***Poster presented at the American Society of Clinical Oncology (ASCO), 2020***

**Fakih MG, et al.**

# CodeBreaK 100: Activity of AMG 510, a novel small molecule inhibitor of $KRAS^{G12C}$, in patients with advanced colorectal cancer

ASCO 2020
Abstract number: 4018

# CodeBreak 100: Activity of AMG 510, a Novel Small Molecule Inhibitor of KRAS$^{G12C}$, in Patients With Advanced Colorectal Cancer


Marwan G. Fakih,[1] Jayesh Desai,[2] Yasutoshi Kuboki,[3] John H. Strickler,[4] Timothy J. Price,[5] Gregory A. Durm,[6] Gerald S. Falchook,[7] Crystal S. Denlinger,[8] John C. Krauss,[9] Geoffrey I. Shapiro,[10] Tae Won Kim,[11] Keunchil Park,[12] Andrew L. Coveler,[13] Pamela N. Munster,[14] Bob T. Li,[15] June Kim,[16] Haby Henary,[16] Gataree Ngarmchamnanrith,[16] David S. Hong[17]

[1]Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, California, USA; [2]Royal Melbourne Hospital/Peter MacCallum Cancer Centre, Victoria, VIC, Australia; [3]Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan; [4]Duke University Medical Center, Durham, North Carolina, USA; [5]The Queen Elizabeth Hospital and University of Adelaide, Woodville South, Australia; [6]Department of Medicine, Division of Hematology/Oncology, Indiana University School of Medicine, Indianapolis, Indiana, USA; [7]Sarah Cannon Research Institute at HealthONE, Denver, Colorado, USA; [8]Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; [9]University of Michigan, Ann Arbor, Michigan, USA; [10]Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA; [11]Department of Oncology, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea; [12]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [13]Department of Medicine, Division of Oncology, University of Washington, Seattle, Washington, USA; [14]Helen Diller Family Comprehensive Cancer Center, San Francisco, California, USA; [15]Memorial Sloan Kettering Cancer, Center, New York, New York, USA; [16]Amgen Inc. Thousand Oaks, California, USA; [17]Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

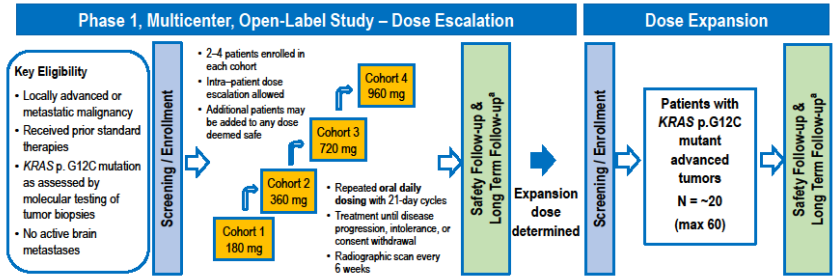

## BACKGROUND

- *Kirsten rat sarcoma viral oncogene homolog (KRAS)* mutations are the most prominent oncogenic driver mutations in cancer; however, no agent directly targeting mutant KRAS has been clinically approved[1]
- *KRAS* p.G12C mutation occurs in ~3% of colorectal cancer (CRC) and is often associated with poor prognosis[2-4]
- For patients with previously treated CRC receiving standard therapies, median PFS was ~2 months with the response rate of less than 2%[5,6]
- Previously, AMG 510 (proposed INN sotorasib), a novel *KRAS*$^{G12C}$ inhibitor, demonstrated a favorable toxicity profile and preliminary efficacy in patients with solid tumors harboring *KRAS* p.G12C; this analysis reports updated data in patients with CRC (NCT03600883)[7]

INN: international nonproprietary name

## METHODS

### Study Schema

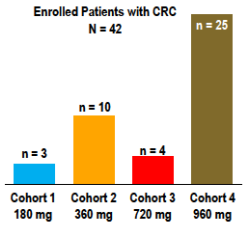



**Primary endpoints:** dose limiting toxicities (DLTs), safety
**Key secondary endpoints:** PK, objective response rate, duration of response, disease control rate, PFS, duration of stable disease

[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




Data cutoff: January 8, 2020

Median follow-up: 7.9 months (range: 4.2–15.9)

- 8 patients were continuing treatment
- 34 patients discontinued
  - 32: due to disease progression
  - 2: requested by patients

### Baseline Characteristics

| Baseline Characteristics | N = 42 |
|---|---|
| Median age (range) – year | 57.5 (33–82) |
| Female – n (%) | 21 (50) |
| ECOG performance at baseline – n (%) | |
| 0 | 17 (40.5) |
| 1 | 25 (59.5) |
| Prior lines of systemic anticancer therapy – n (%) | |
| 1 | 2 (4.8) |
| 2 | 11 (26.2) |
| 3 | 10 (23.8) |
| > 3 | 19 (45.2) |
| Number of prior lines of systemic anticancer therapy – median (range) | 3 (1–4) |

ECOG: Eastern Cooperative Oncology Group.

### Patient Incidence of Adverse Events

| | Treatment-Emergent AEs (TEAEs) N = 42, n (%) | Treatment-Related AEs N = 42, n (%) |
|---|---|---|
| Any grade | 38 (90.5) | 20 (47.6) |
| Grade ≥ 2 | 29 (69.0) | 9 (21.4) |
| Grade ≥ 3 | 13 (31.0) | 2 (4.8) |
| Grade ≥ 4 | 3 (7.1) | 0 (0.0) |
| Dose limiting toxicities | 0 (0.0) | 0 (0.0) |
| Serious AEs | 10 (23.8) | 0 (0.0) |
| Fatal AEs | 3 (7.1) | 0 (0.0) |
| AEs leading to treatment discontinuation | 2 (4.8) | 0 (0.0) |

AE: adverse event.

