IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

KRYSTAL-1: Two-Year Follow-Up of Adagrasib (MRTX849) Monotherapy in Patients With Advanced/Metastatic KRAS^{G12C}-Mutated NSCLC

Shirish M. Gadgeel[1], Pasi A. Jänne[2], Alexander I. Spira[3], Sai-Hong Ignatius Ou[4], Rebecca S. Heist[5], Jose M. Pacheco[6], Melissa L. Johnson[7], Joshua K. Sabari[8], Konstantinos Leventakos[9], Joshua A. Mason[10], Karen Velastegui[10], Xiaohong Yan[10], Richard Chao[10], Gregory J. Riely[11]

[1]Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Virginia Cancer Specialists, Fairfax, VA, USA; US Oncology Research, The Woodlands, TX, USA; [4]University of California Irvine, Chao Family Comprehensive Center, Orange, CA, USA; [5]Massachusetts General Hospital, Boston, MA, USA; [6]University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [7]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN, USA; [8]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Mirati Therapeutics, Inc., San Diego, CA, USA; [11]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA.

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

- 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[1–5]
- Based on Phase 2 Cohort A of the KRYSTAL-1 trial (n=116; median follow-up: 12.9 months; ORR: 42.9%; DOR: 8.5 months), adagrasib has been granted accelerated approval by the FDA in patients with previously treated KRAS^{G12C}-mutated NSCLC[6,7]

Key Eligibility Criteria[a]

- KRAS^{G12C}-mutated unresectable or metastatic NSCLC[b,c]
- ≥18-years-old
- ECOG PS 0–1
- Treated, stable CNS metastases were allowed

Phase 1/1b[5] Dose Escalation and Expansion	**Phase 2 Cohort A[7]** NSCLC Monotherapy Treatment
Adagrasib 600 mg BID **N=16**	**Adagrasib 600 mg BID** **N=116**
Key Endpoints: Safety, tolerability, recommended Phase 2 dose, and efficacy	**Primary Endpoint:** ORR (RECIST v1.1) per BICR **Secondary Endpoints:** DOR, PFS, 1-year survival rate, OS, and safety **Exploratory Endpoints:** Clinical activity in patients with CNS metastases and co-mutations[d]

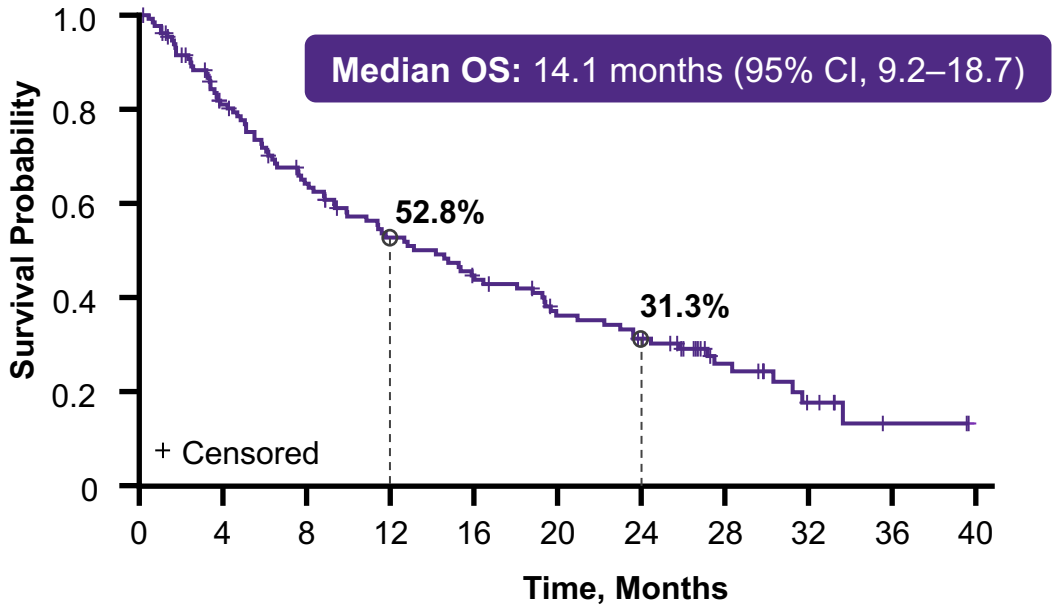
- Here we report 2-year follow-up data for 132 patients in Phase 1/1b dose escalation and expansion cohorts and Phase 2 Cohort A of KRYSTAL-1 (Data as of 1 January 2023; median follow-up: 26.9 months)
- Patients were administered adagrasib 600 mg BID orally (capsule, fasted)
- Baseline characteristics were consistent with those previously reported[5,7]

