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Oncology

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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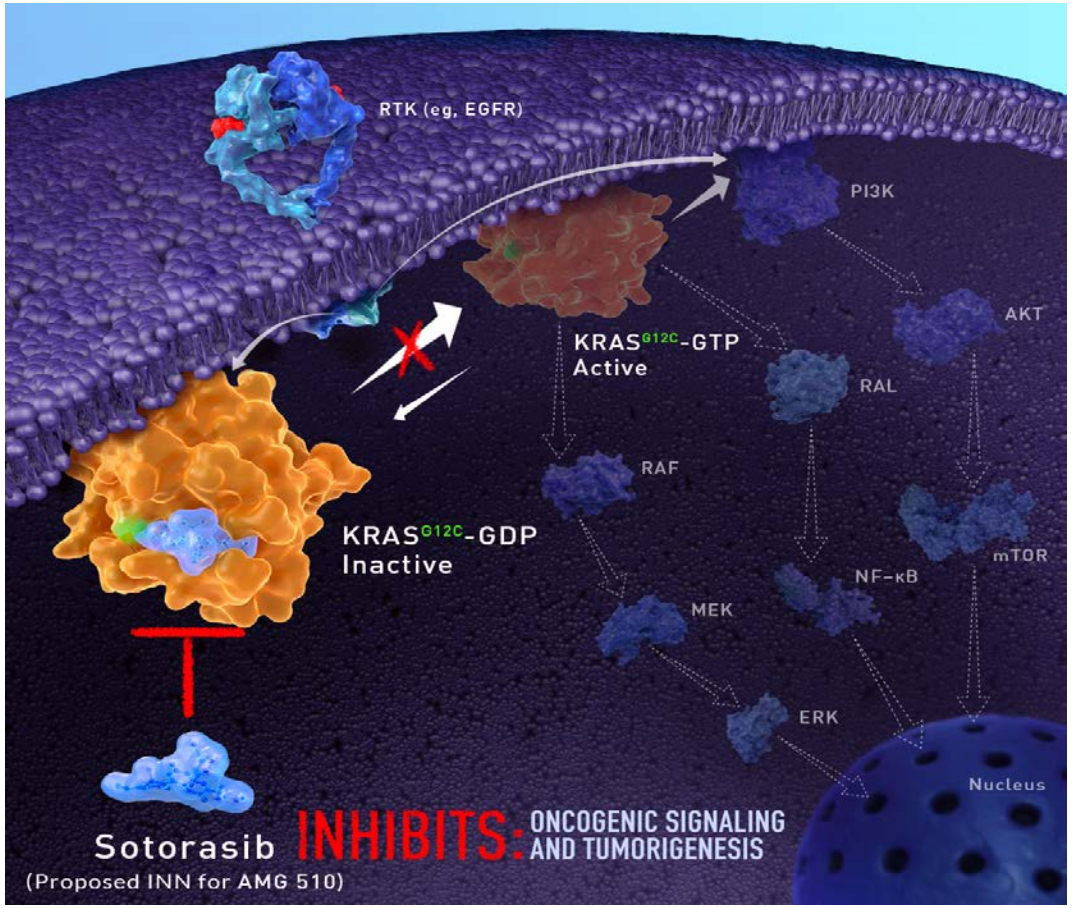
Presented at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020.

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]



AKT, protein kinase B; **EGFR,** epidermal growth factor receptor; **ERK,** extracellular signal-regulated kinase; **GDP,** guanosine diphosphate; **INN,** international non-proprietary name; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **MEK,** mitogen-activated protein kinase kinase; **mTOR,** mammalian target of rapamycin; **NF-κB,** nuclear factor kappa-light-chain-enhancer of activated B cells; **NSCLC,** non-small cell lung cancer; **PI3K,** phophoinositide 3-kinase; **RAF,** rapidly accelerated fibrosarcoma; **RAL,** Ras-like; **RTK,** receptor tyrosine kinase.

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.

Hong DS. Oral presentation at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020.

