ASCO® Gastrointestinal Cancers Symposium

KRYSTAL-1: Updated Activity and Safety of Adagrasib (MRTX849) in Patients (Pts) With Unresectable or Metastatic Pancreatic Cancer (PDAC) and Other Gastrointestinal (GI) Tumors Harboring a KRAS^{G12C} Mutation

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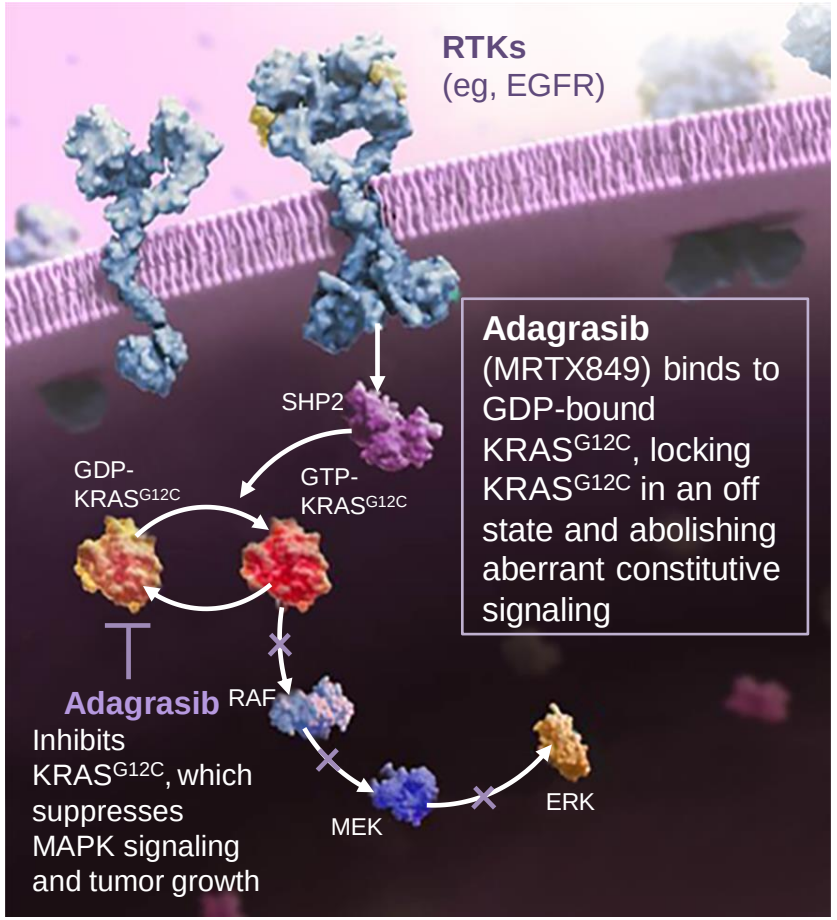
Adagrasib (MRTX849) is a Differentiated, Selective Inhibitor of KRAS^{G12C}

