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MEETING SUMMARY
LOWER GI CANCER HIGHLIGHTS FROM ESMO 2022

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PRACTICE-CHANGING DATA ESMO 2022

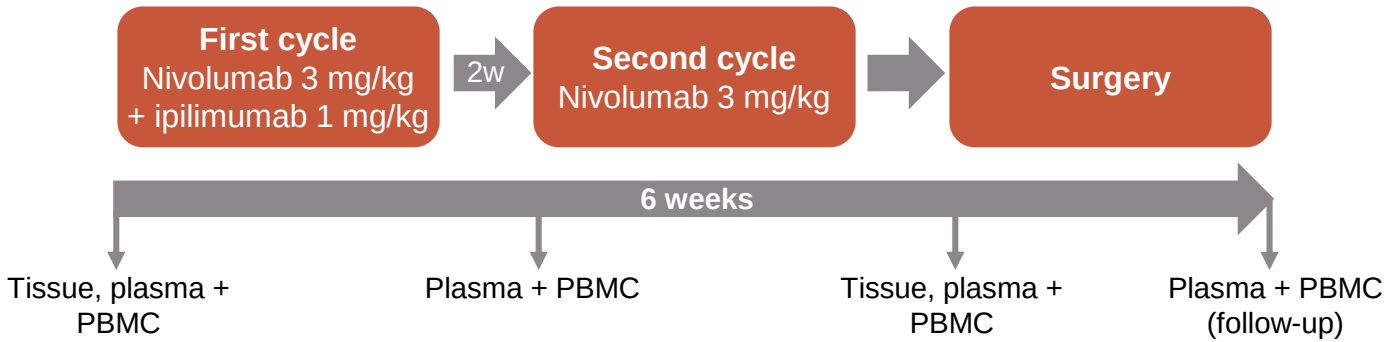
NEOADJUVANT IMMUNE CHECKPOINT INHIBITION IN LOCALLY ADVANCED MMR-DEFICIENT COLON CANCER: THE NICHE-2 STUDY

Chalabi M, et al. ESMO 2022. Abstract #LBA7

MMR, mismatch repair

NICHE-2: BACKGROUND AND STUDY DESIGN

- Approximately 10-15% of colon cancers are mismatch repair deficient (dMMR)[1,2]
- There is a recurrence rate of 20-40% for stage III dMMR tumours despite standard of care chemotherapy[1,2]
- The NICHE-1 study showed that immune checkpoint blockade is highly effective in dMMR colon cancer
- NICHE-2 was an investigator-initiated, non-randomised, multicentre study



Primary Objectives
- Safety and feasibility
- 3-year disease-free survival

Secondary objectives
- Major and complete pathological response rate
- ctDNA dynamics
- Translational research

ctDNA, circulating tumour DNA; PBMC, peripheral blood mononuclear cells; w, weeks

1. Chalabi M, et al. Nat Med 2020, 26(4):566-576; 2. Verschoor Y, et al. J Clin Oncol 2022, 40: 3511-3511, 3. Chalabi M, et al. Ann Oncol. 2022; 33 (suppl_7): S808-S869 (ESMO 2022, oral presentation)

NICHE-2: RESULTS

- Grade 3-4 immune-related adverse events were observed in 4 (4%) patients. 98% of patients underwent timely surgery, meeting the safety primary endpoint
- In the PP population (n=107), baseline radiologic assessment revealed 89% stage III, 77% high-risk stage III, and 64% T4 tumours
- 95% of patients achieved a major pathological response; 67% a pathologic complete response
- With a median follow-up of 13.1 months (1.4-57.4), there have been no disease recurrences

Pathologic response (RVT)		Patients N=107 n (%)
Yes	**(≤50%)**	**106 (99%)**
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10%-50%)	4 (4%)
No	**(≥50%)**	**1 (1%)**