Target dose for expansion & phase 2: **960 mg QD**

| Treatment-related TEAEs of any grade occurring in > 1 patients | N = 42, n (%) |
|---|---|
| Diarrhea | 8 (19.0) |
| Fatigue | 4 (9.5) |
| Nausea | 2 (4.8) |
| Blood creatine phosphokinase increase | 2 (4.8) |
| Anemia | 2 (4.8) |
| Vomiting | 2 (4.8) |

- **Grade 3 treatment-related TEAEs:** diarrhea and anemia, occurring in 1 patient each.

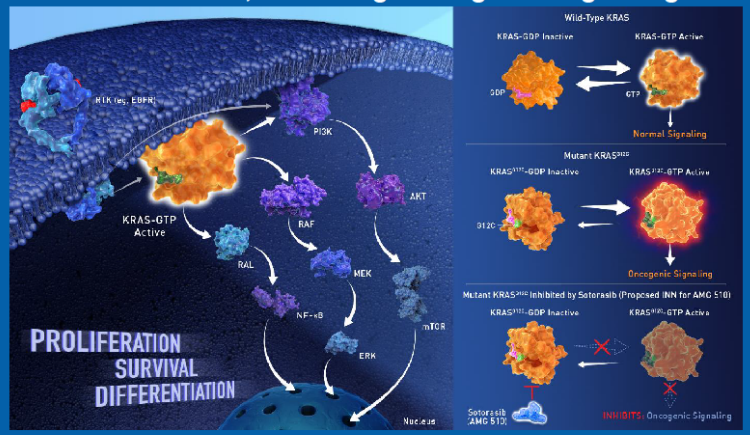
### Tumor Response

| Efficacy outcomes | All dose levels N = 42 n (%) | 960 mg N = 25 n (%) |
|---|---|---|
| Best overall response | | |
| Confirmed partial response – n (%) | 3 (7.1) | 3 (12.0) |
| Stable disease – n (%) | 29 (69.0) | 17 (68.0) |
| Progressive disease – n (%) | 9 (21.4) | 4 (16.0) |
| Not done – n (%)[a] | 1 (2.4) | 1 (4.0) |
| Objective response rate – % (95% CI) | 7.1 (1.50, 19.48) | 12.0 (2.55, 31.22) |
| Disease control rate – % (95% CI) | 76.2 (60.55, 87.95) | 80.0 (59.30, 93.17) |
| Duration of response for 3 responders – months | 1.4+, 4.2+, 4.3+ | 1.4+, 4.2+, 4.3+ |
| Duration of stable disease – months Median (min, max) | 4.2 (2.5+, 11.0) | 4.2 (2.6, 5.7+) |

[a]Patient had clinical progression with no postbaseline measurement.
+: censored value.

- Three of 42 patients (7.1%) with heavily pretreated *KRAS* p.G12C mutant metastatic CRC had durable partial responses to sotorasib (AMG 510)
- In addition to the 3 responders, 29 patients achieved disease control, resulting in a disease control rate of 76.2% and a median PFS of 4.0 months (range: 0.7–11.0)
- Sotorasib (AMG 510) is well tolerated with mild treatment-related toxicities, consistent with previous results
- 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 full author disclosures

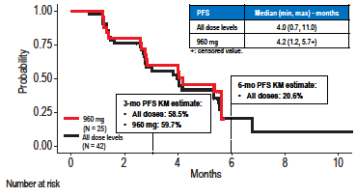




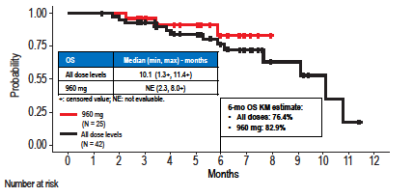
Contact information: Dr. Marwan G. Fakih, email: mfakih@coh.org


## RESULTS (Continued)

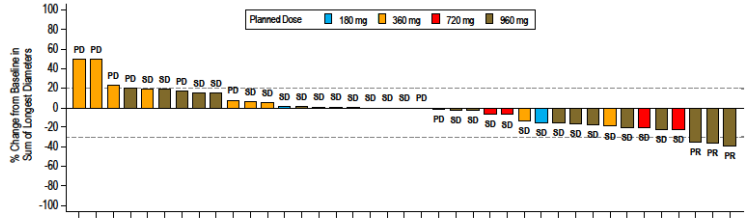
### Progression-Free Survival




### Overall Survival

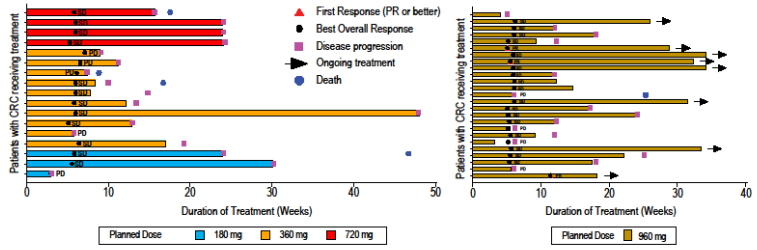



### Tumor Burden Change from Baseline




Three patients are not included in the graph due to missing postbaseline tumor data (1 PD, 1 SD, 1 not done with clinical progression)

### Time to Response and Treatment Over Time

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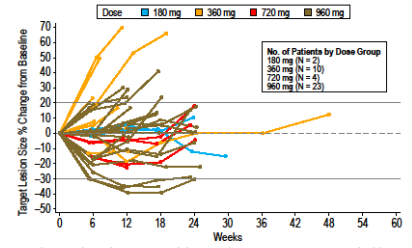


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## REFERENCES


1. Cox AD, Fesik SW, Kimmelman AC, et al. *Nat Rev Drug Discov.* 2014 Nov;13(11):828-851
2. Modest DP, Brodowicz T, Stintzing S, et al. *Oncology* 2012;83:241-247
3. Neumann J, Zeindl-Eberhart E, Kirchner T, et al. *Pathol Res Pract.* 2009;205(12):858-862
4. Jones RP, Sutton PA, Evans JP, et al. *Br J Cancer* 2017;116:923-929.
5. Mayer RJ, Van Cutsem E, Falcone A, et al. *N Engl J Med* 2015;372:1909-19.
6. Grothey A, Van Cutsem E, Sobrero A, et al. Lancet 2013;381:303-12.
7. Govindan R, Fakih MG, Price TJ, et al. *Annals of Oncology* (2019) 30 (suppl_5): v159-v193.