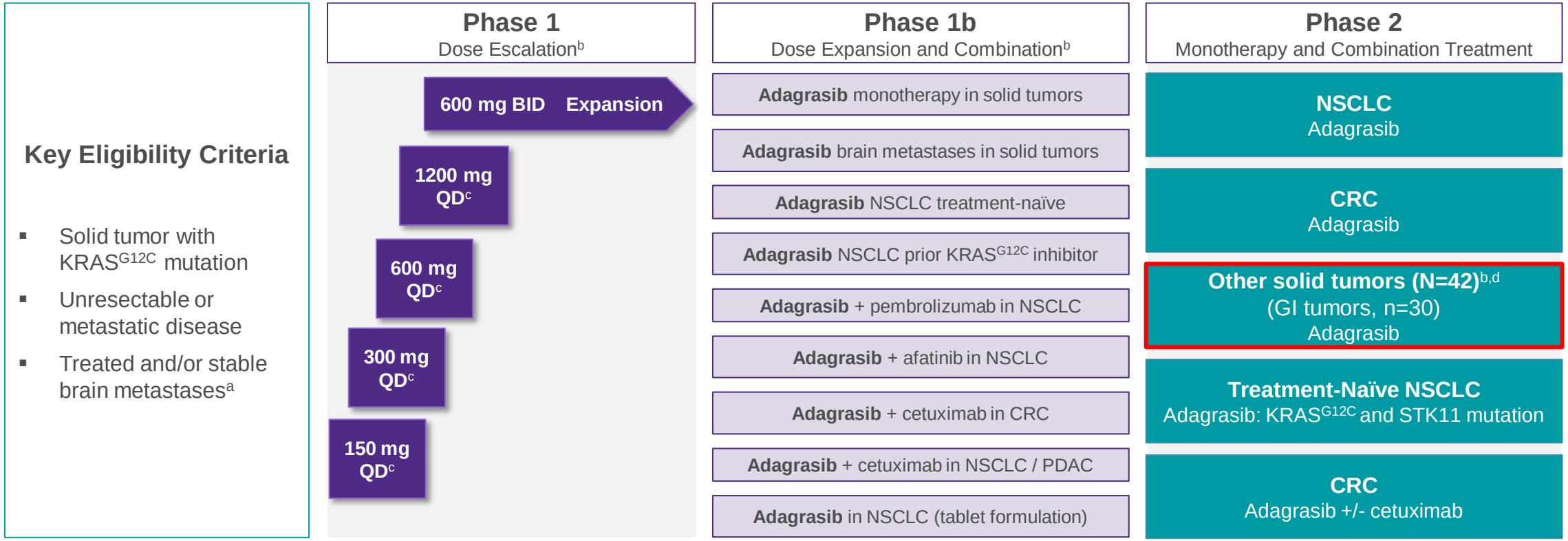
- KRAS mutations occur in approximately 90% of pancreatic cancer[1]; ~2% of these are KRAS^{G12C} mutations[2]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 hours[3,4]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor[5]:
  - Long half-life of ~24 hours
  - Dose-dependent PK
  - CNS penetration
- Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity



CNS, central nervous system; EGFR, epidermal growth factor receptor; PK, pharmacokinetics; RTK, receptor tyrosine kinase.

1. Prior IA, et al. *Cancer Res*. 2012;72(10):2457–2467. 2. Nollmann FI & Alexander Ruess D. *Biomedicines*. 2020;8(8):281. 3. Bos JL, et al. *Cell*. 2007;129:865–877. 4. Shukla S, et al. *Neoplasia*. 2014;16(2):115–128. 5. Hallin J, et al. *Cancer Discov*. 2020;10(1):54–71.

KRYSTAL-1 (849-001) Study Design



Phase 2 Endpoints **Primary:** ORR (RECIST 1.1) **Secondary:** DOR, PFS, OS, safety

- Previously reported data demonstrated clinical activity with adagrasib in patients with various KRAS^{G12C}-mutated solid tumors, including NSCLC, CRC and other tumors such as PDAC, ovarian and endometrial cancers, and cholangiocarcinoma[1–3]
- Here we report preliminary data from a Phase 2 cohort evaluating adagrasib 600 mg BID in patients with previously-treated GI tumors (n=30), excluding CRC, with a focus on PDAC (n=12) and other GI cancers (n=18), with a KRAS^{G12C} mutation

CRC, colorectal cancer; ctDNA, circulating tumor deoxyribonucleic acid; GI, gastrointestinal; NSCLC, non–small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

1. Jänne PA et al. Presented at: 2020 EORTC-NCI-AACR Symposium; Oct 25, 2020. 2. Weiss J et al. Presented at: 2021 ESMO Congress; Sept 19, 2021. 3. Johnson ML et al. Presented at: 2020 EORTC-NCI-AACR Symposium; Oct 25, 2020.

[a]Most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases; [b]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA; [c]Patients subsequently dose escalated up to 600 mg BID; [d]Solid tumors included GI tumors (n=30) and non-GI tumors (n=12).

Data as of 10 September 2021. ClinicalTrials.gov. NCT03785249.

