# Elisrasib (D3S-001) Monotherapy in Advanced *KRAS*$^{G12C}$-Mutant Solid Tumors

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## Background

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene mutations, such as the glycine-to-cysteine substitution at position 12 (G12C), are relatively common in multiple solid tumors, including non–small-cell lung cancer (NSCLC), colorectal cancer (CRC), and pancreatic ductal adenocarcinoma (PDAC). Elisrasib is a next-generation KRAS$^{G12C}$ inhibitor (G12Ci) designed to maximize target engagement efficiency and outpace growth factor-induced nucleotide exchange.

## Methods

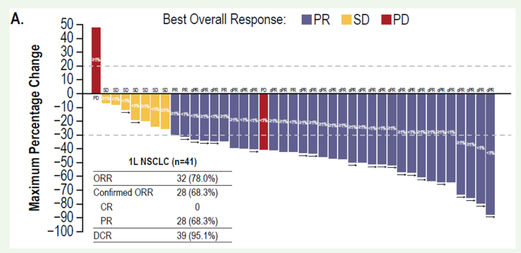
This open-label phase 1/2 trial aimed to evaluate once-daily oral elisrasib (600 mg) for advanced *KRAS*$^{G12C}$-mutant solid tumors. We report the primary analysis of elisrasib monotherapy in 5 cohorts: first-line (1L) non–small-cell lung cancer (NSCLC), previously treated (2L+) NSCLC, previously treated and G12Ci-refractory (3L+) NSCLC, 2L+ colorectal cancer (CRC), and 2L+ pancreatic ductal adenocarcinoma (PDAC). The primary objective was safety/tolerability; secondary objectives included antitumor activity (objective response rate [ORR], duration of response [DOR], progression-free survival [PFS]) and pharmacokinetics.

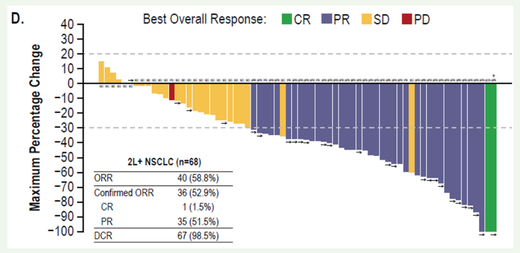
Eligible patients were aged ≥18 years with a metastatic/locally advanced solid tumor, a *KRAS*$^{G12C}$ mutation, no other actionable mutations, measurable disease (RECIST v1.1), an Eastern Cooperative Oncology Group performance status score 0-1, and adequate organ/marrow function. The 1L NSCLC cohort had received no prior systemic therapy for advanced disease and had known PD-L1 expression. The 2L+ NSCLC cohort had received ≥1 prior systemic therapy (no prior KRAS$^{G12C}$ inhibitor); the 3L+ NSCLC cohort was refractory to a prior G12C inhibitor (received 1 prior KRAS$^{G12C}$ inhibitor with best response of complete/partial response or stable disease for ≥6 months). The 2L+ CRC and 2L+ PDAC cohorts had received ≥1 prior therapy line without prior KRAS$^{G12C}$ inhibitors. For all cohorts, patients with neurologically asymptomatic, stable brain metastases were eligible.

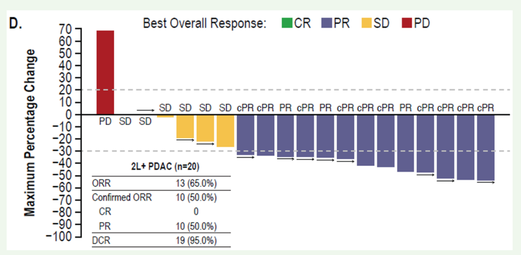
## Results

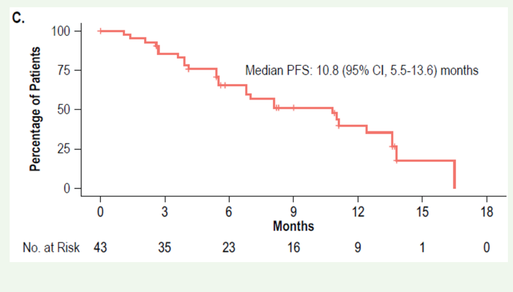
In 1L NSCLC (n=43), ORR was 78.0%, median DOR was 9.7 months, and median PFS was 10.8 months. In 2L+ NSCLC (n=69), ORR was 58.8%, median DOR was 16.5 months, and median PFS was 12.2 months. In 3L+ NSCLC (G12Ci-refractory; n=32), ORR was 32.3%, median DOR was 15.6 months, and median PFS was 8.1 months. In 2L+ CRC (n=34), ORR was 46.9%, median DOR was 13.1 months, and median PFS was 9.5 months. In 2L+ PDAC (n=20), ORR was 65.0%, median DOR was 10.8 months, and median PFS was 13.5 months. The most common treatment-related adverse events (TRAEs) were nausea (64.6%), diarrhea (40.9%), and vomiting (37.9%). TRAEs were primarily grade 1 or 2 and infrequently led to elisrasib dose reduction (8.1%) or discontinuation (1.5%).