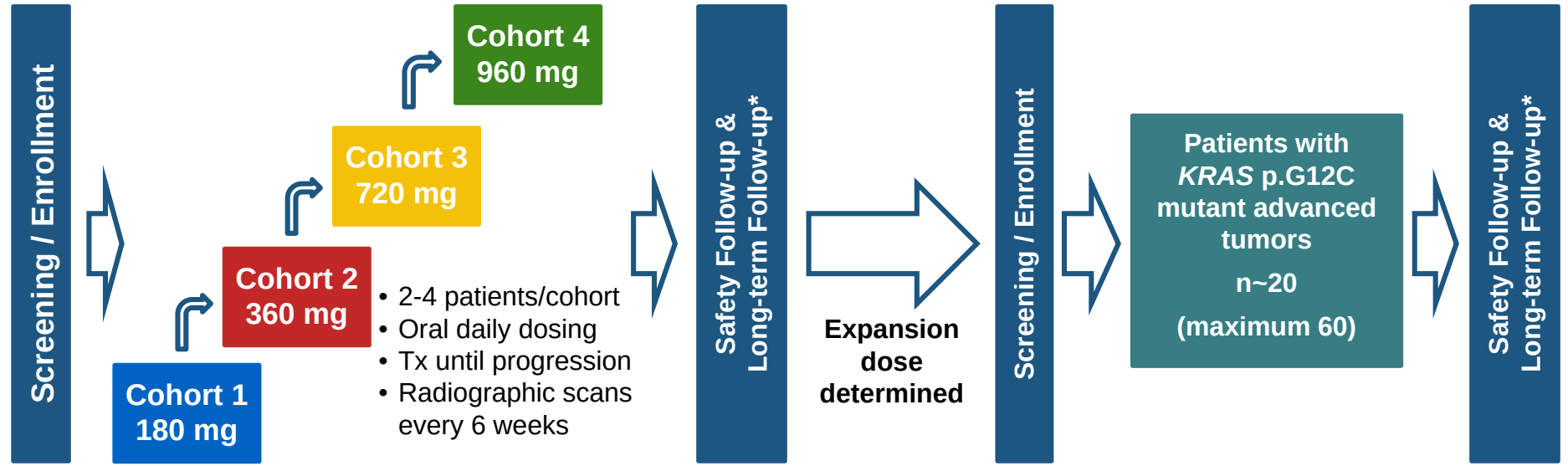
Phase 1 study design (CodeBreaK 100: NCT03600883)

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

Dose Expansion

Key Eligibility

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



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; **DOR,** duration of response; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **ORR,** objective response rate; **PFS,** progression-free survival; **PK,** pharmacokinetic; S**D,** stable disease; **Tx,** treatment.

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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 cut-off: 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-PD-1/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 PS, Eastern Cooperative Oncology Group performance status; **NSCLC,** non-small cell lung cancer; **PD-1/L1,** programmed cell death 1/ligand 1.

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Incidence of 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 AE occurred in 18.6% of patients

Sotorasib monotherapy demonstrated a favorable safety profile

Data cutoff: June 1, 2020.
AE, adverse event.

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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; **ALT,** alanine aminotransferase; **AST,** aspartate aminotransferase; **GGT,** gamma-glutamyl transferase.
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Response to sotorasib

	960 mg (n = 34)	All Patients (n = 59)
Best Overall Response per Investigators' Assessment, n (%) Confirmed Partial Response Stable Disease Progressive Disease Not Evaluable Not Done*	 12 (35.3) 19 (55.9) 2 (5.9) 1 (2.9) 0	 19 (32.2) 33 (55.9) 5 (8.5) 1 (1.7) 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. Evaluation of response is based on RECIST 1.1.
*Patient withdrew consent before tumor assessment. †Confirmed complete or partial response. ‡Confirmed complete or partial response, or stable disease.
CI, confidence interval; **CR,** complete response; **DCR,** disease control rate; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **PR,** partial response; **RECIST,** response evaluation criteria in solid tumors.

