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TREATMENT SEQUENCING IN mCRC: THIRD LINE AND BEYOND

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mCRC, metastatic colorectal cancer

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EDUCATIONAL OBJECTIVES

- Know how to optimise treatment sequencing for mCRC patients third line and beyond
  - Understand the potential treatment options for these patients
  - Understand the available data to support the optimal sequencing of these treatments
  - Know which patient considerations are important when making treatment sequencing decisions
  - Know the best ways to manage toxicities and quality of life through treatment sequencing

mCRC, metastatic colorectal cancer

CLINICAL TAKEAWAYS

- Optimal sequencing of cytotoxic/targeted agents in metastatic colorectal cancer (mCRC) is unclear
- First-line choice of therapy is critical as it affects treatment decisions in later lines
- Molecular profiling has an important role in determining treatment options and sequence
- Physicians should consider patient characteristics, such as comorbidities, prior adverse reactions to treatments, and overall performance status
- Management of adverse events, to minimise the effect on quality of life, while maximising treatment benefit is crucial
- Clinical trials of emerging agents, new treatment combinations, and novel therapies are important for continued improvement in outcomes in these patients

mCRC, metastatic colorectal cancer

TREATMENT SEQUENCING CONSIDERATIONS

KEY FACTORS FOR CONSIDERATION IN THE CRC TREATMENT STRATEGY

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Overall condition and emotional status of patients

- Fit versus unfit for a combination therapy (triplet vs doublet vs monotherapy)
- Eastern Cooperative Oncology Group performance status
- Patient age
- Established comorbidities
- Patient attitude
- Patient disease history (e.g. previous oxaliplatin-based adjuvant treatment)

Tumour characteristics and clinical course

- Indolent versus aggressive tumour
- Disease presentation (synchronous vs metachronous)
- Tumour load
- Mutational status (*RAS* and *BRAF*)

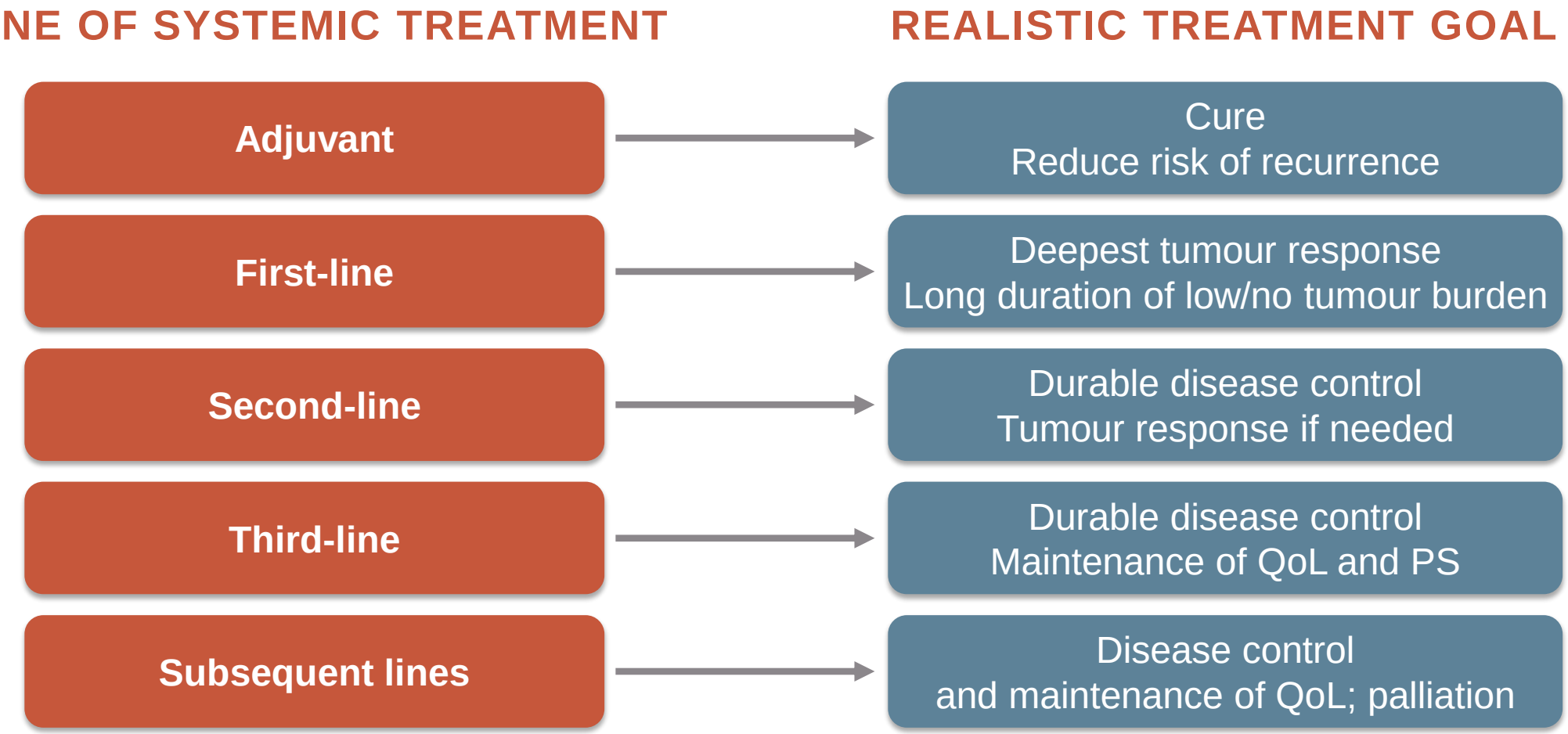
Treatment goal

- Tumour shrinkage to achieve a radical surgery of metastases or palliation of disease-related symptoms
- Disease control to delay progression and worsening of patient's general condition

BRAF, proto-oncogene B-Raf; CRC, colorectal cancer; *RAS, RAS* proto-oncogene GTPase

Argiles G, et al. ESMO Open 2019;4:e000495. doi:10.1136/esmoopen-2019-000495

TREATMENT GOALS ACCORDING TO LINE OF THERAPY



PS, performance status; QoL, quality of life

Argiles G, et al. ESMO Open 2019;4:e000495. doi:10.1136/esmoopen-2019-000495

TREATMENT LINE: DIMINISHING OUTCOMES

- Optimising treatment across multiple lines of therapy in mCRC is challenging, with 1st-line therapy a key to success:

Outcome*	First-line[1-8]	Second-line[9-16]	Third-line and beyond[17-21]
Response rate	38–65%	5–36%	1–31%
Progression-free survival	9–12 months	4–7 months	2–5 months

* Efficacy ranges taken from the targeted/experimental treatment arms of studies reporting the specified outcome (for EGFR trials, results are shown for *RAS* wild-type subsets where applicable)

- When no potential curative path is reached by 1st-line therapy, the question of sequencing gains in importance
- This review explores current treatment approaches in the 3rd-line mCRC setting, including biological aspects affecting sequencing and rechallenge

