Looking Down the Road at the Therapeutic Pipeline

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Agenda

- **Current Landscape for VEGF inhibitors in CRC**

- **Ongoing and Recent VEGF inhibitor trials in mCRC**
  - *AtezoTRIBE trial*
  - *VEGF TKI + IO combinations*

Right Drugs to Right Patients (Biomarker)

Current Landscape (Approved Drugs)

Study	Agent	Line of Rx	RR	PFS (mos)	OS (mos)	HR for OS
AVF2107	Bevacizumab	1st	+ 10%	+ 4.4	+ 4.7	0.66
NO16966	Bevacizumab	1st	NS	+ 1.4	NS	NS
ECOG E3200	Bevacizumab	2nd	+ 14.1%	+ 2.6	+ 2.1	0.75
TML	Bevacizumab	2nd	+ 1.5%	+ 1.6	+ 1.4	0.83
VELOUR	Aflibercept	2nd	+ 3.3%	+ 2.23	+ 1.4	0.82
RAISE	Ramucirumab	2nd	NS	+1.2	+ 1.6	0.84
CORRECT	Regorafenib	Refractory	NS	+ 0.2	+ 1.4	0.77

Hurwitz H et al. *N Engl J Med*. 2004;350(23):2335-2342. Saltz LB et al. *J Clin Oncol*. 2008;26(12):2013-2019. Giantonio BJ et al. *J Clin Oncol*. 2007;25(12):1539-1544. Van Cutsem E et al. ASCO 2012. Abstract 3502. Tournigand C et al. ASCO 2012. Abstract LBA3500. Allegra CJ et al. ASCO 2012. Abstract 3505. de Gramont A et al. ASCO 2011. Abstract 71344. Allegra CJ et al. *J Clin Oncol*. 2009;27(20):3385-3390. Grothey A et al. *Lancet*. 2013;381(9863):303-312.

Anti-angiogenic Agents Tested in Phase 3 Trials in mCRC

Agent	No. of Patients
Semaxanib (SU5416)	2084
Cediranib (AZD 2171)	3194
Sunitinib	1623
Ramucirumab (IMC-1121B)	1050
Brivanib	923
Vatalanib	2023
Bevacizumab (Bev)	> 50 phase 3 studies*

* Clinicaltrials.gov. Accessed 6/21/12.

“Over a decade, over 2,000 trials but few drugs and modest benefits – need biomarkers”

Jayson GC et al. *Nat Rev Clin Oncol*. 2012;9(5):297-303.

Current Landscape (Updated)

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer

Prager GW et al. DOI: 10.1056/NEJMoa2214963

CLINICAL PROBLEM

In patients with refractory metastatic colorectal cancer, oral trifluridine–tipiracil (FTD–TPI) is commonly used as third- or fourth-line therapy. Preliminary research suggests that combining FTD–TPI with the vascular endothelial growth factor inhibitor bevacizumab might extend survival, but more data are needed.

CLINICAL TRIAL

Design: A phase 3, international, randomized trial assessed the efficacy and safety of FTD–TPI plus bevacizumab, as compared with FTD–TPI alone, in adults who had received one or two previous chemotherapy regimens for the treatment of advanced colorectal cancer and had had disease progression or unacceptable adverse effects.

Intervention: 492 patients were assigned to receive oral, twice-daily FTD–TPI at a starting dose of 35 mg per square meter of body-surface area (given on days 1 through 5 and 8 through 12) plus intravenous bevacizumab at a dose of 5 mg per kilogram of body weight (given on days 1 and 15) or FTD–TPI alone in 28-day treatment cycles, which continued until disease progression or unacceptable toxic effects occurred or consent was withdrawn. The primary end point was overall survival.

RESULTS

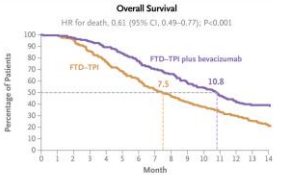
Efficacy: During a median follow-up of approximately 14 months, overall survival was significantly longer in the group that received FTD–TPI plus bevacizumab than in the group that received FTD–TPI alone.

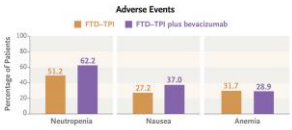
Safety: Neutropenia, nausea, and anemia were the most common adverse events in both groups. The incidence of neutropenia (including events of grade ≥3) and that of nausea and hypertension were higher among patients who received FTD–TPI plus bevacizumab than among those who received FTD–TPI alone. No new safety signals emerged.

LIMITATIONS AND REMAINING QUESTIONS

- Black patients were underrepresented in the trial.

Links: Full Article | NEJM Quick Take | Science behind the Study





CONCLUSIONS

In adults with refractory metastatic colorectal cancer, adding bevacizumab to FTD–TPI prolonged overall survival without introducing new safety concerns.

Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study

Arvind Dasari†, Sara Lonardi‡, Rocío García-Carbonero, Elena Elez, Takayuki Yoshino, Alberto Sobrero, James Yao, Pilar García-Alfonso, Judit Kocsis, Antonio Cubillo Gracian, Andrea Sartore-Bianchi, Torah Satoh, Violaine Randrian, Jiri Tomasek, Geoff Chong, Andrew Scott Poulsen, Toshiki Masuishi, Jeremy Jones, Tibor Csőszi, Chiara Cremolini, Francois Ghiringhelli, Ardaman Shergill, Howard S Hochster, John Krauss, Ali Bassam, Michel Ducreux, Anneli Elme, Laurence Faugeras, Stefan Kasper, Eric Van Cutsem, Dirk Arnold, Shivani Nanda, Zhao Yang, William R Schelman, Marek Kania, Josep Tabernero†, Cathy Eng†, on behalf of the FRESCO-2 Study Investigators‡

Summary

Background There is a paucity of effective systemic therapy options for patients with advanced, chemotherapy-refractory colorectal cancer. We aimed to evaluate the efficacy and safety of fruquintinib, a highly selective and potent oral inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, in patients with heavily pretreated metastatic colorectal cancer.

Methods We conducted an international, randomised, double-blind, placebo-controlled, phase 3 study (FRESCO-2) at 124 hospitals and cancer centres across 14 countries. We included patients aged 18 years or older (≥20 years in Japan) with histologically or cytologically documented metastatic colorectal adenocarcinoma who had received all current standard approved cytotoxic and targeted therapies and progressed on or were intolerant to trifluridine–tipiracil or regorafenib, or both. Eligible patients were randomly assigned (2:1) to receive fruquintinib (5 mg capsule) or matched placebo orally once daily on days 1–21 in 28-day cycles, plus best supportive care. Stratification factors were previous trifluridine–tipiracil or regorafenib, or both, *RAS* mutation status, and duration of metastatic disease. Patients, investigators, study site personnel, and sponsors, except for selected sponsor pharmacovigilance personnel, were masked to study group assignments. The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. A non-binding futility analysis was done when approximately one-third of the expected overall survival events had occurred. Final analysis occurred after 480 overall survival events. This study is registered with ClinicalTrials.gov, NCT04322539, and EudraCT, 2020-000158-88, and is ongoing but not recruiting.

Findings Between Aug 12, 2020, and Dec 2, 2021, 934 patients were assessed for eligibility and 691 were enrolled and randomly assigned to receive fruquintinib (n=461) or placebo (n=230). Patients had received a median of 4 lines (IQR 3–6) of previous systemic therapy for metastatic disease, and 502 (73%) of 691 patients had received more than 3 lines. Median overall survival was 7·4 months (95% CI 6·7–8·2) in the fruquintinib group versus 4·8 months (4·0–5·8) in the placebo group (hazard ratio 0·66, 95% CI 0·55–0·80; p<0·0001). Grade 3 or worse adverse events occurred in 286 (63%) of 456 patients who received fruquintinib and 116 (50%) of 230 who received placebo; the most common grade 3 or worse adverse events in the fruquintinib group included hypertension (n=62 [14%]), asthenia (n=35 [8%]), and hand-foot syndrome (n=29 [6%]). There was one treatment-related death in each group (intestinal perforation in the fruquintinib group and cardiac arrest in the placebo group).

Interpretation Fruquintinib treatment resulted in a significant and clinically meaningful benefit in overall survival compared with placebo in patients with refractory metastatic colorectal cancer. These data support the use of fruquintinib as a global treatment option for patients with refractory metastatic colorectal cancer. Ongoing analysis of the quality of life data will further establish the clinical benefit of fruquintinib in this patient population.

Funding HUTCHMED.