PP, per protocol; RVT, residual viable tumour

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

NICHE-2: SUMMARY

- 4 weeks of treatment resulted in 95% of patients with dMMR achieving a major pathological response, including 67% pathologic complete responses
- Treatment was well tolerated with only 4% of patients experiencing grade 3 or 4 immune-related adverse events
- No disease recurrences after a median follow-up of 13.1 months

Clinical Perspective

- **NICHE-2 results indicate that future treatment schedules for dMMR patients with early colon cancer, are likely to be with immunotherapy rather than chemotherapy**

dMMR, mismatch repair deficient

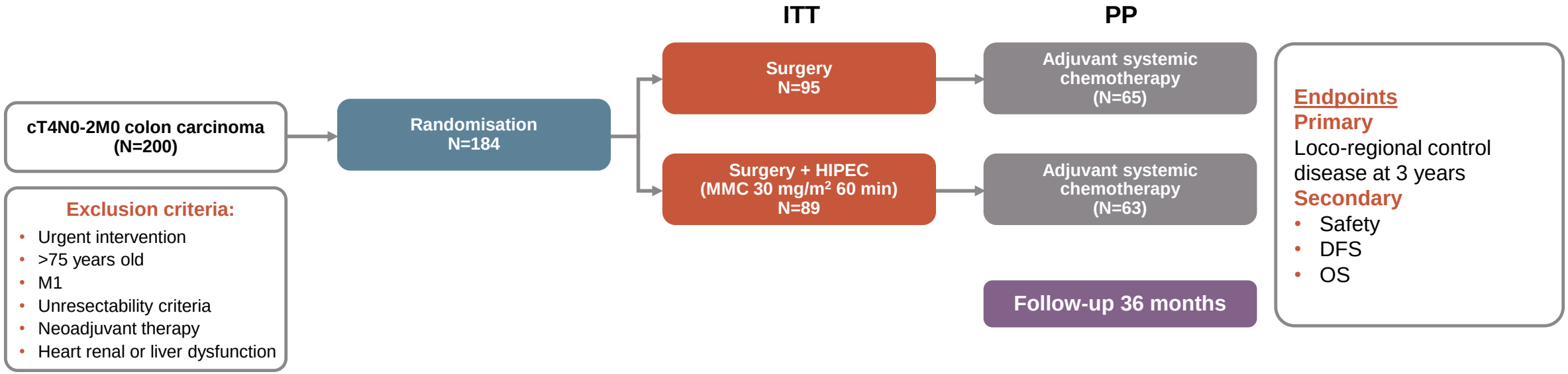
Chalabi M, et al. Ann Oncol. 2022; 33 (suppl_7): S808-S869 (ESMO 2022, oral presentation)

ADJUVANT HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN LOCALLY ADVANCED COLON CANCER (HIPECT4): A RANDOMIZED PHASE 3 STUDY

Arjona-Sanchez A, et al. ESMO 2022. Abstract #314O

HIPECT4: BACKGROUND AND STUDY DESIGN

- Peritoneal metastasis in locally advanced colon cancer is estimated around 25% at 3 years from surgical resection with a poor prognosis
- There is controversy about the results using prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) in this group of patients
- HIPECT4 is an open label, randomised, phase 3, controlled trial to determine the efficacy and safety of adjuvant HIPEC in patients with locally advanced colon cancer.



DFS, disease free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; ITT, intent to treat; M0, non-metastatic; M1, metastatic; min, minute; MMC, mitomycin C; OS, overall survival; PP, per protocol

Arjona-Sanchez A, et al. Ann Oncol. 2022;33 (suppl_7): S136-S196 (ESMO 2022 presentation)

HIPECT4: RESULTS

- 184 patients were recruited and randomised (89 experimental vs 95 control) between November 2015 and January 2021
- Median follow-up of 36 (IQR 27-36) months
- Demographic, tumour features, surgical management and final pathology reports were similar between both groups
- The LC was improved in the experimental arm (35.3 ± 0.4 vs 33.2 ± 0.8 months) with a 3 years LC rate of 97% vs 87% (p=0.025)
- No differences were observed in DFS and OS
- The pT4 subgroup showed a clear benefit of LC in the HIPEC arm
- No differences in morbidity were observed between groups

