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Hong DS, et al.

CodeBreaK 100: Phase 1 study of AMG 510, a novel $KRAS^{G12C}$ inhibitor, in patients with advanced solid tumors other than non–small cell lung cancer (NSCLC) and colorectal cancer (CRC)

ASCO 2020
Abstract number: 3511

CodeBreak 100: Phase 1 Study of AMG 510, a Novel KRAS^{G12C} Inhibitor, in Patients With Advanced Solid Tumors Other Than Non–Small-Cell Lung Cancer (NSCLC) and Colorectal Cancer (CRC)

David S. Hong, MD[1]; James C. Kuo, MBBS, FRACP[2]; Adrian Sacher, MD[3]; Fabrice Barlesi, MD, PhD[4]; Benjamin Besse, MD, PhD[5]; Yasutoshi Kuboki, MD[6]; Grace K. Dy, MD[7]; Vikas Dembla, MD[8]; John C. Krauss, MD[9]; Timothy F. Burns, MD, PhD[10]; June Kim, PhD[11]; Haby Henary, MD[11]; Gataree Ngarmchamnanrith, MD[11]; Bob T. Li, MD, PhD[12]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Scientia Clinical Research, Randwick, AU; [3]Princess Margaret Cancer Centre, University of Toronto, Ontario, Canada; [4]Aix Marseille University, France; [5]Gustave Roussy Institute, Villejuif, France; [6]National Cancer Center Hospital East, Kashiwa, Japan; [7]Rosswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [8]Gibbs Cancer Center, Greer, SC, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA, USA; [11]Amgen Inc, Thousand Oaks, CA, USA; [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA

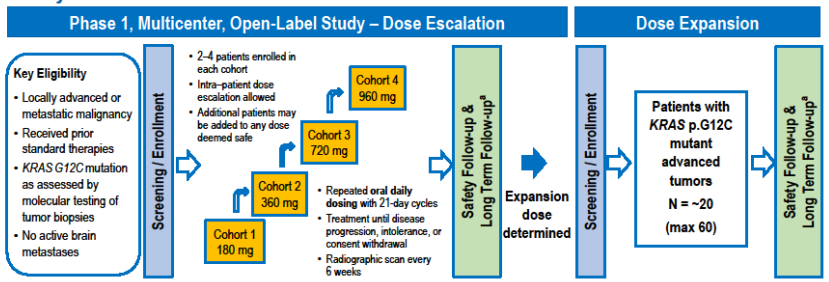
BACKGROUND

- *Kirsten rat sarcoma viral oncogene homolog (KRAS)* is the most commonly mutated oncogene in cancer; yet no agent directly targeting mutant KRAS has been clinically approved[1]
- *KRAS* p.G12C mutation, often associated with poor prognosis, occurs in approximately 13% of NSCLC and 1%–3% of CRC and other solid cancers[2-6]
- Previously, AMG 510 (proposed INN, sotorasib), a novel KRAS^{G12C} inhibitor, demonstrated a favorable toxicity profile and preliminary efficacy in patients with NSCLC and CRC harboring *KRAS* p.G12C[7]
- This analysis reports updated data in patients with other tumor types

INN: international nonproprietary name

METHODS

Study Schema



Primary endpoints: dose limiting toxicities (DLTs), safety
Key secondary endpoints: PK, objective response rate, duration of response, disease control rate, PFS, duration of stable disease

[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

RESULTS

Patients

Tumor types	Number of patients
Pancreatic cancer	10
Appendiceal cancer	4
Endometrial cancer	2
Unknown primary cancer	2
Bile duct cancer	1
Sinonasal cancer	1
Ampullary cancer	1
Small bowel cancer	1
Melanoma	1
Small cell lung cancer	1
Esophageal cancer	1
Total	**25**

Data cutoff: January 8, 2020

Median follow-up: 4.3 (range: 0.1–12.6) months

Dosing schedule: 2 appendiceal cancer patients received 360 mg and 720 mg, respectively; the remaining patients received 960 mg

