Overall survival (OS) of phase 3 CodeBreaK 300 study of sotorasib plus panitumumab (soto+pani) versus investigator's choice of therapy for *KRAS* G12C-mutated metastatic colorectal cancer (mCRC)

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Disclosure

- **Marwan G. Fakih** reports honoraria from Amgen; consulting or advisory roles for Taiho, Bayer, Pfizer, Seattle Genetics, GlaxoSmithKline, Mirati, Roche/Genentech, Essai, Merck, Sanofi, TEMPUS, and Bristol Myers Squibb; and research funding (to the institution) from Verastem, Bristol Myers Squibb, Amgen, Genentech, and Agenus Bio

Presentation Key Takeaways

- **Sotorasib 960 mg + panitumumab is a new standard-of-care therapy for patients with chemorefractory *KRAS* G12C–mutated mCRC**

- **This is supported by the following:**
  - **Previously reported superior PFS for sotorasib 960mg + panitumumab compared to investigator's choice**
  - **Overall survival trend favoring sotorasib 960mg + panitumumab compared to investigator's choice**
  - **Greatly increased objective response rate for sotorasib 960mg + panitumumab compared to investigator's choice**

Background

- The oncogenic *KRAS* G12C mutation is present in ~3% of patients with colorectal cancer (CRC) and may be associated with poor prognosis[1–7]
- There is a biological rationale to combine anti-EGFR therapy with a KRAS^{G12C} inhibitor in this molecular subgroup of patients[8–10]
- In CodeBreaK 300, sotorasib + panitumumab was superior to investigator's choice at the primary analysis of progression-free survival (PFS) in patients with *KRAS* G12C–mutated metastatic CRC (mCRC)[11]
- Here we present the protocol-specified final analysis of overall survival

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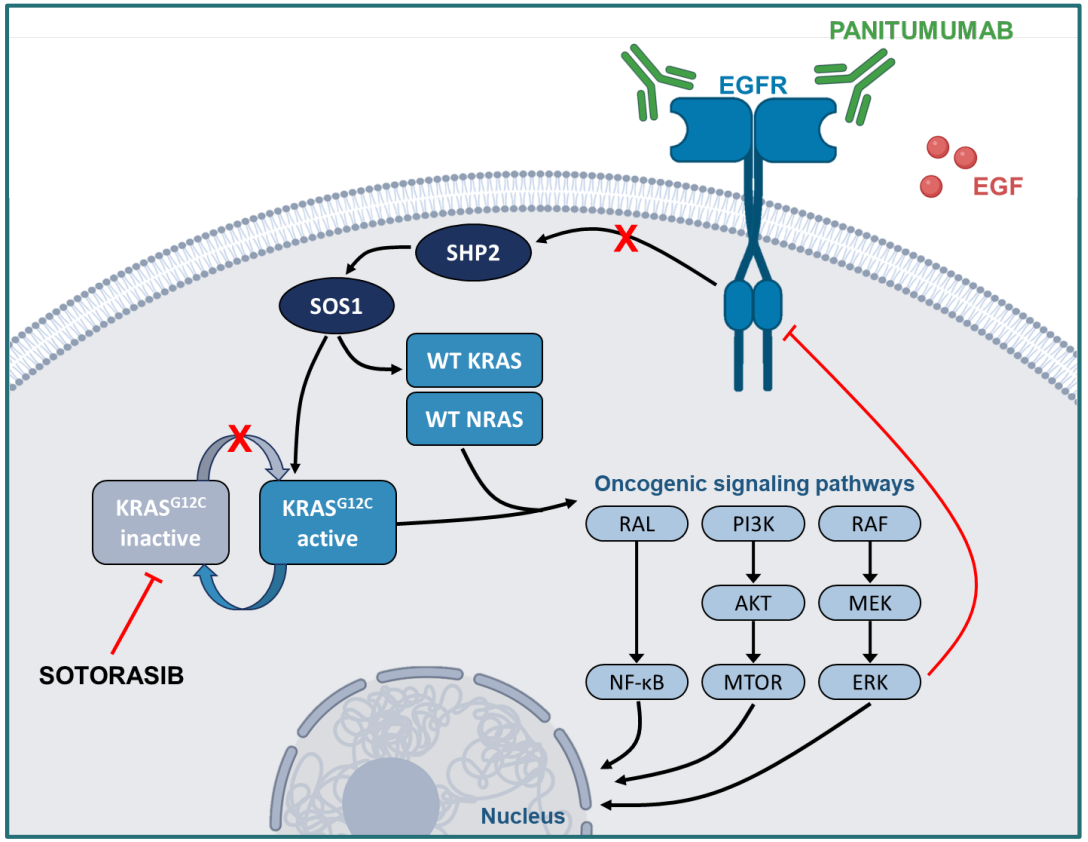
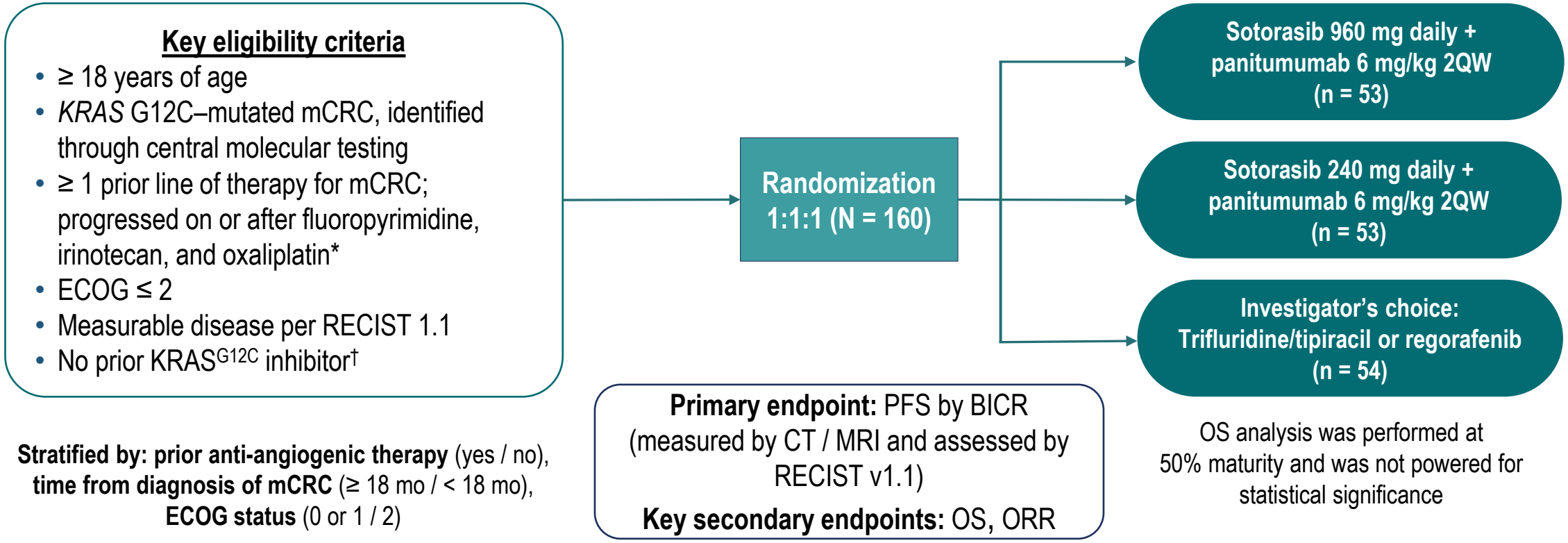


AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; KRAS, Kirsten rat sarcoma; MEK, mitogen-activated extracellular signal-regulated kinase; MTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; NRAS, neuroblastoma Ras viral oncogene homolog; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAL, Ras-related protein; SHP2, Src homology region 2-containing protein tyrosine phosphatase 2; SOS1, son of sevenless homolog 1; WT, wild type.

CodeBreaK 300 Phase 3 Study Design

Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)



*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †Patients with prior treatment with trifluridine and tipiracil and with regorafenib were excluded, where the investigator's choice would be these agents.

2QW, every 2 weeks; BICR, blinded independent central review; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

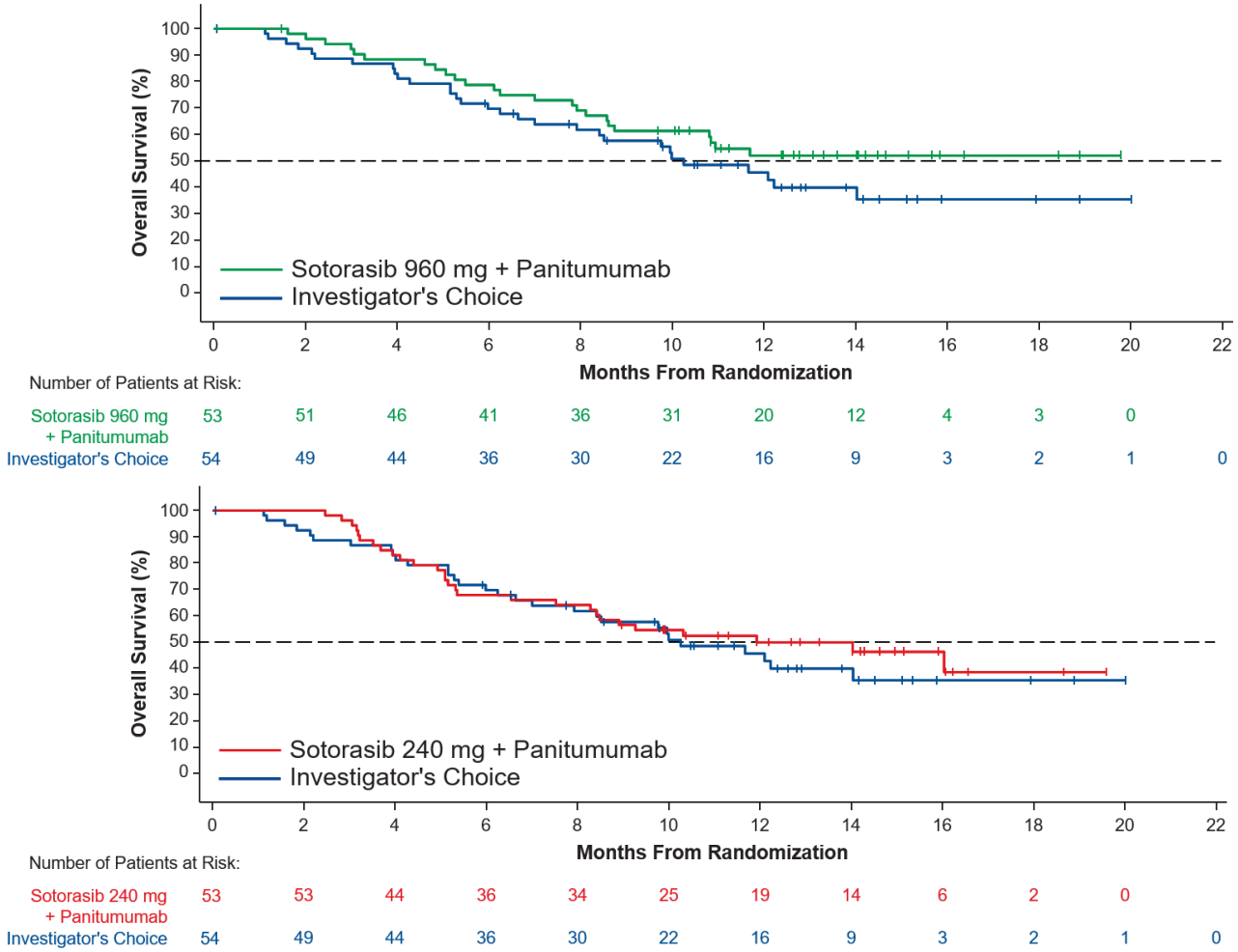
Baseline Characteristics

Characteristic	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Age, median (range), years	63.0 (37–79)	58.0 (35–82)	64.5 (34–81)
Male, n (%)	29 (55)	26 (49)	24 (44)
North America / Europe / Asia / Rest of world, %	9 / 77 / 11 / 2	9 / 53 / 36 / 2	13 / 67 / 20 / 0
ECOG performance status 0 / 1 / 2, %	60 / 36 / 4	55 / 42 / 4	65 / 33 / 2
Tumor sidedness, left / right / unknown, %	53 / 45 / 2	68 / 32 / 0	69 / 30 / 2
Prior lines of therapy, n (%)			
1	7 (13)	8 (15)	9 (17)
≥ 2	46 (87)	45 (85)	45 (83)
Prior oxaliplatin and irinotecan and fluoropyrimidine, n (%)	49 (92)	50 (94)	51 (94)
Prior anti-angiogenic therapy, n (%)	45 (85)	47 (89)	48 (89)
Prior trifluridine and tipiracil, n (%)	7 (13)	7 (13)	6 (11)
Prior regorafenib, n (%)	4 (8)	1 (2)	2 (4)
Prior trifluridine and tipiracil or regorafenib, n (%)	11 (21)	8 (15)	8 (15)

Demographics and baseline characteristics were generally balanced across arms

Data cutoff, 18 December 2023. ECOG, Eastern Cooperative Oncology Group.