Demographics and Baseline Characteristics

	PDAC (n=12)	Other GI cancers (n=18)	Overall GI cancers[a] (n=30)
Median age, y (range)	66.5 (40–80)	64.0 (54–89)	65.5 (40–89)
Female, n (%)	4 (33)	8 (44)	12 (40)
Race, n (%)			
White	7 (58)	13 (72)	20 (67)
Black or African American	1 (8)	2 (11)	3 (10)
Asian / Other	1 (8) / 3 (25)	1 (6) / 2 (11)	2 (7) / 5 (17)
ECOG PS, n (%)			
0 / 1	0 (0) / 12 (100)	6 (33) / 12 (67)	6 (20) / 24 (80)
Tumor type, n			
PDAC	**12**		**12**
Other GI		**18**	**18**
Biliary tract		8	8
Appendiceal		5	5
Gastro-esophageal junction		2	2
Small bowel		2	2
Esophageal		1	1
Prior lines of systemic anticancer therapy			
Median (range)	2.5 (1–4)[b]	2.0 (1–5)	2.0 (1–5)
1 / 2 / 3 / ≥4 / missing, %	8 / 42 / 42 / 8	22 / 39 / 11 / 22 / 6	17 / 40 / 23 / 17 / 3

Percentages may not add up to 100 due to rounding.
ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Excluding CRC; [b]All patients with PDAC received gemcitabine-based regimen(s), and all but 2 received prior fluoropyrimidine-based regimen(s).

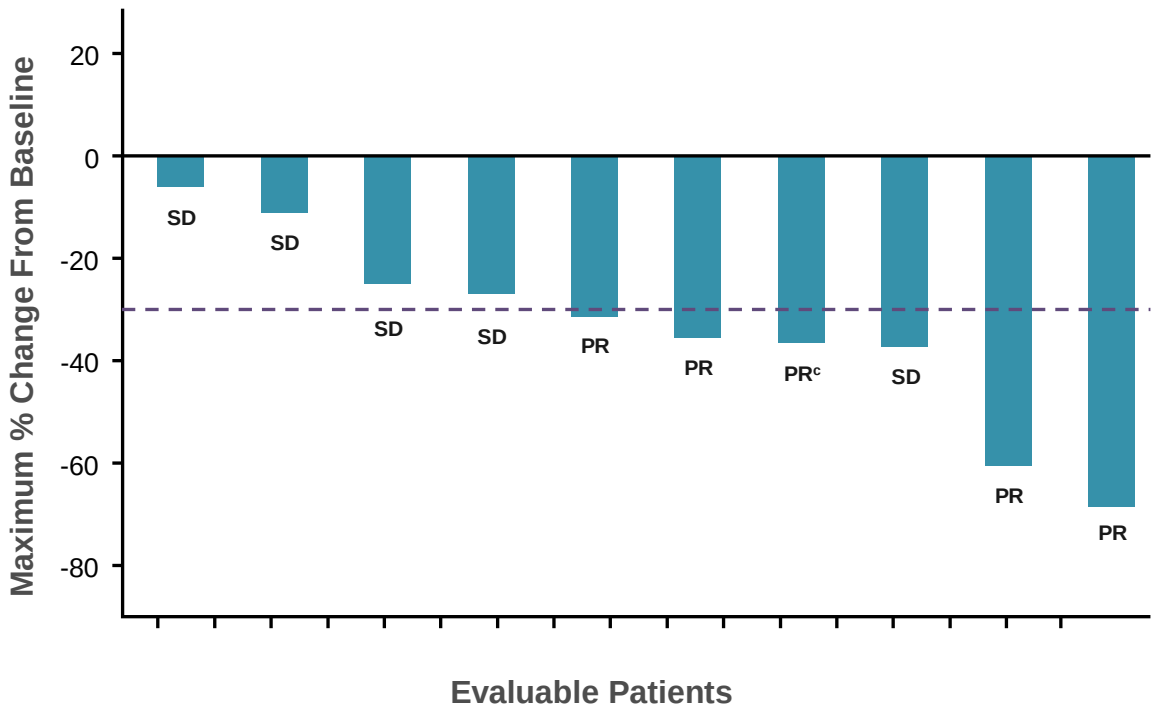
Adagrasib in Patients With PDAC and Other GI Tumors:[a] Objective Response Rate

Efficacy outcome[b], n (%)	PDAC (n=10)[c]	Other GI cancers (n=17)[d]	Overall GI cancers[a] (n=27)[c,d]
Objective response rate	5 **(50)**[e]	6 **(35)**[f]	11 **(41)**[g]
Best overall response			
Complete response (CR)	0 (0)	0 (0)	0 (0)
Partial response (PR)	5 (50)[e]	6 (35)[f]	11 (41)[g]
Stable disease (SD)	5 (50)	11 (65)	16 (59)
Disease control rate	10 **(100)**	17 **(100)**	27 **(100)**

A total of 30 patients were enrolled: 12 PDAC, 18 Other GI.
[a]Excluding CRC; [b]Based on investigator assessment of the clinically evaluable patients (measurable disease with ≥ 1 on-study scan); [c]Evaluable population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; [d]Evaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; [e]Includes 1 unconfirmed PR as of data cut-off; [f]Includes 2 unconfirmed PR as of data cut-off; [g]Includes 3 unconfirmed PR as of data cut-off.
Data as of 10 Sept 2021 (median follow-up: overall, 6.3 months; PDAC, 8.1 months; other GI cancers: 6.3 months).

