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CodeBreaK101 Subprotocol H: Phase 1b Study Evaluating Combination of Sotorasib, a KRAS^{G12C} Inhibitor, and Panitumumab (PMab), an EGFR Inhibitor, in Advanced *KRAS* p.G12C-Mutated Colorectal Cancer (CRC)

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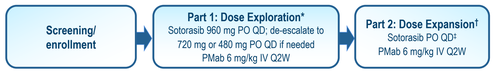
INTRODUCTION

- The *Kirsten rat sarcoma viral oncogene homolog (KRAS)* p.G12C mutation has been identified as an oncogenic driver mutation in colorectal cancer (CRC)[1]
- Sotorasib is a first-in-class specific and irreversible inhibitor of the KRAS^{G12C} protein[2]
  - In the CodeBreaK100 phase 1 trial (NCT03600883), sotorasib monotherapy demonstrated clinical activity in heavily pretreated patients with *KRAS* p.G12C-mutated CRC, with an objective response rate (ORR) of 7.1%[2]
- Panitumumab (PMab), a monoclonal antibody specific to epidermal growth factor receptor (EGFR), is approved for the treatment of *RAS* wild-type CRC[3]
- KRAS^{G12C} inhibition with sotorasib can lead to accumulation of upstream EGFR signaling, which could drive tumor growth via alternative pathways[4]
  - The combination of sotorasib with an EGFR inhibitor may provide complete and deep inhibition of tumor growth, as supported by preclinical evidence[4,5]
- **Herein, the safety and efficacy of sotorasib in combination with PMab in *KRAS* p.G12C-mutated CRC is evaluated in this ongoing phase 1b study (NCT04185883)**

STUDY DESIGN

CodeBreaK101 Subprotocol H Phase 1b



Key eligibility criteria

- Locally advanced or metastatic CRC
- *KRAS* p.G12C mutation as assessed by molecular testing
- ≥ 1 prior treatment for advanced disease

Primary endpoints

- Dose-limiting toxicities
- Adverse events

Key secondary endpoints

- Efficacy: ORR, TTR, DOR, PFS, OS
- Pharmacokinetic profile

Focus herein:

Part 1 Cohort A	Part 2 Cohort A
• Includes patients that received prior KRAS^{G12C} inhibitor or were KRAS^{G12C} inhibitor naïve • **Dosing: 960 mg sotorasib PO QD/ PMab 6 mg/kg IV Q2W**	• Only includes KRAS^{G12C} inhibitor naïve patients • **Dosing: 960 mg sotorasib PO QD/ PMab 6 mg/kg IV Q2W**

*A minimum of 2 patients must be KRAS^{G12C} inhibitor naïve per dose cohort. Herein, we are only presenting data on Part 1 Cohort A in patients treated with 960 mg sotorasib PO QD/PMab 6 mg/kg IV Q2W.
†Patients must be KRAS^{G12C} inhibitor naïve and must have progressed after fluoropyrimidine, oxaliplatin, irinotecan, and an anti-angiogenic agent.
‡Sotorasib PO daily dose identified in the dose exploration phase. Herein, we are only presenting data on Part 2 Cohort A in patients treated with 960 mg sotorasib PO QD/PMab 6 mg/kg IV Q2W.
CRC, colorectal cancer; DOR, duration of response; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; Q2W, every 2 weeks; QD, daily; TTR, time to response.

RESULTS

Baseline Characteristics and Treatment Exposure

	Part 1 + Part 2 Combined Cohort A (N = 31) Sotorasib 960 mg PO QD/PMab 6 mg/kg IV Q2W
Baseline characteristic	
Median age, years (range)	58 (31–79)
Female, n (%)	21 (67.7)
Median lines of therapy for metastatic disease, n (range)	2 (1–10)
Prior sotorasib therapy, n (%)	5 (16.1)
Exposure	
Median treatment duration of combination, week (range)	10.3 (2.1–48.1)

IV, intravenous; PMab, panitumumab; PO, oral; Q2W, every 2 weeks; QD, daily.

