METASTATIC COLORECTAL CANCER & FRESCO-2 PHASE III MRCT

DATA PRESENTATION AND ROUNDTABLE DISCUSSION

Monday September 12, 2022 | 14:00 Paris Time

Nasdaq/AIM:HCM; HKEX:13

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Most discovered in-house

PRODUCT	MOA	INDICATIONS	PARTNER	CHINA[1]	GLOBAL[1]
Fruquintinib	VEGFR 1/2/3	Colorectal, gastric, EMC (multiple I/O & TKI combos)	Lilly (China)	**Marketed** (Colorectal); **Ph.III** (Gastric) **Ph.II reg-intent** (EMC)	**Ph.III U.S., E.U., Japan** (Colorectal)
Surufatinib	VEGFR 1/2/3, FGFR1 & CSF-1R	NET, NEC (multiple I/O combos)	None	**Marketed** (NET) **Marketed** (pNET) **Ph.III** (NEC)	U.S. FDA / EMA MAA discussions ongoing
Savolitinib	MET	NSCLC, kidney, gastric, colorectal[2] (multiple I/O & TKI combos)	AstraZeneca (Worldwide)	**Marketed** (NSCLC mono) **Ph.III** (NSCLC combo) **Ph.II reg-intent** (Gastric)	**Ph.II/III global** (multiple NSCLC) **Ph.III global** (PRCC)
Amdizalisib	PI3Kδ	B-cell malignancies – indolent NHL	None	**Ph.II reg-intent** (FL & MZL)	**Ph.I** U.S., E.U., Aus.
Sovleplenib	Syk	ITP, B-cell malignancies	None	**Ph.Ib** (>200 NHL pts.) **Ph. III** (ITP)	**Ph.I** U.S., E.U., Aus.
Tazemetostat	EZH2	Solid tumors, hematological malignancies	IPSEN Innovation for patient care (ex-China)	**Marketed** (ES & FL, Hainan) **Bridging** (3L FL)	Marketed by Ipsen [3] Global **Ph. Ib/III** (2L FL combo)
HMPL-453	FGFR 1/2/3	Cholangiocarcinoma	None	**Ph.II** (Solid tumors)	-
HMPL-306	IDH 1/2	Hematological malignancies, solid tumors	None	**Ph.I**	**Ph.I**
HMPL-295	ERK (MAPK pathway)	Solid tumors	None	**Ph.I**	-
HMPL-760	3G BTK	Hematological malignancies	None	**Ph.I**	IND cleared, Ph. I activated
HMPL-653	CSF-1R	Solid tumors	None	**Ph. I**	-
HMPL-A83	CD47	mAb – solid tumors, hematological malignancies	None	**Ph.I**	-

[1] Represents the most advanced clinical trial stage and indication; [2] Investigator initiated trials (IITs); [3] Epizyme was acquired by Ipsen in August 2022.

Agenda

1 **Opening Remarks** —  Dr Weiguo Su

2 **FRESCO-2 Data Summary** —  Dr Arvind Dasari

3 **Panel Discussion:**
Metastatic colorectal cancer: where are we now? —  Dr Marek Kania  Dr Weiguo Su

Steering Committee / co-Principal Investigators of the FRESCO-2 study

 Dr Arvind Dasari
 Dr Alberto Sobrero
 Dr Cathy Eng
 Dr James Yao
 Dr Josep Tabernero
 Dr Takayuki Yoshino

5 **Closing Remarks & Q&A** — All

FRESCO-2 Data Summary

Dr Arvind Dasari

Associate Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center

FRESCO-2: A global phase 3 multiregional clinical trial evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer

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Declaration of Interests

Arvind Dasari

- **Grants to Institution**
  - AAA/Novartis, Crinetics, Eisai, Guardant Health, HUTCHMED, Natera
- **Advisory Boards**
  - AAA/Novartis, Crinetics, HUTCHMED, Personalis, Voluntis

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Introduction

- The VEGF pathway is a key mediator of angiogenesis, which is necessary for tumor growth and metastasis[1]
- Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor of VEGFRs-1, -2, and -3[2]
- The phase 3 FRESCO study showed the efficacy and safety of fruquintinib in Chinese patients with mCRC in a 3L+ setting[3]
  - mOS improvement of 2.7 months with fruquintinib vs placebo (9.3 m vs 6.6 m; HR=0.65 [95% CI, 0.51-0.83]; $p<0.001$)
  - mPFS improvement of 1.9 months with fruquintinib vs placebo (3.7 m vs 1.8 m; HR=0.26 [95% CI, 0.21-0.34]; $p<0.001$)
  - Fruquintinib was approved in China in 2018 for 3L+ mCRC
  - Standard of care for mCRC in China differed from global patterns when FRESCO was conducted
- There remains an unmet need for effective treatment options for patients with refractory mCRC
- FRESCO-2 is a global phase 3 study evaluating the efficacy and safety of fruquintinib in more heavily pretreated mCRC patients reflective of current global treatment practices

