Clinical Validation of Plasma Cell-Free DNA (cfDNA) Sequencing in a Phase 2 Cohort of the KRYSTAL-1 Study of Adagrasib in Patients with KRAS^{G12C}-Mutated NSCLC

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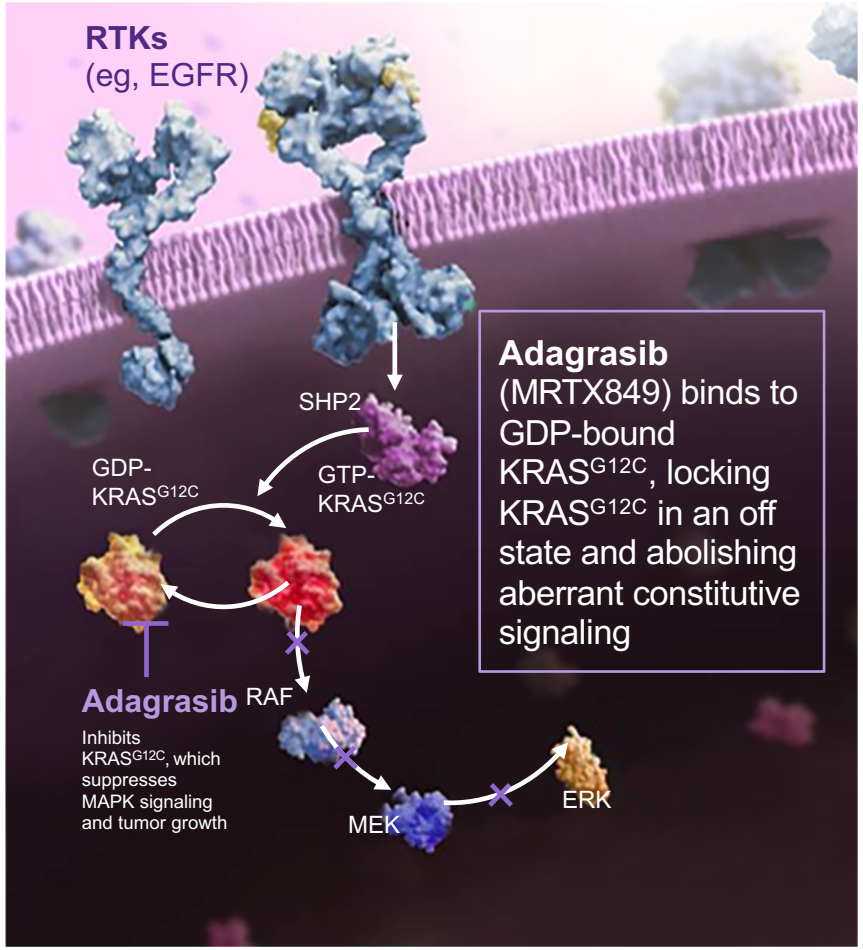
DISCLOSURES

Kenna Anderes

Financial Interest	Relationship(s)
Stock ownership	Mirati Therapeutics, Inc.
Other substantive relationships	Mirati Therapeutics, Inc. (employee)

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

- KRAS mutations occur in approximately 25% of NSCLC,[1] with KRAS^{G12C} mutations occurring in approximately 14% of adenocarcinomas[2]
- Adagrasib is a KRAS^{G12C} inhibitor selected for specific properties, including a long half-life (23 hours), dose-dependent pharmacokinetics, and CNS penetration[3,4]
- Clinical activity with adagrasib has been shown in patients across multiple KRAS^{G12C}-mutated solid tumors, including patients with NSCLC and treated/untreated CNS metastases[4–8]
- Agilent Resolution ctDx FIRST is a liquid biopsy genomic tumor profiling assay, using cfDNA, which is being developed as a companion diagnostic for adagrasib



KRYSTAL-1 (849-001) Phase 2 Cohorts A and B Study Design

Key Eligibility Criteria

- Unresectable or metastatic NSCLC with a KRAS^{G12C} mutation
- Prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy
- Treated, stable CNS metastases were allowed