DFS, disease free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; LC, loco-regional control; OS, overall survival

Arjona-Sanchez A, et al. Ann Oncol. 2022;33 (suppl_7): S136-S196 (ESMO 2022 presentation)

HIPECT4: SUMMARY

- The addition of hyperthermic intraperitoneal chemotherapy with mitomycin C to a complete surgical resection for locally advanced colon cancer improves the LC rate, without increasing morbidity
- This benefit is greatest in the subgroup of patients with pT4 colon cancer.

Clinical Perspective

- **Need to see additional data before making any changes to clinical practice**
- **Challenges previous negative perceptions of HIPEC due to prior negative trials**
- **Need to understand which patients are likely to respond**

HIPEC, hyperthermic intraperitoneal chemotherapy; LC, loco-regional control

Arjona-Sanchez A, et al. Ann Oncol. 2022;33 (suppl_7): S136-S196 (ESMO 2022 presentation)

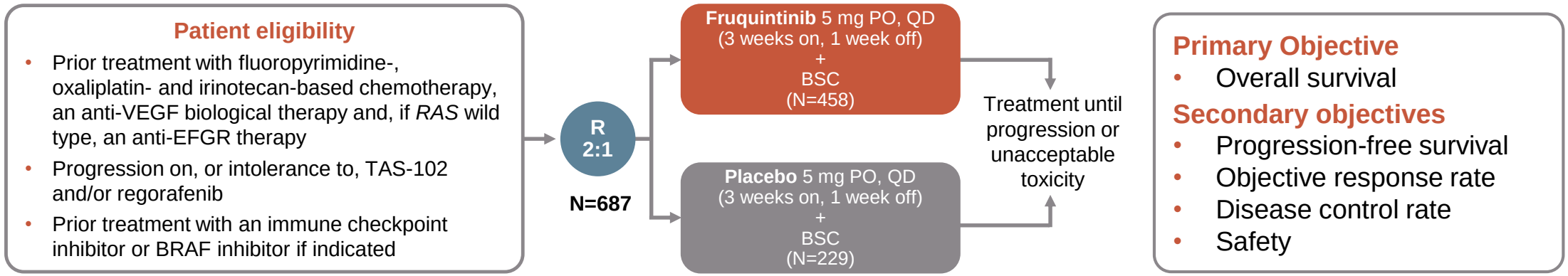
FRESCO-2: A GLOBAL PHASE 3 MULTIREGIONAL CLINICAL TRIAL EVALUATING THE EFFICACY AND SAFETY OF FRUQUINTINIB IN PATIENTS WITH REFRACTORY METASTATIC CRC

Dasari NA, et al. ESMO 2022. Abstract #LBA25

CRC, colorectal cancer

FRESCO-2: BACKGROUND AND STUDY DESIGN

- Effective treatment options are limited for patients (pts) with refractory metastatic colorectal cancer
- Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor or VGFR-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 pts 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, B-Raf; BSC, best supportive care; EFGR, endothelial growth factor; mCRC, metastatic prostate cancer; PO, orally; QD, once a day; RAS, rat sarcoma; R, randomisation; VEGFR, vascular endothelial growth factor receptor

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

FRESCO-2: RESULTS

EFFICACY

Category	Fruquintinib	Placebo
Overall survival		
Events/patients n/N (%)	317/461 (68.8)	173/230 (75.2)
Stratified p-value (log-rank)	P<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	
Progression-free survival		
Events/patients n/N (%)	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	

- Median duration of follow-up:
  - 11.3 months fruquintinib vs 11.2 months placebo
- Patients were heavily pre-treated, with > 70% having received > 3 lines of prior therapy

SAFETY

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%)

CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event

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

FRESCO-2: SUMMARY

- Fruquintinib had a significant and clinically meaningful improvement in OS and PFS in patients with refractory mCRC
- Fruquintinib was well tolerated, with a safety profile consistent with the established profile for monotherapy

Clinical Perspective

- **FRESCO-2 results are consistent with FRESCO and should support a new treatment option in refractory mCRC**

mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival

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

KRYSTAL-1: UPDATED EFFICACY AND SAFETY OF ADAGRASIB (MRTX849) WITH OR WITHOUT CETUXIMAB IN PATIENTS WITH ADVANCED CRC HARBOURING A KRASG12C MUTATION

Klempner S, et al. ESMO 2022. Abstract #LBA24

CRC, colorectal cancer; KRAS, Kirsten rat sarcoma

KRYSTAL-1: BACKGROUND AND STUDY DESIGN

- $KRAS^{G12C}$ mutations are associated with poor prognosis compared with other mutations in patients with CRC and later-line treatment options are limited
- Adagrasib is a $KRAS^{G12C}$ inhibitor and when combined with cetuximab to cause a dual EGFR/$KRAS^{G12C}$ blockade may enhance inhibition of KRAS-dependent signalling and overcome adaptive feedback
- KRYSTAL-1 is a phase 1b/2 CRC cohort study evaluating the safety and efficacy of adagrasib in patients with $KRAS^{G12C}$-mutated advanced solid tumours

Key eligibility criteria

- CRC with a $KRAS^{G12C}$ mutation[a]
- Unresectable or metastatic disease
- Prior systemic treatment for metastatic disease
- No available treatment with curative intent or available standard of care

Phase 1b
CRC combination

Adagrasib 600 mg BID[b] + cetuximab[c] (n=32)

Phase 2
CRC monotherapy

Adagrasib 600 mg BID[b] (n=44)

Study objectives

Phase 1b

- Primary endpoints: safety, RP2D, PK
- Secondary endpoints: ORR (RECIST 1.1), DOR, PFS, OS

Phase 2

- Primary endpoint: ORR (RECIST 1.1)[d]
- Secondary endpoints: safety, DOR, PFS, OS

[a] $KRAS^{G12C}$ mutation detected in tumour tissue and/or ctDNA per protocol. [b] Capsule, fasted. [c] Cetuximab dosing, 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W.
[d] Response was analysed in the clinically evaluable population with local radiology review.

BD, twice a day; CRC, colorectal cancer; ctDNA, circulating tumour DNA; DCR, disease control rate; DOR, duration of response; KRAS, Kirsten rat sarcoma; ORR, objective response rate; OS, overall survival; Q2W, twice weekly; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase 2 dose; PK, pharmacokinetics; PFS, progression-free survival

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

KRYSTAL-1: RESULTS

BASELINE DATA

	Adagrasib N=44	Adagrasib + cetuximab N=32
Median follow-up, months	20.1 months	17.5 months
Median age, years	59	60
Females, %	50%	53%
Median prior lines of systemic therapy, n	3	3
ECOG PS, %		
0	52%	44%
1	48%	56%

EFFICACY

Endpoint	Adagrasib N=44	Adagrasib + cetuximab N=32
ORR, % (n/N)	19% (8/43)	46% (13/28)
DCR, % (n/N)	86% (37/43)	100% (28/28)
Median PFS, months (95% CI)	5.6 months (95% CI: 4.1-8.3)	6.9 months (95% CI: 5.4-8.1)
Median OS, months (95% CI)	19.8 months (95% CI: 12.5-23.0)	13.4 months (95% CI: 9.5-20.1)
Median DOR, months (95% CI)	4.3 months (95% CI: 2.3-8.3)	7.6 months (95% CI: 5.7-NE)
Median TTR, months (95% CI)	1.5 months	1.4 months

SAFETY

- Grade 1 or 2 and 3 or 4 TRAEs occurred in 59% and 34% of pts, respectively, in the monotherapy cohort, and 84% and 16% of pts, respectively, in the combination cohort. No grade 5 TRAE occurred.