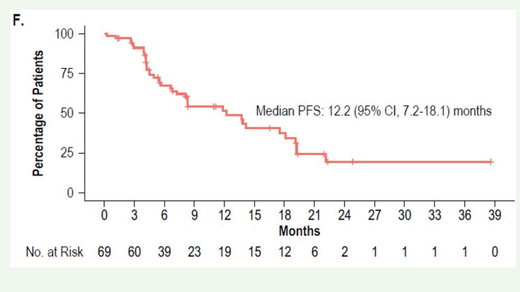
| Event, n (%) | NSCLC (n=144) | | 2L+ CRC (n=34) | | 2L+ PDAC (n=20) | | All patients (n=198) | |
|---|---|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Nausea | 94 (65.3) | 2 (1.4) | 22 (64.7) | 1 (2.9) | 12 (60.0) | 0 | 128 (64.6) | 3 (1.5) |
| Diarrhea | 63 (43.8) | 1 (0.7) | 13 (38.2) | 2 (5.9) | 5 (25.0) | 0 | 81 (40.9) | 3 (1.5) |
| Vomiting | 52 (36.1) | 0 | 19 (55.9) | 0 | 4 (20.0) | 0 | 75 (37.9) | 0 |
| Lipase increased | 38 (26.4) | 3 (2.1) | 5 (14.7) | 1 (2.9) | 2 (10.0) | 0 | 45 (22.7) | 4 (2.0) |
| Amylase increased | 29 (20.1) | 0 | 6 (17.6) | 0 | 1 (5.0) | 0 | 36 (18.2) | 0 |
| Anemia | 22 (15.3) | 0 | 10 (29.4) | 0 | 1 (5.0) | 0 | 33 (16.7) | 0 |
| Decreased appetite | 24 (16.7) | 2 (1.4) | 4 (11.8) | 0 | 1 (5.0) | 0 | 29 (14.6) | 2 (1.0) |
| Neutrophil count decreased | 19 (13.2) | 0 | 7 (20.6) | 2 (5.9) | 0 | 0 | 26 (13.1) | 2 (1.0) |
| White blood cell count decreased | 18 (12.5) | 0 | 4 (11.8) | 0 | 0 | 0 | 22 (11.1) | 0 |
| Hypertriglyceridemia | 19 (13.2) | 1 (0.7) | 2 (5.9) | 0 | 0 | 0 | 21 (10.6) | 1 (0.5) |
| Hyperglycemia | 18 (12.5) | 0 | 2 (5.9) | 0 | 1 (5.0) | 0 | 21 (10.6) | 0 |

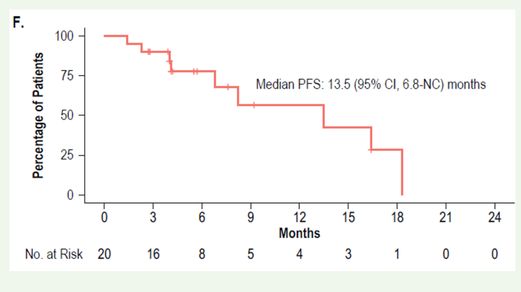



## Conclusion

Elisrasib demonstrated robust and durable efficacy and favorable safety across tumor types and treatment settings, including tumors refractory to first-generation KRAS G12Cis. Elisrasib monotherapy showed promising efficacy as 1L therapy for *KRAS*$^{G12C}$-mutant NSCLC, with an ORR of 78.0% (70.6% in patients with PD-L1 TPS <1%; 83.3% in patients with PD-L1 TPS ≥1%) and median PFS of 10.8 months. To our knowledge, elisrasib is the first KRAS$^{G12C}$ inhibitor to demonstrate efficacy as monotherapy in the 1L NSCLC population.

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