ENA 2020
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32nd Symposium

KRYSTAL-1: Updated Safety and Efficacy Data With Adagrasib (MRTX849) in NSCLC With KRAS^{G12C} Mutation From a Phase 1/2 Study

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Disclosures

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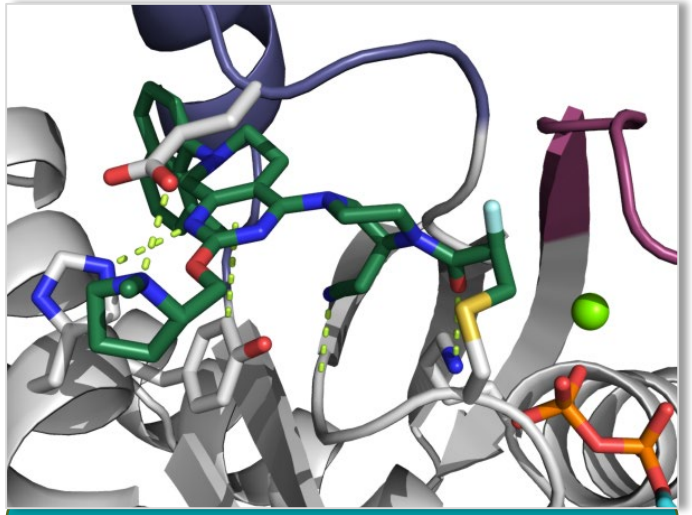
Adagrasib (MRTX849) Is a Differentiated and Selective Inhibitor of KRAS^{G12C}

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma), 3-4% of CRC, and 1-2% of several other cancers[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 dose interval and maximizes depth and duration of antitumor activity

1. Zehir A, Benayed R, Shah RH, et al. *Nat Med*. 2017;23(6):703–713. 2. Schirripa M, Nappo F, Cremolini C, et al. *Clin Colorectal Cancer*. 2020; S1533-0028(20)30067-0.
3. NIH TCGA: The Cancer Genome Atlas. 4. Bos JL, Rehmann H, Wittinghofer A. *Cell*. 2007;129: 865-877. 5. Shukla S, Allam US, Ahsan A, et al. *Neoplasia*. 2014;16(2):115-128;
6. Hallin J, Engstrom LD, Hargis L, et al. *Cancer Discov*. 2020;10(1): 54-71.

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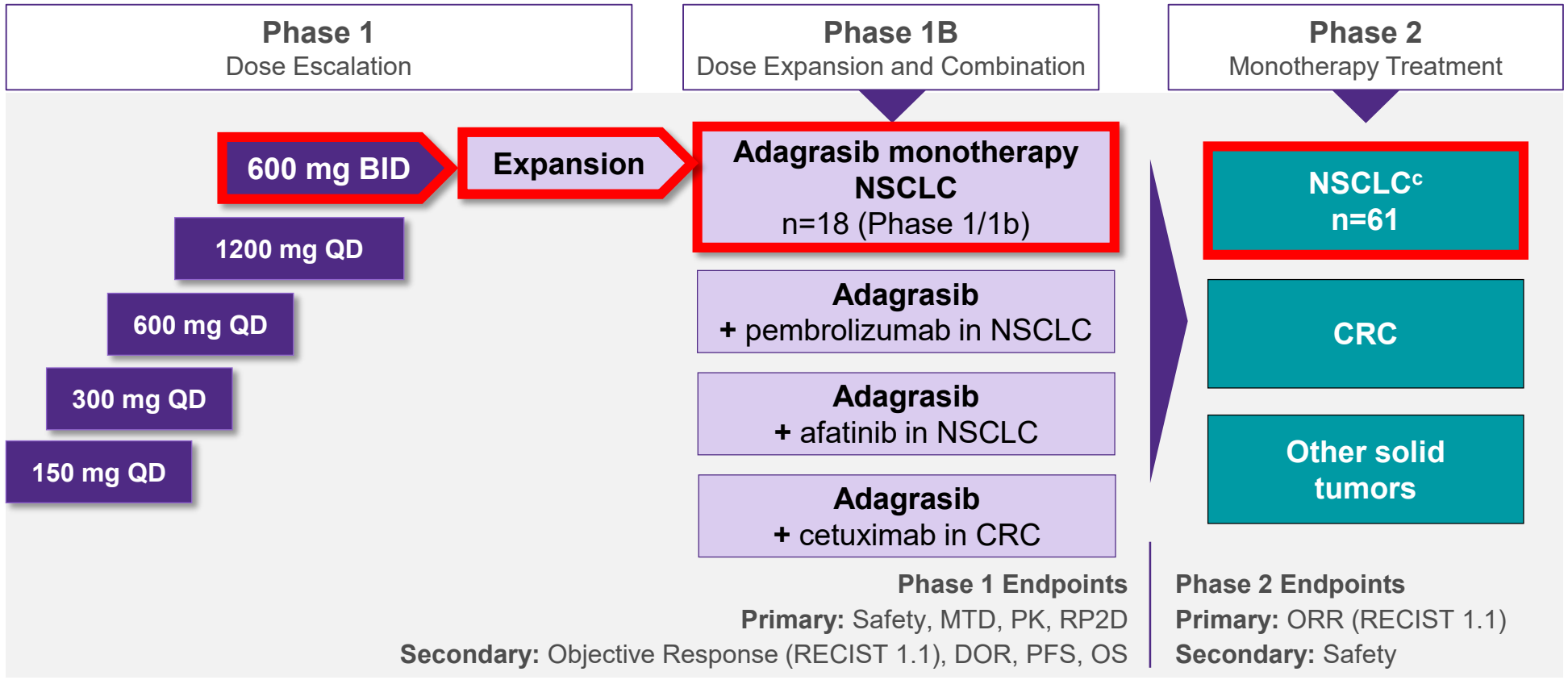
KRYSTAL-1 (849-001) Study Design