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Title Background Mechanism of Action Methods Results Conclusions Acknowledgements

# Background

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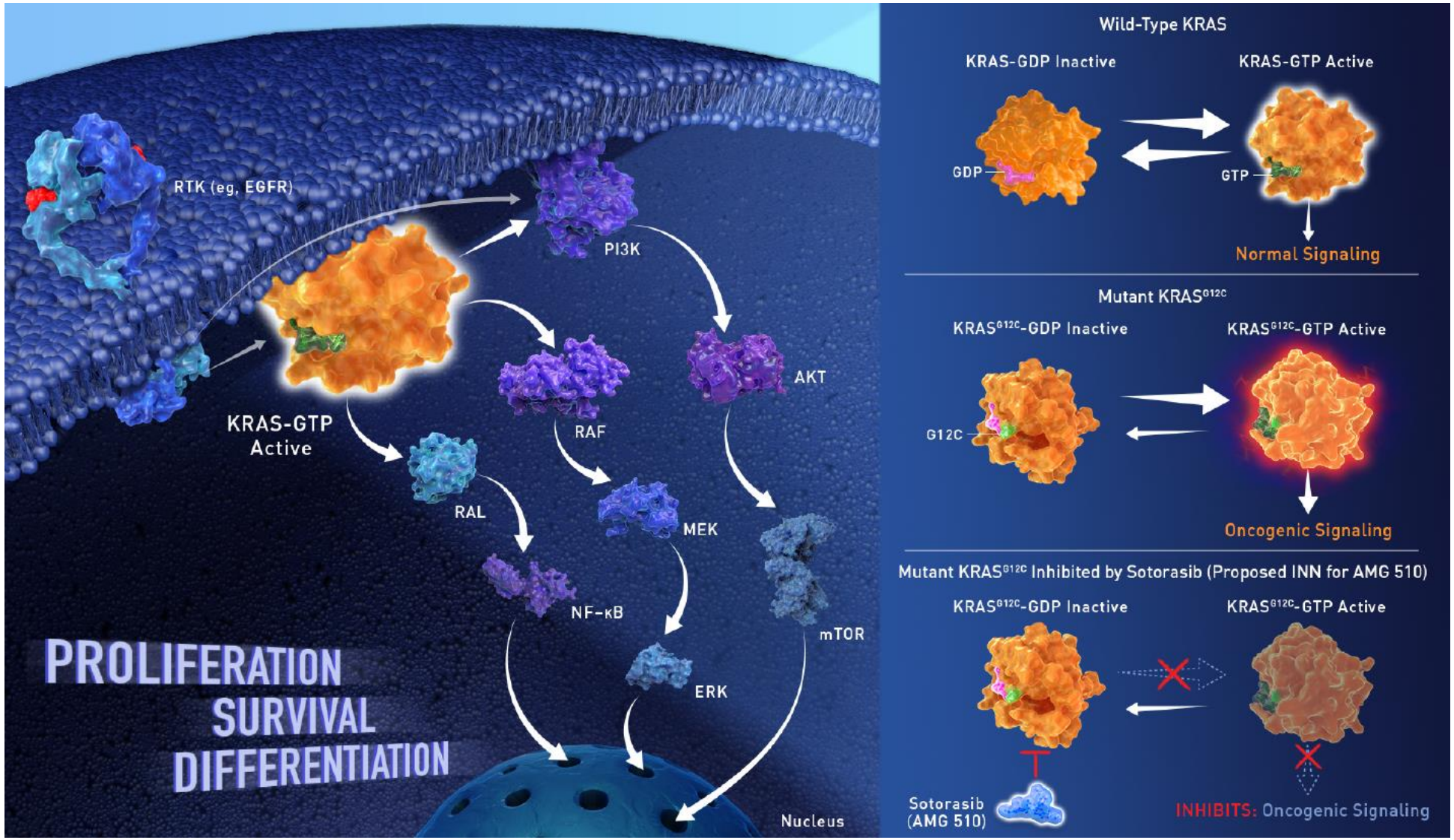
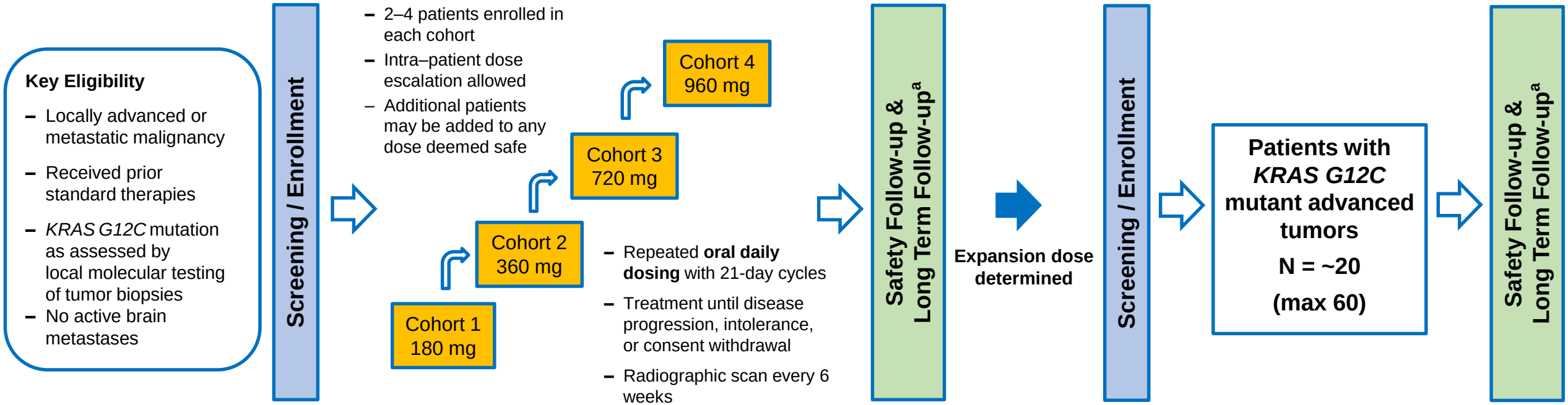
# Sotorasib (AMG 510) locks KRAS$^{G12C}$ in the inactive state, inhibiting oncogenic signaling



