ORIGINAL ARTICLE

Setidegrasib in Advanced Non–Small-Cell Lung Cancer and Pancreatic Cancer

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ABSTRACT

BACKGROUND

The *KRAS* p.G12D variant occurs in 5% of patients with non–small-cell lung cancer (NSCLC) and is the most common substitution variant in pancreatic ductal adenocarcinoma, occurring in 40% of patients, but no targeted therapies directed against this variant are currently approved for clinical use. Setidegrasib (ASP3082) is a first-in-class KRAS G12D–targeted protein degrader.

METHODS

We conducted this phase 1 study to evaluate the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of setidegrasib in patients with previously treated advanced solid tumors harboring *KRAS* p.G12D variants. The primary objectives were to evaluate the safety profile, as indicated by dose-limiting toxic effects and adverse events (the primary end points), and to determine the phase 2 dose. Setidegrasib was administered intravenously once weekly at doses of 10 to 800 mg.

RESULTS

Overall, 203 patients were enrolled. Among the 76 patients who received setidegrasib at a dose of 600 mg, which was ultimately selected as the phase 2 dose, adverse events occurred during treatment in all the patients, with events of grade 3 or higher in 42%. Treatment-related adverse events occurred in 93% of the patients; the most common were transient infusion-related reactions (in 80%) and nausea (in 30%). Adverse events led to discontinuation in 2 patients. Among the 45 patients with NSCLC who received the 600-mg dose, 36% (95% confidence interval [CI], 22 to 51) had a partial response, the median progression-free survival was 8.3 months (95% CI, 4.1 to could not be estimated), and the estimated 12-month overall survival was 59% (95% CI, 40 to 74). Among the 21 patients with metastatic pancreatic ductal adenocarcinoma who received the 600-mg dose as second- or third-line treatment (of whom 67% received setidegrasib as third-line treatment), 24% (95% CI, 8 to 47) had a response, the median progression-free survival was 3.0 months (95% CI, 1.4 to 6.9), and the median overall survival was 10.3 months (95% CI, 4.2 to 13.0).

CONCLUSIONS

Setidegrasib was associated with antitumor activity and a low incidence of treatment discontinuation due to adverse events in patients with previously treated advanced *KRAS* p.G12D–mutated NSCLC or pancreatic ductal adenocarcinoma. (Funded by Astellas Pharma; ClinicalTrials.gov number, NCT05382559.)

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The *KRAS* p.G12D variant occurs in 5% of patients with non–small-cell lung cancer (NSCLC) and is the most common substitution variant in pancreatic ductal adenocarcinoma, occurring in approximately 40% of patients.[1,2] In contrast to the number of therapies approved for use against KRAS G12C, no targeted therapies directed against KRAS G12D are currently approved for clinical use.[3-6] The challenge in classic inhibition of KRAS G12D reflects structural distinctions between the two alleles: whereas KRAS G12C has a reactive cysteine residue that enables covalent inhibitor binding, KRAS G12D lacks this feature and possesses only a shallow switch II pocket, which renders it difficult to target.[7,8] Recent advances have permitted KRAS G12D targeting despite these structural constraints. Several KRAS G12D inhibitors are in development and have been shown to have clinical activity in patients with *KRAS* p.G12D–mutated NSCLC or pancreatic ductal adenocarcinoma.[9-13]

Targeted protein degradation represents a method of treatment that is distinct from small-molecule inhibition and enables catalytic elimination of oncogenic proteins. Setidegrasib (ASP3082) is a first-in-class KRAS G12D–targeted protein degrader that forms a ternary complex among KRAS G12D, a proteolysis-targeting chimera, and von Hippel–Lindau E3 ligase, resulting in selective degradation of KRAS G12D and inhibition of downstream signaling pathways.[8] Here, we report the safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of setidegrasib monotherapy from a first-in-human phase 1 study involving patients with advanced solid tumors, including those with NSCLC and those with pancreatic ductal adenocarcinoma.

METHODS

PATIENTS

Eligible patients were adults who had documented locally advanced unresectable or metastatic solid tumors harboring *KRAS* p.G12D variants according to local or central testing; had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; had a score of 0 to 2 (to be eligible for dose escalation) or 0 to 1 (for dose expansion) on the Eastern Cooperative Oncology Group performance-status scale (range, 0 to 5, with higher scores indicating greater disability); had previously received at least one systemic anticancer therapy but not KRAS G12D or pan-RAS inhibitors or degraders; and did not have symptomatic or untreated central nervous system metastases. Patients with asymptomatic, treated central nervous system metastases were allowed to enroll in the study. After study initiation, amended eligibility criteria excluded patients with pancreatic ductal adenocarcinoma who had a baseline albumin level of 3.0 g per deciliter or lower, given the association of hypoalbuminemia with frailty and early death in patients with advanced pancreatic ductal adenocarcinoma.[14,15] Complete eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

STUDY DESIGN

This phase 1, open-label, international, multicenter study included dose-escalation and dose-expansion cohorts. Patients received setidegrasib at escalating weekly intravenous doses of 10 to 800 mg. Dose escalation was guided by a Bayesian continual reassessment method incorporating dose-limiting toxic effects during the first 21 days of treatment. Dose-limiting toxic effects were defined in the protocol as hematologic adverse events of grade 4 or nonhematologic adverse events of grade 3 or higher, hepatic laboratory abnormalities, infusion-related reactions leading to discontinuation, or a delay in treatment administration for more than 1 week because of treatment-related toxic effects. Initial dose-ranging, dose-expansion cohorts were enrolled at up to two dose levels that had acceptable safety profiles (300 mg and 600 mg in patients with pancreatic ductal adenocarcinoma) to identify the recommended phase 2 dose. Tumor-specific dose-expansion cohorts were enrolled at the dose that was determined to be the phase 2 dose. Treatment continued until the occurrence of disease progression, unacceptable toxic effects, or withdrawal from the study.

