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List of Abbreviations

Abbreviation or Term	Definition/Explanation
AACR	American Association for Cancer Research
ALK	anaplastic lymphoma kinase
BID	twice daily
BICR	Blinded independent central review
CR	complete response
CRC	colorectal cancer
CT	computed tomography
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
GAP	GTPase-activating proteins
GENIE	Genomics Evidence Neoplasia Information Exchange
FDA	Food and Drug Administration
FIH	first-in-human
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
$KRAS^{G12C}$	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
NTrk	neurotrophic tyrosine kinase
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
phase 1 NSCLC group	subjects with *KRAS p.G12C*-mutated advanced NSCLC who were enrolled across 7 different sotorasib monotherapy dose cohorts in phase 1 of Study [redacted]
phase 2 NSCLC group	subjects with KRAS p.G12C-mutated advanced NSCLC who were enrolled phase 2 and treated with 960 mg QD sotorasib monotherapy administered orally
PK	pharmacokinetics
PR	partial response

Abbreviation or Term	Definition/Explanation
PRO	patient-reported outcomes
QD	once daily
RAS	rat sarcoma viral oncogene homolog
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SEER	Surveillance, Epidemiology, and End Results
t_{max}	time to achieve C_{max}
VEGF	vascular endothelial growth factor

1. Background and Overview of Clinical Efficacy

1.1 Introduction

Sotorasib (AMG 510) is a small molecule that specifically binds and irreversibly inhibits the Kirsten rat sarcoma viral oncogene homolog protein (KRAS) with the G12C amino acid substitution ($KRAS^{G12C}$). This Summary of Clinical Efficacy summarizes data to support approval of sotorasib for the treatment of patients with *KRAS* gene with a mutation resulting in a G12C amino acid substitution (*KRAS p.G12C*)-mutated locally-advanced or metastatic non-small cell lung cancer (NSCLC) who have disease progression after receiving prior therapy.

1.1.1 *KRAS p.G12C*-mutated Non-small Cell Lung Cancer

Lung cancer is the leading cause of cancer death, with more than 80% of all lung cancer cases classified as NSCLC. Worldwide, lung cancer (small cell and non-small cell) is the most common cancer occurring in both men and women, with an estimated 2.09 million cases in 2018 (World Health Organization Statistics, 2018). The estimated number of deaths from lung cancer in 2018 was 173 278 in North America, 387 913 in Europe, and 1 068 862 in Asia (Globocan – Lung Cancer, 2018). In 2018, more than 250 000, 470 039, and 1 225 000 new cases of lung cancer were reported in North America, Europe, and Asia, respectively. Advanced NSCLC (stage IIIB and IV) is a serious and life-threatening disease, with a 5-year survival of 5.2% (Surveillance, Epidemiology, and End Results Program, 2019).

A number of proto-oncogene mutations have been implicated in the development of NSCLC. Among these, mutations in the *RAS* family of proto-oncogenes are among the most prevalent. The *RAS* family of proto-oncogenes consists of 3 closely related genes that express guanosine triphosphatases responsible for regulating cellular proliferation and survival (Simanshu et al, 2017; Barbacid, 1987). Different tumor types are associated with mutations in certain isoforms of *RAS*, with *KRAS* being the most frequently mutated isoform in most cancers (Prior et al, 2012).

Of the *KRAS* mutations, an estimated 80% occur at codon 12. The *KRAS p.G12C* mutation in codon 12 is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of guanosine triphosphatase-activating proteins, thereby reducing the hydrolysis of guanosine triphosphate by the KRAS protein. The resulting accumulation of active, guanosine triphosphate-bound KRAS leads to proliferative and survival signaling in tumor cells (Jones et al, 2017). It is estimated that

the *KRAS p.G12C* mutation is present in approximately 13% of lung adenocarcinoma (Biernacka et al, 2016) and has been identified as a putative oncogenic driver in this tumor type (AACR Project GENIE Consortium, 2017; Fernández-Medarde and Santos, 2011). Based on the estimated incidence of the *KRAS p.G12C* mutation in NSCLC (approximately 13% in Western regions and approximately 3% in Asia [Liu et al, 2020; Biernacka et al, 2016]) and the estimated number of worldwide lung cancer cases in 2018, the expected number of new cases diagnosed annually for *KRAS p.G12C*-mutated NSCLC is approximately 33 000 in North America, 61 000 in Europe, and 37 000 in Asia.

The role of *KRAS* mutations in human cancers, including NSCLC, has been known for decades, but no therapies specifically targeting *KRAS p.G12C* mutations have been successfully developed until recently (McCormick, 2019). Oncogenic *KRAS* mutations rarely occur concomitantly with other oncogenic mutations in genes such as the epidermal growth factor receptor gene (Martorell et al, 2017). Thus, most patients with oncogenic *KRAS* mutations, including the *KRAS p.G12C* mutation, are not candidates for currently approved targeted therapies and consequently are typically treated as patients without targetable mutations (ie, with chemotherapy, immunotherapy, or antiangiogenic agents) (Planchard et al, 2018; Van Cutsem et al, 2014).

1.1.2 Natural History of Patients With KRAS p.G12C-mutated NSCLC

To better characterize the natural history of and outcomes for patients with *KRAS pG12C*-mutated advanced NSCLC, and therefore the unmet medical need, Amgen conducted 3 real-world evidence studies in the United States:

- Study [redacted] (N = 743), a retrospective cohort study of patients with *KRAS p.G12C*-mutated advanced NSCLC in the Flatiron Health Foundation Medicine Clinico-Genomic Database.
- Study [redacted] (N = 7069), companion study to Study [redacted] a retrospective cohort study of patients with advanced NSCLC (ie, regardless of *KRAS p.G12C* mutation), in the Flatiron Health-Foundation Medicine Clinico-Genomic Database.
- Study [redacted] (N = 416), a retrospective study of patients with *KRAS p.G12C*-mutated metastatic NSCLC in the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database.

These studies showed that outcomes in second or later lines of therapy for patients with *KRAS p.G12C*-mutated advanced NSCLC were as poor as the overall patient population with advanced NSCLC (Table 1 of Module 2.5, Clinical Overview). These outcomes were consistent in similar patient populations regardless of the line of therapy when

treated with current standard of care. In Study [redacted] and Study [redacted] in second line of therapy in patients with *KRAS p.G12C*-mutated advanced NSCLC and the overall advanced NSCLC population, the median (95% CI) OS was 9.5 (8.1, 13.1) months and 10.2 (9.5, 11.3) months, respectively. The median (95% CI) real-world PFS was 4.0 (2.8, 5.3) months and 4.0 (3.7, 4.4) months, respectively. Similar results were observed in Study [redacted]. Overall survival and real-world PFS decreased with each subsequent line of therapy in all 3 studies.

The review of existing literature showed that the outcomes for patients with advanced NSCLC with the *KRAS p.G12C* mutation are poor with existing therapies in second-line or later, and their prognosis is as poor as the overall advanced the overall population of patients with advanced NSCLC (Wiesweg et al, 2018; Park et al, 2017; Barlesi et al, 2016; Svaton et al, 2016; Johnson et al, 2013).

Therefore, there is a need for additional novel, biomarker driven, anticancer therapies with better efficacy and tolerable safety profiles to address *KRAS p.G12C*-driven tumors.

1.1.3 Rationale for Use of Sotorasib in *KRAS p.G12C*-mutated NSCLC

Sotorasib is a novel small molecule that specifically binds and irreversibly inhibits the $KRAS^{G12C}$ mutant protein. The structure is presented in Figure 1 of Module 2.5, Clinical Overview. Sotorasib binds to the P2 pocket of $KRAS^{G12C}$ adjacent to the altered cysteine at position 12 and the nucleotide binding pocket. The inhibitor contains a thiol reactive portion that covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive, guanosine diphosphate-bound conformation. This blocks the interaction of KRAS with effectors such as RAF, thereby preventing downstream signaling, including the phosphorylation of extracellular-signal-regulated kinase (Canon et al, 2019; Simanshu et al, 2017; Ostrem et al, 2013; Cully and Downward, 2008). Inactivation of KRAS by ribonucleic acid interference or small molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts that have *KRAS* mutations, including the *KRAS p.G12C* mutation (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016). Studies with sotorasib have confirmed these in vitro findings and have likewise demonstrated selective inhibition of cell growth and regression of tumors with *KRAS p.G12C* mutations (Section 2.1 of Module 2.4, Nonclinical Overview).

The primary evidence of efficacy for this marketing application is provided by the phase 2 NSCLC portion of the phase 1/2 Study [redacted] (CodeBreaK 100), with supportive evidence provided by the phase 1 portion. The sotorasib development

program also includes an ongoing confirmatory, active-controlled phase 3 study for the treatment of NSCLC (Study [redacted]), as well as an ongoing phase 1 pharmacokinetic study in subjects of Chinese descent (Study [redacted]), and an ongoing phase 1b master protocol study with sotorasib administered in investigational regimens (as monotherapy and in various combination regimens) in subjects with *KRAS p.G12C*-mutated advanced solid tumors (Study [redacted]). In addition, a full clinical pharmacology program has examined the pharmacokinetics of sotorasib and explored potential drug-drug interactions.

The clinical studies supporting the marketing application are shown in Figure 2 of Module 2.5, Clinical Overview and are listed in Module 5.2, Tabular Listing of All Clinical Studies. Studies that are not included in this marketing application are listed in Appendix 2 of Module 2.5, Clinical Overview.

1.2 Overview of Sotorasib Clinical Program

This Summary of Clinical Efficacy summarizes data to support approval of sotorasib for the treatment of patients with *KRAS p.G12C*-mutated locally-advanced or metastatic NSCLC who have disease progression after receiving prior therapy. The primary support for the proposed indication is based on efficacy results from the subjects with *KRAS p.G12C*-mutated advanced NSCLC enrolled in the pivotal phase-2 portion of Study [redacted]), an ongoing phase 1/2 study evaluating sotorasib for the treatment of *KRAS p.G12C*-mutated advanced NSCLC (hereafter referred as NSCLC), colorectal cancer (CRC), and other solid tumors. Further efficacy support is provided based on the results from the phase-1 portion assessing sotorasib as monotherapy.

The sotorasib development program also includes an ongoing confirmatory, active-controlled phase 3 study for the treatment of NSCLC (Study [redacted] as well as an ongoing phase 1 pharmacokinetics study in subjects of Chinese descent (Study [redacted]), and an ongoing phase 1b master protocol study with sotorasib administered in investigational regimens (as monotherapy and in various combination regimens) in subjects with *KRAS p.G12C*-mutated advanced solid tumors (Study [redacted]). To characterize the initial safety, tolerability, pharmacokinetics, pharmacodynamics, and exposure-response properties of sotorasib, the marketing application also includes 9 clinical pharmacology studies and pharmacokinetic data from the subjects in the pivotal phase 1/2 Study [redacted]

The results of an integrated analysis of safety to support the overall sotorasib development program is provided in Module 2.7.4, Summary of Clinical Safety. The results of clinical pharmacology studies are summarized in Module 2.7.2, Summary of Clinical Pharmacology. The clinical studies supporting the marketing application are shown in Figure 2 of the Clinical Overview (Module 2.5) and are listed in the Tabular Listing of All Clinical Studies, Module 5.2. Studies that are not included in this marketing application are listed in Appendix 2 of the Clinical Overview.

1.3 Overview of Pivotal Study [redacted]

1.3.1 Key Design Aspects

Study [redacted] s an ongoing phase 1/2, open-label, nonrandomized single-group study evaluating the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in subjects with *KRAS p.G12C*-mutated NSCLC, CRC, and other solid tumors.

Phase 1 was a first-in-human (FIH) dose exploration/expansion portion of the study. The primary objectives of the phase-1 portion of the study were to evaluate the safety and tolerability of sotorasib and to estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose (RP2D) of sotorasib in adult subjects with *KRAS p.G12C*-mutated advanced solid tumors. A total of 214 subjects were enrolled in the phase 1 part of the study. The study design for phase-1 portion of Study 20170543 is outlined below and full details are provided in Section 8.1 of Study [redacted] Phase 1.

The phase-1 portion of the study was conducted in 2 parts: part 1 – dose exploration and part 2 – dose expansion. Part 1 had several dose cohorts that evaluated sotorasib administered under different conditions in subjects with *KRAS p.G12C*-mutated advanced solid tumors:

Part 1a: escalating dosing of once daily (QD) sotorasib monotherapy administered orally (180 mg to 960 mg).

Part 1b: 480 mg sotorasib monotherapy twice daily (BID) administered with food.

Part 1d: 960 mg sotorasib QD administered with food.

In part 1c cohort, 360, 720, and 960 mg sotorasib QD in combination with pembrolizumab were evaluated in subjects with NSCLC (combination therapy).

The phase 1 dose expansion (part 2) was to open when the MTD and/or a RP2D had been determined in part 1. Part 2 comprised several cohorts that evaluated sotorasib

administered under different conditions in subjects with *KRAS p.G12C*-mutated advanced solid tumors:

Part 2a: 960 mg sotorasib monotherapy QD.

Part 2b: 480 mg sotorasib monotherapy BID administered with food.

Part 2d: 960 mg sotorasib QD administered with food.

In Part 2c, sotorasib QD in combination with pembrolizumab will be evaluated in subjects with NSCLC

Part 2e: evaluated safety, tolerability, preliminary efficacy, PK and pharmacodynamic parameters of 960 mg QD dosing for sotorasib monotherapy in subjects with previously untreated *KRAS p.G12C*-mutated metastatic NSCLC. In addition, approximately 4 to 6 subjects enrolled in part 2e could participate in a drug-drug interaction substudy of sotorasib with midazolam.

Phase 2 is a pivotal open-label, nonrandomized single-group portion of the study designed to evaluate efficacy and safety/tolerability of sotorasib as monotherapy in subjects with *KRAS p.G12C*-mutated advanced solid tumors (NSCLC, CRC, and other tumors). The dose (and schedule) administered in phase 2 was the RP2D of 960 mg QD (Section 4). The study design for phase-2 portion of Study [redacted] is outlined below and full details are provided in Section 8.1 of Study [redacted] Phase 2.

The primary objective of the phase-2 portion of the study was to evaluate tumor ORR of sotorasib as monotherapy in subjects with *KRAS p.G12C*-mutated advanced solid tumors. Approximately 250 subjects (with at least 105 subjects with NSCLC and 60 subjects with CRC) were to be enrolled. Interim safety reviews were conducted after 30, 50, 70, and 100 subjects had been enrolled and treated with sotorasib for at least 21 days (enrollment was not to be held for completion of these safety reviews). To demonstrate durability of ORR, the phase 2 primary analysis was to occur approximately 8.5 months after 105 evaluable subjects with NSCLC or 60 with CRC had enrolled in the phase-2 portion of the study.

Daily treatment with sotorasib was to continue without interruption (ie, no planned off-treatment days) until disease progression (unless subject is eligible for continued treatment) or until discontinuation of treatment due to protocol-defined reasons including subject request, adverse event, intolerance to sotorasib treatment, noncompliance, or requirement for alternative treatment. Subjects were to have a safety follow-up visit

30 days (+ 7 days) after the last dose of sotorasib or before any new anticancer treatment was started. After the safety follow-up visit, subjects were to be followed long term for health condition, disease status, and subsequent anticancer treatment every 12 weeks (± 2 weeks) from last dose of investigational product for up to 3 years after last subject was enrolled or until withdrawal of consent, loss to follow-up, or subject death, whichever occurred first. Also, for subjects who discontinued study treatment without disease progression or start of subsequent anticancer treatment, tumor assessments were to continue during long-term follow-up every 12 weeks (± 2 weeks) for up to 3 years after last subject enrolled or until disease progression, start of subsequent anticancer treatment, death, withdrawal of consent, loss to follow-up, or end of study.

Eligible subjects were men or women ≥ 18 years of age, with *KRAS p.G12C*-mutated advanced NSCLC, colorectal cancer, or other solid tumors. Enrollment was restricted to subjects with *KRAS p.G12C*-mutated solid tumors as assessed by molecular testing. For NSCLC and CRC tumor types in phase 2, the mutation was confirmed by central testing prior to enrollment. Subjects in phase 2 with NSCLC and CRC tumor types were required to either provide archived tumor tissue samples (formalin fixed, paraffin embedded sample collected within 5 years) or be willing to undergo pretreatment tumor biopsy. Subjects must have received prior therapy (phase 1, except for the previously untreated metastatic NSCLC cohort) or progressed after receiving prior therapy (phase 2). In addition, subjects must have had measurable disease per response evaluation criteria in solid tumors (RECIST) 1.1 criteria; Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (phase 1) or ≤ 1 (phase 2); ability to take oral medications; QTc ≤ 470 msec; and adequate hematological, renal, hepatic, and coagulation laboratory assessments.

As nonclinical data suggest that sotorasib would have no therapeutic effect on tumors lacking *KRAS p.G12C* mutation (Module 2.4, Nonclinical Overview), Study [redacted] only enrolled subjects with tumors that had this mutation. Subject selection for the phase-1 portion of the study was based on a previously-documented *KRAS p.G12C* mutation. In the pivotal phase-2 portion subjects with *KRAS p.G12C*-mutated NSCLC were identified prospectively using local assessments that were then confirmed with central laboratory testing for the mutation before enrollment in the study. Central laboratory testing was performed using the Qiagen *therascreen*® KRAS RGQ polymerase chain reaction (PCR) In Vitro Diagnostic assay, which has CE (certification)

Marking in Europe. Approved diagnostics for testing KRAS pG12C mutational status are available in other regions.

