ASCO® Plenary Series

KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients With Advanced Solid Tumors Harboring a $KRAS^{G12C}$ Mutation

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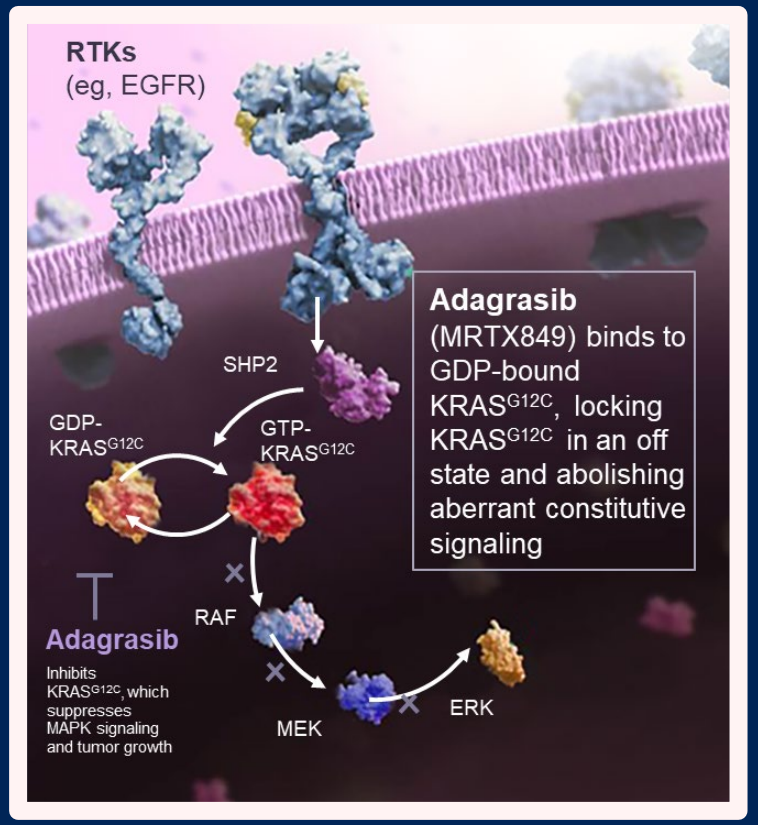
Disclosures

- Consulting/Advisory Board: Zymeworks, Ipsen, Novartis, Janssen

Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- KRAS^{G12C} mutations act as oncogenic drivers in a range of solid tumors:
  - NSCLC (~14%)[1]
  - CRC (3–4%)[1–3]
  - Appendiceal (3–4%)[1,2]
  - Ovarian (0.4%)[1]
  - PDAC (1–3%)[4]
  - Small bowel (1–3%)[1,2]
  - Biliary tract (1%)[2]
  - Endometrial (1.5%)[1]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, was selected for favorable properties, including a long half-life (23 hours), dose-dependent PK and CNS penetration[5–7]
- Adagrasib has been granted accelerated approval by the FDA and is under review by the EMA for the treatment of KRAS^{G12C}-mutated NSCLC
- Adagrasib has been granted breakthrough therapy designation, in combination with cetuximab, for the treatment of patients with KRAS^{G12C}-mutated CRC



KRYSTAL-1 (849-001) Phase 2 Solid Tumors Cohort: Study Design

Key Eligibility Criteria

- Histologically confirmed diagnosis of a solid tumor malignancy with a KRAS^{G12C} mutation[a], excluding NSCLC and CRC
- Unresectable or metastatic disease
- No other available treatment with curative intent[b]
- ECOG PS 0–1

Adagrasib 600 mg oral BID[c]
N=64[d]

Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1)
- Secondary endpoints: DOR, PFS, OS and safety

- Preliminary data from this Phase 2 cohort evaluating adagrasib (600 mg oral BID) in patients with previously treated GI tumors (N=30; excluding CRC) demonstrated clinical activity and manageable safety (median follow-up: 6.3 months)[8]
- Here we report updated data from this Phase 2 cohort of patients with KRAS^{G12C}-mutated solid tumors, other than NSCLC and CRC (data cutoff: October 1, 2022; median follow-up: 16.8 months)

[a]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA per protocol; [b]Patients were ineligible for, declined or had no available standard-of-care treatment option; [c]All patients who received adagrasib initially received a capsule formulation and 18 patients (29%) later transitioned to a tablet formulation; [d]64 patients were enrolled and 63 patients had received ≥1 dose of adagrasib at data cutoff

