Supplementary Appendix

Supplement to: 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. DOI: 10.1056/NEJMoa2208470

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Sotorasib in *KRAS* p.G12C–mutated Advanced Pancreatic Cancer

Table of contents

Supplementary Methods

Trial assessments

Objective response (OR) was defined as complete response (CR) or partial response (PR) with confirmatory repeat assessment at least 4 weeks after the first detection of response. Time to response (TTR) was defined as the time from the start of treatment with sotorasib to the first objective tumor response. Duration of response (DoR) was measured from first CR or PR until progressive disease or death, whichever was earlier. Disease control rate (DCR) was defined as the proportion of patients with OR or stable disease [standard deviation (SD); minimum time interval ≥ 5 weeks for SD]. Progression-free survival (PFS) was defined as the start of treatment until disease progression or death from any cause, whichever occurred first. Overall survival (OS) was defined as the start of treatment to death.

Treatment-emergent adverse events (TEAEs) included all adverse events (AEs) that began after the first dose of sotorasib through 30 days after the end of treatment. Treatment-related AEs (TRAEs) were TEAEs considered to be related to sotorasib by the investigator.

Baseline plasma samples were analyzed for genomic alterations in cell-free DNA using the Guardant360 assay (Guardant Health, Palo Alto, CA), with mutations reported per test manufacturer's specifications. Variants were then filtered down to retain somatic single-nucleotide variants (SNVs) or insertions or deletions (INDELs) that were nonsynonymous or affecting a splice (acceptor/donor/regional) site, and non-aneuploid copy number variations (CNVs). If the oncogene/tumor suppressing gene status was known, only increases from known oncogenes or CNV decreases from known tumor suppressing genes were retained.

Trial oversight

The trial was funded by the sponsor, Amgen, and was designed by employees of the sponsor in collaboration with the investigators. The data were collected by investigators and analyzed by statisticians employed by the sponsor. The responses were assessed by BICR. A medical writer employed by the sponsor supported the authors in drafting of the manuscript and provided editorial assistance. All authors contributed to the data interpretation, reviewed the draft manuscript, and provided input for revisions. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Statistical analysis

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later was used to code all events categorized as AEs to a system organ class and a preferred term. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

No imputation was done for time-to-event endpoints. For safety summary of TRAEs, an AE with unknown treatment relation was assumed to be a TRAE (one case, grade 1 frequent bowel movements).

Supplementary Results

Trial population

Among select regimens, 29 (76.3%) patients received prior FOLFIRINOX, 25 (65.8%) received prior gemcitabine with nab-paclitaxel, and 17 (44.7%) received both. Five (13.2%) patients received a prior regimen of 5-FU with nanoliposomal irinotecan. A total of 17 (44.7%) patients received FOLFIRINOX and 14 (36.8%) received gemcitabine with nab-paclitaxel as 1L treatment.

Supplementary Figures

Figure S1. Patient Disposition.

