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

Poster/Abstract no. 519

Tanios S. Bekaii-Saab[1], Alexander I. Spira[2], Rona Yaeger[3], Gary L. Buchschacher Jr.[4], Autumn J. McRee[5], Joshua K. Sabari[6], Melissa L. Johnson[7], Minal Barve[8], Navid Hafez[9], Karen Velastegui[10], James G. Christensen[10], Thian Kheoh[10], Hirak Der-Torossian[10], Shirish M. Gadgeel[11]

1. Department of Medical Oncology and Hematology, Mayo Clinic, Scottsdale, Arizona, USA; 2. Virginia Cancer Specialists, Fairfax, Virginia, NEXT Oncology, Virginia, US Oncology Research, The Woodlands, Texas, USA; 3. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; 4. Kaiser Permanente Southern California, Los Angeles, California, USA; 5. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; 6. Perlmutter Cancer Center, New York University Langone Health, New York, New York, USA; 7. Sarah Cannon Research Institute, Tennessee Oncology, Nashville, Tennessee, USA; 8. Mary Crowley Cancer Research, Dallas, Texas, USA; 9. Yale Cancer Center, New Haven, Connecticut, USA; 10. Mirati Therapeutics, Inc., San Diego, California, USA; 11. Henry Ford Cancer Institute/Henry Ford Health System, Detroit, Michigan, USA

Background

Adagrasib (MRTX849)

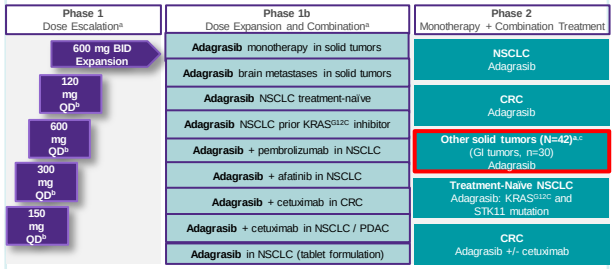
- KRAS mutations occur in approximately 90% of PDAC[1]; ~2% of these are KRAS^{G12C} mutations[2]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 hours[3,4]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, irreversibly and selectively binds 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 pharmacokinetics
  - Central nervous system 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
- Previously reported data demonstrated clinical activity with adagrasib in various KRAS^{G12C}-mutated solid tumors, including non–small-cell lung cancer (NSCLC), colorectal cancer (CRC) and other tumors such as PDAC, ovarian and endometrial cancers, and cholangiocarcinoma[6–8]

Methods

Study Design

- KRYSTAL-1 (NCT03785249) is a Phase 1/2 trial evaluating adagrasib in patients with solid tumors harboring a KRAS^{G12C} mutation

Figure 1. KRYSTAL-1 Study Design.



BID, twice daily; ctDNA, circulating tumor DNA; QD, once daily.
[a]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA; [b]Patients subsequently dose escalated up to 600 mg BID; [c]Solid tumors included GI tumors (n=30) and non-GI tumors (n=12).

Key Eligibility Criteria

- Solid tumor with KRAS^{G12C} mutation
- Unresectable or metastatic disease
- Treated and/or stable brain metastases (most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases)

Phase 2 Endpoints

- **Primary**: Objective Response Rate according to RECIST 1.1
- **Secondary**: Duration of response (DOR); Progression-free survival (PFS); Overall survival; Safety

Results

Adagrasib in Patients With Other Solid Tumors

- 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 (**Figure 1** and **Table 1**)
- Data cut-off 10 September 2021; median follow-up: PDAC, 8.1 months; other GI cancers, 6.3 months; overall, 6.3 months

Results

Table 1. 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 Unresectable or Metastatic PDAC

- Response rate was 50% (5/10), including 1 unconfirmed PR; DCR was 100% (10/10) (**Table 2** and **Figure 2A**)
- Median time to response (TTR) was 2.8 months; median DOR was 6.97 months (**Figure 2B**)
- Median PFS was 6.6 months (95% CI 1.0–9.7)
- Treatment was ongoing in 50% (5/10) of patients

Adagrasib in Patients With Other GI Tumors

- Response rate for biliary tract cancer was 50% (4/8), including 2 unconfirmed PRs (**Figure 3A**)
  - 1 PR each was observed for GEJ (1/1) and small bowel cancer (1/2)
  - DCR was 100% (17/17 patients)
- Median TTR was 1.3 months; median DOR was 7.85 months (**Figure 3B**)
- Median PFS was 7.85 (95% CI 6.90–11.30)
- Treatment was ongoing in 65% (11/17) of patients