CI, confidence interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment related adverse events; TTR, time to responseKlempner S, et al. Ann Oncol. 2022; 33 (suppl_7): S808-S869 (ESMO 2022, oral presentation)

KRYSTAL-1: SUMMARY

- Adagrasib is well tolerated as monotherapy and with cetuximab
- Both mono- and combination therapies showed clinical activity in heavily pretreated pts with KRASG12C mutated CRC, with more sustained responses with the combination
- Adagrasib + cetuximab is being investigated in 2L CRC in the Phase 3 KRYSTAL-10 trial (NCT04793958)

Clinical Perspective

- **The role of these treatment combinations in mCRC needs to be better defined in larger, randomised trials**

2L, second line; KRAS, Kirsten rat sarcoma; (m)CRC, (metastatic) colorectal cancer

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

SOTORASIB IN COMBINATION WITH PANITUMUMAB IN REFRACTORY KRAS G12C-MUTATED CRC: SAFETY AND EFFICACY FOR PHASE 1B FULL EXPANSION COHORT (CodeBreaK 101)

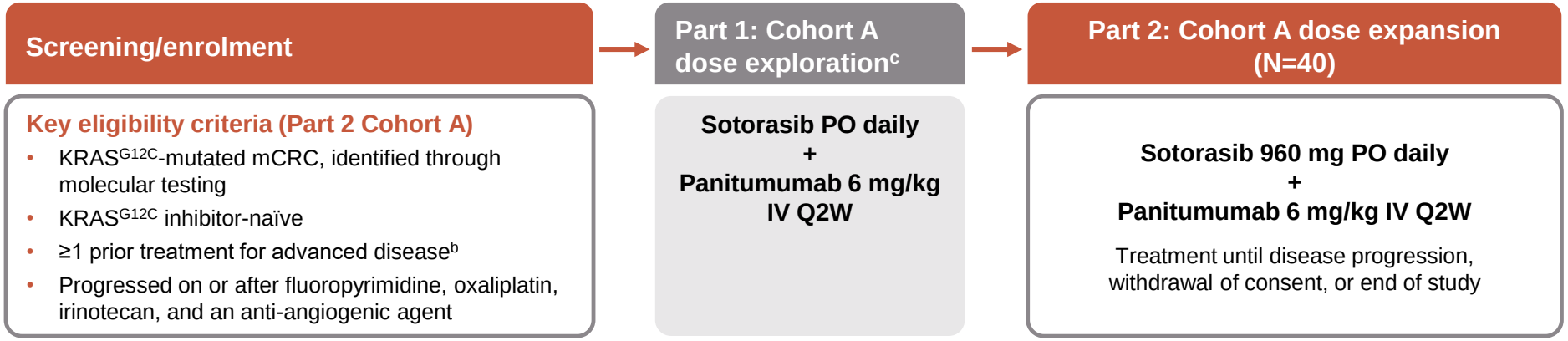
Kuboki Y, et al. ESMO 2022. Abstract #315O

CRC, colorectal cancer; KRAS, Kirsten rat sarcoma

CodeBreaK 101: BACKGROUND AND STUDY DESIGN

- Early data from the CodeBreaK 101 phase Ib dose exploration (n=8) and expansion (n=18) cohorts showed promising antitumour activity for the combination of sotorasib and panitumumab in chemorefractory KRAS^{G12C}-mutated mCRC
- Results from the fully enrolled dose expansion cohort of 40 pts with refractory mCRC are reported

Phase 1b, multicentre study[a]: Sotorasib (KRASG12C inhibitor) + panitumumab (EGFR antibody) in chemorefractory KRAS^{G12C}-mutated mCRC



Primary endpoint: Safety/tolerability
Secondary endpoints: **Anti-tumour efficacy** (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) **and PK**