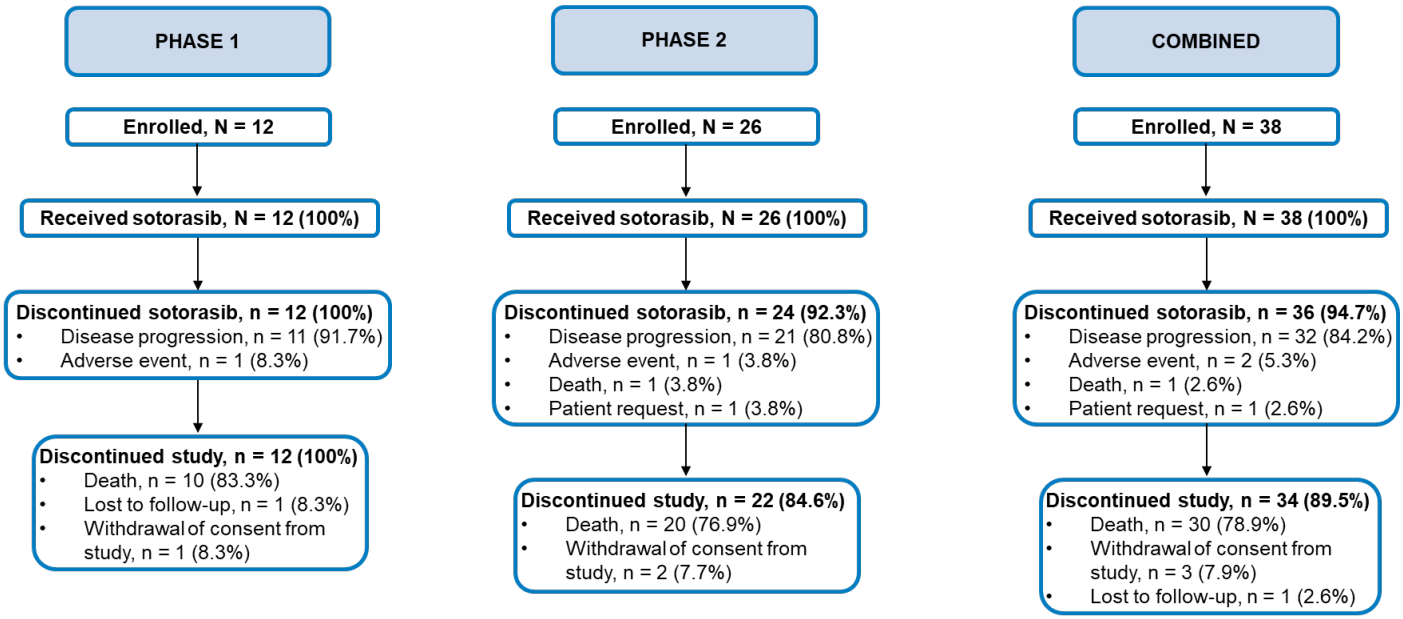
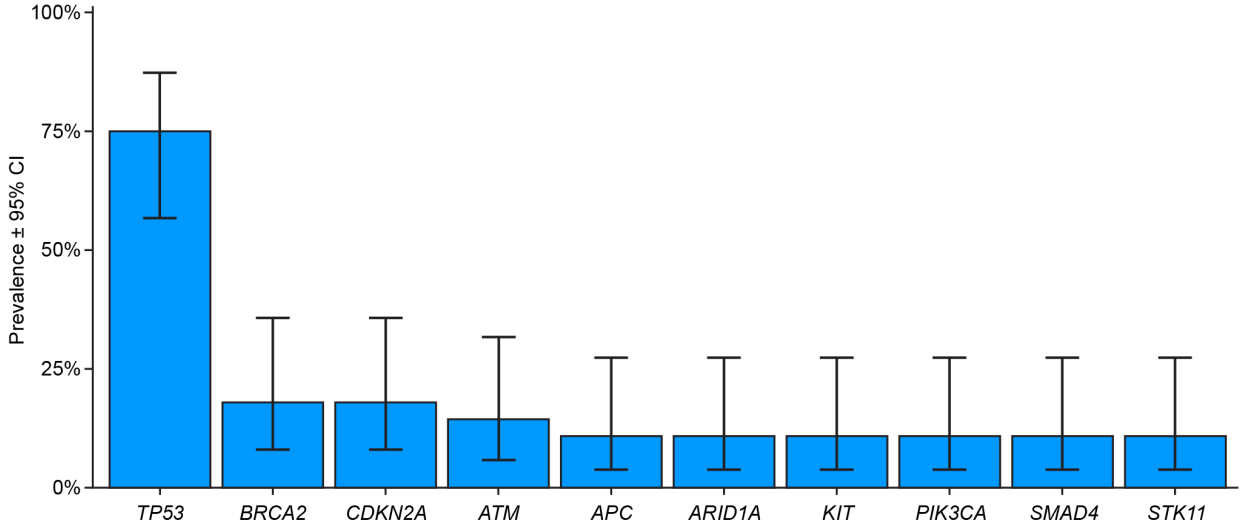
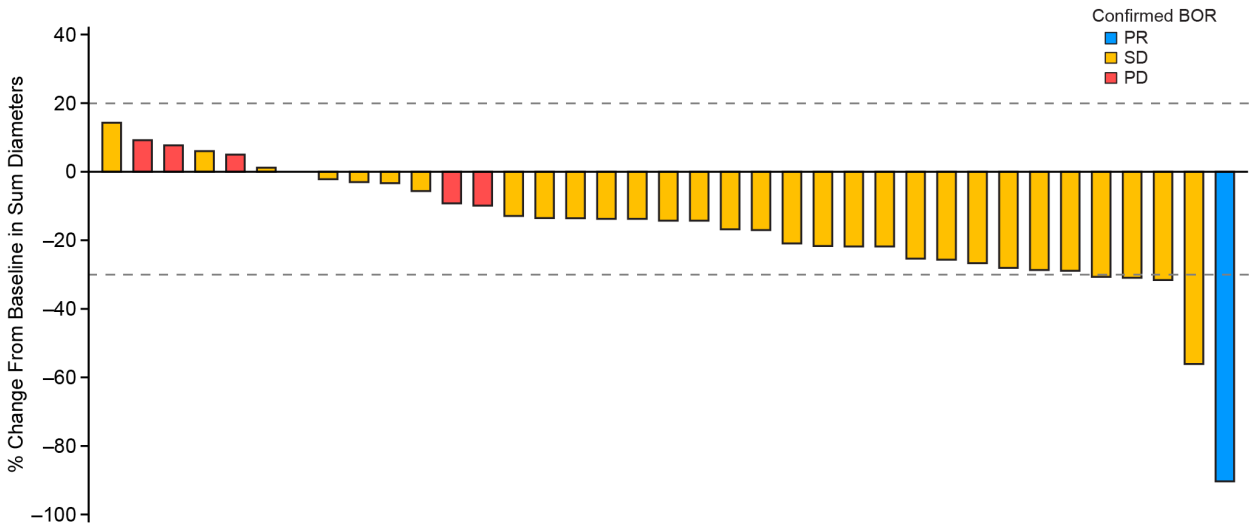