ASSESSMENTS

Tumors were assessed by computed tomography or magnetic resonance imaging at screening, every 6 weeks during treatment, and every 9 weeks during follow-up until the occurrence of disease progression, the receipt of new anticancer therapy, death, withdrawal from the study, or loss to follow-up. Tumor response was assessed by investigators according to RECIST, version 1.1. Adverse events were graded according to the

National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Plasma concentrations of setidegrasib were evaluated in the dose-escalation and dose-expansion cohorts. Blood and tissue samples were obtained for pharmacodynamic evaluation. Paired tumor biopsy samples were obtained at baseline and after one cycle of setidegrasib treatment (days 23 through 28). Additional details are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.

END POINTS

The primary objectives were to evaluate the safety profile, as indicated by dose-limiting toxic effects and adverse events (the primary end points), and to determine the maximum tolerated dose and the recommended phase 2 dose of setidegrasib. Secondary end points were objective response (partial or complete response), duration of response, and disease control according to RECIST, version 1.1; pharmacokinetics; and effects on KRAS G12D protein levels in tumors. Exploratory end points included progression-free survival according to RECIST, version 1.1; overall survival; and pharmacodynamic effects.

TRIAL OVERSIGHT

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Council for International Organizations of Medical Sciences, and the International Council for Harmonisation guidelines for Good Clinical Practice. An institutional review board or independent ethics committee at each participating institution approved the protocol. All the patients provided written informed consent. The sponsor designed the trial in collaboration with the investigators and collected and analyzed the data. All the authors had access to the data, interpreted the data, and participated in manuscript revision. The first draft was written by a medical writer employed by the sponsor. The authors vouch for the completeness and accuracy of the data and for adherence of the study to the protocol.

STATISTICAL ANALYSIS

Objective response and disease control were summarized with Clopper–Pearson 95% confidence intervals. The median duration of response, progression-free survival, and overall survival were estimated with the Kaplan–Meier method. No formal hypothesis testing was planned. Pharmacokinetic and pharmacodynamic analyses were summarized with descriptive statistics. The confidence intervals were exploratory in nature, have not been adjusted for multiplicity, and cannot be interpreted as hypothesis tests. All analyses were performed in the safety analysis population, which included patients who received at least one dose of setidegrasib.

RESULTS

PATIENTS

Between June 21, 2022, and April 24, 2025, a total of 203 patients (59 with NSCLC, 124 with pancreatic ductal adenocarcinoma, and 20 with other solid tumors) were enrolled across 28 centers in five countries; 123 patients were in the dose-escalation cohort and 80 were in the dose-expansion cohort (40 with NSCLC and 40 with pancreatic ductal adenocarcinoma). At the safety data cutoff on October 9, 2025, a total of 24 patients (20 with NSCLC and 4 with pancreatic ductal adenocarcinoma) were still receiving treatment (Fig. S1 in the Supplementary Appendix). Disease progression was the most common reason for treatment discontinuation (among 152 of 179 patients [85%] who discontinued treatment).

The recommended phase 2 dose of setidegrasib, 600 mg, administered intravenously once weekly, was selected on the basis of results of analyses of safety, pharmacokinetics (Fig. S2), pharmacodynamics (Fig. 1 and Figs. S3 and S4), and efficacy. In the dose-ranging, dose-expansion cohorts, an objective response was observed in a higher percentage of the patients receiving the 600-mg dose than of those receiving the 300-mg dose, and the safety profile was similar for these two doses. Corresponding increases in systemic exposure and the level of KRAS G12D degradation further supported the selection of 600 mg as the recommended, clinically feasible dose, given that the 800-mg dose was determined not to be clinically relevant because of the large volume and extended infusion time needed as a result of low solubility.

The baseline characteristics of all 203 patients and of the patients according to setidegrasib dose levels are summarized in Table S1. The baseline characteristics of the 76 patients who received setidegrasib at a dose of 600 mg (45 with NSCLC and 31 with pancreatic ductal adenocarcinoma) across both the dose-escalation and dose-expansion cohorts are summarized in

Table 1 and Table S2. The median age was 68 years (range, 36 to 81) among patients with NSCLC and 65 (range, 36 to 79) among patients with pancreatic ductal adenocarcinoma. The median number of previous lines of anticancer therapy was 2 (range, 1 to 5) in both groups. Among the patients with NSCLC, 42 (93%) had previously received platinum-based chemotherapy plus an immune checkpoint inhibitor. Among the patients with pancreatic ductal adenocarcinoma, 26 (84%) had previously received gemcitabine plus paclitaxel or nab-paclitaxel and 16 (52%) had previously received a modified FOLFIRINOX regimen (folinic acid, fluorouracil, irinotecan, and oxaliplatin). Results of exploratory analyses of co-occurring genetic alterations of interest are shown in Table S3 and S4. The study population was generally representative of patients with solid tumors harboring *KRAS* p.G12D mutations; Black patients were underrepresented (Table S5).

SAFETY

In the dose-escalation cohort, dose-limiting toxic effects occurred in 3 of 123 patients (2%) (Table S6). The maximum tolerated dose was not reached. The median relative dose intensity with setidegrasib at a dose of 600 mg was 97.8% (range, 46.7 to 102.4), and 67 of 76 patients (88%) had a relative exposure intensity of at least 80%. The median duration of setidegrasib exposure at a dose of 600 mg was 16.6 weeks (range, 1.0 to 72.3).

