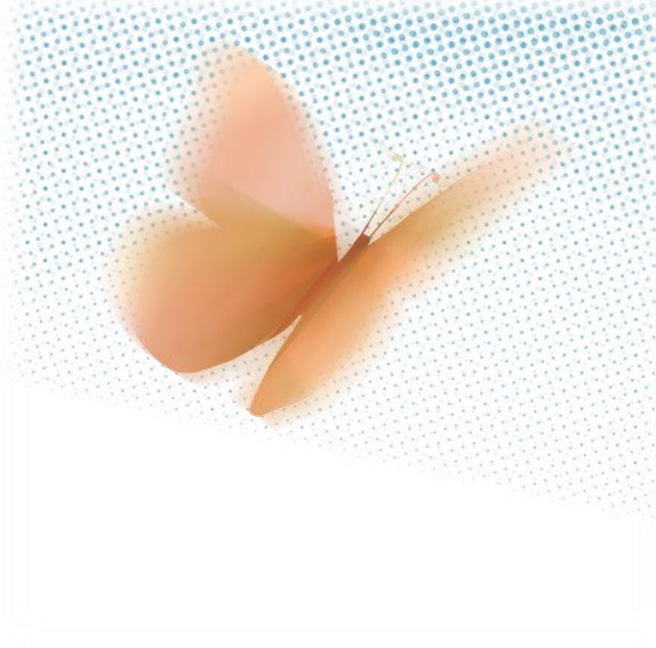
European Lung Cancer Virtual Congress



KRYSTAL-1: ACTIVITY AND PRELIMINARY PHARMACODYNAMIC (PD) ANALYSIS OF ADAGRASIB (MRTX849) IN PATIENTS (PTS) WITH ADVANCED NON–SMALL-CELL LUNG CANCER (NSCLC) HARBORING KRAS^{G12C} MUTATION

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DECLARATION OF INTERESTS

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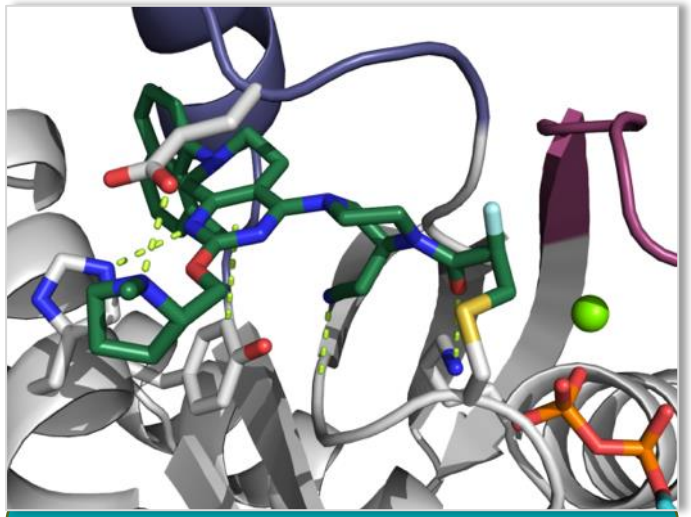
Adagrasib (MRTX849) Is a Differentiated, Selective Inhibitor of KRAS^{G12C}

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma)[1-3]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 h[4,5]
- Adagrasib is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state[6]
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor:
  - Potent covalent inhibitor of KRAS^{G12C} (cellular IC_{50}: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS^{G12C} protein vs wild-type KRAS
  - Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution



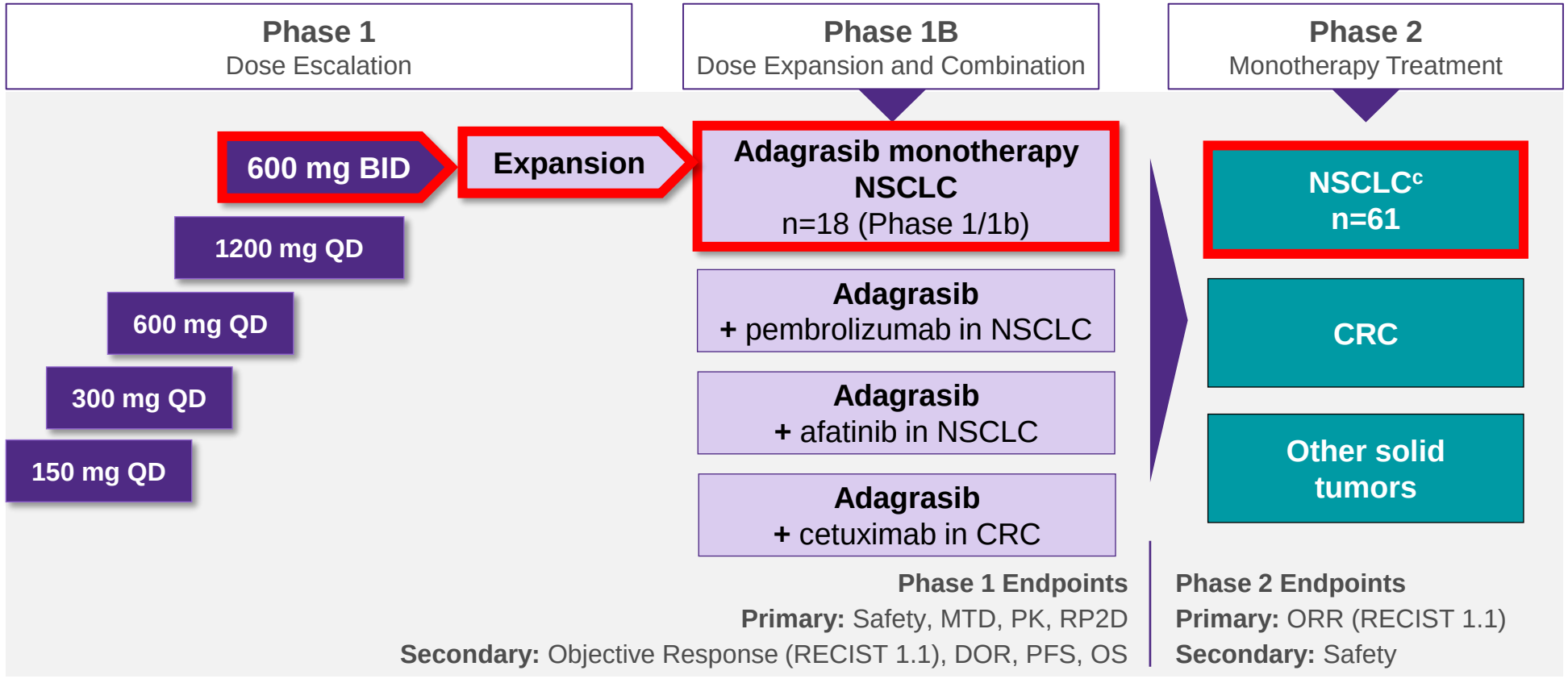
Adagrasib Crystal Structure

Hypothesis: Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dosing interval and maximizes depth and duration of antitumor activity.

KRYSTAL-1 (849-001) Study Design

Key Eligibility Criteria
Up to n=391

- Solid tumor with KRAS^{G12C} mutation
- Unresectable or metastatic disease
- Progression on or following treatment with a PD-1/L1 inhibitor in combination with or following chemotherapy (NSCLC)[a]
- Treated and/or stable brain metastases[b]



- Here we report data for 79 patients evaluating adagrasib 600 mg BID in patients with previously treated NSCLC in Phase 1/1b (n=18; median follow-up, 9.6 months) and Phase 2 (n=61); pooled (n=79) median follow-up, 3.6 months
- Exploratory data will be presented, including PD markers, gene set enrichment analyses, and immune transcript analyses
- Clinical outcome data cutoff date: 30 August 2020

[a]Applies to the majority of NSCLC cohorts. [b]Most cohorts allow patients with brain metastases if adequately treated and stable; additional Phase 1/1b cohort allows limited brain metastases. [c]Primary NSCLC cohort eligibility based on a tissue test; KRAS^{G12C} testing for entry was performed locally or centrally using a sponsor preapproved test. ClinicalTrials.gov. NCT03785249.

Patient Demographics and Baseline Characteristics: NSCLC

	Phase 1/1b 600 mg BID (n=18)	Phase 1/1b and 2 600 mg BID (n=79)
Median age, y (range)	65 (40-76)	65 (25-85)
Female, n (%)	11 (61%)	45 (57%)
Race, n (%)		
White	15 (83%)	67 (85%)
Black	3 (17%)	5 (6%)
Asian	0 (0%)	5 (6%)
Other	0 (0%)	2 (3%)
ECOG PS, n (%)		
0	8 (44%)	17 (22%)
1	10 (56%)	62 (78%)
Current/former smokers	16 (89%)	75 (95%)
Nonsquamous histology, n (%)	18 (100%)	76 (96%)
Prior lines of anticancer therapy[a], median (range)	3 (1-9)	2 (1-9)
Prior anti–PD-1/L1 inhibitor, n (%)	16 (89%)	73 (92%)

[a]Phase 2 patients with NSCLC received prior treatment with platinum regimens.
Data as of 30 August 2020. The pooled dataset includes data from the NSCLC Phase 1/1b and Phase 2 600 mg BID cohorts.