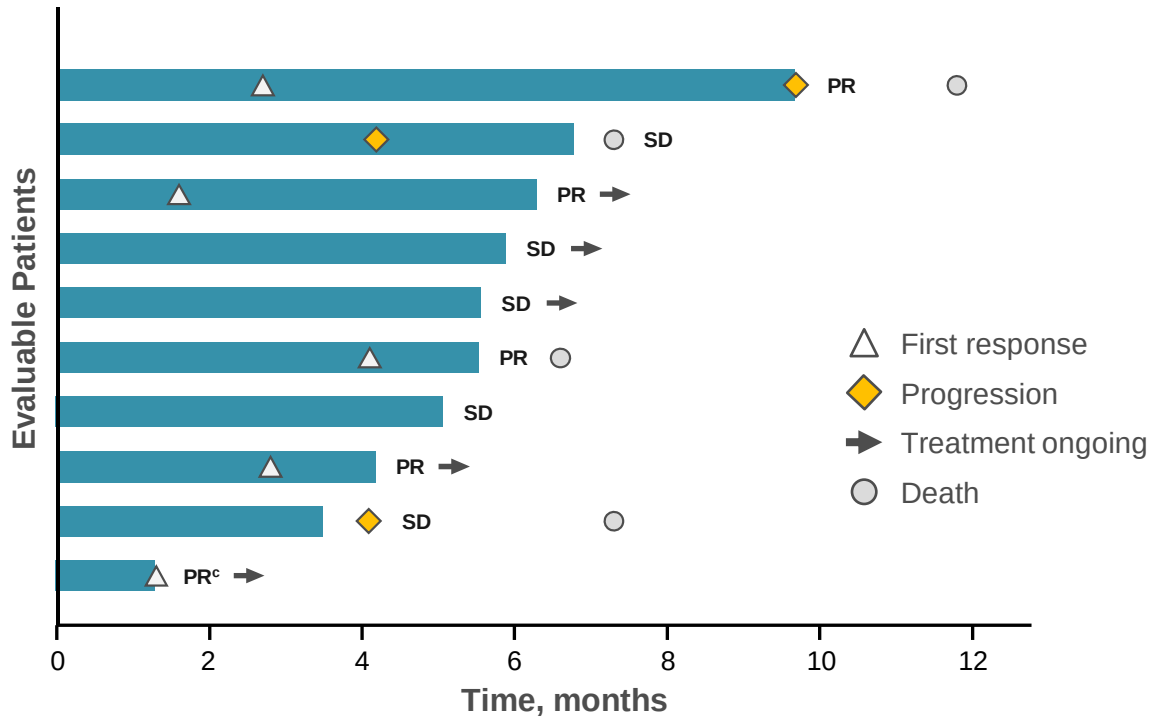
Adagrasib in Patients With Unresectable or Metastatic PDAC: Best Tumor Change From Baseline and Duration of Treatment

Best Tumor Change From Baseline (n=10)[a,b]



- Response rate: 50% (5/10), including 1 unconfirmed PR
- SD: 50% (5/10 patients)
- DCR: 100% (10/10 patients)

Duration of Treatment (n=10)[a,b]