Introduction

Colorectal cancer is the third most diagnosed cancer and second leading cause of cancer-related deaths worldwide.[1] Approximately 50% of patients with colorectal cancer develop distant metastases during their disease course; the overall 5-year survival rate for such patients is 15%.[2,3] Standard initial systemic treatments for metastatic colorectal cancer include chemotherapy and targeted therapies, as appropriate.[3,4] Later-line non-selective treatment options include the oral agents trifluridine–tipiracil and regorafenib, a multikinase inhibitor, which have shown incremental effects on median overall survival.[3,4] Consequently, there is an unmet need for safe and effective treatments for

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See Comment page 4

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FDA approves trifluridine and tipiracil with bevacizumab for previously treated metastatic colorectal cancer

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FDA approves fruquintinib in refractory metastatic colorectal cancer

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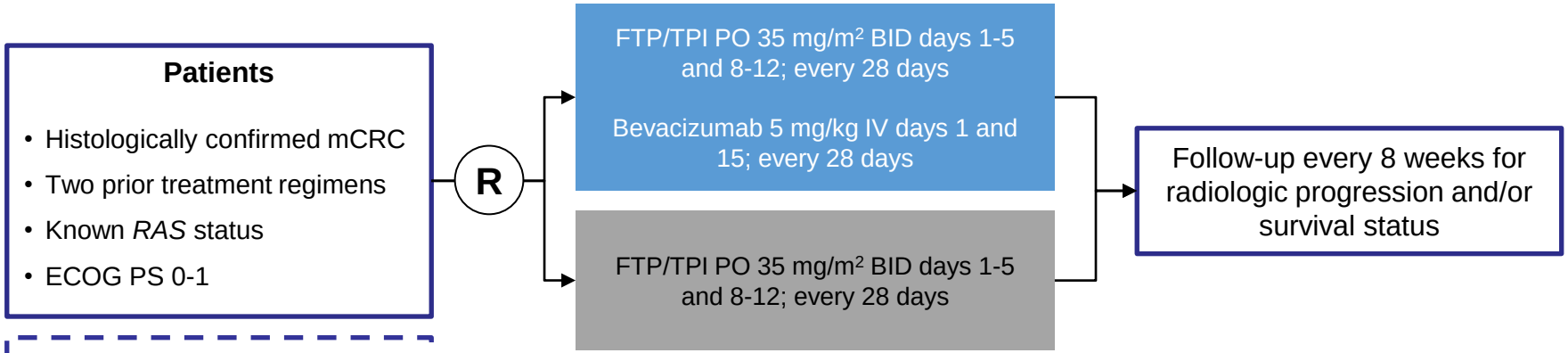
SUNLIGHT Study Design

- An open-label, randomized, phase 3 study in patients with refractory mCRC



Primary endpoint: OS in full analysis set
Secondary endpoints: PFS
DCR
ORR
Safety profile
QoL

Statistical considerations
- Sample size: 490 (245 per arm)
- Expected OS HR: 0.70 (30% reduction in risk of death) with 90% power
- Required OS events: 331
- No planned interim analysis

Tabernero J et al. ASCO GI 2023. Abstract 4.

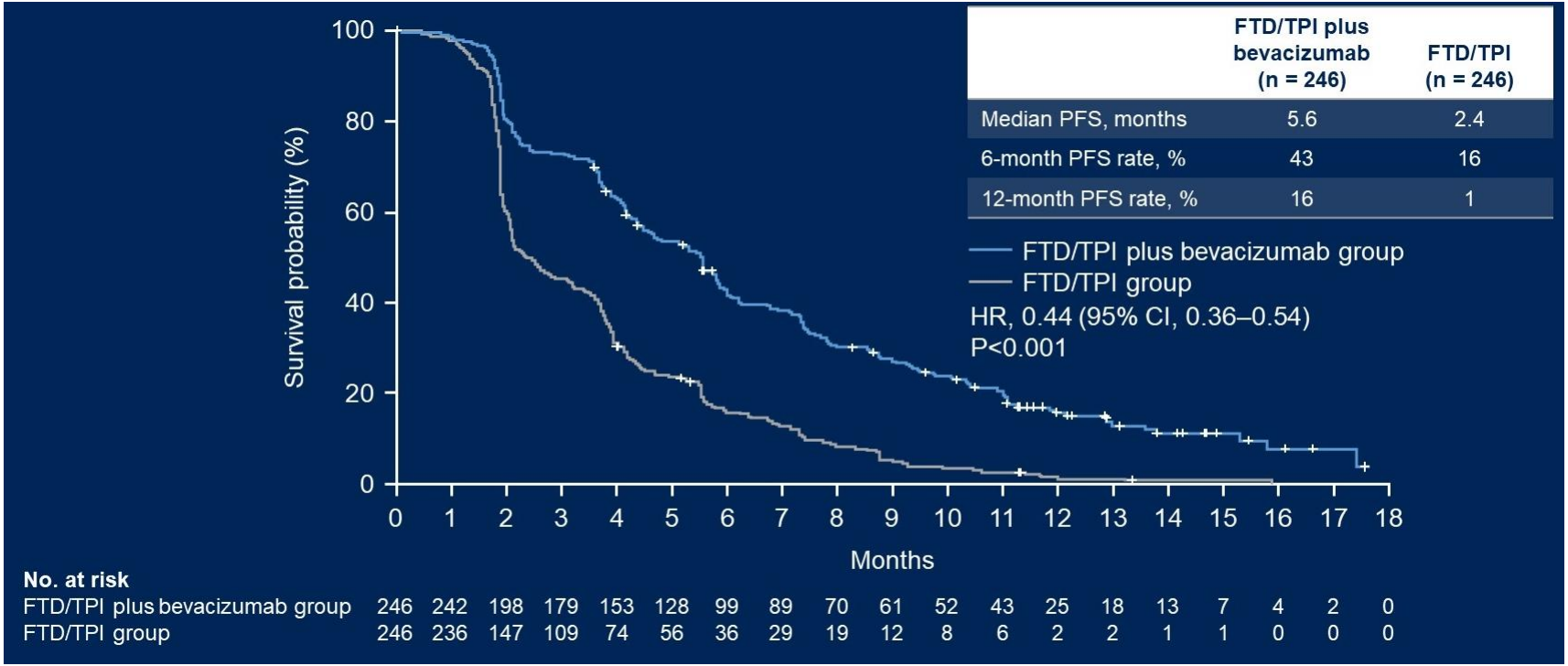
SUNLIGHT: Key Baseline Characteristics

Characteristic		FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Age	Median (range), years	62 (20–84)	64 (24–90)
	<65 years, n (%)	146 (59)	129 (52)
	≥65 years, n (%)	100 (41)	117 (48)
Sex, n (%)	Male	122 (50)	134 (55)
Region	European Union	158 (64)	157 (64)
	North America	8 (3)	8 (3)
	Rest of the world	80 (33)	81 (33)
Primary tumor localization, n (%)	Right	62 (25)	77 (31)
	Left	184 (75)	169 (69)
Time from diagnosis of first metastasis to randomization,[a] n (%)	<18 months	104 (42)	105 (43)
	≥18 months	142 (58)	141 (57)
***RAS* status,[a] n (%)**	Mutant	171 (70)	170 (69)
	Wild-type	75 (31)	76 (31)
Prior treatment with anti-VEGF, n (%)	Yes	188 (76)	188 (76)
Prior treatment with bevacizumab, n (%)	No	68 (28)	69 (28)
	Yes	178 (72)	177 (72)
ECOG PS, n (%)	0	119 (48)	106 (43)
	1	127 (52)	139 (57)
	2	0	1 (0.4)[b]

[a] As documented in the Interactive Web Response System set for randomization. [b] Patient had an ECOG PS of 1 at randomization but was assessed as having an ECOG PS of 2 on day 1, cycle 1.
ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; VEGF, vascular endothelial growth factor.

Tabernero J et al. ASCO GI 2023. Abstract 4.

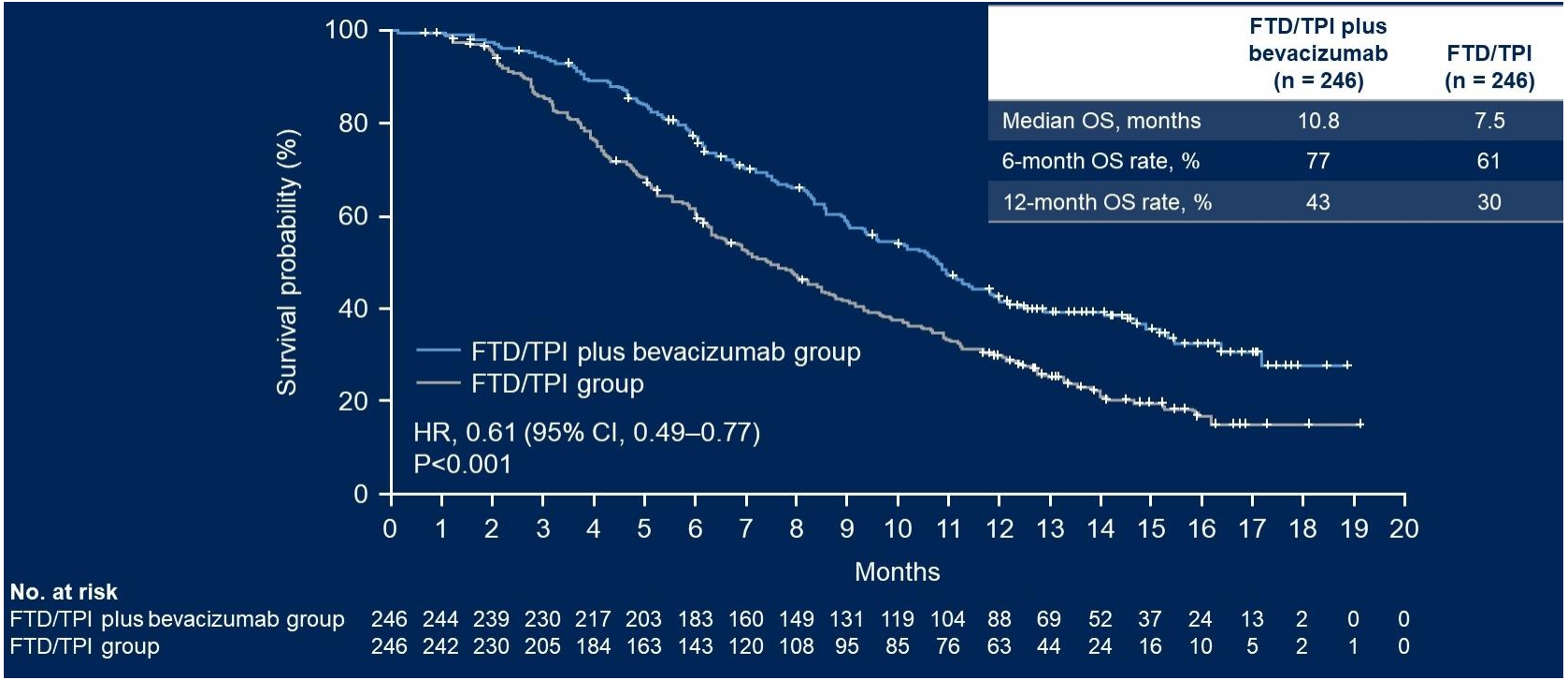
SUNLIGHT: PFS in Full Analysis Set



	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median PFS, months	5.6	2.4
6-month PFS rate, %	43	16
12-month PFS rate, %	16	1

Tabernero J et al. ASCO GI 2023. Abstract 4.