[a]Patients enrolled in Phase 2 Cohort A also had prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy. [b]KRAS^{G12C} mutation detected in tumor tissue or ctDNA by sponsor-approved local or central laboratory testing. [c]Phase 1/1b also enrolled patients with other KRAS^{G12C}-mutated unresectable or metastatic solid tumors. [d]Genetic alterations detected in tumor tissue and/or ctDNA NGS assay at baseline

ClinicalTrials.gov. NCT03785249

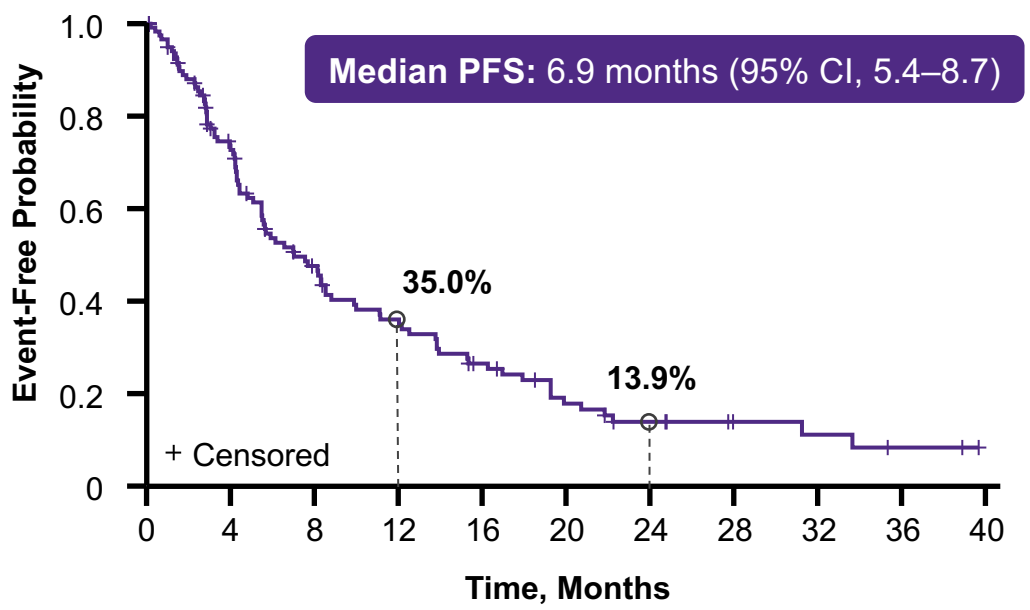
Efficacy Outcomes at Two-Years

Overall Survival (N=132)



Patients at risk 132 98 74 59 48 37 30 16 7 2 0

Progression-Free Survival (N=128)



128 78 46 33 23 14 9 5 4 2 0

- Objective responses were observed in 43% of patients (55/128); DCR was 80%
- Median DOR was 12.4 months (95% CI, 7.0–15.1)[a]