Phase 2
NSCLC Monotherapy

Adagrasib 600 mg BID (capsule, fasted)

Cohort A[a]
KRAS^{G12C} mutation detected in **tumor tissue**[b]

Cohort B[c]
KRAS^{G12C} mutation detected by **liquid biopsy**[b]

Study Objectives

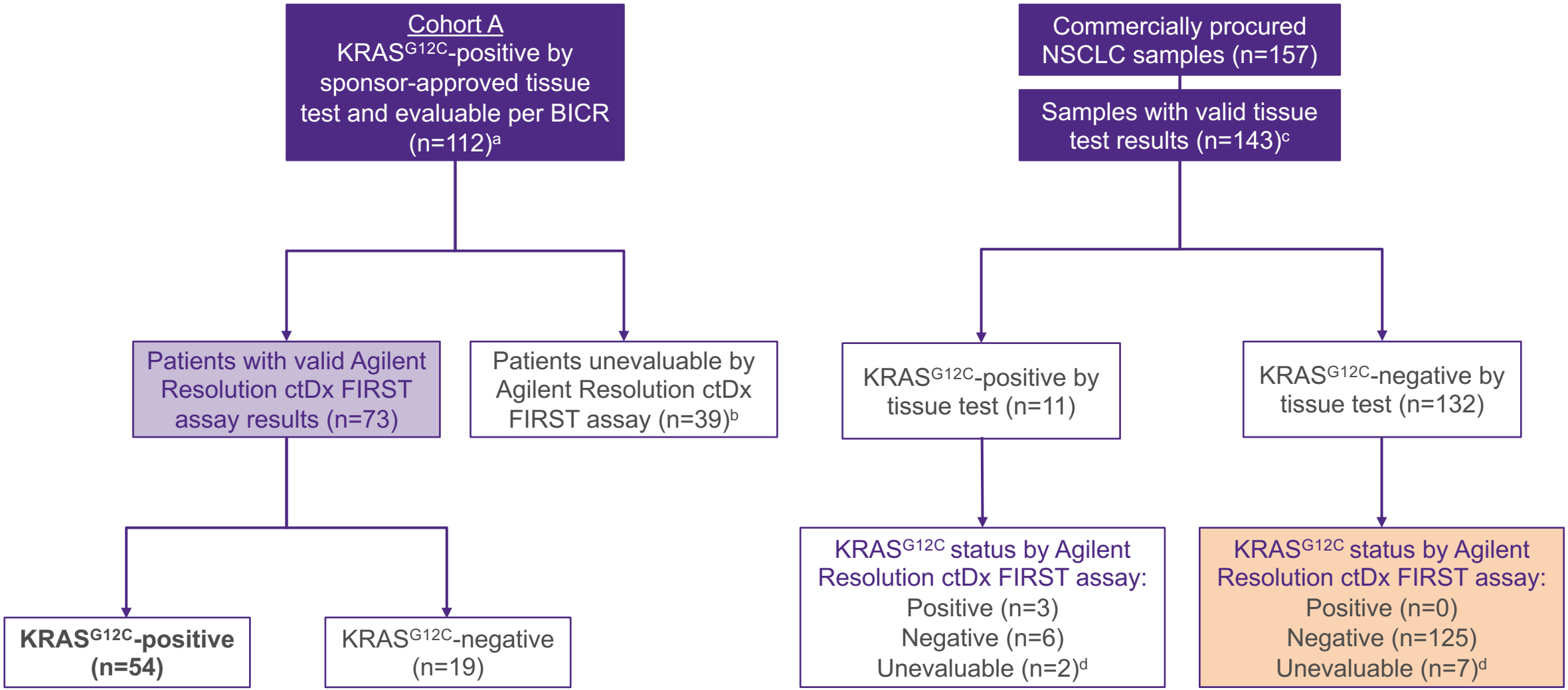
- Primary endpoint: ORR (RECIST 1.1) by BICR
- Secondary endpoints: DOR, PFS, OS, safety