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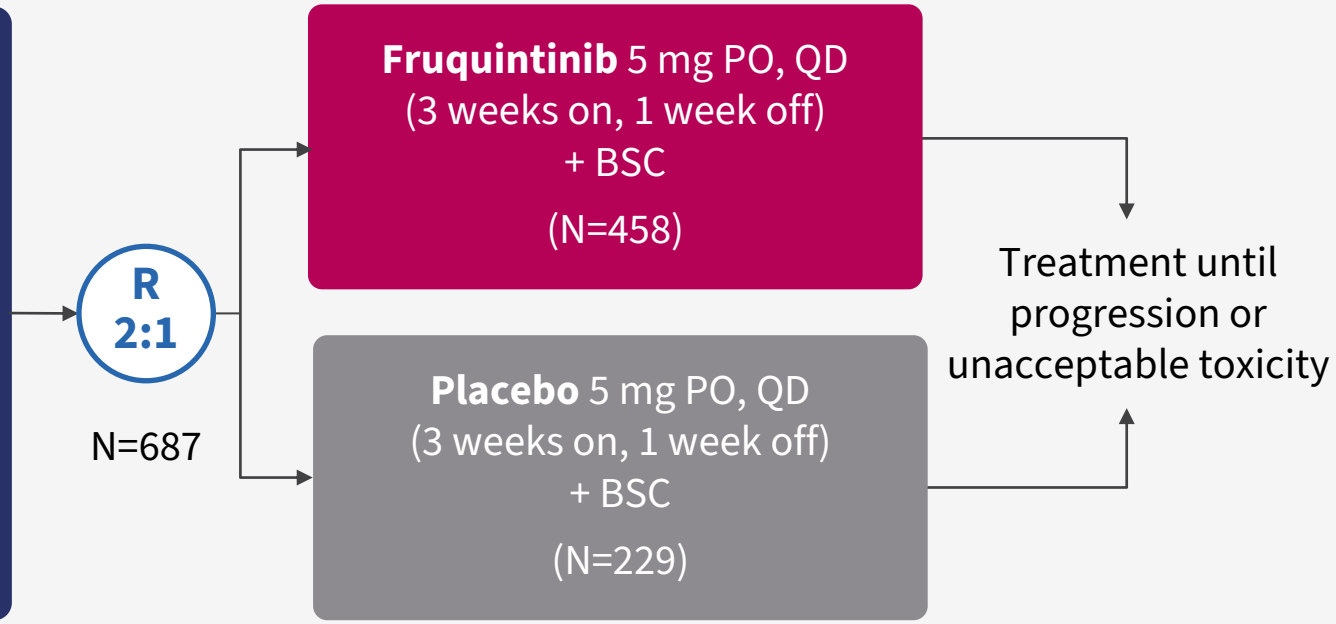
1. Hicklin DJ et al. *J Clin Oncol* 2005; 2. Sun Q et al. *Cancer Biol Ther* 2014. 3. Li J et al. *JAMA* 2018.

FRESCO-2 Study Design

Patient Eligibility

- Prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild type, an anti-EGFR therapy
- Progression on, or intolerance to, TAS-102 and/or regorafenib
- Prior treatment with an immune checkpoint inhibitor or BRAF inhibitor if indicated



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 treated with prior regorafenib was limited to 344 patients (50%)

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BSC, best supportive care.
NCT04322539.

Study Objectives and Statistical Assumptions

- Objectives
  - **Primary: Overall Survival**
  - Key Secondary: Progression-Free Survival
  - Other Secondary: Objective Response Rate, Disease Control Rate, Safety

- Sample Size
  - 687 patients (480 OS events) would provide 90% power to detect a difference in OS with a HR of 0.73 at a 2-sided α of 0.05
  - Median OS assumption in the placebo arm is 5.0 months and median OS in fruquintinib arm is 6.8 months
  - Non-binding interim futility analysis at one-third (160) of OS events

- Safety monitored by independent data monitoring committee

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Patient and Disease Characteristics

