# Additional Practice-Informing Adverse Event Patterns and Management in the KRYSTAL-1 Phase 2 Study of Adagrasib (MRTX849) in Patients With KRAS$^{G12C}$-Mutated NSCLC

Poster 1133P

Jun Zhang[1], Konstantinos Leventakos[2], Ticiana A. Leal[3], Nathan A. Pennell[4], Minal Barve[5], Scott Paulson[6], Lyudmila Bazhenova[7], Melissa L. Johnson[8], Richard C. Chao[9], Karen Velastegui[9], Chunlin Qian[9], Alexander I. Spira[10]

1. University of Kansas Medical Center, Kansas City, KS, USA; 2. Mayo Clinic, Rochester, MN, USA; 3. Winship Cancer Institute, Emory University, Atlanta, GA, USA; 4. Cleveland Clinic, Cleveland, OH, USA; 5. Mary Crowley Cancer Research, Dallas, TX, USA; 6. Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; 7. UC San Diego Moores Cancer Center, La Jolla, CA, USA; 8. Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN, USA; 9. Mirati Therapeutics, Inc., San Diego, CA, USA; 10. Virginia Cancer Specialists, Fairfax, VA, USA

## Background

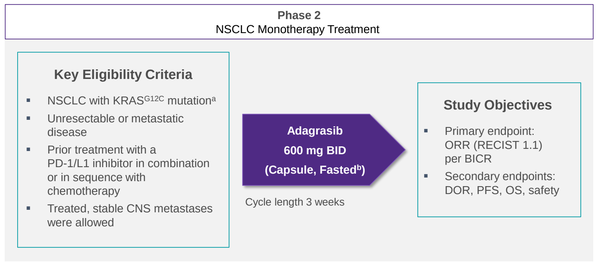
- KRAS mutations occur in approximately 25% of non-small cell lung cancers (NSCLC)[1], with KRAS$^{G12C}$ mutations occurring in approximately 14% of adenocarcinomas[2]
- Adagrasib is a KRAS$^{G12C}$ inhibitor selected for favorable properties, including a long half-life (23 hours), dose-dependent pharmacokinetics, and central nervous system (CNS) penetration
- Adagrasib has previously demonstrated a manageable safety profile and clinical activity in 116 patients with previously treated KRAS$^{G12C}$-mutated NSCLC (objective response rate [ORR] 43%; median overall survival 12.6 months*), including patients with CNS metastases
  - Treated, stable CNS metastases (intracranial ORR 33% per mRANO-BM; n=33)[3]
  - Active, untreated CNS metastases (intracranial ORR 32% per mRANO-BM; n=19)[4]

## Methods

### Study Design

- KRYSTAL-1 is a multicohort Phase 1/2 study of adagrasib in patients with advanced solid tumors harboring a KRAS$^{G12C}$ mutation (**Figure 1**)
- Efficacy and safety for Cohort A, a Phase 2 study with registrational intent, has previously been reported[3]
- Here we report additional practice-informing safety analyses from Cohort A evaluating adagrasib capsules 600 mg orally BID (fasted state†) in patients with previously treated NSCLC (N=116; **Table 1**)

**Figure 1.** KRYSTAL-1 Study Design




[a]KRAS$^{G12C}$ mutation detected in tumor tissue and/or ctDNA; [b]Taken on an empty stomach following an overnight fast or ≥2 hours after previous meal and ≥1 hour before next meal; BICR, blinded independent central review; BID, twice daily; ctDNA, circulating tumor DNA; DOR, duration of response; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival

### Additional Safety Analyses

- Time to onset of treatment-related adverse events (TRAEs)
- Time to resolution of TRAEs
- Management of TRAEs

## Results

- Data cut-off October 15, 2021; median follow-up 12.9 months (95% CI, 11.8–13.5)*
- Median duration of treatment was 5.7 months (range, 0–19.6)

*Data cut-off for overall survival January 15, 2022; median follow up 15.6 months
†Taken on an empty stomach following an overnight fast or ≥2 hours after previous meal and ≥1 hour before next meal

## Results

**Table 1.** Demographics and Baseline Characteristics

| | Adagrasib Monotherapy (N=116)[a] |
|---|---|
| **Median age, years (range)** | 64 (25–89) |
| **Female sex, n (%)** | 65 (56%) |
| **Race, n (%)** | |
| White | 97 (84%) |
| Black or African American | 9 (8%) |
| Asian / Other | 5 (4%) / 5 (4%) |
| **ECOG PS, n (%)[b]** | |
| 0 / 1 | 18 (16%) / 97 (84%) |
| **Histology, n (%)** | |
| Adenocarcinoma | 113 (97%) |
| Squamous | 3 (3%) |
| **Smoking history, n (%)** | |
| Never smoker | 5 (4%) |
| Current smoker / former smoker | 11 (10%) / 100 (86%) |
| **Prior lines of systemic therapy, n (%)** | |
| 1 | 50 (43%) |
| 2 | 40 (35%) |
| 3+ | 26 (22%) |
| **Prior platinum-based therapy and/or checkpoint inhibitor therapy, n (%)[c]** | |
| Received prior platinum-based therapy only | 2 (2%) |
| Received both | 114 (98%) |
| **Baseline metastases, n (%)** | |
| Bone | 46 (40%) |
| CNS | 24 (21%) |
| Adrenal | 22 (19%) |
| Liver | 19 (16%) |