- Adagrasib has demonstrated a manageable safety profile and clinical activity in patients with KRAS^{G12C}-mutated NSCLC (cohort A, n=116)[4]
- In a bridging design verification study, the clinical validity of the Agilent Resolution ctDx FIRST assay was evaluated in a retrospective sensitivity analysis of patients with paired plasma/tissue samples enrolled in cohort A[d] or commercially procured NSCLC samples
- Additionally, we report the first analysis from the prospective cohort B enrolling patients with KRAS^{G12C}-mutated NSCLC detected by liquid biopsy (n=60)

[a]Registrational cohort; [b]KRAS^{G12C} mutation detected by sponsor-approved tests; [c]Exploratory cohort including patients who did not have tissue to test or a positive KRAS^{G12C} tissue test; [d]Plasma samples were collected at baseline and on-study for correlative analyses

ClinicalTrials.gov. NCT03785249

Patient Disposition for Sensitivity Analysis in Cohort A and Commercially Procured NSCLC Samples



[a]A total of 116 patients were enrolled in cohort A; full analysis set per BICR excludes 4 patients who did not have measurable disease at baseline; [b]Patients unevaluable due to no sample available (n=20) or insufficient cfDNA (n=19); [c]Of the 157 commercial NSCLC samples, 14 samples had no valid tissue test results; [d]Samples were extracted but either did not meet the required cfDNA assay input of 15 ng or failed QC steps

Positive and Negative Percent Agreements in Sensitivity Analysis from Cohort A and Commercially Procured NSCLC Samples

		Cohort A (n=112)			Commercially procured NSCLC samples (n=143)		
		Agilent Resolution ctDx FIRST			Agilent Resolution ctDx FIRST		
		Positive	Negative	NE	Positive	Negative	NE
Tissue result	Positive	54	19[a]	39	3[b]	6[b]	2
	Negative	NA	NA	NA	0	125	7

- Overall, 198 matched plasma/tissue samples were included in the sensitivity analysis
- The positive percent agreement was **54/73 (74%)** in cohort A samples
- The negative percent agreement was **125/125 (100%)** in commercially procured samples

[a]Agilent Resolution ctDx FIRST results confirmed by orthogonal method (ddPCR assay using cfDNA) in 16/18 samples; 1 sample had insufficient cfDNA input mass for orthogonal testing;
[b]Agilent Resolution ctDx FIRST results confirmed by orthogonal method (ddPCR assay using cfDNA)

Demographics and Baseline Characteristics in Cohorts A and B

Characteristic	Cohort A (n=112)[a]	Cohort A with valid Agilent Resolution ctDx FIRST assay results (n=73)	Cohort B (n=60)
Median age, years (range)	64 (25–89)	64 (25–89)	64 (39–82)
Female sex, n (%)	62 (55)	40 (55)	38 (63)
Race, n (%)			
White	93 (83)	59 (81)	55 (92)
Black or African American	9 (8)	6 (8)	2 (3)
Asian / Other	5 (5) / 5 (5)	4 (6) / 4 (6)	2 (3) / 1 (2)
ECOG PS, n (%)			
0 / 1	18 (16) / 93 (83)[b]	15 (21) / 58 (80)	12 (20) / 48 (80)
Histology, n (%)			
Non-squamous / Squamous	109 (97) / 3 (3)	71 (97) / 2 (3)	56 (97) / 2 (3)[c]
Disease type, n (%)			
Locally advanced / Metastatic	12 (11) / 100 (89)	11 (15) / 62 (85)	3 (5) / 55 (95)[c]
Smoking history, n (%)			
Never smoker / Current smoker / Former smoker	5 (5) / 11 (10) / 96 (86)	3 (4) / 4 (6) / 66 (90)	3 (5) / 11 (18) / 46 (77)
Tissue test for enrollment, n (%)			
Foundation One / IMPACT / Other	25 (22) / 14 (13) / 73 (65)	19 (26) / 11 (15) / 43 (59)	NA
Liquid biopsy test for enrollment, n (%)			
Foundation Medicine / Guardant Health / Other	NA	NA	6 (10) / 28 (48) / 4 (7)
Resolution Bioscience	NA	NA	20 (35)[c]