Among the 76 patients who received setidegrasib at a dose of 600 mg (Table 2), adverse events of any grade that emerged during treatment occurred in all the patients, and treatment-related adverse events of any grade occurred in 71 patients (93%); however, attribution of treatment relatedness is imprecise in a first-in-human study. Adverse events led to discontinuation in 2 patients. The most common treatment-related adverse events occurring in at least 20% of the patients were infusion-related reactions (in 61 patients [80%]) and nausea (in 23 [30%]). Among infusion-related reactions, the most reported events were pruritus and rash (in 23 patients each [30%]) and urticaria (in 19 [25%]). No infusion-related reactions of grade 3 or higher were observed. Infusion-related reactions led to temporary interruption of treatment in 48 patients (63%) but did not lead to discontinuation of treatment. Infusion-related reactions occurred most frequently during the first infusion of setidegrasib (in 59 patients [78%]) and occurred less frequently after subsequent infusions. Overall, 32 patients (42%)

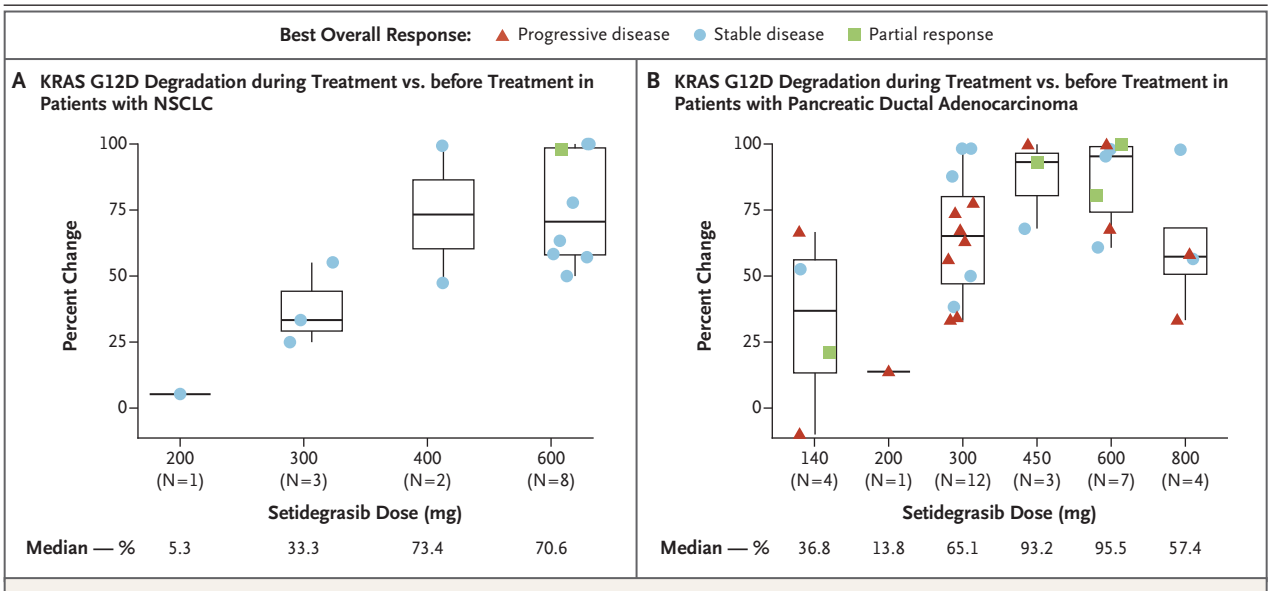

Figure 1. KRAS G12D Protein Degradation.

Shown is the level of KRAS G12D degradation in patients with non–small-cell lung cancer (NSCLC) and in those with pancreatic ductal adenocarcinoma. The horizontal lines within the boxes indicate the medians, and the lower and upper box limits represent quartile 1 and quartile 3, respectively. The lower whiskers represent 1.5 times the quartile 1 value or the minimum if within that range, and the upper whiskers represent 1.5 times the quartile 3 value or the maximum if within that range.

had adverse events of grade 3 or higher that emerged during treatment; treatment-related adverse events of grade 3 or higher occurred in 7 patients (9%; 2 patients [3%] had an increased alanine aminotransferase level, 2 [3%] had neutropenia, 2 [3%] had a decreased neutrophil count, 1 [1%] had iron deficiency anemia, and 1 [1%] had cholangitis [1 patient had both neutropenia and cholangitis]). Serious treatment-related adverse events (Table S7) and treatment-related adverse events that led to dose reduction were observed in 4 patients each (5%) (Table 2); no treatment-related adverse events led to treatment discontinuation or death. Adverse events according to dose levels are summarized in Table S6.

PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetic profile of setidegrasib is shown in Figure S2. With setidegrasib at a dose of 600 mg, the maximum plasma concentration (±SD) was 54.3±21.7 μg per milliliter, and the median time to reach a maximum plasma con-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients Who Received 600 mg of Setidegrasib Monotherapy.*

Characteristic	All Patients (N=76)	NSCLC (N=45)	PDAC (N=31)
Median age (range) — yr	66 (36–81)	68 (36–81)	65 (36–79)
Female sex — no. (%)	41 (54)	28 (62)	13 (42)
Race — no./total no. (%)†			
White	31/54 (57)	23/33 (70)	8/21 (38)
Asian	22/54 (41)	10/33 (30)	12/21 (57)
Black or African American	1/54 (2)	0	1/21 (5)
ECOG performance-status score of 1 — no. (%)‡	56 (74)	35 (78)	21 (68)
Median lines of previous anticancer therapy (range)	2 (1–5)	2 (1–5)	2 (1–5)
Lines of previous anticancer therapy — no. (%)			
1	26 (34)	19 (42)	7 (23)
2	27 (36)	13 (29)	14 (45)
≥3	23 (30)	13 (29)	10 (32)
Disease stage IV — no. (%)§	74 (97)	43 (96)	31 (100)
Distant metastasis — no. (%)¶			
Bone	—	17 (38)	—
Lymph node	—	17 (38)	—
Liver	—	9 (20)	23 (74)
Brain	—	6 (13)	—
Type of previous anticancer therapy — no. (%)‖			
Platinum-based chemotherapy and immune checkpoint inhibitor	—	42 (93)	—
Gemcitabine plus paclitaxel or nab-paclitaxel	—	—	26 (84)
Modified FOLFIRINOX	—	—	16 (52)

* For characteristics relevant to specific tumor types, data are shown for that group only; dashes appear in the other columns. NSCLC denotes non–small-cell lung cancer, and PDAC pancreatic ductal adenocarcinoma.
† Race was reported by the patient in the case-report form. The total numbers were the numbers of patients with nonmissing data; data were missing for 22 patients (12 with NSCLC and 10 with PDAC).
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
§ Anatomical staging was performed at screening; stage IV, IVA, IVB, and IVC were classified as stage IV.
¶ Shown are the selected metastatic sites of interest.
‖ Shown are the selected therapies of interest. Modified FOLFIRINOX consisted of folinic acid, fluorouracil, irinotecan, and oxaliplatin.