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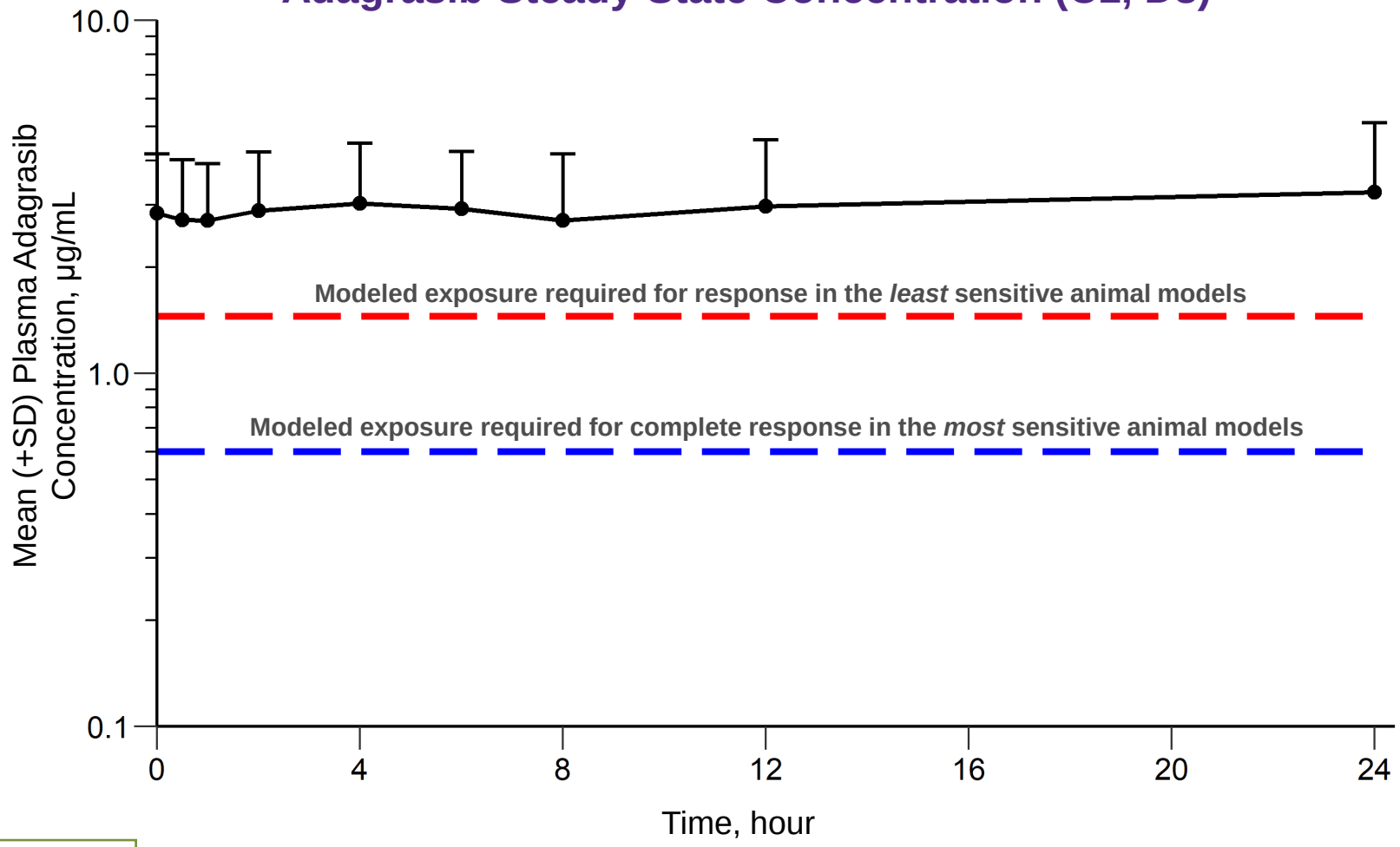
Adagrasib at 600 mg BID Exhibits Favorable PK Properties; Exposure Maintained Above Target Plasma Thresholds Throughout Full Dosing Interval



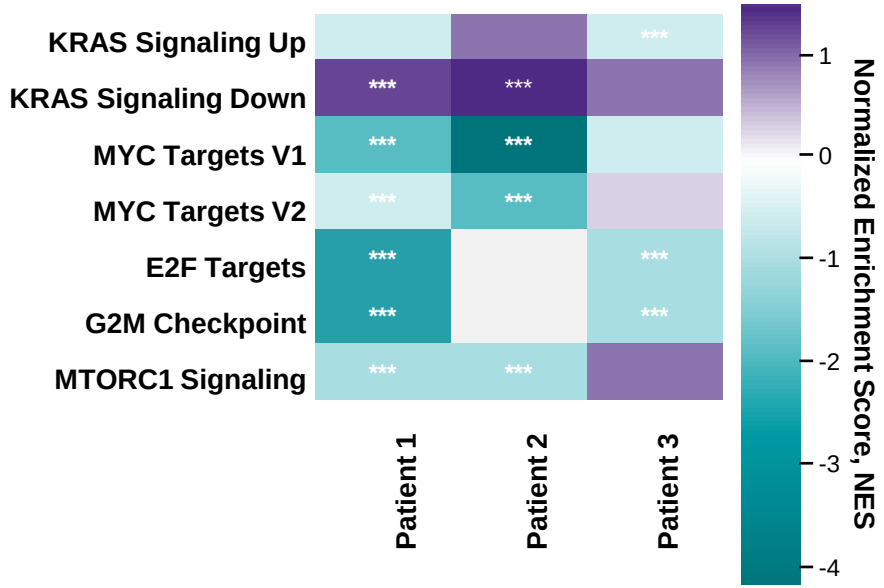
PK Properties Summary:

- C_{ave} of 2.63 µg/mL is 2- to 5-fold above target threshold for the full dosing interval
- C_{ave} PK parameter best matched to nonclinical antitumor activity
- Low peak to trough ratio at steady state (~1.27)
- **Half-life ~ 24 hours**
- Extensive volume of distribution predicted based on nonclinical studies