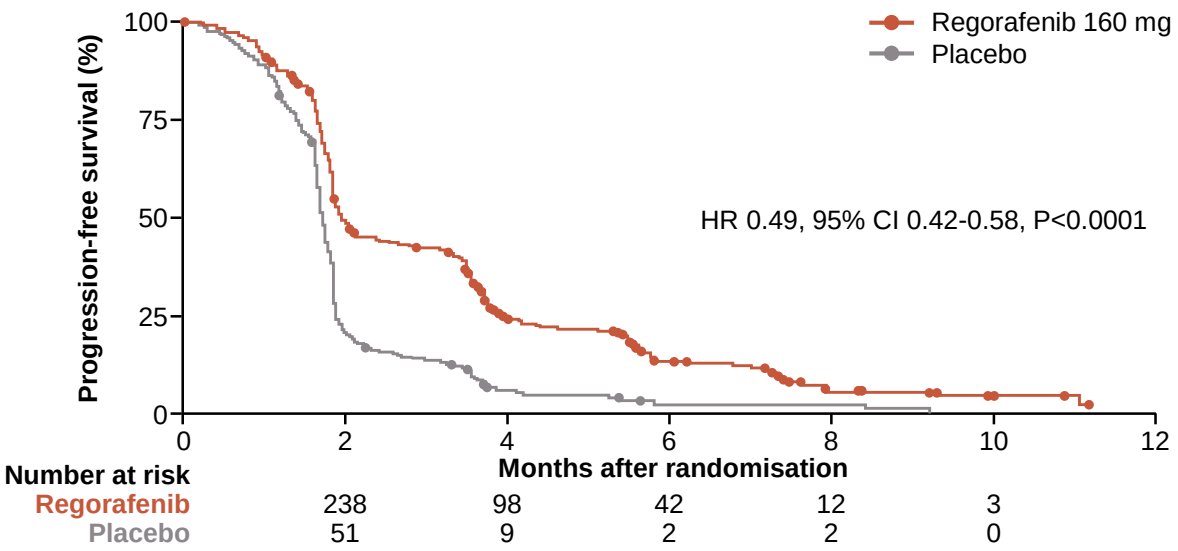
EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; *RAS, RAS* proto-oncogene GTPase

1. Saltz LB, et al. J Clin Oncol. 2008;26:2013-9; 2. Heinemann V, et al. Lancet Oncol. 2014;15:1065-75; 3. Douillard JY, et al. J Clin Oncol. 2010;28:4697-705; 4. Loupakis F, et al. N Engl J Med. 2014;371:1609-18; 5. Douillard JY, et al. Ann Oncol. 2014;25:1346-55; 6. Falcone A, et al. J Clin Oncol. 2007;25:1670-6; 7. Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-9; 8. Venook AP, et al. JAMA. 2017;317:2392-2401; 9. Giantonio BJ, et al. J Clin Oncol. 2007;25:1539-44; 10. Peeters M, et al. J Clin Oncol. 2010; 28:4706-13; 11. Bennouna J, et al. Lancet Oncol. 2013;14:29-37; 12. Van Cutsem E, et al. J Clin Oncol. 2012;30:3499-506; 13. Tabernero J, et al. Lancet Oncol. 2015;16:499-508; 14. Sobrero AF, et al. J Clin Oncol. 2008;26:2311-9; 15. Seymour MT, et al. Lancet Oncol. 2013;14:749-59; 16. Peeters M, et al. Ann Oncol. 2014;25:107-16; 17. Amado RG, et al. J Clin Oncol. 2008;26:1626-34; 18. Grothey A, et al. Lancet. 2013;381:303-12; 19. Karapetis CS, et al. N Engl J Med. 2008;359:1757-65; 20. Mayer RJ, et al. N Engl J Med. 2015;372:1909-19; 21. Kim TW, et al. Br J Cancer. 2016;115:1206-14

PHASE 3 DATA INFLUENCING TREATMENT DECISIONS

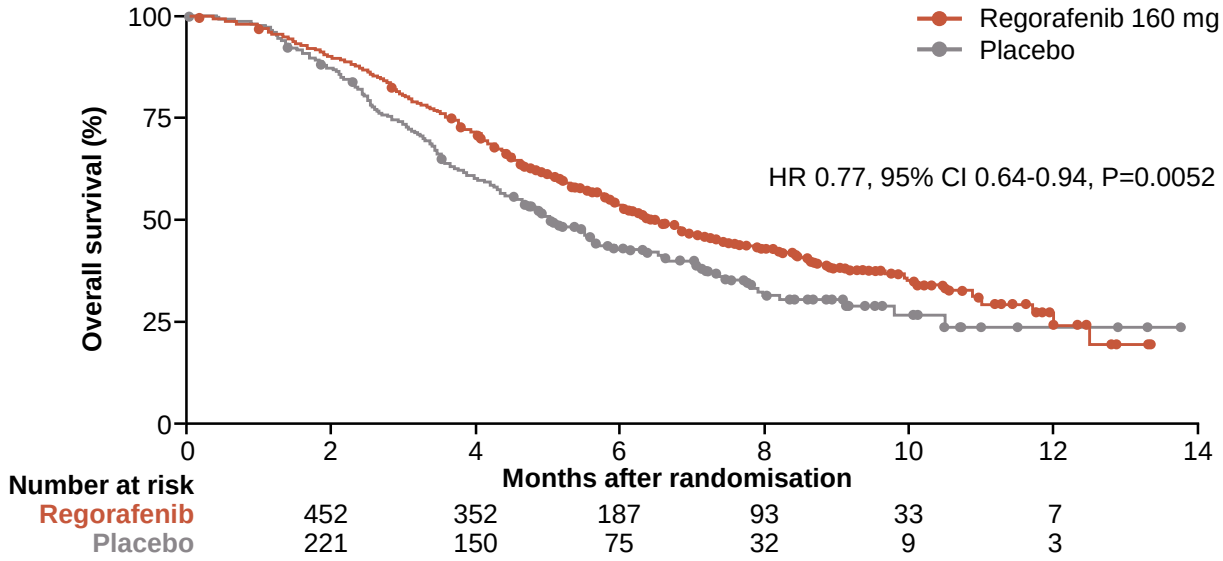
CORRECT STUDY: REGORAFENIB VS PLACEBO PROLONGED PFS AND OS IN REFRACTORY mCRC PATIENTS

PROGRESSION-FREE SURVIVAL



PFS: 1.9 mo vs. 1.7 mo (HR 0.49; p<0.0001)

OVERALL SURVIVAL



OS: 6.4 mo vs. 5.0 mo (HR 0.77; p= 0.0052)

Tumour response:

ORR: 1.0% vs. 0.4% (p=0.19)

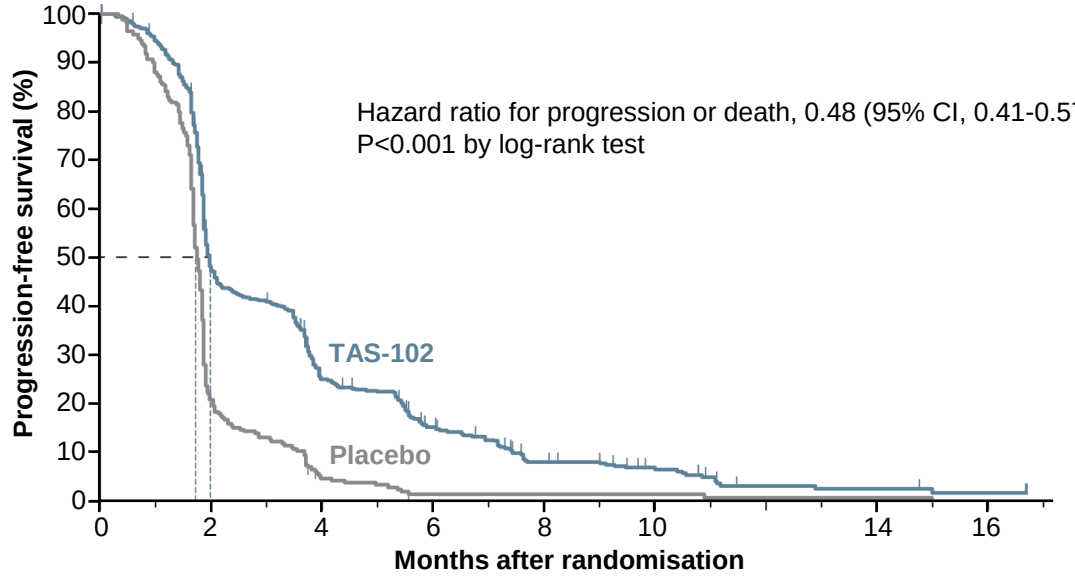
DCR: 41% vs. 15% (p<0.0001)

