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Durability of clinical benefit and biomarkers in patients with advanced non-small cell lung cancer (NSCLC) treated with AMG 510 (sotorasib): CodeBreaK 100

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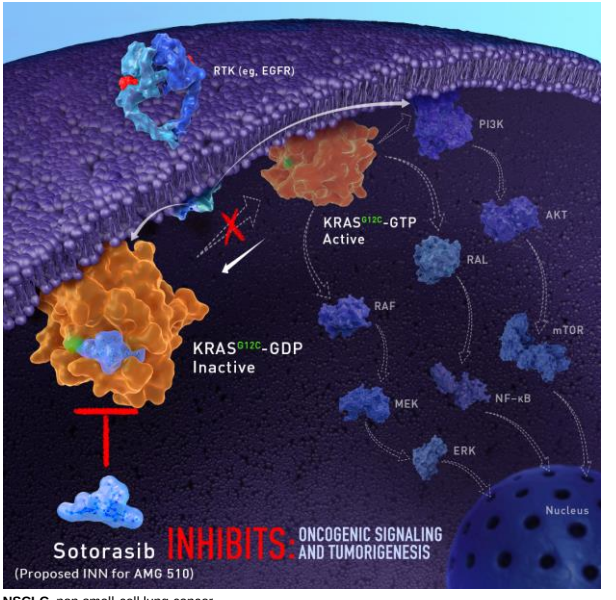
Sotorasib is a first-in-class KRAS^{G12C} inhibitor

- *KRAS* p.G12C mutation is found in approximately 13% of NSCLC, 3-5% of colorectal cancer, and 1%–3% of other solid tumors[1-6]

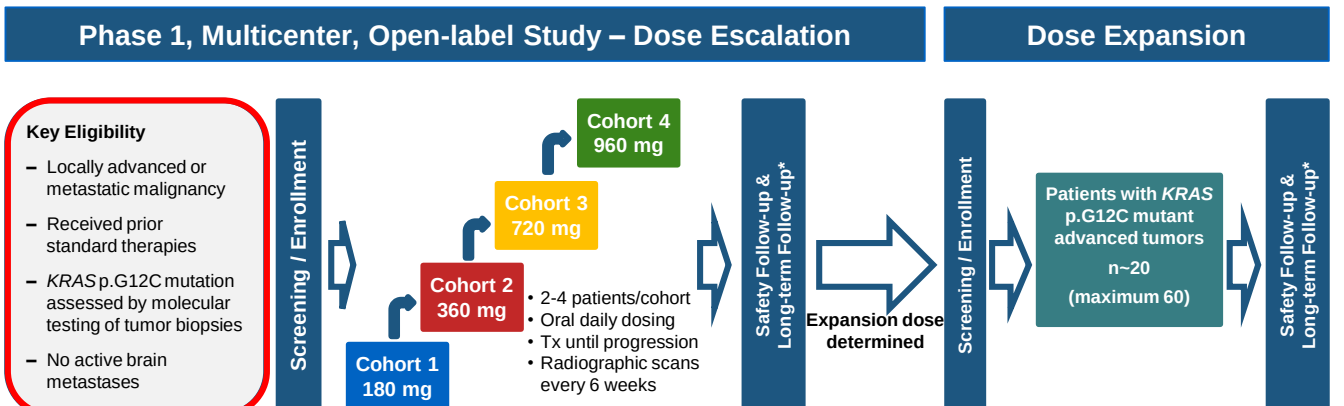
- Sotorasib (proposed INN for AMG 510) is a novel, highly-selective, first-in-class KRAS^{G12C} inhibitor that has demonstrated anticancer activity and a manageable safety profile in patients with *KRAS* p.G12C mutant solid tumors[5,7]



GDP, guanosine diphosphate; **INN,** international nonproprietary name; ***KRAS,*** *Kirsten rat sarcoma* viral oncogene homolog; **NSCLC,** non-small cell lung cancer

1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198. **2.** Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862. **3.** Jones RP, et al. *Br J Cancer.* 2017;116:923-929. **4.** Wiesweg M, et al. *Oncogene.* 2019;38:2953-2966; **5.** Canon J, et al. *Nature.* 2019;575:217-223. **6.** Zhou L, et al. *Med Oncol.* 2016;33:32. **7.** Govindan R, et al. Presented at: European Society for Medical Oncology; September 27–October 1, 2019; Barcelona, Spain. Abstract #446PD.