This Summary of Clinical Efficacy (SCE) summarizes response data from 123 subjects (the phase 2 full analysis set) and overall survival data from 126 subjects (the phase 2 safety analysis set) with NSCLC treated with 960 mg QD sotorasib monotherapy (phase 2 NSCLC group) from primary analysis of the phase-2 portion of the study that occurred at the data cutoff date 01 September 2020. This SCE also provides the efficacy data from 124 subjects with NSCLC who were enrolled across 7 different sotorasib monotherapy dose cohorts (phase 1 NSCLC group) from interim analysis of the phase-1 portion of study that occurred at the data cutoff date 06 July 2020.

1.3.2 Appropriateness of Efficacy Endpoints

As previously treated patients with *KRAS p.G12C*-mutated advanced NSCLC receive limited benefit from currently available therapies (Section 1.1), data from a nonrandomized study in this patient population may be considered adequate to support marketing approval of novel therapies (US Food and Drug Administration [FDA] Guidance for Industry, 2015; EMA, 2015).

To reduce bias in this single-group study, tumor response assessments were conducted by an independent, external radiologic central laboratory (blinded independent central review [BICR]) using RECIST 1.1 criteria (US FDA 2015; Eisenhauer et al, 2009). The data received by the external reading radiologist was limited to only that which was relevant to an independent assessment of tumor response and disease progression. The reading radiologist was blinded to all other data.

The primary endpoint in the phase-2 portion of Study [redacted] to support marketing approval is the ORR (ORR = complete response + partial response), which has been used as a surrogate endpoint in support of marketing approval in uncontrolled, single-group studies in advanced solid tumors (Hierro et al, 2019; Drilon et al, 2018; Oxnard et al, 2016).

A clinically meaningful ORR to support marketing approval was identified after considering historical literature of outcomes after standard-of-care treatment in patients with NSCLC. For subjects with advanced or metastatic NSCLC, multiple large phase 3 trials have demonstrated ORR in ≥ second line (after first-line platinum-containing chemotherapy doublets, typically cisplatin/pemetrexed) of 5.5% to 13 % with chemotherapy (typically a taxane) and 9.7% to 22.5% with chemotherapy plus a VEGFR

inhibitor (Gridelli et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007). For subject with NSCLC, a large phase 3 trial (REVEL) for second-line treatment after disease progression on platinum-based therapy showed that an ORR of 23% (95% CI: 20, 26) was observed with ramucirumab plus docetaxel (Garon et al 2014, Cyramza® Prescribing Information). Therefore, in phase-2 portion of the study, the benchmark ORR of 23% was selected to exclude from the lower limit of 95% CI in the phase-2 portion of Study [redacted] in subjects with NSCLC.

The [redacted] study population is generally similar to the NSCLC population eligible for the phase-2 portion of Study [redacted] however, subjects in the [redacted]L study were only in second-line treatment, whereas subjects in Study [redacted] are in second to fourth line of treatment. Since the subject population in Study [redacted] had received more previous lines of treatment than those in the [redacted] study, using the benchmark of ORR 23% would demonstrate a clinically meaningful improvement over current standard of care.

Since the clinical significance of ORR is generally assessed by both its magnitude and duration, duration of response (DOR) was also evaluated as a key secondary endpoint. The secondary endpoints of time to response, disease control rate (DCR), PFS, and OS also provide additional support to the efficacy of sotorasib.

1.3.3 Statistical Methodology

To avoid potential bias due to differences in subject characteristics or other aspects of treatment between phase 1 and phase 2 of the study, the efficacy analysis was conducted separately for data from phase 1 and phase 2. All efficacy data reported for this marketing application are based on cutoff dates of 06 July 2020 (phase 1 interim analysis) and 01 September 2020 (phase 2 primary analysis).

For phase-1 portion of the study, sample sizes were based on practical considerations and were consistent with conventional oncology studies with the objective to estimate the MTD and evaluate initial safety and tolerability. Up to 283 subjects were to be enrolled, approximately 49 subjects in part 1 (dose exploration) and 154 subjects in part 2 (dose expansion). Additionally, a total of 40 to 80 subjects were allowed to be enrolled as backfill into 1 or more cohorts in phase 1 at doses that had been deemed to be safe and tolerable.

For phase-2 portion of the study, approximately 250 subjects were to be enrolled (at least 105 subjects with NSCLC and 60 subjects with CRC). The phase-2 portion of the

study targeted an ORR higher than a prespecified benchmark rate to exclude based on the lower limit of the 95% CI for the observed ORR for each tumor type (NSCLC or CRC). A sample size of 105 subjects for NSCLC would provide approximately a 90% probability that the lower limit of the ORR 95% CI exceeds the tumor-specific benchmark ORR assuming the true ORR improvement is 15%. The minimum observed ORR that would exclude the benchmark ORR with 105 NSCLC subjects was 32%.

The primary and secondary efficacy endpoints and the corresponding statistical methods of analysis for phase 1 and phase-2 portions of the study are summarized in Table 1.

The phase 2 primary analysis was to occur approximately 8.5 months after 105 subjects with NSCLC or 60 subjects with CRC were enrolled in the phase-2 portion of the study, whichever occurred earlier. The study team was blinded to the efficacy data to protect the data integrity. The primary analysis data cutoff date was determined based on the assumption from the data from phase 1 subjects with previously treated NSCLC who were in 960 mg sotorasib monotherapy (fasted) dose cohort and achieved an objective response. The data indicated that most responders achieved responses by the first or second scan (ie, 1.5 to 3 months from the start of treatment).

All primary response-related efficacy analyses for phase 2 were conducted on the phase 2 full analysis set, which consisted of all subjects enrolled in phase 2 who received ≥ 1 dose of sotorasib and had 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1. Overall survival was evaluated on the phase 2 safety analysis set which consisted of all subjects enrolled in phase 2 who received ≥ 1 dose of sotorasib. For further details, refer to the Study [redacted] statistical analysis plan (SAP) in Module 5.

Table 1. Efficacy Endpoints and Statistical Methods

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
Primary[a]		
objective response rate (ORR)	Proportion of subjects with a best overall response of confirmed complete response or confirmed partial response, measured by CT or MRI and assessed per RECIST 1.1 by blinded independent central review (BICR). Complete response and partial response required CT or MRI repeat assessment at least 4 weeks after the first detection of response.	The number and percentage of subjects with a best overall response of complete response, partial response, stable disease, progressive disease, not evaluable was provided. Objective response rate was summarized with Clopper-Pearson exact 95% CI[b]. Subjects without a post-baseline tumor assessment were considered nonresponders.
Secondary[a]		
duration of response (DOR)	Time from first partial response or complete response to disease progression per RECIST 1.1 or death, whichever was earlier. The DOR was calculated only for subjects who achieved a confirmed best overall response of partial response or complete response per RECIST 1.1.	Summarized with Kaplan-Meier median, quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months)
disease control rate (DCR)	Proportion of subjects whose best overall response was complete response, partial response, or stable disease > 5 weeks.	Summarized as for ORR.
time to response (TTR)	Time from the date of the first dose of sotorasib to the date of the first partial response or complete response. The TTR was calculated only for subjects who achieved a confirmed best overall response of partial response or complete response per RECIST 1.1.	Summarized by the nonmissing sample size (n), mean, standard deviation, median, minimum, and maximum for responders.
progression-free survival (PFS)	Time from the date of the first dose of sotorasib to the date of disease progression (assessed per RECIST 1.1 by BICR) or death due to any cause.	Summarized with Kaplan-Meier curves, median, quartiles, and rates for selected timepoints (eg, 6 and 12 months).

Footnotes defined on last page of table.

Table 1. Efficacy Endpoints and Statistical Methods

Efficacy Endpoint	Definition	Statistical Test
overall survival (OS)	Time from the date of the first dose of sotorasib until the date of death due to any cause.	Summarized with Kaplan-Meier curves, median, quartiles, and rates for selected timepoints (eg, 12 months).
duration of stable disease (phase 1 only)	Time from the date of the first dose of sotorasib to the date of disease progression or death due to any cause. Only calculated in subjects with best overall response of stable disease.	Summarized as for DOR.

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BICR = blinded independent central review; CI = confidence interval; CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; RECIST = response evaluation criteria in solid tumors

[a] Primary and secondary endpoints in this table are based on the phase-2 portion of the study and the phase-1 parts other than part 2e. All efficacy endpoints were primary endpoints for phase 1 part 2e.

[b] Clopper and Pearson, 1934

Source: Study [redacted] *Statistical Analysis Plan*

2. Summary of Results of Individual Studies: Study [redacted]

Study Number/Title: [redacted] A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation (CodeBreaK 100)

Methods: Study [redacted] is an ongoing phase 1/2, nonrandomized single-group, open-label study evaluating the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in subjects with *KRAS p.G12C*-mutated NSCLC, CRC, and other solid tumor types.

The primary objectives of the phase-1 portion of the study were to evaluate the safety and tolerability of sotorasib and to estimate the MTD and/or a RP2D of sotorasib in adult subjects with *KRAS p.G12C*-mutated advanced solid tumors. The primary objective of the phase-2 portion of the study was to evaluate tumor ORR of sotorasib as monotherapy as assessed by BICR using by RECIST 1.1 criteria in subjects with *KRAS p.G12C*-mutated advanced solid tumors. The phase 2 primary analysis was to occur approximately 8.5 months after 105 evaluable subjects with NSCLC or 60 with CRC had enrolled in the phase-2 portion of the study, whichever occurred earlier. The study team was blinded to the efficacy data to protect the data integrity. The primary analysis data cutoff date was determined based on the assumption from the data from the phase-1 portion of Study [redacted] that most responders achieved responses by the first or second scan (ie, 1.5 to 3 months from the start of treatment).

A summary of results for subjects with NSCLC treated with sotorasib monotherapy from the interim analysis of the phase-1 portion of the study (phase 1 NSCLC group, data cutoff date 06 July 2020) and the primary analysis of the phase-2 portion of the study (phase 2 NSCLC group, data cutoff date 01 September 2020) is presented below. Full description of the results for this study is provided in Study [redacted] Phase 1, Study [redacted] Phase 2, and Study [redacted] PRO.

Amgen has performed assessment of the impact of COVID-19 pandemic situation on Study [redacted], including the impact of changes implemented to ensure subject safety and continuity of the study (Section 8.9.1 of Study [redacted] Phase 1 and Section 8.9.1 of Study [redacted] Phase 2). The outcomes from this assessment demonstrated that a

low impact was expected from the observed deviations due to COVID-19 on the characterization and inference making on the primary and secondary efficacy endpoints (ORR and duration of response) and safety assessments.

Results:

Phase 1

Subject Disposition

A total of 124 subjects in phase 1 NSCLC group were enrolled in 7 dose cohorts in phase-1 portion of the study to be treated with sotorasib monotherapy. As of the data cutoff date of 06 July 2020, of the 124 subjects, 75 (60.5%) discontinued investigational product. Of the 55 subjects (44.4%) who discontinued the study, 44 subjects (35.5%) died and 11 subjects (8.9%) withdrew consent.

Baseline Demographics

- Sex: 46 men (37.1%); 78 women (62.9%)
- Age: mean (SD; range): 67.6 (7.9; 49, 86) years
- Race: 101 white (81.5%); 12 Asian (9.7%); 6 black (4.8%); 5 other (4.0%)

Efficacy Results:

The tumor response was evaluated by contrast-enhanced magnetic resonance imaging/computed tomography (MRI/CT) according to RECIST 1.1 by BICR. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4 weeks after the first documentation of response and could have been delayed until the next scheduled scan to avoid unnecessary procedures.

As the phase-1 portion of Study [redacted] study was a FIH study, the effect of food on safety, tolerability, and PK of sotorasib was evaluated in a food effect assessment substudy (Protocol Section 3.1.1.1.5 in Section 16.1.1 of Study [redacted] Phase 1). The results of this substudy indicate that sotorasib can be taken with or without food. The phase-1 portion of the study had 2 dose cohorts for which 960 mg QD sotorasib monotherapy was administered to previously untreated NSCLC subjects: 1 cohort for subjects in the fasted state (part 1a and part 2a) and 1 dose cohort for subjects in the fed state (part 1d and part 2d). In this SCE, the word "(fasted)" in the name of the "960

mg QD sotorasib monotherapy (fasted)" dose cohort is used only to differentiate between these 2 cohorts.

Efficacy results for subjects with previously untreated NSCLC in phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort are provided in Table 2. Additional efficacy data for other sotorasib monotherapy dose cohorts are provided in Section 3.2.3.

Table 2. Summary of Efficacy Results for Subjects With Previously Treated NSCLC in Phase 1 960 mg QD Sotorasib Monotherapy (Fasted) Dose Cohort (N = 34)

Endpoint	Median	95% CI	Median Follow-up Time (Range) (Months)
ORR (%)	47.1	29.78, 64.87	-
DCR (%)	94.1	80.32, 99.28	-
DOR (months)	NE	4.2, NE	9.0 (1.5, 15.0)
Duration of stable disease (months)	2.9	2.6, 5.2	12.5 (1.3, 12.5)
TTR (months)	1.41 (range: 0.8, 8.3)	-	-
PFS (months)	5.3	3.1, 8.1	11.1 (1.2+, 16.3)
KM estimate at 6 months	42.9	25.5, 59.2	-
KM estimate at 12 months	31.2	15.6, 48.2	-
OS (months)	7.6	6.3, NE	12.2 (2.5+, 17.1)
KM estimate at 6 months	72.2	53.3, 84.4	-
KM estimate at 12 months	41.2	23.8, 57.9	-

- = not applicable; + = censored; BICR = blinded independent central review; DCR = disease control rate, DOR = duration of response; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = response evaluation criteria in solid tumors; TTR = time to response

[a] The tumor response was evaluated by contrast-enhanced magnetic resonance imaging/computed tomography (MRI/CT) according to RECIST 1.1 by BICR. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4 weeks after the first documentation of response and could have been delayed until the next scheduled scan to avoid unnecessary procedures.

Pharmacokinetics:

During dose exploration (part 1 of phase 1), sotorasib was administered orally either QD as a monotherapy over a dose range of 180 mg to 960 mg or BID as a monotherapy at 480 mg. Geometric mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from time zero to 24 hours postdose (AUC_{0-24h}) parameters for both day 1 and day 8 were less than dose proportional. No accumulation was observed with multiple dosing at all dose levels tested. With 480 mg BID dosing,

geometric mean $AUC_{0\text{-}24h}$ increased, compared with 960 mg QD dosing, on both day 1 and day 8 of dosing.

During dose expansion (part 2), sotorasib was administered QD at the 960 mg dose to subjects with *KRAS p.G12C*-mutated advanced solid tumors as a monotherapy in the fasted and fed states (part 2a and part 2d). Geometric mean C_{max} and $AUC_{0\text{-}24h}$ were similar to the results observed for the 960 mg QD dose cohorts during dose exploration (part 1).

Safety Results

As of the data cutoff date for phase 1 (06 July 2020), a total of 124 subjects in the safety analysis set of the phase 1 NSCLC group received ≥ 1 dose of sotorasib monotherapy. The mean (SD) number of cycles started was 6.0 (5.2) and mean (SD) duration of treatment was 19.47 (15.67) weeks.

Of 124 subjects, 121 (97.6%) had treatment-emergent adverse events, 72 subjects (58.1%) had grade ≥ 3 adverse events, and 59 subjects (47.6%) had serious adverse events. Twenty-one subjects (16.9%) had fatal adverse events; none of the events were considered related to sotorasib per investigator. Forty subjects (32.3%) had adverse events leading to dose modification of sotorasib and 12 subjects (9.7%) had adverse events leading to discontinuation of sotorasib.

Conclusions:

- No dose-limiting toxicities were observed in any cohort. The RP2D for sotorasib was determined to be 960 mg QD, which was the highest dose tested. Sotorasib was safe and had acceptable tolerability across dose levels tested in monotherapy.
- Of 34 subjects in the ORR analysis set for phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort, 16 subjects had confirmed partial response, for an ORR of 47.1% (95% CI: 29.78, 64.87). The median (range) follow-up time for DOR was 9.0 (1.5, 15.0) months. The Kaplan-Meier estimate of median DOR was not reached (95% CI: 4.2, NE). Among 16 responders, the DOR was at least 3 months in 12 subjects (75.0%), at least 6 months in 5 subjects (31.3%), at least 9 months in 4 subjects (25.0%), and 1 subject (6.3%) had a DOR of at least 12 months.
- Sotorasib exposure after QD administration, as assessed by C_{max} and $AUC_{0\text{-}24h}$, increased in a less than dose-proportional manner in the dose range of 180 mg to 960 mg. No accumulation was observed at the dose levels tested (180 mg to 960 mg). After 960 mg QD sotorasib administration to subjects in the fasted or fed states, sotorasib exposure was similar between the fed state and the fasted state.

- Based on review of the totality of evidence including safety and efficacy, 960 mg QD was selected as the proposed dose for the intended patient population

Phase 2

Subject Disposition

A total of 126 subjects enrolled in the phase 2 NSCLC group. As of the data cutoff date of 01 September 2020, of the 126 subjects in the phase 2 NSCLC group who were treated with 960 mg QD sotorasib monotherapy, 89 subjects (70.6%) discontinued sotorasib. Of the 57 subjects (45.2%) who discontinued the study, 47 subjects (37.3%) died and 10 subjects (7.9%) withdrew consent.

Baseline Demographics

- Sex: 63 men (50.0%); 63 women (50.0%)
- Age: mean (SD; range): 62.9 (9.3; 37, 80) years
- Race: 103 white (81.7%); 19 Asian (15.1%); 2 black (1.6%), 2 other (1.6%)

Efficacy Results:

Efficacy results for phase 2 subjects with previously untreated NSCLC treated with 960 mg QD sotorasib monotherapy are provided in Table 3 and described in detail in Section 3.2.