# Methods

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

## Dose Expansion




**Primary endpoints:** dose limiting toxicities (DLTs), safety
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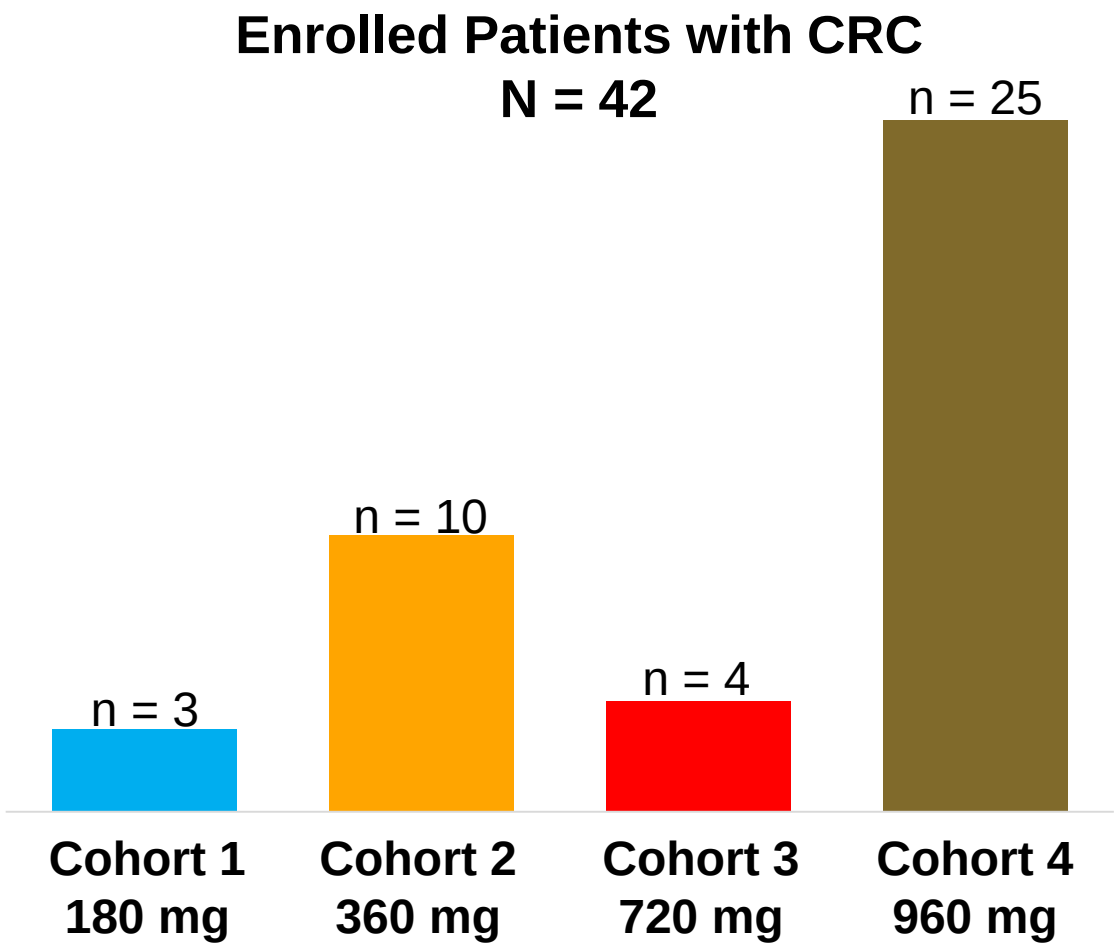
# Results (1 of 10)

***Patients***




Data cutoff: January 8, 2020

Median follow-up: 7.9 (range: 4.2–15.9) months

- 8 patients were continuing treatment
- 34 patients discontinued
  - 32: due to disease progression
  - 2: requested by patients

# Results (2 of 10)

***Baseline Characteristics***

| Baseline characteristics | N = 42 |
|---|---|
| Median age – year (range) | 57.5 (33–82) |
| Female – n (%) | 21 (50) |
| ECOG performance status at baseline – n (%)<br>0<br>1 | <br>17 (40.5)<br>25 (59.5) |
| Prior lines of systemic anticancer therapy – n (%)<br>1<br>2<br>3<br>> 3 | <br>2 (4.8)<br>11 (26.2)<br>10 (23.8)<br>19 (45.2) |
| Number of prior lines of systemic anticancer therapy – median (range) | 3 (1–4) |

ECOG: Eastern Cooperative Oncology Group.

