COR2ED

THE HEART OF MEDICAL EDUCATION

LONG-TERM RESPONSE IN ADVANCED COLORECTAL CANCER

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AUG 2023

DEVELOPED BY GI CONNECT

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Acknowledgement and disclosures

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- **Assoc. Prof. Gerald Prager** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies:
  - Amgen, AstraZeneca, Bayer, BMS, Incyte, Merck Serono, MSD, Servier, Takeda

EDUCATIONAL OBJECTIVES

- Understand the considerations for achieving a long-term response in advanced colorectal cancer:
  - How to view CRC treatment as a continuum of care
  - What to consider when making treatment decisions
  - Which treatment options are available for CRC patients' 3rd line and beyond

CRC, colorectal cancer

CLINICAL TAKEAWAYS

- Treatment of advanced colorectal cancer (CRC) should be considered as a continuum of care and patients should be offered as many life prolonging therapies as possible
- Decision-making at each stage of therapy should consider patients' suitability and tolerability, tumour biomarkers and prior exposure to chemotherapies and/or targeted agents
- There are a number of treatment options for CRC patients third-line and beyond that should be considered such as regorafenib, trifluridine/tipiracil as well as consideration of clinical trials and rechallenge with chemotherapy or anti-EGFR

EGFR, epidermal growth factor receptor

INTRODUCTION

- With the introduction of targeted therapy over the past two decades, the life expectancy of patients with metastatic CRC (mCRC) has improved significantly from 12 to 30-40 months in various studies[1]
- More than 50% of patients are now receiving treatment in the third-line setting[2]
- We cannot predict which patients will achieve a long-term response but there are some clinical factors that can help decision-making:
  - Left sided tumours even in the metastatic setting have a better prognosis than right sided[3-5]
  - Molecular markers, among them *BRAF* mutations as a worse prognostic marker but with specific treatment options for these patients[6]
  - Clinically useful predictive biomarkers aid clinical decision making, such as the presence of *KRAS* gene mutations predicting a lack of benefit from anti-EGFR therapy[7]

BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homologue

1. Novakova-Jiresova A, et al. Cancer Manag Res. 2020;12:5365-5372; 2. Tampellini M, et al. Clin Colorectal Cancer. 2017;16(4):372-376;
3. Loupakis F, et al. J Natl Cancer Inst. 2015;107(3):dju427; 4. Brule SY, et al. J Clin Oncol 2013; 31 (Suppl):3528; 5. Petrelli F, et al. JAMA Oncol. 2017;3(2):211-219;
6. Sahin IH, et al. JCO Oncol Pract2021;17(12):723-730; 7. Koncina E, et al. Cancers. 2020;12(2):319

PATIENT CHARACTERISTICS AND CONSIDERATIONS

KEY FACTORS FOR CONSIDERATION IN THE CRC TREATMENT STRATEGY

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 (ECOG PS)
- 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 (e.g. *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, rat sarcoma viral oncogene homologue

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

MOLECULAR ANALYSIS IN mCRC IS THE MAINSTAY OF TREATMENT DECISION-MAKING

- Several biomarkers are used to inform treatment selection and understand the prognosis for patients with mCRC[1]
- Around 70% of ***RAS* wild-type CRCs** simultaneously harbour heterogeneous genomic alterations involved in EGFR and other signalling pathways that confer **resistance to anti-EGFR monoclonal antibodies therapy**[2]
- ***BRAF* V600E** is a well-established oncogenic driver mutation **associated with highly aggressive behaviour in CRC**[3]
  - ***BRAF* V600E–mutant CRC is associated with resistance to chemotherapy and EGFR–directed therapies**, leading to shorter survival outcomes compared with wild-type *BRAF*
  - **BRAF inhibitors combined with EGFR blockade create a synergistic effect**, resulting in significant therapeutic efficacy in colon cancer with *BRAF* V600E mutation
  - The *BRAF* V600E mutation is also associated with MMR–deficient CRC, which is highly responsive to immune checkpoint inhibitor therapy
- **MMR enzyme deficiency** caused by mutations in MMR genes **is a predictive and prognostic factor, especially in the early stage of CRC**[4]
  - Patients with CRCs that are microsatellite instability (MSI) and high somatic tumour mutation burden (TMB) have shown encouraging outcomes after receiving immunotherapy[5,6]
- ***HER2* is an emerging biomarker for CRC**[7]

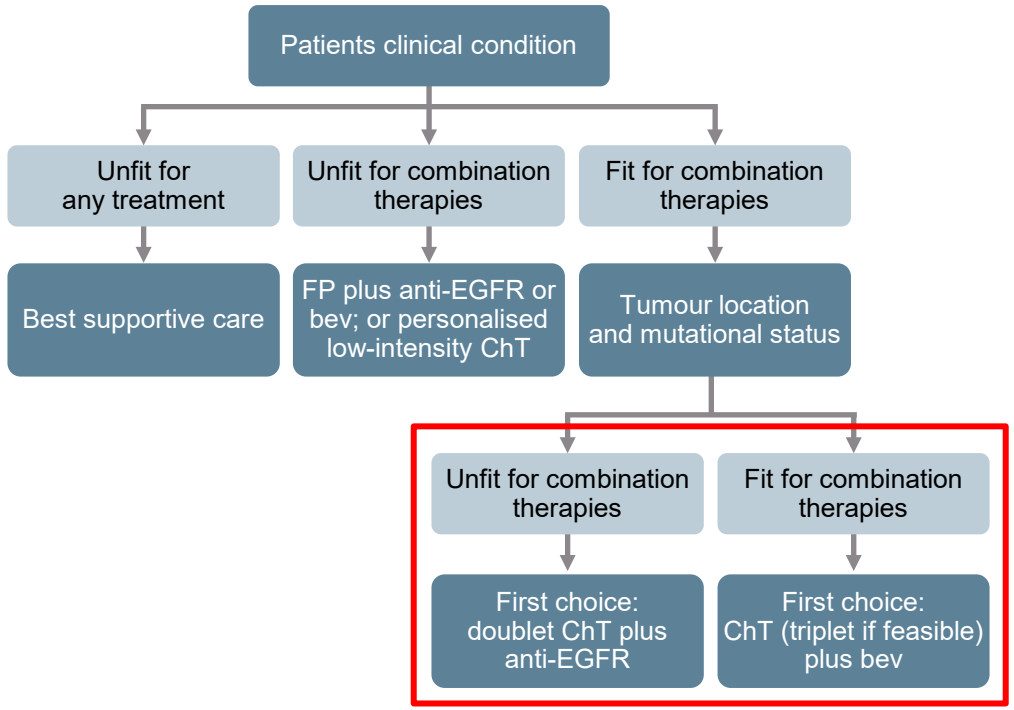
BRAF, proto-oncogene B-Raf; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; (m)CRC, (metastatic) colorectal cancer; MMR, mismatch repair; RAS, rat sarcoma viral oncogene homologue