Demographic and Baseline Characteristics

Characteristic	Adagrasib monotherapy (N=64)
Median age, years (range)	65 (21–89)
Female, n (%)	33 (51.6)
Ethnicity, n (%)	
White	48 (75.0)
Black or African American	6 (9.4)
Asian / Other	3 (4.7) / 7 (10.9)
ECOG PS, n (%)[a]	
0 / 1	24 (37.5) / 39 (60.9)
Tumor Type[b], n	
PDAC[c]	21
BTC[d,e]	12
Appendiceal	10
Ovarian	5
Unknown primary	4
GEJ/esophageal	4
Endometrial	3
Small bowel	3
Breast	1
Glioblastoma	1
Prior Lines of systemic anticancer therapy	
Median (range)	2 (0–7)
0 / 1 / 2 / 3 / ≥4, %	7.8 / 21.9 / 35.9 / 18.8 / 15.6

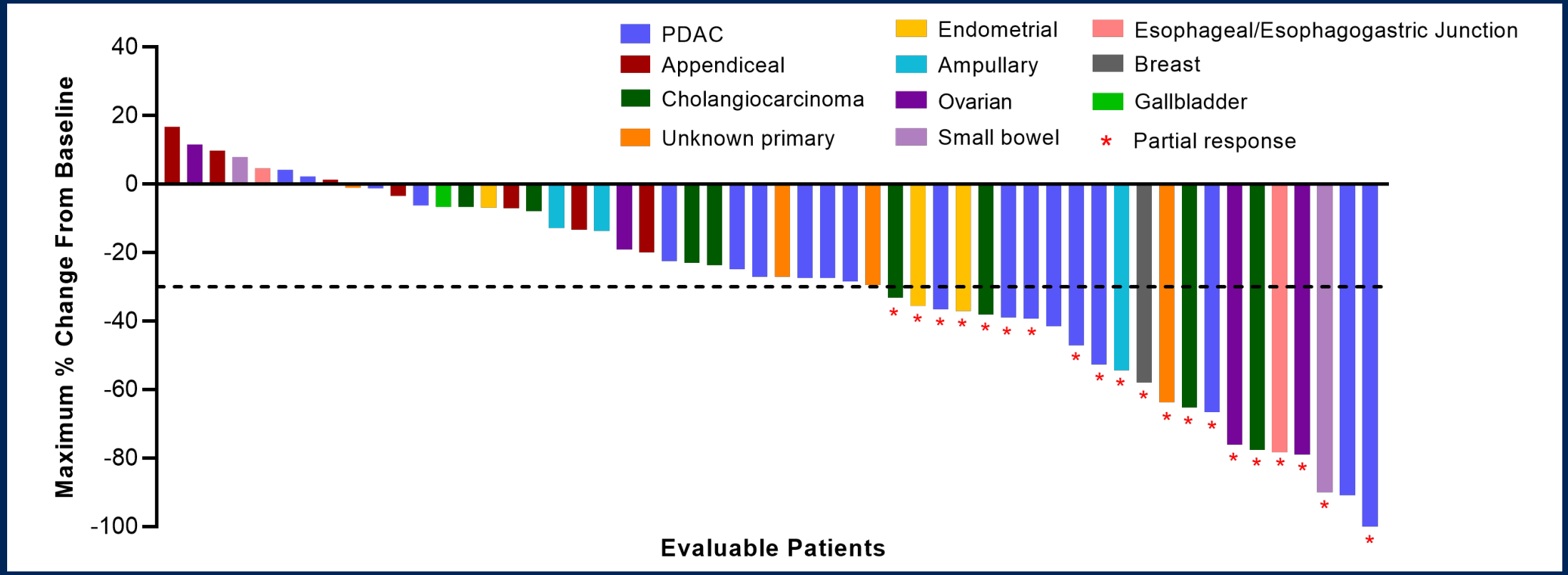
[a]ECOG PS was unavailable for one patient (1.6%); [b]Excluding non-small cell lung cancer and colorectal cancer; [c]For patients with PDAC, 81.0% previously received gemcitabine-based regimen(s) and 85.7% received prior fluoropyrimidine-based regimen(s); [d]Includes cholangiocarcinoma, ampullary and gallbladder tumors; [e]For patients with biliary tract cancer, 83.3% received gemcitabine-based regimen(s) and 66.7% received prior fluoropyrimidine-based regimen(s). Data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With Solid Tumors[a]: Objective Response Rate