SUNLIGHT: OS in Full Analysis Set (Primary Endpoint)



	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30

Tabernero J et al. ASCO GI 2023. Abstract 4.

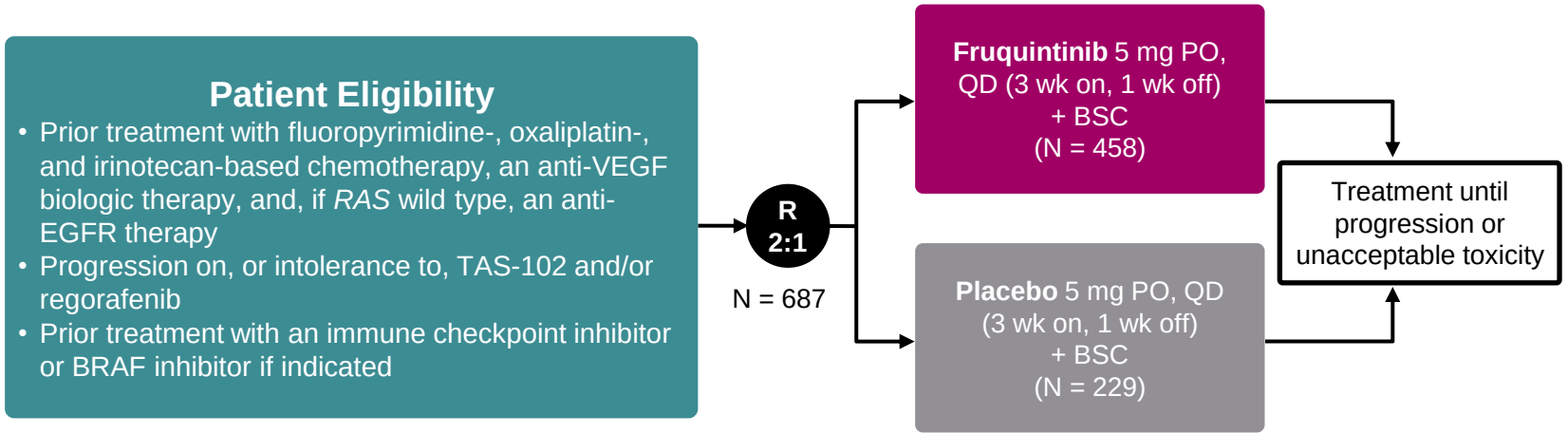
SUNLIGHT:TEAEs in ≥20% of Patients

	FTD/TPI plus bevacizumab (n = 246)		FTD/TPI (n = 246)	
TEAE, n (%)	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 were more common in the combination group; there was one case of febrile neutropenia with FTD/TPI plus bevacizumab versus six with FTD/TPI

Tabernero J et al. ASCO GI 2023. Abstract 4.

FRESCO-2 Study Design



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 mo vs >18 mo)

Note: To ensure the patient population is reflective of clinical practice, the number of patients treated with prior regorafenib was limited to 344 (50%).
BSC, best supportive care.
NCT04322539.

FRESCO-2: Patient and Disease Characteristics (ITT population[a])

Characteristic		Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Age	Median (range), yr	64 (25-82)	64 (30-86)
	≥65 yr, n (%)	214 (46.4)	111 (48.3)
Sex, n (%)	Female	216 (46.9)	90 (39.1)
Region, n (%)	North America	82 (17.8)	42 (18.3)
	Europe	329 (71.4)	166 (72.2)
	Asia Pacific	50 (10.8)	22 (9.6)
ECOG PS, n (%)	0	196 (42.5)	102 (44.3)
	1	265 (57.5)	128 (55.7)
Primary site at first diagnosis, n (%)	Colon left	192 (41.6)	92 (40.0)
	Colon right	97 (21.0)	53 (23.0)
	Colon left and right	4 (0.9)	2 (0.9)
	Colon unknown	25 (5.4)	13 (5.7)
	Rectum only	143 (31.0)	70 (30.4)
Liver metastases, n (%)	Yes	339 (73.5)	156 (67.8)

Characteristic (cont.)		Fruquintinib + BSC (N = 461)	Placebo + BSC (N = 230)
Duration of metastatic disease, n (%)	≤18 mo	37 (8.0)	13 (5.7)
	>18 mo	424 (92.0)	217 (94.3)
RAS status, n (%)	Wild type	170 (36.9)	85 (37.0)
	Mutant	291 (63.1)	145 (63.0)
BRAF V600E mutation, n (%)	No	401 (87.0)	198 (86.1)
	Yes	7 (1.5)	10 (4.3)
	Other/Unknown	53 (11.5)	22 (9.6)
Prior lines of therapy (metastatic disease)	Median (range), n	5 (2-16)	5 (2-12)
	≤3, n (%)	125 (27.1)	64 (27.8)
	>3, n (%)	336 (72.9)	166 (72.2)
Prior therapies, n (%)	VEGF inhibitor	445 (96.5)	221 (96.1)
	EGFR inhibitor	180 (39.0)	88 (38.3)
Prior TAS-102 and/or regorafenib, n (%)	TAS-102	240 (52.1)	121 (52.6)
	Regorafenib	40 (8.7)	18 (7.8)
	Both	181 (39.3)	91 (39.6)

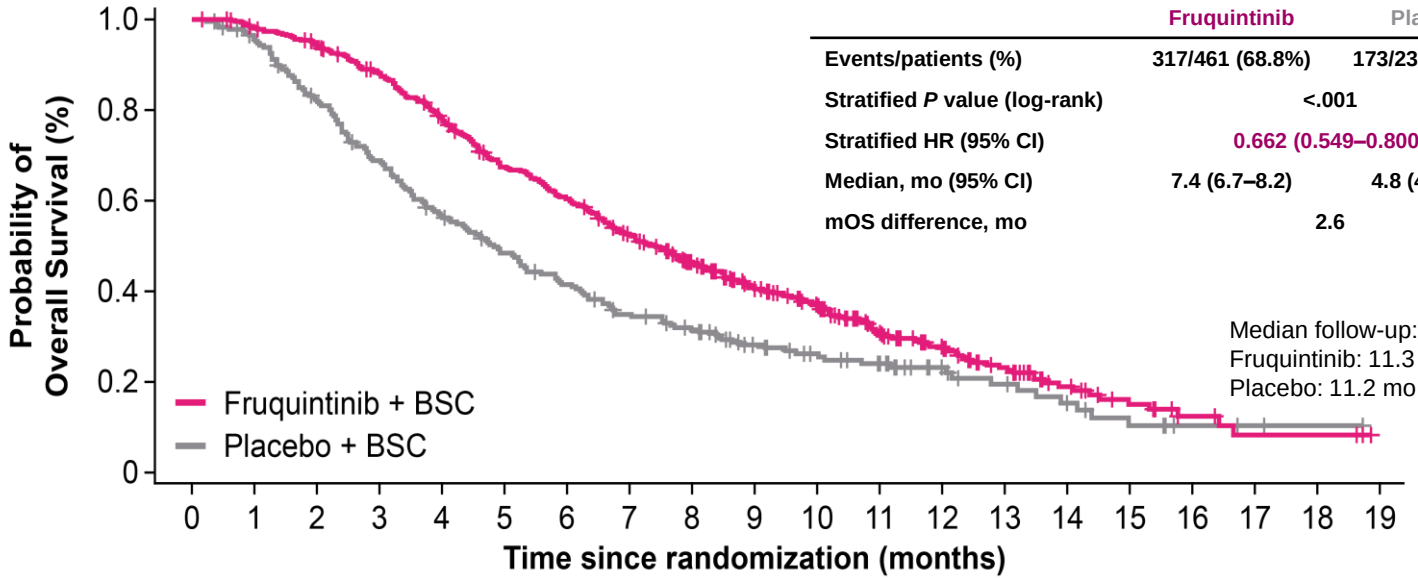
[a] Enrollment: Sep 2020 to Dec 2021; data cutoff: June 24, 2022.
BSC, best supportive care; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; *RAS*, rat sarcoma; mo, months; VEGF, vascular endothelial growth factor; yr, year.

Dasari NA et al. ESMO 2022. Abstract LBA25.