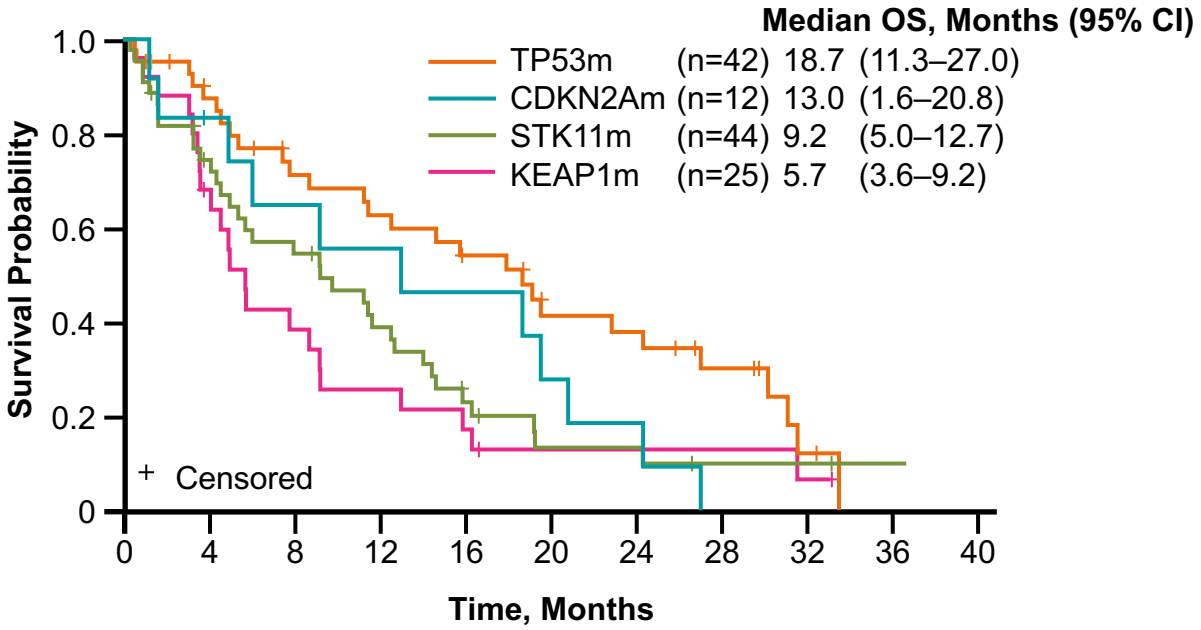
Results are based on BICR. Missing, n=1. Full analysis set defined as all patients who had measurable disease at baseline and received ≥1 dose of adagrasib;18 patients were not evaluable due to not having post-baseline measurement in target lesions

[a]Twelve-month event-free rate was 50.6% (95% CI, 36.1–63.5)

Data as of 1 January 2023 (median follow-up: 26.9 months)

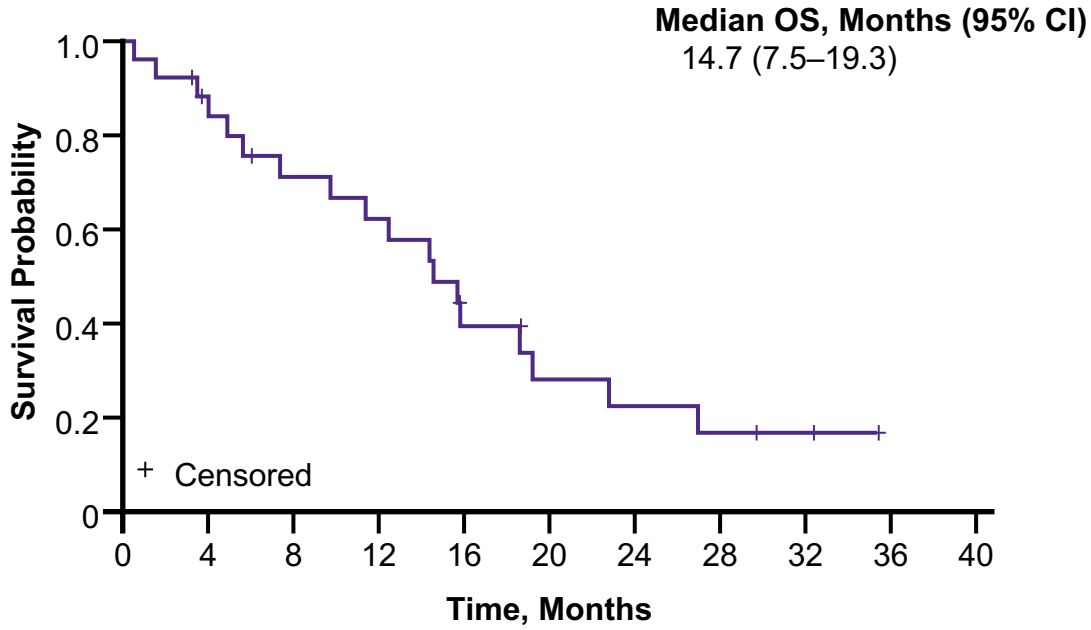
Overall Survival and Progression-Free Survival in Patients With Tumors Harboring Co-Mutations or With Baseline CNS Metastases

Overall Survival According to Co-Mutations at Baseline[a]