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival

Grothey A, et al. Lancet. 2013;381:303-12

RECOURSE STUDY: TAS-102 PROLONGED PFS AND OS IN REFRACTORY mCRC PATIENTS

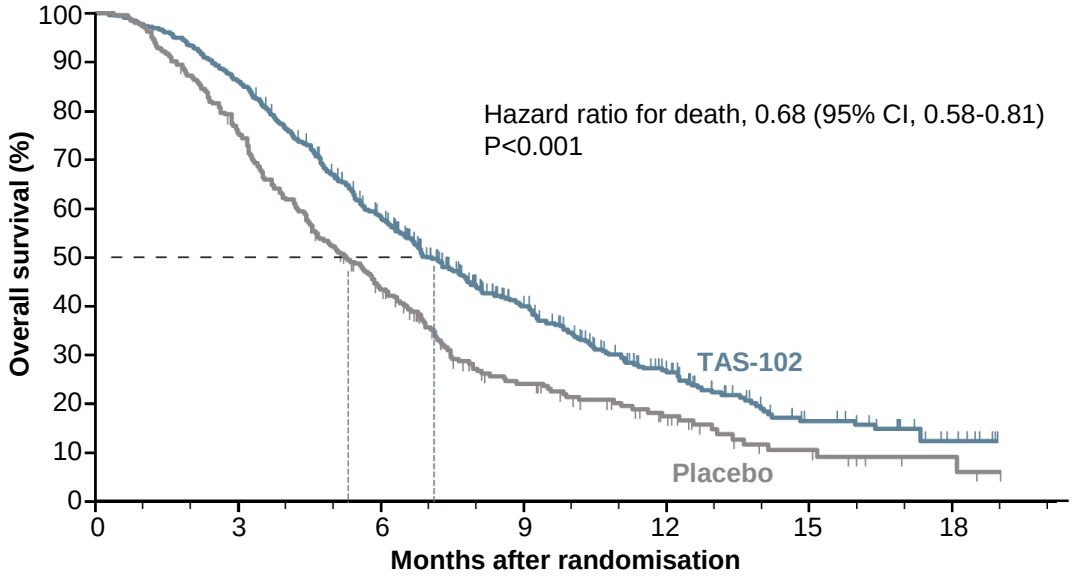
PROGRESSION-FREE SURVIVAL



Number at risk									
TAS-102	534	238	121	66	30	18	5	4	2
Placebo	266	51	10	2	2	2	1	1	0

PFS: 2.0 mo vs. 1.7 mo (HR 0.48; p<0.001)

OVERALL SURVIVAL



Number at risk							
TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

OS: 7.1 mo vs. 5.3 mo (HR 0.68; p<0.001)

<u>Tumour response:</u>

ORR: 1.6% vs. 0.4% (p=0.29)

DCR: 44% vs. 16% (p<0.001)

CI, confidence interval; DCR, disease control rate; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival; TAS-102, trifluridine/tipiracil

Mayer RJ, et al N Engl J Med. 2015;372:1909-19

INFLUENCE OF SAFETY PROFILE IN PATIENTS BEYOND THE SECOND LINE

MOST COMMONLY REPORTED (≥25%) SIDE EFFECTS FOR TAS-102 AND REGORAFENIB IN PHASE 3 CLINICAL STUDIES[1,2]

TAS-102 (N=533)[1]			Regorafenib (N=500)[2,a]		
	Overall (%)	Grade ≥3 (%)		Overall (%)	Grade ≥3 (%)
Leucopenia	77	21	Hand-foot skin reaction	47	17
Anaemia	77	18	Fatigue	47	10
Neutropaenia	67	38	Diarrhoea	34	7
Nausea	48	2	Anorexia	30	3
Thrombocytopaenia	42	5	Voice changes	29	<1
Decreased appetite	39	4	Hypertension	28	7
Fatigue	35	4	Oral mucositis	27	3
Diarrhoea	32	3	Rash/desquamation	26	6

[a]Treatment-related adverse events from start of treatment to 30 days after end of treatment

Please note that these drugs have not been compared in head-to-head studies. The information is presented for information purposes only

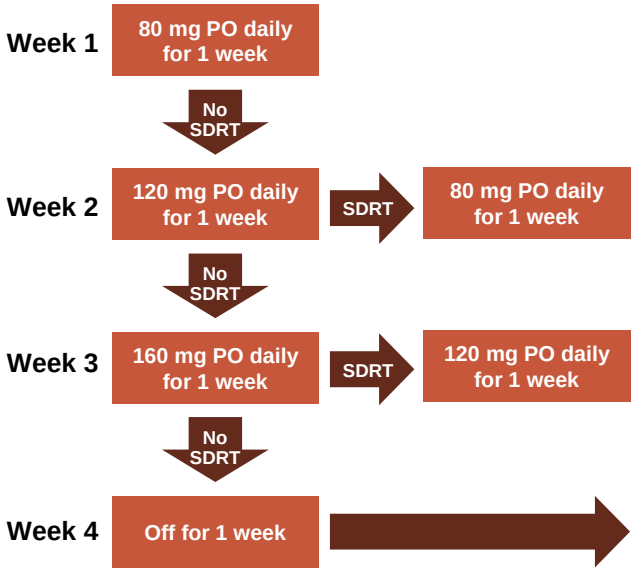
TAS-102, trifluridine/ tipiracil

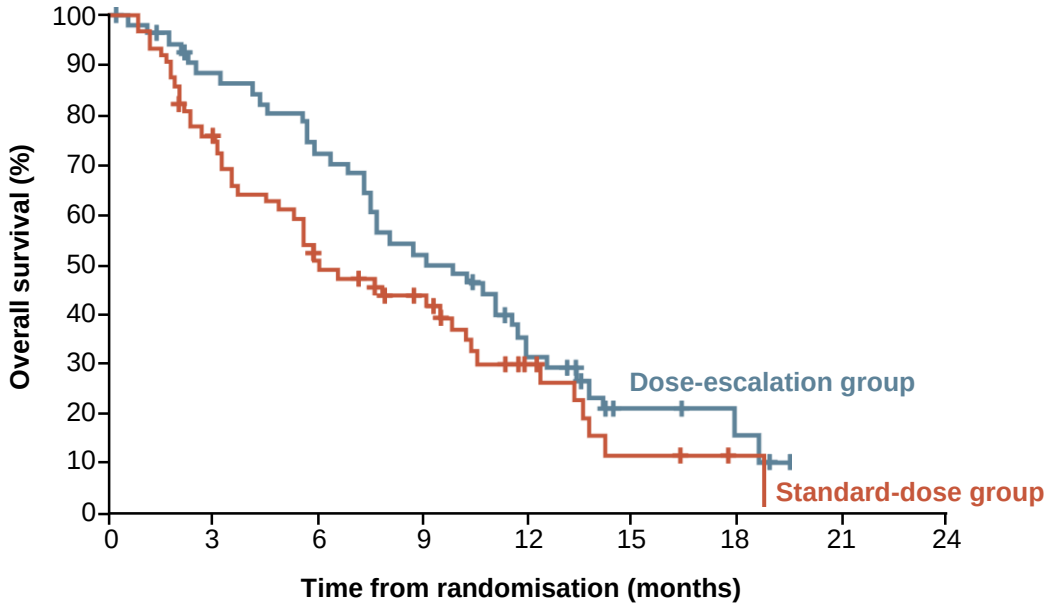
Adapted from Argiles G, et al. ESMO Open 2019;4:e000495. doi:10.1136/esmoopen-2019-000495

1. Mayer RJ, et al. N Engl J Med. 2015;372:1909-19; 2. Grothey A, et al. Lancet. 2013;381:303-12

DOSE-ESCALATED STRATEGY FOR MANAGEMENT OF ADVERSE EVENTS WITH REGORAFENIB

PHASE 2 ReDOS STUDY





Number at risk (number censored)

Dose escalation	54 (0)	44 (4)	36 (4)	26 (4)	14 (4)	5 (11)	3 (12)	0 (14)	–
Standard dose	62 (0)	45 (2)	28 (3)	21 (7)	10 (12)	3 (14)	1 (16)	0 (16)	–