Primary Endpoint: OS

ITT Population

	Fruquintinib	Placebo
Events/patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified *P* value (log-rank)	<.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)
mOS difference, mo	2.6	



Median follow-up:
Fruquintinib: 11.3 mo
Placebo: 11.2 mo

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

Subsequent anticancer medication balanced between the 2 arms: **29.4% fruquintinib arm** vs **34.3% placebo arm**

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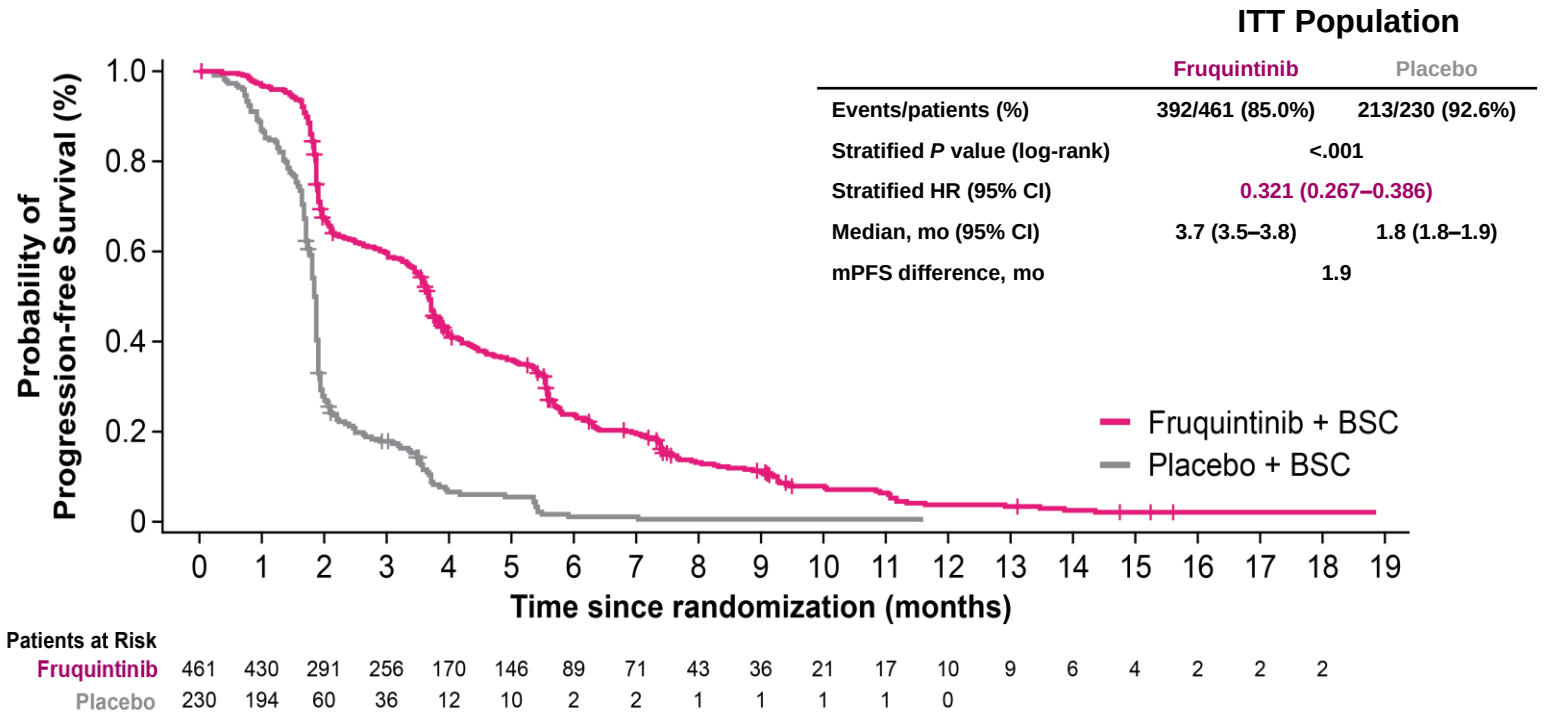
PFS



Dasari NA et al. ESMO 2022. Abstract LBA25.

Most Common TEAEs: SAFETY Population

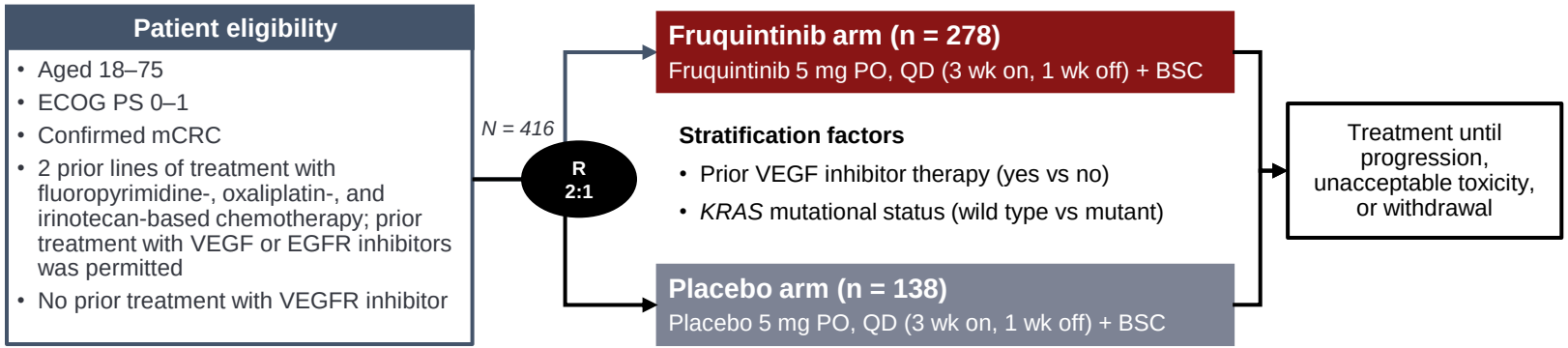
(any grade ≥ 15% in either arm)

TEAE, n (%)	Fruquintinib (n = 456)		Placebo (n = 230)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE	451 (98.9)	286 (62.7)	213 (92.6)	116 (50.4)
Hypertension	168 (36.8)	62 (13.6)	20 (8.7)	2 (0.9)
Asthenia	155 (34.0)	35 (7.7)	52 (22.6)	9 (3.9)
Decreased appetite	124 (27.2)	11 (2.4)	40 (17.4)	3 (1.3)
Diarrhea	110 (24.1)	16 (3.5)	24 (10.4)	0
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Fatigue	91 (20.0)	18 (3.9)	37 (16.1)	2 (0.9)
Hand-foot syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Abdominal pain	83 (18.2)	14 (3.1)	37 (16.1)	7 (3.0)
Nausea	79 (17.3)	3 (0.7)	42 (18.3)	2 (0.9)
Proteinuria	79 (17.3)	8 (1.8)	12 (5.2)	2 (0.9)
Constipation	78 (17.1)	2 (0.4)	22 (9.6)	0
Dysphonia	74 (16.2)	0	12 (5.2)	0

Dasari NA et al. ESMO 2022. Abstract LBA25.

FRESCO (NCT02314819): Study Design

Phase 3, Conducted in China



Primary Endpoint	Secondary Endpoints		Statistical Assumptions
Overall survival	Key • Progression-free survival • ORR • DCR	Other • DOR • Safety	Sample size • ~400 patients (280 OS events) would provide 80% power to detect a difference in OS with a HR of 0.70 at a 2-sided P value of .05 • Median OS assumption in the placebo arm is 6.3 mo, and median OS in fruquintinib arm is 9.0 mo

BSC, best supportive care; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PO, orally; QD, once a day; R, randomization; VEGF(R), vascular endothelial growth factor (receptor).

Li J et al. *JAMA*. 2018;319(24):2486-2496.

FRESCO: Patient and Disease Characteristics (ITT Population)

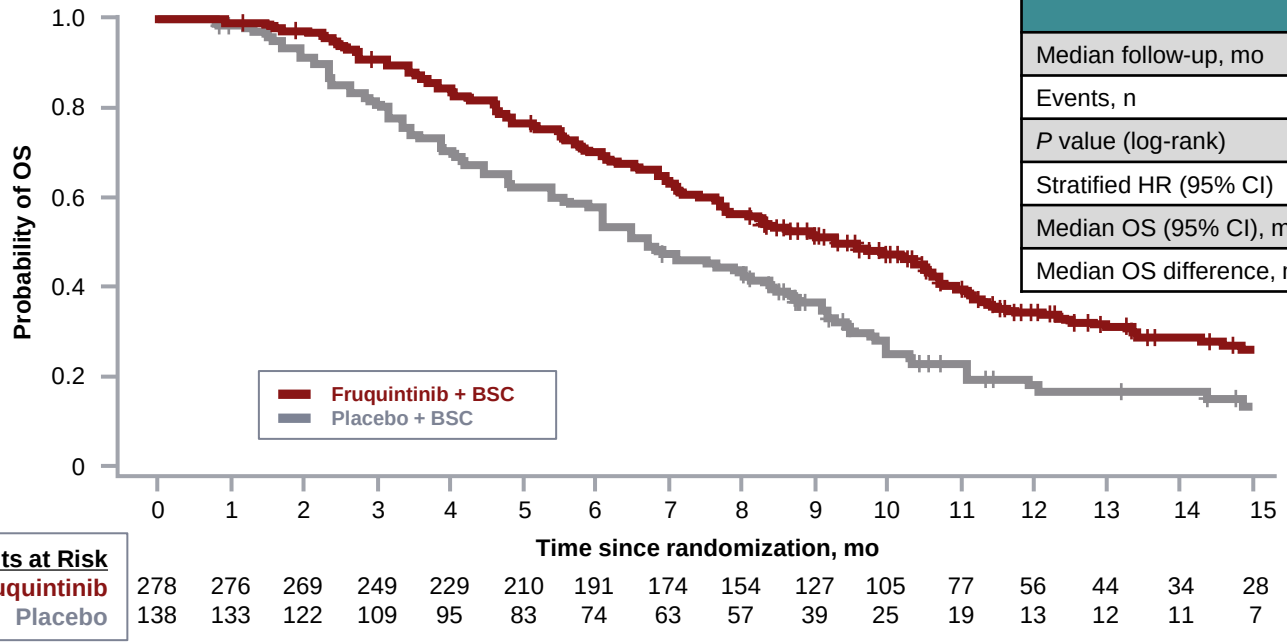
Characteristic		Fruquintinib + BSC (n = 278)	Placebo + BSC (n = 138)
Age	Median (range), yr	55 (23–75)	57 (24–74)
	<65 yr	228 (82.0)	110 (79.7)
Sex, n (%)	Male	158 (56.8)	97 (70.3)
ECOG PS, n (%)[a]	1	201 (72.3)	101 (73.2)
Time from first diagnosis to randomization	Median (range), yr	1.8 (0.1–9.7)	2.0 (0.3–9.8)
CRC stage at first diagnosis, n (%)	I	8 (2.9)	4 (2.9)
	II	34 (12.2)	18 (13.0)
	III	118 (42.4)	51 (37.0)
	IV	117 (42.1)	63 (45.7)
	Missing information	1 (0.4)	2 (1.4)
Primary disease site at first diagnosis, n (%)	Colon	147 (52.9)	70 (50.7)
	Rectum	125 (45.0)	60 (43.5)
	Colon and rectum	6 (2.2)	7 (5.1)
	Missing information[b]	0	1 (0.7)
KRAS status, n (%)	Wild type	157 (56.5)	74 (53.6)