22 patients had been followed up for ≥ 7 weeks and were evaluable for response

At cutoff, 12 patients discontinued treatment

Baseline Characteristics

Baseline Characteristics	N = 25
Median age (range) – year	60.0 (40–75)
Female – n (%)	9 (36.0)
ECOG performance at baseline – n (%)	
0	7 (28.0)
1	14 (56.0)
2	4 (16.0)
Prior lines of systemic anticancer therapy – n (%)	
1	4 (16.0)
2	5 (20.0)
3	6 (24.0)
> 3	9 (36.0)
Missing	1 (4.0)
Number of prior lines of anticancer therapy – median (range)	3 (1–4)

ECOG: Eastern Cooperative Oncology Group.

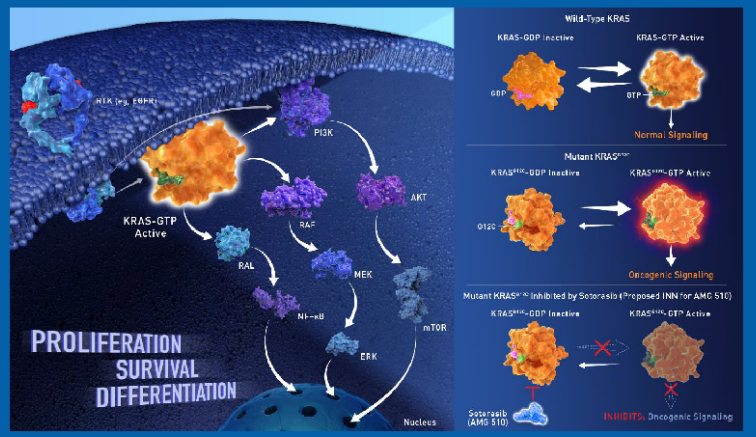
REFERENCES

1. Cox AD, Fesik SW, Kimmelman AC, et al. *Nat Rev Drug Discov.* 2014 Nov;13(11):828-851.
2. Nadal E, Chen G, Prensner JR, et al. *J Thorac Oncol.* 2014;9:1513-1522.
3. Ouerhani S, Elgaaied AB. *Cancer Biomark.* 2011;10:259-266.
4. Jones RP, Sutton PA, Evans JP, et al. *Br J Cancer.* 2017;116:923-929.
5. Modest DP, Brodowicz T, Stintzing S, et al. *Oncology.* 2012;83:241–247.
6. Biernacka A, Tsongalis PD, Peterson JD, et al. *Cancer Genet.* 2016;209:195-198.
7. Govindan R, Fakih MG, Price TJ, et al. *Annals of Oncology.* (2019) 30 (suppl_5): v159-v193.

CONCLUSIONS

- Sotorasib (AMG 510) was well tolerated in patients with advanced *KRAS* p.G12C mutant solid tumors other than NSCLC and CRC
  - The safety profile was largely consistent with that reported previously
  - Toxicities were mild and manageable, and there were no treatment-related AEs that led to discontinuation of treatment
- A confirmed partial response was observed in 3 patients with appendiceal cancer, melanoma, and endometrial cancer, respectively
- Six of 8 evaluable patients with pancreatic cancer achieved stable disease; 3 of them had best tumor burden reduction of ~30% from baseline
- Eight (36.4%) of 22 evaluable patients were still on treatment as of cutoff
- Phase 2 part of CodeBreak 100 is ongoing (NCT03600883)

Sotorasib (AMG 510) Locks KRAS^{G12C} in the Inactive State, Inhibiting Oncogenic Signaling



- This study is funded by Amgen Inc.
- Yang Li PhD (Amgen Inc.) provided medical writing assistance
- Refer to the QR code for the poster file and author disclosures

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RESULTS (Continued)

Patient Incidence of Adverse Events

	All treatment-emergent AEs (TEAEs) N = 25, n (%)	All treatment-related TEAEs N = 25, n (%)
Any grade	20 (80.0)	9 (36.0)
Grade ≥ 2	17 (68.0)	4 (16.0)
Grade ≥ 3	15 (60.0)	2 (8.0)
Grade ≥ 4	4 (16.0)	0 (0.0)
Dose limiting toxicity	0 (0.0)	0 (0.0)
Serious adverse events	13 (52.0)	1 (4.0)
Fatal adverse events	4 (16.0)	0 (0.0)
AEs leading to treatment discontinuation	3 (12.0)	0 (0.0)