Phase 1 study design (CodeBreaK100: NCT03600883)



Primary endpoint: safety
Secondary endpoints include: PK, ORR, DOR, DCR, PFS, duration of SD

*30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long-term follow-up.

DCR, disease control rate; **DLT,** dose-limiting toxicity; **DOR,** duration of response; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **ORR,** objective response rate; **PFS,** progression-free survival; **PK,** pharmacokinetic; **RP2D,** recommended phase 2 dose; **SD,** stable disease; **Tx**, treatment.

Disposition and baseline characteristics of patients with NSCLC

Dose cohort	# patients (N = 59)
180 mg	3
360 mg	16
720 mg	6
960 mg†	**34**

†identified as the Phase II dose in NSCLC

- Data cutoff: June 1, 2020
- Median follow-up: 11.7 (range: 4.8–21.2) months
- 14 patients were continuing treatment
- 45 patients discontinued
  - 35: disease progression
  - 5: death
  - 4: patient request
  - 1: adverse event

Baseline Characteristic	960 mg (n = 34)	All Patients (N = 59)
Median age – years (range)	68 (49–83)	68 (49–83)
Female – n (%)	18 (52.9)	35 (59.3)
Current/former smoker	30 (88.2)	53 (89.8)
Prior anti-PD1/L1 therapy	28 (82.4)	53 (89.8)
Prior platinum-based chemo	34 (100.0)	59 (100.0)
ECOG PS score – n (%)		
0	8 (23.5)	12 (20.3)
1	26 (76.5)	45 (76.3)
2	0 (0.0)	2 (3.4)
Median prior systemic anticancer therapy for metastatic disease – n (range)	2 (0–10)	3 (0–10)
Prior systemic anticancer therapy – n (%)		
0	2 (5.9)	2 (3.4)
1	12 (35.3)	13 (22.0)
2	8 (23.5)	14 (23.7)
3	6 (17.7)	11 (18.6)
≥ 4	6 (17.7)	19 (32.2)
Brain metastasis	12 (35.3)	18 (30.5)

ECOG, Eastern Cooperative Oncology Group; **NSCLC,** non-small cell lung cancer

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Incidence of all treatment-emergent adverse events

Events – n (%)	All Patients (N = 59)			
	Any Grade	Grade ≥3	Grade ≥4	Fatal
Treatment-emergent AEs				
Any	58 (98.3)	37 (62.7)	17 (28.8)	13 (22.0)
Serious	30 (50.8)	27 (45.8)	16 (27.1)	13 (22.0)
Led to Discontinuation	5 (8.5)	5 (8.5)	3 (5.1)	3 (5.1)
Treatment-related AEs				
Any	39 (66.1)	11 (18.6)	1 (1.7)	0 (0.0)
Serious	2 (3.4)	1 (1.7)	1 (1.7)	0 (0.0)
Led to Discontinuation	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)

- No dose-limiting toxicities were reported
- No treatment-related fatal AEs were reported
- Grade 3 or 4 treatment-related AEs occurred in 18.6% of patients

Sotorasib monotherapy demonstrated a favorable safety profile

Data cutoff: June 1, 2020.
*__AE,__ adverse event; __TEAE,__ treatment-emergent adverse event.

Treatment-related AEs (incidence ≥ 5% or grade ≥ 3)

Treatment-related Adverse Events	All Patients (N = 59) n (%)		
	Any Grade	Grade ≥3	Grade ≥4
Any	39 (66.1)	11 (18.6)	1 (1.7)
Diarrhea	15 (25.4)	3 (5.1)	0 (0.0)
ALT increased	12 (20.3)	6 (10.2)	1 (1.7)*
AST increased	12 (20.3)	3 (5.1)	0 (0.0)
Fatigue	6 (10.2)	0 (0.0)	0 (0.0)
Nausea	6 (10.2)	0 (0.0)	0 (0.0)
Alkaline phosphatase increased	5 (8.5)	2 (3.4)	0 (0.0)
Decreased appetite	4 (6.8)	0 (0.0)	0 (0.0)