Table 3. Summary of Efficacy Results for Phase 2 Subjects With Previously Treated NSCLC (N = 123)

Endpoint	Median	95% CI	Median Follow-up Time (Range) (Months)
ORR (%)[a]	37.4	28.84, 46.58	-
DCR (%)[a]	80.5	72.37, 87.08	-
DOR (months)[a]	8.4	6.9, 8.4	6.9 (1.3, 8.4+)
TTR (months)[a]	1.35 (range: 1.2, 6.1)	-	-
PFS (months)	6.7	4.9, 8.1	8.3 (0.3, 11.5+)
KM estimate at 3 months	67.5	58.2, 75.2	
KM estimate at 6 months	51.5	41.9, 60.4	-
OS (months)	12.0	9.5, NE	9.3 (1.1+, 12.2)
KM estimate at 6 months	75.5	66.8, 82.2	-
KM estimate at 12 months	51.6	36.7, 64.5	-

- = not applicable; + = censored; BICR = blinded independent central review; DCR = disease control rate, DOR = duration of response; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = response evaluation criteria in solid tumors; TTR = time to response

[a] The tumor response was evaluated by contrast-enhanced magnetic resonance imaging/computed tomography (MRI/CT) according to RECIST 1.1 by BICR. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4 weeks after the first documentation of response and could have been delayed until the next scheduled scan to avoid unnecessary procedures.

Pharmacokinetics:

In phase 2 of this study, 960 mg sotorasib monotherapy was administered QD to fasted subjects. Geometric mean sotorasib C_{max} and $AUC_{0\text{-}24h}$ were similar to those for phase 1 cohorts.

Patient-reported Outcomes

The PRO-related objective in phase 2 was to explore the changes in cancer-specific symptoms and overall health status using PRO instruments validated for use in lung cancer. Overall, compliance with the protocol-specified schedule for PRO completion was high, which allowed for an informative exploration of the PRO data. At baseline, 78% of subjects completed at least 1 PRO assessment and the PRO compliance rate at each timepoint (percent of subjects completing a PRO assessment among those expected to complete an assessment) was > than 85% for cycles 2 to 6, > 70% for cycles 7 to 13, and < 60% during later cycles. At enrollment into the study, subjects in the phase 2 NSCLC group reported a high symptomatic burden and impaired physical

function and quality of life which was comparable to normative values for patients with NSCLC and higher than the general population (Scott et al, 2008). Over time, a trend toward improvement (or stabilization) was observed in the severity of key lung cancer symptoms of cough, dyspnea and chest pain. Few subjects reported bother due to treatment-related side effects associated with sotorasib. Among those who reported symptom bother, most subjects described their symptoms as mild.

Safety

As of the data cutoff date, a total of 126 subjects in safety analysis set of the phase 2 NSCLC group received ≥ 1 dose of sotorasib. The mean (SD) number of cycles started was 8.0 (4.7) and mean (SD) duration of treatment was 25.12 (14.55) weeks.

Of 126 subjects, 125 (99.2%) had treatment-emergent adverse events, 75 subjects (59.5%) had grade ≥ 3 adverse events, and 63 subjects (50.0%) had serious adverse events. Eighteen subjects (14.3%) had fatal adverse events; none of the fatal events were considered related to sotorasib per investigator. Twenty-eight subjects (22.2%) had adverse events leading to interruption of investigational product and 11 subjects (8.7%) had adverse events leading to discontinuation of investigational product.

Conclusions

- Forty-six subjects in the full analysis set of the phase 2 NSCLC group achieved a partial response or complete response for an ORR of 37.4% (95% CI: 28.84, 46.58). The study met its primary endpoint: the lower bound of the 95% CI excluded the prespecified benchmark ORR of 23%. Of 46 responders, 2 subjects (1.6%) achieved complete response and 44 subjects (35.8%) achieved partial response. The median (95% CI) DOR for the 46 objective responders was 8.4 (6.9, 8.4) months. Therefore, durable objective response was achieved in a large percentage of subjects treated with sotorasib.
  Of the 99 subjects in the full analysis set who had prior treatment with both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1, ORR (95% CI) was 32.3% (23.3, 42.5) and median (95% CI) duration of response was not estimable (6.9, not estimable) months.
- Of 126 subjects in the safety analysis set of the phase 2 NSCLC group, 125 (99.2%) had treatment-emergent adverse events, 75 subjects (59.5%) had grade ≥ 3 adverse events, and 63 subjects (50.0%) had serious adverse events. Eighteen subjects (14.3%) had fatal adverse events; none of the events were considered related to sotorasib per investigator. Twenty-eight subjects (22.2%) had adverse events leading to interruption of investigational product and 11 subjects (8.7%) had adverse events leading to discontinuation of investigational product. Overall, 960 mg QD dose of sotorasib had a tolerable safety profile.

- Geometric mean sotorasib C_{max} and AUC_{0-24h} were similar to those for phase 1 cohorts.
- A trend toward improvement (or stabilization) was observed in the PRO assessments of the severity of key lung cancer symptoms of cough, dyspnea and chest pain.

3. Comparison and Analyses of Results Across Studies

All the efficacy data for this marketing application were obtained from Study [redacted] which consisted of the FIH phase-1 portion and the pivotal phase-2 portion. The primary evidence for efficacy for this marketing application is the evaluation of the data for subjects with previously treated NSCLC who received sotorasib monotherapy in the pivotal phase-2 portion of phase 1/2 Study [redacted] (phase 2 NSCLC group), as reflected in a durable objective response in a large percentage of subjects and supported by the totality of clinically meaningful response measures.

Therefore, this SCE primarily focuses on efficacy data collected in the phase-2 portion of the study for subjects in the phase 2 NSCLC group. Efficacy results for subjects with *KRAS p.G12C*-mutated CRC and other *KRAS p.G12C*-mutated solid tumors are provided in the Study [redacted] Phase 2 CSR.

Efficacy data from the phase-1 portion of the study will also be summarized in this SCE for both previously treated and previously untreated subjects with NSCLC who received sotorasib monotherapy (phase 1 NSCLC group). Efficacy data for previously treated subjects with NSCLC treated with sotorasib combination therapy with pembrolizumab are summarized in Study [redacted] Phase 1 CSR.

3.1 Study Populations

3.1.1 Analysis Sets

3.1.1.1 Phase 2

The phase 2 full analysis set included all subjects enrolled in phase 2 who received ≥ 1 dose of sotorasib and had ≥ 1 measurable lesion at baseline as assessed by BICR using RECIST 1.1. The primary analysis for phase 2 tumor response and other efficacy-related endpoints was performed on this dataset. The phase 2 full analysis set for the phase 2 NSCLC group comprised 123 subjects.

The phase 2 investigator efficacy analysis set included all subjects enrolled in phase 2 who received ≥ 1 dose of sotorasib and had ≥ 1 measurable lesion at baseline as assessed by the investigator using RECIST 1.1. This dataset was used for sensitivity analysis of response-related efficacy endpoints using assessment per investigator. The phase 2 investigator efficacy analysis set for the phase 2 NSCLC group comprised 126 subjects.

The phase 2 safety analysis set included all subjects enrolled in phase 2 who received ≥ 1 dose of sotorasib and was used for analysis of all safety endpoints, unless noted

otherwise, and for analysis of OS. The phase 2 safety analysis set for the phase 2 NSCLC group comprised 126 subjects.

3.1.1.2 Phase 1

The phase 1 full analysis set included all subjects enrolled in phase 1 who received ≥ 1 dose of sotorasib and had ≥ 1 measurable lesion at baseline as assessed by BICR using RECIST 1.1. The phase 1 full analysis set for NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort comprised 34 subjects and was used for analyses of PFS.

The phase 1 ORR analysis set included all subjects in the phase 1 full analysis set who have had the opportunity to be followed for ≥ 7 weeks starting from day 1. The 7-week time-point was chosen because the first post-baseline tumor assessment was scheduled to occur at 6 ± 1 week after cycle 1 day 1. Subjects who stopped disease assessments before 7 weeks were included in this analysis set if the data cutoff was ≥ 7 weeks after their first dose date. Interim analysis for phase 1 efficacy was performed on this dataset. The phase 1 ORR analysis set for NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort comprised 34 subjects.

The phase 1 safety analysis set included all subjects enrolled in phase 1 who received ≥ 1 dose of sotorasib and was used for analysis of all safety endpoints, unless noted otherwise, and for analysis of OS. The phase 1 safety analysis set for the NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort comprised 34 subjects.

3.1.2 Subject Disposition

3.1.2.1 Phase 2

A total of 126 subjects enrolled in the phase 2 NSCLC group (Table 4). As of the data cutoff date of 01 September 2020, of the 126 subjects in the phase 2 NSCLC group who were treated with sotorasib monotherapy, 89 subjects (70.6%) discontinued sotorasib.

Of the 57 subjects (45.2%) who discontinued the study, 47 subjects (37.3%) died and 10 subjects (7.9%) withdrew consent.

Table 4. Subject Disposition with Discontinuation Reason (Phase 2 Enrolled Subjects)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
Enrolled – n (%)	126 (100.0)
Investigational product accounting – n (%)	
Subjects who never received sotorasib	0 (0.0)
Subjects who received sotorasib	126 (100.0)
Subjects who discontinued sotorasib	89 (70.6)
Adverse event	11 (8.7)
Decision by sponsor	0 (0.0)
Lost to follow-up	0 (0.0)
Death	1 (0.8)
Subject request	5 (4.0)
Pregnancy	0 (0.0)
Noncompliance	1 (0.8)
Disease progression	70 (55.6)
Requirement for alternative therapy	1 (0.8)
Protocol specified criteria	0 (0.0)
Study completion accounting – n (%)	
Subjects continuing study	69 (54.8)
Subjects who discontinued study	57 (45.2)
Decision by sponsor	0 (0.0)
Lost to follow-up	0 (0.0)
Death	47 (37.3)
Withdrawal of consent from study	10 (7.9)

Phase 2 data cutoff date of 01 September 2020.
N = Number of enrolled subjects, n = Number of subjects with observed data.
Percentages based on subjects enrolled.
Sixty-eight subjects failed screening in phase 2 NSCLC group.
Source: Study [redacted] Phase 2 CSR Table 14b-1.1

3.1.2.2 Phase 1

Table 5 provides a summary of subject disposition for 124 subjects in phase 1 NSCLC group who were enrolled across 7 dose cohorts in phase-1 portion of the study to be treated with sotorasib monotherapy as described in Section 1.3.1. As of the data cutoff date of 06 July 2020, of the 124 subjects, 75 (60.5%) discontinued investigational product. The primary reasons for treatment discontinuation were progression of disease (53 subjects, 42.7%), adverse event (12 subjects, 9.7%), and subject request (6 subjects, 4.8%). Of the 55 subjects (44.4%) who discontinued the study, 44 subjects (35.5%) died and 11 subjects (8.9%) withdrew consent.

Table 5. Subject Disposition with Discontinuation Reason (Phase 1 NSCLC Monotherapy Enrolled Subjects)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3) n (%)	Phase 1 NSCLC 360 mg QD Fasted (N = 16) n (%)	Phase 1 NSCLC 720 mg QD Fasted (N = 6) n (%)	Phase 1 NSCLC 960 mg QD Fasted (N = 34) n (%)	Phase 1 NSCLC 480 mg BID Fed (N = 21) n (%)	Phase 1 NSCLC 960 mg QD Fed (N = 14) n (%)	Phase 1 NSCLC 1L 960 mg QD Fasted[a] (N = 30) n (%)	Phase 1 NSCLC Mono Total (N = 124) n (%)
Enrolled – n (%)	3 (100.0)	16 (100.0)	6 (100.0)	34 (100.0)	21 (100.0)	14 (100.0)	30 (100.0)	124 (100.0)
Investigational product accounting – n (%)								
Subjects who never received sotorasib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who received sotorasib	3 (100.0)	16 (100.0)	6 (100.0)	34 (100.0)	21 (100.0)	14 (100.0)	30 (100.0)	124 (100.0)
Subjects who discontinued sotorasib	3 (100.0)	13 (81.3)	6 (100.0)	25 (73.5)	10 (47.6)	5 (35.7)	13 (43.3)	75 (60.5)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	5 (14.7)	4 (19.0)	1 (7.1)	2 (6.7)	12 (9.7)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)	4 (3.2)
Subject request	0 (0.0)	3 (18.8)	0 (0.0)	1 (2.9)	1 (4.8)	1 (7.1)	0 (0.0)	6 (4.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disease progression	3 (100.0)	10 (62.5)	5 (83.3)	19 (55.9)	5 (23.8)	3 (21.4)	8 (26.7)	53 (42.7)
Requirement for alternative therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol specified criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 5. Subject Disposition with Discontinuation Reason (Phase 1 NSCLC Monotherapy Enrolled Subjects)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3) n (%)	Phase 1 NSCLC 360 mg QD Fasted (N = 16) n (%)	Phase 1 NSCLC 720 mg QD Fasted (N = 6) n (%)	Phase 1 NSCLC 960 mg QD Fasted (N = 34) n (%)	Phase 1 NSCLC 480 mg BID Fed (N = 21) n (%)	Phase 1 NSCLC 960 mg QD Fed (N = 14) n (%)	Phase 1 NSCLC 1L 960 mg QD Fasted[a] (N = 30) n (%)	Phase 1 NSCLC Mono Total (N = 124) n (%)
Study completion accounting – n (%)								
Subjects continuing study	0 (0.0)	7 (43.8)	1 (16.7)	12 (35.3)	15 (71.4)	10 (71.4)	24 (80.0)	69 (55.6)
Subjects who discontinued study	3 (100.0)	9 (56.3)	5 (83.3)	22 (64.7)	6 (28.6)	4 (28.6)	6 (20.0)	55 (44.4)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	2 (66.7)	7 (43.8)	5 (83.3)	19 (55.9)	4 (19.0)	1 (7.1)	6 (20.0)	44 (35.5)
Withdrawal of consent from study	1 (33.3)	2 (12.5)	0 (0.0)	3 (8.8)	2 (9.5)	3 (21.4)	0 (0.0)	11 (8.9)

BID = twice a day; mono = sotorasib monotherapy; N = Number of enrolled subjects, n = Number of subjects with observed data; SCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; QD = once daily

Phase 1 data cutoff date of 06 July 2020

Percentages based on number of subjects enrolled.

Number of subjects screen-failed in phase 1: 38

[a] Four subjects enrolled in sotorasib phase 1 NSCLC 1L 960 mg QD fasted cohort were later identified by site investigators to have had prior treatments in metastatic setting or in non-metastatic setting with an administration completed within 6 months prior to study enrollment.

Source: Study [redacted] Phase 1 CSR Table 14j-1.1

3.1.3 Baseline Demographics and Characteristics

3.1.3.1 Phase 2

The baseline demographics for the phase 2 NSCLC group are provided in Table 6. Half of the subjects enrolled in the study were women (50.0%) and most were white (81.7%). The median age was 63.5 years (range: 37 to 80 years). Baseline disease characteristics and prior treatments are provided in Table 7.

Most subjects in the phase 2 NSCLC group had nonsquamous NSCLC (99.2%) and stage IV disease at screening (96.0%). Subjects had a median of 2 prior lines of therapy. Of 126 subjects, 42.9%, 34.9%, 22.2%, and 0% had 1, 2, 3, $\geq$ 4 prior lines of anticancer therapies, respectively. Most subjects (89.7%) had received and progressed on platinum-based chemotherapy, 92.1% had received and progressed on immunotherapy, and 81.0% had received and progressed after having received both therapies. Consistent with real-world data described in Section 1.1, some subjects had co-mutations in *TP53* (10.3%) and *STK11* (5.6%). Less than 3% of subjects had other co-mutations; among them, no subjects had co-mutations in *ALK* or *ROS*. The identification of co-mutations was performed locally and was reported as entered by the study centers on the case report form Most subjects (92.9%) were current or former smokers. As required by the enrollment criteria, all subjects in the phase 2 NSCLC group had ECOG performance status of 0 or 1.

Overall, 96.8% of subjects had metastatic disease. Subjects with active brain metastases were not eligible for this study, but subjects with treated and stable brain metastases were eligible to enroll. This is due to having no safety and efficacy data in this population and in keeping with the standard of treating active brain metastases with surgery or radiation before initiating pharmacotherapy.