AE: adverse events

Target dose for expansion: 960 mg QD

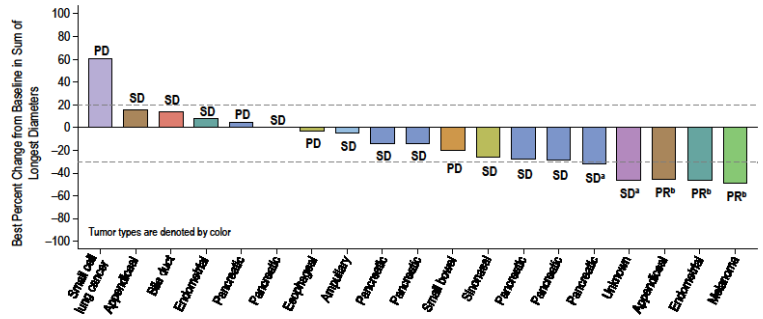
- Treatment-related TEAEs reported in > 1 patients
  - Diarrhea (2/25)
  - Fatigue (2/25)
- Grade 3 treatment-related TEAEs
  - Diarrhea (1/25)
  - Pneumonia (1/25)

Tumor Response

Best tumor response	N = 25
Confirmed partial response – n	3
Tumor types (n)	Appendiceal (1), Melanoma (1), Endometrial (1)
Stable disease – n	13
Tumor types (n)	Pancreatic (6), Appendiceal (2), Ampullary (1), Bile duct (1), Endometrial (1), Sinonasal (1), Unknown primary (1)
Progressive disease – n	6
Tumor types (n)	Pancreatic (2), Appendiceal (1), Small cell lung cancer (1), Esophageal (1), Small bowel cancer (1)
Not evaluable[a] – n	3
Tumor types (n)	Pancreatic (2), Unknown primary (1)

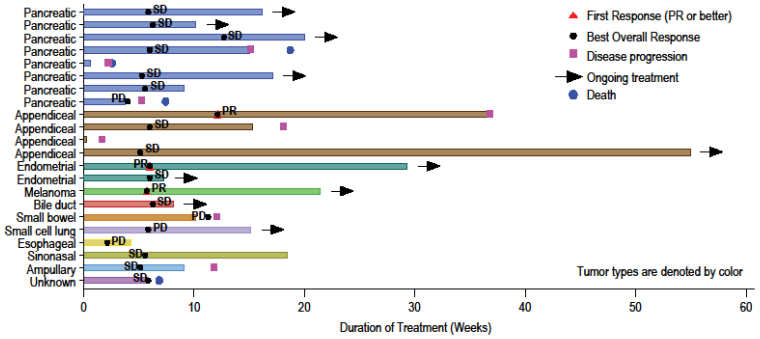
[a]Patients hadn't been followed up for > 7 weeks as of the cutoff

Tumor Burden Change From Baseline



Three patients are not included due to missing postbaseline tumor data: 2 patients with appendiceal cancer (1 PD, 1 SD) and 1 with pancreatic cancer (PD)
[a]Patients had unconfirmed PR; [b]Of 3 patients with confirmed PR, 1 with appendiceal cancer received 720 mg and the other 2 received 960 mg.

