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


†Deputy Chair of the Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
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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\(^5\),\(^7\)

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

Phase 1 study design (CodeBreaK100: NCT03600883)

**Phase 1, Multicenter, Open-label Study – Dose Escalation**

**Key Eligibility**
- Locally advanced or metastatic malignancy
- Received prior standard therapies
- KRASp.G12C mutation assessed by molecular testing of tumor biopsies
- No active brain metastases

**Cohort 1** 180 mg
- 2-4 patients/cohort
- Oral daily dosing
- Tx until progression
- Radiographic scans every 6 weeks

**Cohort 2** 360 mg

**Cohort 3** 720 mg

**Cohort 4** 960 mg

**Primary endpoint:** safety

**Secondary endpoints include:** PK, ORR, DOR, DCR, PFS, duration of SD

**Dose Expansion**

**Patients with KRAS p.G12C mutant advanced tumors**
- n~20 (maximum 60)

**Screening / Enrollment**
- Expansion dose determined

*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

<table>
<thead>
<tr>
<th>Dose cohort</th>
<th># patients (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 mg</td>
<td>3</td>
</tr>
<tr>
<td>360 mg</td>
<td>16</td>
</tr>
<tr>
<td>720 mg</td>
<td>6</td>
</tr>
<tr>
<td>960 mg†</td>
<td>34</td>
</tr>
</tbody>
</table>

†identified as the Phase II dose in NSCLC

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

- 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

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer
Incidence of all treatment-emergent adverse events

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

- 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)

<table>
<thead>
<tr>
<th>Treatment-related Adverse Events</th>
<th>All Patients (N = 59) n (%)</th>
<th>All Patients (N = 59) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Any</td>
<td>39 (66.1)</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (25.4)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>12 (20.3)</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>AST increased</td>
<td>12 (20.3)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (10.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (10.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>5 (8.5)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (6.8)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

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

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.

<table>
<thead>
<tr>
<th>Best Overall Response per Investigators’ Assessment, n (%)</th>
<th>960 mg (n = 34)</th>
<th>All patients (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed Partial Response</td>
<td>12 (35.3)</td>
<td>19 (32.2)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>19 (55.9)</td>
<td>33 (55.9)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2 (5.9)</td>
<td>5 (8.5)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>1 (2.9)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Not Done*</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

- 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.
Tumor burden change from baseline

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.

Tumor reduction was seen across all dose levels.
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
- Duration of stable disease‡
  Median of 4.0
  (1.4 to 10.9+) months
10/19 responders still in response

Patients with SD, n = 33
- Duration of response* †
  Median of 4.0
  (1.4 to 10.9+) months
- Duration of stable disease‡
  Median of 4.0
  (1.4 to 10.9+) months

Number of Patients at Risk:
59 56 51 39 25 23 18 16 9 7 4 3 3 1 0

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**

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

$n = 32$ patients with evaluable results

**NSCLC Tissue: PD-L1 IHC 22C3 pharmDx assay**

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

$n = 18$ patients with evaluable results

**NSCLC Plasma: Illumina TruSight Oncology 500 ctDNA assay**

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

$n = 33$ patients with evaluable results

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.

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

- Sotorasib (previously known as AMG 510) is a novel, highly-selective, first-in-class, oral KRAS<sup>G12C</sup> inhibitor<sup>1</sup>
- 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)<sup>2-5</sup>

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.

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David S. Hong, MD, Funda Meric-Bernstam, MD, Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Marwan G. Fakih, MD, Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, California, USA

John H. Strickler, MD, Duke University Medical Center, Durham, North Carolina, USA

Jayesh Desai, MD, Royal Melbourne Hospital/Peter MacCallum Cancer Centre, Victoria, VIC, Australia

Gregory A. Durm, MD, Department of Medicine, Division of Hematology/Oncology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Geoffrey I. Shapiro, MD, PhD, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

Gerald S. Falchook, MD, Sarah Cannon Research Institute at HealthONE, Denver, Colorado, USA

Timothy J. Price, MBBS, FRACP, DHLthSc, The Queen Elizabeth Hospital and University of Adelaide, Woodville South, Australia

Adrian Sacher, MD, MMSc, FRCP, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

Crystal S. Denlinger, MD, FACP, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

Yung-Jue Bang, MD, PhD, Seoul National University College of Medicine, Seoul, South Korea

Grace K. Dy, MD, Roswell Park Cancer Institute, Buffalo, New York, USA

John C. Krauss, MD, University of Michigan, Ann Arbor, Michigan, USA

Yasutoshi Kuboki, MD, Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan

James C. Kuo, MD, Scientia Clinical Research, Randwick, Australia

Andrew L. Coveler, MD, Department of Medicine, Division of Oncology, University of Washington, Seattle, Washington, USA

Keunchil Park, MD, PhD, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Tae Won Kim, MD, PhD, Department of Oncology, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, South Korea

Fabrice Barlesi, MD, PhD, Aix Marseille Universite, University, CNRS, INSERM, CRCM, Assistance Publique Hôpitaux de Marseille, Marseille, France

Pamela N. Munster, MD, University of California San Francisco, San Francisco, California, USA

Suresh S. Ramalingam, MD, FASCO, Winship Cancer Institute of Emory University, Atlanta, USA

Timothy F. Burns, MD, PhD, University of Pittsburgh Medical Center Hillman Cancer Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Haby Henary, MD, Jude Ngang, PharmD, Gataaree Ngarmchamanrith, MD, June Kim, PhD, Brett E. Houk, PhD, Jude Canon, PhD, J. Russell Lipford, PhD, Gregory Friberg, MD, Amgen Inc. Thousand Oaks, California, USA

Bob T. Li, MD, MPH, Piro Lito, MD, PhD, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Ramaswamy Govindan, MD, Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, Missouri, USA

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Dr. David S. Hong
†Deputy Chair of the Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Please reach out by email with any questions:
dshong@mdanderson.org