1. Yekeduz E, et al. Cureus. 2022;14(4):e24175; 2. Dienstmann R, et al. Am Soc Clin Oncol Educ Book. 2015;35:e149-156;
3. Sahin IH, et al. JCO Oncol Pract 2021;17(12):723-730; 4. Molinari C, et al. Int J Mol Sci. 2018;19:3733; 5. Le DT, et al. N Engl J Med. 2015;372:2509-2520;
6. Overman MJ, et al. Lancet Oncol. 2017;18:1182-1191; 7. Djaballah S, et al. Am Soc Clin Oncol Educ Book. 2022;42:219-232

TUMOUR SIDEDNESS AND TREATMENT CONSIDERATIONS

- A retrospective analysis of data from the CALGB/SWOG 80405 trial found that patients whose cancer originated in the left side of the colon lived more than a year longer after initial treatment than patients whose disease originated in the right side of the colon[1]
- The study also linked tumour location to the likelihood of benefit from specific targeted therapies used to treat patients with colorectal cancer[1]
- Tumour sidedness may also be predictive of response to treatment; greater benefit from treatment with an anti-EGFR therapy was observed in patients with RAS wild-type disease who had left-sided tumours than in patients with right-sided tumours[1,2]
- Bevacizumab plus chemotherapy may provide greater clinical benefit than anti-EGFR therapies in patients with right-sided tumours[2]
- Anti-EGFR therapy when added to an irinotecan-based regimen has been shown to have significant activity in patients with irinotecan-refractory colorectal cancer[3]

Tailoring first-line treatment for patients with mCRC



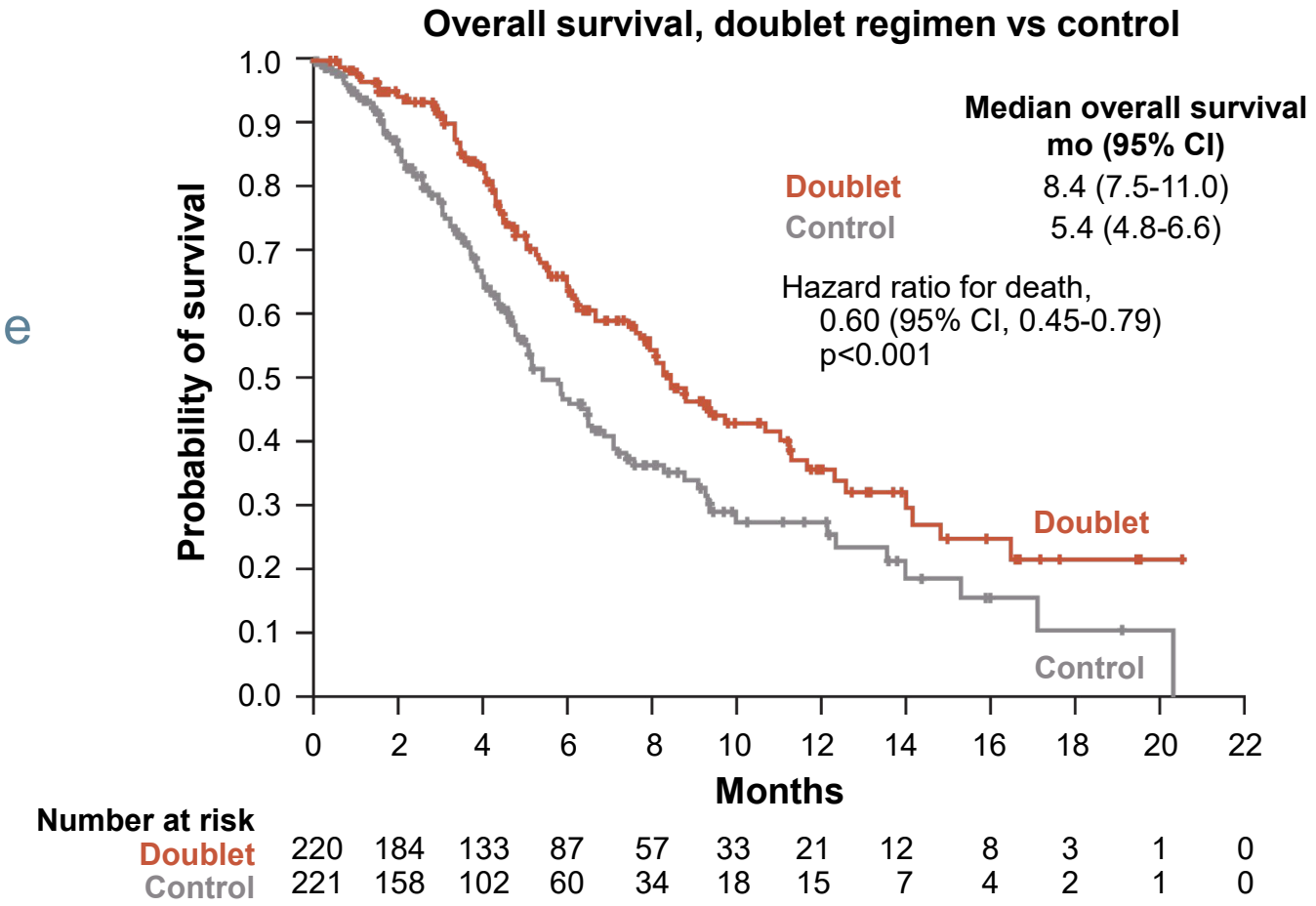
bev, bevacizumab; ChT, chemotherapy; EGFR, epidermal growth factor receptor; FP fluoropyrimidine; mCRC, metastatic colorectal cancer; RAS, rat sarcoma viral oncogene homologue

Figure adapted from: Cremolini C, et al. Gastrointestinal tumours, Essentials for Clinicians (2nd Edition, Chapter 7), ESMO Press 2021

1. Venook, AP, et al. J Clin Oncol. 2016;34 no. 15_suppl:3504-3504; 2. Arnold D, et al. Ann Oncol. 2017;28(8):1713-1729; 3. Cunningham D, et al. New Engl J Med. 2004;351:337-345;