Table 6. Baseline Demographics (Phase 2 Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Sex - n (%)	
Men	63 (50.0)
Women	63 (50.0)
Ethnicity - n (%)	
Hispanic or Latino	2 (1.6)
Not Hispanic or Latino	116 (92.1)
Missing	8 (6.3)
Race - n (%)	
American Indian or Alaska Native	0 (0.0)
Asian	19 (15.1)
Black or African American	2 (1.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)
White	103 (81.7)
Multiple	0 (0.0)
Other	2 (1.6)
Age (years)	
n	126
Mean	62.9
SD	9.3
Median	63.5
Q1, Q3	56.0, 70.0
Min, Max	37, 80
Age group – n (%)	
18 to 64 years	67 (53.2)
65 to 74 years	49 (38.9)
75 to 84 years	10 (7.9)
≥ 85 years	0 (0.0)

N = Number of subjects in the analysis set; n = Number of subjects in the corresponding category; NSCLC = non-small cell lung cancer; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.
Phase 2 data cutoff date of 01 September 2020.
Source: Study [redacted] Phase 2 CSR Table 14b-2.1

Table 7. Baseline Characteristics (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
ECOG status at baseline[a] – n (%)	
0	38 (30.2)
1	88 (69.8)
2	0 (0.0)
Weight (kg)	
n	126
Mean	71.08
SD	17.14
Median	70.65
Q1, Q3	57.70, 83.00
Min, max	36.8, 122.7
Height (cm)	
n	123
Mean	167.83
SD	9.20
Median	168.80
Q1, Q3	161.00, 175.00
Min, Max	146.0, 188.0
Prior line of anticancer therapy – n (%)	
0	0 (0.0)
1	54 (42.9)
2	44 (34.9)
3	28 (22.2)
≥ 4	0 (0.0)
Median (number of prior lines)	2

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Table 7. Baseline Characteristics (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Type of prior anticancer therapy[b] - n (%)	
Chemotherapy	115 (91.3)
Platinum-base chemotherapy	113 (89.7)
Immunotherapy	116 (92.1)
Checkpoint inhibitor	116 (92.1)
Anti PD-1 or anti PD-L1	115 (91.3)
Platinum-base chemotherapy and anti PD-1 or anti PD-L1[c]	102 (81.0)
Hormonal therapy	0 (0.0)
Targeted biologics	30 (23.8)
Anti-VEGF biological therapy	25 (19.8)
Targeted small molecules	9 (7.1)
Other	1 (0.8)
Histopathology type - n (%)	
Squamous	1 (0.8)
Nonsquamous	125 (99.2)
Mutations[c] - n (%)	
ATM	1 (0.8)
BRAF	1 (0.8)
CTNNB1	1 (0.8)
EGFR	3 (2.4)
FBXW7	1 (0.8)
GNAS	2 (1.6)
KEAP1	1 (0.8)
KIT	1 (0.8)
KRAS	126 (100.0)
MET	2 (1.6)
MYC	1 (0.8)
PIK3CA	2 (1.6)
RB1	1 (0.8)
SMARCA4	1 (0.8)
SMARCB1	1 (0.8)
STK11	7 (5.6)
TP53	13 (10.3)

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Table 7. Baseline Characteristics (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Metastatic - n (%)	
Yes	122 (96.8)
No	4 (3.2)
Liver metastasis- n (%)	
Yes	26 (20.6)
No	100 (79.4)
Brain metastasis- n (%)	
Yes	26 (20.6)
No	100 (79.4)
Smoking history- n (%)	
Never	6 (4.8)
Current	15 (11.9)
Former	102 (81.0)
Missing	3 (2.4)
Region- n (%)	
North America	79 (62.7)
Europe	30 (23.8)
Asia	12 (9.5)
Rest of the world	5 (4.0)
Best response to last prior therapy[d] - n (%)	
Complete response	1 (0.8)
Partial response	12 (9.5)
Stable disease	33 (26.2)
Progressive disease	48 (38.1)
Unevaluable	1 (0.8)
Unknown / not applicable / not done	27 (21.4)
Missing	4 (3.2)
Disease stage at screening - n (%)	
Stage I	0 (0.0)
Stage II	0 (0.0)
Stage III	5 (4.0)
Stage IV	121 (96.0)

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CTNNB1 = catenin beta 1; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FBXW7 = F-box/WD repeat-containing protein 7; GNAS = guanine nucleotide binding protein, alpha stimulating activity polypeptide; KEAP1 = Kelch-like ECH-associated protein 1; KRAS = Kirsten rat sarcoma viral oncogene homolog; N = Number of subjects in the analysis set; n = Number of subjects in the corresponding category; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; PI3KCA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD-L1 = programmed death ligand 1; Q1 = first quartile; Q3 = third quartile; QD = once daily; RB1 = retinoblastoma 1; SD = standard deviation; STK11 = serine/threonine kinase 11; TP53 = tumor protein p53

Phase 2 data cutoff date of 01 September 2020.
[a] Baseline ECOG is measured at cycle 1 day 1 pre-dose. Subject may satisfy ECOG enrollment eligibility during screening period, but subsequently had baseline ECOG = 2 prior to first dose. ECOG 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 = Dead.
[b] Each subject may have multiple prior therapies. Types of prior anticancer therapies were adjudicated and include therapies given in any treatment setting.
[c] Based on available data at local site as entered on case report form.
[d] Subjects with no prior lines of therapy were excluded. Number of prior lines and best response on prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.
Source: *Study [redacted] Phase 2 CSR Table 14n-2.2*

A summary of relevant baseline medical and surgical histories for the NSCLC full analysis set is provided in Study [redacted] Phase 2 CSR Table 14n-2.3.

3.1.3.2 Phase 1

Table 8 provides a summary of subject baseline demographics for 124 subjects in phase 1 NSCLC group. Baseline demographic characteristics were generally similar between the cohorts. Most subjects enrolled in the study were white (81.5%) and women (62.9%). The median (range) age was 68.0 (49 to 86) years. Baseline disease characteristics and prior treatments for these subjects are provided in Table 9.

Most subjects in phase 1 NSCLC group (98.4%) were disease stage IV at screening and most subjects had an ECOG performance status of 0 or 1 (27 subjects, 21.8%; and 91 subjects, 73.4%; respectively); 6 subjects (4.8% had an ECOG performance status of 2). Among 124 subjects in phase 1 NSCLC group, the median number of prior lines of therapy was 2, with 23 subjects (18.5%) having received at least 4 prior lines of therapy. Overall, most subjects had received prior platinum-based chemotherapy (102 subjects, 82.3%), checkpoint inhibitor therapy (90 subjects, 72.6%) or had previously received both therapies (89 subjects, 71.8%). Most subjects (92.7%) were current or former smokers. Approximately one-fourth of subjects had metastases to the liver (25.0%) or brain (27.6%), and almost half (46.0%) had metastases to bone. Per protocol, all subjects (100%) had *KRAS p.G12C*-mutated NSCLC as assessed by molecular testing of tumor biopsy specimens.

Demographic and baseline characteristics for subjects in the previously treated 960 mg QD sotorasib monotherapy (fasted) dose cohort were generally consistent with the overall phase 1 NSCLC group.

Table 8. Baseline Demographics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Sex - n (%)								
Men	1 (33.3)	5 (31.3)	2 (33.3)	16 (47.1)	9 (42.9)	4 (28.6)	9 (30.0)	46 (37.1)
Women	2 (66.7)	11 (68.8)	4 (66.7)	18 (52.9)	12 (57.1)	10 (71.4)	21 (70.0)	78 (62.9)
Ethnicity - n (%)								
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (3.3)	2 (1.6)
Not Hispanic or Latino	3 (100.0)	14 (87.5)	6 (100.0)	33 (97.1)	19 (90.5)	13 (92.9)	28 (93.3)	116 (93.5)
Missing	0 (0.0)	2 (12.5)	0 (0.0)	1 (2.9)	1 (4.8)	1 (7.1)	1 (3.3)	6 (4.8)
Race - n (%)								
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	1 (6.3)	0 (0.0)	6 (17.6)	0 (0.0)	0 (0.0)	5 (16.7)	12 (9.7)
Black or African American	0 (0.0)	1 (6.3)	1 (16.7)	1 (2.9)	1 (4.8)	1 (7.1)	1 (3.3)	6 (4.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	3 (100.0)	14 (87.5)	5 (83.3)	26 (76.5)	18 (85.7)	12 (85.7)	23 (76.7)	101 (81.5)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	2 (9.5)	1 (7.1)	1 (3.3)	5 (4.0)

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Table 8. Baseline Demographics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Age (years)								
n	3	16	6	34	21	14	30	124
Mean	65.0	65.8	67.0	66.2	68.0	70.1	69.0	67.6
SD	8.7	7.0	7.3	8.6	7.6	7.9	8.1	7.9
Median	61.0	67.5	68.0	68.0	69.0	69.5	70.5	68.0
Q1, Q3	59.0, 75.0	60.0, 69.0	63.0, 72.0	57.0, 73.0	64.0, 73.0	65.0, 77.0	64.0, 74.0	61.0, 73.0
Min, max	59, 75	55, 78	55, 76	49, 83	53, 80	58, 86	54, 83	49, 86
Age group – n (%)								
18 to 64 years	2 (66.7)	7 (43.8)	2 (33.3)	11 (32.4)	6 (28.6)	3 (21.4)	9 (30.0)	40 (32.3)
65 to 74 years	0 (0.0)	6 (37.5)	3 (50.0)	19 (55.9)	11 (52.4)	7 (50.0)	14 (46.7)	60 (48.4)
75 to 84 years	1 (33.3)	3 (18.8)	1 (16.7)	4 (11.8)	4 (19.0)	3 (21.4)	7 (23.3)	23 (18.5)
≥ 85 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (0.8)

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BID = twice a day; mono = sotorasib monotherapy; N = Number of subjects in the analysis set; n = Number of subjects in the corresponding category; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.
Phase 1 data cutoff date of 06 July 2020.
Source: *Study [redacted] Phase 1 CSR Table 14j-2.1*

Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
ECOG status at baseline[a] – n (%)								
0	0 (0.0)	4 (25.0)	0 (0.0)	8 (23.5)	3 (14.3)	3 (21.4)	9 (30.0)	27 (21.8)
1	2 (66.7)	12 (75.0)	5 (83.3)	26 (76.5)	16 (76.2)	11 (78.6)	19 (63.3)	91 (73.4)
2	1 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	2 (9.5)	0 (0.0)	2 (6.7)	6 (4.8)
Weight (kg)								
n	3	16	6	34	21	14	30	124
Mean	70.43	65.87	62.43	70.01	66.26	71.25	66.63	67.81
SD	22.50	9.25	15.23	17.23	14.76	17.36	13.55	14.96
Median	58.20	68.45	58.73	69.15	62.90	73.95	67.19	66.70
Q1, Q3	56.70, 96.40	55.65, 72.30	56.70, 72.80	58.40, 80.40	54.90, 80.70	58.40, 85.40	55.80, 73.00	56.40, 77.65
Min, max	56.7, 96.4	52.3, 79.2	41.6, 86.0	38.4, 109.5	45.8, 100.7	45.6, 103.6	44.6, 94.6	38.4, 109.5

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Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Height (cm)								
N	3	16	6	34	20	14	28	121
Mean	161.87	164.32	166.32	166.75	165.62	168.62	160.90	164.96
SD	16.84	5.74	8.00	8.93	8.15	10.21	9.73	9.13
Median	158.00	163.50	164.60	165.10	165.55	167.69	161.30	165.10
Q1, Q3	147.30, 180.30	160.00, 168.80	161.00, 167.50	161.30, 170.50	157.85, 173.00	164.00, 175.00	153.65, 167.80	158.20, 170.30
Min, max	147.3, 180.3	157.0, 174.0	159.0, 181.2	151.0, 183.5	151.0, 178.5	149.9, 190.5	144.5, 180.3	144.5, 190.5
Prior line of anticancer therapy – n (%)								
0	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	26 (86.7)	28 (22.6)
1	1 (33.3)	0 (0.0)	1 (16.7)	11 (32.4)	13 (61.9)	6 (42.9)	2 (6.7)	34 (27.4)
2	0 (0.0)	3 (18.8)	1 (16.7)	10 (29.4)	6 (28.6)	4 (28.6)	1 (3.3)	25 (20.2)
3	1 (33.3)	2 (12.5)	2 (33.3)	5 (14.7)	2 (9.5)	2 (14.3)	0 (0.0)	14 (11.3)
≥ 4	1 (33.3)	11 (68.8)	2 (33.3)	6 (17.6)	0 (0.0)	2 (14.3)	1 (3.3)	23 (18.5)
Median (number of prior lines)	3	4	3	2	1	2	0	2

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Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Type of prior anticancer therapy[b]								
Chemotherapy	3 (100.0)	16 (100.0)	6 (100.0)	34 (100.0)	20 (95.2)	14 (100.0)	9 (30.0)	102 (82.3)
Immunotherapy	3 (100.0)	16 (100.0)	6 (100.0)	28 (82.4)	20 (95.2)	13 (92.9)	4 (13.3)	90 (72.6)
Hormonal therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Targeted biologics	1 (33.3)	4 (25.0)	1 (16.7)	6 (17.6)	3 (14.3)	3 (21.4)	1 (3.3)	19 (15.3)
Targeted small molecules	1 (33.3)	5 (31.3)	1 (16.7)	9 (26.5)	1 (4.8)	0 (0.0)	0 (0.0)	17 (13.7)
Chemo-embolization	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Radiosensitizer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	1 (0.8)
Not applicable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (70.0)	21 (16.9)
Other	0 (0.0)	1 (6.3)	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.4)
Disease stage at screening - n (%)								
Stage I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stage III	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.3)	2 (1.6)
Stage IV	3 (100.0)	16 (100.0)	6 (100.0)	33 (97.1)	21 (100.0)	14 (100.0)	29 (96.7)	122 (98.4)

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Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Selected prior therapy regimen/agent[b] - n (%)								
Anti PD-1 or anti PD-L1	3 (100.0)	16 (100.0)	6 (100.0)	28 (82.4)	20 (95.2)	13 (92.9)	4 (13.3)	90 (72.6)
Platinum-base chemotherapy	3 (100.0)	16 (100.0)	6 (100.0)	34 (100.0)	20 (95.2)	14 (100.0)	9 (30.0)	102 (82.3)
Platinum-base chemotherapy and anti PD-1 or anti PD-L1[c]	3 (100.0)	16 (100.0)	6 (100.0)	28 (82.4)	19 (90.5)	13 (92.9)	4 (13.3)	89 (71.8)
Anti-VEGF biological therapy	1 (33.3)	5 (31.3)	1 (16.7)	7 (20.6)	2 (9.5)	3 (21.4)	1 (3.3)	20 (16.1)
Fluoropyrimidine	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Bevacizumab	1 (33.3)	2 (12.5)	1 (16.7)	4 (11.8)	0 (0.0)	3 (21.4)	1 (3.3)	12 (9.7)
Checkpoint inhibitor	3 (100.0)	16 (100.0)	6 (100.0)	28 (82.4)	20 (95.2)	13 (92.9)	4 (13.3)	90 (72.6)
Histopathology type								
Squamous	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	2 (9.5)	0 (0.0)	1 (3.3)	4 (3.2)
Nonsquamous	2 (66.7)	16 (100.0)	6 (100.0)	33 (97.1)	19 (90.5)	14 (100.0)	29 (96.7)	119 (96.0)

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Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Mutations[c]								
EGFR	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	2 (1.6)
ALK	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
BRAF	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (3.3)	2 (1.6)
STK11	0 (0.0)	3 (18.8)	0 (0.0)	3 (8.8)	1 (4.8)	2 (14.3)	6 (20.0)	15 (12.1)
TP53	2 (66.7)	2 (12.5)	1 (16.7)	2 (5.9)	4 (19.0)	0 (0.0)	8 (26.7)	19 (15.3)
ATM	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.8)	0 (0.0)	0 (0.0)	2 (6.7)	5 (4.0)
Metastatic								
Yes	3 (100.0)	16 (100.0)	6 (100.0)	34 (100.0)	20 (95.2)	14 (100.0)	28 (93.3)	121 (97.6)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	2 (6.7)	3 (2.4)
Liver metastasis								
Yes	0 (0.0)	6 (37.5)	1 (16.7)	8 (23.5)	5 (23.8)	4 (28.6)	7 (23.3)	31 (25.0)
No	3 (100.0)	10 (62.5)	5 (83.3)	26 (76.5)	16 (76.2)	10 (71.4)	23 (76.7)	93 (75.0)

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Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Brain metastasis								
Yes	0 (0.0)	5 (31.3)	0 (0.0)	12 (35.3)	8 (38.1)	2 (14.3)	7 (23.3)	34 (27.4)
No	3 (100.0)	11 (68.8)	6 (100.0)	22 (64.7)	13 (61.9)	12 (85.7)	23 (76.7)	90 (72.6)
Smoking history								
Never	0 (0.0)	1 (6.3)	1 (16.7)	4 (11.8)	0 (0.0)	1 (7.1)	2 (6.7)	9 (7.3)
Current	1 (33.3)	2 (12.5)	0 (0.0)	1 (2.9)	2 (9.5)	2 (14.3)	2 (6.7)	10 (8.1)
Former	2 (66.7)	13 (81.3)	5 (83.3)	29 (85.3)	19 (90.5)	11 (78.6)	26 (86.7)	105 (84.7)
Region								
North America	3 (100.0)	14 (87.5)	5 (83.3)	29 (85.3)	19 (90.5)	12 (85.7)	28 (93.3)	110 (88.7)
Europe	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Asia	0 (0.0)	1 (6.3)	0 (0.0)	4 (11.8)	0 (0.0)	0 (0.0)	1 (3.3)	6 (4.8)
Rest of the world	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	2 (9.5)	2 (14.3)	1 (3.3)	6 (4.8)

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Table 9. Baseline Characteristics
(Phase 1 NSCLC Monotherapy in Safety Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	Phase 1 NSCLC 960 mg QD Fasted (N = 34)	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)	Phase 1 NSCLC Mono Total (N = 124)
Best response to last prior therapy[d]								
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	0 (0.0)	1 (6.3)	0 (0.0)	1 (2.9)	3 (14.3)	1 (7.1)	1 (3.3)	7 (5.6)
Stable disease	0 (0.0)	3 (18.8)	1 (16.7)	7 (20.6)	5 (23.8)	4 (28.6)	1 (3.3)	21 (16.9)
Progressive disease	0 (0.0)	7 (43.8)	3 (50.0)	19 (55.9)	6 (28.6)	5 (35.7)	2 (6.7)	42 (33.9)
Unevaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown/not applicable/not done	3 (100.0)	3 (18.8)	2 (33.3)	5 (14.7)	6 (28.6)	3 (21.4)	0 (0.0)	22 (17.7)
Missing	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	1 (4.8)	1 (7.1)	0 (0.0)	4 (3.2)

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BID = twice a day; mono = sotorasib monotherapy; ECOG = Eastern Cooperative Oncology Group; N = Number of subjects in the analysis set; n = Number of subjects in the corresponding category; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.