- Median PFS: KEAP1m, 4.1 months (95% CI, 2.7–5.6); STK11m, 4.2 months (3.9–6.1); CDKN2Am, 8.4 months (1.2–11.9); TP53m, 8.7 months (5.0–12.1)

Overall Survival in Patients With CNS Metastases at Baseline (n=26)



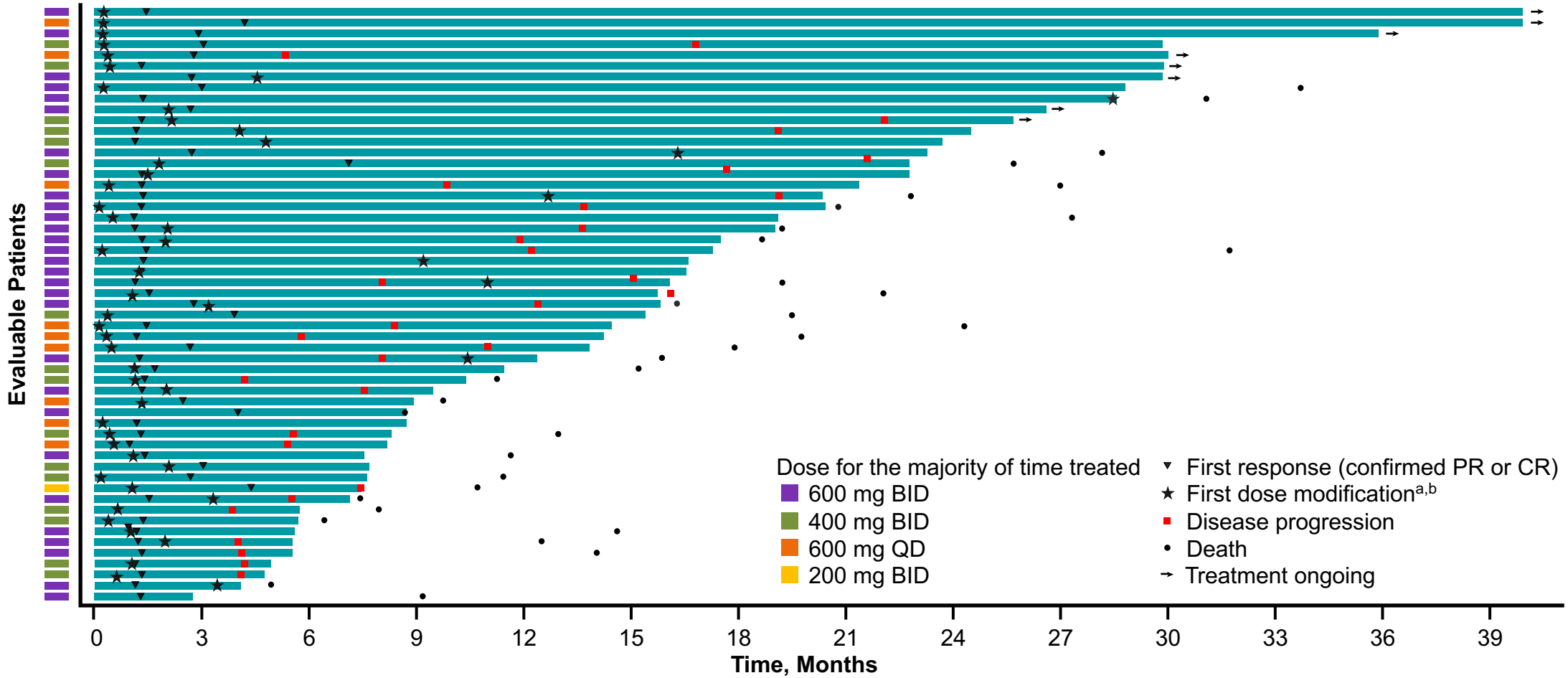
- Median PFS for patients with CNS metastases at baseline was 6.9 months (95% CI, 4.1–11.9)

PFS results are based on BICR. Full analysis set defined as all patients who had measurable disease at baseline and received ≥1 dose of adagrasib. Baseline CNS metastases were stable and treated