ENCORAFENIB PLUS CETUXIMAB IMPROVES SURVIVAL IN PREVIOUSLY TREATED PATIENTS WITH *BRAF* V600E–MUTANT mCRC

- In the BEACON CRC study, treatment with doublet therapy (encorafenib plus cetuximab) improved OS, ORR, and PFS in previously treated patients in the metastatic setting compared with standard chemotherapy[a]



[a] Standard chemotherapy: cetuximab and irinotecan or cetuximab and FOLFIRI

BRAF, proto-oncogene B-Raf; CI, confidence interval; FOLFIRI, folinic acid, fluorouracil and irinotecan; (m)CRC, (metastatic) colorectal cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Kopetz S, et al. N Engl J Med. 2019;381:1632-1643; Tabernero J, et al. J Clin Oncol. 2021;39(4):273-284

ANTI-EGFR PLUS IRINOTECAN BASED CHEMOTHERAPY HAS BENEFIT IN IRINOTECAN-REFRACTORY CRC

- Cetuximab has clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer

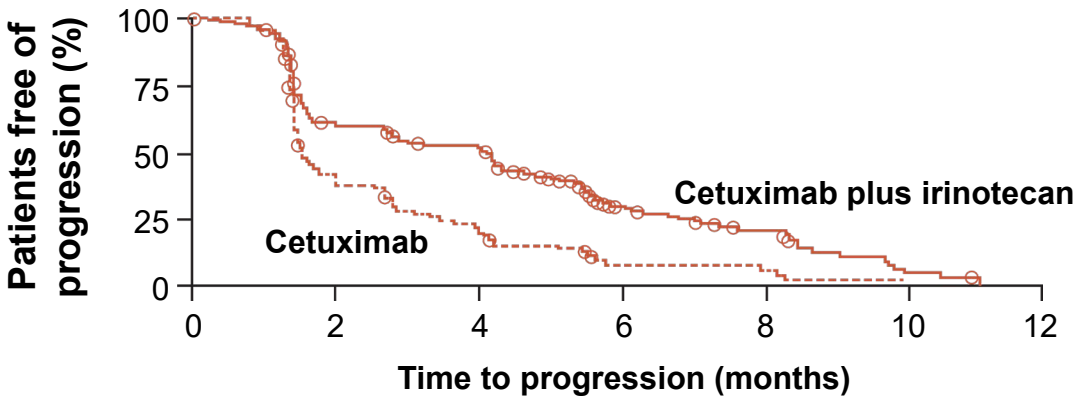
RATES OF RADIOLOGIC RESPONSE*

Subgroup and variable	Cetuximab plus irinotecan n=218	Cetuximab n=111
Response – n (%)		
Complete response	0	0
Partial response	50 (22.9)	12 (10.8)
Stable disease	71 (32.6)	24 (21.6)
Progressive disease	68 (31.2)	59 (53.2)
Could not be evaluated	29 (13.3)	16 (14.4)

Patients treated with cetuximab plus irinotecan vs cetuximab, achieved:

- Overall response: 22.9% vs 10.8%, p=0.007
- Disease control rate: 55.5% vs 32.4%, p<0.001

TIME TO DISEASE PROGRESSION IN THE TWO STUDY GROUPS



The hazard ratio for disease progression in the combination-therapy group as compared with the monotherapy group was 0.54 (95 percent confidence interval, 0.42 to 0.71) (p<0.001 by the log-rank test). The points on the curves represent the dates on which a patient's data were censored

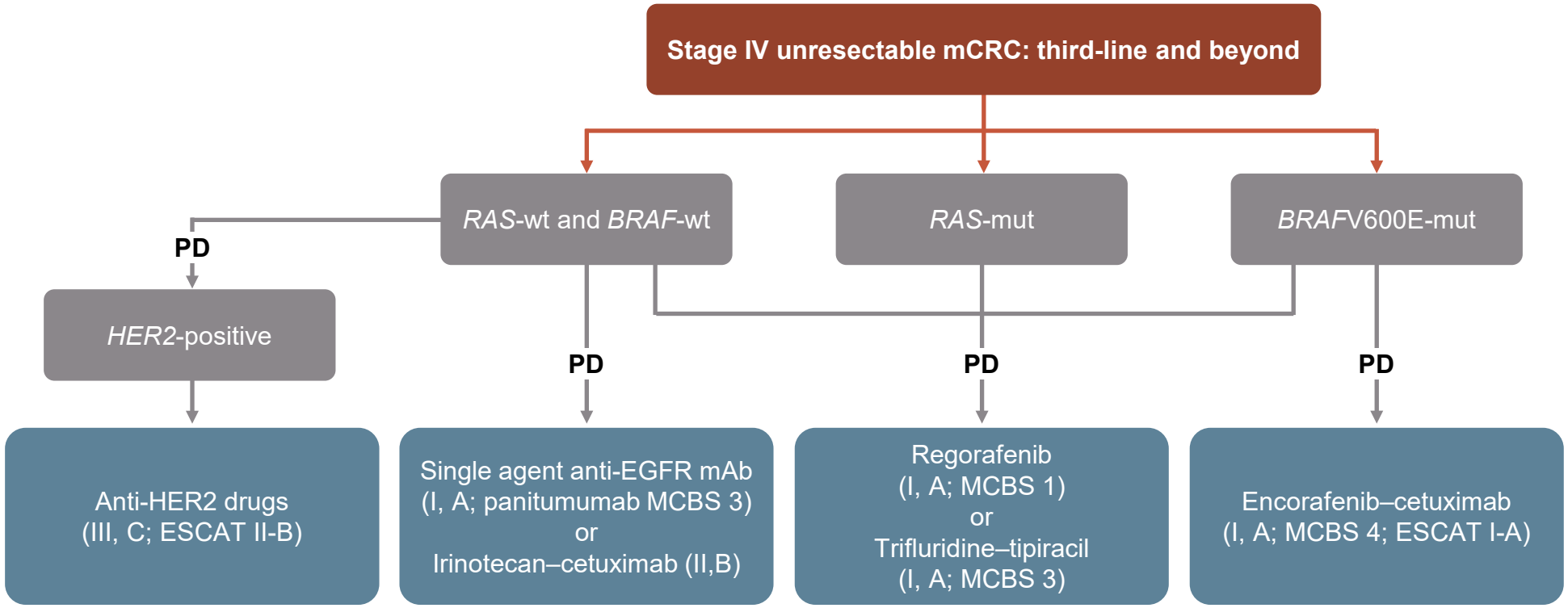
CI, confidence interval; CRC, colorectal cancer; EGFR, epidermal growth factor receptor