Efficacy outcome	Overall solid tumors, n (%) (n=57)[b]
Objective response rate	20 (35.1)
Best overall response	
Complete response	0 (0.0)
Partial response	20 (35.1)
Stable disease	29 (50.9)
Progressive disease	5 (8.8)
Not evaluable	3 (5.3)
Disease control rate	49 (86.0)

[a]Excluding non-small cell lung cancer and colorectal cancer; [b]Per BICR; full analysis set excludes 6 patients who did not have measurable disease at baseline per BICR
Per investigator assessment (n=63): objective response rate n=19 (30.2%), complete response n=0 (0.0%), partial response n=19 (30.2%), stable disease n=36 (57.1%), progressive disease n=5 (7.9%), disease control rate n=55 (87.3%)
Data as of October 1, 2022 (median follow-up: 16.8 months)

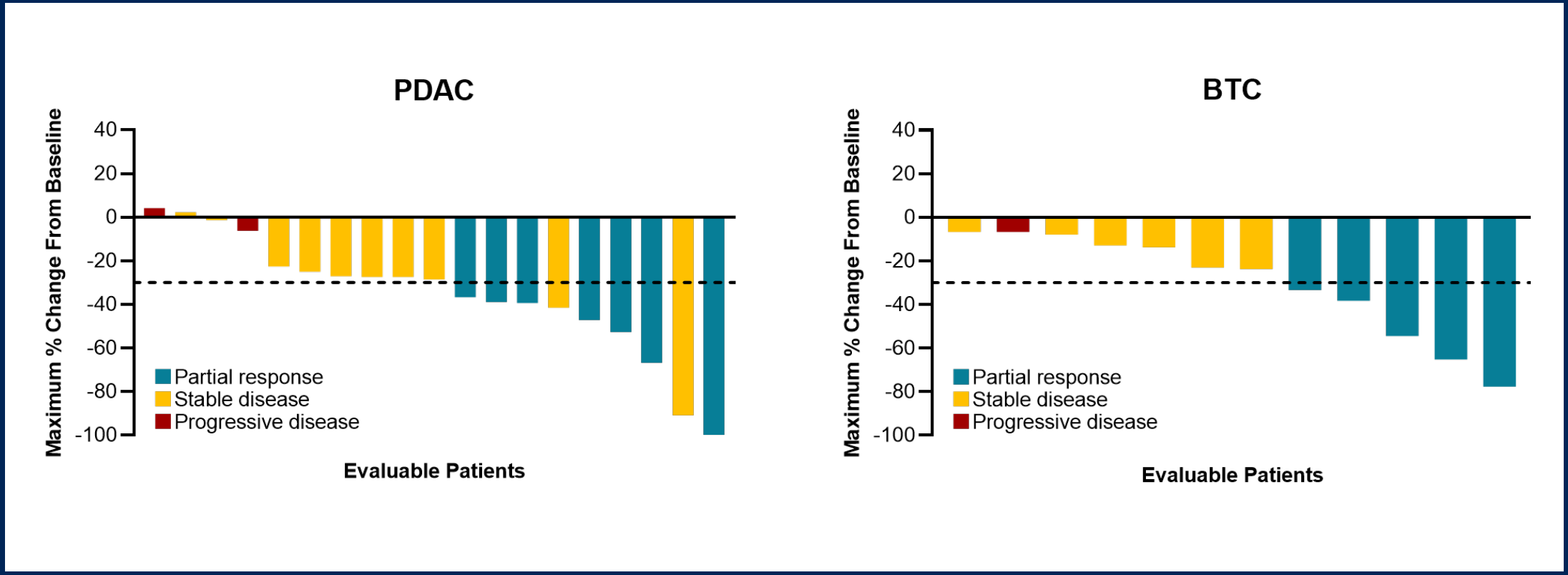
Adagrasib in Patients With Solid Tumors[a]: Best Tumor Change From Baseline



- Confirmed objective responses were observed in 20/57 patients (35.1%)
- Disease control was observed in 49/57 patients (86.0%)

[a]Excluding non-small cell lung cancer and colorectal cancer
All results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With PDAC and BTC: Best Tumor Change From Baseline



- Confirmed ORR of 33.3% (7/21 patients)
- Disease control was observed in 17/21 (81.0%) patients

- Confirmed ORR of 41.7% (5/12 patients)
- Disease control was observed in 11/12 (91.7%) patients