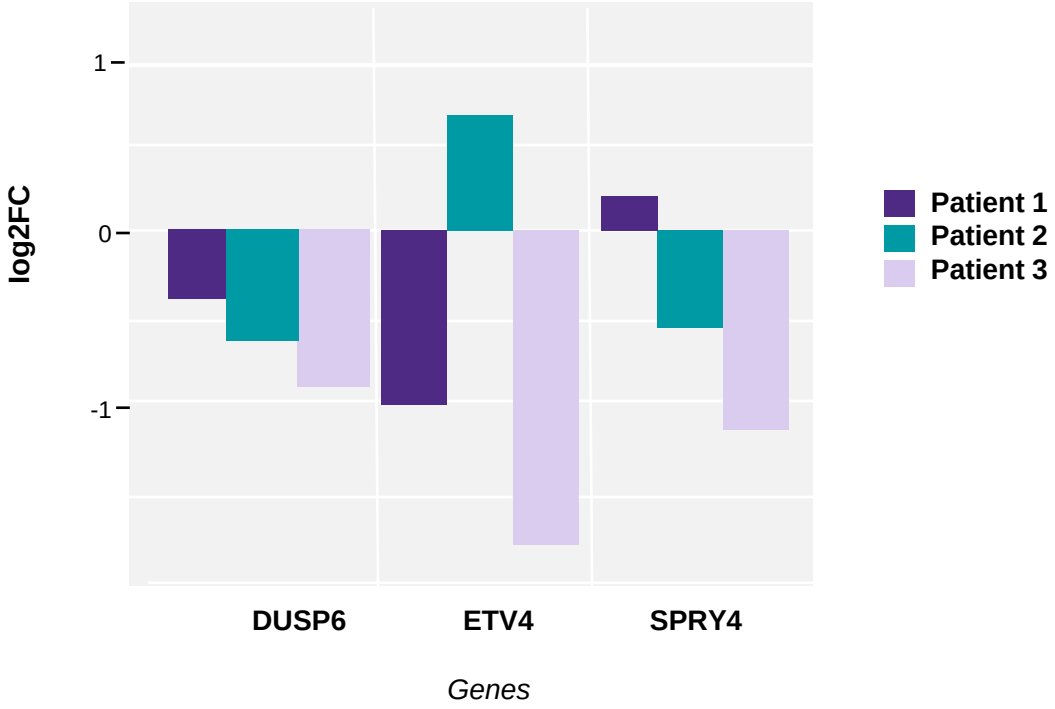
[a]Includes 14 patients with NSCLC, 1 patient with CRC, and 2 patients with appendiceal cancer from Phase 1/1b. Data as of 18 March 2020.

Mechanistic Biomarker Analyses Suggest Downregulation of KRAS/MAPK Pathway Genes in Tumor Tissue from Adagrasib-Treated Patients

Gene Set Enrichment Analysis (GSEA) Post-Adagrasib (Cycle 1, Day 8)



KRAS Signaling Subset–Fold Changes by Patient



- GSEA demonstrated significantly altered hallmark pathways, including MYC, KRAS, E2F, G2M, and MTORC1 in patient tumors following adagrasib treatment (n=3 NSCLC)
- MAPK target genes downregulated in several post–adagrasib-treated biopsies
- Robust plasma coverage of KRAS is consistent with evidence of KRAS/ERK pathway inhibition in tumor tissue

Note: Tumor biopsies from patients with NSCLC treated at 600 mg BID were harvested at baseline and cycle 1, day 8 (adagrasib steady state) and were subjected to targeted RNA sequencing analysis. *** refers to a false discovery rate (FDR) < 0.25.

Incidence of Treatment-Related Adverse Events

	All Cohorts Pooled, 600 mg BID[a] (n=110)		
TRAEs[b,c], %	**Any Grade**	**Grades 3-4**	**Grade 5**
Any TRAEs	85%	30%	2%
Most frequent TRAEs[a,d], %			
Nausea	54%	2%	0%
Diarrhea	51%	0%	0%
Vomiting	35%	2%	0%
Fatigue	32%	6%	0%
Increased ALT	20%	5%	0%
Increased AST	17%	5%	0%
Increased blood creatinine	15%	0%	0%
Decreased appetite	15%	0%	0%
QT prolongation	14%	3%	0%
Anemia	13%	2%	0%

- Grade 5 TRAEs included pneumonitis in a patient with recurrent pneumonitis (n=1) and cardiac failure (n=1)
- 4.5% of TRAEs led to discontinuation of treatment

[a]Includes patients pooled from Phase 1/1b and Phase 2 NSCLC (n=79), and CRC and Phase 2 other tumor cohorts (n=31). [b]Includes events reported between the first dose and 30 August 2020. [c]The most common treatment-related SAEs reported (2 patients each) reported were diarrhea (grade 1, grade 2) and hyponatremia (both grade 3). [d]Occurred in ≥10%. Data as of 30 August 2020.

Adagrasib in Patients With NSCLC: ORR in Pooled Dataset

Efficacy Outcome[a], n (%)	Phase 1/1b, NSCLC 600 mg BID (n=14)	Phase 1/1b and 2, NSCLC 600 mg BID (n=51)
Objective Response Rate	6 (43%)	23 (45%)[b]
Best Overall Response		
Complete Response (CR)	0 (0%)	0 (0%)
Partial Response (PR)	6 (43%)	23 (45%)
Stable Disease (SD)	8 (57%)	26 (51%)
Progressive Disease (PD)	0 (0%)	1 (2%)
Not Evaluable (NE)	0 (0%)	1 (2%)[c]
Disease Control	14 (100%)	49 (96%)

[a]Based on investigator assessment of the clinically evaluable patients (measurable disease with ≥1 on-study scan); 14/18 patients (Phase 1/1b) and 51/79 patients (Phase 1/1b and 2 pooled) met these criteria. [b]At the time of the 30 August 2020 data cutoff, 5 patients had unconfirmed PRs. All 5 PRs were confirmed by scans that were performed after the 30 August 2020 data cutoff. [c]One patient had tumor reimaging too early for response assessment.
Data as of 30 August 2020. The pooled dataset includes data from the NSCLC Phase 1/1b and Phase 2 600 mg BID cohorts.