Cunningham D, et al. N Engl J Med. 2004;351:337-345

THIRD LINE TREATMENT OPTIONS

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

ESMO CLINICAL PRACTICE GUIDELINES

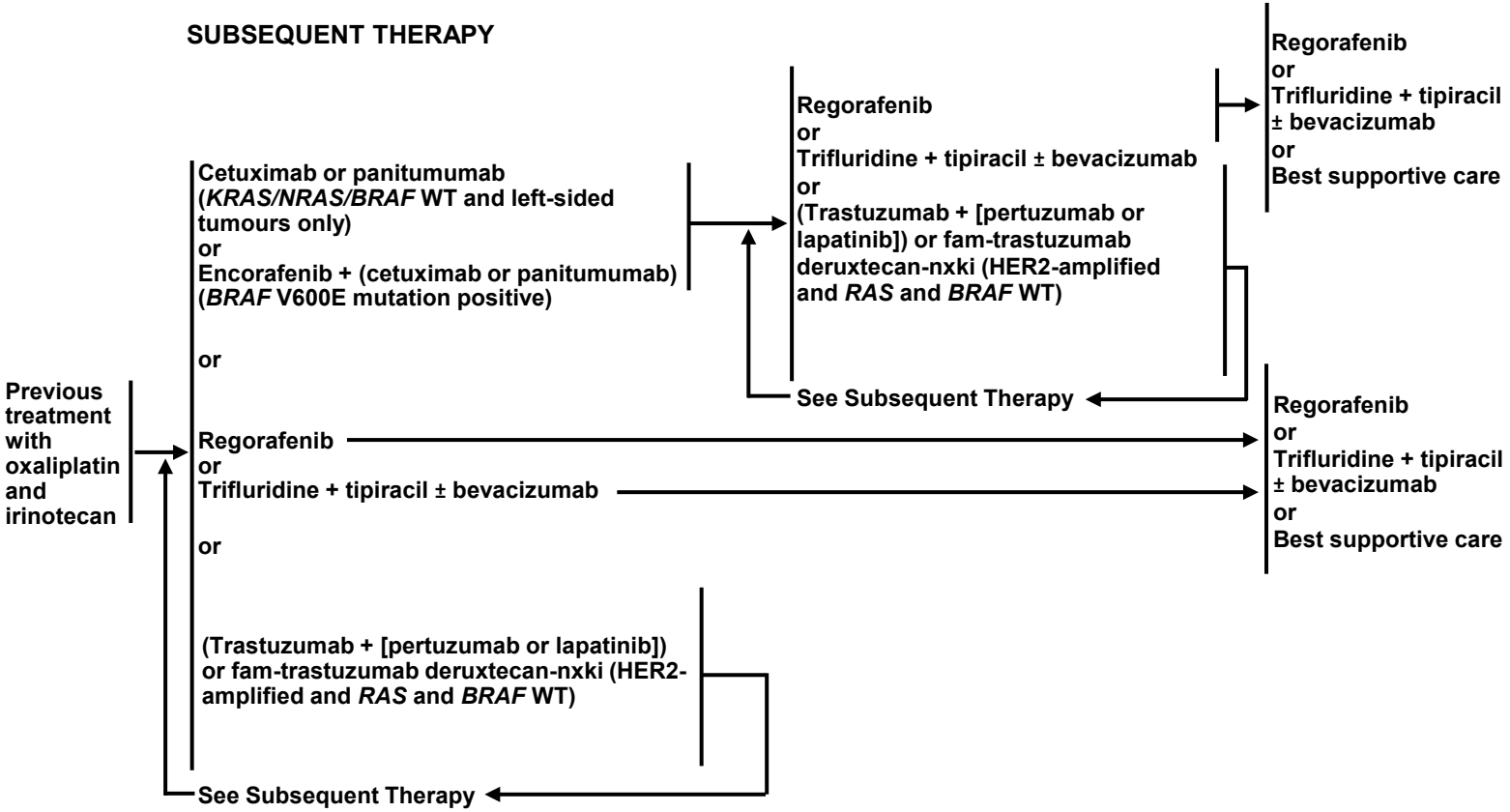


BRAF, proto-oncogene B-Raf; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO Magnitude of Clinical Benefit Scale;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

Cervantes A, et al. Ann Oncol. 2022;4(1):10-32

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC CRC

NCCN CLINICAL PRACTICE GUIDELINES

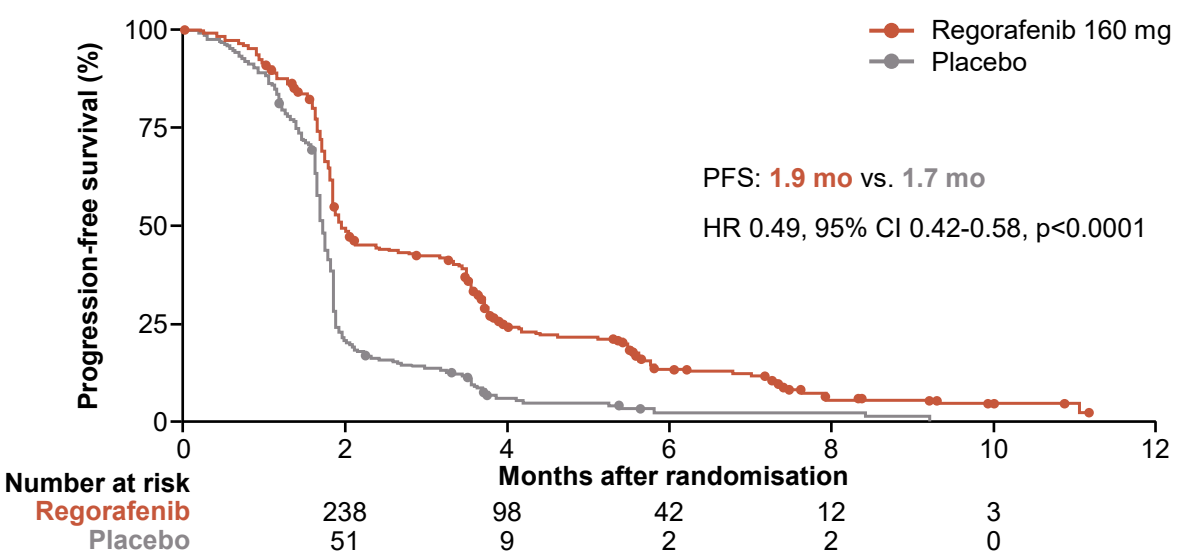


BRAF, proto-oncogene B-Raf; CRC, colorectal cancer; dMMR, deficient mismatch repair; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; MSI-H, microsatellite instability-high; NCCN, National Comprehensive Cancer Network; NRAS, neuroblastoma ras viral oncogene homolog; RAS, rat sarcoma viral oncogene homologue; WT, wild-type