Table 2. Adverse Events in Patients Who Received 600 mg of Setidegrasib Monotherapy.

Event	Patients (N=76)
Adverse events that emerged during treatment — no. (%)	
Any	76 (100)
Grade ≥3	32 (42)
Serious	25 (33)
Leading to treatment interruption	59 (78)
Leading to dose reduction	4 (5)
Leading to permanent discontinuation	2 (3)
Treatment-related adverse events — no. (%)	
Any	71 (93)
Grade ≥3	7 (9)
Alanine aminotransferase increased	2 (3)
Neutropenia*	2 (3)
Neutrophil count decreased	2 (3)
Iron deficiency anemia	1 (1)
Cholangitis*	1 (1)
Serious	4 (5)
Leading to treatment interruption	53 (70)
Infusion-related reactions	48 (63)
Noninfusion-related-reaction adverse events	8 (11)
Leading to dose reduction	4 (5)
Leading to permanent discontinuation	0
Occurring in ≥20% of patients	
Infusion-related reactions	61 (80)
Nausea	23 (30)
Infusion-related reactions	
Cycle — no./total no. (%)†	
Cycle 1, week 1	59/76 (78)
Cycle 1, week 2	10/62 (16)
Cycle 1, week 3	12/60 (20)
Cycle 2	20/65 (31)
Cycle 3	8/56 (14)
Cycle 4	8/54 (15)
Cycle 5	4/46 (9)
Cycle 6	2/40 (5)
Grade ≥3 — no. (%)	0
Occurring in ≥20% of patients — no. (%)	
Pruritus	23 (30)
Rash	23 (30)
Urticaria	19 (25)

* One patient had both neutropenia and cholangitis.
† Shown are the numbers of patients with at least one infusion-related reaction that emerged during the cycle and week divided by the number of patients.

centration was 3.9 hours (range, 2.0 to 5.9). The mean elimination half-life was 34.9±5.91 hours. No accumulation occurred with once-weekly dosing. The area under the curve increased more than dose-proportionally with escalating doses.

The level of KRAS G12D degradation from the baseline level in paired tumor-biopsy samples from patients receiving treatment increased dose-proportionally, with an observed plateau at doses of at least 450 mg (Fig. 1). An example of the KRAS G12D immunohistochemical assessment at baseline and during treatment in one patient is shown in Figure S3. With setidegrasib at a dose of 600 mg, the level of KRAS G12D degradation, shown as the median percent change from baseline, was 70.6% in patients with NSCLC and 95.5% in patients with pancreatic ductal adenocarcinoma. Setidegrasib was shown to lead to a molecular response with changes in the *KRAS* p.G12D variant allele frequency as early as treatment cycle 1 (Fig. S4). In patients with NSCLC, the median greatest percent change from baseline in the frequency of the *KRAS* p.G12D variant allele in circulating tumor DNA was 98.2% (95% CI, 100.0 to 79.9) in 20 patients with stable disease or a partial response as compared with 21.6% in 2 patients with progressive disease; in patients with pancreatic ductal adenocarcinoma, the median greatest percent change from baseline was 91.3% (95% CI, 96.7 to 78.1) in 10 patients with stable disease or a partial response as compared with 49.6% (95% CI, 62.1 to 15.3) in 8 patients with progressive disease. Among patients with stable disease or a partial response, clearance (variant allele frequency of 0 or below the limit of detection) was shown to have occurred in 11 patients with NSCLC and in 5 patients with pancreatic ductal adenocarcinoma, and a reduction of more than 50% was shown to have occurred in 17 and 9 patients, respectively.

EFFICACY IN NSCLC

Efficacy was assessed in the 45 patients with NSCLC who received setidegrasib at a dose of 600 mg as second-line of treatment or later. As of the efficacy data cutoff on November 10, 2025, the median duration of follow-up was 9.7 months (95% CI, 9.1 to 12.4). The greatest changes from baseline in tumor size and the time to response and duration of treatment are shown in Figure 2A and 2B, respectively. An objective response was observed in 16 patients (36%; 95% CI, 22 to 51); a partial response, pending confirmation, was observed in 1 patient, and a confirmed partial response was

observed in 15 patients (Table S8). Among these 15 patients, the median time to a response was 1.4 months (range, 1.2 to 8.1). The Kaplan–Meier estimate of the percentage of patients with a response at 6 months was 76% (95% CI, 41 to 92). The median progression-free survival was 8.3 months (95% CI, 4.1 to could not be estimated) (Fig. 2C). The Kaplan–Meier estimate of overall survival at 6 months was 77% (95% CI, 62 to 87) and at 12 months was 59% (95% CI, 40 to 74) (Fig. 2D). Among the 32 patients who received setidegrasib at a dose of 600 mg as second- or third-line treatment, an objective response was observed in 12 patients (38%; 95% CI, 21 to 56), and the median progression-free survival was 11.2 months (95% CI, 5.6 to could not be estimated) (Fig. 2C).

EFFICACY IN PANCREATIC DUCTAL ADENOCARCINOMA

Efficacy was assessed in the 21 patients with pancreatic ductal adenocarcinoma who received setidegrasib at a dose of 600 mg as second-line (7 patients) or third-line (14 patients) treatment. As of the efficacy data cutoff on November 10, 2025, the median duration of follow-up was 15.2 months (95% CI, 6.3 to could not be estimated). The greatest changes from baseline in tumor size and the time to response and duration of treatment are shown in Figure 3A and 3B, respectively. An objective response was observed in 5 patients with confirmed partial response (24%; 95% CI, 8 to 47). Among these 5 patients, the median time to response was 4.1 months (range, 1.3 to 8.2), and the median duration of response was 4.2 months (95% CI, 2.7 to could not be estimated). The median progression-free survival was 3.0 months (95% CI, 1.4 to 6.9) (Fig. 3C). The median overall survival was 10.3 months (95% CI, 4.2 to 13.0) (Fig. 3D).