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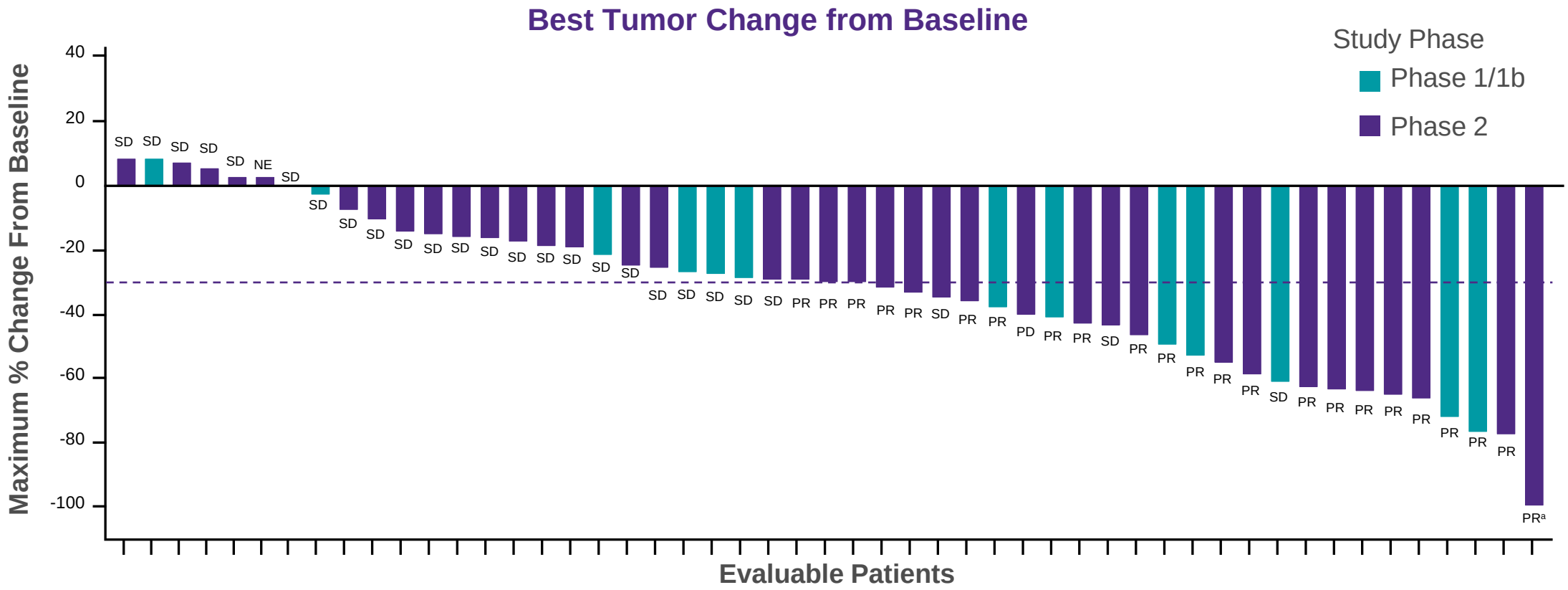
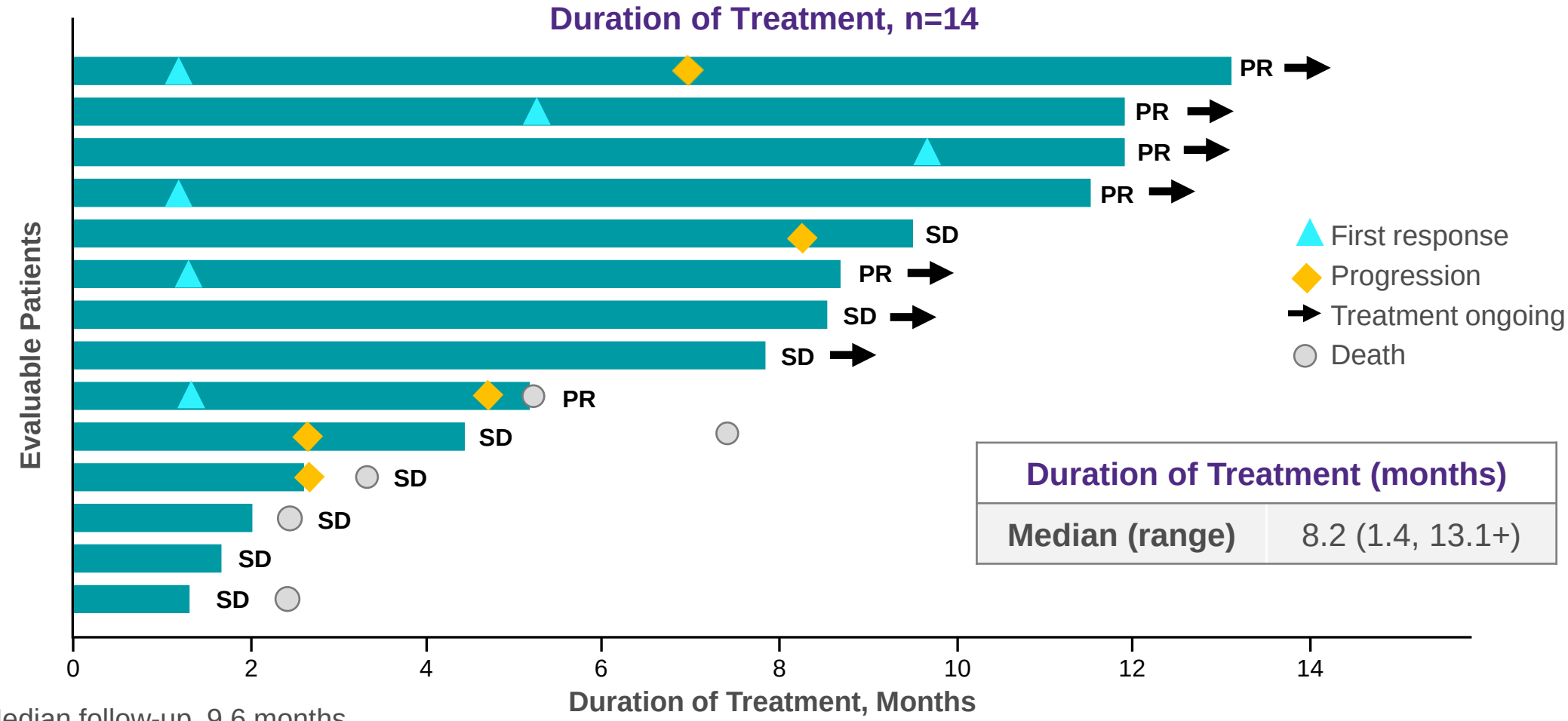
Adagrasib 600 mg BID in Patients With NSCLC: Best Tumor Change From Baseline