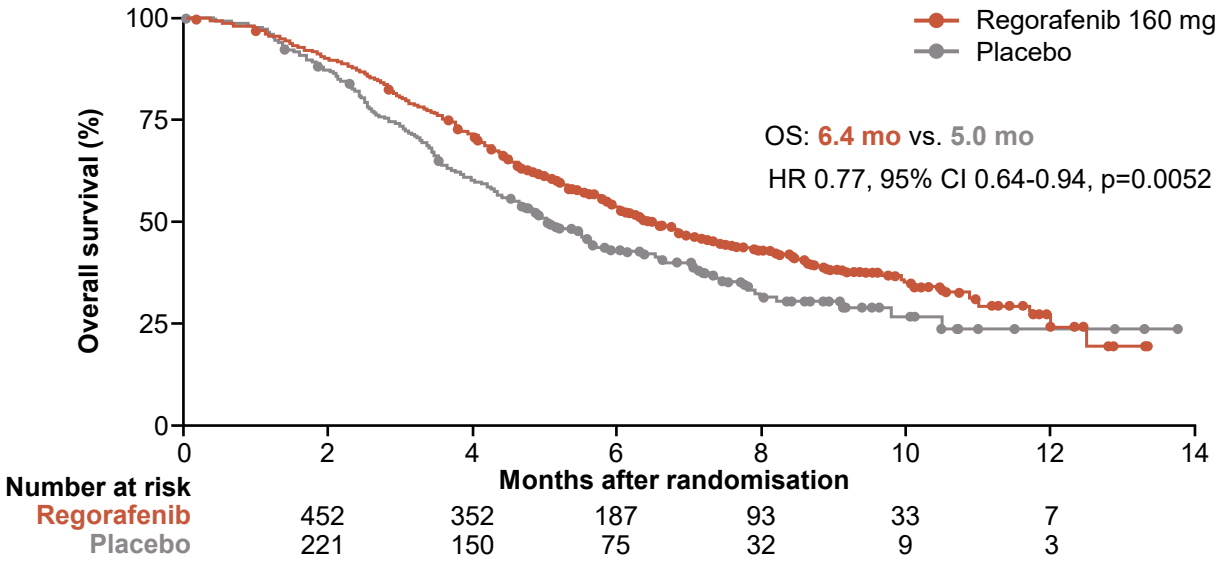
NCCN guidelines, Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed July 2023

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

PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



Tumour response:

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

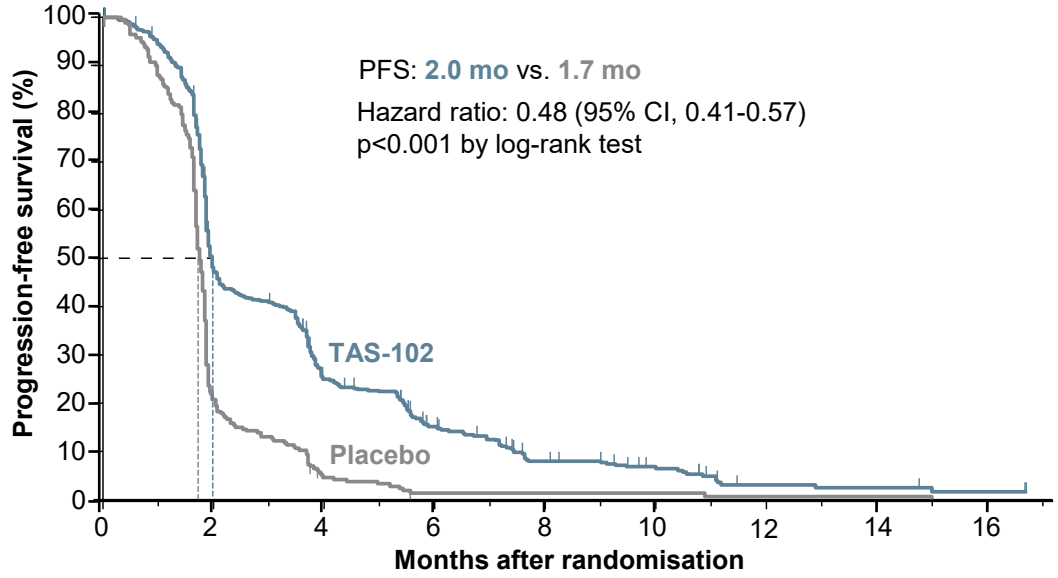
DCR: 41% vs. 15% (p<0.0001)

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;381:303-312

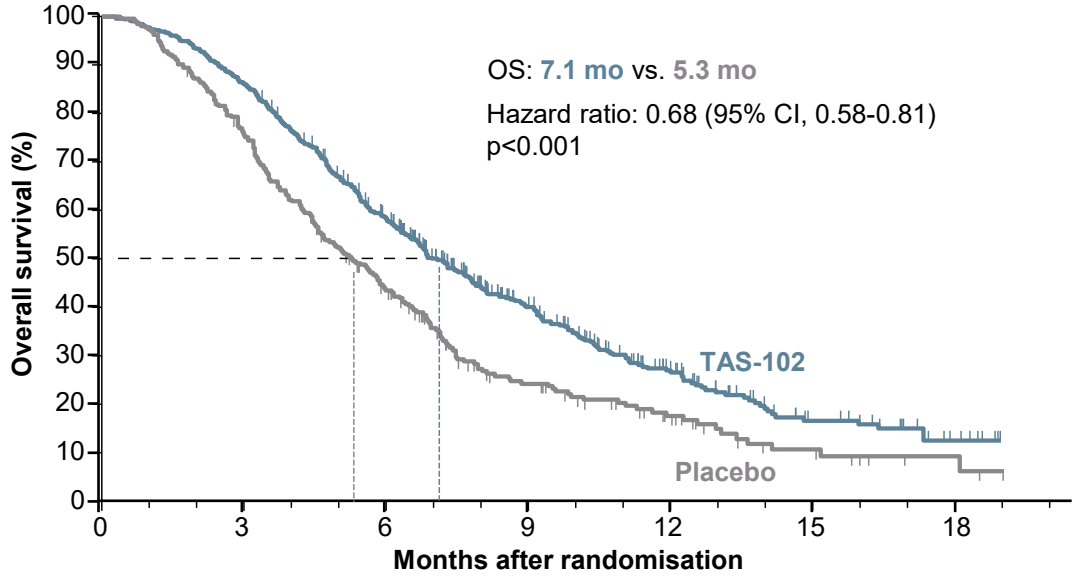
RECOURSE STUDY: TAS-102 PROLONGED PFS AND OS IN REFRACTORY mCRC PATIENTS

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

OVERALL SURVIVAL



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

Tumour response:

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;372:1909-1919

SAFETY PROFILE IN PATIENTS BEYOND THE SECOND LINE

MOST COMMONLY REPORTED (≥25%) ADVERSE EVENTS 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
Neutropenia	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
Vomiting	28	2			

[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

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

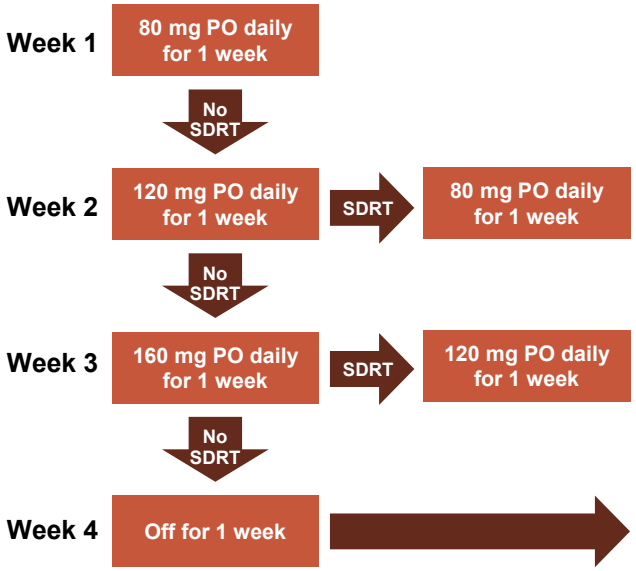
TAS-102, trifluridine/ tipiracil

1. Mayer RJ, et al. N Engl J Med. 2015;372:1909-1919; 2. Grothey A, et al. Lancet. 2013;381:303-312

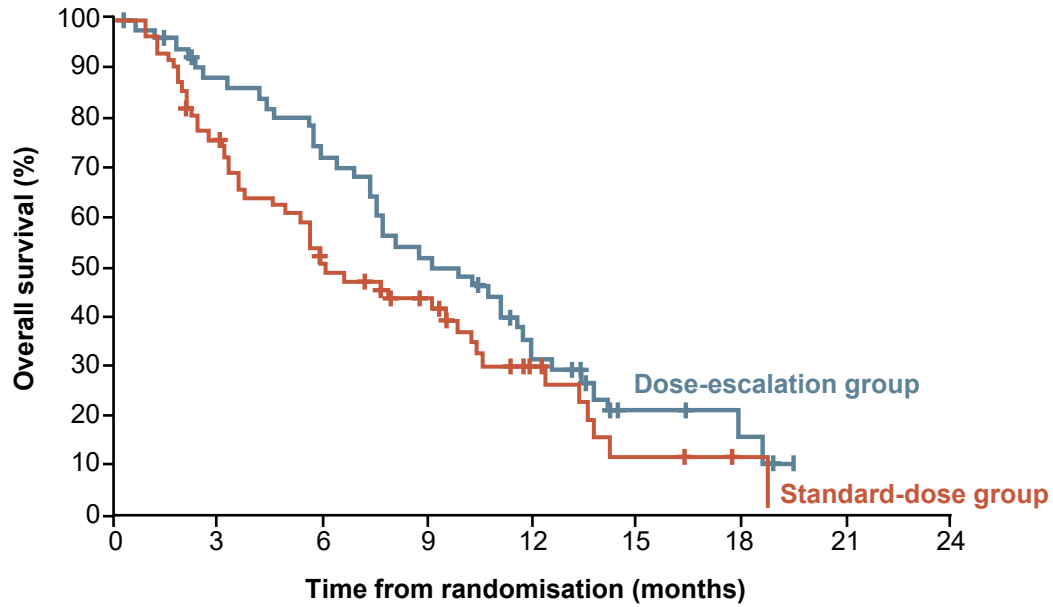
DOSE-ESCALATED STRATEGY FOR MANAGEMENT OF ADVERSE EVENTS WITH REGORAFENIB

- ReDOS study: no significant difference in overall survival between dose escalation and standard dosing

A DOSE-ESCALATION SCHEDULE FOR REGORAFENIB TO MINIMISE TOXICITIES[1]



PHASE 2 ReDOS STUDY[2]



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

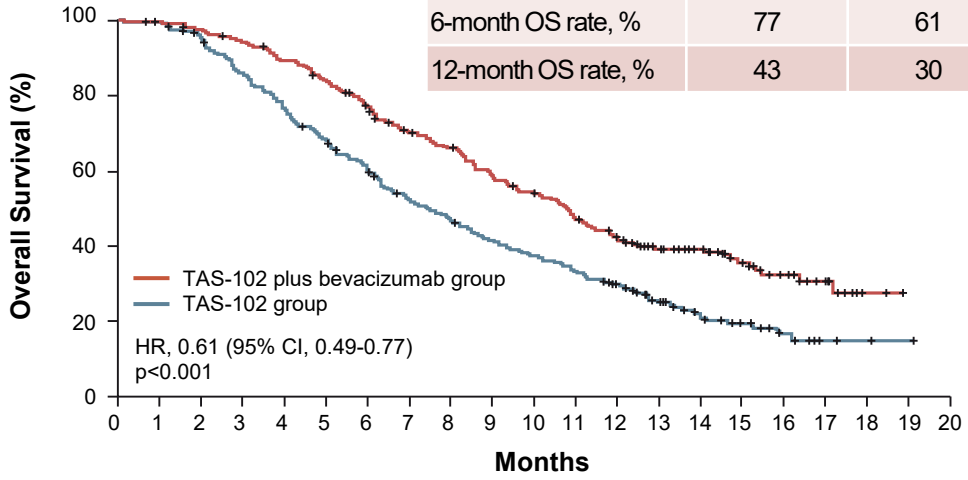
1. Grothey A. Clin Adv Hematol Oncol. 2015;13(8):514-517; 2. Bekaii-Saab TS, et al. Lancet Oncol. 2019;20(8):1070-1082