Treatment-related Adverse Events	All Patients (N = 59) n (%)		
	Any Grade	Grade ≥3	Grade ≥4
Vomiting	4 (6.8)	0 (0.0)	0 (0.0)
Abdominal distension	3 (5.1)	0 (0.0)	0 (0.0)
Abdominal pain	3 (5.1)	0 (0.0)	0 (0.0)
Anemia	2 (3.4)	2 (3.4)	0 (0.0)
Lymphocyte count decreased	2 (3.4)	1 (1.7)	0 (0.0)
GGT increased	1 (1.7)	1 (1.7)	0 (0.0)
Hepatitis	1 (1.7)	1 (1.7)	0 (0.0)
Hyponatremia	1 (1.7)	1 (1.7)	0 (0.0)

Data cutoff: June 1, 2020.
***Grade 4 ALT increase which resolved to baseline with dose reduction and glucocorticoid taper.
AE, adverse event; **alk phos,** alkaline phosphatase; **ALT,** alanine aminotransferase; **AST,** aspartate aminotransferase, **GGT,** gamma-glutamyl transferase

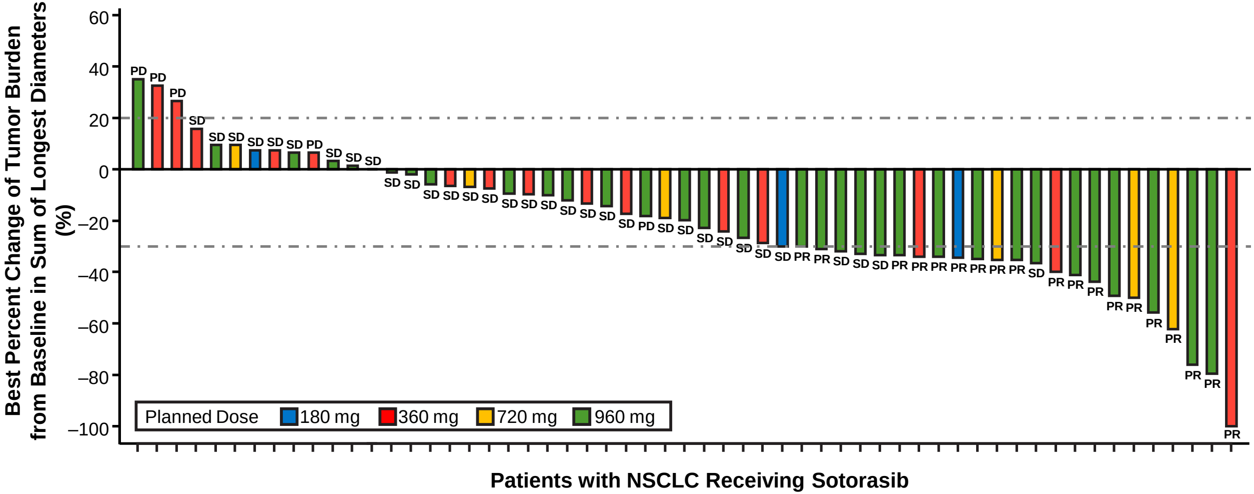
Response to sotorasib

	960 mg (n = 34)	All patients (N = 59)
Best Overall Response per Investigators' Assessment, n (%)		
Confirmed Partial Response	12 (35.3)	19 (32.2)
Stable Disease	19 (55.9)	33 (55.9)
Progressive Disease	2 (5.9)	5 (8.5)
Not Evaluable	1 (2.9)	1 (1.7)
Not Done*	0 (0.0)	1 (1.7)
Confirmed Objective Response Rate†, % (95% CI)	35.3 (19.8, 53.5)	32.2 (20.6, 45.6)
Disease Control Rate‡, % (95% CI)	91.2 (76.3, 98.1)	88.1 (77.1, 95.1)

- Tumor shrinkage of any magnitude from baseline was observed in 42 patients (71.2%) at the first week 6 assessment
- At the 960 mg dose (n = 34), confirmed ORR was 35.3% and DCR was 91.2%
  - 960 mg dose was identified as the Phase II dose in NSCLC