[a] NCT04185883; EudraCT 2020-004721-23. [b] For patients with tumours known to be microsatellite instability high, prior checkpoint inhibitor therapy is required if clinically appropriate and locally available for that indication. [c] Dose exploration is completed

DCR, disease control rate; DOR, duration of response; IV; intravenous; KRAS, Kirsten rat sarcoma; mCRC, metastatic castration resistant prostate cancer; ORR, objective response rate; OS, overall survival; Q2w, every 2 weeks; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; pt, patient; RECIST, Response Evaluation Criteria in Solid Tumours; TTR, time to response

Kuboki Y, et al. Ann Oncol. 2022; 33 (suppl_7): S136-S196 (ESMO 2022 oral presentation)

CodeBreaK 101: RESULTS

- **Baseline characteristics:** 75% female, median age 57.5 years, median prior lines of therapy was 2
- **Safety findings** were consistent with known profiles of the individual drugs. No TRAEs resulted in discontinuation of either drug
- Sotorasib PK exposures were consistent to those observed in monotherapy studies

SAFETY

TRAE	N=40 n (%)
TRAE, any grade	37 (93)
Attributed to sotorasib	26 (65)
Attributed to panitumumab	37 (93)
Grade 3 TRAE[a]	9 (23)
Grade 4 TRAE	0
Fatal TRAE	0
TRAE leading to dose interuptions/reductions	
Attributed to sotorasib	6 (15)
Attributed to panitumumab	10 (25)
TRAE leading to discontinuation of either drug	0

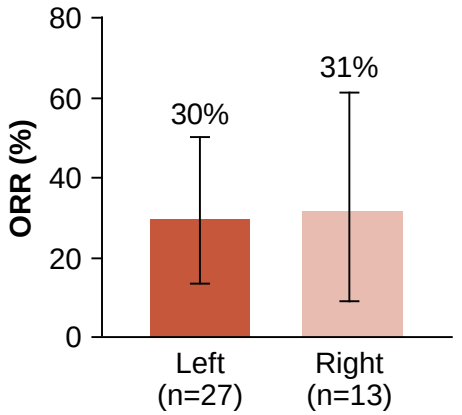
Data cutoff: June 24, 2022.
[a]Grade 3 TRAEs were rash (n=2, 5%), anaemia, fatigue, peripheral oedema, cellulitis, pustular rash, salmonellosis, skin infection, hypomagnesaemia, malignant neoplasm progression, pulmonary embolism, dermatitis acneiform, and pruritis (n=1 patient each, 3%)

EFFICACY

Response by investigator assessment	N=40 n (%)
ORR confirmed (95% CI)	**12 (30)** (16.6, 46.5)
Complete response	0
Partial response	12 (30)
Stable disease[a]	25 (63)
Progressive disease	3 (8)
DCR (95% CI)	**37 (93)** (79.6, 98.4)

Data cutoff: June 24, 2022.
[a]Minimum requirement for stable disease was 5 weeks.
DCR, disease control rate; mCRC, metastatic colorectal cancer; ORR, objective response rate

ORR subgroup analysis by primary tumour location



CI, confidence interval; DCR, disease control rate; ORR, objective response rate; PK, pharmacokinetics; TRAEs, treatment related adverse events

Kuboki Y, et al. Ann Oncol. 2022; 33 (suppl_7): S136-S196 (ESMO 2022 oral presentation)

CodeBreak 101: SUMMARY

- Sotorasib plus panitumumab was safe and tolerable in these chemorefractory patients with KRASG12C-mutated mCRC
- A 3-fold higher response rate (30% ORR) was observed than previously seen with sotorasib monotherapy, with no apparent difference based on tumour location

Clinical Perspective

- **The global phase 3 study, CodeBreaK300 (NCT05198934) will provide further data on the combination of sotorasib plus panitumumab vs standard of care in patients with KRAS^{G12C}-mutated mCRC**

KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Kuboki Y, et al. Ann Oncol. 2022; 33 (suppl_7): S136-S196 (ESMO 2022 oral presentation)