SUNLIGHT: TAS-102 PLUS BEVACIZUMAB IMPROVES OUTCOMES IN REFRACTORY mCRC

- TAS-102 plus bevacizumab improved OS and PFS in refractory CRC patients

OVERALL SURVIVAL (PRIMARY ENDPOINT)

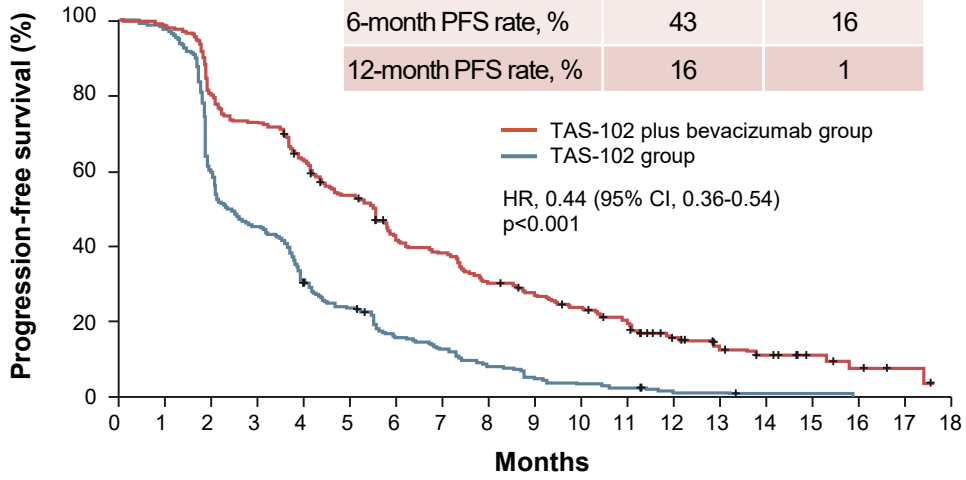
	TAS-102 plus bevacizumab (N=246)	TAS-102 (N=246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30



No. at risk																				
TAS-102 plus bevacizumab group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
TAS-102 group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

PROGRESSION-FREE SURVIVAL

	TAS-102 plus bevacizumab (N=246)	TAS-102 (N=246)
Median PFS, months	5.6	2.4
6-month PFS rate, %	43	16
12-month PFS rate, %	16	1



No. at risk																				
TAS-102 plus bevacizumab group	246	242	198	179	153	128	99	89	70	61	52	43	25	18	13	7	4	2	0
TAS-102 group	246	236	147	109	74	56	36	29	19	12	8	6	2	2	1	1	0	0	0

CI, confidence interval; HR, hazard ratio; (m)CRC, (metastatic) colorectal cancer; OS, overall survival; PFS, progression-free survival; TAS-102, trifluridine/tipiracil

Tabernero J, et al. J Clin Oncol. 2023;41(suppl 4; abstr 4) (ASCO GI 2023, oral presentation); Prager G, et al. N Engl J Med. 2023; 388:1657-1667

SUNLIGHT: SAFETY RESULTS

OVERALL SAFETY

Event (any cause), n (%)	TAS-102 plus bevacizumab (N=246)	TAS-102 (N=246)
Overall AEs	241 (98)	241 (98)
TAS-102-related AEs	221 (90)	200 (81)
Bevacizumab-related AEs	119 (48)	NA
Severe (grade ≥3) AEs	178 (72)	171 (70)
Serious AEs	61 (25)	77 (31)
Treatment-related deaths	0	0
AEs leading to withdrawal from the study	31 (13)	31 (13)

Dose modification, n (%)	TAS-102 plus bevacizumab (N=246)	TAS-102 (N=246)
Dose reductions	40 (16)	30 (12)
Dose delays	171 (70)	131 (53)

TEAEs IN ≥20% OF ALL PATIENTS

TEAE, n (%)	TAS-102 plus bevacizumab (N=246)		TAS-102 (N=246)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	153 (62)	106 (43)	126 (51)	79 (32)
Nausea	91 (37)	4 (2)	67 (27)	4 (2)
Anemia	71 (29)	15 (6)	78 (32)	27 (11)
Asthenia	60 (24)	10 (4)	55 (22)	10 (4)
Fatigue	53 (22)	3 (1)	40 (16)	9 (4)
Diarrhea	51 (21)	2 (1)	46 (19)	6 (2)
Decreased appetite	50 (20)	2 (1)	38 (15)	3 (1)

- Hypertension (10% vs 2%), nausea and neutropenia occurred more frequently in the combination group
  - One case of febrile neutropenia with TAS-102 plus bevacizumab versus six with TAS-102

AE, adverse event; TAS-102, trifluridine/tipiracil; TEAE, treatment emergent adverse event

Tabernero J, et al. J Clin Oncol. 2023;41(suppl 4; abstr 4) (ASCO GI 2023, oral presentation); Prager G, et al. N Engl J Med. 2023; 388:1657-1667

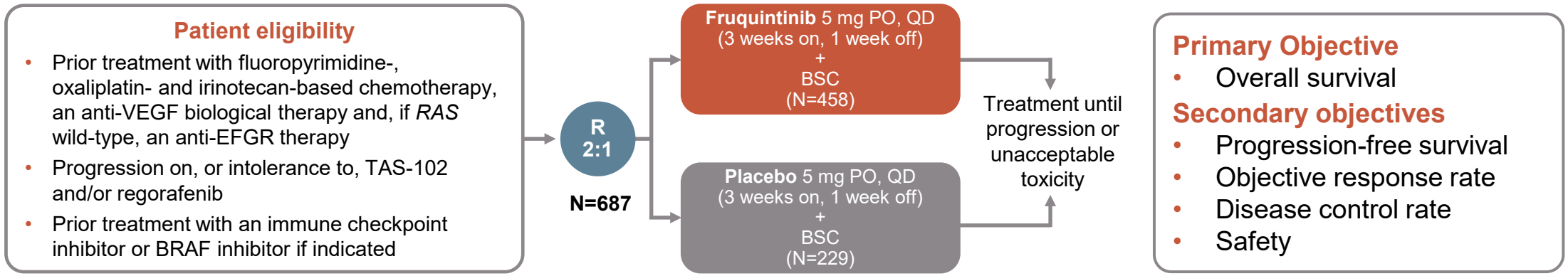
AFTER REGORAFENIB AND TAS-102 ± BEV WHAT NEXT?