[a]Co-mutations were evaluated in tissue and/or ctDNA. CDKN2Am includes homozygous deletions and inactivating mutations. Number of patients analyzed for each co-mutation: KEAP1, n=97; TP53, n=111; STK11, n=106; CDKN2A, n=70. PFS for patients with STK11m/KEAP1wt and STK11m/KEAP1m was 4.2 months (95% CI, 2.8–8.1) and 5.0 months (95% CI, 1.1–8.1), respectively. OS for patients with STK11m/KEAP1wt and STK11m/KEAP1m was 11.5 months (95% CI, 5.4–14.5) and 5.7 months (95% CI, 1.6–15.9), respectively

Data as of 1 January 2023 (median follow-up: 26.9 months)

Duration of Treatment in Responders, Including Patients With Dose Modification



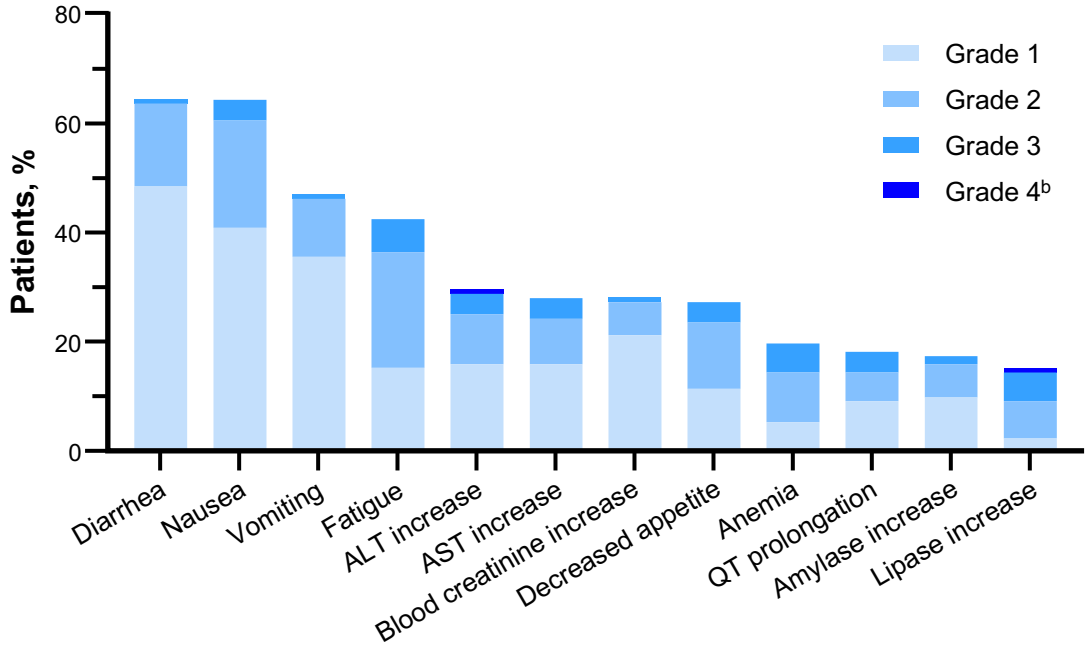
- Dose modifications were not associated with shorter treatment duration; all 33 patients (60%) who had DOT >1 year and all 12 patients (22%) who had DOT >2 years had dose modifications[b]
- For all patients with a dose modification[c], 1-year OS was 53.3% and 2-year OS was 32.1%

All results are based on BICR. [a]Time to first dose modification due to any cause, including missed dose, AE, or others. [b]Dose modification included any interruption or reduction. [c]128/132 (97%) of patients had any dose modification. 68/132 (52%) of patients had a dose reduction

Data as of 1 January 2023 (median follow-up: 26.9 months)