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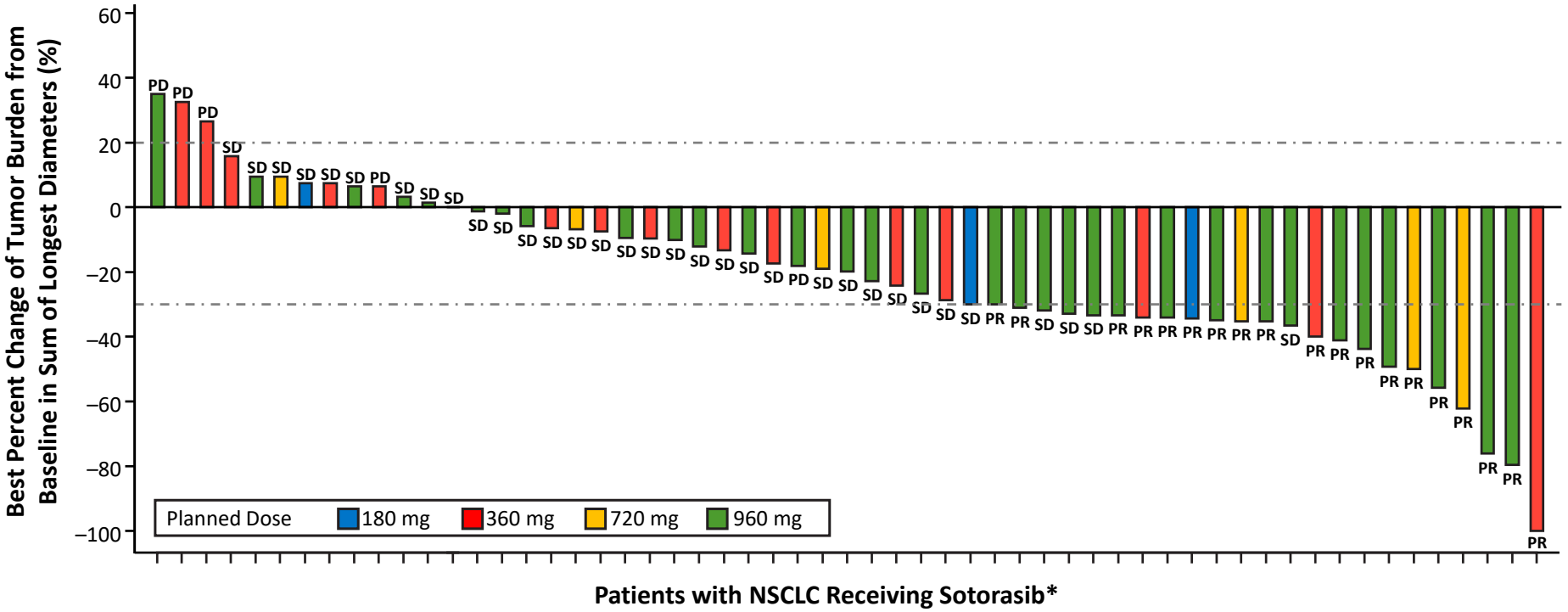
Tumor burden change from baseline



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.