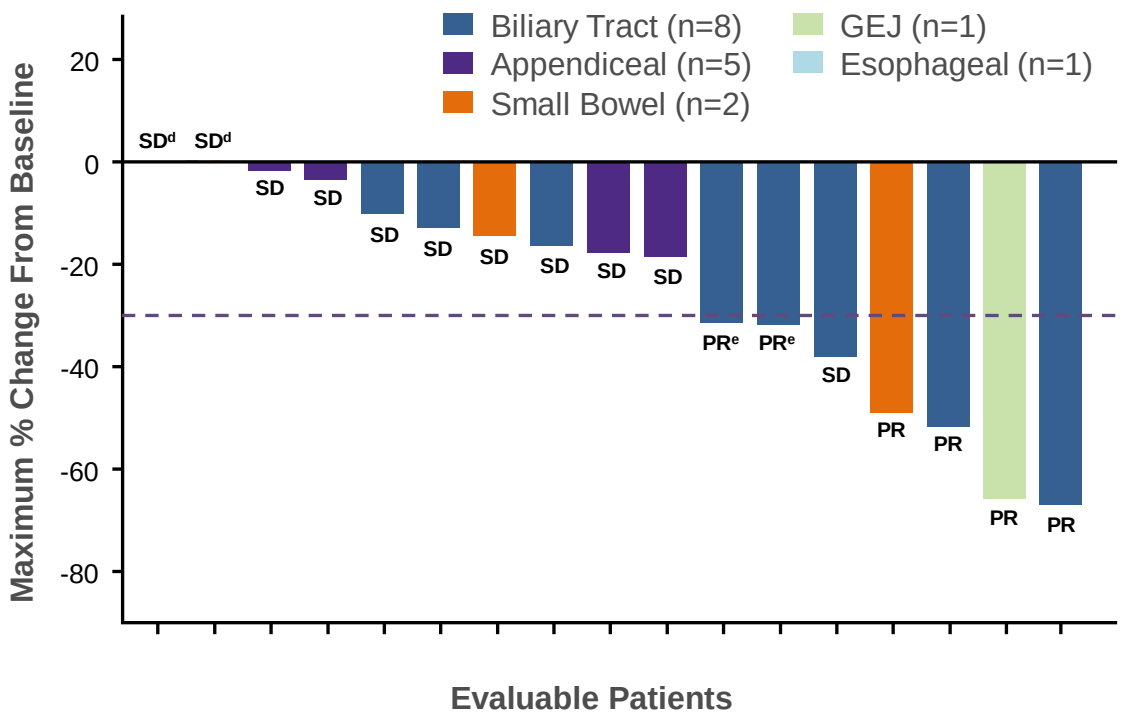


- Median TTR: 2.8 months
- Median DOR: 6.97 months
- Median PFS: 6.6 months (95% CI 1.0–9.7)
- Treatment ongoing in 50% (5/10) of patients

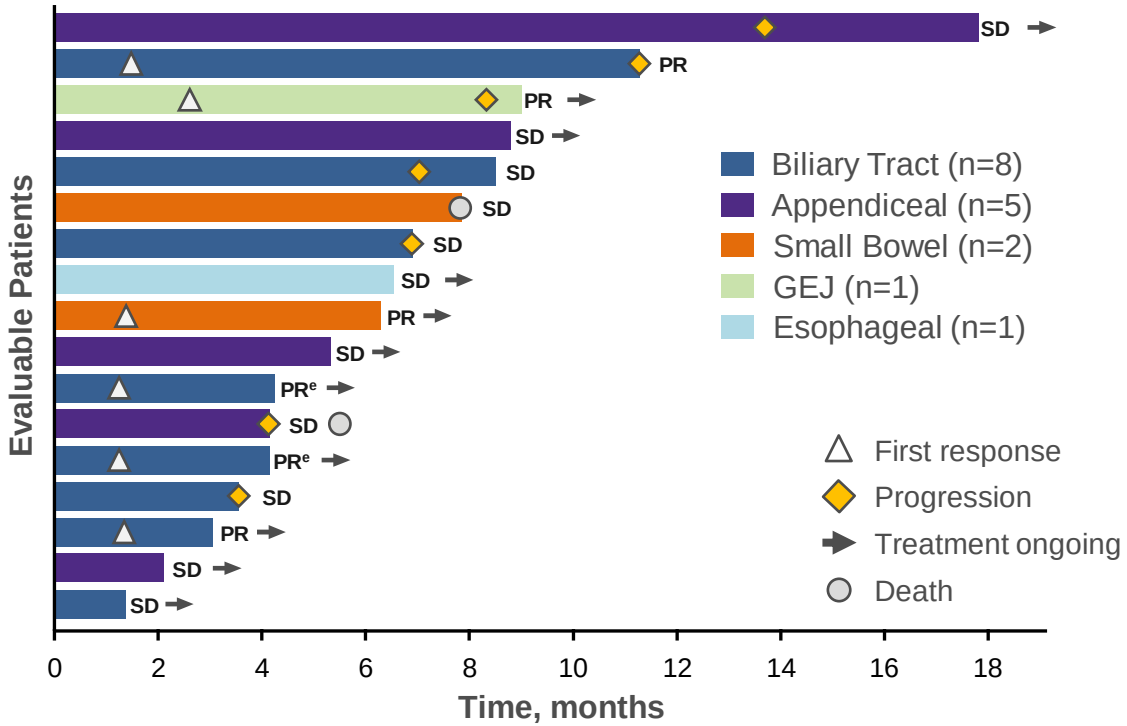
DCR, disease control rate; DOR, duration of response; PR, partial response; SD, stable disease; TTR, time to response.
[a]Evaluable population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; [b]All results are based on investigator assessments; [c]At data cut-off, 1 patient had unconfirmed PR.
Data as of 10 Sept 2021 (median follow-up: 8.1 months).