Data cutoff: June 1, 2020. *Patient withdrew consent before tumor assessment. †Confirmed complete or partial response. ‡Confirmed complete or partial response, or stable disease.
**Patients with NSCLC who had available post-baseline tumor data (n = 57); Evaluation of response is based on RECIST 1.1.
CI, confidence interval; **DCR,** disease control rate; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **PR,** partial response; **RECIST**, response evaluation criteria in solid tumors

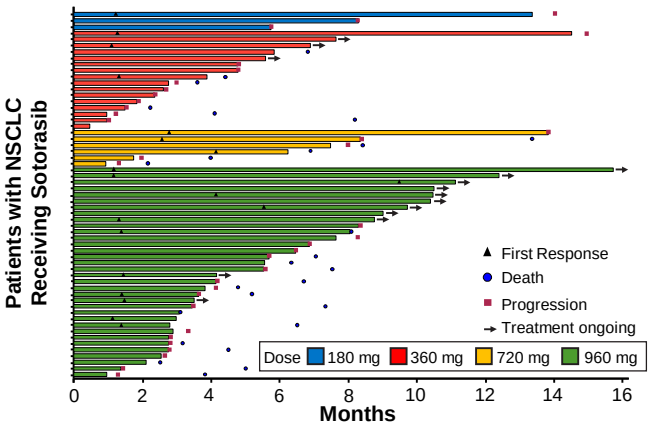
Tumor burden change from baseline

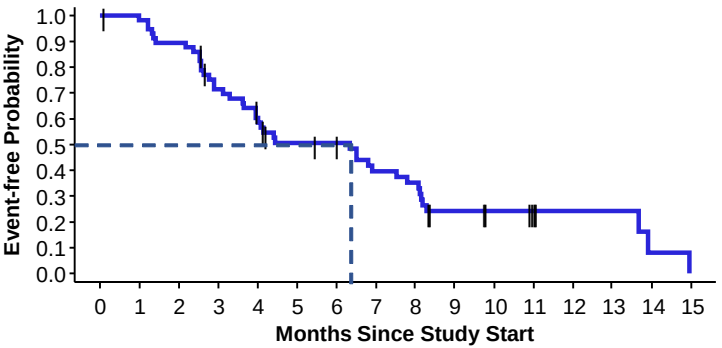


Tumor reduction was seen across all dose levels

Data cutoff: June 1, 2020.
*Patients with NSCLC who had available post-baseline tumor data (n = 57); Evaluation of response is based on modified RECIST 1.1.
NSCLC, non-small cell lung cancer; **PD,** progressive disease; **PR,** partial response; **RECIST,** response evaluation criteria in solid tumors; **SD,** stable disease.

Durability of clinical benefit and progression-free survival





Confirmed PR, n = 19

Duration of response*

Median of 10.9
(1.1+ to 13.6) months

10/19 responders still in response†

Patients with SD, n = 33

Duration of stable disease‡

Median of 4.0
(1.4 to 10.9+) months

Median PFS: 6.3 (range 0.0+ to 14.9) months

*Duration of response was measured from first evidence of PR/CR to disease progression or death due to any cause, whichever was earlier. ‡Duration of SD was measured from the start of the treatment until the criteria for disease progression were met or death, whichever was earlier. †At data cutoff of June 1, 2020; + Indicates censored value; median follow-up time was 11.7 (range 4.8-21.2) months.
NSCLC, non-small cell lung cancer; **PR,** partial response; **SD,** stable disease. **PFS**, progression-free survival

Patient case

Demographics:

- 59 y.o. Male; *KRAS* p.G12C mutant metastatic NSCLC in Dec, 2013

Treatment history:

- Progressed on 5 prior therapies
  - 3 targeted therapies (erlotinib, dasatinib, M3541[ATM inhibitor])
  - Chemotherapy (carboplatin/pemetrexed)
  - Checkpoint inhibitor (nivolumab)
- Gamma knife for brain lesions
- Patient started sotorasib (360 mg) since Dec 2018

Biomarkers:

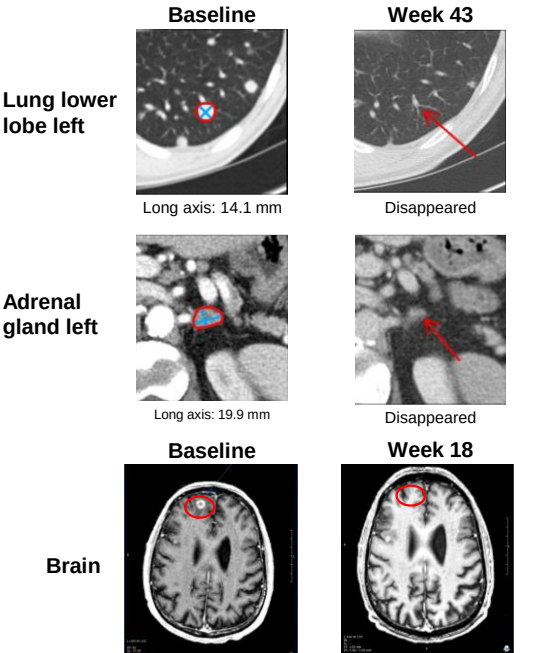
- STK11 co-mutation identified in plasma

Response to Sotorasib:

- Complete response in target lesions; partial response overall
- Time to response: 1.4 months
- Duration of response: 13.6 months
- Response in CNS (brain metastasis) was seen
- Recently progressed in non-target lesions after ~ 1.5 years in response

Adverse events:

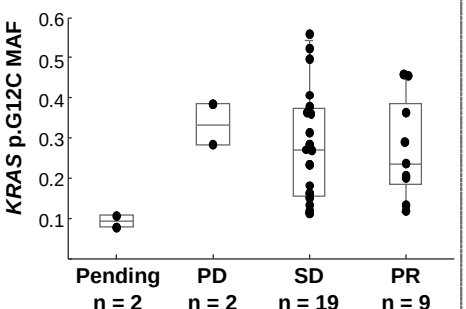
- No DLTs or grade 3/4 AEs related to sotorasib
- No dose reduction/discontinuation due to AEs
- Sotorasib-related AEs: nausea (grade 1), vomiting (grade 1), and hypophosphatemia (grade 2)



*AE, adverse event; ATM, ataxia telangiectasia mutated; CNS, central nervous system; DLT, dose limiting toxicity; NSCLC, non-small cell lung cancer

Sotorasib demonstrates clinical activity across a range of *KRAS* p.G12C MAFs, PD-L1 tissue expression levels, and plasma TMB levels

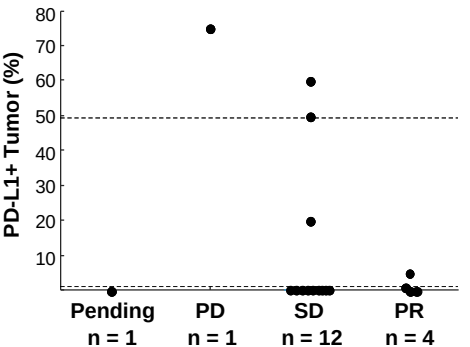
NSCLC Tissue: Qiagen Comprehensive Cancer Panel



n = 32 patients with evaluable results

KRAS p.G12C MAF by response:
- Wilcoxon p = 1 for SD vs PR
- Wilcoxon p = 0.43 for PD vs PR + SD

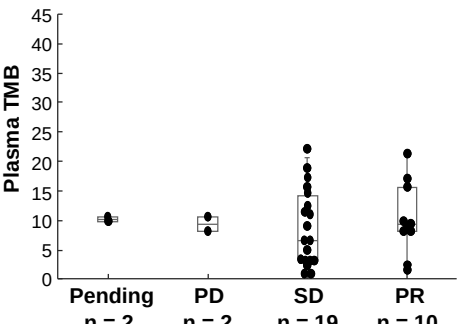
NSCLC Tissue: PD-L1 IHC 22C3 pharmDx assay



n = 18 patients with evaluable results

PD-L1+ Tumor % by response:
- Wilcoxon p = 0.73 for SD vs PR
- Wilcoxon p = 0.12 for PD vs PR + SD