# Results (3 of 10)

## *Patient Incidence of Adverse Events*

| | Treatment-Emergent AEs (TEAEs) N = 42, n (%) | Treatment-related TEAEs N = 42, n (%) |
|---|---|---|
| Any grade<br>Grade ≥ 2<br>Grade ≥ 3<br>Grade ≥ 4 | 38 (90.5)<br>29 (69.0)<br>13 (31.0)<br>3 (7.1) | 20 (47.6)<br>9 (21.4)<br>2 (4.8)<br>0 (0.0) |
| Dose-limiting toxicities | 0 (0.0) | 0 (0.0) |
| Serious AEs | 10 (23.8) | 0 (0.0) |
| Fatal AEs | 3 (7.1) | 0 (0.0) |
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AE: adverse event

| Treatment-related TEAEs of any grade occurring in > 1 patient | N = 42, n (%) |
|---|---|
| Diarrhea | 8 (19.0) |
| Fatigue | 4 (9.5) |
| Nausea | 2 (4.8) |
| Blood creatine phosphokinase increase | 2 (4.8) |
| Anemia | 2 (4.8) |
| Vomiting | 2 (4.8) |

- **Grade 3 treatment-related TEAEs**: diarrhea and anemia, occurring in 1 patient each

**Target dose for expansion: 960 mg daily.**

# Results (4 of 10)

## *Tumor Response*

| Efficacy outcomes | All dose levels N = 42, n (%) | 960 mg N = 25, n (%) |
|---|---|---|
| Best overall response | | |
| Confirmed partial response – n (%) | 3 (7.1) | 3 (12.0) |
| Stable disease – n (%) | 29 (69.0) | 17 (68.0) |
| Progressive disease – n (%) | 9 (21.4) | 4 (16.0) |
| Not done – n (%)[a] | 1 (2.4) | 1 (4.0) |
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| Duration of response for 3 responders – months | 1.4+, 4.2+, 4.3+ | 1.4+, 4.2+, 4.3+ |
| Median duration of stable disease – months (min, max) | 4.2 (2.5+, 11.0) | 4.2 (2.6, 5.7+) |

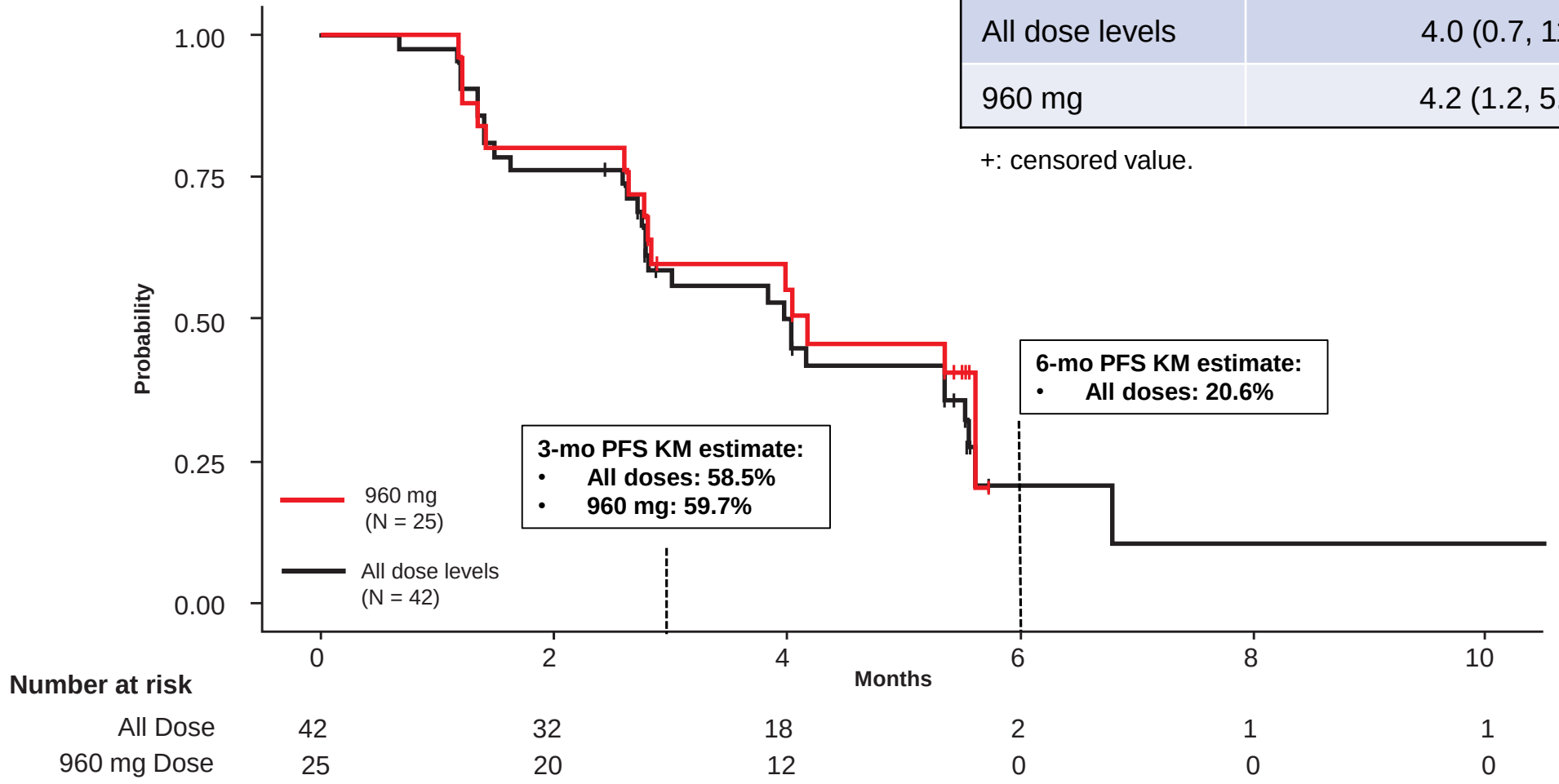
[a]Patient had clinical progression with no postbaseline measurement.
+: censored value.

# Results (5 of 10)

## *Progression-Free Survival*

| PFS | Median – months (min, max) |
|---|---|
| All dose levels | 4.0 (0.7, 11.0) |
| 960 mg | 4.2 (1.2, 5.7+) |

+: censored value.