Characteristic (cont.)		Fruquintinib + BSC (n = 278)	Placebo + BSC (n = 138)
Primary tumor location at first diagnosis, n (%)	Left[c]	214 (77.0)	115 (83.3)
	Right[d]	56 (20.1)	21 (15.2)
	Left and right	4 (1.4)	0
	Unknown	4 (1.4)	1 (0.7)
	Missing information	0	1 (0.7)
Metastases, n (%)	Multiple	265 (95.3)	134 (97.1)
	Liver	185 (66.5)	102 (73.9)
Prior antitumor treatment, n (%)	Chemotherapy[e]	278 (100)	138 (100)
	Radiation therapy	85 (30.6)	39 (28.3)
	Surgery	264 (95.0)	125 (90.6)
Prior therapy, n (%)	2L or 3L chemotherapy[f]	190 (68.3)	98 (71.0)
	VEGF inhibitors[g]	84 (30.2)	41 (29.7)
	EGFR inhibitors[h]	40 (14.4)	19 (13.8)
Prior chemotherapy with VEGF and EGFR inhibitors[i]	Neither	167 (60.1)	83 (60.1)
	VEGF only	71 (25.5)	36 (26.1)
	EGFR only	27 (9.7)	14 (10.1)
	Both	13 (4.7)	5 (3.6)

[a] All eligible patients had ECOG PS = 0 or 1 (0 = fully active, able to carry on all predisease activities without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. [b] Referred to cecum. [c] Splenic flexure, descending colon, transverse colon, sigmoid colon, rectum. [d] Cecum, ascending colon, hepatic flexure. [e] And pharmacologic treatment. [f] Systemic. [g] Included 120 patients who had received bevacizumab (fruquintinib arm, 83; placebo arm, 37) and 5 patients who had received aflibercept (fruquintinib arm, 1; placebo arm, 4). [h] Cetuximab. [i] No patients received VEGFR inhibitor.

Li J et al. *JAMA*. 2018;319(24):2486-2496.

FRESCO: Primary Endpoint – OS (ITT Population)



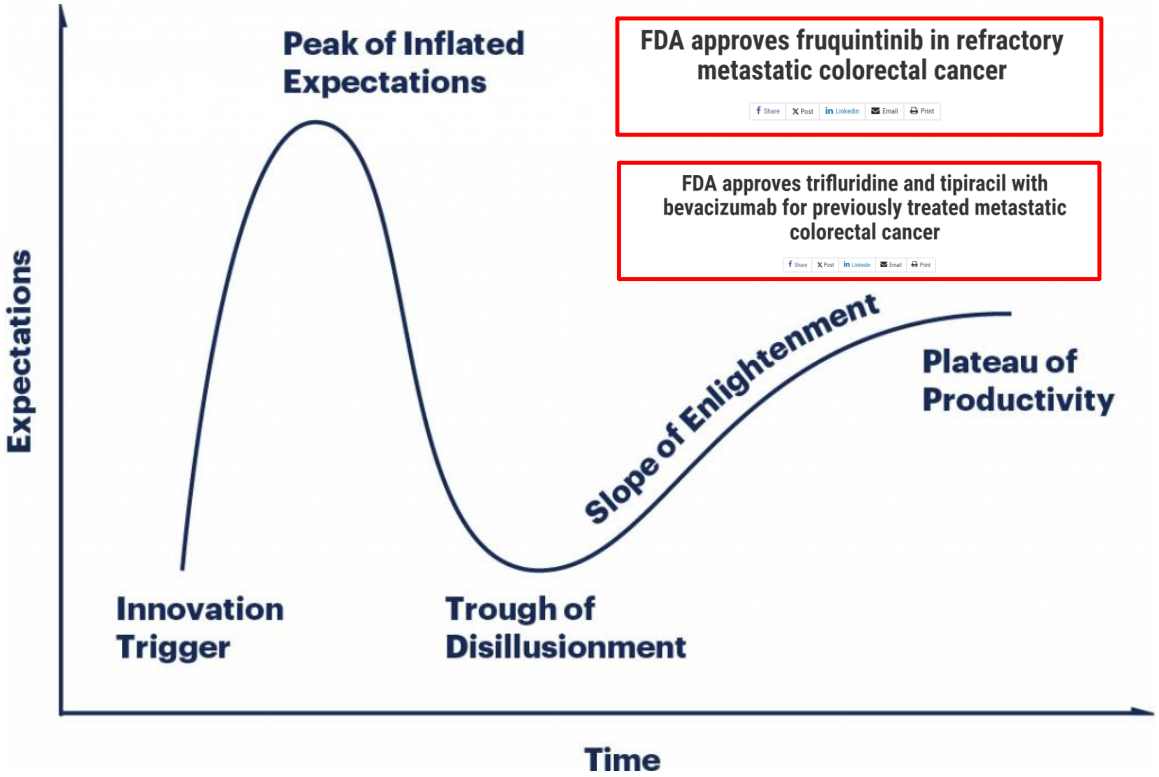
	Fruquintinib + BSC (n = 278)	Placebo + BSC (n = 138)
Median follow-up, mo	13.3	13.2
Events, n	297	
P value (log-rank)	<.001	
Stratified HR (95% CI)	0.65 (0.51–0.83)	
Median OS (95% CI), mo	9.30 (8.18–10.45)	6.57 (5.88–8.11)
Median OS difference, mo	2.73	

Subsequent anticancer medication between the 2 arms:
42.4% fruquintinib vs **50.7% placebo**

Data cutoff: January 17, 2017.
BSC, best supportive care; HR, hazard ratio; ITT, intention-to-treat; mo, months; OS, overall survival.

Li J et al. *JAMA*. 2018;319(24):2486-2496.

Current Landscape (Updated) – Sign of Things to Come?



Gartner Hype Cycle

Agenda

- **Current Landscape for VEGF inhibitors in CRC**

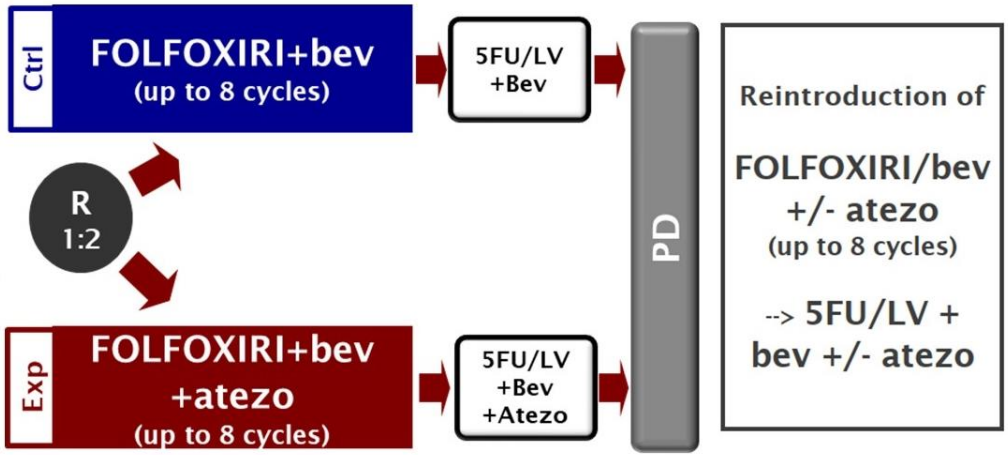
- **Ongoing and Recent VEGF inhibitor trials in mCRC**
  - *AtezoTRIBE trial*
  - *VEGF TKI + IO combinations*

Right Drugs to Right Patients (Biomarker)

AtezoTRIBE: Study Design

Key eligibility criteria

- Previously untreated, unresectable and RECIST v1.1-measurable mCRC
- Age 18-75 years
- ECOG PS ≤ 2 (ECOG PS= 0 if age= 71-75 years)
- Adjuvant oxaliplatin-containing chemotherapy not allowed
- Adjuvant fluoropyrimidine monotherapy allowed if more than 6 months elapsed between the end of adjuvant and first relapse
- Adequate bone marrow, liver and renal functions
- No contraindications to ICI

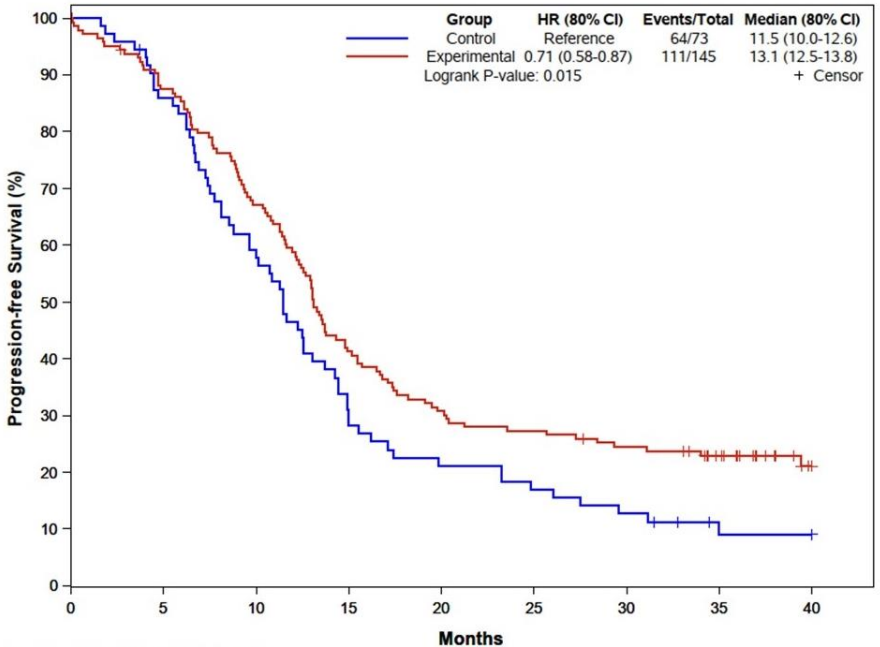


Stratification factors: center; ECOG PS (0 *vs* 1-2); primary turmour location (right *vs* left or rectum); previous adj chemotherapy (yes *vs* no)
Participating centers: 22 Italian sites

Primary endpoint: Progression-Free Survival
Sample size: Assuming a median PFS of 12 months in the control arm, 201 pts (129 PFS events) would provide 85% power to detect a difference in PFS in favour of the experimental arm with a HR of 0.66 at a one-sided α of 0.10.