Among all 31 patients with pancreatic ductal adenocarcinoma who received setidegrasib at a dose of 600 mg (i.e., as second-line treatment or later), an objective response was observed in 6 patients (19%). A post hoc analysis of data from patients who met amended eligibility criteria with a baseline albumin level of more than 3.0 g per deciliter is shown in Figure S5.

DISCUSSION

This phase 1, first-in-human study involving patients with advanced, previously treated NSCLC or pancreatic ductal adenocarcinoma evaluated the safety profile and clinical activity of setidegrasib, a first-in-class, selective KRAS G12D–targeted protein degrader, administered at a dose of 600 mg intravenously once weekly. Overall, 42% of the patients who received setidegrasib at a dose of 600 mg had adverse events of grade 3 or higher; adverse events led to discontinuation in 2 patients. Infusion-related reactions were the most common treatment-related adverse events (occurring in 80% of the patients). All were events of grade 1 or 2, occurred predominantly during the first infusion, and were managed during subsequent infusions with protocol-specified measures, including infusion-rate modification, temporary interruption, and antihistamine administration. None of the patients discontinued treatment owing to infusion-related reactions. Most of the other treatment-related adverse events were also of grade 1 or 2. Overall, 9% of the patients had treatment-related adverse events of grade 3 or higher with setidegrasib at a dose of 600 mg; no treatment-related gastrointestinal or dermatologic adverse events of grade 3 or higher were noted. In phase 1–2 studies of KRAS G12D inhibitors in patients with *KRAS* p.G12D–mutated solid tumors, the incidence of treatment-related adverse events of grade 3 or higher ranged widely, from approximately 1 to 30%.[9-12,16] In a phase 1 study of the pan-RAS inhibitor daraxonrasib in patients with *KRAS* p.G12X mutations, the incidence of treatment-related adverse events of grade 3 or higher was approximately 35% in patients with pancreatic ductal adenocarcinoma and 16% in patients with NSCLC.[17,18] Cross-trial comparisons should be interpreted with caution.

The setidegrasib safety profile supports investigation of setidegrasib in combination therapies; this approach is being evaluated in additional patient cohorts in this trial. Although intravenous administration can require additional clinical resources, it avoids reliance on gastrointestinal absorption, which may be impaired in patients with advanced cancer, and provides tighter exposure control and more predictable pharmacokinetics. These advantages, along with the transient nature of infusion-related reactions and the lack of gastrointestinal treatment-related adverse events of grade 3 or higher at the recommended phase 2 dose of setidegrasib, may support an improved safety profile and treatment adherence and may facilitate adoption of possible combination regimens.