Figure S2. Most Common (> 10%) Co-driver Mutations.



CI, confidence interval

Figure S3. Best Percentage Change From Baseline in the Tumor Burden Per Investigator's Assessment.



BOR, best objective response; PR, partial response; PD, progressive disease; SD, stable disease.

Table S1. Details of Therapeutic Regimens Received by the Patients Who Discontinued Sotorasib.

Patient	Treatment
1	Capecitabine followed by oxaliplatin
2	Radiotherapy
3	Irinotecan
4	GNP
5	Combination of sotorasib and MEK inhibitor
6	PA18-0712
7	FOLFOX
8	FOLFOX followed by olaparib
9	5-FU/irinotecan liposomal injection/leucovorin followed by capecitabine
10	Combination of gemcitabine and nab-paclitaxel

5-FU, 5-fluorouracil; FOLFOX, leucovorin, 5-FU, and oxaliplatin; GNP, gemcitabine plus nab-paclitaxel; MEK, mitogen-activated extracellular signal–regulated kinase.

Table S2. Efficacy of Sotorasib as per Investigator's Assessment.

	Phase 1 (n = 12)	Phase 2 (n = 26)	Combined phase 1/2 (n = 38)
Best overall response, n (%)			
Confirmed CR	0	0	0
Confirmed PR	1 (8.3)	0 (0.0)	1 (2.6)
SD	8 (66.7)	23 (88.5)	31 (81.6)
PD	2 (16.7)	3 (11.5)	5 (13.2)
Not evaluable	0	0	0
Not assessed	1 (8.3)	0	1 (2.6)
ORR, % (95% CI)	8.3 (0.2–38.5)	0 (0.0–13.2)	2.6 (0.1–13.8)
DCR, % (95% CI)	75.0 (42.8–94.5)	88.5 (69.9–97.6)	84.2 (68.8–94.0)
Time to objective response, months, median (range)*	1.4 (1.4–1.4)	Not applicable†	1.4 (1.4–1.4)
Median DoR, months (95% CI)*	Not applicable†	Not applicable†	Not applicable†

*Calculated among confirmed responders.
†Kaplan-Meier estimate is not provided due to the small number of responders.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table S3. Summary of PFS as Assessed by the BICR Committee and per Investigator's Assessment.