Antoniotti C et al. ASCO 2023. Abstract 3500.

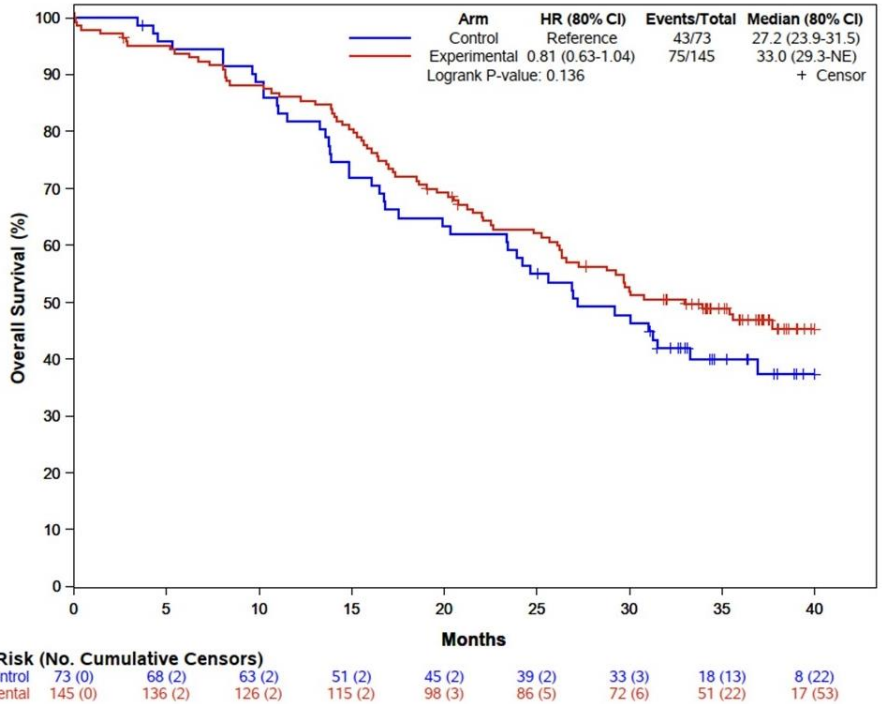
AtezoTRIBE: Updated PFS (ITT)



Cut-off date: January 23rd, 2023. At median follow-up: 37.0 months (IQR: 34.3-40.5)

Antoniotti C et al. ASCO 2023. Abstract 3500.

AtezoTRIBE: OS (ITT)

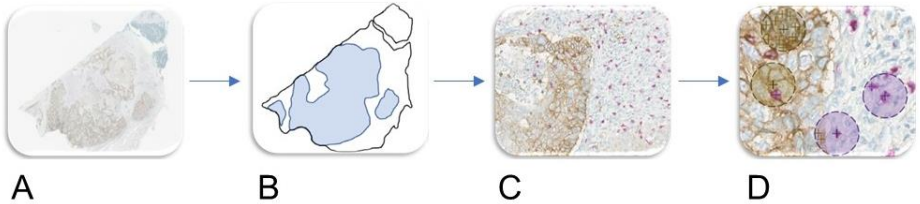


Cut-off date: January 23rd, 2023. At median follow-up: 37.0 months (IQR: 34.3-40.5)

Antoniotti C et al. ASCO 2023. Abstract 3500.

Immunoscore IC – More Than TILs Evaluation

CD8+ and PD-L1+ cell densities and proximity between them, by means of IHC and digital pathology



High IS-IC: high density of CD8+ and PD-L1+ cells and proximity between them
Low IS-IC: low density of CD8+ and PD-L1+ cells and proximity between them

Concordance between Immunoscore IC and TILs*

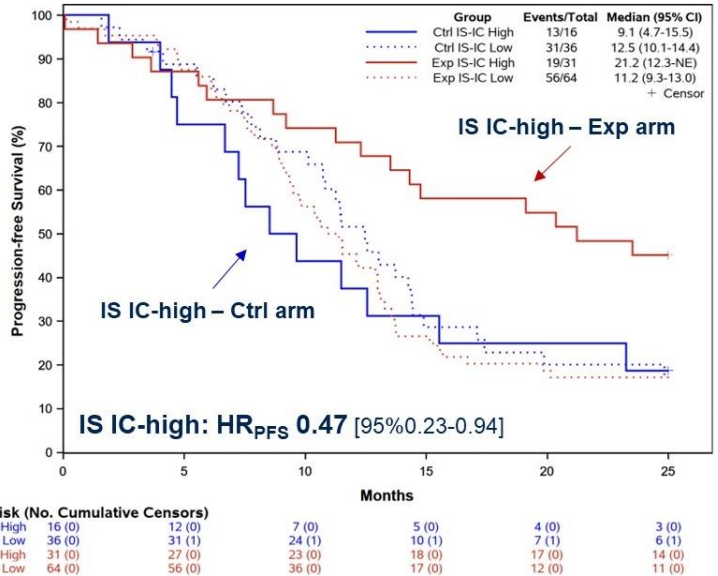
	TILs-HIGH	TILs-LOW	*K* of Cohen
Immunoscore IC-HIGH	21 (39%)	24 (25%)	*0.15*
Immunoscore IC-LOW	33 (61%)	73 (75%)	

*assessed by means of optical microscope

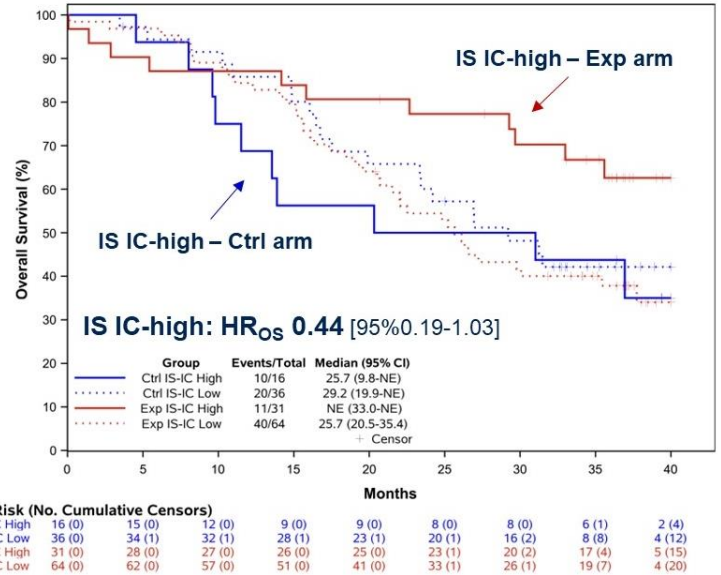
Antoniotti C et al. ASCO 2023. Abstract 3500. Antoniotti C et al. *Lancet Oncol.* 2022;23(7):876-887. Moretto R et al. *J Immunother Cancer.* 2023;11(4):e006633.

AtezoTRIBE: Outcomes According to Immunoscore IC and Arm (pMMR Cohort)

Progression-Free Survival



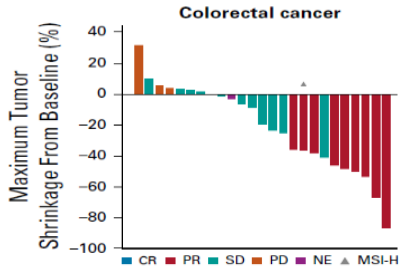
Overall Survival



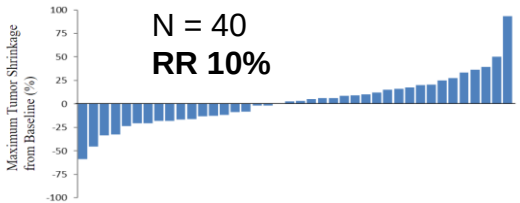
Antoniotti C et al. ASCO 2023. Abstract 3500.