RESULTS (continued)

Treatment-Related Adverse Events (TRAEs)

- No dose-limiting toxicities (DLT) were observed during the first 28 days (DLT evaluation period)
- The majority of TRAEs were grade 1–2 in severity

Variable	Part 1 + Part 2 Combined Cohort A (N = 31) Sotorasib 960 mg PO QD/PMab 6 mg/kg IV Q2W
TRAE any grade, n (%)	23 (74.2)
Related to sotorasib	14 (45.2)
Related to PMab	23 (74.2)
Grade 3 TRAE, n (%)	4 (12.9)*
Grade 4 TRAE, n	0
Fatal TRAE, n	0
TRAE leading to dose modification, n (%)	
Sotorasib	3 (9.7)†
PMab	2 (6.5)‡

*One patient experienced grade 3 hypokalemia, hypomagnesemia, dry skin, and rash (PMab-related); PMab dose modified. One experienced grade 3 dermatitis acneiform and myalgia (PMab-related); PMab dose modified only for dermatitis acneiform. One experienced grade 3 diarrhea (sotorasib-related); sotorasib dose modified. One experienced grade 3 cellulitis, edema peripheral, and dermatitis acneiform (PMab-related); sotorasib and PMab dose not changed.
†One patient had diarrhea, one patient had fatigue, and another patient had hypokalemia, resulting in dose modification of sotorasib.
‡One patient had dermatitis acneiform and another patient had dry skin, rash, hypokalemia, and hypomagnesemia, resulting in dose modification of PMab.
IV, intravenous; PMab, panitumumab; PO, oral; Q2W, every 2 weeks; QD, daily; TRAE, treatment related adverse event.

Sotorasib in combination with PMab was well tolerated, with no fatal TRAEs

Most Common TRAEs (Occurring in > 10% Of Combined Cohort)

Variable	Part 1 + Part 2 Combined Cohort A (N = 31) Sotorasib 960 mg PO QD/PMab 6 mg/kg IV Q2W	
	All grades	Grade ≥ 3* (No grade 4 or 5 events reported)
Total TRAEs, n (%)	23 (74.2)	4 (12.9)
Dermatitis acneiform	17 (54.8)	2 (6.5)
Dry skin	8 (25.8)	1 (3.2)
Nausea	8 (25.8)	0
Diarrhea	7 (22.6)	1 (3.2)
Hypokalemia	5 (16.1)	1 (3.2)
Hypomagnesemia	5 (16.1)	1 (3.2)
Pruritus	4 (12.9)	0
Rash	4 (12.9)	1 (3.2)

*Other grade 3 TRAEs reported included cellulitis, peripheral edema, and myalgia.
IV, intravenous; PMab, panitumumab; PO, oral; Q2W, every 2 weeks; QD, daily; TRAE, treatment related adverse event.

Tumor Response for Sotorasib Combination with PMab

Response assessed by investigator	Part 1 Cohort A (n = 8) Sotorasib 960 mg / PMab 6 mg/kg	Part 2 Cohort A (n = 18) Sotorasib 960 mg / PMab 6 mg/kg	Part 1 + Part 2 Combined Cohort A (N = 26)*
Disease control rate, n (%)	6 (75.0)	15 (83.3)	21 (80.8)
ORR, % (95% CI)			
Confirmed	12.5 (0.3, 52.7)	16.7 (3.6, 41.4)	15.4
Confirmed and unconfirmed†	12.5 (0.3, 52.7)	33.3 (13.3, 59.0)	26.9
Partial response, n (%)			
Confirmed	1 (12.5)	3 (16.7)	4 (15.4)
Confirmed and unconfirmed†	1 (12.5)	6 (33.3)	7 (26.9)
Stable disease, n (%)	5 (62.5)	12 (66.7)	17 (65.4)
Progressive disease, n (%)	1 (12.5)	2 (11.1)	3 (11.5)
Not done, n (%)	1 (12.5)	1 (5.6)	2 (7.7)

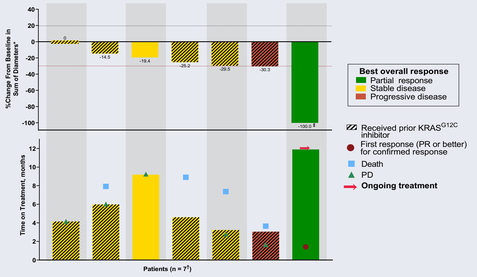
*Efficacy analysis set includes all patients who received ≥ 1 dose of investigational products, have ≥ 1 measurable lesions at baseline assessed using RECIST 1.1, and have the opportunity to be followed for ≥ 7 weeks starting from day 1.
†Includes patients with unconfirmed partial response, awaiting confirmatory scan.
ORR, objective response rate; PMab, panitumumab.