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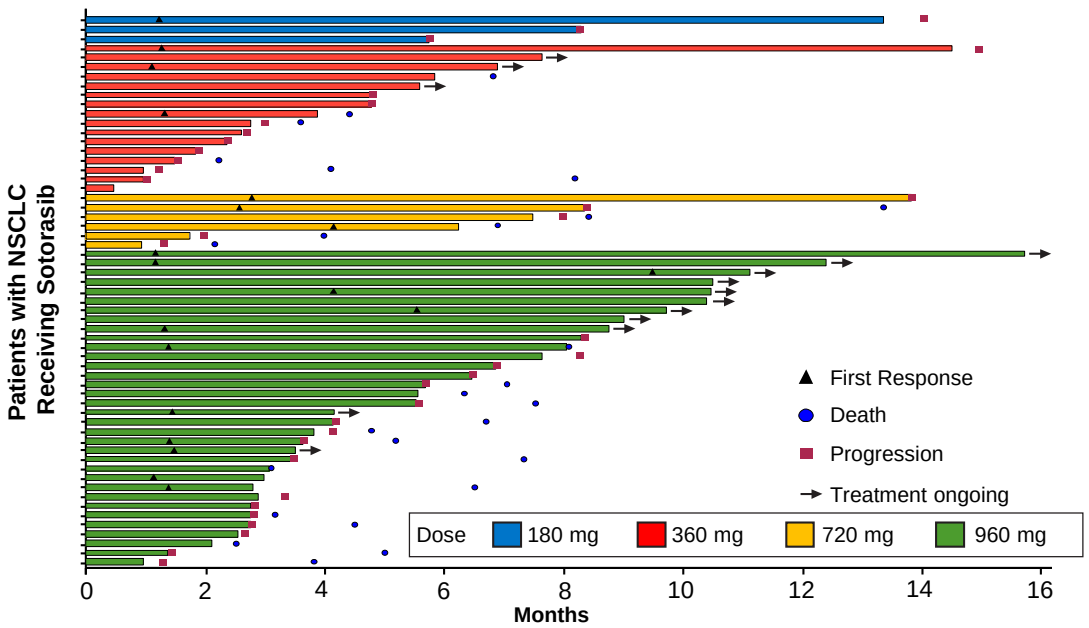
Duration of clinical benefit and progression-free survival



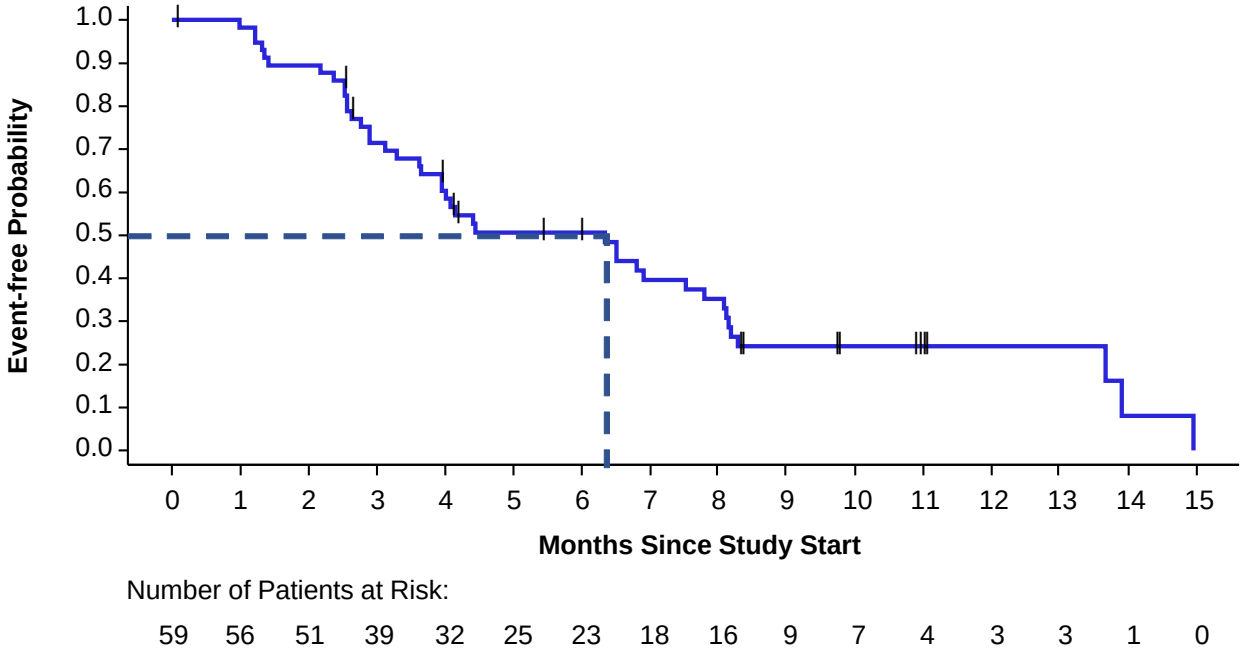
Confirmed PR, n = 19

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. †At data cutoff of June 1, 2020.
‡Duration of SD was measured from the start of the treatment until the criteria for disease progression were met or death, whichever was earlier. + Indicates censored value.
Median follow-up time was 11.7 (range 4.8-21.2) months.