ITT Population

Enrollment: Sep 2020 to Dec 2021

Data Cutoff: 24 June 2022

Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Age, y	Median (range)	64 (25, 82)	64 (30, 86)
	≥ 65	214 (46.4)	111 (48.3)
Sex	Female	216 (46.9)	90 (39.1)
	Male	245 (53.1)	140 (60.9)
Region	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	0	196 (42.5)	102 (44.3)
	1	265 (57.5)	128 (55.7)
Primary site at 1st diagnosis	Colon left	192 (41.6)	92 (40.0)
	Colon right	97 (21.0)	53 (23.0)
	Colon left & 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	Yes	339 (73.5)	156 (67.8)

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

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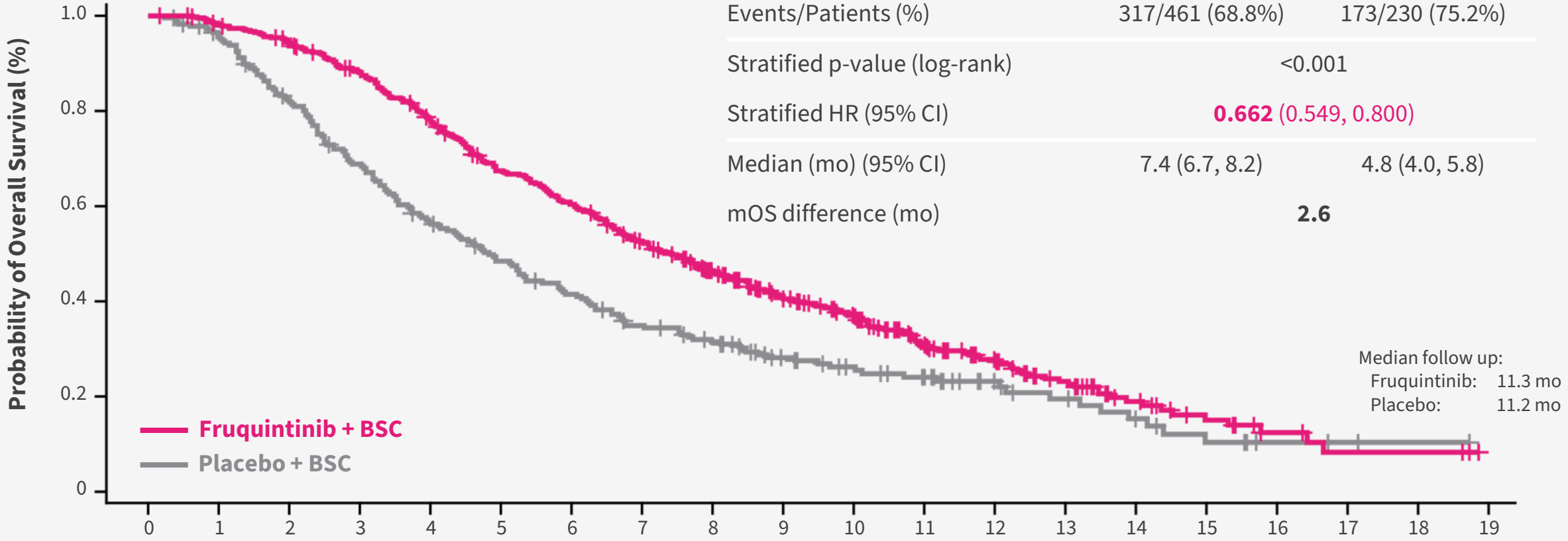
Primary Endpoint: Overall Survival

	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)
mOS difference (mo)	**2.6**	



Patients at Risk

Fruquintinib	461	449	429	395	349	297	266	224	187	143	113	76	58	41	23	14	7	4	4	0
Placebo	230	219	184	153	125	105	89	73	63	45	37	34	20	15	10	6	3	2	1	0

Subsequent anti-cancer medication balanced between the two arms: **29.4% in fruquintinib arm** vs. **34.3% placebo arm**