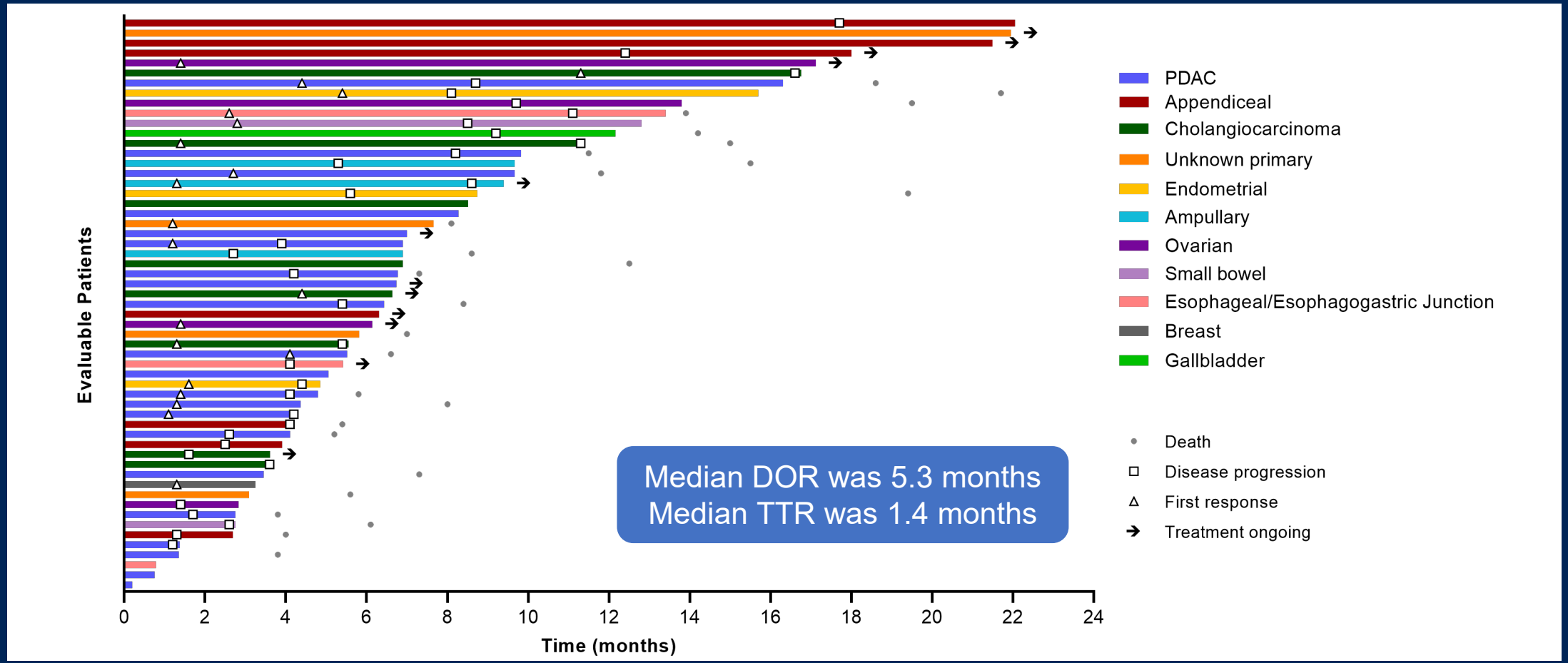
All results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With Solid Tumors[a]: Response by Tumor Type

Tumor Type	n	ORR, n (%)	DCR, n (%)
All patients	**57[b]**	**20 (35.1)**	**49 (86.0)**
PDAC	**21**	**7 (33.3)**	**17 (81.0)**
BTC	**12**	**5 (41.7)**	**11 (91.7)**
Other GI Tumors	**12**	**2 (16.7)**	**10 (83.3)**
Appendiceal	7	0 (0.0)	6 (85.7)
Small Bowel	2	1 (50.0)	2 (100.0)
GEJ/esophageal	3	1 (33.3)	2 (66.7)
Gynecological tumors	**7**	**4 (57.1)**	**6 (85.7)**
Ovarian	4	2 (50.0)	3 (75.0)
Endometrial	3	2 (66.7)	3 (100.0)
Other tumors	**5**	**2 (40.0)**	**5 (100.0)**
Unknown Primary	4	1 (25.0)	4 (100.0)
Breast	1	1 (100.0)	1 (100.0)