CR, complete response; **NSCLC,** non-small cell lung cancer; **PFS,** progression-free survival; **PR,** partial response; **SD,** stable disease.

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Patient case

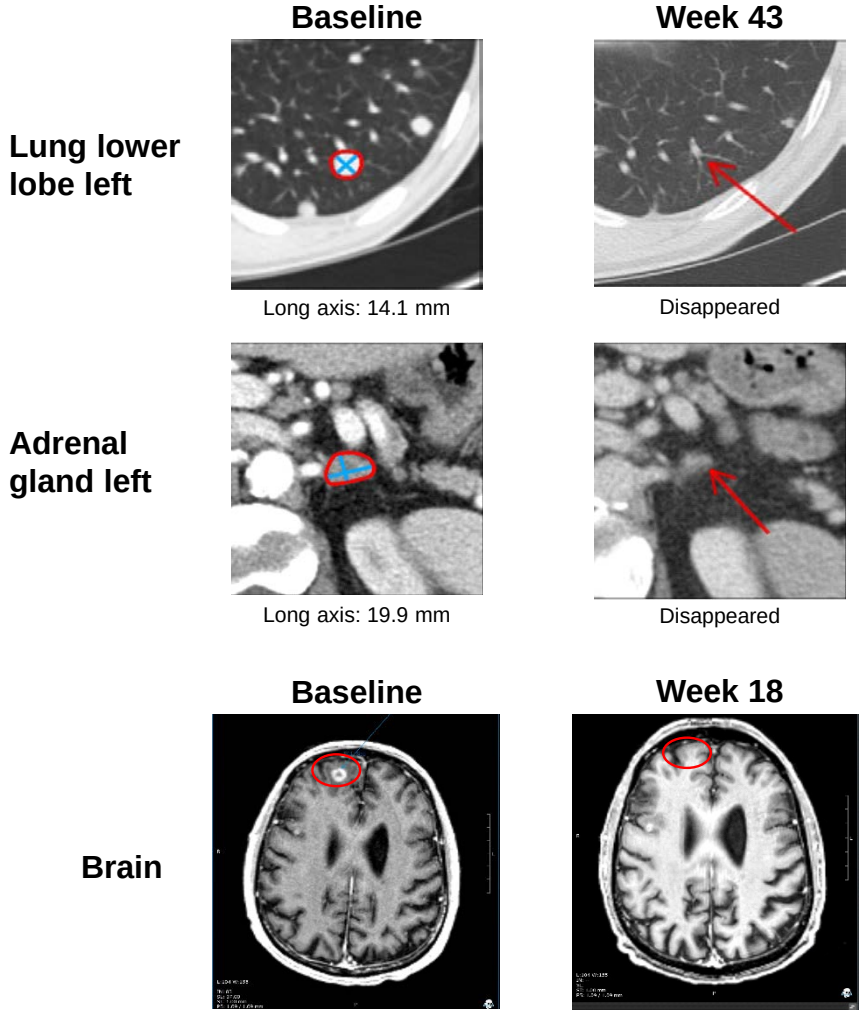
Demographics:
- 59 y.o. Male; *KRAS* p.G12C mutant metastatic NSCLC in Dec, 2013

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 kinase; **CNS,** central nervous system; **DLT,** dose-limiting toxicity; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **NSCLC,** non-small cell lung cancer; **STK11,** serine/threonine kinase 11.