Dose-escalated arm: regorafenib initiated at 80 mg/day, increased weekly up to 160 mg/day if no significant drug-related toxicities
Standard-dose arm: regorafenib 160 mg/day

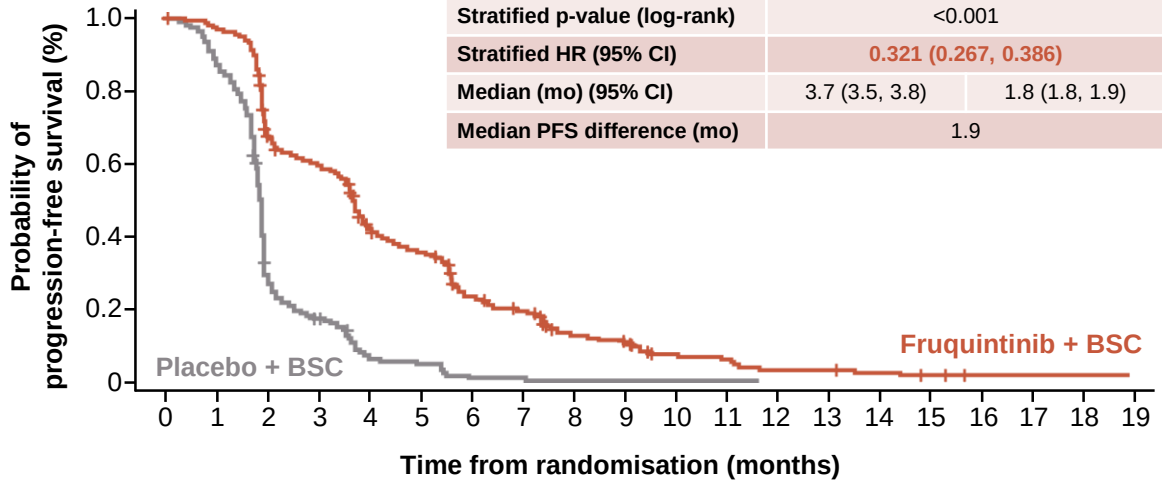
PO, by mouth; SDRT, significant drug-related toxicities

Bekaii-Saab TS, et al. Lancet Oncol. 2019;20(8):1070-82; Grothey A. Clin Adv Hematol Oncol. 2015;13(8):514-7

FRESCO-2: FRUQUINTINIB PROLONGED OS AND PFS IN PATIENTS WITH REFRACTORY mCRC

PROGRESSION-FREE SURVIVAL

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



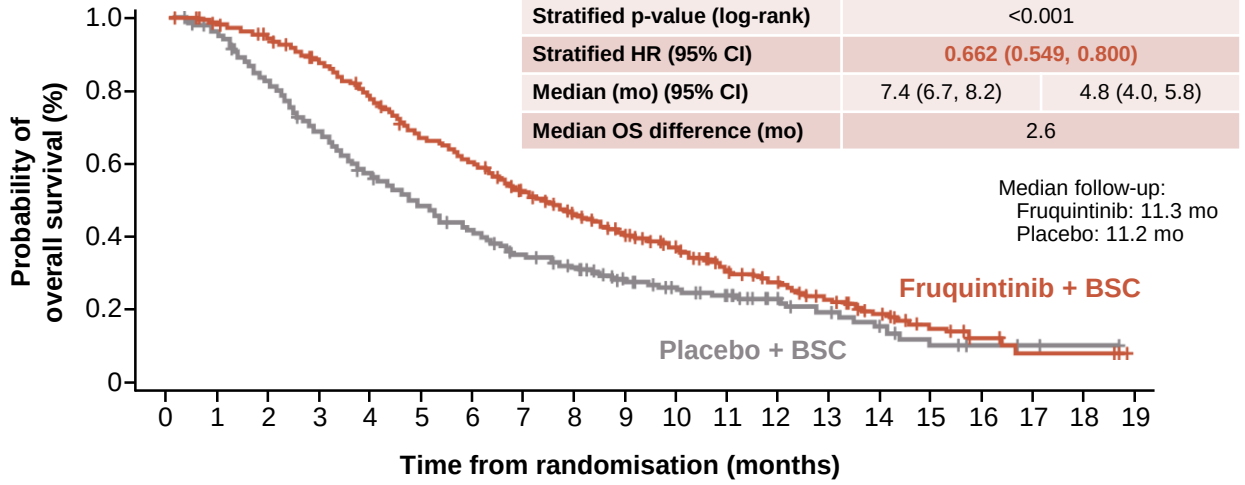
Patients at risk

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

PFS: 3.7 mo vs. 1.8 mo (HR 0.32; p<0.001)

OVERALL SURVIVAL

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



Patients at risk

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

OS: 7.4 mo vs. 4.8 mo (HR 0.66; p<0.001)

Tumour response:

ORR: 1.5% vs. 0.0% (p=0.059)

DCR: 55.5% vs. 16.1% (p<0.001)

BSC, best supportive care; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; mCRC, metastatic colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival

Dasari NA, et al. Ann Oncol. 2022;33(suppl_7):S808-S869 (ESMO 2022 oral presentation)

FRESCO-2: SAFETY RESULTS

Category, n (%)	Fruquintinib (N=456)	Placebo (N=230)
Any TEAE	**451 (98.9)**	**213 (92.6)**
Grade ≥3	286 (62.7)	116 (50.4)
Treatment-related Grade ≥3	164 (36.0)	26 (11.3)
Leading to death	48 (10.5)	45 (19.6)
Any serious TEAE	**171 (37.5)**	**88 (38.3)**
Grade ≥3	162 (35.5)	85 (37.0)
TEAEs leading to dose modifications		
Dose interruption	247 (54.2)	70 (30.4)
Dose reduction	110 (24.1)[a]	9 (3.9)
Dose discontinuation	93 (20.4)[b]	49 (21.3)

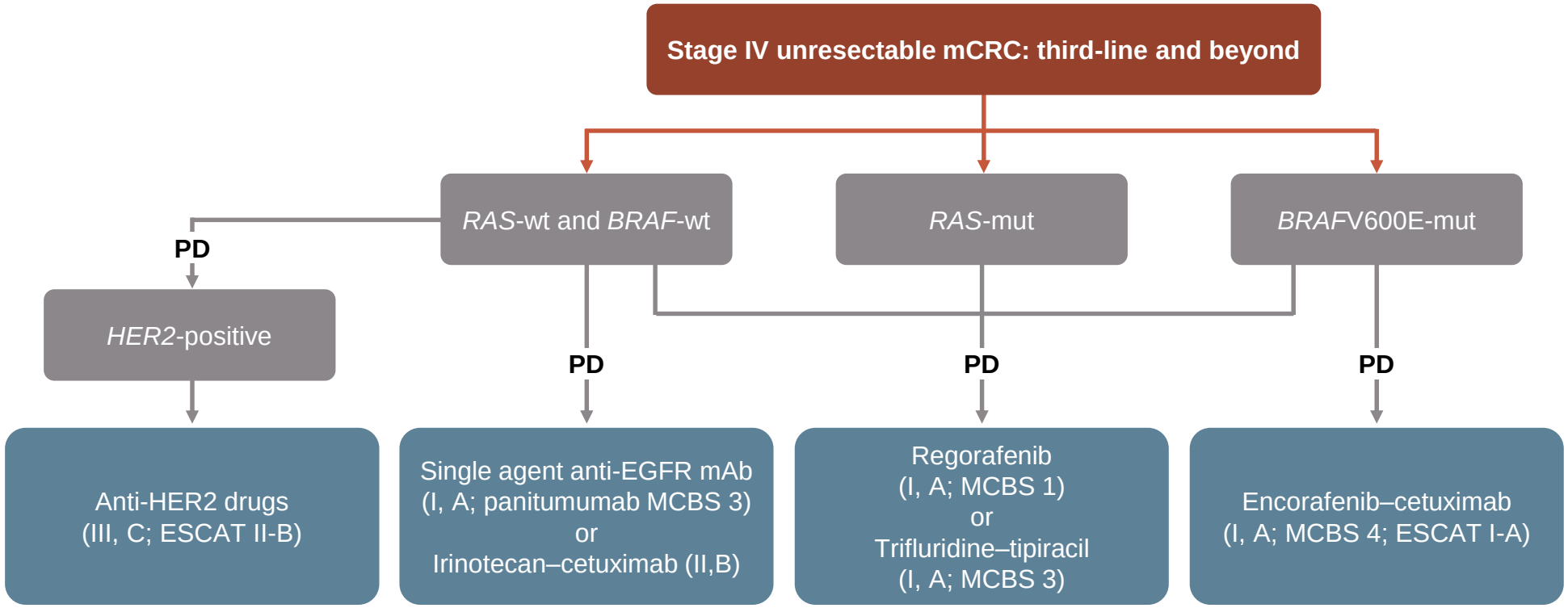
[a] Most common TEAEs leading to dose reduction in fruquintinib arm: hand-foot syndrome (5.3%), hypertension (3.7%), and asthenia (3.5%)
[b] Most common TEAE leading to dose discontinuation in the fruquintinib arm: asthenia (1.5%)