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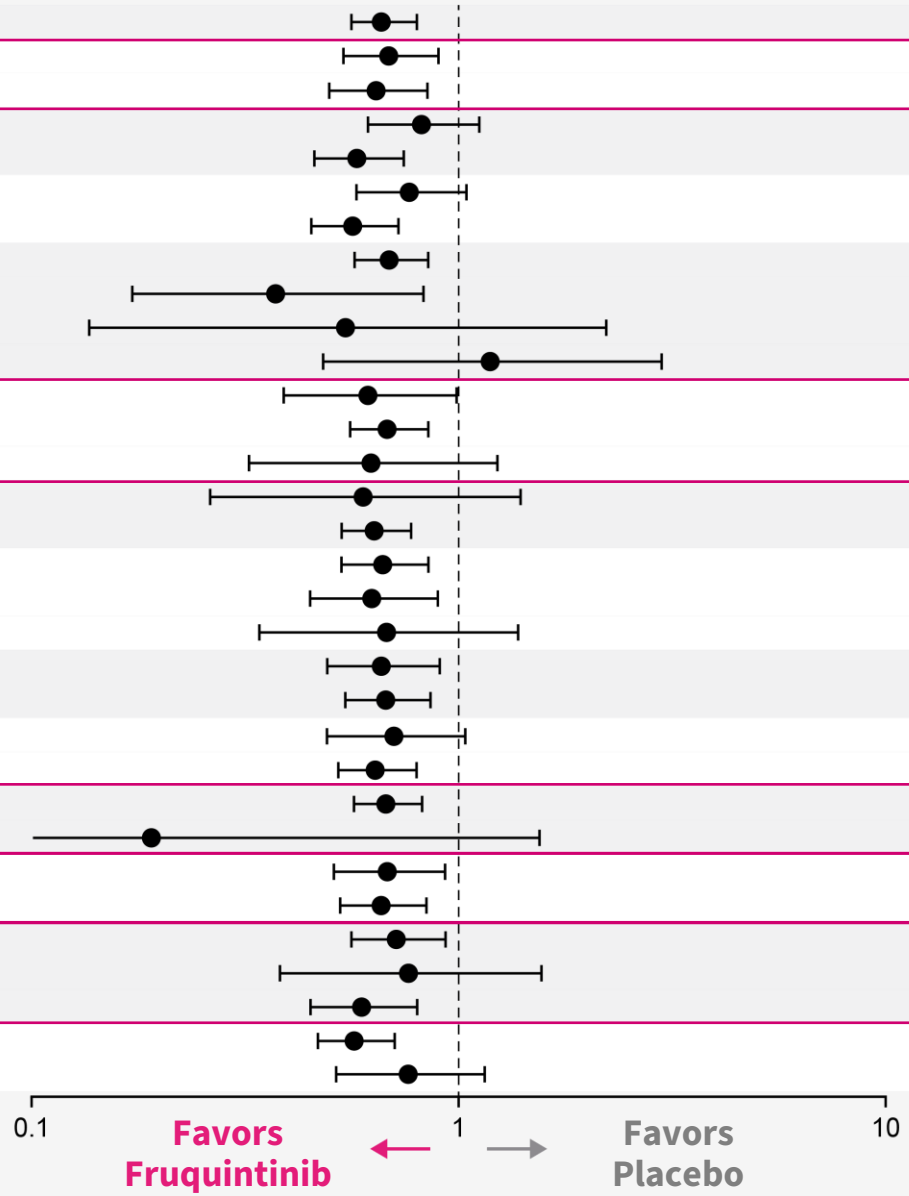
OS Subgroup Analysis

ITT Population

Subgroup		Fruquintinib n/N	Placebo n/N	HR (95% CI)
ITT population		317/461	173/230	0.662 (0.549, 0.800)
Age	< 65	171/247	89/119	0.694 (0.534, 0.903)
	≥ 65	146/214	84/111	0.648 (0.494, 0.851)
Sex	Female	149/216	61/90	0.828 (0.609, 1.125)
	Male	168/245	112/140	0.584 (0.456, 0.749)
ECOG PS	0	121/196	67/102	0.775 (0.573, 1.050)
	1	196/265	106/128	0.571 (0.499, 0.728)
Race	Caucasian	260/367	145/192	0.696 (0.567, 0.854)
	Asian	24/43	14/18	0.377 (0.171, 0.833)
	African American	7/13	5/7	0.550 (0.135, 2.231)
	Other	26/38	9/13	1.199 (0.478, 3.008)
Region	North America	50/82	29/42	0.620 (0.387, 0.995)
	Europe	237/329	130/166	0.688 (0.554, 0.855)
	Asia Pacific	30/50	14/22	0.631 (0.321, 1.241)
Duration of metastatic disease	≤ 18 mo	30/37	8/13	0.605 (0.260, 1.406)
	> 18 mo	287/424	165/217	0.642 (0.529, 0.779)
Primary tumor site at 1st diagnosis	Colon	195/279	109/137	0.672 (0.528, 0.855)
	Rectum	99/143	49/70	0.633 (0.446, 0.900)
	Colon and Rectum	23/39	15/23	0.686 (0.339, 1.388)
RAS status	WT	119/170	62/85	0.667 (0.489, 0.909)
	Mutant	198/291	111/145	0.683 (0.539, 0.865)
# of prior treatment lines in metastatic disease	≤ 3	80/125	45/64	0.714 (0.488, 1.043)
	>3	237/336	128/166	0.645 (0.519, 0.802)
Prior VEGFi	Yes	306/445	167/221	0.683 (0.565, 0.827)
	No	11/16	6/9	0.193 (0.024, 1.557)
Prior EGFRi	Yes	127/180	64/88	0.689 (0.507, 0.936)
	No	190/281	109/142	0.666 (0.524, 0.846)
Prior TAS-102 and Regorafenib	TAS-102	165/240	88/121	0.723 (0.557, 0.938)
	Regorafenib	25/40	12/18	0.772 (0.379, 1.573)
	Both	127/181	73/91	0.600 (0.447, 0.805)
Liver metastases	Yes	255/339	132/156	0.576 (0.465, 0.713)
	No	62/122	41/74	0.771 (0.513, 1.158)