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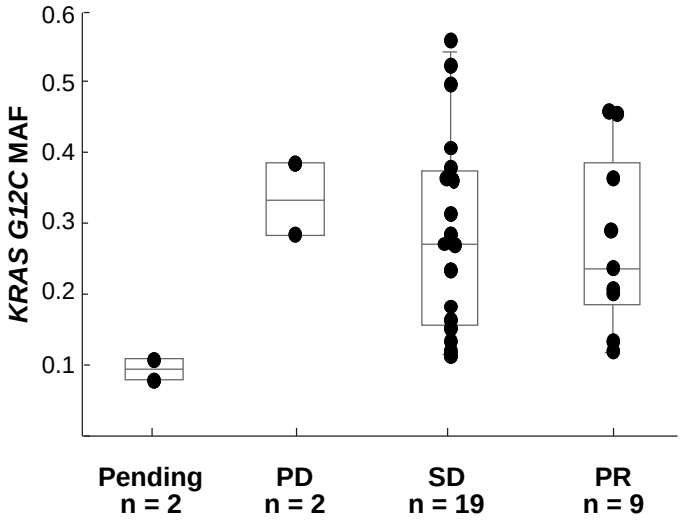
Sotorasib demonstrates clinical activity across a range of *KRAS* p.G12C MAFs, PD-L1 tissue expression levels, and plasma TMB levels

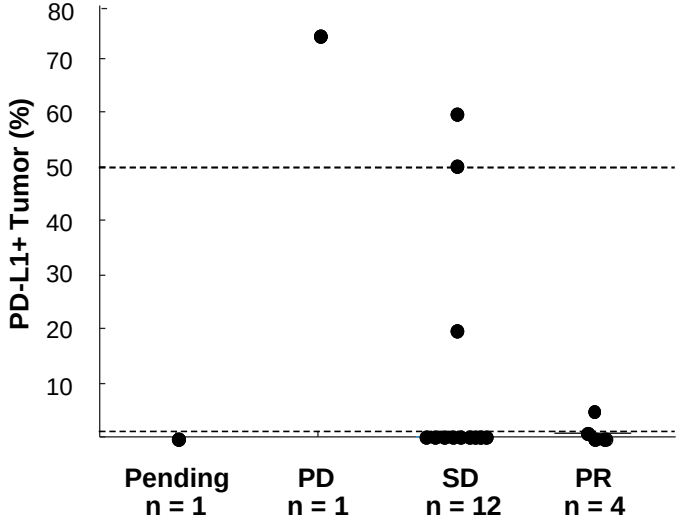
NSCLC Tissue: Qiagen Comprehensive Cancer Panel



n = 32 patients (NSCLC) 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

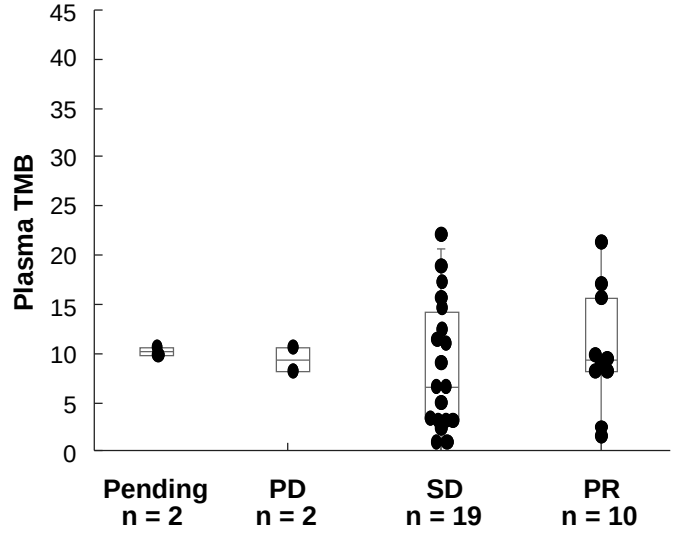
NSCLC Tissue: PD-L1 IHC 22C3 pharmDx assay



n = 18 patients (NSCLC) 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 (NSCLC) 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.

ctDNA, circulating tumor DNA; **DNA,** deoxyribose nucleic acid; **IHC,** immunohistochemistry; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **MAF,** mutation allele frequency (mutants read/total reads); **NSCLC,** non-small cell lung cancer; **PD,** progressive disease; **PD-L1,** programmed death ligand 1; **PR,** partial response; **SD,** stable disease; **TMB,** tumor mutational burden.