Phase 1 data cutoff date of 06 July 2020. Phase 2 data cutoff date of 01 September 2020.

[a] Baseline ECOG is measured at C1D1 pre-dose. Subject may satisfy ECOG enrollment eligibility during screening period, but subsequently had baseline ECOG = 2 prior to first dose. ECOG 0 = Fullyactive, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 = Dead.

[b] Each subject may have multiple prior therapies. Types of prior anticancer therapies were adjudicated and include therapies given in any treatment setting. Four subjects enrolled in AMG 510 960 mg QD 1L NSCLC fasted cohort were later identified by site investigators to have had prior treatments in metastatic setting or in non-metastatic setting with an administration completed within 6 months prior to study enrollment.

[c] Based on available data at local site as entered on case report form.

[d] Subjects with 0 prior line of therapy are excluded. Number of prior lines and best response on prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.

Source: Study [redacted] Phase 1 CSR Table 14j-2.2

3.2 Comparison of Efficacy Results of All Studies

The tumor response was evaluated by contrast-enhanced MRI/CT according to RECIST 1.1 by BICR and by the local investigator. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4 weeks after the first documentation of response and could have been delayed until the next scheduled scan to avoid unnecessary procedures.

3.2.1 Phase 2: Primary Efficacy Endpoint

Forty-six subjects in the full analysis set of phase 2 NSCLC group achieved a partial response or complete response as assessed per RECIST 1.1 by the BICR, for an ORR of 37.4% (95% CI: 28.84, 46.58) (Table 10 and Figure 1). The lower bound of the 95% CI excluded the prespecified benchmark ORR from the [redacted] study of 23% (95% CI: 20, 26) (Cyramza Prescribing Information, 2020). Of the 46 responders, 2 subjects (1.6%) achieved complete response and 44 subjects (35.8%) achieved partial response (Table 10).

Per the local investigator assessment, 126 subjects had ≥ 1 measurable assessment at baseline (investigator efficacy analysis set), as opposed to 123 subjects per BICR assessment. Thirty-eight subjects in the investigator efficacy analysis set of phase 2 NSCLC group had an objective response as assessed by the investigator, for an ORR of 30.2% (95% CI: 22.31, 38.97) (Study [redacted] Phase 2 CSR Table 14n-4.1.3). Concordance in assessment by BICR and by the investigator was 82.9% for objective response (Study [redacted] Phase 2 CSR Table 14n-4.5.2).

Among the 99 subjects in the full analysis set who had prior treatment with both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1, 32 subjects achieved a partial or complete response, for an ORR of 32.3% (95% CI: 23.3, 42.5) (Table 19).

Table 10. Summary of Objective Response (Assessed by BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Best objective response - n (%)	
Complete response (CR)	2 (1.6)
Partial response (PR)	44 (35.8)
Stable disease	53 (43.1)
Progressive disease (PD)	20 (16.3)
Not evaluable (NE)	2 (1.6)
Not done	2 (1.6)
Objective response rate (ORR)	
Number of overall responders - N1 (%)	46 (37.4)
95% CI[a]	(28.84, 46.58)

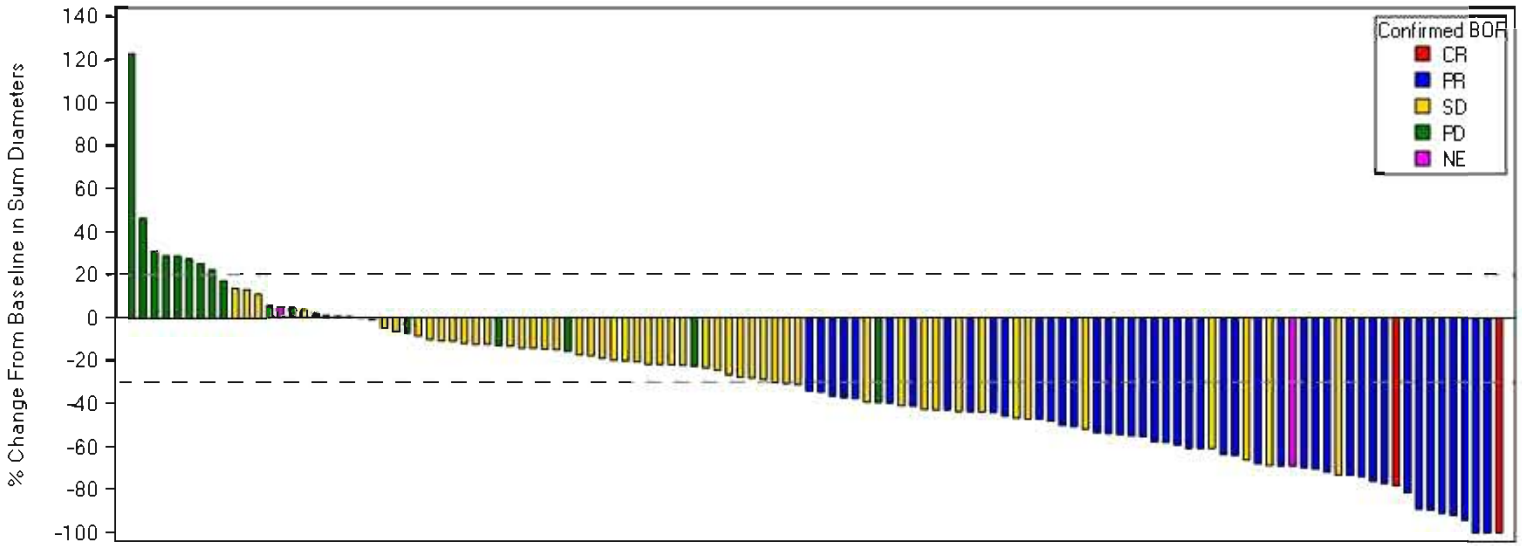
BICR = blinded independent central review; N = Number of subjects in the analysis set; n = Number of subjects with observed data; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors

Phase 2 data cutoff date of 01 September 2020.

[a] Exact 95% confidence interval was calculated using the Clopper-Pearson method.

Source: Study [redacted] Phase 2 CSR Table 14n-4.1.1

Figure 1. Waterfall Plot of Best Tumor Shrinkage by Central Review (Phase 2 NSCLC Full Analysis Set)



Phase 2 data cut-off date 01SEP2020
Percent change from baseline in sum of diameters only considers tumor assessments prior to and include the 1st assessment where timepoint response is progressive disease, and prior to start of next anti-cancer therapy
Three subjects without baseline target lesions and 3 subjects without post-baseline percent changes are not shown
One CR whose reduction <100% is because target lesions are in lymph nodes

[redacted]

BOR = best overall response, CR = complete response, PD = progressive disease, PR = partial response, NE = not evaluable, NSCLC = non-small cell lung cancer, SD = stable disease

Percent change from baseline in sum of diameters only considers tumor assessments before and including the first assessment where time point response is progressive disease Three subjects without baseline target lesions and 3 subjects without post-baseline percent changes are not shown

One CR whose reduction <100% is because target lesions are in lymph nodes

Source Figure 14n-4 1 401 of Study [redacted] *Phase 2*

3.2.2 Phase 2: Secondary Efficacy Endpoints

3.2.2.1 Duration of Response

The DOR (calculated only for those subjects with a confirmed complete response or partial response per RECIST 1.1) was defined as the time from first objective response to disease progression as assessed by BICR per RECIST 1.1 or death due to any cause, whichever was earlier. Responses were censored at the last assessment not confirming disease progression.

As of the data cutoff date, the Kaplan-Meier estimate of median (range) follow-up time for DOR was 6.9 (1.3, 8.4+) months. Among the 46 objective responders in the full analysis set of the phase 2 NSCLC group, 32 subjects (69.6%) were censored; of those, 28 subjects (60.9%) were on study without disease progression (Study [redacted] Phase 2 CSR Table 14n-4.1.1). The Kaplan-Meier estimate of median (95% CI) DOR for the 46 objective responders was 8.4 (6.9, 8.4) months (Table 11, Figure 2). As of the data cutoff date, 76.1% of subjects had DOR $\geq$ 3 months and 50.0% of subjects had DOR $\geq$ 6 months.

Subject-level data for DOR for the 46 responders are shown in the swimmer plot in Figure 3. Among the 46 responders as assessed by BICR, 24 subjects (52.2%) were still on treatment with ongoing responses as of the data cutoff date and 41 subjects (89.1%) had at least 6 months of follow-up post-onset of responses (Listing 16n-2.6.401 of Study [redacted] Phase 2 CSR). Of the remaining 5 responders who had less than 6 months of follow-up after response, 1 responder had 5.9 months of follow-up and 4 responders were late responders who achieved the first onset of responses at 4.2 to 6.1 months, and the follow-up time since onset of response was between 3.2 to 5.1 months (Listing 16n-2.6.401 of Study [redacted] Phase 2 CSR).

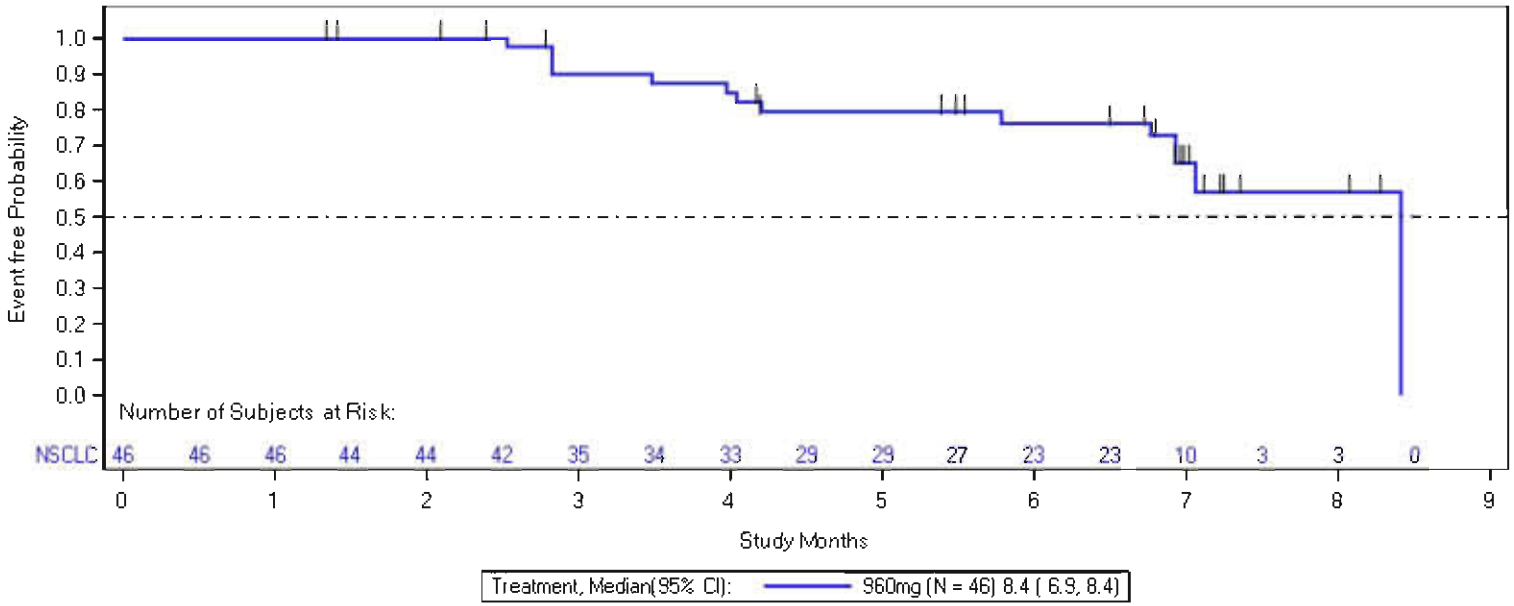
For the 32 subjects in the full analysis set who had prior treatment with both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 and achieved a partial or complete response, the Kaplan-Meier estimate of median (95% CI) DOR was not estimable (6.9, not estimable) months (Table 14n-4.4.1).

**Table 11. Duration of Response
(Response Assessed By BICR per RECIST 1.1 Criteria)
(Phase 2 NSCLC in Full Analysis Set)**

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Duration of objective response (DOR)[a]	
Observed duration ≥ 3 months - n (%)	35 (76.1)
Observed duration ≥ 6 months - n (%)	23 (50.0)
Observed duration ≥ 9 months - n (%)	0 (0.0)
Observed duration ≥ 12 months - n (%)	0 (0.0)
Duration of response (KM) (months)	
25th percentile (95% CI)	6.8 (3.5, 7.1)
Median (95% CI)	8.4 (6.9, 8.4)
75th percentile (95% CI)	8.4 (NE, NE)
Min, Max (+ for censored)	1.3+, 8.4
Kaplan-Meier estimate (95% CI)[b]	
At 3 months	89.9 (75.3, 96.1)
At 6 months	76.2 (59.1, 86.9)
At 9 months	0.0 (NE, NE)
At 12 months	0.0 (NE, NE)
Follow-up time for DOR[c] (KM) (months)	
25th percentile (95% CI)	5.5 (2.8, 6.7)
Median (95% CI)	6.9 (5.6, 7.0)
75th percentile (95% CI)	7.1 (7.0, 8.1)
Min, Max (+ for censored)	1.3, 8.4+

Phase 2 data cutoff date 01 September 2020.
BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; N = Number of subjects in the analysis set; n = Number of subjects with observed data; KM = Kaplan-Meier; N = Number of subjects in the analysis set. N = Number of subjects with observed data; NE = not estimable; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
; Months are derived as days x (12/365.25).
[a] Duration of response is calculated among confirmed responders N1.
[b] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
[c] Follow-up time is measured by reversing the status indicator for censored and events.
Source: Study [redacted] Phase 2 CSR Table 14n-4.1.1

**Figure 2. Kaplan-Meier Plot of Duration of Response
(Response Assessed By BICR per RECIST 1.1 Criteria)
(Phase 2 NSCLC Responders in Full Analysis Set)**



Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
Censor indicated by vertical bar |
NE = Not Estimable.
Radiological Progression or Death (whichever occurs earlier after confirmed CR/PR) is an event.

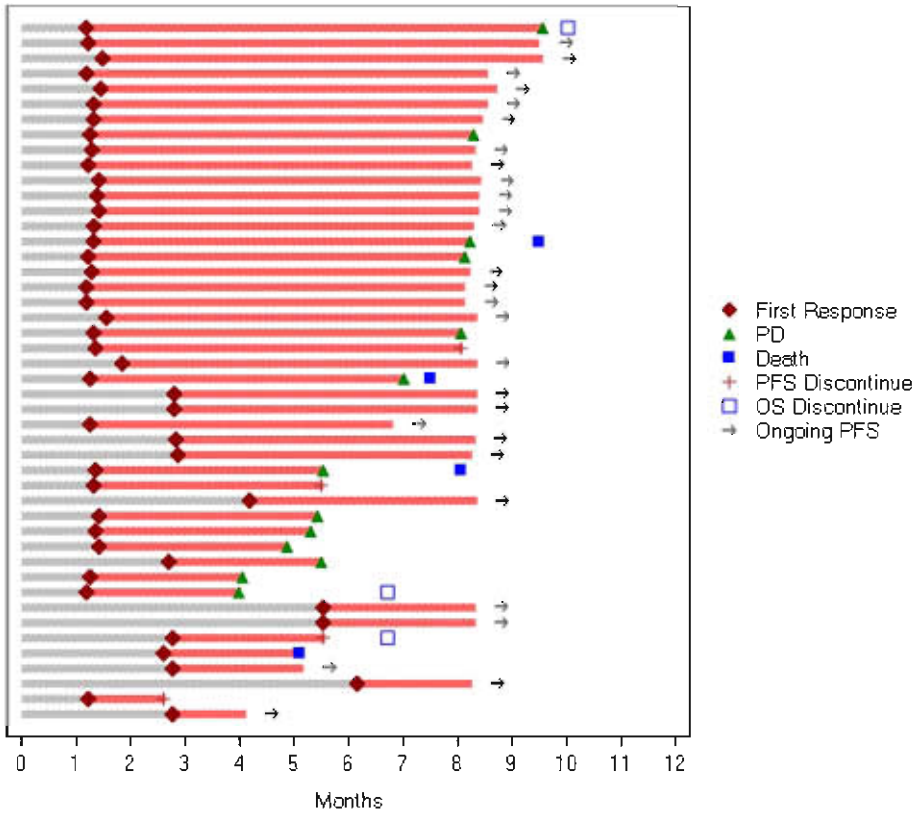
[redacted]

BICR = blinded independent central review; CI = confidence interval; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors

Phase 2 data cutoff date of 01 September 2020. Censor indicated by vertical bar. Radiological progression or death (whichever occurs earlier after confirmed partial response or confirmed complete response) is an event.

Source: Study [redacted] Phase 2 CSR Figure 14n-4.1.1

**Figure 3. Swimmer Plot of Duration of Response
(Response Assessed By BICR per RECIST 1.1 Criteria)
(Phase 2 NSCLC Responders in Full Analysis Set)**



Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
'PFS Discontinue' indicates PFS censor due to no post-baseline assessment, withdrew consent, started of new anti-cancer therapy, missed two or more consecutive tumor assessments, off study due to sponsor decision, or lost to follow-up.
'OS Discontinue' indicate OS censor due to withdrew consent, completed study, off study due to sponsor decision, or lost to follow-up.