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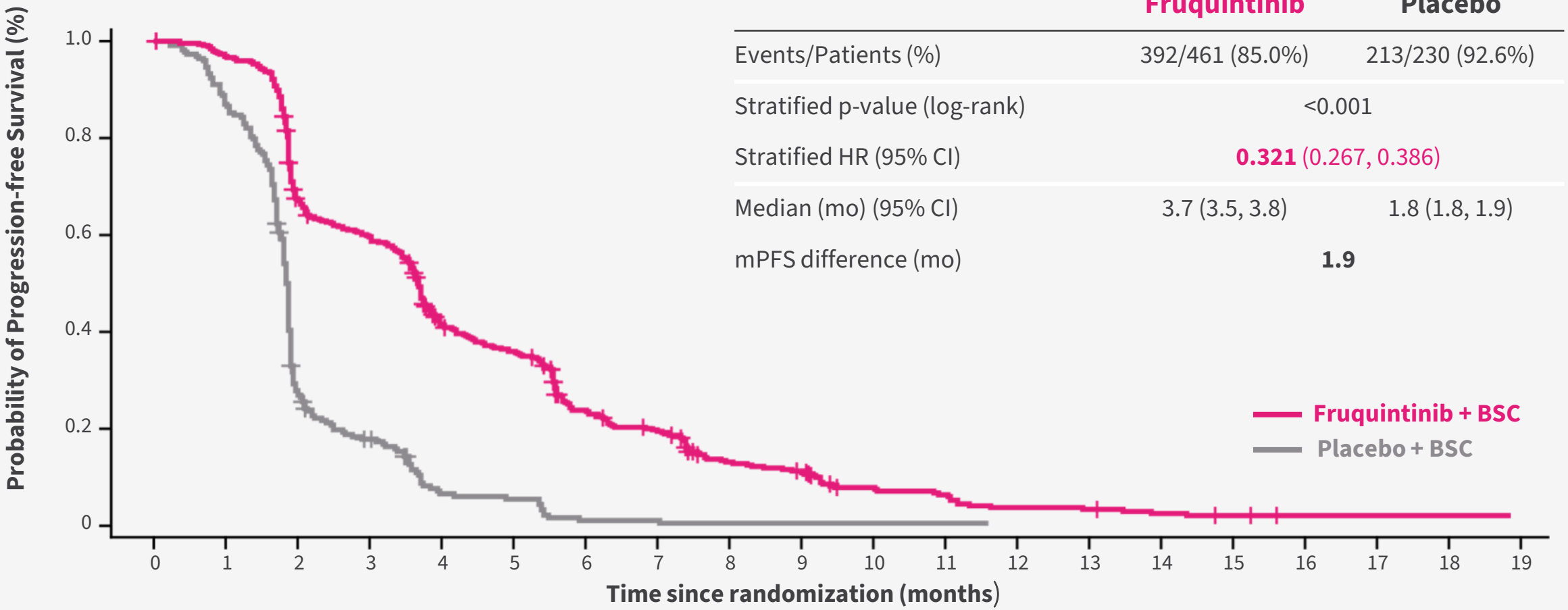
Progression-Free Survival



	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)
mPFS 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						