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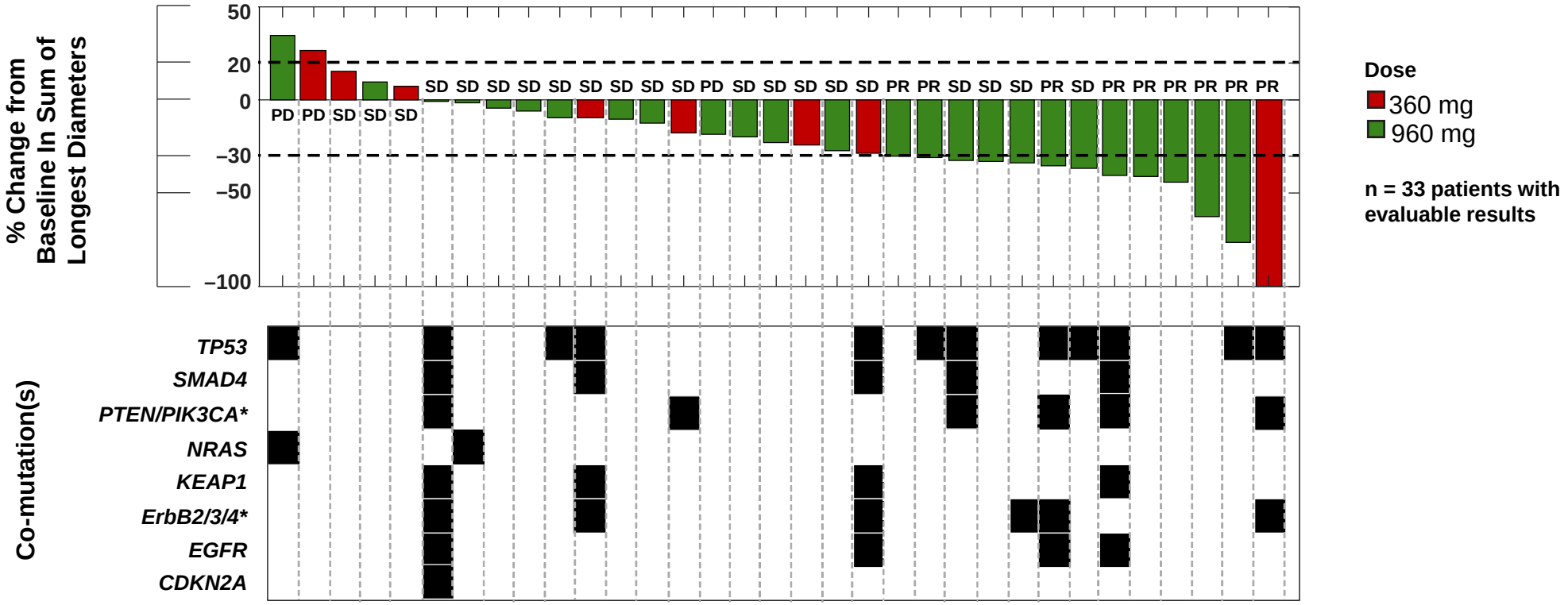
Response to sotorasib is demonstrated across a range of tissue co-mutational profiles



*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.

CDKN2A, cyclin-dependent kinase inhibitor 2A; **EGFR,** epidermal growth factor receptor; **ErbB,** avian erythroblastosis oncogene B; **KEAP1,** Kelch-like ECH-associated protein 1; **NRAS,** neuroblastoma rat sarcoma viral oncogene homolog; **PD,** progressive disease; **PI3KCA,** phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; **PR,** partial response; **PTEN,** phosphatase and tensin homolog; **SD,** stable disease; **SMAD4,** mothers against decapentaplegic homolog 4; **TP53,** tumor protein 53.

Hong DS, et al. Presented at: European Society for Medical Oncology Virtual Congress 2020, September 19–21, 2020; Abstract #3076.

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 with NSCLC
- 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; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **MAF,** mutational allele frequeny; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **PD-L1,** programmed death ligand 1; **PFS,** progression-free survival; **TMB,** tumor mutational burden.

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

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