bev, bevacizumab; TAS-102, trifluridine/tipiracil

FRESCO-2: BACKGROUND AND STUDY DESIGN

AFTER REGORAFENIB AND/OR TAS-102

- Effective treatment options are limited for patients with refractory metastatic colorectal cancer
- Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor of VEGFR-1, -2 and -3 and was approved in China in the 3L+ mCRC setting based on results from the FRESCO trial
- FRESCO-2 evaluated fruquintinib in more heavily pre-treated patients reflecting current global practices



Stratification factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months

Note: to ensure the patient population is reflective of clinical practice, the number of patients with prior regorafenib was limited to 344 patients (50%); TAS-102, trifluridine and tipiracil hydrochloride

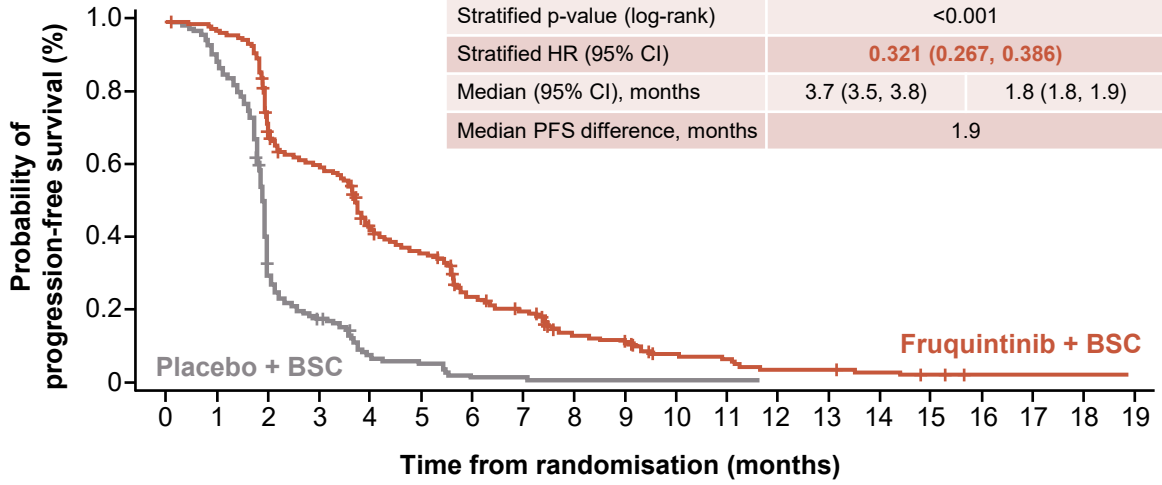
3L, third line; BRAF, proto-oncogene B-Raf; BSC, best supportive care; EFGR, endothelial growth factor; mCRC, metastatic prostate cancer; PO, orally; QD, once a day; R, randomisation; RAS, rat sarcoma viral oncogene homologue; VEGF(R), vascular endothelial growth factor (receptor); TAS-102, trifluridine/tipiracil

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

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 (95% CI), months	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Median PFS difference, months	1.9	



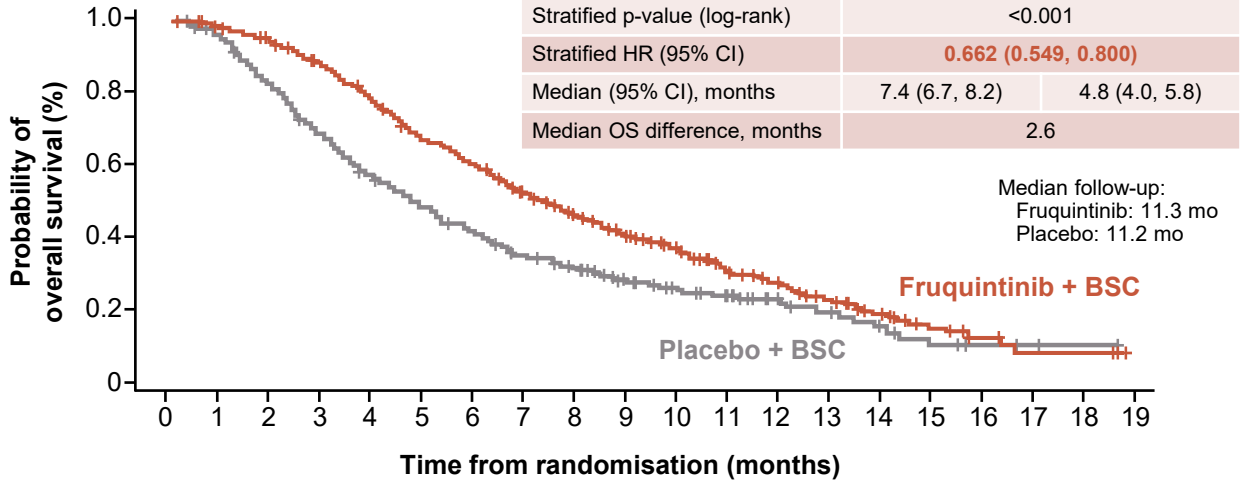
Patients at risk

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 (95% CI), months	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Median OS difference, months	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)

<u>Tumour response:</u>
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

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SUMMARY

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SEQUENTIAL TREATMENT CONSIDERATIONS FOR ADVANCED COLON CANCER

Treatment of advanced CRC should be considered as a continuum of care.
Decision-making at each stage of therapy should account for patient suitability and tolerability, tumour biomarkers, and prior exposure to chemotherapies and/or targeted agents.

Initial systemic therapy:
Is the patient considered appropriate for intensive therapy?

Consider the patient's prior treatments. Have they received a previous:
Oxaliplatin-based chemotherapy?
Irinotecan-based chemotherapy?
Oxaliplatin- and irinotecan-based regimen?
FP without oxaliplatin/irinotecan?

Consider the results of molecular testing. Is the patient's tumour:
KRAS/NRAS/BRAF wild-type?
BRAF V600E-positive?
dMMR/MSI-H?
HER2-amplified, RAS wild-type?

Consider the location of the patient's tumour:
Left- or right sided?

Please refer to relevant treatment guidelines for the full details of the decision-making pathway and treatment options at each stage

BRAF, proto-oncogene B-Raf; CRC, colorectal cancer; FP, fluoropyrimidine; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homologue; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; NRAS, neuroblastoma RAS viral oncogene homolog; RAS, rat sarcoma viral oncogene homologue

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