TEAE, treatment-emergent adverse event

Dasari NA, et al. Ann Oncol. 2022;33 (suppl_7):S808-S869 (ESMO 2022 oral presentation)

MANAGEMENT OF STAGE IV UNRESECTABLE mCRC IN THIRD-LINE THERAPY AND BEYOND

ESMO CLINICAL PRACTICE GUIDELINES

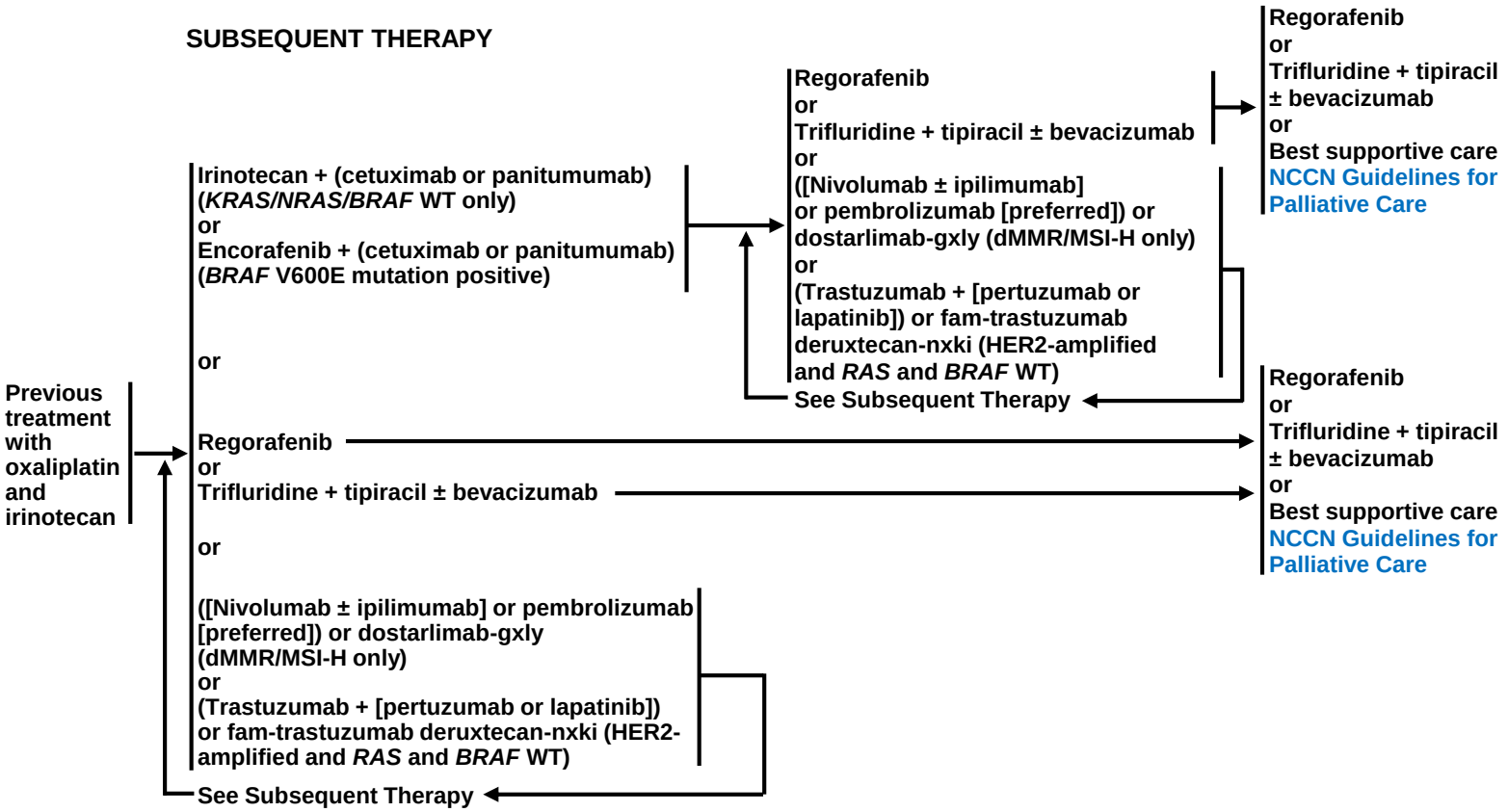


BRAF, proto-oncogene B-Raf; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutant; PD, progressive disease; *RAS, RAS* proto-oncogene GTPase; wt, wild-type

Cervantes A, et al. Ann Oncol. 2022 Oct 25;S0923-7534(22)04192-8. doi: https://doi.org/10.1016/j.annonc.2022.10.003

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC CRC

NCCN CLINICAL PRACTICE GUIDELINES



BRAF, proto-oncogene B-Raf; dMMR, deficient mismatch repair; HER2, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma virus; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; *NRAS*, *NRAS* Proto-Oncogene GTPase; *RAS, RAS* proto-oncogene GTPase; WT, wild-type

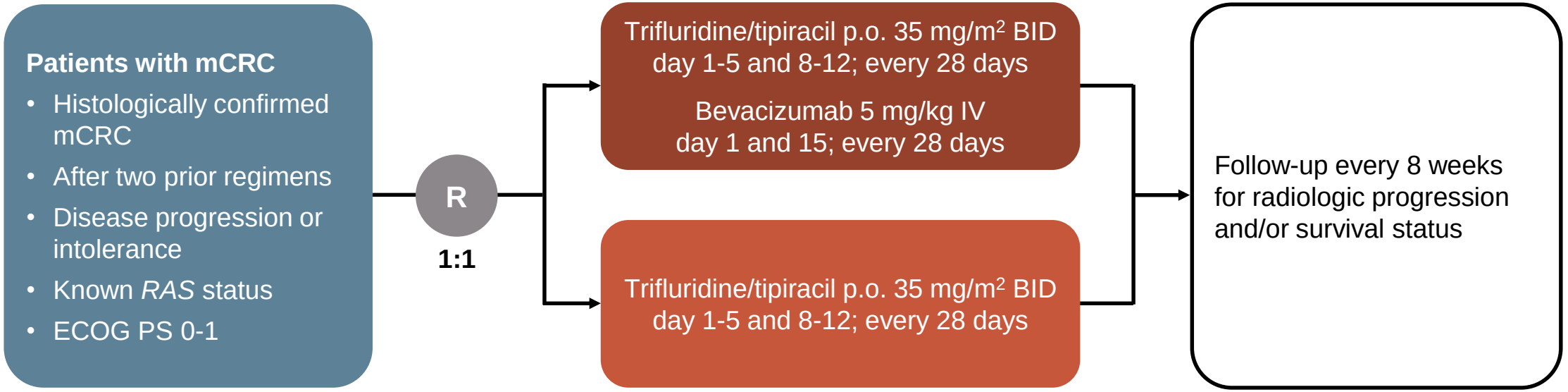
NCCN guidelines, Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed December 2022