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PFS Subgroup Analysis

ITT Population

Subgroup		Fruquintinib n/N	Placebo n/N	HR (95% CI)
ITT population		392/461	213/230	0.321 (0.267, 0.386)
Age	< 65	214/247	111/119	0.329 (0.255, 0.424)
	≥ 65	178/214	102/111	0.314 (0.241, 0.410)
Sex	Female	190/216	81/90	0.351 (0.263, 0.468)
	Male	202/245	132/140	0.302 (0.237, 0.385)
ECOG PS	0	169/196	90/102	0.264 (0.197, 0.354)
	1	223/265	123/128	0.351 (0.277, 0.446)
Race	Caucasian	312/367	176/192	0.313 (0.255, 0.383)
	Asian	37/43	17/18	0.286 (0.140, 0.584)
	African American	9/13	7/7	0.081 (0.014, 0.468)
	Other	34/38	13/13	0.525 (0.248, 1.110)
Region	North America	64/82	36/42	0.261 (0.163, 0.417)
	Europe	283/329	158/166	0.324 (0.261, 0.401)
	Asia Pacific	45/50	19/22	0.271 (0.144, 0.509)
Duration of metastatic disease	≤ 18 mo	35/37	11/13	0.361 (0.166, 0.787)
	> 18 mo	357/424	202/217	0.300 (0.249, 0.363)
Primary tumor site at 1st diagnosis	Colon	241/279	127/137	0.294 (0.231, 0.375)
	Rectum	118/143	64/70	0.315 (0.225, 0.441)
	Colon and Rectum	33/39	22/23	0.386 (0.202, 0.739)
RAS status	WT	145/170	76/85	0.333 (0.245, 0.454)
	Mutant	247/291	137/145	0.318 (0.254, 0.399)
# of prior treatment lines in metastatic disease	≤ 3	108/125	57/64	0.280 (0.192, 0.409)
	>3	284/336	156/166	0.334 (0.270, 0.412)
Prior VEGFi	Yes	377/445	206/221	0.335 (0.278, 0.402)
	No	15/16	7/9	0.020 (0.001, 0.385)
Prior EGFRi	Yes	154/180	79/88	0.325 (0.239, 0.440)
	No	238/281	134/142	0.310 (0.247, 0.391)
Prior TAS-102 and Regorafenib	TAS-102	210/240	111/121	0.367 (0.287, 0.470)
	Regorafenib	29/40	16/18	0.292 (0.139, 0.611)
	Both	153/181	86/91	0.285 (0.212, 0.382)
Liver metastases	Yes	297/339	149/156	0.291 (0.234, 0.362)
	No	95/122	64/74	0.334 (0.235, 0.476)

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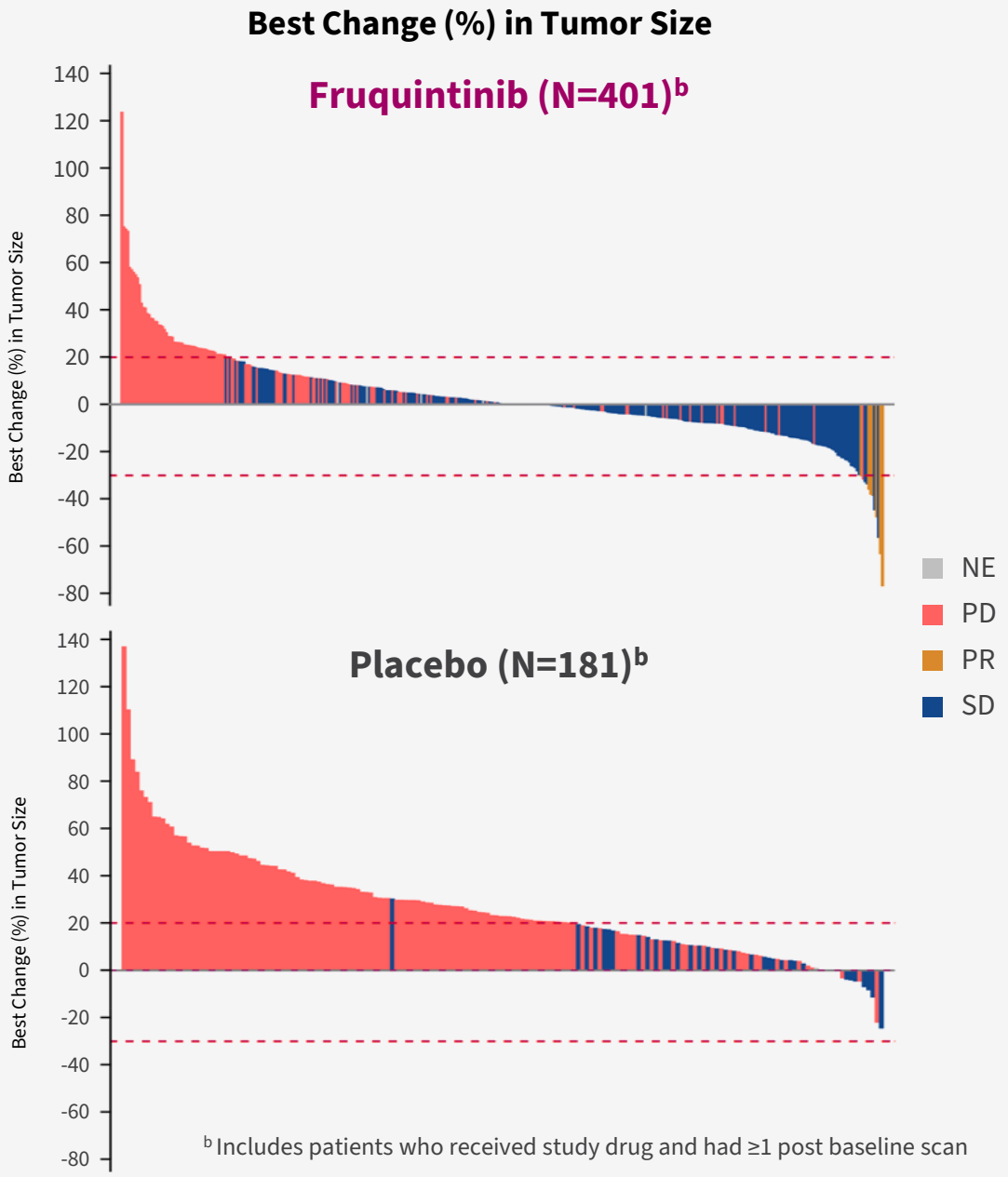
Anti-Tumor Activity