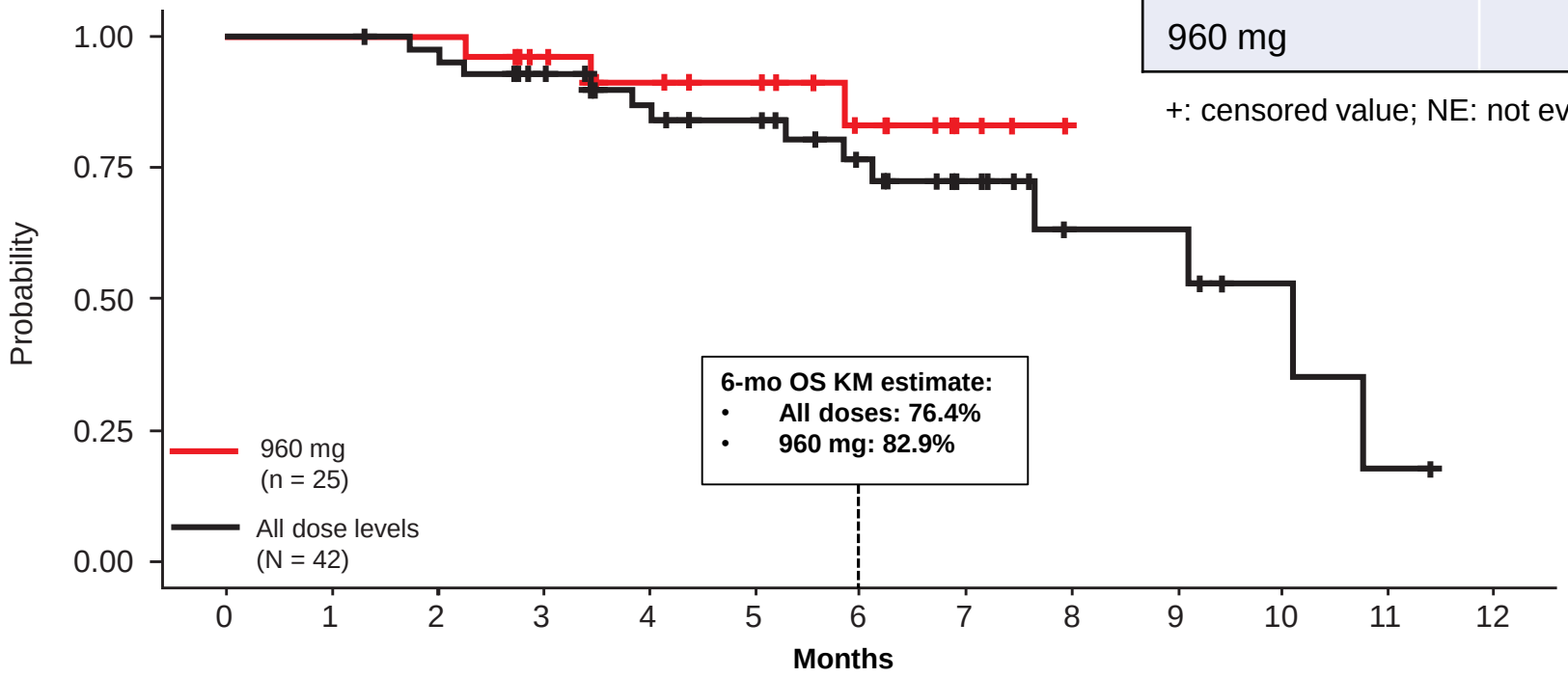


# Results (6 of 10)

## *Overall Survival*

| OS | Median – months (min, max) |
|---|---|
| All dose levels | 10.1 (1.3+, 11.4+) |
| 960 mg | NE (2.3, 8.0+) |

+: censored value; NE: not evaluable.

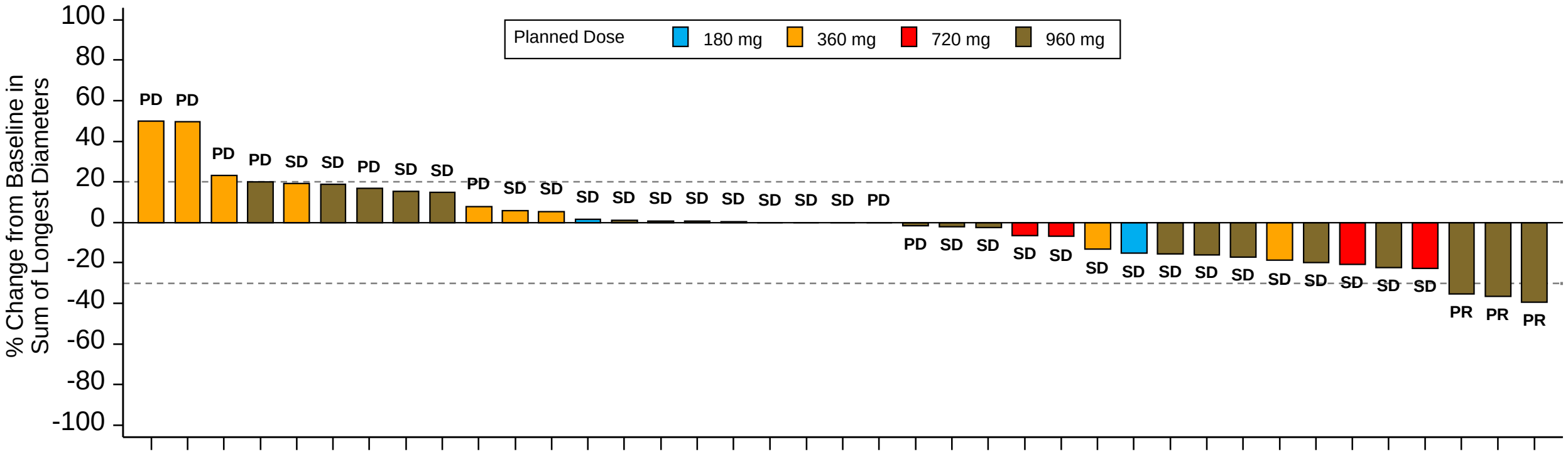



**Number of patients at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| All Dose | 42 | 40 | 29 | 19 | 6 | 3 | 0 |
| 960 mg | 25 | 25 | 17 | 9 | 0 | | |