- Clinical benefit (DCR) observed in 96% (49/51) of patients

[a]Two timepoint assessments of CR were separated by recurrent disease associated with treatment interruption due to hypoxia; this patient remains on treatment and in 2 consecutive scans (1 after August 30 data cutoff) demonstrated 100% tumor regression in target and nontarget lesions after resuming treatment.
Data as of 30 August 2020. The pooled dataset includes data from NSCLC Phase 1/1b and Phase 2 600 mg BID cohorts.

Duration of Treatment in Patients With NSCLC Treated With Adagrasib 600 mg BID in Phase 1/1b



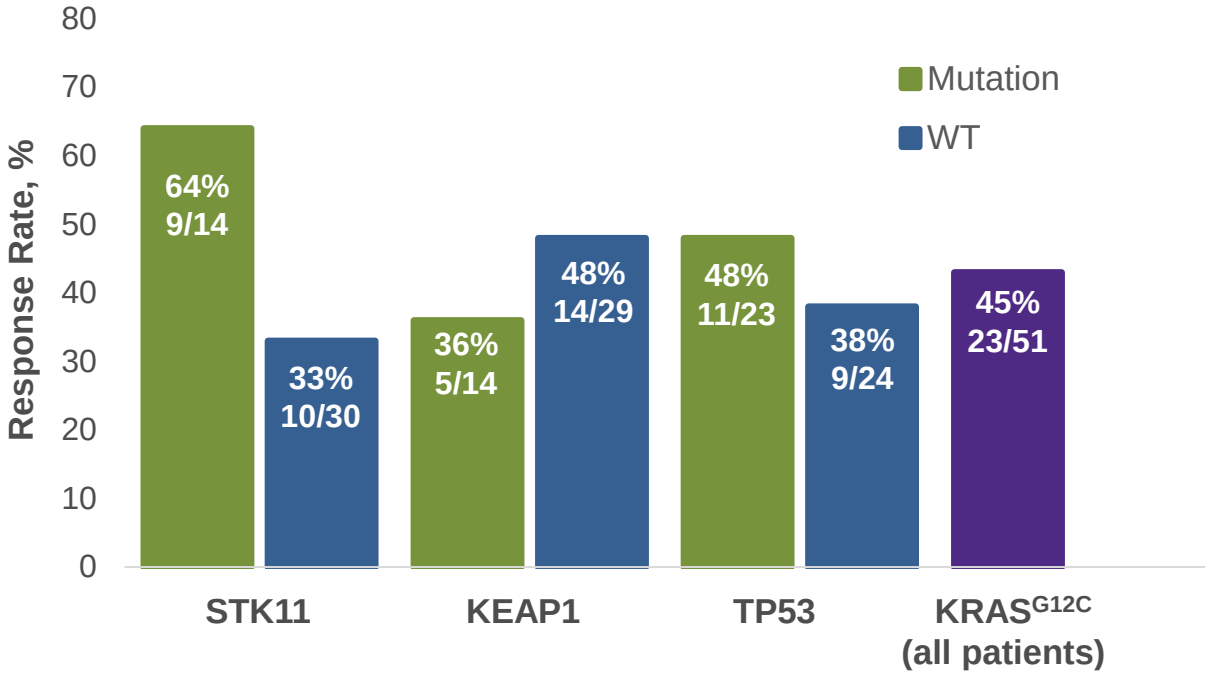
Duration of Treatment (months)	
Median (range)	8.2 (1.4, 13.1+)

- Median follow-up, 9.6 months
- 5 of the 6 responders remain on treatment; treatment is ongoing for >11 months for the majority of patients with responses (4/6)
- Median time to response, 1.5 months