Category	Fruquintinib (N=461)	Placebo (N=230)
Confirmed ORR (CR + PR) [a]	7 (1.5)	0
Adjusted difference (95% CI)	1.5 (0.4, 2.7)	
Two-sided p-value	0.059	
Disease Control Rate (CR + PR + SD)	**256 (55.5)**	**37 (16.1)**
Adjusted difference (95% CI)	39.4 (32.8, 46.0)	
Two-sided p-value	< 0.001	

[a] No CR reported

- Tumor assessments were performed every 8 weeks until disease progression



[b] Includes patients who received study drug and had ≥1 post baseline scan

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Study Drug Exposure

Category	Fruquintinib (N=456)[a]	Placebo (N=230)[a]
Cycles received, median (Q1, Q3)	3.00 (2.00, 6.00)	2.00 (1.00, 3.00)
Relative dose intensity (%), median (Q1, Q3)	91.63 (74.13, 99.52)	97.62 (86.67, 100.00)
Number of patients with drug interruption, n (%)	312 (68.4)	110 (47.8)
Number of patients with any dose reduction, n (%)	121 (26.5)	10 (4.3)
Reduction from 5 mg to 4 mg	121 (26.5)	10 (4.3)
Reduction from 4 mg to 3 mg	45 (9.9)	0

[a] Of 5 patients assigned to the fruquintinib arm, 3 did not receive fruquintinib treatment and 2 patients received placebo instead. Two patients assigned to the placebo arm did not receive treatment.

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Overview of TEAEs

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 the 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%)

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Most Common TEAEs
(Any Grade ≥ 15% in Either Arm)

TEAE	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

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Conclusions

- FRESCO-2 met the primary endpoint of OS
  - mOS improvement of 2.6 months with fruquintinib vs placebo (7.4 m vs 4.8 m; HR=0.66 [95% CI, 0.55-0.80]; $p < 0.001$)
  - OS improvement was consistent across all pre-specified subgroups
- FRESCO-2 met the key secondary endpoint of PFS
  - mPFS improvement of 1.9 months with fruquintinib vs placebo (3.7 m vs 1.8 m; HR=0.32 [95% CI, 0.27-0.39]; $p < 0.001$)
  - PFS improvement was consistent across all pre-specified subgroups
- Fruquintinib was well tolerated with a safety profile consistent with the previously established monotherapy profile
- The FRESCO-2 results are consistent with those of FRESCO and support a new global oral treatment option for patients with refractory mCRC, which enriches the continuum of care for these patients

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Panel Discussion with Select Members of Steering Committee Metastatic Colorectal Cancer: Where Are We Now?