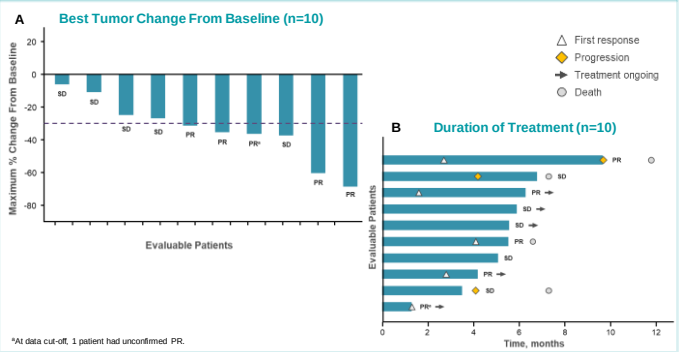
Table 2. Objective Response Rate in Patients With PDAC and Other GI Tumors[a].

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 (DCR)	10 **(100)**	17 **(100)**	27 **(100)**

[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; [f]Includes 2 unconfirmed PRs; [g]Overall 3 unconfirmed PRs.

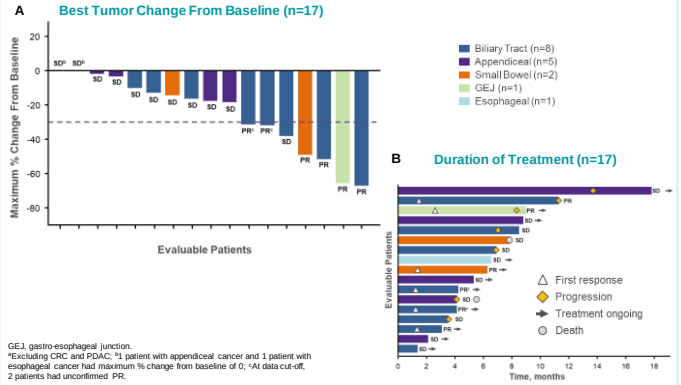
Results

Figure 2. Adagrasib in Patients With Unresectable or Metastatic PDAC.



[a]At data cut-off, 1 patient had unconfirmed PR.

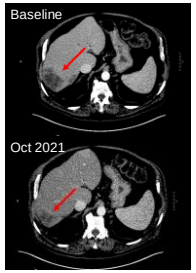
Figure 3. Adagrasib in Patients With Other GI Tumors[a].



GEJ, gastro-esophageal junction.
[a]Excluding CRC and PDAC; [b]1 patient with appendiceal cancer and 1 patient with esophageal cancer had maximum % change from baseline of 0; [c]At data cut-off, 2 patients had unconfirmed PR.

Patient Case: Response in PDAC Harboring a KRAS^{G12C} Mutation

- 76-year-old female with locally advanced adenocarcinoma of the pancreas
- Diagnosis January 2020
- Treatment history and best overall response:
  - gemcitabine, abraxane (January–July 2020): SD;
  - pembrolizumab, GVAX pancreas vaccine, CSF1R inhibitor (August 2020 – January 2021): SD
- Disease progression February 2021
- Adagrasib 600 mg BID started March 2021
  - September 2021 (cycle 8), SD (-25%)
  - October 2021, PR (-38%) after data cut-off
  - December 2021, confirmed PR (-38%) after data cut-off
- No treatment-related adverse events (TRAEs)
- Patient remains on study



Results

Table 3. Safety Summary: TRAEs in Patients With Other Advanced Solid Tumors[a]

Most Frequent TRAEs[b]	Overall (N=42)[c]		Overall GI cancers[d] (n=30)	
TRAEs, %	**Any Grade**	**Grades 3–4**	**Any Grade**	**Grades 3–4**
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

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Excluding NSCLC and CRC; [b]Occurring in ≥10% of patients; [c]Overall population included 12 non-GI cancers (ovarian [n=4], endometrial [n=2], breast [n=1], glioblastoma [n=1], and unknown primary [n=4]); [d]Excluding CRC.

Safety

- No Grade 5 TRAEs were observed (**Table 3**)
- No TRAEs led to discontinuation

Summary

- Adagrasib monotherapy demonstrated promising clinical activity and 100% DCR 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)[6–8]
- 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

References

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

Acknowledgments

- The patients and their families for making this trial possible
- The clinical study teams and investigators for their work and contributions
- This study is supported by Mirati Therapeutics, Inc.
- The authors would like to thank Igor Rybkin for his role at Henry Ford Health System for his contribution to this study
- All authors contributed to and approved this presentation; writing and editorial assistance were provided by Flaminia Fenoaltea, MSc, and Alex Coulthard, BSc, of Ashfield MedComms, funded by Mirati Therapeutics, Inc.

Tanios S. Bekaii-Saab: bekaii-saab.tanios@mayo.edu