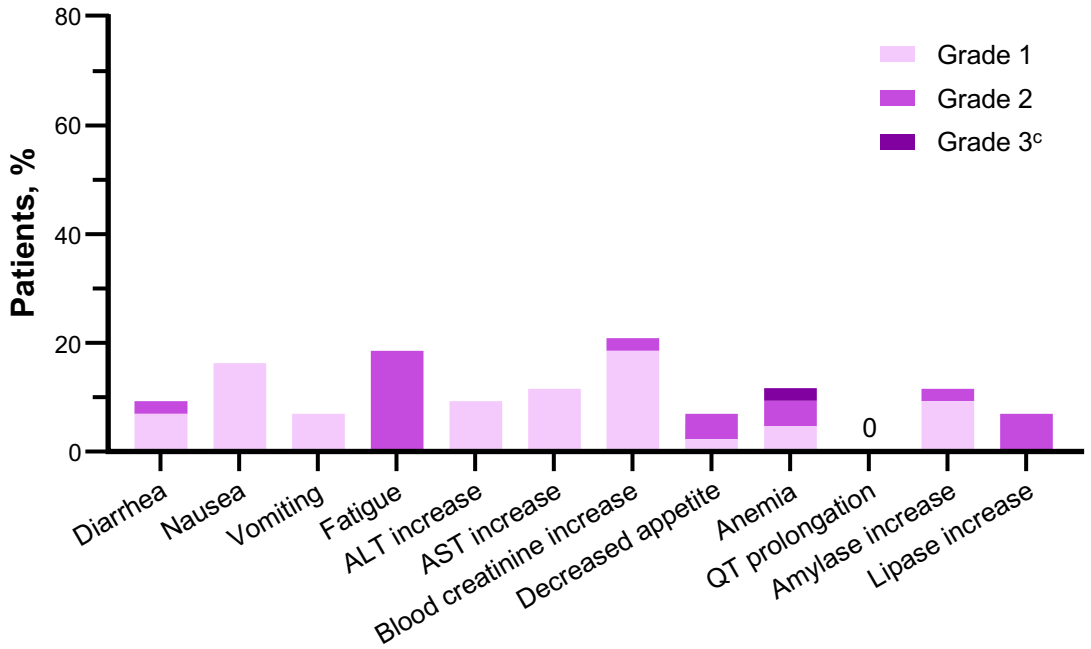
Treatment-Related Adverse Events and Long-Term Safety

TRAEs in Patients Overall (N=132)[a]



- ≥1 TRAE occurred in 128/132 (97%) patients
- 0/12 (0%) patients[d] who received IO <30 days before adagrasib had Grade ≥3 hepatotoxicity[e]
- One patient discontinued treatment due to Grade 3 hepatotoxicity

TRAEs With New Onset >1 Year (N=43)



- 43/132 patients (32.6%) received adagrasib for >1 year
- 29 of these 43 patients (67%) had a new onset TRAE after >1 year
- New onset Grade ≥2 GI TRAEs occurred in 1 patient (2%; Grade 2 diarrhea); no patients had Grade ≥2 hepatotoxicity with onset >1 year

[a]Any-grade TRAEs that occurred in >15% of patients. Overall, Grade 5 events occurred in 3 patients: cardiac failure [n=1], pneumonitis [n=1], and pulmonary hemorrhage [n=1]. Overall, TRAEs led to dose reduction in 68/132 patients (52%), dose interruption in 83/132 patients (63%), and discontinuation of study drug in 12/132 patients (9%). [b]Overall, Grade 4 events comprised: neutrophil count decrease (n=2 [2%]), febrile neutropenia (n=1 [1%]), ejection fraction decrease (n=1 [1%]), ALT increase (n=1 [1%]), lipase increase (n=1 [1%]), white blood cell count decrease (n=1 [1%]), and hypokalemia (n=1 [1%]). [c]Grade 3 events that occurred >1 year after treatment onset comprised: ejection fraction decrease (n=1 [2%]), platelet count decrease (n=1 [2%]), cardiac failure (n=1 [2%]), anemia (n=1 [2%]), and nervous system disorder (n=1 [2%]). [d]Ten patients from Cohort A and 2 from Phase I/Ib. [e]Hepatotoxicity included increased ALT/AST, increased liver function test, and mixed liver injury. In patients who received IO >30 days before adagrasib, 7 patients experienced Grade 3 treatment-related hepatotoxicity; 1 patient experienced Grade 4 treatment-related hepatotoxicity (ALT increase)

Data as of 1 January 2023 (median follow-up: 26.9 months)

Conclusions and Future Directions

- In this pooled analysis of patients with previously treated KRAS^{G12C}-mutated NSCLC, adagrasib demonstrated durable efficacy, with a median OS of 14.1 months and 2-year OS rate of 31%
- Exploratory analyses suggested durable clinical benefit in patients with treated, stable CNS metastases at baseline (median OS of 14.7 months), with clinical benefit noted across most baseline co-mutations
- Adagrasib had a manageable long-term safety profile; most TRAEs with onset >1 year were of low grade and included fewer GI TRAEs
- Treatment management by dose modification did not lead to a decrease in OS (2-year OS rate of 32%)
- Adagrasib was associated with a low rate of Grade ≥3 hepatotoxicity and was not observed in any patients who received adagrasib within 30 days of prior IO
- A confirmatory Phase 3 study is evaluating adagrasib vs docetaxel in previously treated patients with KRAS^{G12C}-mutated NSCLC, in North America, Europe, Asia, and Australia (KRYSTAL-12; NCT04685135)