[a]Excluding non-small cell lung cancer and colorectal cancer; [b]Per BICR; full analysis set excludes 6 patients who did not have measurable disease at baseline per BICR
Data as of October 1, 2022 (median follow-up: 16.8 months)

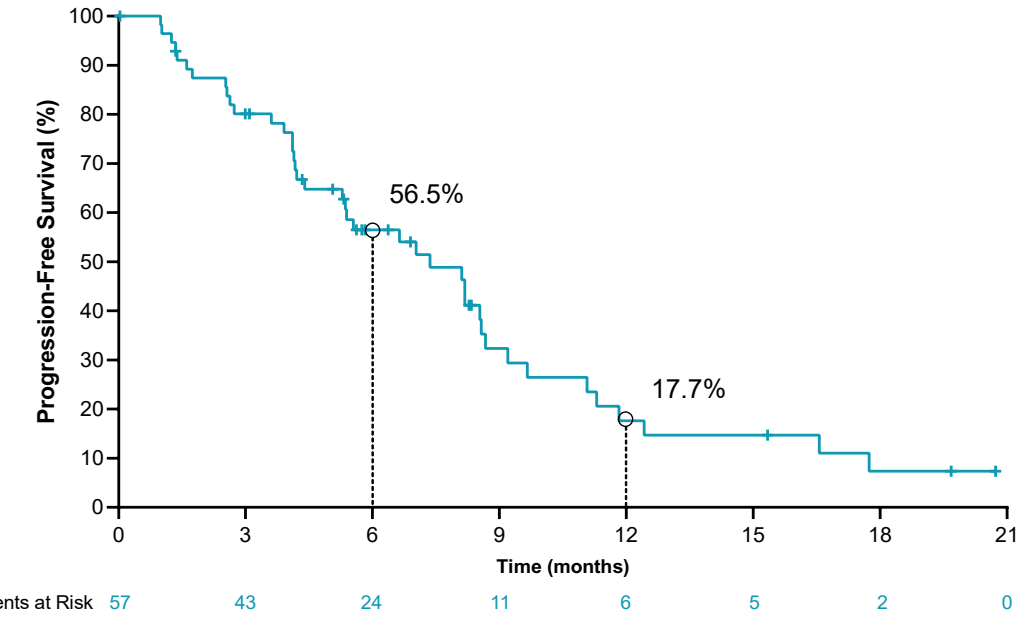
Adagrasib in Patients With Solid Tumors[a]: Duration of Treatment



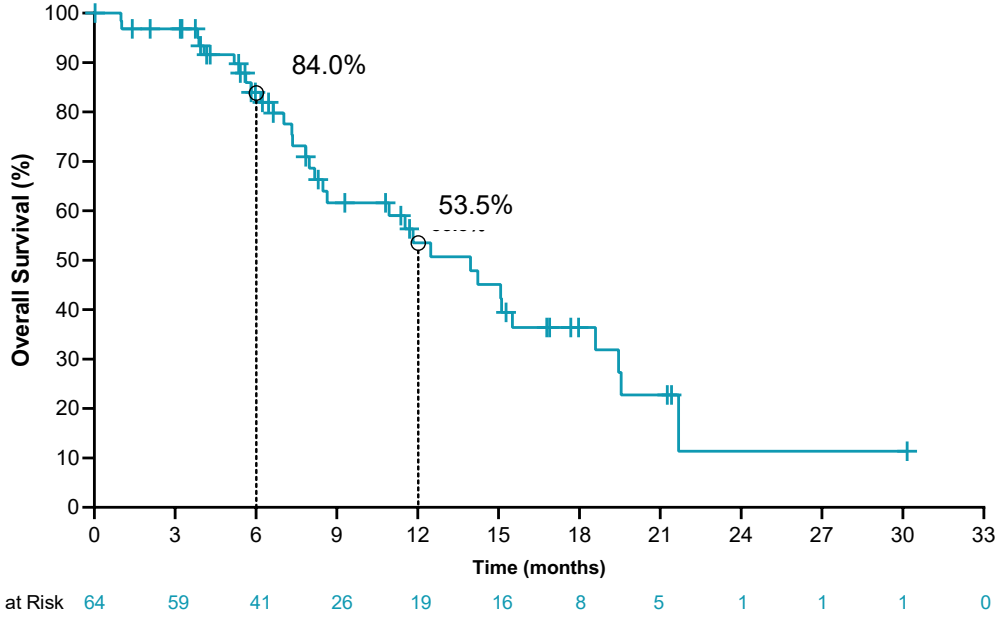
[a]Excluding non-small cell lung cancer and colorectal cancer
All results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With Solid Tumors[a]: Progression-Free Survival and Overall Survival