	BICR Assessment			Investigator Assessment		
	Phase 1 (n = 12)	Phase 2 (n = 26)	Combined phase 1/2 (n = 38)	Phase 1 (n = 12)	Phase 2 (n = 26)	Combined phase 1/2 (n = 38)
Patient status						
Events, n (%)	11 (91.7)	18 (69.2)	29 (76.3)	12 (100.0)	25 (96.2)	37 (97.4)
PD	6 (50.0)	13 (50.0)	19 (50.0)	7 (58.3)	19 (73.1)	26 (68.4)
Death due to any cause	5 (41.7)	5 (19.2)	10 (26.3)	5 (41.7)	6 (23.1)	11 (28.9)
Censored, n (%)	1 (8.3)	8 (30.8)	9 (23.7)	0 (0.0)	1 (3.8)	1 (2.6)
On study without disease progression	0 (0.0)	2 (7.7)	2 (5.3)	0 (0.0)	1 (3.8)	1 (2.6)
Missed more than one consecutive assessments	0 (0.0)	3 (11.5)	3 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)
Started new anti-cancer therapy	1 (8.3)	1 (3.8)	2 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent	0 (0.0)	2 (7.7)	2 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Progression-free survival (KM), months						
25th percentile (95% CI)	1.58 (0.59–2.76)	2.79 (1.41–3.98)	2.69 (1.41–3.32)	2.10 (0.59–3.68)	2.92 (1.61–4.17)	2.76 (1.45–3.68)
Median (95% CI)	2.79 (1.22–4.30)	5.45 (3.32–7.82)	3.98 (2.79–5.59)	3.88 (0.92–4.30)	5.14 (3.32–6.83)	4.16 (3.32–5.39)
75th percentile (95% CI)	4.22 (2.76–NE)	8.25 (5.45–NE)	7.06 (4.30–NE)	4.22 (3.68–NE)	7.82 (5.45–8.77)	6.83 (4.47–8.25)

Min, Max (+ for censored)	0.6, 5.6	1.0, 11.0+	0.6, 11.0+	0.6, 8.9	1.0, 11.0	0.6, 11.0
KM estimate (95% CI)[a]						
At 3 months	41.67 (15.25–66.53)	72.02 (50.04–85.59)	62.09 (44.48–75.56)	58.33 (27.01–80.09)	73.08 (51.69–86.15)	68.42 (51.15–80.67)
At 6 months	0.00 (NE–NE)	45.19 (24.43–63.91)	31.61 (16.65–47.72)	8.33 (0.51–31.11)	34.62 (17.46–52.48)	26.32 (13.69–40.81)
At 9 months	0.00 (NE–NE)	14.12 (2.66–34.76)	9.88 (1.95–25.62)	0.00 (NE–NE)	7.69 (1.34–21.73)	3.95 (0.38–15.34)
Follow-up time for PFS[b] (KM) (months)						
25th percentile (95% CI)	4.34 (4.34–NE)	5.39 (1.58–8.80)	4.90 (4.34–8.80)	NE (NE–NE)	8.80 (8.80–NE)	8.80 (8.80–NE)
Median (95% CI)	NE (4.34–NE)	8.80 (4.90–NE)	8.80 (4.90–NE)	NE (NE–NE)	NE (8.80–NE)	NE (8.80–NE)
75th percentile (95% CI)	NE (4.34–NE)	10.97 (8.08–NE)	10.97 (8.08–NE)	NE (NE–NE)	NE (8.80–NE)	NE (8.80–NE)
Min, Max (+ for censored)	0.6+, 5.6+	1.0+, 11.0	0.6+, 11.0	0.6+, 8.9+	1.0+, 11.0+	0.6+, 11.0+

CI, confidence interval; KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; PD, progressive disease; PFS, progression-free survival.

Table S4: Full List of Treatment-related Adverse Events by System Organ Class and Preferred Term and Worst Grade.