Overall, 27% achieved response (including unconfirmed response awaiting confirmation) and 81% achieved disease control

Tumor Response and Treatment Duration

Part 1 Cohort A (n = 7†)
Sotorasib 960 mg/ PMab 6 mg/kg

- 5 patients had received prior KRAS^{G12C} inhibitor
- 3 patients were KRAS^{G12C} inhibitor naïve

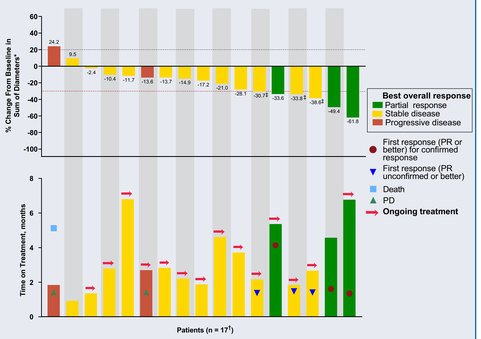


*Only considers tumor assessments prior to and including the first assessment where timepoint response is progressive disease, and prior to the start of the next anti-cancer therapy.
†Includes patients who received ≥ 1 dose of investigational product, have ≥ 1 RECIST 1.1 measurable lesions at baseline, and have been followed for ≥ 7 weeks from the day one; 1 patient was not able to be included here as withdrawn from study before post-baseline tumor assessment.
‡This patient had 100% reduction in target lesion size, but still had non-target lesions present.
PMab, panitumumab.

Four out of 5 patients who had prior KRAS^{G12C} treatment showed tumor shrinkage from 15%–30%; 2 patients who did not have prior KRAS^{G12C} treatment had 19%–100% tumor shrinkage
The majority of the patients (80%) with prior KRAS^{G12C} inhibitor exposure had a best response of stable disease

Part 2 Cohort A (n = 17†)
Sotorasib 960 mg/ PMab 6 mg/kg

- Only includes KRAS^{G12C} inhibitor naïve patients



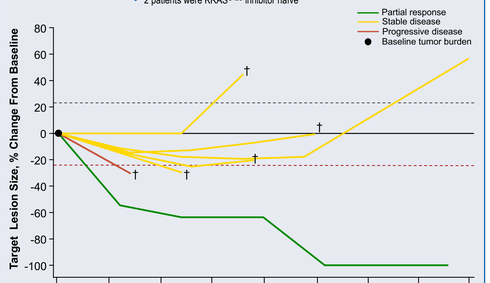
*Only considers tumor assessments prior to and including the first assessment where timepoint response is progressive disease, and prior to the start of the next anti-cancer therapy.
†Includes patients who received ≥ 1 dose of investigational product, have ≥ 1 RECIST 1.1 measurable lesions at baseline, and have been followed for ≥ 7 weeks from the day one; 1 patient was not able to be included here as withdrawn from study before post baseline tumor assessment.
‡Patient has partial response which has not yet been confirmed by a second scan; therefore, currently stable disease.
PMab, panitumumab.

Decrease in target lesion size was observed in the majority (15/17) of this chemotherapy refractory mCRC population treated in dose expansion.
Among these 15 patients, 14 remain on treatment with 2 patients remaining on treatment after 6 months
Median time for progression-free survival can not yet be estimated

Change in Target Lesions Over Time

Part 1 Cohort A (n = 7†)
Sotorasib 960 mg/ PMab 6 mg/kg

- 5 patients had received prior KRAS^{G12C} inhibitor
- 2 patients were KRAS^{G12C} inhibitor naïve

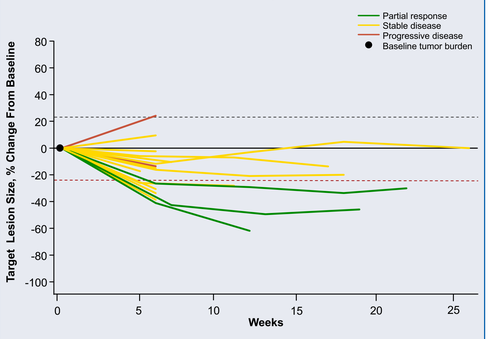


*Includes patients who received ≥ 1 dose of investigational product, have ≥ 1 RECIST 1.1 measurable lesions at baseline, and have been followed for ≥ 7 weeks from the day one; 1 patient was not able to be included here as withdraw from study before post baseline tumor assessment.
†Patients received prior KRAS^{G12C} inhibitor.
PMab, panitumumab.