[redacted]

BICR = blinded independent central review; CI = confidence interval; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PFS = progression-free survival; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
The grey bar represents the time to first response (complete response or partial response) among confirmed responders; the pink bar represents the duration of response.
"PFS Discontinue" indicates PFS censor due to no post-baseline assessment, consent withdrawal, start of new anticancer therapy, or if a subject missed ≥ 2 consecutive tumor assessments, was removed from the study due to sponsor decision, or was lost to follow-up.
"OS Discontinue" indicates OS censor due to consent withdrawal, completed study, or if a subject was taken off study due to sponsor decision.
Source: Study [redacted] Phase 2 CSR Figure 14n-4.1.2

3.2.2.2 Disease Control Rate

The DCR (defined as the proportion of subjects whose best objective response was confirmed complete response, partial response, or stable disease ≥ 5 weeks per RECIST 1.1 criteria assessed by BICR) for subjects in phase 2 NSCLC group was 80.5% (95% CI: 72.37; 87.08) (Table 12). Of 123 subjects in the full analysis set of the phase 2 NSCLC group, 53 subjects (43.1%) had stable disease (Table 10).

Table 12. Disease Control Rate (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC Responders in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Disease control rate (DCR) - n (%)	99 (80.5)
95% CI[a]	(72.37, 87.08)

BICR = blinded independent central review; CI = confidence interval; N = Number of subjects in the analysis set; n = Number of subjects with observed data; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
[a] Exact 95% confidence interval was calculated using the Clopper-Pearson method
Source: Study [redacted] Phase 2 CSR Table 14n-4.1.1

3.2.2.3 Time to Response

Time to response was measured from the date of the first dose of sotorasib to the date of the first complete response or partial response observed; calculated only for subjects who achieved a best objective response of confirmed partial response or better per RECIST 1.1 criteria assessed by BICR.

Among the 46 responders in the full analysis set of the phase 2 NSCLC group, the median (range) time to response was 1.35 (1.2, 6.1) months, with 70% of responses occurring within the first 7 weeks (Table 13).

**Table 13. Time to Response
(Response Determined per RECIST 1.1 Criteria by BICR)
(Phase 2 NSCLC in Full Analysis Set)**

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Time to objective response (months)[a]	
Number of subjects with objective response	46
Mean (SD)	1.95 (1.23)
Median	1.35
Q1, Q3	1.25, 2.69
Min, max	1.2, 6.1

BICR = blinded independent central review; N = Number of subjects in the analysis set; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
[a] Time to response are calculated among confirmed responders N1.
Source: Study [redacted] Phase 2 CSR Table 14n-4.1.1

3.2.2.4 Progression-free Survival

Progression-free survival was measured from the date of the first dose of sotorasib to the date of disease progression (as determined per RECIST 1.1 criteria by BICR) or death due to any cause, whichever occurred first. Subjects who had no disease progression and did not die while on study were censored at the last disease assessment date.

The Kaplan-Meier estimate of median (range) follow-up time for PFS was 8.3 (0.3, 11.5+) months. As of the data cutoff date, the percentage of subjects in the full analysis set of the phase 2 NSCLC group with event of disease progression or death were 48.8% and 8.1%, respectively (Table 14). Of 123 subjects in the phase 2 NSCLC full analysis set, 53 subjects (43.1%) were censored and of those, 40 subjects (32.5%) were on study without disease progression as of the data cutoff date, 6 subjects (4.9%) started new anticancer therapy, 4 subjects (3.3%) missed more than 1 consecutive assessment, and 3 subjects (2.4%) withdrew consent.

The Kaplan-Meier estimate of median PFS in the phase 2 NSCLC group was 6.7 (95% CI: 4.9, 8.1) months (Table 12, Figure 4). The median PFS as assessed by the investigator (6.8; 95% CI: 5.5, 8.3) was generally consistent with that as assessed by BICR (Table 14n-4.2.3).

The Kaplan-Meier PFS probability estimates at 6, 9, and 12 months were 51.5% (95% CI: 41.9, 60.4), 36.2% (95% CI: 26.7, 45.8), 0.0 (NE, NE), respectively.

Concordance in assessment by BICR and by the investigator was 78.0% and 65.0% for progressive disease status and progressive disease status and timing, respectively (Study [redacted] Phase 2 CSR Table 14n-4.5.3).

Table 14. Summary of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Subject Status	
Events - n (%)	70 (56.9)
Progressive disease	60 (48.8)
Death due to any cause	10 (8.1)
Censored - n (%)	53 (43.1)
On study without disease progression	40 (32.5)
No evaluable post-baseline disease assessment	0 (0.0)
Missed more than 1 consecutive assessments	4 (3.3)
Started new anticancer therapy	6 (4.9)
Withdrew consent	3 (2.4)
Off study due to sponsor decision	0 (0.0)
Lost to follow-up	0 (0.0)

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Table 14. Summary of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Progression-free survival (KM) (months)	
25th percentile (95% CI)	2.8 (1.6, 3.9)
Median (95% CI)	6.7 (4.9, 8.1)
75th percentile (95% CI)	11.5 (9.6, 11.5)
Min, Max (+ for censored)	0.3+, 11.5
Kaplan-Meier estimate (95% CI)[a]	
At 3 months	67.5 (58.2, 75.2)
At 6 months	51.5 (41.9, 60.4)
At 9 months	36.2 (26.7, 45.8)
At 12 months	0.0 (NE, NE)
Follow-up time for PFS[b] (KM) (months)	
25th percentile (95% CI)	6.8 (5.4, 8.2)
Median (95% CI)	8.3 (8.2, 8.3)
75th percentile (95% CI)	8.4 (8.3, 9.5)
Min, Max (+ for censored)	0.3, 11.5+

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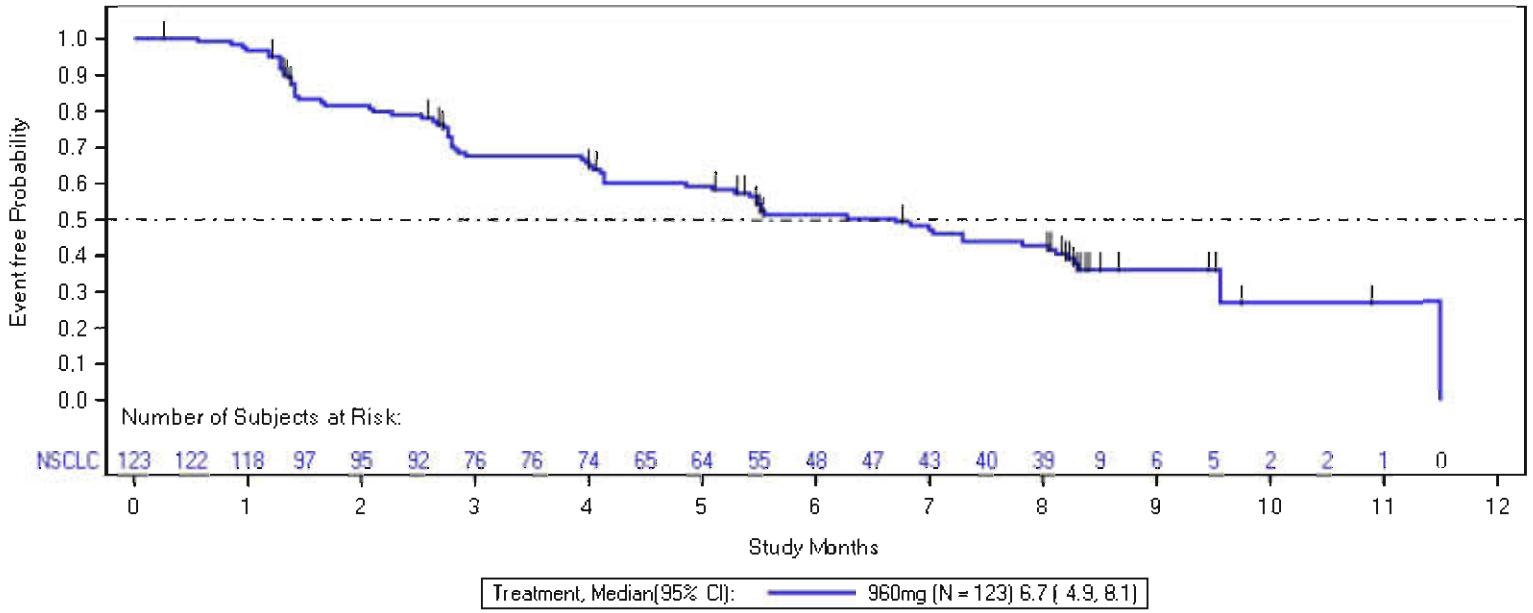
BICR = blinded independent central review; CI = confidence interval; KM = Kaplan-Meier; N = Number of subjects in the analysis set; NE = not evaluable; NSCLC = non-small cell lung cancer; PFS = progression-free survival; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors.
Phase 2 data cutoff date of 01 September 2020
[a] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
[b] Follow-up time is summarized by reversing the status indicator for censored and events.
Source: *Study [redacted] Phase 2 CSR Table 14n-4.2.1*

Figure 4. Kaplan-Meier Plot of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)



Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
Censor indicated by vertical bar |
NE = Not Estimable.
Radiological Progression or Death (whichever occurs earlier) is an event.

[redacted]

BICR = blinded independent central review; CI = confidence interval; NSCLC = non-small cell lung cancer; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
Censor indicated by vertical bar. Radiological progression or death (whichever occurs earlier) is an event.
Source: Study [redacted] Phase 2 CSR Figure 14n-4.2.1

3.2.2.5 Overall Survival

The median (range) follow-up time for OS was 9.3 (1.1+, 12.2) months. As of the data cutoff date, of 126 subjects in the phase 2 NSCLC safety analysis set, 48 subjects (38.1%) died (Table 15) and 78 subjects (61.9%) were censored. Of those 78 subjects, 69 subjects (54.8%) were alive at the last follow-up visit and 9 subjects (7.1%) withdrew consent.

The Kaplan-Meier estimate of median (95% CI) OS was 12.0 months (9.5, NE). The Kaplan-Meier estimates of survival were 89.5% at 3 months, 75.5% at 6 months, 63.4% at 9 months, and 51.6% at 12 months. A Kaplan-Meier plot for OS is shown in Figure 5.

Table 15. Summary of Overall Survival (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Subject Status	
Events - n (%)	48 (38.1)
Death due to any cause	48 (38.1)
Censored - n (%)	78 (61.9)
Alive at last follow-up	69 (54.8)
Lost to follow-up	0 (0.0)
Withdrew consent	9 (7.1)
Off study due to sponsor decision	0 (0.0)
Overall survival (KM) (months)	
25th percentile (95% CI)	6.0 (4.1, 7.9)
Median (95% CI)	12.0 (9.5, NE)
75th percentile (95% CI)	NE (12.0, NE)
Min, max (+ for censored)	1.1, 12.2+

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Footnotes defined on last page of table.

Table 15. Summary of Overall Survival (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Kaplan-Meier estimate (95% CI)[a]	
At 3 months	89.5 (82.7, 93.8)
At 6 months	75.5 (66.8, 82.2)
At 9 months	63.4 (53.8, 71.5)
At 12 months	51.6 (36.7, 64.5)
Follow-up time for OS[b] (KM) (months)	
25th percentile (95% CI)	8.5 (7.3, 8.8)
Median (95% CI)	9.3 (9.0, 9.5)
75th percentile (95% CI)	9.8 (9.6, 10.2)
Min, Max (+ for censored)	1.1+, 12.2

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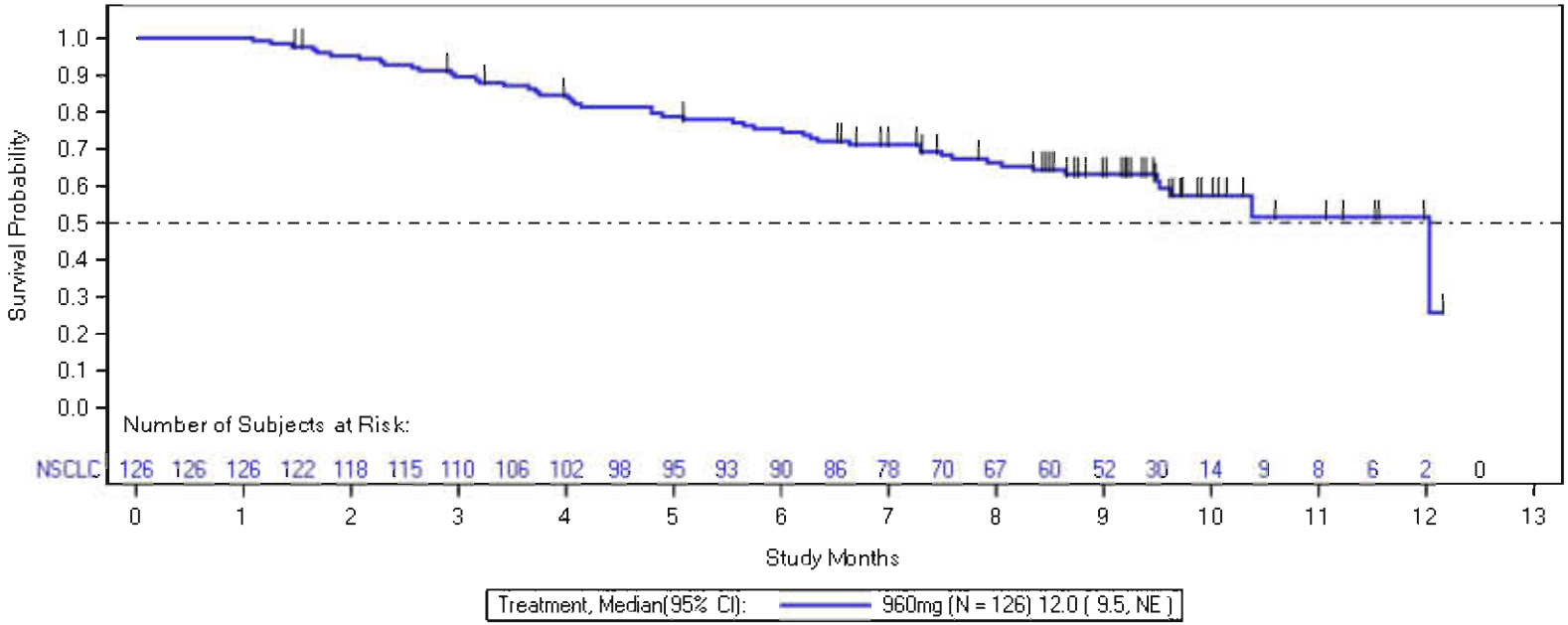
CI = confidence interval; KM = Kaplan-Meier; N = Number of subjects in the analysis set; NE = not evaluable; NSCLC = non-small cell lung cancer; OS = overall survival; QD = once daily.
Phase 2 data cutoff date of 01 September 2020
[a] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
[b] Follow-up time is summarized by reversing the status indicator for censored and events.
Survival status may include publicly available records (where permitted) searched by investigator after subject ended study.
Source: Study [redacted] Phase 2 CSR Table 14n-4.3.1

Figure 5. Kaplan-Meier Plot of Overall Survival (Phase 2 NSCLC in Safety Analysis Set)



Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
Censor indicated by vertical bar |
NE = Not Estimable.
Death is an event.

[redacted]

CI = confidence interval; NSCLC = non-small cell lung cancer
Phase 2 data cutoff date of 01 September 2020.
Censor indicated by vertical bar. Death is an event.
Source: Study [redacted] Phase 2 CSR Figure 14n-4.3.1

3.2.3 Phase 1: Efficacy Endpoints

The efficacy results for 34 subjects with previously treated NSCLC in the ORR analysis set of the phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort are presented below. Since the sotorasib dose used in this cohort was identical to the dose used in the phase-2 portion of the study, the efficacy data presented below are supportive of the phase 2 NSCLC efficacy data package. The results for efficacy endpoints for other dose cohorts in the phase 1 NSCLC group are provided in Table 16, Table 17, and Table 18 and are described in detail in Study [redacted] Phase 1.

Of 34 subjects with previously treated NSCLC in the ORR analysis set of the phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort, 16 subjects had a confirmed partial response, for an ORR of 47.1% (95% CI: 29.78, 64.87).

The Kaplan-Meier estimate of median (range) follow-up time for DOR was 9.0 (1.5, 15.0) months. The Kaplan-Meier estimate of median DOR was not reached (95% CI: 4.2, NE). Among the 16 responders, the DOR was at least 3 months in 12 subjects (75.0%), at least 6 months in 5 subjects (31.3%), at least 9 months in 4 subjects (25.0%), and 1 subject (6.3%) had a DOR of at least 12 months. The median (range) TTR was 1.41 (0.8, 8.3) months.

The Kaplan-Meier estimate of median (range) follow-up time for PFS was 11.1 (1.2+, 16.30) months. As of the data cutoff date, the percentage of subjects who had PFS events of disease progression or death were 50.0% and 11.8%, respectively (Table 17). Overall, 13 subjects (38.2%) in that dose cohort were censored and of those, 10 subjects (29.4%) were on study without disease progression as of the data cutoff date, 2 subjects (5.9%) had missed > 1 consecutive assessments, and 1 subject (2.9%) withdrew consent. The Kaplan-Meier estimate of median PFS was 5.3 (95% CI: 3.1, 8.1) months. The Kaplan-Meier PFS probability estimate (95% CI) was 42.9% (25.5, 59.2) at 6 months and 31.2% (15.6, 48.2) at 12 months.

As of the data cutoff date, Kaplan-Meier estimate of the median (range) follow-up time for OS was 12.2 (2.5+, 17.1) months (Table 18). As of the data cutoff date, of 34 subjects in the phase 1 NSCLC safety analysis set, 19 subjects (55.9%) died and 15 subjects (44.1%) were censored. Of those 15 subjects, 12 subjects (35.3%) were alive at the last follow-up visit and 3 subjects (8.8%) withdrew consent. The Kaplan-Meier estimate of median OS was 7.6 (95% CI: 6.3, NE) months. The

Kaplan-Meier estimate (95% CI) of survival was 72.2% (53.3, 84.4) at 6 months and 41.2% (23.8, 57.9) at 12 months.