WHAT'S NEXT?
COMBINING TS INHIBITORS WITH ANTI-VEGF STRATEGIES

TS, thymidylate synthase; VEGF, vascular endothelial growth factor

SUNLIGHT PHASE 3 STUDY

TAS-102 + BEVACIZUMAB

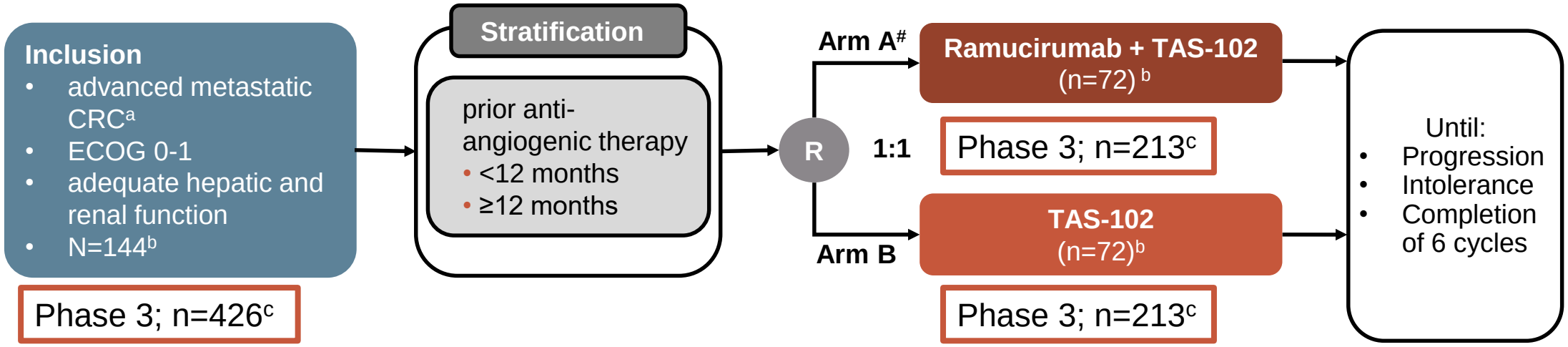


BID, twice a day; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; mCRC, metastatic colorectal cancer; p.o., by mouth; R, randomisation; *RAS, RAS* proto-oncogene GTPase; TAS-102, trifluridine/tipiracil

Tabernero J, et al. Future Oncol. 2021;17:16:1977-85

RAMTAS-STUDY (AIO-KRK-0316/ASS): PHASE 3, ONGOING

RAMUCIRUMAB + TAS-102



[a] failure or intolerance to fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic drugs (bevacizumab, aflibercept, ramucirumab or regorafenib and (if indicated) cetuximab or panitumumab
[b] enrolment for the phase 2 trial (study changed status from a phase 2 to a phase 3 trial with accompanying changes in enrolment numbers)
[c] estimated enrolment for the phase 3 trial

CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; R, randomisation; TAS-102, trifluridine/tipiracil

https://www.clinicaltrials.gov/ct2/show/NCT03520946. Accessed December 2022

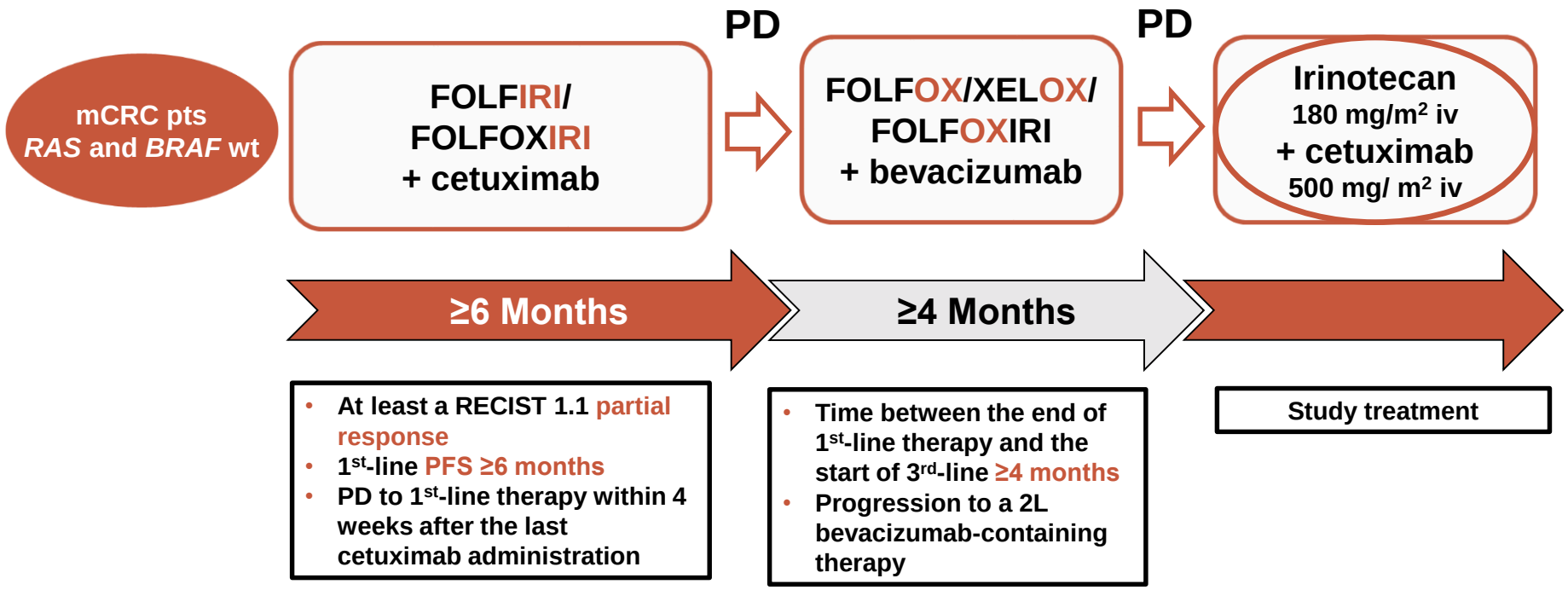
RECHALLENGE WITH ANTI-EGFR

EGFR, epidermal growth factor receptor

CRICKET STUDY

A PHASE 2 SINGLE-ARM TRIAL

Phase 2, non-comparative, study
N = 28 pts

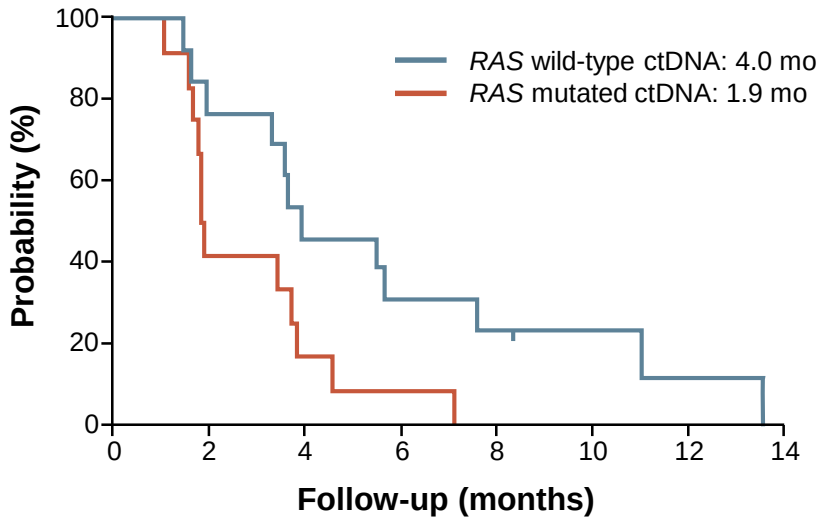


BRAF, proto-oncogene B-Raf; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin and irinotecan; iv, intravenous; mCRC, metastatic colorectal cancer; PD, progressive disease; PFS, progression-free survival; *RAS, RAS* proto-oncogene GTPase; RECIST, response evaluation criteria in solid tumours; wt, wild-type; XELOX, capecitabine plus oxaliplatin