Time to Response and Treatment Over Time



CodeBreaK 100: Phase 1 study of AMG 510, a novel KRAS^{G12C} inhibitor, in patients with advanced solid tumors other than non–small cell lung cancer (NSCLC) and colorectal cancer (CRC)

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- Previously, AMG 510 (proposed INN, sotorasib), a novel KRAS^{G12C} inhibitor, demonstrated a favorable toxicity profile and preliminary efficacy in patients with NSCLC and CRC harboring *KRAS* p.G12C[7]
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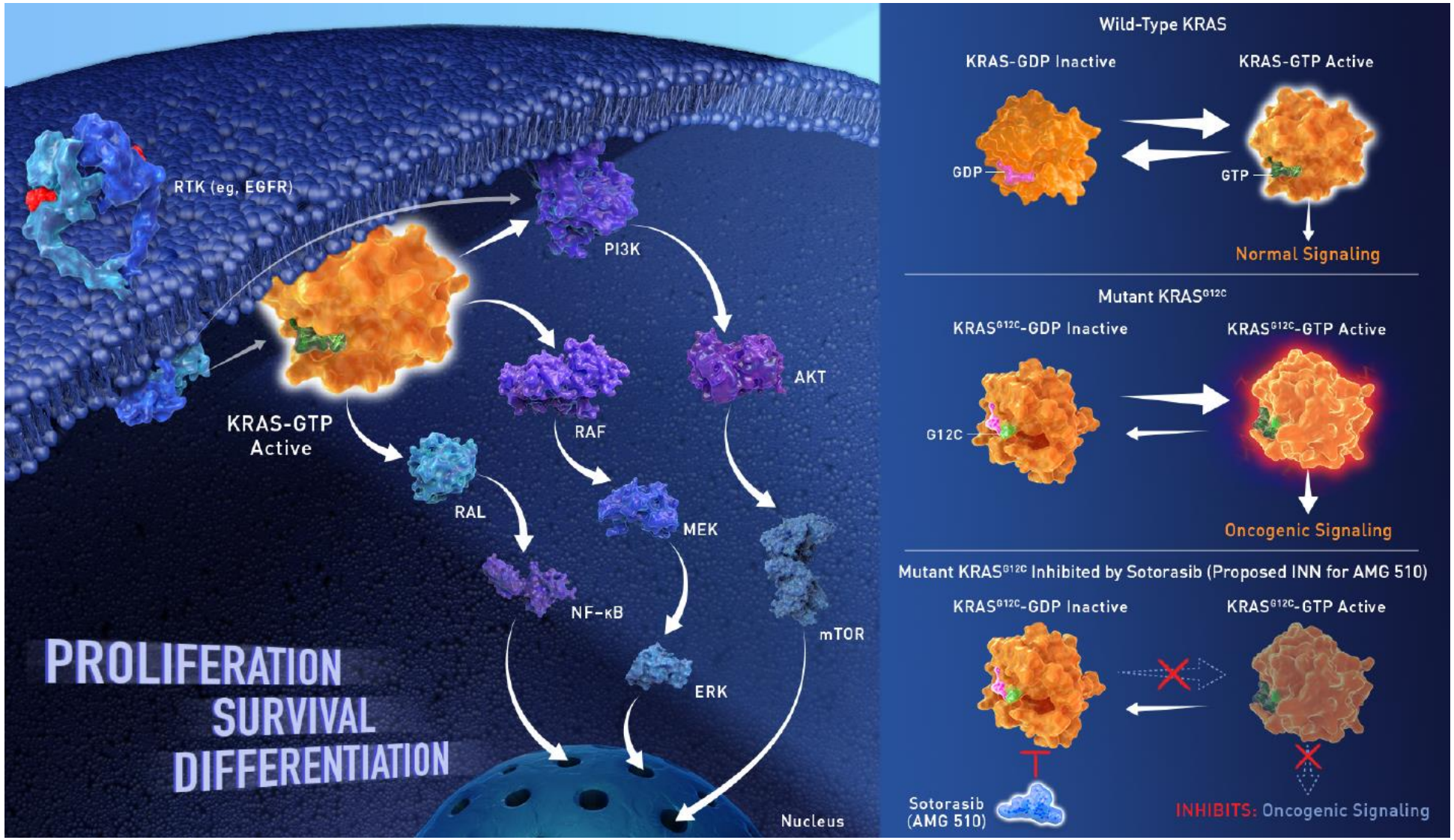
Sotorasib (AMG 510) locks KRAS^{G12C} in the inactive state, inhibiting oncogenic signaling