Overall, these efficacy data are consistent with the phase 2 NSCLC efficacy results, showing that durable objective response was achieved in a large percentage of subjects with advanced KRAS p.G12C-mutated NSCLC treated with 960 mg QD sotorasib monotherapy.

Moreover, among 59 subjects treated with different doses of sotorasib monotherapy (180 mg to 960 mg QD [fasted]; phase 1 part 1a and part 2a) in the phase 1 ORR analysis set, 24 subjects had a confirmed objective response. Among these 24 responders, the DOR was at least 3 months in 19 subjects (79.2%), at least 6 months in 10 subjects (41.7%), at least 9 months in 7 subjects (29.2%), at least 12 months in 2 subjects (8.3%) (Table 16).

Table 16. Summary of Objective Response
(Response Assessed By BICR per RECIST 1.1 Criteria)
(Phase 1 NSCLC monotherapy in ORR Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 11)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 28)
Best overall response - n (%)							
Complete response (CR)							
Confirmed	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	1 (9.1)	[redacted]
Confirmed and unconfirmed awaiting confirmatory scan	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	1 (9.1)	
Partial response (PR)							
Confirmed	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	3 (14.3)	2 (18.2)	[redacted]
Confirmed and unconfirmed awaiting confirmatory scan	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	5 (23.8)	4 (36.4)	
Stable disease (SD)	2 (66.7)	10 (62.5)	3 (50.0)	**16 (47.1)**	12 (57.1)	6 (54.5)	[redacted]
Progressive disease (PD)	0 (0.0)	1 (6.3)	0 (0.0)	**2 (5.9)**	3 (14.3)	0 (0.0)	
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	
Not done	0 (0.0)	1 (6.3)	0 (0.0)	**0 (0.0)**	3 (14.3)	2 (18.2)	
Objective response rate (ORR)							
Confirmed - N1 (%)	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	3 (14.3)	3 (27.3)	[redacted]
95% CI[a]	(0.84, 90.57)	(7.27, 52.38)	(11.81, 88.19)	**(29.78, 64.87)**	(3.05, 36.34)	(6.02, 60.97)	[redacted]
Confirmed and unconfirmed awaiting confirmatory scan - n (%)	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	5 (23.8)	5 (45.5)	[redacted]
95% CI[a]	(0.84, 90.57)	(7.27, 52.38)	(11.81, 88.19)	**(29.78, 64.87)**	(8.22, 47.17)	(16.75, 76.62)	[redacted]

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Table 16. Summary of Objective Response (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 1 NSCLC monotherapy in ORR Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 11)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 28)
Disease control rate (DCR) - n (%)	3 (100.0)	14 (87.5)	6 (100.0)	**32 (94.1)**	15 (71.4)	9 (81.8)	
95% CI[a]	(29.24, 100.00)	(61.65, 98.45)	(54.07, 100.00)	**(80.32, 99.28)**	(47.82, 88.72)	(48.22, 97.72)	
Duration of objective response (DOR)[b]							
Observed duration ≥ 3 months - n (%)	1 (100.0)	4 (100.0)	2 (66.7)	**12 (75.0)**	0 (0.0)	1 (33.3)	
Observed duration ≥ 6 months - n (%)	1 (100.0)	2 (50.0)	2 (66.7)	**5 (31.3)**	0 (0.0)	0 (0.0)	
Observed duration ≥ 9 months - n (%)	1 (100.0)	1 (25.0)	1 (33.3)	**4 (25.0)**	0 (0.0)	0 (0.0)	
Observed duration ≥ 12 months - n (%)	0 (0.0)	1 (25.0)	0 (0.0)	**1 (6.3)**	0 (0.0)	0 (0.0)	
Duration of response (KM) (months)							
25th percentile (95% CI)	-	-	-	**4.7 (3.0, NE)**	-	-	
Median (95% CI)	-	-	-	**NE (4.2, NE)**	-	-	
75th percentile (95% CI)	-	-	-	**NE (5.1, NE)**	-	-	
Min, Max (+ for censored)	9.5, 9.5	3.1, 13.6	2.8, 10.9	**1.5+, 15.0+**	1.4+, 1.5+	1.4+, 4.9+	
Kaplan-Meier estimate (95% CI)[c]							
At 3 months	-	-	-	**92.3 (56.6, 98.9)**	-	-	
At 6 months	-	-	-	**53.7 (21.0, 78.1)**	-	-	
At 9 months	-	-	-	**53.7 (21.0, 78.1)**	-	-	
At 12 months	-	-	-	**53.7 (21.0, 78.1)**	-	-	
Follow-up time for DOR[d] (KM) (months)							
25th percentile (95% CI)	-	-	-	**4.1 (1.5, 9.0)**	-	-	
Median (95% CI)	-	-	-	**9.0 (4.1, 11.0)**	-	-	
75th percentile (95% CI)	-	-	-	**9.8 (9.0, 15.0)**	-	-	
Min, Max (+ for censored)	9.5+, 9.5+	3.1+, 13.6+	2.8+, 10.9+	**1.5, 15.0**	1.4, 1.5	1.4, 4.9	

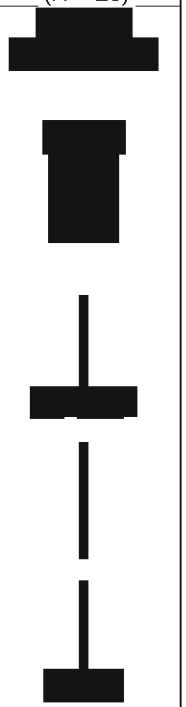

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Table 16. Summary of Objective Response
(Response Assessed By BICR per RECIST 1.1 Criteria)
(Phase 1 NSCLC monotherapy in ORR Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 11)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 28)
Duration of stable disease[b]							
Observed duration ≥ 3 months - n (%)	2 (100.0)	4 (40.0)	2 (66.7)	**7 (43.8)**	1 (8.3)	3 (50.0)	[redacted]
Observed duration ≥ 6 months - n (%)	1 (50.0)	0 (0.0)	1 (33.3)	**3 (18.8)**	0 (0.0)	0 (0.0)	
Observed duration ≥ 9 months - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (6.3)**	0 (0.0)	0 (0.0)	
Observed duration ≥ 12 months - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (6.3)**	0 (0.0)	0 (0.0)	
Duration of stable disease (KM) (months)							
25th percentile (95% CI)	-	2.6 (2.2, 3.6)	-	**2.6 (2.5, 2.8)**	2.8 (2.6, 3.2)	-	[redacted]
Median (95% CI)	-	3.6 (2.2, 4.0)	-	**2.9 (2.6, 5.2)**	3.2 (2.6, 3.2)	-	
75th percentile (95% CI)	-	4.0 (2.6, 4.8)	-	**5.3 (2.9, NE)**	3.2 (NE, NE)	-	
Min, Max (+ for censored)	4.4, 8.3	1.0+, 4.8	2.2, 7.8	**1.3+, 12.5+**	1.2+, 3.2	2.6+, 4.1+	
Follow-up time for duration of stable disease[d] (KM) (months)							
25th percentile (95% CI)	-	2.4 (1.0, NE)	-	**12.5 (1.3, 12.5)**	2.0 (1.2, 2.8)	-	[redacted]
Median (95% CI)	-	NE (1.0, NE)	-	**12.5 (NE, NE)**	2.8 (1.3, 3.0)	-	[redacted]
75th percentile (95% CI)	-	NE (NE, NE)	-	**12.5 (NE, NE)**	3.0 (2.8, NE)	-	
Min, Max (+ for censored)	4.4+, 8.3+	1.0, 4.8+	2.2+, 7.8+	**1.3, 12.5**	1.2, 3.2+	2.6, 4.1	
Time to objective response (months)[b]							
Number of subjects with objective response	1	4	3	**16**	3	3	[redacted]
Mean (SD)	1.25 (NE)	1.65 (0.59)	2.74 (1.46)	**2.24 (2.16)**	1.28 (0.11)	1.25 (0.07)	[redacted]
Median	1.25	1.36	2.79	**1.41**	1.22	1.25	
Min, max	1.2, 1.2	1.3, 2.5	1.2, 4.2	**0.8, 8.3**	1.2, 1.4	1.2, 1.3	

BID = twice a day; mono = sotorasib monotherapy; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.

Phase 1 data cutoff date of 06 July 2020. Months are derived as days x 12/365.25.Kaplan-Meier estimates were not provided if the analysis set had < 10 subjects. Only minimum and maximum values were provided.

[a] Exact 95% confidence interval was calculated using the Clopper-Pearson method.

[b] Time to response and duration of response are calculated among confirmed responders N1. Duration of stable disease is calculated among subjects with best overall response of stable disease.

[c] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.

[d] Follow-up time is measured by reversing the status indicator for censored and events.

Source: Study [redacted] Phase 1 CSR Table 14j-4.1.1

Table 17. Summary of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 1 NSCLC Monotherapy Full Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)
Subject status							
Events - n (%)	3 (100.0)	11 (68.8)	6 (100.0)	**21 (61.8)**	7 (33.3)	2 (14.3)	[redacted]
Progressive disease	3 (100.0)	8 (50.0)	3 (50.0)	**17 (50.0)**	6 (28.6)	1 (7.1)	[redacted]
Death due to any cause	0 (0.0)	3 (18.8)	3 (50.0)	**4 (11.8)**	1 (4.8)	1 (7.1)	[redacted]
Censored - n (%)	0 (0.0)	5 (31.3)	0 (0.0)	**13 (38.2)**	14 (66.7)	12 (85.7)	[redacted]
On study without disease progression	0 (0.0)	1 (6.3)	0 (0.0)	**10 (29.4)**	12 (57.1)	8 (57.1)	[redacted]
No evaluable post-baseline disease assessment	0 (0.0)	1 (6.3)	0 (0.0)	**0 (0.0)**	2 (9.5)	3 (21.4)	[redacted]
Missed more than 1 consecutive assessments	0 (0.0)	2 (12.5)	0 (0.0)	**2 (5.9)**	0 (0.0)	0 (0.0)	[redacted]
Started new anticancer therapy	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	[redacted]
Withdrew consent	0 (0.0)	1 (6.3)	0 (0.0)	**1 (2.9)**	0 (0.0)	1 (7.1)	[redacted]
Off study due to sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	[redacted]
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	[redacted]

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Table 17. Summary of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 1 NSCLC Monotherapy Full Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)
Progression-free Survival (KM) (months)							[redacted]
25th percentile (95% CI)	-	2.6 (1.2, 3.9)	-	**2.8 (2.5, 4.3)**	2.6 (1.1, 3.2)	NE (0.7, NE)	
Median (95% CI)	-	4.0 (2.6, 6.7)	-	**5.3 (3.1, 8.1)**	3.2 (2.6, 3.2)	NE (2.7, NE)	
75th percentile (95% CI)	-	6.7 (3.9, 14.9)	-	**NE (6.3, NE)**	3.2 (NE, NE)	NE (NE, NE)	
Min, max (+ for censored)	4.4, 10.7	0.0+, 14.9	2.2, 13.7	**1.2, 16.3+**	0.0+, 3.2	0.0+, 6.0+	
Kaplan-Meier estimate (95% CI)[a]							[redacted]
At 3 months	-	68.1 (35.4, 86.8)	-	**69.3 (50.4, 82.2)**	61.2 (31.0, 81.5)	79.5 (39.3, 94.5)	
At 6 months	-	25.5 (6.2, 51.2)	-	**42.9 (25.5, 59.2)**	0.0 (NE, NE)	79.5 (39.3, 94.5)	
At 9 months	-	17.0 (2.7, 41.9)	-	**31.2 (15.6, 48.2)**	0.0 (NE, NE)	NE (NE, NE)	
At 12 months	-	17.0 (2.7, 41.9)	-	**31.2 (15.6, 48.2)**	0.0 (NE, NE)	NE (NE, NE)	
Follow-up time for PFS[b] (KM) (months)							[redacted]
25th percentile (95% CI)	-	2.4 (0.0, NE)	-	**10.9 (3.0, 11.1)**	1.3 (0.0, 2.7)	1.3 (0.0, 2.7)	
Median (95% CI)	-	8.3 (2.4, NE)	-	**11.1 (5.6, 12.5)**	2.7 (1.3, 2.8)	2.7 (0.0, 4.1)	
75th percentile (95% CI)	-	NE (8.3, NE)	-	**12.5 (11.1, 16.3)**	2.8 (2.7, NE)	4.1 (2.7, 6.0)	
Min, max (+ for censored)	4.4+, 10.7+	0.0, 14.9+	2.2+, 13.7+	**1.2+, 16.3**	0.0, 3.2+	0.0, 6.0	

BID = twice a day; mono = sotorasib monotherapy; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.

Phase 1 data cutoff date of 06 July 2020.

Kaplan-Meier estimates was not provided if the analysis had < 10 subjects. Only minimum and maximum values were provided.

[a] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.

[b] Follow-up time is summarized by reversing the status indicator for censored and events.

Source: Study [redacted] Phase 1 CSR Table 14j-4.2.1

Table 18. Summary of Overall Survival
(Phase 1 – NSCLC Monotherapy Safety Analysis Set)

	NSCLC 180 mg QD Fasted (N = 3)	NSCLC 360 mg QD Fasted (N = 16)	NSCLC 720 mg QD Fasted (N = 6)	**NSCLC 960 mg QD Fasted (N = 34)**	NSCLC 480 mg BID Fed (N = 21)	NSCLC 960 mg QD Fed (N = 14)	NSCLC 1L 960 QD Fasted (N = 30)
Subject status							
Events - n (%)	2 (66.7)	7 (43.8)	5 (83.3)	**19 (55.9)**	4 (19.0)	1 (7.1)	[redacted]
Death due to any cause	2 (66.7)	7 (43.8)	5 (83.3)	**19 (55.9)**	4 (19.0)	1 (7.1)	
Censored - n (%)	1 (33.3)	9 (56.3)	1 (16.7)	**15 (44.1)**	17 (81.0)	13 (92.9)	
Alive at last follow-up	0 (0.0)	7 (43.8)	1 (16.7)	**12 (35.3)**	15 (71.4)	10 (71.4)	
Withdrew consent	1 (33.3)	2 (12.5)	0 (0.0)	**3 (8.8)**	2 (9.5)	3 (21.4)	
OS (KM) (months)							
25th percentile (95% CI)	-	4.4 (2.2, 8.2)	-	**5.2 (3.2, 7.1)**	4.1 (1.2, 6.7)	NE (0.7, NE)	[redacted]
Median (95% CI)	-	8.2 (4.1, NE)	-	**7.6 (6.3, NE)**	4.1 (4.1, 6.7)	NE (NE, NE)	
75th percentile (95% CI)	-	NE (8.2, NE)	-	**NE (8.1, NE)**	6.7 (4.1, 6.7)	NE (NE, NE)	
Min, max (+ for censored)	7.8, 18.6	0.5+, 18.2+	2.2, 15.1+	**2.5, 17.1+**	1.2, 6.7	0.4+, 6.6+	

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Table 18. Summary of Overall Survival
(Phase 1 – NSCLC Monotherapy Safety Analysis Set)

	NSCLC 180 mg QD Fasted (N = 3)	NSCLC 360 mg QD Fasted (N = 16)	NSCLC 720 mg QD Fasted (N = 6)	**NSCLC 960 mg QD Fasted (N = 34)**	NSCLC 480 mg BID Fed (N = 21)	NSCLC 960 mg QD Fed (N = 14)	NSCLC 1L 960 QD Fasted (N = 30)
Kaplan-Meier estimate (95% CI)[a]							
At 3 months	-	93.3 (61.3, 99.0)	-	**97.1 (80.9, 99.6)**	88.9 (61.8, 97.2)	92.3 (56.6, 98.9)	[redacted]
At 6 months	-	71.8 (41.1, 88.4)	-	**72.2 (53.3, 84.4)**	44.4 (1.1, 86.5)	92.3 (56.6, 98.9)	
At 9 months	-	47.9 (20.0, 71.4)	-	**41.2 (23.8, 57.9)**	0.0 (NE, NE)	NE (NE, NE)	
At 12 months	-	47.9 (20.0, 71.4)	-	**41.2 (23.8, 57.9)**	0.0 (NE, NE)	NE (NE, NE)	
Follow-up time for OS[b] (KM) (months)							
25th percentile (95% CI)	-	7.8 (0.5, 8.4)	-	**11.3 (6.0, 12.2)**	2.4 (1.4, 2.9)	1.6 (0.4, 4.1)	[redacted]
Median (95% CI)	-	8.4 (6.9, 9.8)	-	**12.2 (11.3, 13.5)**	3.1 (2.2, 3.5)	4.1 (1.3, 4.6)	
75th percentile (95% CI)	-	9.8 (8.2, 18.2)	-	**13.5 (12.2, 17.1)**	3.6 (3.2, NE)	4.6 (4.1, 6.6)	
Min, max (+ for censored)	7.8+, 18.6+	0.5, 18.2	2.2+, 15.1	**2.5+, 17.1**	1.2+, 6.7+	0.4, 6.6	[redacted]

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- = not calculated; BID = twice daily; CI = confidence interval; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; QD= once daily; OS = overall survival

Data cutoff date 06 July 2020

OS was defined as the interval from the start of treatment to death due to any cause (whichever came first).

KM estimates were not provided if the analysis set had fewer than 10 subjects. Only min, max were provided.

[a] 95% CIs were based on estimated variance for log-log transformation of the KM survival estimate.