Overall median PFS was 7.4 months (95% CI 5.3–8.6)



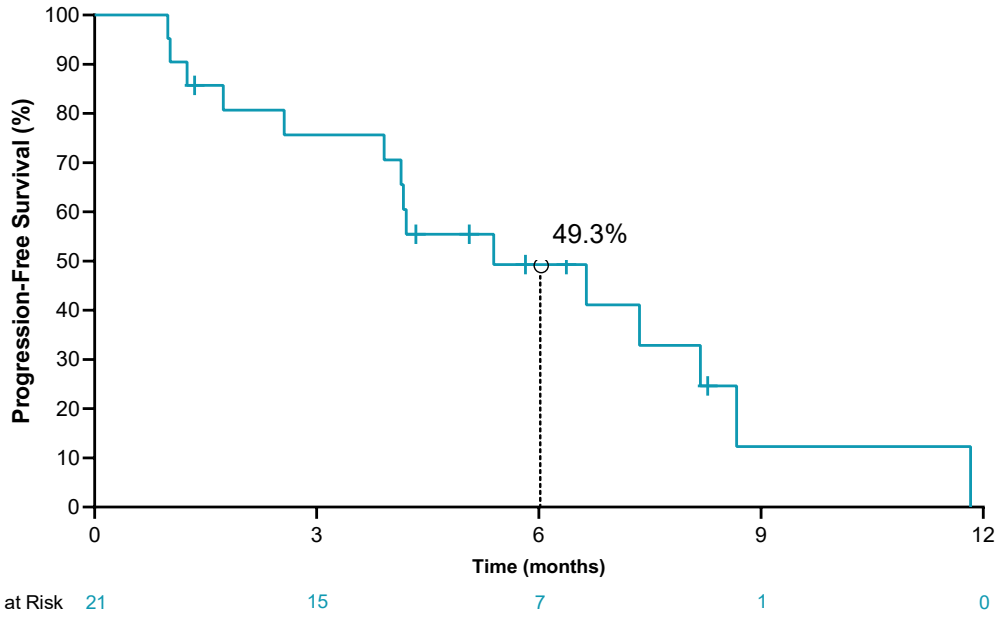
Overall median OS was 14.0 months (95% CI 8.5–18.6)



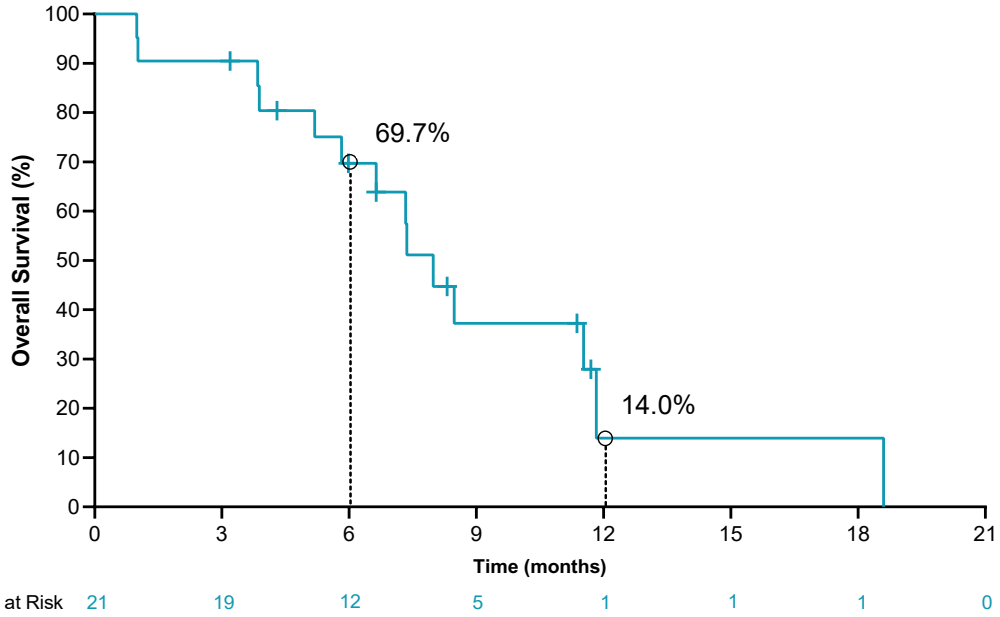
[a]Excluding non-small cell lung cancer and colorectal cancer
PFS results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With PDAC: Progression-Free Survival and Overall Survival