Secondary Endpoint: Protocol-Specified Final OS in Intent-to-Treat Population



	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median (95% CI) OS, months*	NE (8.6–NE)	11.9 (7.5–NE)	10.3 (7.0–NE)
HR (95% CI)†	0.70 (0.41–1.18)	0.83 (0.49–1.39)	–
P-value (2-sided)‡	0.20	0.50	–
Number of deaths (%)	24 (45)	28 (53)	30 (56)

- **After a median follow-up of 13.6 months, sotorasib (240 mg and 960 mg) + panitumumab showed a trend of improved OS versus investigator's choice, with 30% reduction in risk of death for sotorasib 960 mg + panitumumab**

*Estimated using the Kaplan-Meier method, 95% CIs from log-log transformation. †HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk and a longer OS for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib]. ‡*P*-value from stratified log-rank test. Data cutoff, 18 December 2023. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Subsequent Anticancer Therapy

Characteristic	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Patients with subsequent anti-cancer therapy, n (%)	**23 (43)**	**27 (51)**	**33 (61)**
$KRAS^{G12C}$ inhibitors			
Any $KRAS^{G12C}$ inhibitor	**1 (2)**	**0**	**17 (31)**
$KRAS^{G12C}$ inhibitor + EGFR antibody	**0**	**0**	**15 (28)**
$KRAS^{G12C}$ inhibitor + other	**0**	**0**	**2 (4)**
$KRAS^{G12C}$ inhibitor monotherapy	**1 (2)**	**0**	**0**
Control arm agents			
Regorafenib or trifluridine / tipiracil	15 (28)	22 (42)	14 (26)
Regorafenib	8 (15)	6 (11)	8 (15)
Trifluridine and tipiracil	12 (23)	19 (36)	6 (11)
Anti-angiogenics			
Bevacizumab	9 (17)	12 (23)	7 (13)
Aflibercept	0	0	0
Ramucirumab	1 (2)	0	0
Chemotherapy agents			
Oxaliplatin	5 (9)	3 (6)	2 (4)
Irinotecan	1 (2)	3 (6)	4 (7)
Fluoropyrimidine	15 (28)	23 (43)	13 (24)
Other	6 (11)	6 (11)	3 (6)

EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma.

Additional Outcomes

Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Objective response rate, % (95% CI)*	30 (18.3–44.3)	8 (2.1–18.2)	2 (0–9.9)
Duration of response, median (range),† months (+, censored)	10.1 (3.1–12.9+)	– (5.6–11.2+)	– (5.2–5.2)
PFS per BICR (ad hoc analysis at final OS DCO)			
Events, n (%)	36 (68)	42 (79)	38 (70)
Median (95% CI),† months	5.8 (4.2–7.5)	4.0 (3.7–5.9)	2.0 (1.9–3.9)
HR (95% CI)‡	0.46 (0.29–0.72)	0.57 (0.37–0.88)	

- No new safety findings were observed

*ORR 95% CI using Clopper-Pearson method. †Kaplan-Meier estimates with 95% CIs from log-log transformation. Evaluation was only done if at least 10 patients. ‡HRs and 95% CIs from stratified Cox proportional hazards model. HR < 1.0 indicates a lower risk for [sotorasib + panitumumab] versus [trifluridine and tipiracil or regorafenib].
Data cutoff, 18 December 2023. BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival.

Conclusions

- While CodeBreaK 300 was not powered to detect a statistically significant difference in OS, the study showed a trend toward improved OS for patients with mCRC randomized to sotorasib 960 mg + panitumumab
  - After a median follow-up of 13.6 months, median OS was not reached with sotorasib 960 mg + panitumumab versus 10.3 months with investigator's choice (HR 0.70, 95%CI 0.41-1.18)
- Updated ORR was 30% (sotorasib 960 mg + panitumumab) versus 2% (investigator's choice)
- Sotorasib 960 mg + panitumumab showed a median DOR of 10.1 months
- **These results support the use of sotorasib 960 mg + panitumumab as a new standard-of-care therapy for patients with chemorefractory *KRAS* G12C–mutated mCRC**

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

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Patient Lay Summary

- This phase 3 clinical trial evaluated combination therapy with sotorasib, an oral medication that targets the $KRAS^{G12C}$ protein, and panitumumab, an antibody that targets the EGFR protein, for patients who previously received treatment for metastatic colorectal cancer
  - Two doses of sotorasib (960mg and 240mg) were evaluated in combination with panitumumab compared to physician's choice therapy of either trifluridine and tipiracil or regorafenib

- In the previously reported primary objective of the study, the combination of sotorasib at the 960mg dose plus panitumumab effectively prolonged progression-free survival compared to physician's choice therapy

- This longer-term analysis evaluated overall survival, a key secondary objective of the trial
  - After 13.6 months, median overall survival was not yet reached for patients receiving sotorasib 960 mg plus panitumumab; median overall survival was 10.3 months with physician's choice therapy
  - In this analysis, 30% of patients who received sotorasib 960 mg plus panitumumab responded to treatment compared to 2% that responded to physician's choice therapy. This result was not evaluated for statistical significance

These results support the use of sotorasib and panitumumab combination therapy as a new standard-of-care therapy for patients with chemorefractory *KRAS* G12C–mutated metastatic colorectal cancer