Methods

Phase 1, Multicenter, Open-Label Study – Dose Escalation

Key Eligibility

- Locally advanced or metastatic malignancy
- Received prior standard therapies
- *KRAS G12C* mutation as assessed by local molecular testing of tumor biopsies
- No active brain metastases

Screening / Enrollment

- 2–4 patients enrolled in each cohort
- Intra–patient dose escalation allowed
- Additional patients may be added to any dose deemed safe

Cohort 1 180 mg

Cohort 2 360 mg

Cohort 3 720 mg

Cohort 4 960 mg

- Repeated **oral daily dosing** with 21-day cycles
- Treatment until disease progression, intolerance, or consent withdrawal
- Radiographic scan every 6 weeks

Safety Follow-up & Long Term Follow-up[a]

Expansion dose determined

Dose Expansion

Screening / Enrollment

Patients with *KRAS* p.G12C mutant advanced tumors

N = ~20

(max 60)

Safety Follow-up & Long Term Follow-up[a]

Primary endpoints: dose limiting toxicities (DLTs), safety
Key secondary endpoints: PK, objective response rate, duration of response, disease control rate, PFS, duration of stable disease

[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

Results (1 of 6)

Patients

Tumor types	Number of patients
Pancreatic cancer	10
Appendiceal cancer	4
Endometrial cancer	2
Unknown primary cancer	2
Bile duct cancer	1
Sinonasal cancer	1
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Small bowel cancer	1
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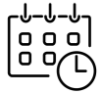
Total	**25**



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Dosing schedule: 2 appendiceal cancer patients received 360mg and 720mg, respectively; the remaining patients received 960mg

22 patients had been followed up for ≥ 7 weeks and were evaluable for response

At cutoff, 12 patients discontinued treatment

Results (2 of 6)

Baseline Characteristics

Baseline Characteristics	N = 25
Median age (range) – year	60 (40–75)
Female – n (%)	9 (36)
ECOG performance status at baseline – n (%) 0 1 2	 7 (28) 14 (56) 4 (16)
Prior lines of systemic anticancer therapy – n (%) 1 2 3 > 3 Missing	 4 (16) 5 (20) 6 (24) 9 (36) 1 (4)
Number of prior lines of anticancer therapy – median (range)	3 (1–4)

ECOG: Eastern Cooperative Oncology Group.

Results (3 of 6)

Patient Incidence of Adverse Events

	All treatment-emergent AEs (TEAEs) N = 25, n (%)	All treatment-related TEAEs N = 25, n (%)
Any grade Grade ≥ 2 Grade ≥ 3 Grade ≥ 4	20 (80) 17 (68) 15 (60) 4 (16)	9 (36) 4 (16) 2 (8) 0 (0)
Dose limiting toxicity	0 (0)	0 (0)
Serious AEs	13 (52)	1 (4)
Fatal AEs	4 (16)	0 (0)
AEs leading to treatment discontinuation	3 (12)	0 (0)

- **Treatment-related TEAEs reported in > 1 patients**
  - **Diarrhea (2/25)**
  - **Fatigue (2/25)**
- **Grade 3 treatment-related TEAEs**
  - **Diarrhea (1/25)**
  - **Pneumonia (1/25)**

AE: adverse events

Target dose for expansion: 960 mg daily.

Results (4 of 6)