[a]103 patients (89%) had metastatic disease and 13 (11%) had locally advanced disease; [b]Missing, n=1; [c]78 patients (67%) had received checkpoint inhibitor therapy as their immediate prior line of therapy; ECOG PS, Eastern Cooperative Oncology Group performance status

### Treatment-Related Adverse Events

- TRAEs of any grade occurred in 97% of patients; 53% of TRAEs were grade 1–2, 45% of patients experienced a grade ≥3 TRAE (**Table 2**)
- There were 2 grade 5 TRAEs (cardiac failure [n=1] and pulmonary hemorrhage [n=1])
- Gastrointestinal (GI)-related TRAEs (diarrhea, nausea or vomiting) of any grade occurred in 85% of patients, and 30% of patients had increased ALT or AST
  - The majority of these TRAEs were grade 1–2

**Table 2.** Treatment-Related Adverse Events

| Event | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Any TRAE, n (%)** | 113 (97%) | 21 (18%) | 40 (35%) | 47 (41%) | 3 (3%) |
| **Most common TRAEs, n (%)[a]** | | | | | |
| Diarrhea | 73 (63%) | 56 (48%) | 16 (14%) | 1 (1%) | 0 |
| Nausea | 72 (62%) | 44 (38%) | 23 (20%) | 5 (4%) | 0 |
| Vomiting | 55 (47%) | 42 (36%) | 12 (10%) | 1 (1%) | 0 |
| Fatigue | 47 (41%) | 19 (16%) | 23 (20%) | 5 (4%) | 0 |
| ALT increase | 32 (28%) | 16 (14%) | 11 (10%) | 4 (3%) | 1 (1%) |
| Blood creatinine increase | 30 (26%) | 21 (18%) | 8 (7%) | 1 (1%) | 0 |
| AST increase | 29 (25%) | 15 (13%) | 10 (9%) | 4 (3%) | 0 |
| Decreased appetite | 28 (24%) | 10 (9%) | 14 (12%) | 4 (3%) | 0 |
| Anemia | 21 (18%) | 6 (5%) | 9 (8%) | 6 (5%) | 0 |
| Amylase increase | 20 (17%) | 11 (10%) | 8 (7%) | 1 (1%) | 0 |
| Electrocardiogram QT prolonged | 19 (16%) | 10 (9%) | 4 (3%) | 5 (4%) | 0 |

[a]Occurring in >15% of patients (any grade); ALT, alanine transaminase; AST, aspartate aminotransferase

## Results

### Dose Reductions, Interruptions and Discontinuations

- TRAEs led to dose reductions in 52% of patients and dose interruptions (dose held until AEs resolved to grade ≤1 or baseline) in 61% of patients (**Table 3**); the most common reasons were GI-related (nausea, vomiting, diarrhea), hepatic (ALT/AST), and fatigue
- Responses were seen regardless of dose interruptions or reductions
  - Among patients with a tumor response (n=48), 21 maintained 600 mg BID all or most of the time, while 20 patients received 400 mg BID, 5 received 600 mg QD, and 1 patient received 200 mg BID for the majority of treatment; 1 patient had multiple dose reductions
  - GI-related TRAEs led to a dose reduction in 23 patients (20%)
- TRAEs led to discontinuation in 8 patients (7%)

**Table 3.** TRAEs Leading to Dose Reduction or Interruption

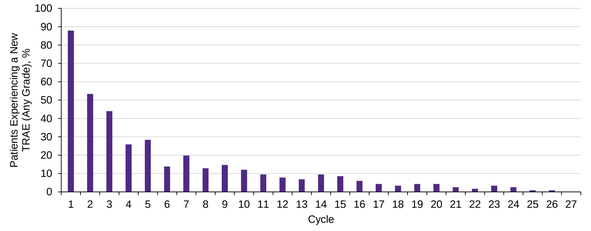
| Event | Adagrasib Monotherapy (N=116) |
|---|---|
| **TRAEs leading to dose reduction, n (%)** | 60 (52%) |
| GI-related TRAEs[a] | 23 (20%) |
| ALT increase | 12 (10%) |
| AST increase | 7 (6%) |
| **TRAEs leading to dose interruption, n (%)** | 71 (61%) |
| GI-related TRAEs[a] | 26 (22%) |
| ALT increase | 11 (10%) |
| AST increase | 10 (9%) |
| **TRAEs leading to discontinuation, n (%)** | 8 (7%) |

[a]Mostly diarrhea, nausea or vomiting. Some patients experienced abdominal pain (n=1), dyspepsia (n=1) or pancreatitis (n=1) that led to dose reductions and abdominal pain (n=2), abdominal distension (n=1) or pancreatitis (n=1) that led to dose interruptions

### Time to Onset and Resolution of TRAEs

- Overall, >92% of new onset TRAEs occurred within the first 3 cycles (**Figure 2**)