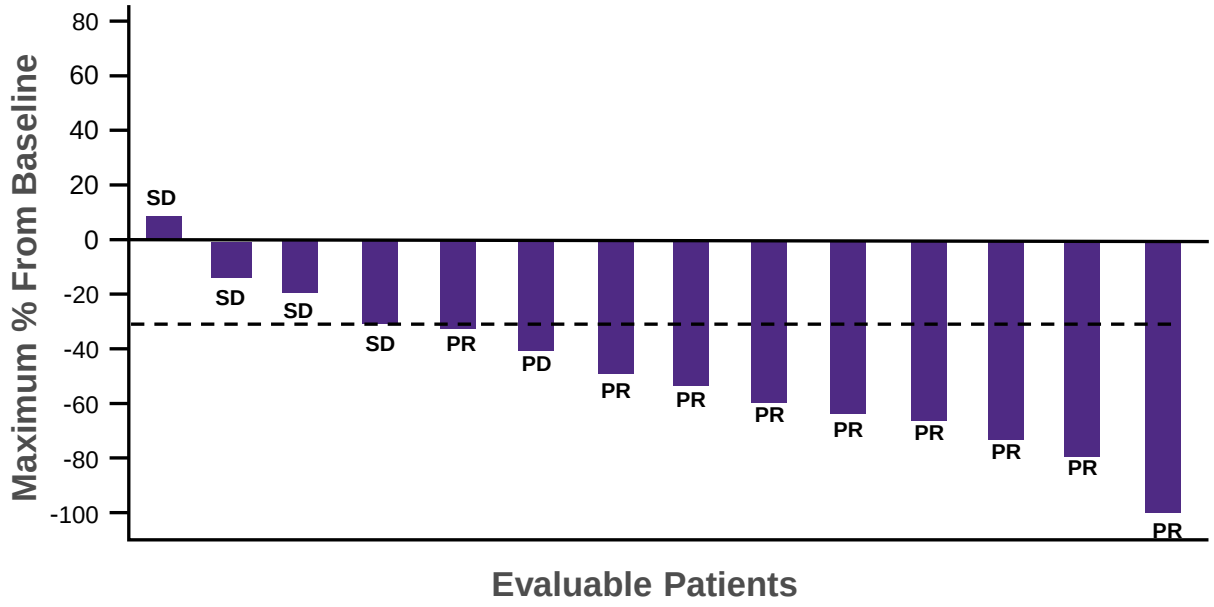
Data as of 30 August 2020.

Preliminary Exploratory Correlative Analysis of Co-Mutations With KRAS^{G12C}, Including STK11, and Response Rate in Patients With NSCLC Treated With Adagrasib

ORR in Patients Harboring KRAS^{G12C} Co-mutations



Best Tumor Change From Baseline for Patients Harboring KRAS^{G12C} and STK11 Co-mutations

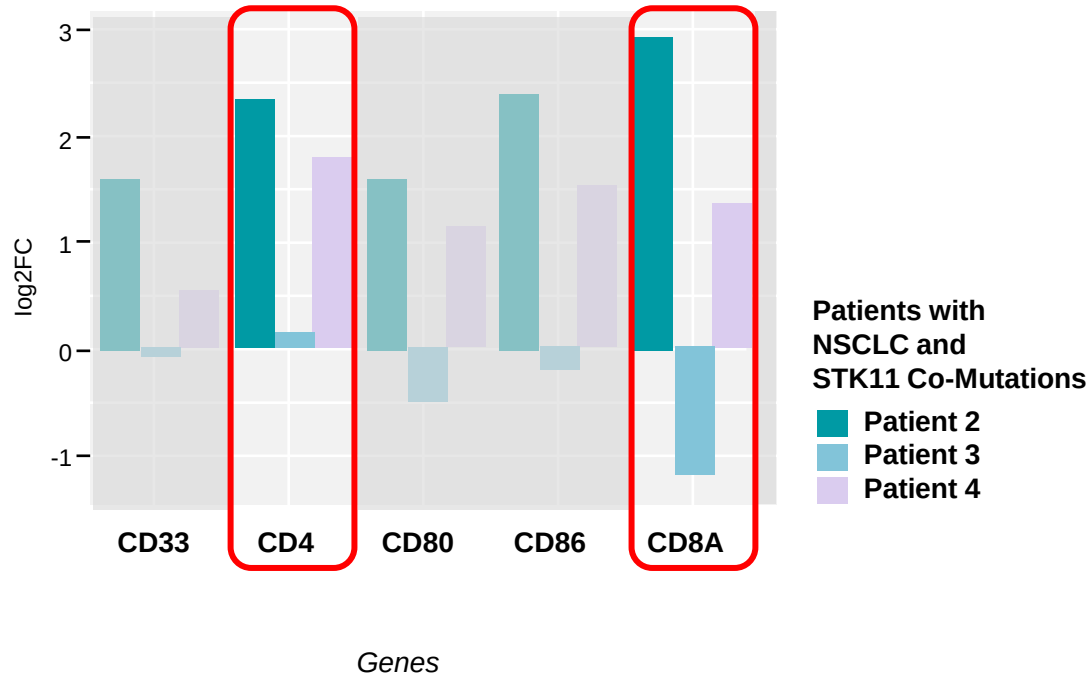


- Baseline NGS reports reviewed for exploratory correlative analysis for all patients with NSCLC with available mutation data[a]
- **64% ORR** in patients with tumors harboring KRAS^{G12C} and STK11 co-mutations
- No apparent trend with KEAP1, TP53, or other common mutations and response rate