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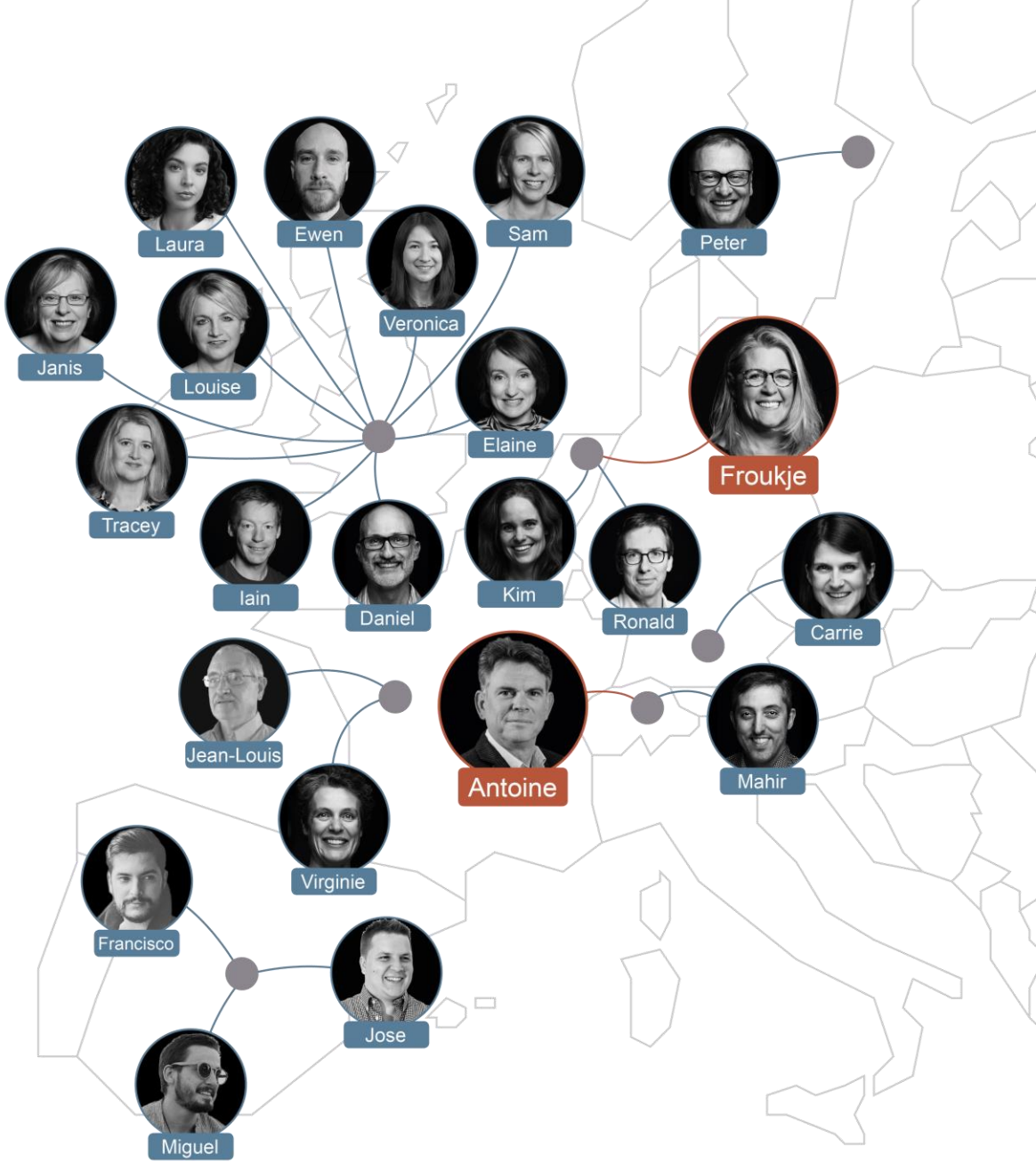

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