PDAC median PFS was 5.4 months (95% CI 3.9–8.2)



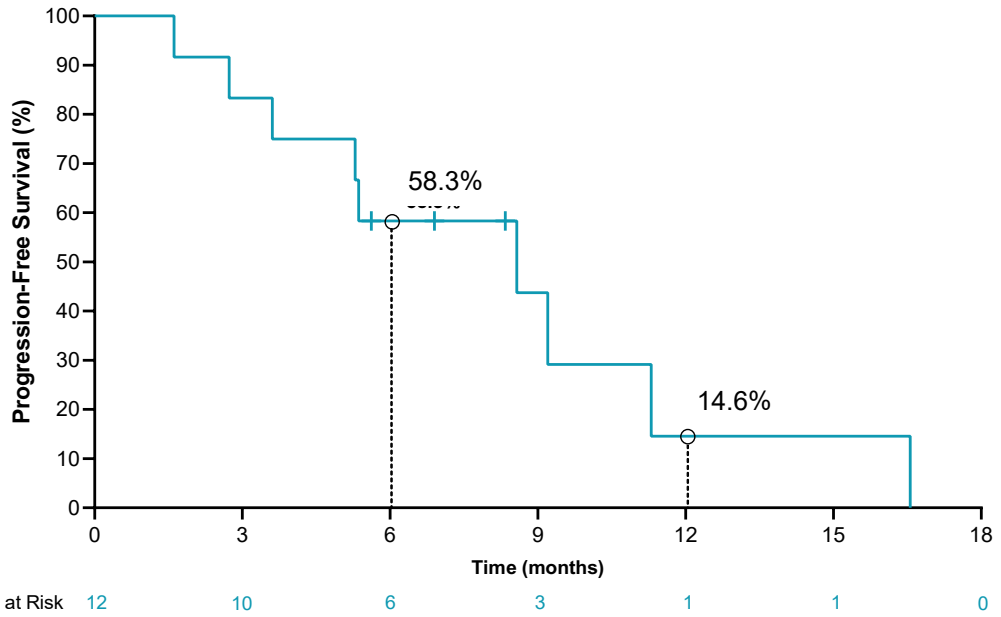
PDAC median OS was 8.0 months (95% CI 5.2–11.8)



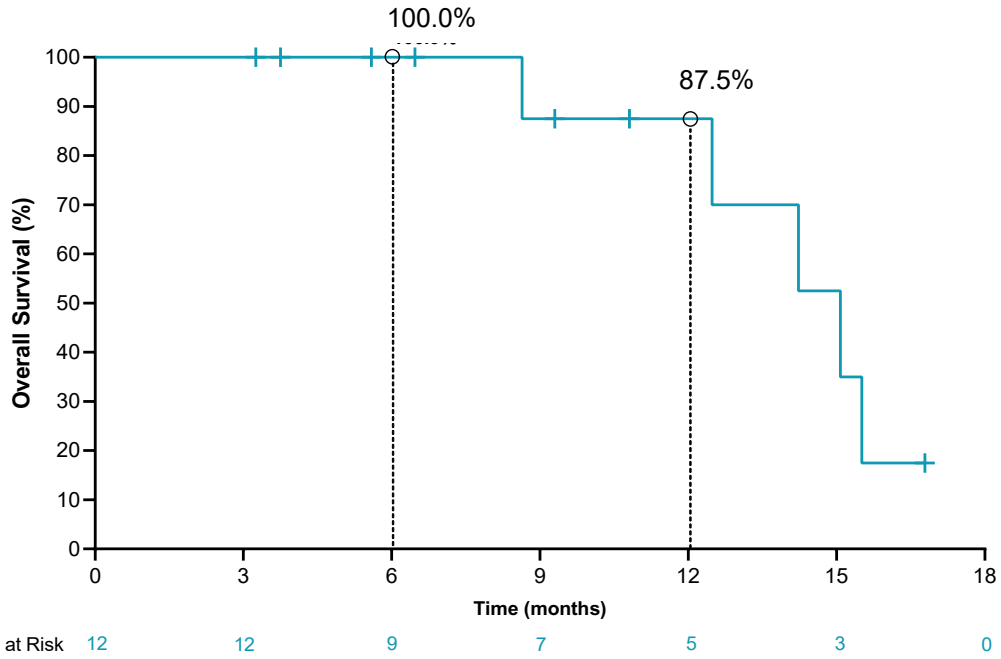
PFS results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With BTC[a]: Progression-Free Survival and Overall Survival