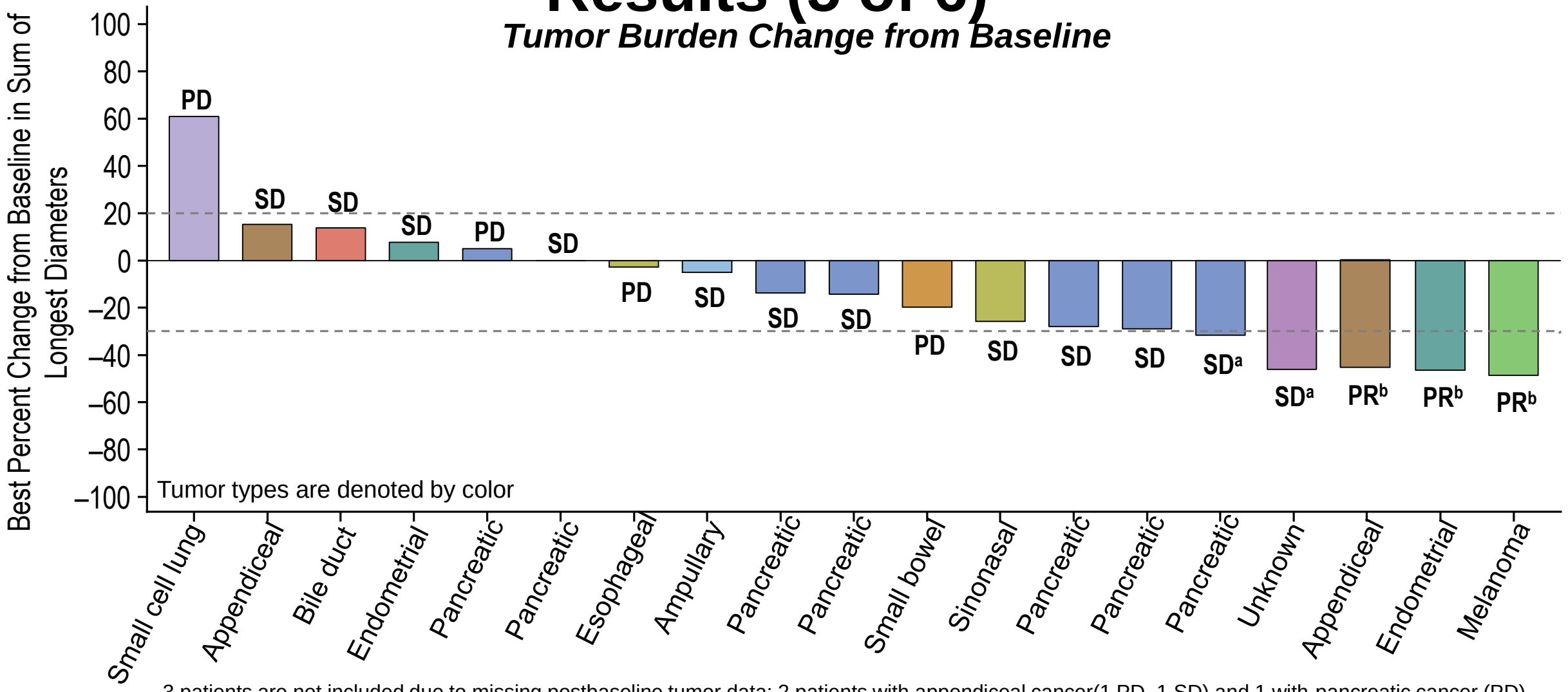
Tumor Response

Best tumor response	N = 25
Confirmed partial response – n Tumor types (n)	**3** Appendiceal (1) Melanoma (1) Endometrial (1)
Stable disease – n Tumor types (n)	**13** Pancreatic (6) Appendiceal (2) Ampullary (1) Bile duct (1) Endometrial (1) Sinonasal (1) Unknown primary (1)
Progressive disease – n Tumor types (n)	**6** Pancreatic (2) Appendiceal (1) Small cell lung cancer (1) Esophageal (1) Small bowel cancer (1)
Not evaluable[a] – n Tumor types (n)	**3** Pancreatic (2) Unknown primary (1)

[a]Patients hadn't been followed up for > 7 weeks as of the cutoff

Results (5 of 6)