# Results (7 of 10)

## *Tumor Burden Change from Baseline*

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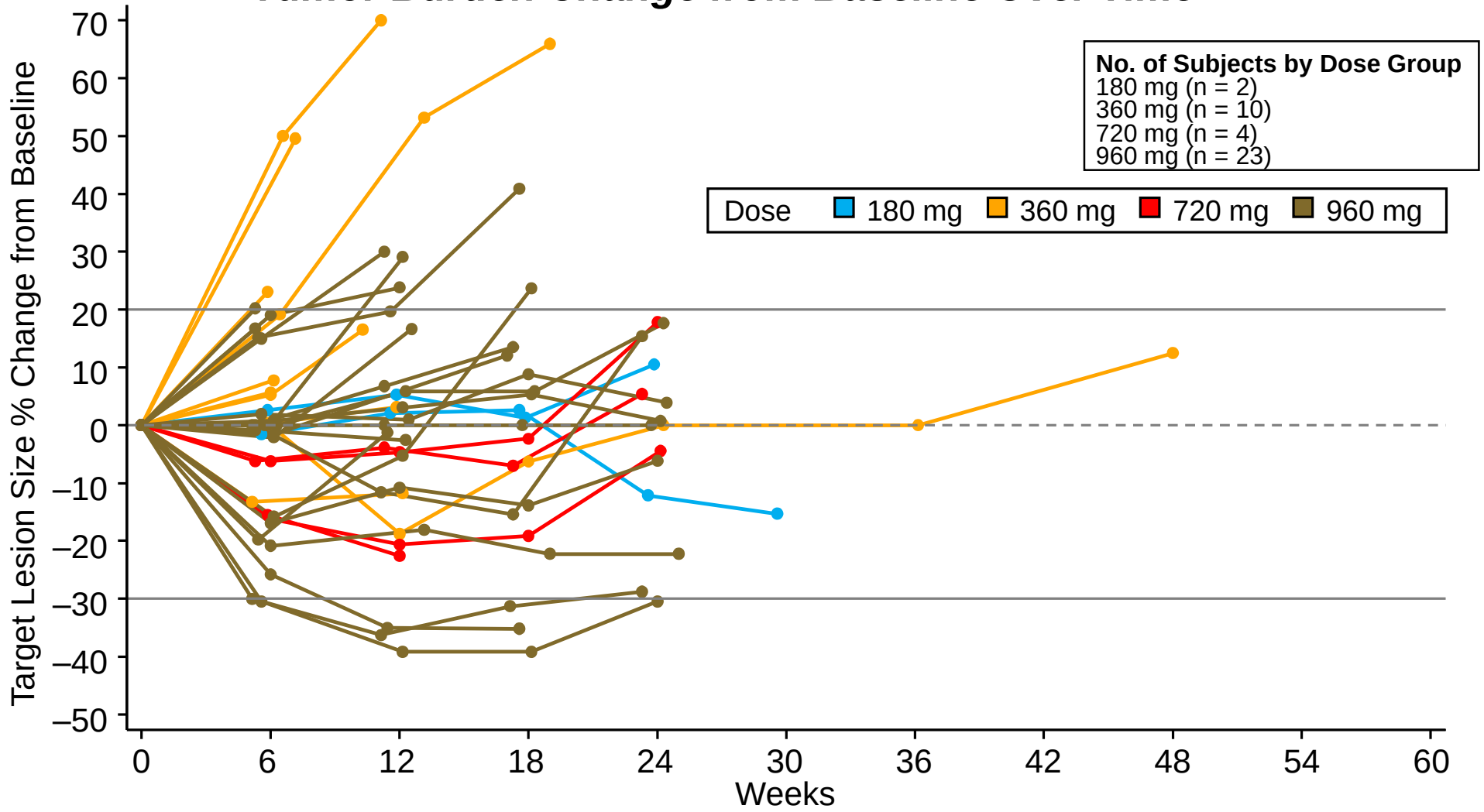
# Results (8 of 10)

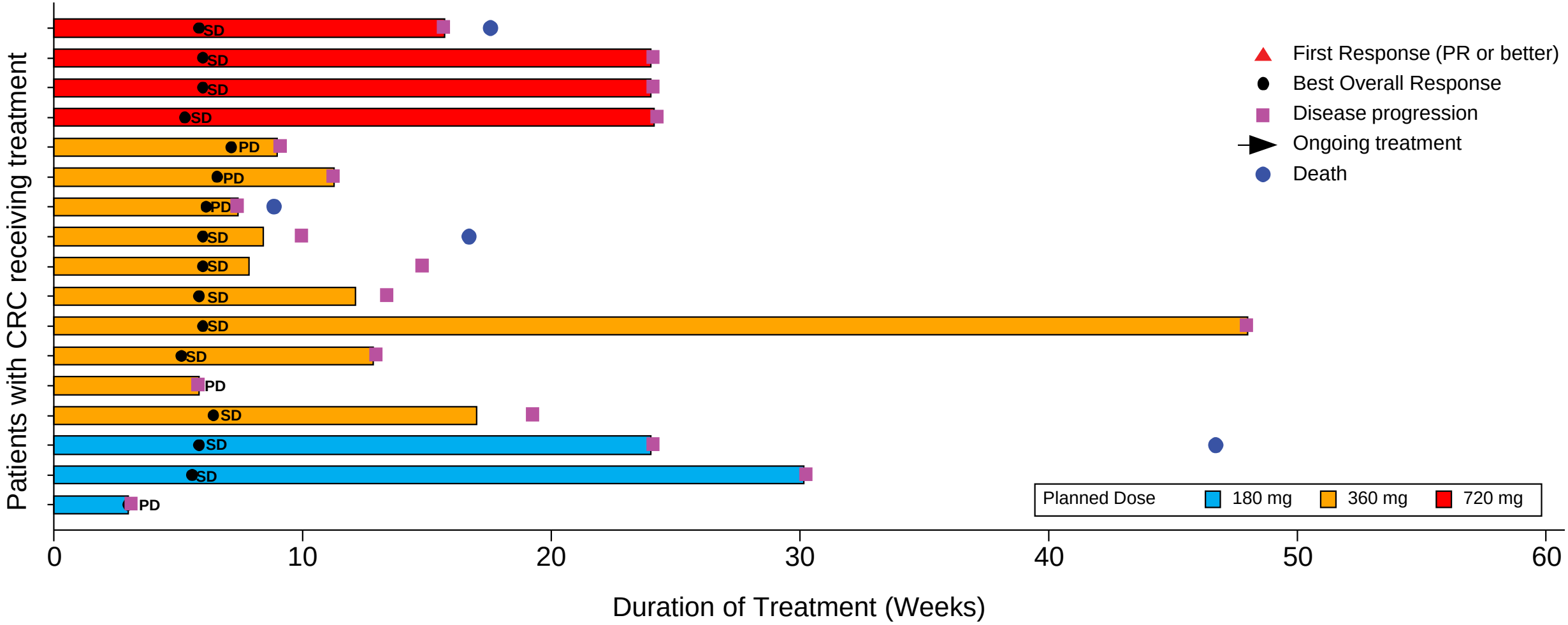
## *Tumor Burden Change from Baseline Over Time*