BTC median PFS was 8.6 months (95% CI 2.7–11.3)



BTC median OS was 15.1 months (95% CI 8.6–NE)



[a]BTC includes ampullary, cholangiocarcinoma and gallbladder tumors
PFS results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

Adagrasib in Patients With Solid Tumors[a]: Treatment-Related Adverse Events

TRAEs, n (%)	Overall solid tumors (N=63)			
	Any Grade	Grade 1	Grade 2	Grade 3
Any TRAEs	**61 (96.8)**	**16 (25.4)**	**28 (44.4)**	**16 (25.4)**
Most Frequent TRAEs[b]				
Nausea	31 (49.2)	23 (36.5)	7 (11.1)	1 (1.6)
Diarrhea	30 (47.6)	21 (33.3)	8 (12.7)	1 (1.6)
Fatigue	26 (41.3)	12 (19.0)	10 (15.9)	4 (6.3)
Vomiting	25 (39.7)	20 (31.7)	4 (6.3)	1 (1.6)
Blood creatinine increase	10 (15.9)	7 (11.1)	3 (4.8)	0 (0.0)
Anemia	9 (14.3)	3 (4.8)	5 (7.9)	1 (1.6)
AST increase	9 (14.3)	7 (11.1)	0 (0.0)	2 (3.2)
Decreased appetite	9 (14.3)	5 (7.9)	4 (6.3)	0 (0.0)
Peripheral edema	9 (14.3)	7 (11.1)	2 (3.2)	0 (0.0)
Electrocardiogram QT prolongation	8 (12.7)	3 (4.8)	1 (1.6)	4 (6.3)
Dysgeusia	7 (11.1)	6 (9.5)	1 (1.6)	0 (0.0)

- There was one Grade 4 TRAE (febrile neutropenia) and no Grade 5 TRAEs
- TRAEs led to dose reduction in 25 patients (39.7%) and dose interruptions in 28 patients (44.4%)
- No TRAEs led to treatment discontinuation

[a]Excluding non-small cell lung cancer and colorectal cancer; [b]Any grade occurring in ≥10% of patients
Data as of October 1, 2022 (median follow-up: 16.8 months); all 63 patients initially received a capsule formulation and 18 patients (29%) later transitioned to a tablet formulation

Conclusions

- This KRYSTAL-1 cohort is the largest phase 2 tumor agnostic dataset to evaluate KRAS^{G12C}-mutated solid tumors, excluding NSCLC and CRC
- Adagrasib monotherapy demonstrated clinically meaningful activity in a variety of KRAS^{G12C}-mutated solid tumors, for which no standard-of-care treatment options are available
- Clinical activity of adagrasib in patients with PDAC and BTC is noteworthy, as chemotherapy has limited clinical activity in these patient populations in the second-line setting[9,10]
- Adagrasib monotherapy is well tolerated and has a manageable safety profile
- KRAS^{G12C}-targeted agents may represent a novel, tumor agnostic treatment option for patients with solid tumors harboring a KRAS^{G12C} mutation

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Abbreviations

AST, aspartate aminotransferase
BICR, blinded independent central review
BID, twice daily
BTC, biliary tract cancer
CI, confidence interval
CNS, central nervous system
CRC, colorectal cancer
DCR, disease control rate
DOR, duration of response
ECOG PS, Eastern Cooperative Oncology Group Performance Status
EGFR, epidermal growth factor receptor
ERK, extracellular signal-regulated kinase
FDA, Food and Drug Administration
GI, gastrointestinal
GEJ, gastroesophageal junction
GDP, guanosine diphosphate
GTP, guanosine triphosphate
KRAS, kirsten rat sarcoma viral oncogene homolog
MEK, mitogen-activated protein kinase kinase
NE, not evaluable
NSCLC, non-small cell lung cancer
ORR, objective response rate
OS, overall survival
PD, progressive disease
PDAC, pancreatic ductal adenocarcinoma
PK, pharmacokinetics
PFS, progression-free survival
PR, partial response
RAF, rapidly accelerated fibrosarcoma
RTK, receptor tyrosine kinase
SHP2, Src homolog domain-containing phosphatase 2
TRAE, treatment-related adverse event
TTR, time to response