PD1 Combos in pMMR CRC: Low Level Activity in Non-Liver Met Population

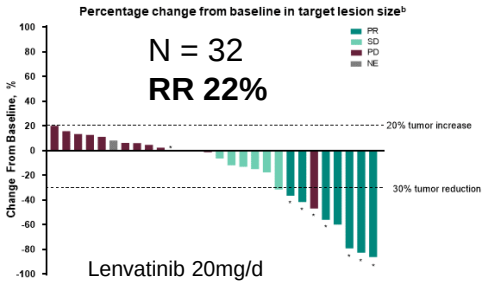
REGONIVO / EPOC1603



MOFFITT PHASE 1/1B



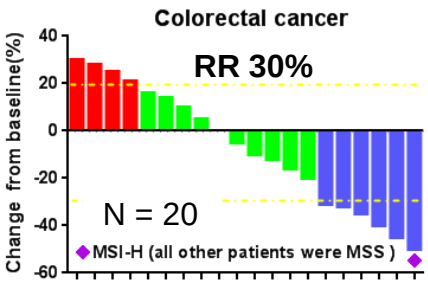
LEAP-005



Lenvatinib 20mg/d
Pembro 200mg q3wks

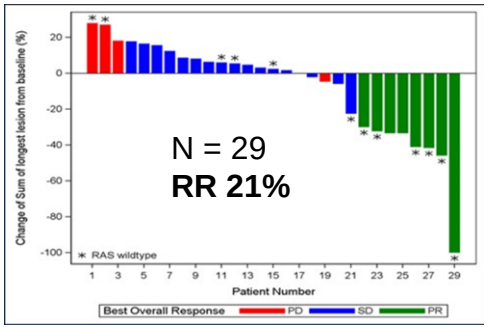
Regorafenib 80mg/d 21on/7off and Nivolumab 3mg/kg q2wks

Xiamen University Phase 2



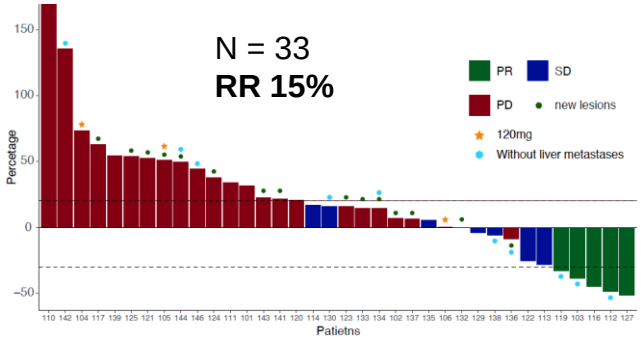
Apatinib 250mg D1-28
Camrelizumab 200mg D1/15

CAMILLA Phase 2



Cabozantinib 40 mg qd
Durvalumab 1500 mg iv q4 w

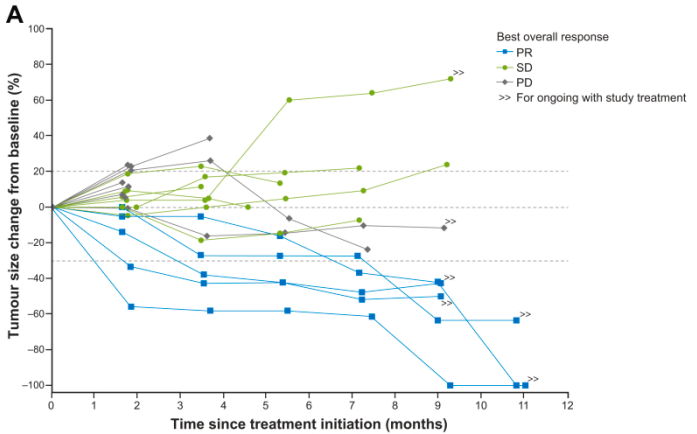
REGOTORI



Regorafenib 80mg/d 21on/7off
Toripalimab 3mg/kg q2wks

Fukuoka S et al. *J Clin Oncol*. 2020;38(18):2053-2061. Kim R et al. ESMO 2021. Abstract PD-2. Xiao L et al. ESMO 2020. Abstract 442P. Gomez-Roca C et al. ASCO 2021. Abstract 94. Saeed A et al. ASCO GI 2022. Abstract 135. Wang et al. ESMO 2022. Abstract 433P. Slide acknowledgement: Overman, M.

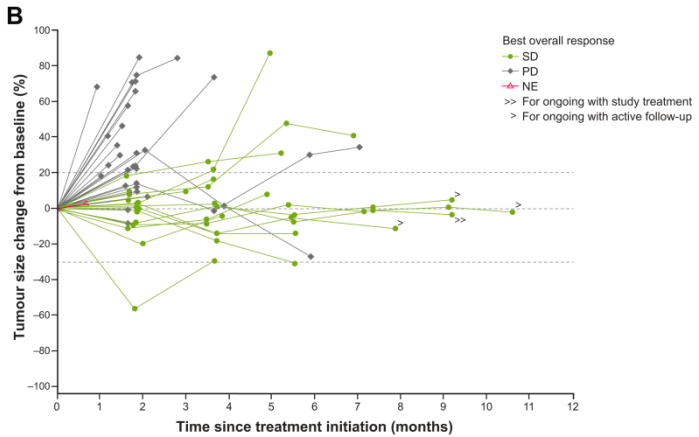
REGONIVO in pMMR CRC: Liver vs Non-Liver Met Population



N = 70, single arm

Primary Endpoint: ORR

Without liver mets = 22%

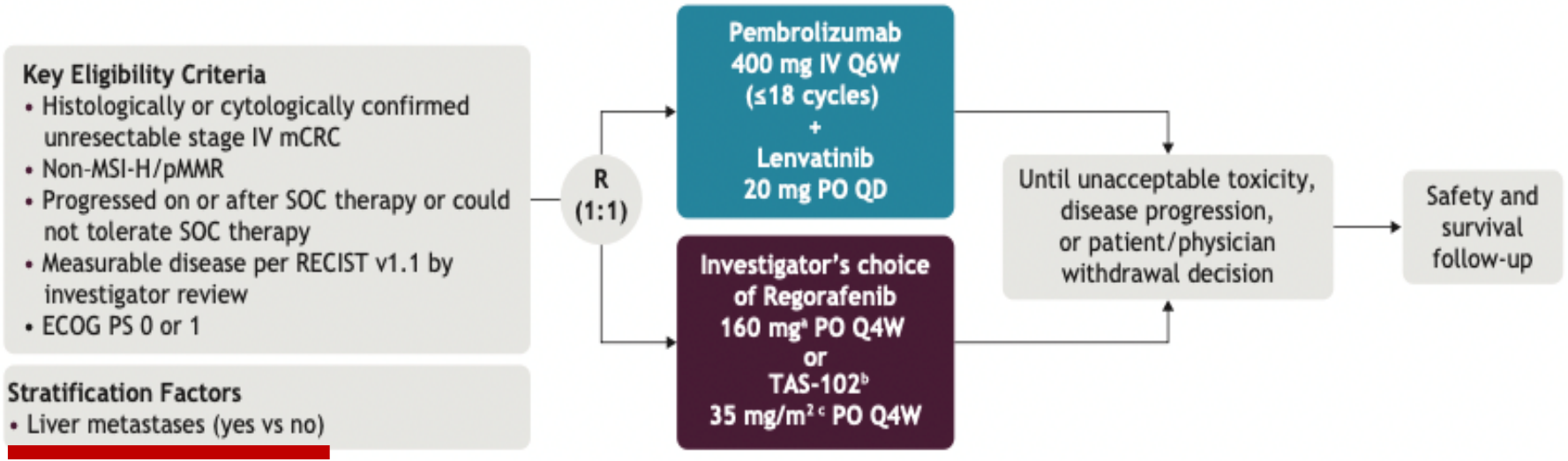


With liver mets = 0%

Fukuoka S et al. *J Clin Oncol*. 2020;38(18):2053-2061. Kim R et al. ESMO 2021. Abstract PD-2.

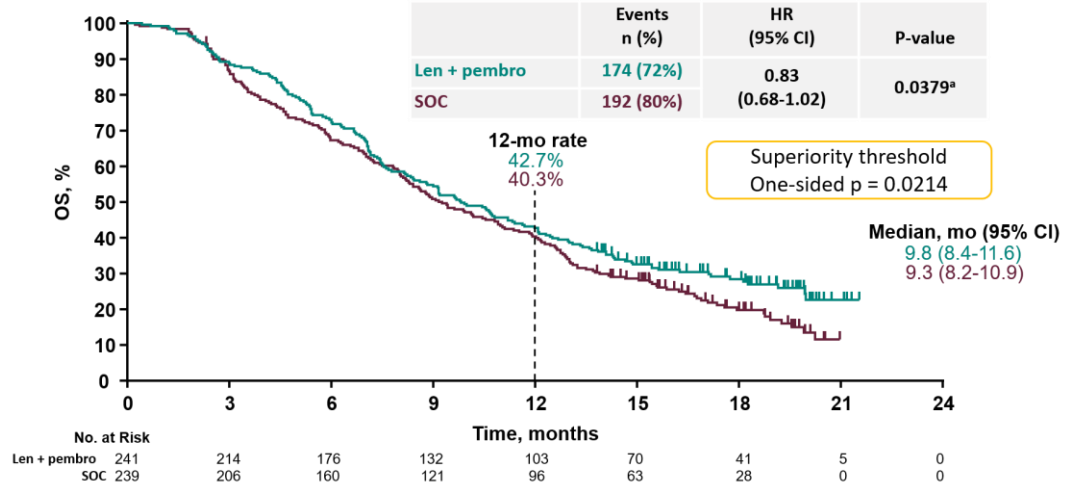
LEAP-017 Phase 3

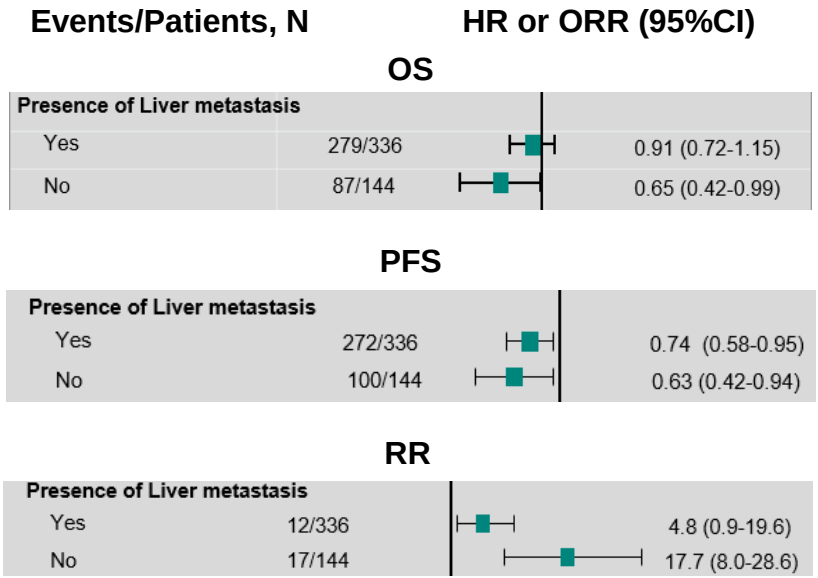
Global, Randomized, Open-Label Trial (NCT04776148)



Yoshino T et al. ESMO 2021. Abstract 506TiP.