Adagrasib in Patients With Other GI Tumors:[a] Best Tumor Change From Baseline and Duration of Treatment

Best Tumor Change From Baseline (n=17)[b,c]



Duration of Treatment (n=17)[b,c]



- Response rate:
  - Biliary tract cancer: 50% (4/8), including 2 unconfirmed PRs
  - GEJ and small bowel cancer: 1 PR each
- DCR: 100% (17/17 patients)

- Median TTR: 1.3 months
- Median DOR: 7.85 months
- Median PFS: 7.85 months (95% CI 6.90–11.30)
- Treatment ongoing in 65% (11/17) of patients

DCR, disease control rate; DOR, duration of response; GEJ, gastro-esophageal junction; PR, partial response; SD, stable disease; TTR, time to response.
[a]Excluding CRC and PDAC; [b]Evaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; [c]All results are based on investigator assessments; [d]1 patient with appendiceal cancer and 1 patient with esophageal cancer had maximum % change from baseline of 0; [e]At data cut-off, 2 patients had unconfirmed PR.
Data as of 10 Sept 2021 (median follow-up: 6.3 months).

Adagrasib in Patients With Other Advanced Solid Tumors:[a] Incidence of Treatment-Related Adverse Events

Most Frequent TRAEs[b]	Overall (N=42)[c]		Overall GI cancers[d] (n=30)	
TRAEs, %	**Any Grade**	**Grade 3**	**Any Grade**	**Grade 3**
Any TRAEs	91	21	87	27
Most frequent TRAEs, %				
Nausea	48	2	50	3
Vomiting	43	0	40	0
Diarrhea	43	0	37	0
Fatigue	29	7	33	10
AST increase	19	2	20	3
Blood creatinine increase	19	0	17	0
Anemia	17	2	20	3
Peripheral edema	17	0	17	0
QT prolongation	14	5	13	7
ALT increase	12	2	13	3
Dysgeusia	12	0	13	0

- No Grade 4 or 5 TRAEs
- No TRAEs led to discontinuation

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
[a]Excluding NSCLC and CRC; [b]Occurring in ≥10% of patients; [c]Overall population included 12 other non-GI cancers (ovarian [n=4], endometrial [n=2], breast [n=1], glioblastoma [n=1], and unknown primary [n=4]); [d]Excluding CRC.
Data as of 10 Sept 2021 (median follow-up: 6.3 months).

Conclusions

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life that enables exposure above a target threshold throughout the dosing interval
- Adagrasib monotherapy demonstrated promising clinical activity and 100% disease control in previously treated patients with PDAC and other GI (non-CRC) tumors harboring a KRAS^{G12C} mutation
  - Of the tumor histologies with >5 patients evaluable, response rates for PDAC and biliary tract cancer were 50%
- Adagrasib has now demonstrated responses across multiple tumor types (NSCLC, CRC, PDAC, biliary tract, GEJ, small bowel, ovarian and endometrial cancers)[1–3]
- Adagrasib monotherapy is well tolerated and has a manageable safety profile
- Further exploration of adagrasib is ongoing in the KRYSTAL-1 trial (NCT03785249), and a newly initiated early access program (NCT05162443) is available to this patient population

1. Jänne PA et al. Presented at: 2020 EORTC-NCI-AACR Symposium; October 25, 2020. 2. Weiss J et al. Presented at: 2021 ESMO Congress; 19 September 2021. 3. Johnson ML et al. Presented at: 2020 EORTC-NCI-AACR Symposium; October 25, 2020.

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