For the responder in this cohort, a 100% reduction in target lesion size was observed
Best response seen in patients with prior KRAS^{G12C} exposure was stable disease

Part 2 Cohort A (n = 17)*
Sotorasib 960 mg/ PMab 6 mg/kg

- Only includes KRAS^{G12C} inhibitor naïve patients

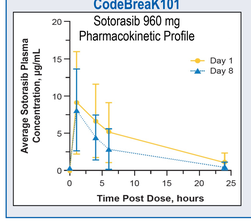


*Includes patients who received ≥ 1 dose of investigational product, have ≥ 1 RECIST 1.1 measurable lesions at baseline, and have been followed for ≥ 7 weeks from the day one; 1 patient was not able to be included here as withdraw from study before post baseline tumor assessment.
PMab, panitumumab.

The majority of patients had a decrease in target lesion size; this decrease appears to be durable

Sotorasib Pharmacokinetics

Study: Subpart Sotorasib 960 mg	Treatment	Day 1* t_{max}, h (range)†	Day 1* C_{max}, µg/mL (mean, CV%)	Day 1* AUC_{0-24h} h*µg/mL (mean, CV%)	Day 8* t_{max}, h (range)†	Day 8* C_{max}, µg/mL (mean, CV%)	Day 8* AUC_{0-24h} h*µg/mL (mean, CV%)
CodeBreaK101: (NCT04185883): Part 1 + Part 2, Cohort A (N = 42–49)	Sotorasib in combination with PMab	1.0 (1.0–6.0)	8.01 (9.91, 66)	77.2 (96.2, 76) [n = 47]	1.0 (1.0–6.0) [n = 48]	7.50 (8.80, 54) [n = 48]	51.7 (61.0, 78) [n = 42]
CodeBreaK100: (NCT03600883) Part 2D Cohort (N = 11–14)	Sotorasib monotherapy	1.9 (0.48–5.9)	9.71 (11.5, 65)	103 (122, 64) [n = 12]	2.0 (0.52–4.2)	6.50 (7.24, 52)	50.3 (58.8, 62) [n = 11]



*Data presented as GeoMean for all parameters except for t_{max}, which is presented as median. Values reported to 3 significant figures except for t_{max} and CV%, which are presented as 2 significant figures and the nearest integer, respectively.
†Reported t_{max} from CodeBreaK101 is based on nominal time; t_{max} from CodeBreaK100 is based on actual time.
AUC_{0-24h}, area under the concentration-time curve from time 0–24 h postdose; C_{max}, maximum observed drug concentration; t_{max}, time to reach C_{max}.

Sotorasib exposures were similar to those observed in monotherapy study

CONCLUSIONS

- The combination of sotorasib (960 mg orally daily) and panitumumab (6 mg/kg IV every 2 weeks) was safe and tolerable in these chemorefractory patients with *KRAS* p.G12C-mutated CRC
  - Adverse events were consistent with known adverse events for sotorasib and panitumumab
- Although follow up is short in this interim analysis, response rates of the combination of sotorasib and panitumumab were:
  - 15.4% confirmed ORR
  - 26.9% ORR (including unconfirmed response awaiting confirmation)
  - These ORR were numerically higher than sotorasib monotherapy in *KRAS* p.G12C-mutated CRC (7.1% ORR)[2]
- Sotorasib in combination with panitumumab is associated with signals of early promising efficacy in patients with *KRAS* p.G12C-mutated CRC

DECLARATION OF INTERESTS

Study sponsored by Amgen Inc.
Marwan Fakih has the following disclosures:
- Speaking engagement (self): Amgen Inc.
- Advisory board (self): Array BioPharma, Bayer
- Advisory board (to institution): AstraZeneca
- Grant (to institution): Novartis

Please see abstract for coauthor disclosures

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