	Phase 1 (n = 12)	Phase 2 (n = 26)	Combined phase 1/2 (n = 38)
Number of subjects reporting treatment-related adverse events	5 (41.7)	11 (42.3)	16 (42.1)
Any system organ class	5 (41.7)	11 (42.3)	16 (42.1)
Any preferred term	5 (41.7)	11 (42.3)	16 (42.1)
Grade 1 or 2	5 (41.7)	5 (19.2)	10 (26.3)
Grade 3	0 (0.0)	6 (23.1)	6 (15.8)
Blood and lymphatic system disorders	2 (16.7)	1 (3.8)	3 (7.9)
Anemia	2 (16.7)	1 (3.8)	3 (7.9)
Grade 1 or 2	2 (16.7)	1 (3.8)	3 (7.9)
Thrombocytopenia	1 (8.3)	0 (0.0)	1 (2.6)
Grade 1 or 2	1 (8.3)	0 (0.0)	1 (2.6)
Gastrointestinal disorders	2 (16.7)	4 (15.4)	6 (15.8)
Diarrhea	2 (16.7)	2 (7.7)	4 (10.5)
Grade 1 or 2	2 (16.7)	0 (0.0)	2 (5.3)

Grade 3	0 (0.0)	2 (7.7)	2 (5.3)
Abdominal pain	1 (8.3)	1 (3.8)	2 (5.3)
Grade 1 or 2	1 (8.3)	0 (0.0)	1 (2.6)
Grade 3	0 (0.0)	1 (3.8)	1 (2.6)
Abdominal distension	0 (0.0)	2 (7.7)	2 (5.3)
Grade 1 or 2	0 (0.0)	2 (7.7)	2 (5.3)
Constipation	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Frequent bowel movements	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Nausea	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
General disorders and administration site conditions	2 (16.7)	3 (11.5)	5 (13.2)
Asthenia	1 (8.3)	0 (0.0)	1 (2.6)
Grade 1 or 2	1 (8.3)	0 (0.0)	1 (2.6)
Fatigue	1 (8.3)	3 (11.5)	4 (10.5)

Grade 1 or 2	1 (8.3)	1 (3.8)	2 (5.3)
Grade 3	0 (0.0)	2 (7.7)	2 (5.3)
Hepatobiliary disorders	0 (0.0)	1 (3.8)	1 (2.6)
Drug-induced liver injury	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Infections and infestations	0 (0.0)	1 (3.8)	1 (2.6)
Hepatitis B reactivation	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Investigations	1 (8.3)	1 (3.8)	2 (5.3)
Transaminases increased	1 (8.3)	0 (0.0)	1 (2.6)
Grade 1 or 2	1 (8.3)	0 (0.0)	1 (2.6)
Alanine aminotransferase increased	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	1 (3.8)	1 (2.6)
Aspartate aminotransferase increased	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	0 (0.0)	0 (0.0)

Grade 3	0 (0.0)	1 (3.8)	1 (2.6)
Blood alkaline phosphatase increased	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Neutrophil count decreased	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
White blood cell count decreased	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Metabolism and nutrition disorders	0 (0.0)	1 (3.8)	1 (2.6)
Hypophosphatemia	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	1 (3.8)	1 (2.6)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (7.7)	2 (5.3)
Pleural effusion	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	1 (3.8)	1 (2.6)
Pulmonary embolism	0 (0.0)	1 (3.8)	1 (2.6)
Grade 1 or 2	0 (0.0)	0 (0.0)	0 (0.0)

Grade 3	0 (0.0)	1 (3.8)	1 (2.6)
Skin and subcutaneous tissue disorders	1 (8.3)	0 (0.0)	1 (2.6)
Rash	1 (8.3)	0 (0.0)	1 (2.6)
Grade 1 or 2	1 (8.3)	0 (0.0)	1 (2.6)
Vascular disorders	1 (8.3)	0 (0.0)	1 (2.6)
Hypertension	1 (8.3)	0 (0.0)	1 (2.6)
Grade 1 or 2	1 (8.3)	0 (0.0)	1 (2.6)