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CLOSING REMARKS

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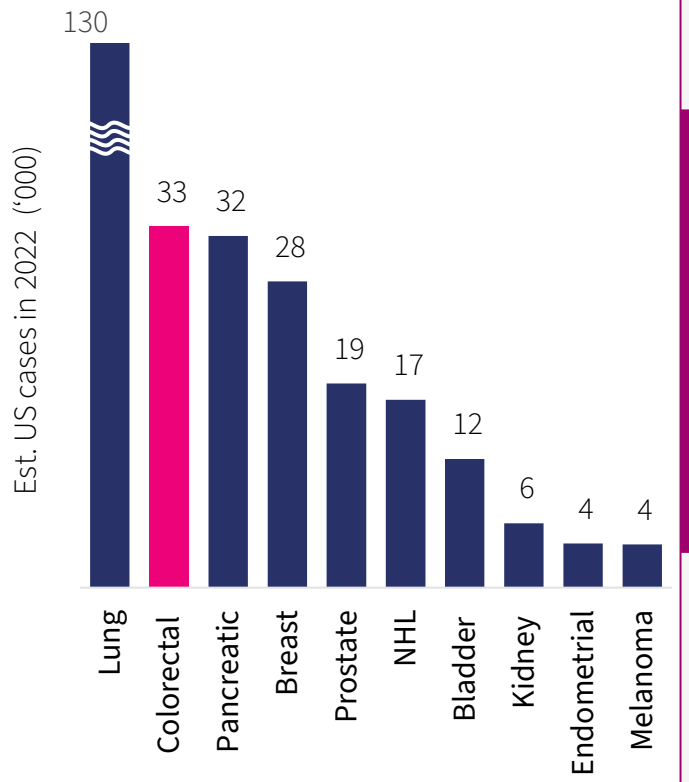
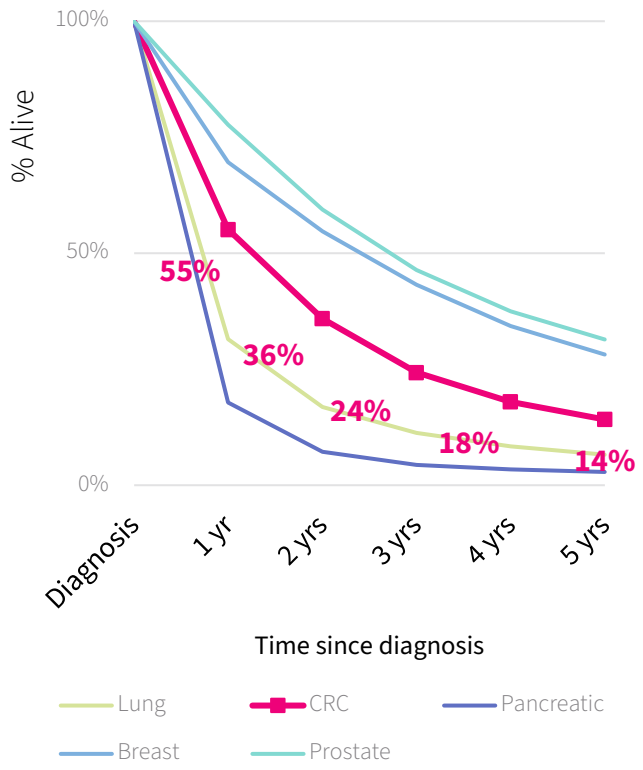
Colorectal cancer a significant burden…

…but there are still limited treatment options for most patients

Second most common metastatic cancer diagnosis



Patients diagnosed with metastatic disease have low 5-year relative survival rate



Unmet medical need

- **Limited use of approved 3L treatments**
  - Regorafenib (approved Q3 2012)
  - TAS-102 (approved Q3 2015)
- **Chemotherapy, anti-VEGF & anti-EGFR agents used across all lines**
- **Newer treatment options focus on discrete actionable mutations**
  - ~10% of patients have BRAF mutation [1]
  - ~15% of patients have MSI-H or dMMR disease [2]

Note: Epidemiology data are sourced from SEER, for the U.S.

[1] D'Haene N, et al. Clinical application of targeted next-generation sequencing for colorectal cancer patients: a multicentric Belgian experience. *Oncotarget*. 2018;9(29):20761-20768. Published 2018 Apr 17. doi:10.18632/oncotarget.25099

[2] André T, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med*. 2020;383(23):2207-2218. doi:10.1056/NEJMoa2017699

Q&A

Thank you

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