[b] Follow-up time was summarized by reversing the status indicator for censored and events.

Source: Study [redacted] Phase 1 CSR Table 14j-4.3.1

3.3 Comparison of Results in Subpopulations (Phase 2)

Subgroup analyses for ORR included the following subgroups: age at baseline, prior lines of anticancer therapy, prior immunotherapy treatment, prior platinum-based chemotherapy, PD-L1 protein expression, ECOG status, race, sex, histopathology type, presence of metastases, presence of liver, brain, or bone metastasis, smoking history, and region (Table 19 and Figure 6). Except for the subgroup of prior platinum-based chemotherapy and presence of brain metastases, no notable treatment-by-subgroup effects were observed for any subgroups, showing that sotorasib treatment effect was generally consistent between the subgroups.

Subjects who had not received prior platinum-based chemotherapy had a higher ORR than the overall subject population and subjects who had previously received prior platinum-based therapy. Subjects with brain metastasis had lower ORR than the overall subject population. However, the subgroup analysis interpretation in a single-group study may be limited because of the small sample size of each subgroup.

Table 19. Subgroup Analysis of Objective Response (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123) Events[a]/Subjects (%) (95% CI)
Age at baseline	
< 65 years	21/65 (32.3) (21.2, 45.1)
≥ 65 years	25/58 (43.1) (30.2, 56.8)
Prior lines of anticancer therapy	
1	22/53 (41.5) (28.1, 55.9)
2	14/43 (32.6) (19.1, 48.5)
> 2	10/27 (37.0) (19.4, 57.6)
Prior anti PD-1 or anti PD-L1	
Yes	41/112 (36.6) (27.7, 46.2)
No	5/11 (45.5) (16.7, 76.6)
Prior platinum-based chemotherapy	
Yes	37/110 (33.6) (24.9, 43.3)
No	9/13 (69.2) (38.6, 90.9)
Prior platinum-based chemotherapy and prior anti PD-1 or anti PD-L1	
Yes	32/99 (32.3) (23.3, 42.5)
No	14/24 (58.3) (36.6, 77.9)
PD-L1 protein expression[b]	
< 1%	16/33 (48.5) (30.8, 66.5)
≥ 1% and < 50%	9/22 (40.9) (20.7, 63.6)
≥ 50%	9/34 (26.5) (12.9, 44.4)
ECOG status at baseline	
0	16/37 (43.2) (27.1, 60.5)
1	30/86 (34.9) (24.9, 45.9)
Race	
White	42/101 (41.6) (31.9, 51.8)
Black	0/2 (0.0) (0.0, 84.2)
Asian	3/18 (16.7) (3.6, 41.4)
Other	1/2 (50.0) (1.3, 98.7)
Sex	
Male	26/61 (42.6) (30.0, 55.9)
Female	20/62 (32.3) (20.9, 45.3)
Histopathology type	
Squamous	0/1 (0.0) (0.0, 97.5)
Nonsquamous	46/122 (37.7) (29.1, 46.9)
Metastatic	
Yes	44/119 (37.0) (28.3, 46.3)
No	2/4 (50.0) (6.8, 93.2)
Liver metastasis	
Yes	9/26 (34.6) (17.2, 55.7)
No	37/97 (38.1) (28.5, 48.6)
Brain metastasis	
Yes	4/26 (15.4) (4.4, 34.9)
No	42/97 (43.3) (33.3, 53.7)

Footnotes defined on last page of table.

Table 19. Subgroup Analysis of Objective Response (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123) Events[a]/Subjects (%) (95% CI)
Bone metastasis	
Yes	19/58 (32.8) (21.0, 46.3)
No	27/65 (41.5) (29.4, 54.4)
Smoking history	
Never	1/5 (20.0) (0.5, 71.6)
Current	4/15 (26.7) (7.8, 55.1)
Former	41/100 (41.0) (31.3, 51.3)
Region	
North America	35/79 (44.3) (33.1, 55.9)
Europe	8/28 (28.6) (13.2, 48.7)
Asia	1/11 (9.1) (0.2, 41.3)
Rest of the world	2/5 (40.0) (5.3, 85.3)

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BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; N = Number of subjects in the analysis set; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand 1; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors

Phase 2 data cutoff date of 01 September 2020.

Types of prior anticancer therapies were adjudicated and include therapies given in any treatment setting. Number of prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.

Subject(s) with unknown or missing subgroup value are not included.

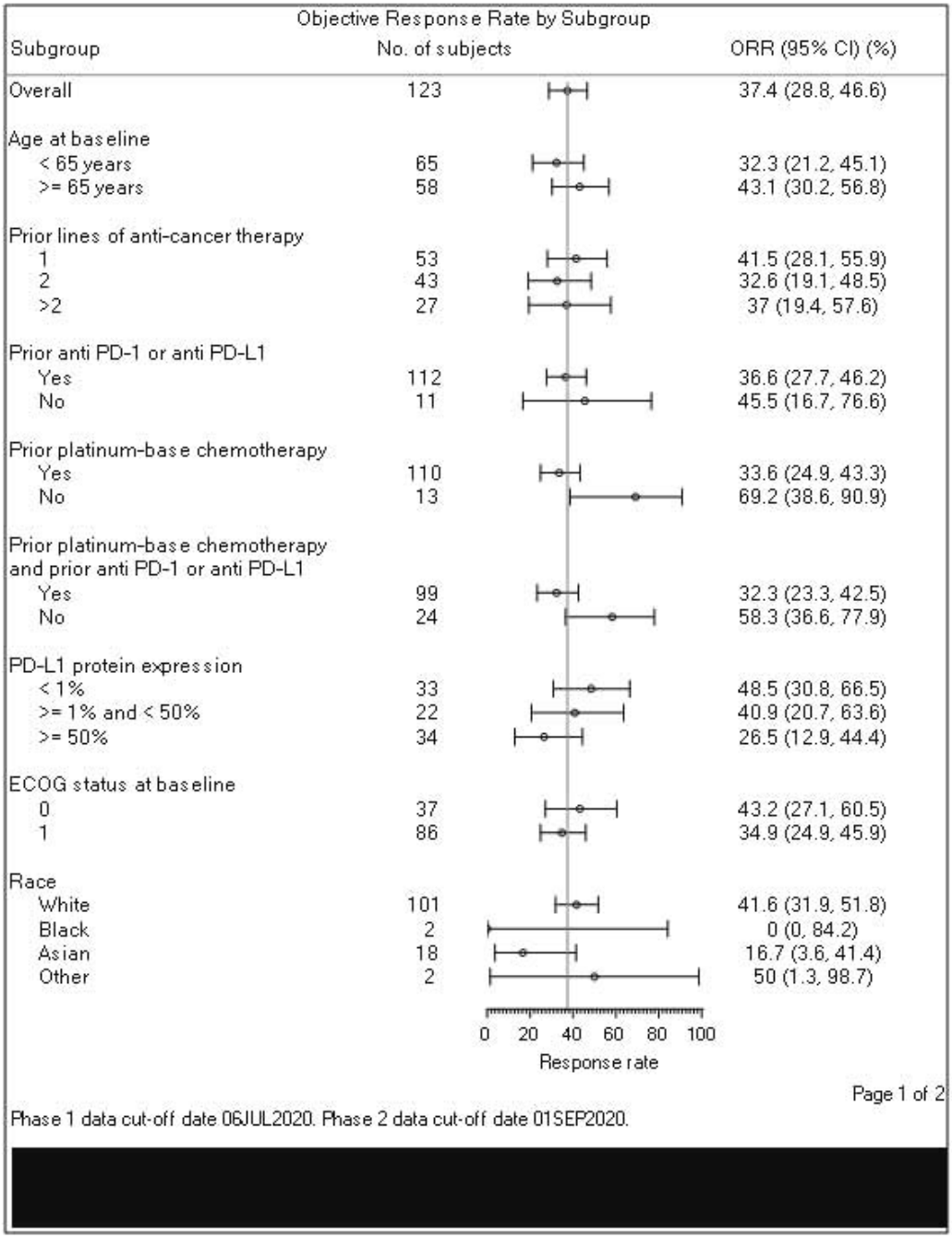
Exact 95% confidence interval was calculated using the Clopper-Pearson method.

[a] Events are confirmed response (partial response or complete response).

[b] Per local data availability

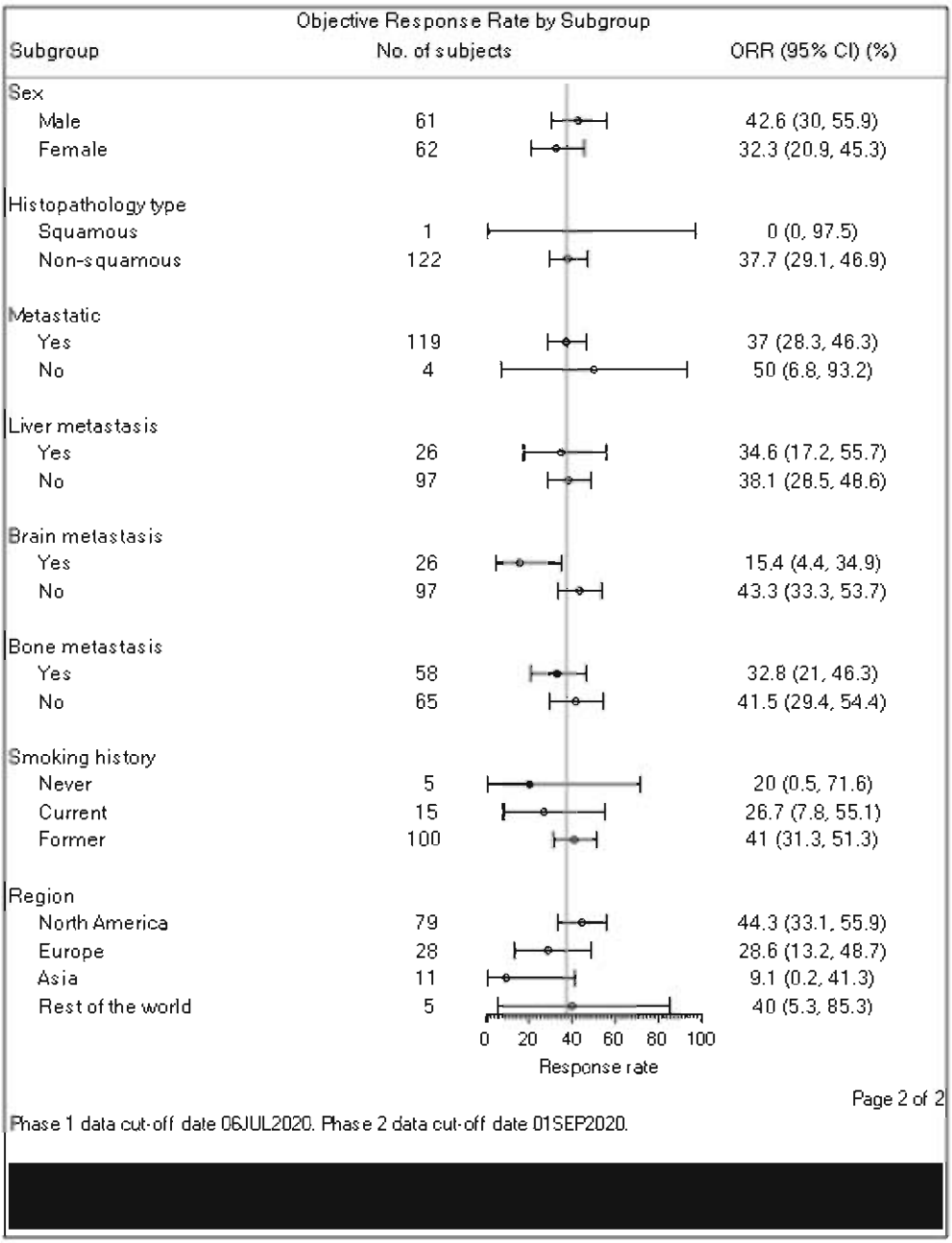
Source: *Study [redacted] Phase 2 CSR Table 14n-4.1.2*

Figure 6. Objective Response Rate by Subgroup Analysis (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)



Footnotes defined on next page of figure.

Figure 6. Objective Response Rate by Subgroup Analysis (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)



BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; No = Number of subjects in the analysis set; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand 1; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
Source: *Study [redacted] Phase 2 CSR Figure 14n-4.5.1*

4. Analysis of Clinical Information Relevant to Dosing Recommendations

In vitro, sotorasib covalently binds the $KRAS^{G12C}$ protein in its inactive, GDP-bound state and locks it in the inactive state. In vivo, reactivation of $KRAS^{G12C}$ mutant protein after exposure to sotorasib would require resynthesis of the mutant protein.

In vivo pharmacodynamic studies have validated the hypothesis that a single brief exposure of sotorasib, even below the cellular concentration that produces a 90% inhibition of activity (IC90), can significantly inhibit KRAS signaling for up to 48 hours. Similarly, in vivo efficacy studies in nonclinical species with human tumor xenografts have demonstrated that exposures of sotorasib above the cellular pERK IC90 for > 2 hours resulted in tumor regressions. Finally, in vivo efficacy studies in a mouse syngeneic tumor model suggested that much less sotorasib exposure is required for tumor regression in immunocompetent animals (Module 2.4 Nonclinical Overview).

The following doses of sotorasib were examined in phase 1 of Study [redacted] 180, 360, 720, and 960 mg QD. No MTD was reached and no DLT was observed (Study [redacted] Phase 1).

In subjects with *KRAS p.G12C*-mutated advanced solid tumors, increases in sotorasib exposure from 180 to 960 mg once daily were less than dose proportional based on preliminary data (Table 2 of Module 2.7.2, Summary of Clinical Pharmacology). Sotorasib does not accumulate with multiple oral dosing.

Based on review of the totality of evidence including safety and efficacy, 960 mg QD was selected as the proposed dose for the intended patient population. Population pharmacokinetic analysis identified no clinically meaningful differences in sotorasib pharmacokinetics based on sex, race, disease status, body weight, age, or mild renal/hepatic impairment, suggesting no dose adjustments are necessary based on these covariates.

An analysis evaluating the relationship between the explored dose levels and tumor response to treatment, in terms of average tumor shrinkage from baseline within first 7 and 13 weeks after treatment, was conducted in previously treated subjects with NSCLC who received sotorasib monotherapy (fasted state) in the phase-1 portion of Study [redacted] (Figure 3 of Module 2.5, Clinical Overview). Due to the limited sample size of enrolled subjects in the explored dose cohorts, this analysis was only conducted in the 360- and 960-mg QD cohorts where 16 and 34 subjects were enrolled, respectively. The result concluded that the average tumor shrinkage from baseline is

numerically larger in the 960-mg QD cohort than in the 360-mg QD cohort within the first 7 and 13 weeks.

Overall, 190 subjects with NSCLC were treated with 960 mg QD sotorasib monotherapy (fasted) in Study [redacted]. This subject population includes 34 subjects in phase 1 and 126 subjects in phase 2 with previously treated NSCLC, and 30 subjects in phase 1 with previously untreated NSCLC (Table 4 and Table 5). Of the 190 subjects, 18 subjects (9.5%) had adverse events leading to discontinuation of sotorasib (ISS Table 14b-6.1.1). Therefore, the 960 mg dose was associated with a low rate for discontinuation due to adverse events and sotorasib had comparable safety profiles across dose levels.

In summary, the 960 mg QD dose of sotorasib has been shown to be efficacious with a tolerable safety profile.

5. Persistence of Efficacy and/or Tolerance Effects

The exposure to sotorasib and data on persistence of efficacy for subjects with previously treated NSCLC treated with 960 mg QD sotorasib monotherapy (fasted) are described below. The exposure data and efficacy results for other doses, as well as other tumors, are provided in Study [redacted] Phase 1 and Study [redacted] Phase 2 clinical study reports.

As of the 06 July 2020 data cutoff date for phase 1 and 01 September 2020 data cutoff for phase 2, 26 and 88 subjects with NSCLC were treated with 960 mg QD sotorasib monotherapy (fasted) for ≥ 3 months in phase 1 and phase 2 of the study, respectively, 16 and 60 subjects for ≥ 6 months, 9 and 36 subjects for ≥ 9 months, and 6 and 0 subjects for ≥ 12 months. The median (Q1, Q3) number of doses received was 168.0 (84.0, 319.0) (range = 40 to 454 doses) and 168.0 (68.0, 266.0) (range = 7 to 360) for phase 1 subjects in the NSCLC group and phase 2 subjects in the NSCLC group, respectively. The maximum number of 960 mg QD sotorasib monotherapy(fasted) doses received by subjects with NSCLC in phase 1 and phase 2 was 454 and 360, respectively, and the maximum duration on treatment was 17 and 12 months (Study [redacted] Phase 1 CSR Table 14j-5.1and Study [redacted] Phase 2 CSR Table 14b-5.1).

In phase 1 and phase 2, among the 16 and 46 objective responders among subjects with NSCLC treated with 960 mg QD sotorasib monotherapy (fasted), the median DOR was not reached (95% CI: 4.2 months, NE) and 8.4 (6.9, 8.4) months, respectively. The median PFS as assessed by BICR per RECIST 1.1 criteria for subjects in phase 2 NSCLC group was 6.7 (95% CI: 4.9, 8.1) months. The Kaplan-Meier PFS probability estimate at 6 and 9 months were 51.5% (95% CI: 41.9, 60.4) and 36.2% (95% CI: 26.7, 45.8), respectively. The median (95% CI) OS was 12.0 months (9.5, NE).

These data demonstrate that sotorasib effect on tumor response is durable and that tolerance to the beneficial effects of sotorasib does not develop over the durations studied in most subjects.

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