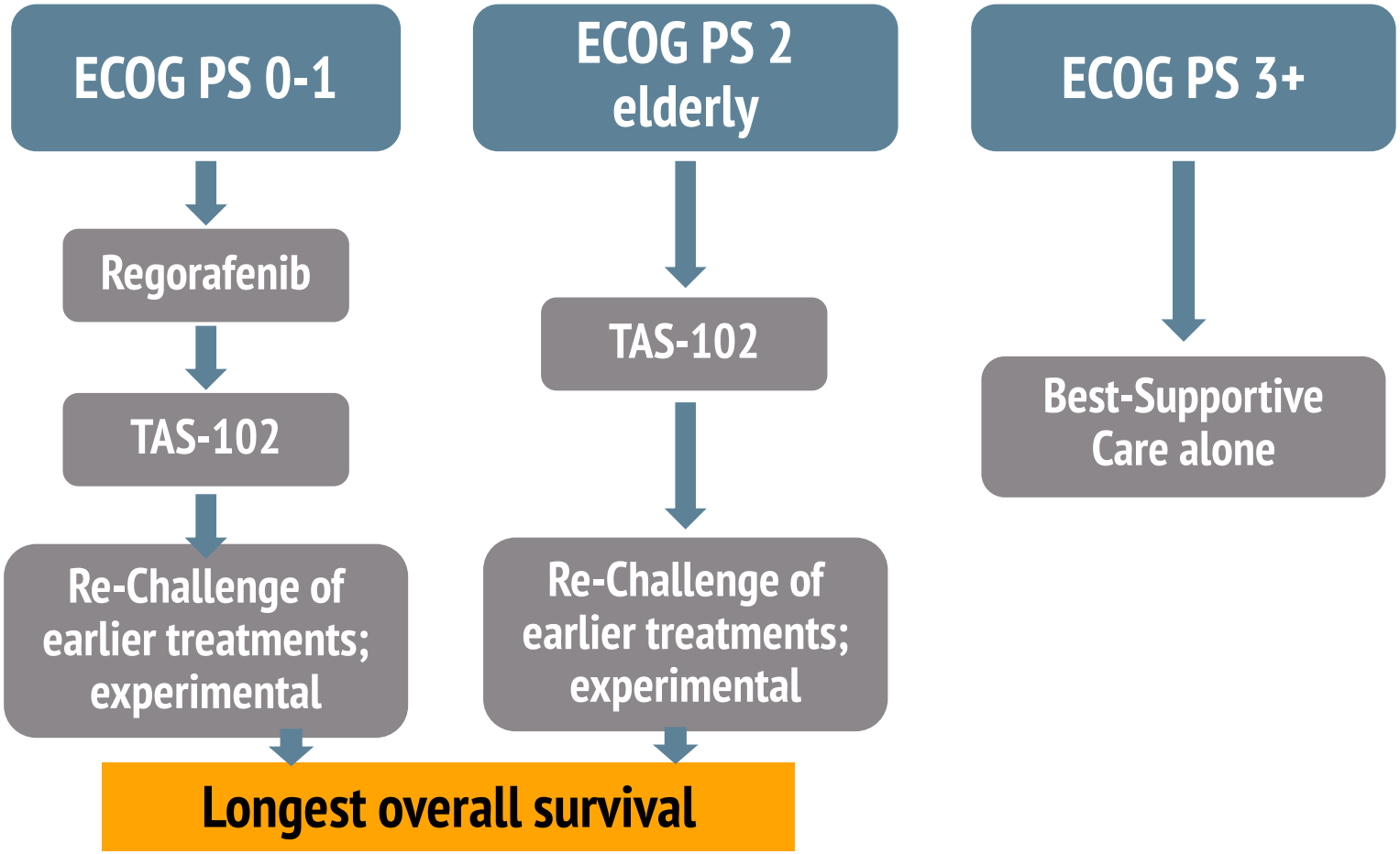

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ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; RAS, rat sarcoma; VEGF, vascular endothelial growth factor; WT, wild type

SUMMARY

Experience from CCC-Vienna, Austria

Regorafenib as well as trifluridine/tipiracil are effective drugs with manageable toxicity

Most common side effects differ substantially, but QOL is maintained

More lines of treatment are beneficial and improve the prognosis

Regorafenib should be given earlier, while trifluridine/tipiracil seems to be beneficial in all lines

The younger and fit patient seems to be preferable for regorafenib

Flexible dosing of regorafenib seems to be feasible

Experimental treatment concepts according to the molecular profile or re-challenging of earlier lines are subject of clinical trials or should ONLY be applied if NO STANDARD treatment options are available.

QOL, quality of life

SUMMARY OF THE ARGUMENTS PRESENTED

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DISCLAIMER

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Please note:

The views presented do not reflect the Experts' own opinions but are intended to represent opposing perspectives on the topic of discussion

Disclosures:

- Dr. Heinz-Josef Lenz has received financial support/sponsorship for research support, consultation or speaker fees from the following companies: Bayer, Boehringer Ingelheim, BMS, Merck Serono

SUMMARY FOR TREATMENT SEQUENCING & FLEXIBLE DOSING

Experience from CCC-Vienna, Austria

Regorafenib as well as trifluridine/tipiracil are effective drugs with manageable toxicity

Most common side effects differ substantially, but QOL is maintained

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Regorafenib should be given earlier, while trifluridine/tipiracil seems to be beneficial in all lines

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Flexible dosing of regorafenib seems to be feasible

Experimental treatment concepts according to the molecular profile or re-challenging of earlier lines are subject of clinical trials or should ONLY be applied if NO STANDARD treatment options are available.

QOL, quality of life
Gerald Prager, M.D.

SUMMARY AGAINST TREATMENT SEQUENCING & FOR FLEXIBLE DOSING

- Sequencing does not apply to the later line setting
- Pre-treated patients with MSI-high mCRC should receive checkpoint inhibitors
- Regorafenib may be a preferred choice for patients <65-70 years old, with good general conditions and no liver impairment
- When choosing regorafenib, available evidence strongly suggest to be "open-minded" about flexible dosing
- In the case of availability of ctDNA assessment and RAS wt ctDNA, even in the absence of phase III evidence, anti-EGFR rechallenge may be a good, more tailored option

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