Tumor Burden Change from Baseline



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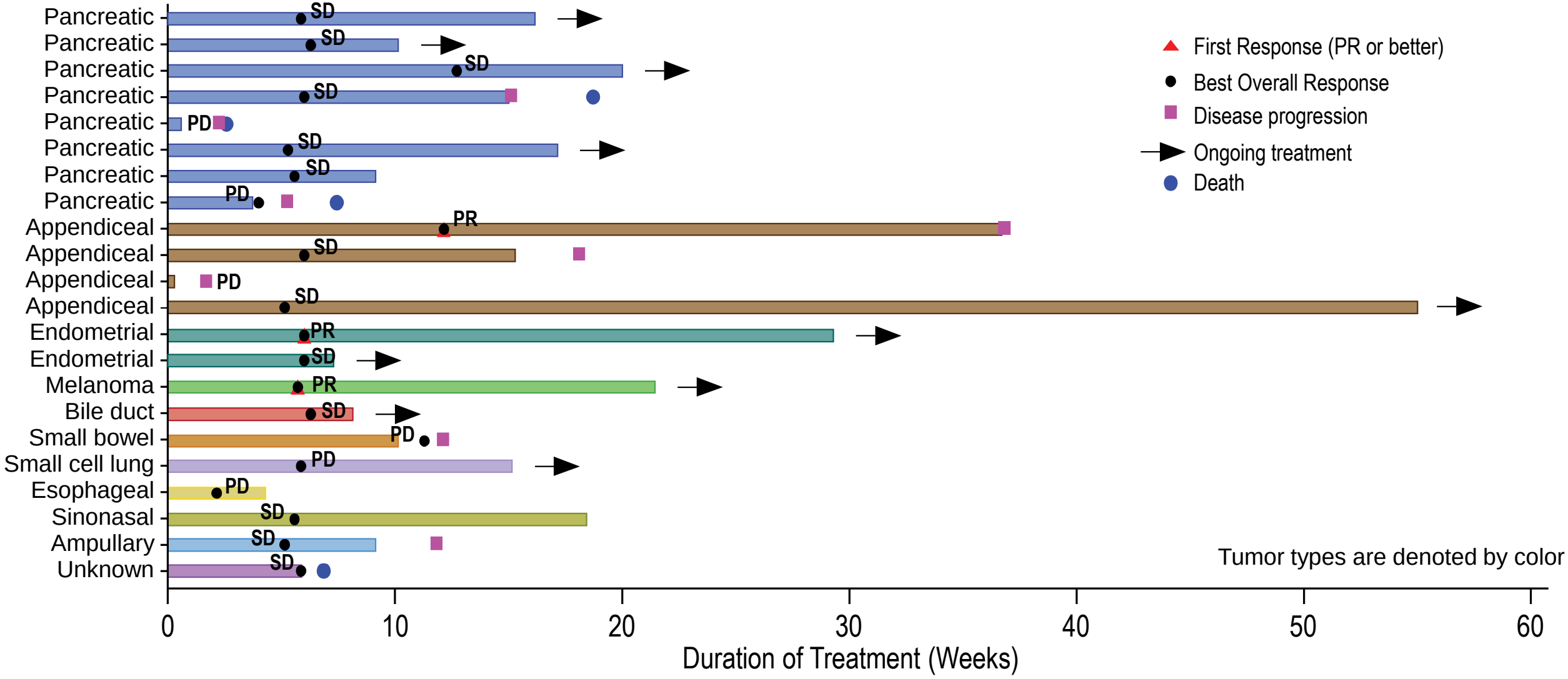
Results (6 of 6)

Time to Response and Treatment Over Time



Conclusions

- Sotorasib (AMG 510) was well tolerated in patients with advanced *KRAS* p.G12C mutant solid tumors other than NSCLC and CRC
  - The safety profile was largely consistent with that reported previously
  - Toxicities were mild and manageable, and there were no treatment-related AEs that led to discontinuation of treatment
- A confirmed partial response was observed in 3 patients with appendiceal cancer, melanoma, and endometrial cancer, respectively
- Six of 8 evaluable patients with pancreatic cancer achieved stable disease; 3 of them had best tumor burden reduction of ~30% from baseline
- Ten (45.5%) of 22 evaluable patients were still on treatment as of cutoff
- Phase 2 part of CodeBreaK 100 is ongoing (NCT03600883)

Acknowledgments

This study is funded by Amgen Inc. (ClinicalTrials.gov identifier: NCT03600883)

Yang Li, PhD (Amgen Inc.) provided medical writing assistance