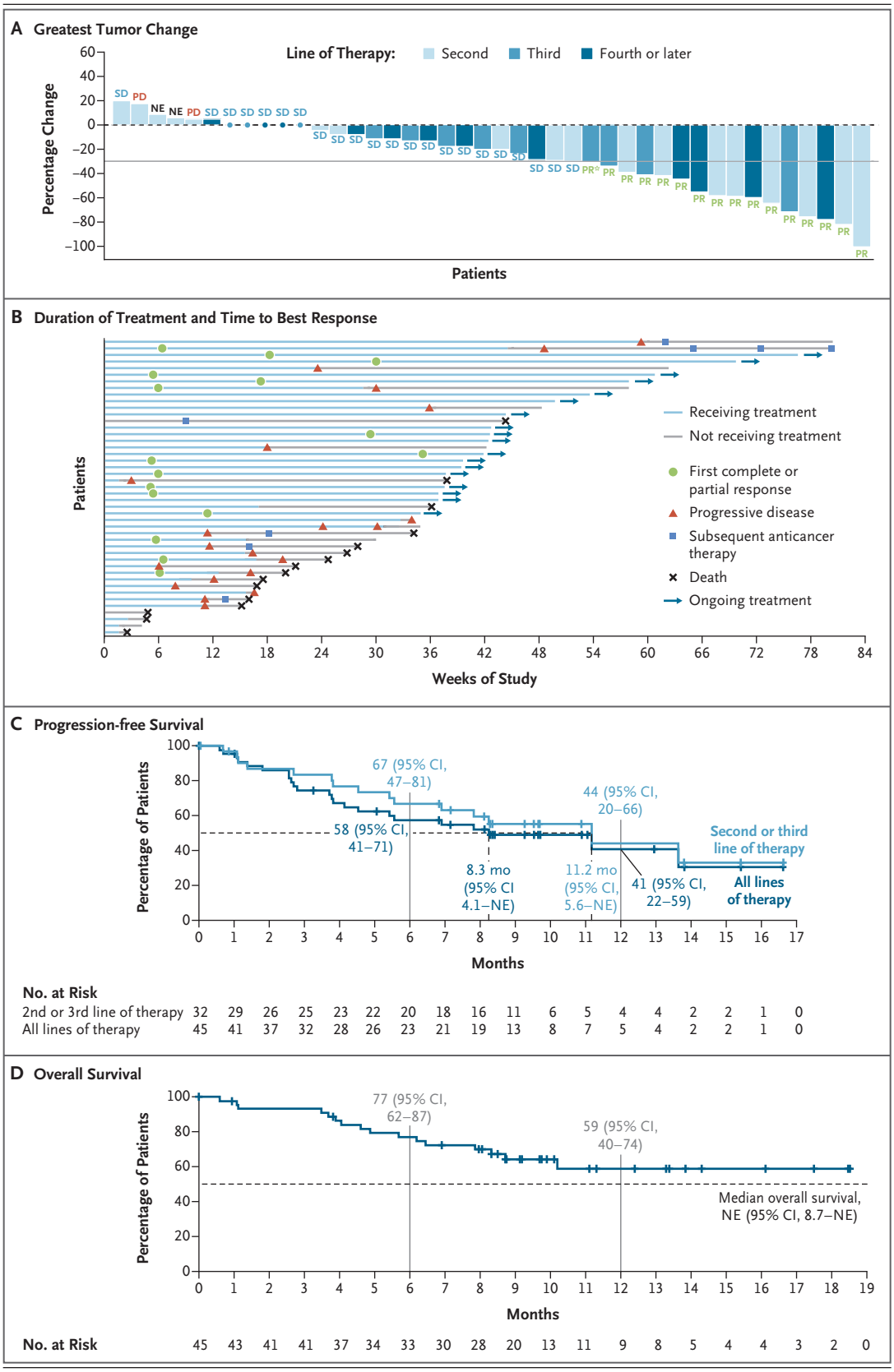

Figure 2 (facing page). Efficacy in Patients with NSCLC.

Data are shown for patients with NSCLC who received 600 mg of setidegrasib monotherapy as second-line treatment or later. Panel A shows the greatest tumor change from baseline, Panel B the time to response and duration of treatment, Panel C progression-free survival, and Panel D overall survival. The gray line in Panel A represents partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The asterisk indicates an unconfirmed partial response according to RECIST, version 1.1. The dashed line in Panels C and D represents the median. NE denotes could not be estimated, PD progressive disease, PR partial response, and SD stable disease.

In patients with NSCLC, the antitumor activity of setidegrasib (objective response in 36% of all the patients [i.e., those receiving setidegrasib as second-line treatment or later]; objective response with setidegrasib as second- or third-line therapy in 38%) and the median progression-free survival (8.3 months; median progression-free survival with setidegrasib as second- or third-line therapy, 11.2 months) are encouraging when compared with those associated with the currently recommended regimens for patients with previously treated NSCLC. Docetaxel with or without ramucirumab is associated with an objective response observed in approximately 9 to 23% of patients and a median progression-free survival of approximately 3.0 to 4.5 months.[19-23] Our results are similar to phase 1 results of KRAS G12D inhibitors in patients with *KRAS* p.G12D–mutated NSCLC (objective response in approximately 30 to 60% of patients; median progression-free survival, approximately 6.5 to 8.5 months) and to phase 1 results of second- or third-line daraxonrasib in patients with *KRAS* p.G12X–mutated NSCLC (objective response in 38% of patients; median progression-free survival, 9.8 months).[9-11,18] These findings highlight the clinical activity of setidegrasib and support its therapeutic potential in this molecularly defined population.

Outcomes with available second-line chemotherapy regimens for metastatic pancreatic ductal adenocarcinoma remain limited — the median progression-free survival is typically less than 3 months, and the median overall survival is approximately 6 months.[24-30] No established standard therapy is available for third-line treatment. In this study, we observed that among the 21 patients with metastatic pancreatic ductal adenocarcinoma who received setidegrasib at a dose of 600 mg as second- or third-line therapy (7 and 14 patients, respectively), an objective response occurred in 24%, the median progression-free survival was 3.0 months, and the median overall survival was 10.3 months. Early-phase studies of KRAS G12D inhibitors showed that an objective response occurred in 20 to 40% of patients with previously treated pancreatic ductal adenocarcinoma, with mature survival data pending.[11,12] Phase 1 results of second-line daraxonrasib in patients with metastatic pancreatic ductal adenocarcinoma showed that an objective response occurred in 35% of patients, the median progression-free survival was 8.5 months, and the median overall survival was 13.1 months.[17] We previously showed that setidegrasib-mediated KRAS G12D degradation may result in more durable inhibition of downstream signaling pathways than KRAS G12D inhibition.[8] A similar result was shown by Feng and colleagues in a direct comparison of a pan-KRAS–targeted protein degrader and inhibitor.[31] These observations suggest that elimination of a target protein by degradation may have resistance distinct from that of targeted inhibition. Further studies will be needed to evaluate this possibility.

The median level of KRAS G12D degradation was 70.6% and 95.5% in patients with NSCLC and pancreatic ductal adenocarcinoma, respectively, and the median greatest percent change from baseline in *KRAS* p.G12D variant allele frequency in circulating tumor DNA in patients with stable disease or a partial response was 90% or higher in both groups. Although degradation of tumor KRAS G12D confirms target engagement, reductions in circulating tumor DNA provide a dynamic measure of the treatment effect and show a closer concordance with clinical outcomes. In addition, tumor-specific signaling dependencies and the heterogeneity of the tumor microenvironment may contribute to variable efficacy across tumor types. Further research is needed to define the biologic determinants of response.

This study had limitations. Because this was a first-in-human phase 1 study, the sample size was limited, the duration of follow-up was relatively short, and the study was not designed to