Cremolini S, et al. JAMA Oncol. 2019;5(3):343-350

CRICKET TRIAL: ANTI-EGFR RE-CHALLENGE

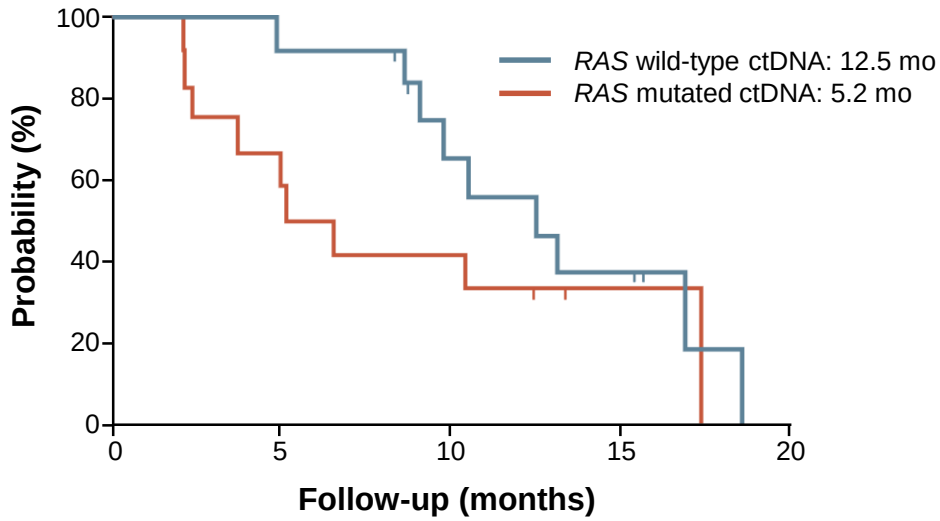
PROGRESSION-FREE SURVIVAL



Number at risk								
Wild-type ctDNA	13	10	6	4	3	2	1	0
Mutated ctDNA	12	5	2	1	0	0	0	0

PFS: 4.0 mo vs. 1.9 mo (median overall: 3.4 mo)

OVERALL SURVIVAL



Number at risk					
Wild-type ctDNA	13	12	7	4	0
Mutated ctDNA	12	7	5	1	0

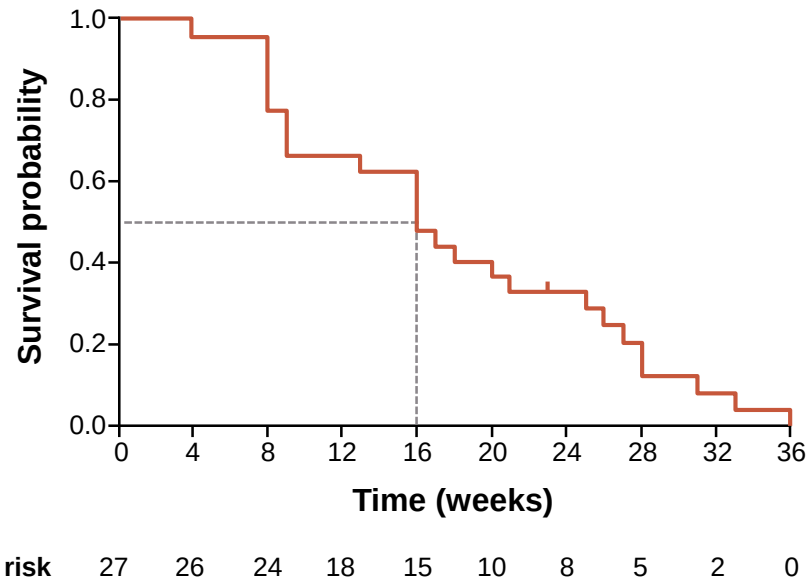
OS: 12.5 mo vs. 5.2 mo (median OS 9.8 mo)

<u>Tumour response:</u>
ORR: 21%
DCR: 54%

ctDNA, circulating tumour DNA; DCR, disease control rate; EGFR, epidermal growth factor receptor; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival; *RAS, RAS* proto-oncogene GTPase

Cremolini C, et al JAMA Oncol. 2019;5(3):343-350

CHRONOS TRIAL: ANTI-EGFR RE-CHALLENGE



Median PFS: 16.4 weeks (9-25)

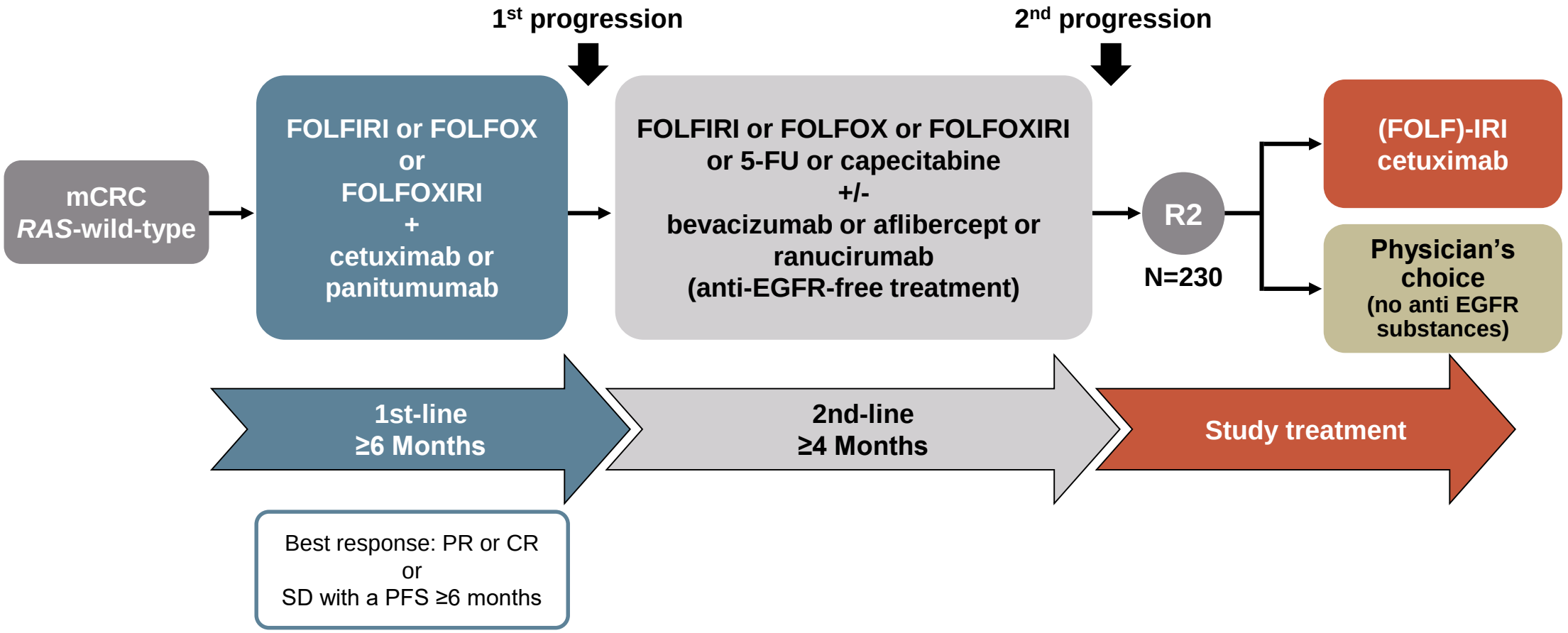
Best response RECIST 1.1 by centralised revision	N	%
Responses (PR+CR)	**8**	**30%**
Partial response	**8***	**30%**
Stable disease ≥4 mo	9	33%
Stable disease <4 mo	2	7%
Control of disease (PR+SD ≥4 mo)	**17**	**63%**
Progressive disease	8	30%
Total	**27**	**100%**