Acknowledgments

- The patients and their families for making this trial possible
- The clinical study teams and investigators for their work and contributions
- Skye Sully from Mirati Therapeutics, Inc. for her support in data delivery
- This study is supported by Mirati Therapeutics, Inc.
- All authors contributed to and approved this presentation; writing and editorial assistance, under the direction of the authors, were provided by Hannah Preston, BSc, of Ashfield MedComms, an Inizio Company, and funded by Mirati Therapeutics, Inc.

Investigators

John Adams
USOR, Texas Oncology, Arlington

Scott Anderson
Goldschmidt Cancer Center

Minal Barve
Mary Crowley Cancer Research

Lyudmila Bazhenova
University of California San Diego

David Berz
Beverly Hills Cancer Center

David Ellison
USOR, Charleston Hematology Oncology Associates

Shirish M. Gadgeel
Henry Ford Cancer Institute/ Henry Ford Health System

David Hakimian
USOR, Illinois Cancer Specialists

Rebecca S. Heist
Massachusetts General Hospital

Pasi A. Jänne
Dana-Farber Cancer Institute

Melissa L. Johnson
Sarah Cannon Research Institute

Scott Kruger
USOR, Virginia Oncology Associates

Konstantinos Leventakos
Mayo Clinic, Rochester

Yanyan Lou
Mayo Clinic, Jacksonville

Kristi McIntyre
USOR, Texas Oncology, Presbyterian Cancer Center Dallas

Jamal Misleh
USOR, Medical Oncology Hematology Consultants

Marcelo V. Negrao
MD Anderson Cancer Center

Sai-Hong Ignatius Ou
University of California Irvine

Jose M. Pacheco
University of Colorado

Kyriakos P. Papadopolous
START San Antonio

Nathan A. Pennell
Cleveland Clinic

Gregory J. Riely
Memorial Sloan Kettering Cancer Center

Richard Rosenberg
USOR, Arizona Oncology Associates

Joshua Sabari
Perlmutter Cancer Center

Alexander I. Spira
Virginia Cancer Specialists

Nataliya Uboha
University of Wisconsin Carbone Cancer Center

Anthony Van Ho
USOR, Compass Oncology

Jared Weiss
University of North Carolina

Edwin Yau
Roswell Park Comprehensive Center

Jun Zhang
University of Kansas

References

1. Negrao MV, et al. J Clin Oncol 2023;JCO2300046.
2. Sabari JK, et al. Clin Cancer Res 2022;28:3318–28.
3. Hallin J, et al. Cancer Discov 2020;10:54–71.
4. Jänne PA, et al. Presented at 2020 EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; Oct 25, 2020.
5. Ou SI, et al. J Clin Oncol 2022;40:2530–38.
6. US Food and Drug Administration. 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-adagrasib-kras-g12c-mutated-nsclc. (Accessed 08/01/2023).
7. Jänne PA, et al. N Engl J Med 2022;387:120–31.

Abbreviations

AE, adverse event

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BICR, blinded independent central review

BID, twice daily

CDKN2A, cyclin-dependent kinase inhibitor 2A

CI, confidence interval

CNS, central nervous system

CR, complete response

ctDNA, circulating tumor DNA

DCR, disease control rate

DOR, duration of response

DOT, duration of treatment

ECOG PS, Eastern Cooperative Oncology Group Performance Status

FDA, Food and Drug Administration

GI, gastrointestinal

IO, immunotherapy

KEAP1, kelch-like ECH-associated protein 1

KRAS, Kirsten rat sarcoma viral oncogene homolog

NGS, next-generation sequencing

NSCLC, non-small cell lung cancer

ORR, objective response rate

OS, overall survival

PD-1, programmed cell death-protein 1

PD-L1, programmed cell death-ligand 1

PFS, progression-free survival

PK, pharmacokinetics

PR, partial response

QD, once daily

RECIST, Response Evaluation Criteria In Solid Tumors

STK11, serine/threonine kinase 11

TP53, tumor protein P53

TRAE, treatment-related adverse event