[a]Full analysis set per BICR excludes 4 patients who did not have measurable disease at baseline; [b]Missing, n=1; [c]Results reported for BICR-evaluable patients only (n=58)

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC in Cohorts A and B: Tumor Response by BICR

Efficacy outcome	Cohort A (n=112)	Cohort A with valid Agilent Resolution ctDx FIRST assay results (n=73)	Cohort B (n=58)[a]
Objective response rate			
n (%)	48 (43)	32 (44)	23 (40)
95% CI	34–53	32–56	27–53
Best overall response, n (%)			
Complete response	1 (1)	1 (1)	1 (2)
Partial response	47 (42)	31 (43)	22 (38)
Stable disease	41 (37)	26 (36)	25 (43)
Progressive disease	6 (5)	4 (6)	4 (7)
Not evaluable	17 (15)	11 (15)	6 (10)
Disease control rate, n (%)	89 (80)	58 (79)	48 (83)

- For patients in cohort A who were KRAS^{G12C}-positive by tissue test and by the Agilent Resolution ctDx FIRST assay, ORR was **46%** (25/54)
- Safety results observed in cohort B were consistent with cohort A,[4] with TRAEs of any grade occurring in 97% of patients
  - 50% grade 1/2; 40% grade 3; 5% grade 4[b]; most frequent TRAEs were diarrhea, nausea, and vomiting
  - There was one grade 5 TRAE (acute respiratory failure)[c]

[a]Full analysis set per BICR excludes 2 patients who did not have measurable disease at baseline; [b]Grade 4 TRAEs included 1 case each of hypotension, hypoxia, pericardial effusion, sepsis, ventricular fibrillation, and ventricular tachycardia; [c]Patient had a history of pulmonary disease

Cohort A: Data as of October 15, 2021 (median follow-up: 12.9 months); Cohort B: Data as of December 31, 2021 (median follow-up: 12.3 months)

Conclusions

- This retrospective analysis of the registrational Phase 2 cohort A from KRYSTAL-1 demonstrated high concordance between tissue and the Agilent Resolution ctDx FIRST liquid biopsy assay (PPA, 74%)
- ORR was similar in KRAS^{G12C}-positive patients identified by plasma or tissue testing in the registrational cohort A (46% vs 43%, respectively)
- In the first prospective analysis of a KRAS^{G12C} inhibitor in patients enrolled exclusively by liquid biopsy, adagrasib demonstrated encouraging clinical efficacy (ORR, 40%; DCR, 83%)
- These results suggest that liquid biopsy can accurately identify patients with NSCLC harboring a KRAS^{G12C} mutation who may respond to adagrasib

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Abbreviations

BICR, blinded independent central review
BID, twice daily
CI, confidence interval
CNS, central nervous system
cfDNA, cell-free DNA
DCR, disease control rate
ddPCR, droplet digital polymerase chain reaction
DOR, duration of response
ECOG PS, Eastern Cooperative Oncology Group Performance Status
EGFR, epidermal growth factor receptor
ERK, extracellular signal-regulated kinase
GDP, guanosine diphosphate
GTP, guanosine triphosphate
KRAS, Kirsten rat sarcoma virus
MAPK, mitogen-activated protein kinase
MEK, mitogen-activated protein kinase kinase
NA, not applicable
NE, not evaluable
NSCLC, non-small cell lung cancer
ORR, objective response rate
OS, overall survival
PD-1/L1, programmed death-1/ligand 1
PFS, progression-free survival
PPA, positive percent agreement
QC, quality control
RAF, rapidly accelerated fibrosarcoma kinase
RECIST, Response Evaluation Criteria in Solid Tumors
RTK, receptor tyrosine kinase
SHP2, Src homology phosphatase 2
TRAE, treatment-related adverse event