**Figure 2.** TRAE Onset by Cycle

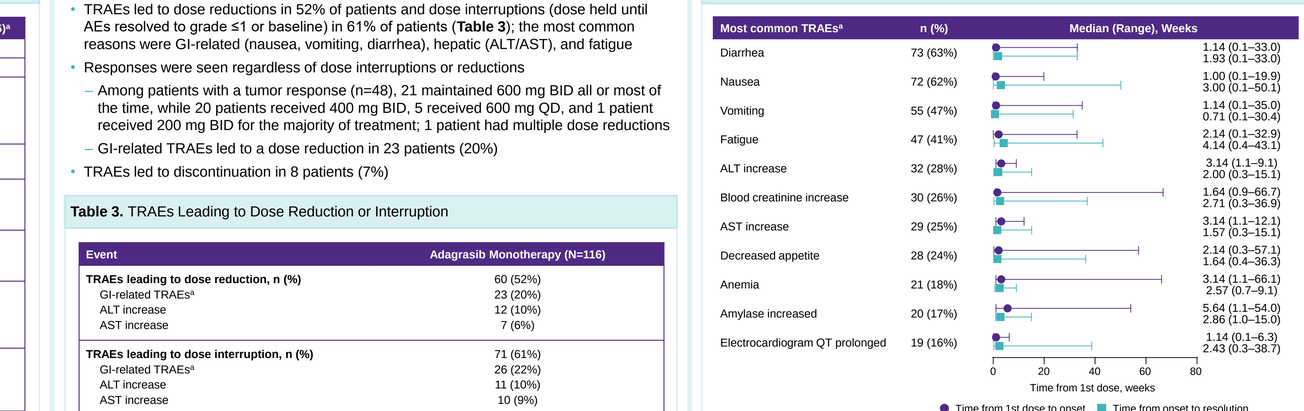



Cycle length 3 weeks

- Median time to onset was 3 days (range 1–231) for GI TRAEs and 22 days (range 8–63) for increased ALT and AST (**Figure 3**)
- Median time to resolution after initial occurrence of GI TRAEs was 14 days (range 1–351) and for increased ALT and AST was 12 days (range 2–106)
- GI TRAEs were manageable with dose reductions/interruptions and supportive medications (including provision as prophylaxis and as needed), with concomitant antidiarrheals used in 48% and antiemetics/antinauseants used in 87% of cases
- Overall, 14% and 11% of patients underwent dose reductions/interruptions for ALT and AST increases, respectively

## Results

**Figure 3.** Time to Onset and Resolution of TRAEs




[a]Occurring in >15% of patients (any grade)

## Summary

- Adagrasib, administered as capsules in a fasted state, demonstrated a manageable AE profile in patients with pretreated, advanced, KRAS$^{G12C}$-mutated NSCLC
- Most TRAEs were low grade, occurred early in treatment, and resolved quickly, resulting in a low (7%) discontinuation rate
- The most common TRAEs (GI-related, hepatic) were manageable with dose reductions/interruptions and supportive medications
- Adagrasib is currently being evaluated in a tablet formulation, administered both fed and fasted, which is hypothesized to improve tolerability, particularly for GI-related TRAEs

## References

1. Pakkala S, et al. *JCI Insight* 2018;3(15):e120858.
2. Nassar AH, et al. *N Engl J Med* 2021;384(2):185–7.
3. Jänne PA, et al. *New Engl J Med* 2022;387:120–31.
4. Sabari JK, et al. *ASCO Annual Meeting* 2022;LBA9009.

## Acknowledgments & Disclosures

- Dr Zhang has the following conflicts of interest to disclose: invited speaker for AstraZeneca, Regeneron, MJH Life Sciences, Sanofi, Novartis; advisory board for AstraZeneca, Hengrui; research grant from AstraZeneca, Biodesix, Nilogen, Genentech, Mirati Therapeutics; project lead for AstraZeneca, Biodesix, Nilogen, Genentech, Mirati Therapeutics; principal investigator for AstraZeneca, Biodesix, Nilogen, Genentech, Mirati Therapeutics; training for Novartis; sponsorship/funding from Abbvie, AstraZeneca, BeiGene, Genentech, Hengrui, Merck, Mirati Therapeutics, Nilogen, Novartis; advisory role for AstraZeneca, Eli Lilly, Nexus Health, Bayer, Biodesix, Hengrui, Novartis, Novocure, Bristol Myers Squibb, Sanofi, Takeda Oncology, Cardinal Health, Daiichi Sankyo, Mirati Therapeutics
- The authors would like to thank the patients for their participation, as well as site staff and clinical study teams for their work and contributions
- This study is supported by Mirati Therapeutics, Inc.
- Clinical trial registry number: NCT03785249
- All authors contributed to and approved this presentation; William F. Bleker contributed to the development and review of this presentation and abstract; writing and editorial assistance was provided by Rebecca Benatan, BSc, of Ashfield MedComms, an Inizio company, funded by Mirati Therapeutics, Inc.





Author contact: jzhang3@kumc.edu