Three patients are not included in the graph due to missing postbaseline tumor data (1 PD, 1 SD, 1 not done with clinical progression)

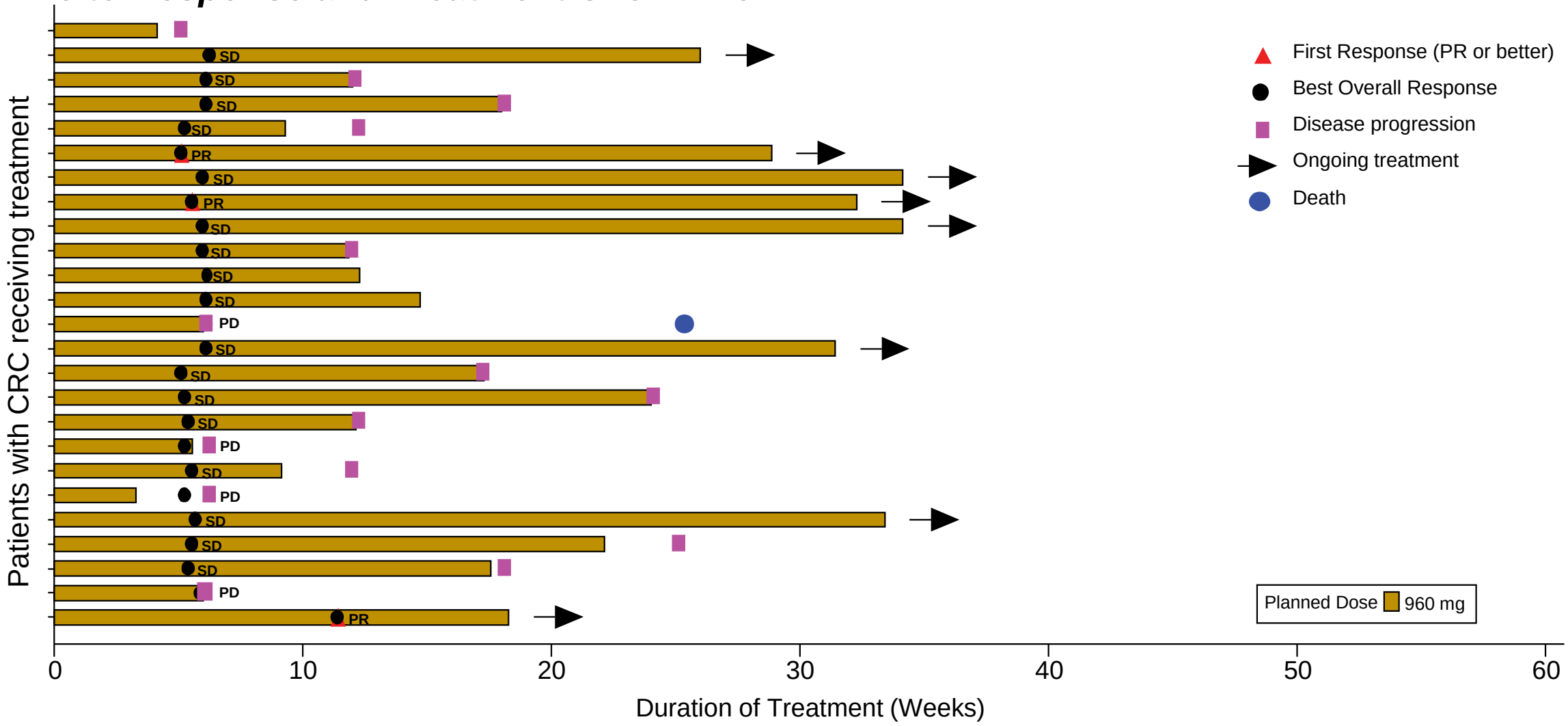
# Results (9 of 10)

## *Time to Response and Treatment Over Time*



# Results (10 of 10)

## *Time to Response and Treatment Over Time*



# Conclusions

- Three of 42 patients (7.1%) with heavily pretreated *KRAS p.G12C* mutant metastatic CRC had confirmed durable partial responses to sotorasib (AMG 510)
- In addition to the 3 responders, 29 patients achieved disease control, resulting in a disease control rate of 76.2% and a median PFS of 4.0 months (range: 0.7–11.0)
- Sotorasib (AMG 510) is well tolerated with mild treatment-related toxicities, consistent with previous results
- 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