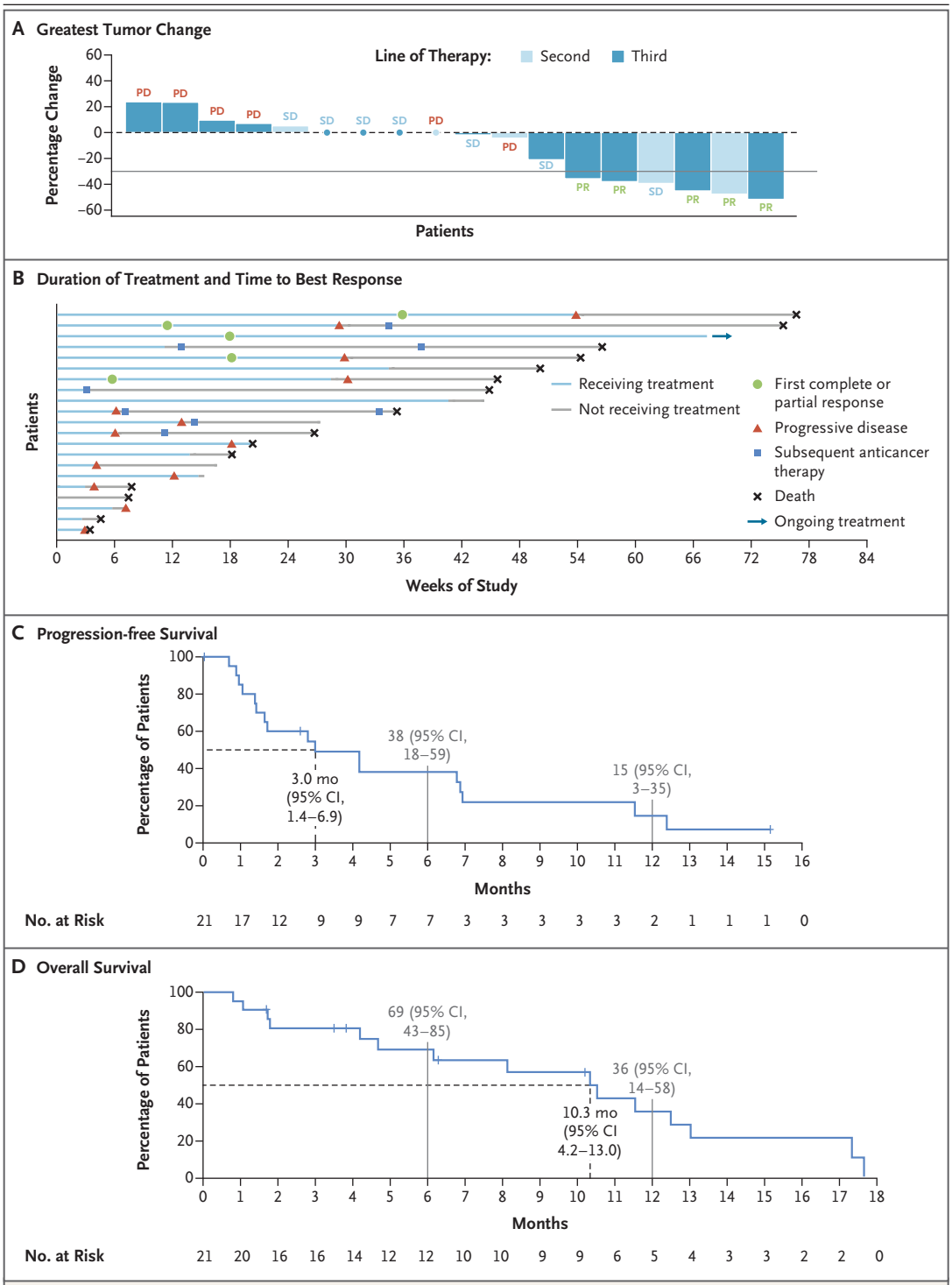

Figure 3. Efficacy in Patients with Pancreatic Ductal Adenocarcinoma.

Data are shown for patients with pancreatic ductal adenocarcinoma who received 600 mg of setidegrasib monotherapy as second- or third-line treatment. Panel A shows the greatest tumor change from baseline, Panel B the time to response and duration of treatment, Panel C progression-free survival, and Panel D overall survival. The gray line in Panel A represents partial response according to RECIST, version 1.1. The dashed line in Panels C and D represents the median.

compare efficacy across tumor types or against standard-of-care therapies. The median duration of follow-up was shorter in patients with NSCLC than in those with pancreatic ductal adenocarcinoma (9.7 vs. 15.2 months). In addition, biomarker analyses were exploratory, and predictors of response to KRAS G12D degradation remain to be defined. These limitations highlight the need for further investigation in larger, disease-specific studies.

This first-in-human study showed that selective KRAS G12D–targeted protein degradation with setidegrasib was associated with mainly low-grade, transient infusion-related adverse events, with few discontinuations and no treatment-related adverse events leading to death. Preliminary antitumor activity was observed in patients with advanced NSCLC and in those with advanced pancreatic ductal adenocarcinoma. Setidegrasib, a first-in-class protein degrader targeting mutant KRAS protein, was shown to have clinical activity, which establishes targeted protein degradation as a viable new method of treatment for patients with *KRAS* p.G12D–driven solid tumors. These results support continued clinical development of setidegrasib in rational combination strategies in these patients.

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REFERENCES

1. Lee JK, Sivakumar S, Schrock AB, et al. Comprehensive pan-cancer genomic landscape of KRAS altered cancers and real-world outcomes in solid tumors. NPJ Precis Oncol 2022;6:91.
2. Varghese AM, Perry MA, Chou JF, et al. Clinicogenomic landscape of pancreatic adenocarcinoma identifies KRAS mutant dosage as prognostic of overall survival. Nat Med 2025;31:466-77.
3. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung cancer, version 4.2024, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2024;22:249-74.
4. Li H, Li X, Li T, et al. Research progress and challenges in the treatment of oncogene-addicted non-small cell lung cancer. Cancer Biol Med 2025;22:1353-71.
5. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non–small-cell lung cancer harboring a *KRAS*^{G12C} mutation. N Engl J Med 2022;387:120-31.
6. Strickler JH, Satake H, George TJ, et al. Sotorasib in *KRAS* p.G12C-mutated advanced pancreatic cancer. N Engl J Med 2023;388:33-43.
7. Wang X, Allen S, Blake JF, et al. Identification of MRTX1133, a noncovalent, potent, and selective KRAS^{G12D} inhibitor. J Med Chem 2022;65:3123-33.