LEAP-017: Lenvatinib/Pembro in pMMR CRC





Primary Endpoint OS: NEGATIVE

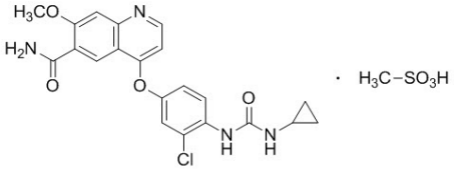
	Lenvatinib + Pembrolizumab	SOC
Characteristics, n (%)	**N = 241**	**N = 239**
Presence of liver metastases		
Yes	168 (69.7)	168 (70.3)
No	73 (30.3)	71 (29.7)

Trends seen in no liver met population

Kawazoe A et al. WCGC 2023. Abstract LBA-5. Slide acknowledgement: Overman, M.

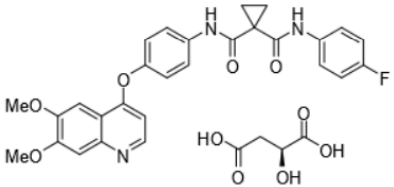
Do We Know Which VEGF TKI to Use?

Lenvatinib



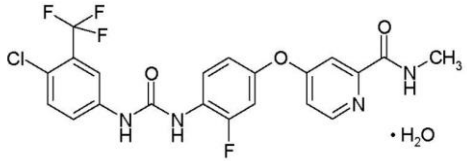
VEGFR1-3, FGFR1-4 PDGFRα, KIT, RET and FRS2α phosphorylation

Cabozantinib



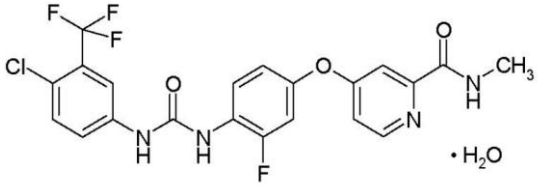
MET, VEGFR1-3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2

Regorafenib



RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R

Fruquintinib



VEGFR1-3

JAMA Oncology | Original Investigation

Regorafenib, Ipilimumab, and Nivolumab for Patients With Microsatellite Stable Colorectal Cancer and Disease Progression With Prior Chemotherapy

A Phase 1 Nonrandomized Clinical Trial

Marwan Fakih, MD; Jaideep Sandhu, MBBS, MPH; Dean Lim, MD; Xiaochen Li, PhD; Sierra Li, PhD; Chongkai Wang, MS, MD

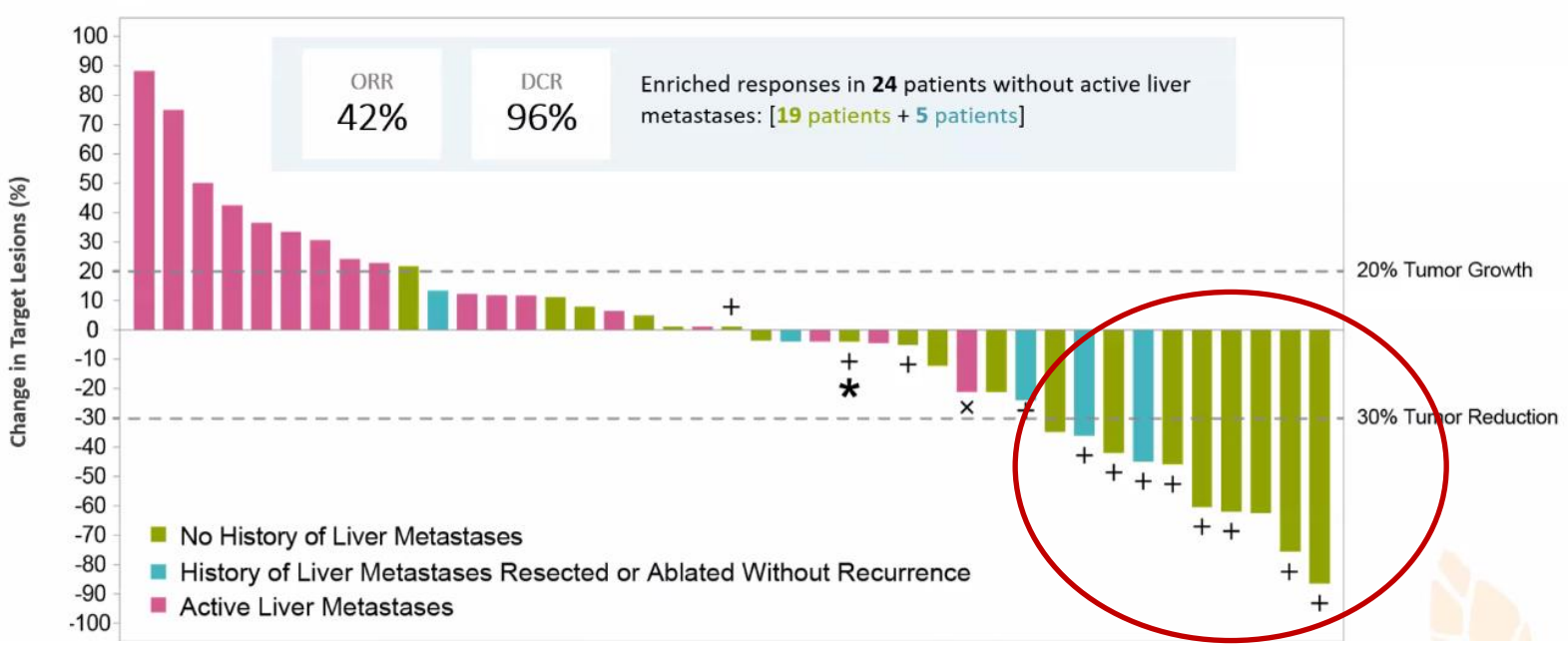
3 + 3 dose de-escalation study with an effectiveness expansion cohort at the RP2D.

	No liver metastases (n = 22)	Liver metastases (n = 7)
ORR, (%)	40.9	0
PFS, median, months	6	2
OS, median, months	> 22	7

Fakih M et al. *JAMA Oncol.* 2023;9(5):627-634.

PD1 Combos in pMMR CRC: low level activity in non liver met population

AGENUS



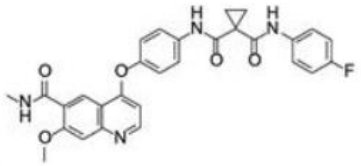
Botensilimab + Balstilimab

Wang et al. ASCO 2020; GI ESMO 2022; Slide acknowledgement: Overman, M

STELLAR-303 Study Design

A

XL092



Kinase	Kinase inhibition,
MET	3.0 ± 0.27
VEGFR2	15.0 ± 0.95
AXL	5.8 ± 0.38
MER	0.6 ± 0.054
TYRO3	NA

Global, open-label, randomized phase 3 study

Previously treated *RAS*wt or *RAS*mut mCRC
(N≈600; 400 *RAS*wt and 200 *RAS*mut patients)

- Measurable disease per RECIST v1.1 by investigator
- ECOG performance status 0 or 1
- Radiographically progressed on, refractory to, or intolerant to SOC therapy for mCRC*
- Progressed during treatment with or within 3 months of most recent SOC therapy
- Patients with MSI-H or dMMR disease are excluded

1:1

XL092 100 mg PO QD
+ **atezolizumab** 1200 mg IV Q3W

Stratification factors
- Geographical region (Asia, other)
- Documented *RAS* status (wt, mut)
- Presence of liver metastases (yes, no)

Regorafenib 160 mg PO QD
(first 21 days of 28-day cycles)

Tumor assessment Q8W through Week 49, then Q12W thereafter per RECIST v1.1

Treatment until lack of clinical benefit or intolerable toxicity

Endpoints
- **Primary efficacy:** Overall survival in the *RAS*wt population
- **Other efficacy:** PFS, ORR, and DOR per RECIST v1.1 by investigator, OS, and change in tumor markers in the *RAS*wt and *RAS*mut populations, and all randomized patients
- **Additional:** Safety, quality of life, changes in biomarkers, pharmacokinetics, immunogenicity of atezolizumab, and healthcare utilization

*SOC must have included all of the following: fluoropyrimidine, irinotecan and oxaliplatin ± anti-VEGF monoclonal antibody, anti-EGFR monoclonal antibody for *RAS*wt patients, BRAF inhibitor for patients with known *BRAF V600E* mutations

Hsu J et al. *Mol Cancer Ther*. 2023;22(2):179-191. Hecht JR et al. ASCO 2023. Abstract TPS3630.

Agenda

- **Current Landscape for VEGF inhibitors in CRC**

Established role for VEGF inhibition across the continuum of care in mCRC

- **Ongoing and Recent VEGF inhibitor trials in mCRC**
  - *AtezoTRIBE trial*
  - *VEGF TKI + IO combinations*

Right Drugs to Right Patients (Biomarker) – intriguing data and signals for biomarkers for anti-VEGF therapy (finally!)