NSCLC Plasma: Illumina TruSight Oncology 500 ctDNA assay

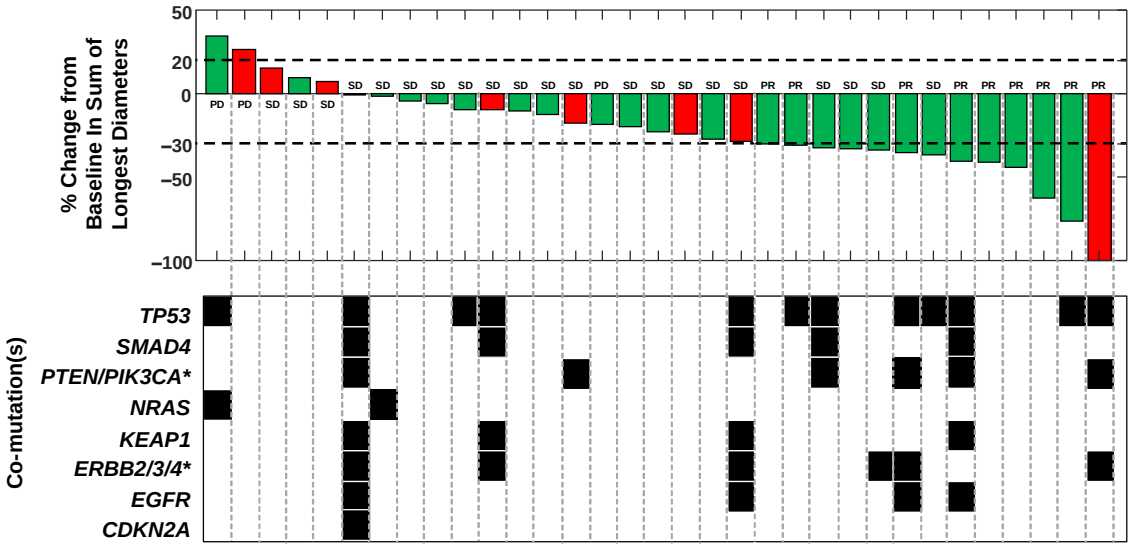


n = 33 patients with evaluable results

NSCLC TMB by response:
- Wilcoxon p = 0.60 for SD vs PR
- Wilcoxon p = 0.90 for PD vs PR + SD

Response data used for biomarker analyses were from June 1, 2020 cutoff. **IHC**, immunohistochemistry; **MAF**, mutational allele frequency, defined as mutant reads/total reads; **NSCLC**, non-small cell lung cancer; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **TMB**, tumor mutational burden.

Response to sotorasib is demonstrated across a range of tissue co-mutational profiles



*Mutations detected in one or multiple of these genes

Sotorasib demonstrates clinical activity across a range of tissue co-mutational profiles. No clear tissue co-mutational profile correlates with response to sotorasib.

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Summary

- Sotorasib (previously known as AMG 510) is a novel, highly-selective, first-in-class, oral $KRAS^{G12C}$ inhibitor[1]
- Sotorasib showed a favorable safety profile:
  - No dose-limiting toxicities
  - No treatment-related fatal AEs
  - Grade 3 or 4 treatment-related AEs occurred in 18.6% of patients
- Sotorasib demonstrated durable disease control in heavily pre-treated patients with NSCLC:
  - Confirmed ORR: 32.2% for all patients; 35.3% for 960 mg cohort
  - DCR: 88.1% for all patients; 91.2% for 960 mg cohort
  - Median PFS was 6.3 months in all patients, with median duration of response of 10.9 months
- 960 mg dose of sotorasib was identified as the Phase II dose in NSCLC
- Sotorasib demonstrates clinical activity in NSCLC across a range of *KRAS* p.G12C MAFs, PD-L1 expression levels, TMB plasma levels, and co-mutational profiles
- Additional CodeBreaK trials evaluating sotorasib as monotherapy or in combination with other anticancer agents are currently underway (CodeBreaK 100, CodeBreaK 200, CodeBreaK 101, CodeBreaK 105)[2-5]

AE, adverse event; **DCR,** disease control rate; **INN,** international nonproprietary name; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **PFS,** progression-free survival.

1. Canon J, et al. *Nature*. 2019;575:217-223. **2.** NCT03600883. **3.** NCT04303780. **4.** NCT04185883. **5.** NCT04380753.

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