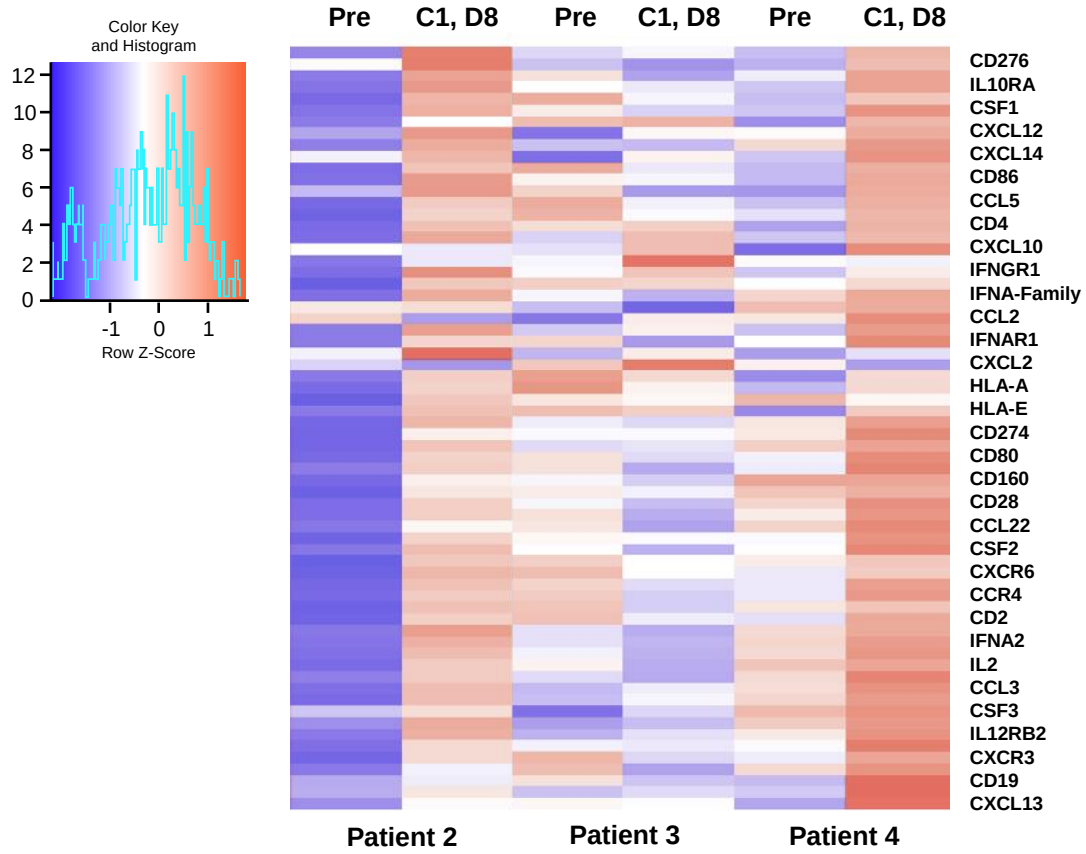
[a]Analysis includes key mutations detected at baseline in tumor and/or plasma that commonly occur with KRAS^{G12C}. Mutations included as positive include nonsense, frameshift, splice site, and recurrent mutations predicted to have deleterious impact, and excluded variants of unknown significance.
Data as of 30 August 2020. Based on unaudited data.

Tumors Harboring STK11 Co-mutations Were Immune "Cold" at Baseline and Exhibited Increased Immune Response Transcripts After Treatment With Adagrasib

Immune Biology Subset Fold Changes by Patient



Immune Transcripts Pre– and Post–Adagrasib Treatment



- Low expression of immune transcripts in pretreatment tumors with STK11 co-mutations suggests an immune "cold" phenotype
- Increase in immune transcripts and activation of IFN signatures, (eg, CD4, CD8), observed in 2 of 3 patients after adagrasib treatment
- **Hypothesis:** Adagrasib treatment recruits T cells into the tumor and may reverse STK11-mediated immune suppression

Note: Patient 4 had 5% tumor present on the post–adagrasib-treated tumor biopsy at C1D8.

Conclusions

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life and extensive predicted target coverage throughout the dosing interval
- Adagrasib is well tolerated and provides durable responses and broad disease control to patients with NSCLC harboring KRAS^{G12C} mutations
- In an exploratory genomic analysis, ORR was higher in patients with tumors harboring KRAS^{G12C} and STK11 co-mutations
- Initial biomarker analyses post-treatment with adagrasib indicate downregulation of KRAS/MAPK pathway genes and an increase in immune transcripts in patients with STK11 co-mutations
- Adagrasib is being evaluated as 1L monotherapy in patients with NSCLC with KRAS^{G12C} and STK11 co-mutations in a new cohort of KRYSTAL-1

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Abbreviations

ALT = alanine aminotransferase

AST = aspartate aminotransferase

BID = twice daily

C_{ave} = average plasma concentration

CBR = clinical benefit rate

CR = complete response

CRC = colorectal cancer

CSF = cerebrospinal fluid

DCR = disease control rate

DOR = duration of response

ECOG = Eastern Cooperative Oncology Group

IC_{50} = half maximal inhibitory concentration

IFN = interferon

MTD = maximum tolerated dose

NE = not evaluable

NSCLC = non–small-cell lung cancer

ORR = objective response rate

OS = overall survival

PD = progressive disease

PFS = progression-free survival

PK = pharmacokinetics

PR = partial response

PS = performance status

QD = once daily

RP2D = recommended Phase 2 dose

SAE = serious adverse event

SD = stable disease

TRAE = treatment-related adverse event