* Two PR were unconfirmed

CR, complete response; EGFR, epidermal growth factor receptor; mo, months; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumours; SD, stable disease

Sartore-Bianchi A, et al. J Clin Oncol. 2021;39,no. 15_suppl:3506-3506 (ASCO 2021. Abstract #3506, oral presentation)

FIRE-4 STUDY (AIO KRK-0114)
PHASE 3



5-FU, fluorouracil; CR, complete response; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil, oxaliplatin and irinotecan; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin and irinotecan; mCRC, metastatic colorectal cancer; PFS, progression-free survival; PR, partial response; R, randomisation; *RAS, RAS* proto-oncogene GTPase; SD, stable disease

https://clinicaltrials.gov/ct2/show/NCT02934529. Accessed December 2022; Heinemann V, et al. World congress on GI Cancer 2022 (SO-16, oral presentation)

OTHER TREATMENT STRATEGIES IN DEVELOPMENT

MOLECULARLY SELECTED TRIALS

Study	ClinicalTrials.gov identifier	Treatments	Patient population	Recruitment stage	Primary completion date
CodeBreak 300[1]	NCT05198934	• Sotorasib plus panitumumab • Investigator's choice (TAS-102 or regorafenib)	Previously treated (at least 1 line of therapy) mCRC subjects with *KRAS* G12C mutation (N=153)	Recruiting	April 2023
MOUNTAINEER[2]	NCT03043313	• Tucatinib combined with trastuzumab • Tucatinib monotherapy	HER2 positive mCRC patients (N=117)	Active, not recruiting	March 2022
DESTINY-CRC02[3]	NCT04744831	• Trastuzumab deruxtecan	Patients with HER2-expressing metastatic colorectal cancer (N=122)	Active, not recruiting	February 2023

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; *KRAS*, Kirsten rat sarcoma virus

1. https://clinicaltrials.gov/ct2/show/NCT05198934. Accessed December 2022. 2. https://www.clinicaltrials.gov/ct2/show/NCT03043313. Accessed December 2022.
3. https://clinicaltrials.gov/ct2/show/NCT04744831. Accessed December 2022

NON-MOLECULARLY SELECTED TRIALS

Study	ClinicalTrials.gov identifier	Treatments	Patient population	Recruitment stage	Primary completion date
MK-7902-017/E7080-G000-325/LEAP-017[1]	NCT04776148	• Lenvatinib + pembrolizumab • Standard of care (TAS-102 or regorafenib)	mCRC (N=434)	Active, not recruiting	January 2024
RELATIVITY-123[2]	NCT05328908	• Relatlimab-nivolumab fixed-dose combination • Investigator's choice (TAS-102 or regorafenib)	Non-MSI-H/dMMR CRC participants who failed at least 1 but no more than 4 prior lines of therapy for metastatic disease (N=700)	Recruiting	January 2025

dMMR, deficient mismatch repair; CRC, colorectal cancer; mCRC, metastatic CRC; MSI-H, microsatellite instability high

https://clinicaltrials.gov/ct2/show/NCT04776148. Accessed December 2022. 2. https://clinicaltrials.gov/ct2/show/NCT05328908. Accessed December 2022

SUMMARY

SUMMARY

- The **increased number of potential treatment options for mCRC** along with the use of some agents in more than one line or as adjuvant therapy can **make the treatment landscape appear complex**
- **Treatment choice will depend on multiple factors** including:
  - molecular characterisation of the tumour
  - treatment goal
  - overall condition
  - tumour load
  - clinical course
- **Recommended treatments** in the 3L setting include: regorafenib, TAS-102, anti-EGFR, in *RAS*- and *BRAF* wild-type patients not previously treated with EGFR antibodies
- **The refractory setting in CRC is a moving field**. We look forward other treatment strategies, in molecularly and non-molecularly selected patients

3L, third line; *BRAF*, proto-oncogene B-Raf; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; mCRC, metastatic CRC; *RAS, RAS* proto-oncogene GTPase; TAS-102, trifluridine/tipiracil

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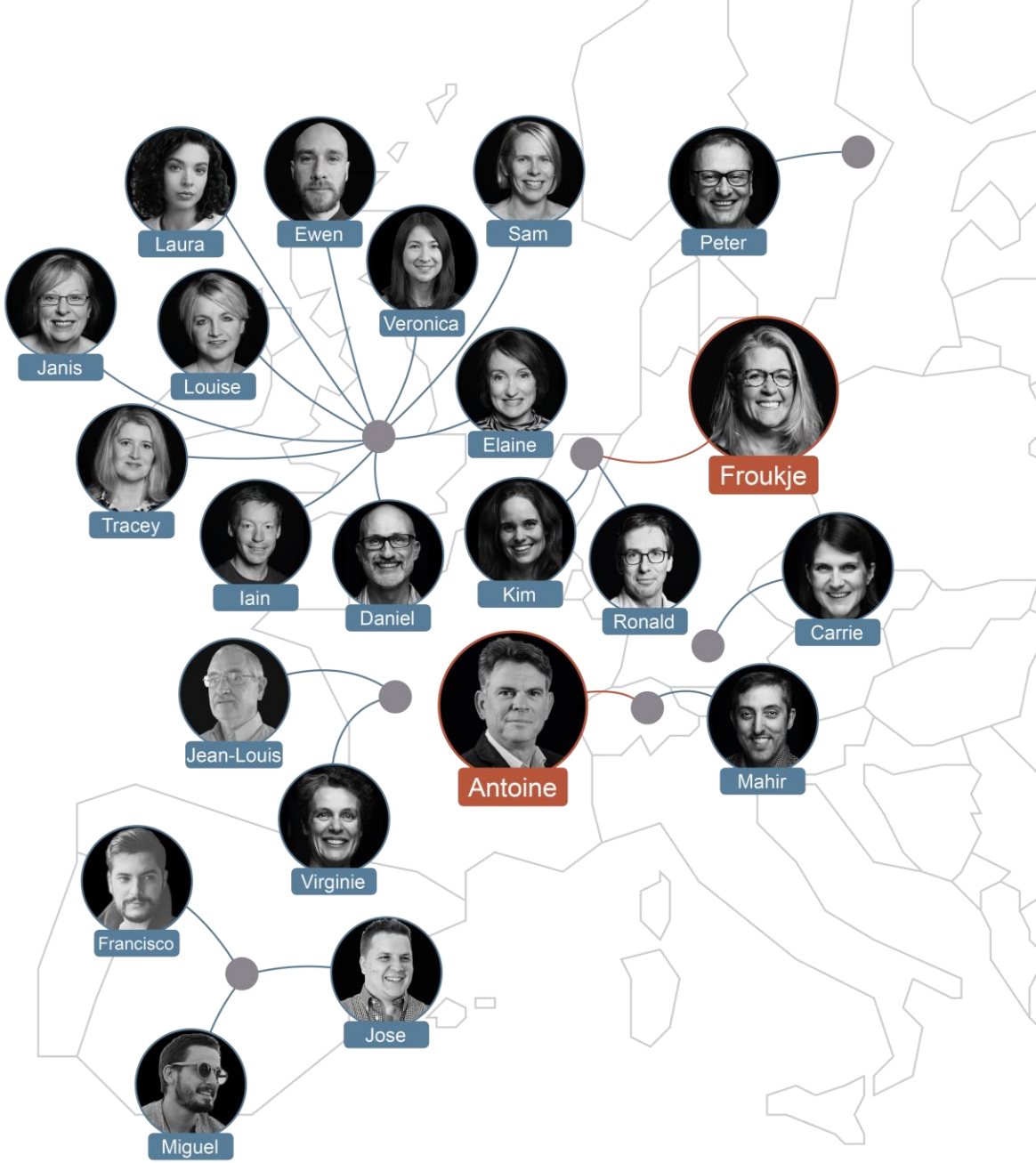

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