8. Yoshinari T, Nagashima T, Ishioka H, et al. Discovery of KRAS(G12D) selective degrader ASP3082. Commun Chem 2025; 8:254.
9. Arbour KC, Tawee T, Yaeger R, et al. Preliminary safety and antitumor activity of zoldonrasib (RMC-9805), an oral, RAS(ON) G12D-selective, tri-complex inhibitor in patients with KRAS G12D non-small cell lung cancer (NSCLC) from a phase 1 study in advanced solid tumors. Cancer Res 2025;85:Suppl 2:CT019. abstract (https://aacrjournals.org/cancerres/article/85/8_Supplement_2/CT019/762489/Abstract-CT019-Preliminary-safety-and-antitumor).
10. Lu S, Li Z, Ai X, et al. Efficacy and Safety of GFH375 in advanced non-small cell lung cancer patients with KRAS G12D mutation. J Thorac Oncol 2025;20: Suppl 1:S59-S60. abstract (https://www.jto.org/article/S1556-0864(25)01160-8/abstract).
11. Xiong A, Zhou C, Zhang Y, et al. KRAS G12D inhibitor HRS-4642 in patients with KRAS G12D-mutant advanced solid tumors: a phase I trial. Ann Oncol 2025; 36:Suppl 2:S558-S559. abstract (https://www.annalsofoncology.org/article/S0923-7534(25)02404-4/fulltext).
12. Zhou A, Li Z, Sun Y, et al. Efficacy and safety of GFH375 monotherapy in previously treated advanced KRAS G12D-mutant pancreatic ductal adenocarcinoma (PDAC). Ann Oncol 2025;36:Suppl 2:S1626. abstract (https://www.annalsofoncology.org/article/S0923-7534(25)04869-0/fulltext).
13. Wainberg ZA, Henry JT, Park H, et al. Preliminary phase 1 results of INCB161734, a novel oral Kirsten rat sarcoma (KRAS) G12D inhibitor, as monotherapy or in combination with chemotherapy for advanced/metastatic pancreatic duct adenocarcinoma (PDAC). J Clin Oncol 2026;44:Suppl:654. abstract (https://ascopubs.org/doi/10.1200/JCO.2026.44.2_suppl.654).
14. Westgaard A, Pirnat A, Hjermstad MJ, Aass N, Kaasa S, Dajani OF. Prognostic value of performance status, albumin, and CRP in last-line chemotherapy for pancreatic vs. other gastrointestinal cancers — simple tools matter. Curr Oncol 2024;31: 5462-71.
15. Yamada S, Shimada M, Morine Y, et al. Significance of frailty in prognosis after surgery in patients with pancreatic ductal adenocarcinoma. World J Surg Oncol 2021;19:94.
16. Spira AI, Papadopoulos KP, Kim DW, et al. Preliminary safety, antitumor activity, and circulating tumor DNA (ctDNA) changes with RMC-9805, an oral, RAS(ON) G12D-selective tri-complex inhibitor in patients with KRAS G12D pancreatic ductal adenocarcinoma (PDAC) from a phase 1 study in advanced solid tumors. J Clin Oncol 2025;43:Suppl:724. abstract (https://ascopubs.org/doi/10.1200/JCO.2025.43.4_suppl.724).
17. Garrido-Laguna I, Wolpin BM, Park W, et al. Safety, efficacy, and on-treatment circulating tumor DNA (ctDNA) changes from a phase 1 study of RMC-6236, a RAS(ON) multi-selective, tri-complex inhibitor, in patients with RAS mutant pancreatic ductal adenocarcinoma (PDAC). J Clin Oncol 2025;43:Suppl:722. abstract (https://ascopubs.org/doi/10.1200/JCO.2025.43.4_suppl.722).
18. Punekar SR, Hong DS, Luo J, et al. Safety and clinical activity of daraxonrasib (RMC-6236) in RAS mutant non-small cell lung cancer (NSCLC). J Thorac Oncol 2025;20:Suppl 1:S10-S11. abstract (https://www.jto.org/article/S1556-0864(25)00201-1/fulltext).
19. Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-73.
20. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373:1627-39.
21. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with $KRAS^{G12C}$ mutation: a randomised, open-label, phase 3 trial. Lancet 2023; 401:733-46.
22. Mok TSK, Yao W, Duruisseaux M, et al. KRYSTAL-12: phase 3 study of adagrasib versus docetaxel in patients with previously treated advanced/metastatic non-small cell lung cancer (NSCLC) harboring a $KRAS^{G12C}$ mutation. J Clin Oncol 2024; 42:Suppl:LBA8509. abstract (https://ascopubs.org/doi/10.1200/JCO.2024.42.17_suppl.LBA8509).
23. Owen DH, Halmos B, Puri S, et al. Therapy for stage IV non-small cell lung cancer without driver alterations: ASCO living guideline, version 2025.1. J Clin Oncol 2025;43(24):e45-e58.
24. Wang-Gillam A, Li C-P, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387: 545-57.
25. Chiorean EG, Guthrie KA, Philip PA, et al. Randomized phase II study of PARP inhibitor ABT-888 (veliparib) with modified FOLFIRI versus FOLFIRI as second-line treatment of metastatic pancreatic cancer: SWOG S1513. Clin Cancer Res 2021;27:6314-22.
26. Hecht JR, Lonardi S, Bendell J, et al. Randomized phase III study of FOLFOX alone or with pegilodecakin as second-line therapy in patients with metastatic pancreatic cancer that progressed after gemcitabine (SEQUOIA). J Clin Oncol 2021;39:1108-18.
27. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. JAMA 2021;326:851-62.
28. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021;19:439-57.
29. Huffman BM, Basu Mallick A, Horick NK, et al. Effect of a MUC5AC antibody (NPC-1C) administered with second-line gemcitabine and nab-paclitaxel on the survival of patients with advanced pancreatic ductal adenocarcinoma: a randomized clinical trial. JAMA Netw Open 2023; 6(1):e2249720.
30. De La Fouchardière C, Malka D, Cropet C, et al. Gemcitabine and paclitaxel versus gemcitabine alone after 5-fluorouracil, oxaliplatin, and irinotecan in metastatic pancreatic adenocarcinoma: a randomized phase III PRODIGE 65-UCGI 36-GEMPAX UNICANCER study. J Clin Oncol 2024;42:1055-66.
31. Feng J, Xiao X, Xia X, et al. A pan-KRAS inhibitor and its derived degrader elicit multifaceted anti-tumor efficacy in KRAS-driven cancers. Cancer Cell 2025; 43(10):1866-1884.e12.