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 following or in combination with chemotherapy (NSCLC)[a]
- Treated and/or stable brain metastases[b]



- Previously reported data from Phase 1 demonstrated clinical activity with adagrasib (MRTX849) in patients with pretreated KRAS^{G12C} NSCLC and CRC
- 600 mg BID was chosen as the RP2D
- 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 mo) and Phase 2 (n=61); pooled (n=79) median follow-up, 3.6 mo
- Data cut-off 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 pre-approved test. ClinicalTrials.gov. NCT03785249.

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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. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

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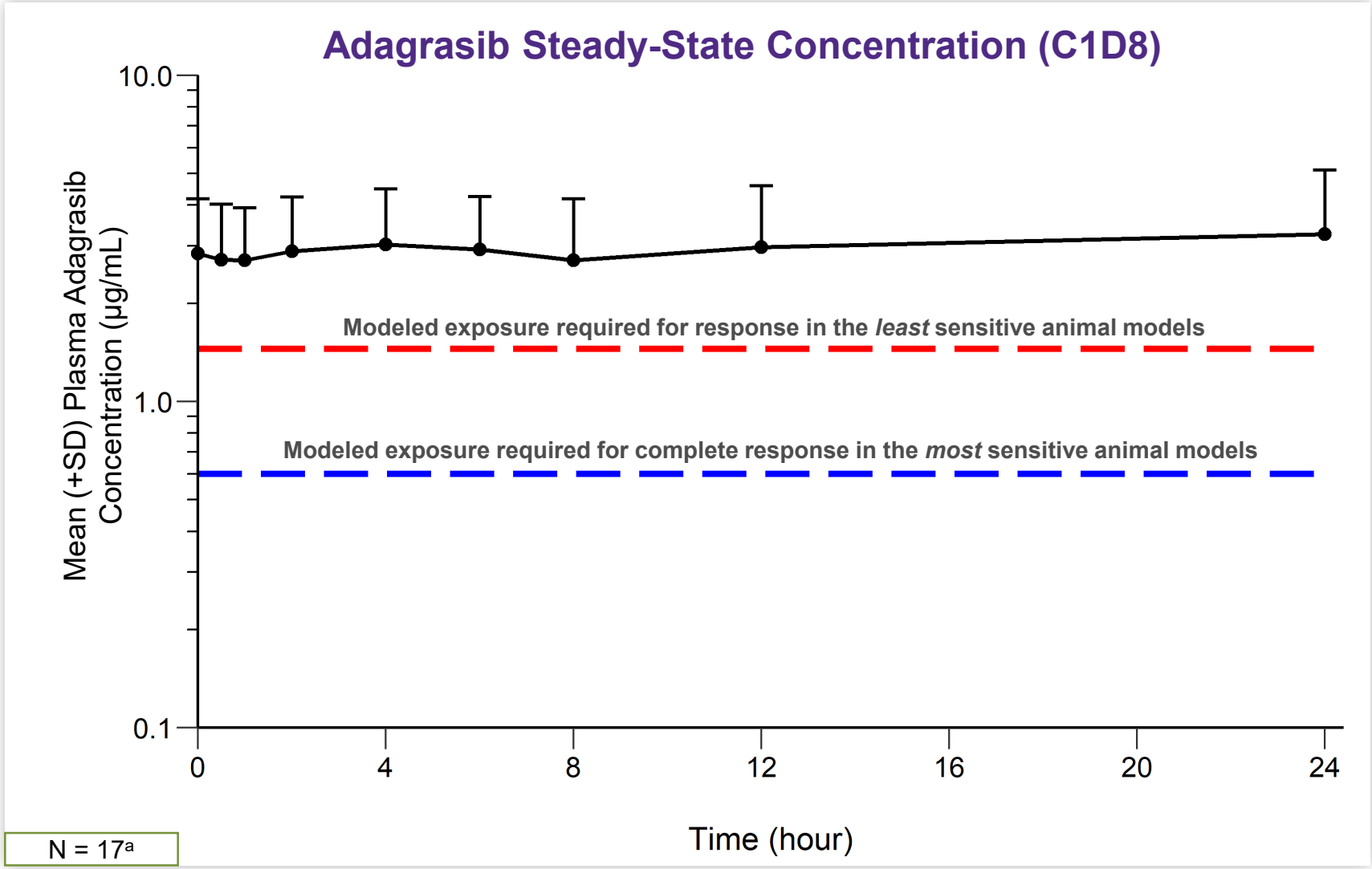
Adagrasib at 600 mg BID Exhibits Favorable PK Properties; Exposure Maintained Above Target Plasma Thresholds Throughout Full Dosing Interval



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

PK Properties Summary:

- C_{ave} of 2.63 µg/mL is 2-5-fold above target threshold for full dose interval
- C_{ave} PK parameter best matched to nonclinical antitumor activity
- Low peak to trough ratio at steady state (~1.27)
- **$t_{1/2}$ ~ 24 hours**
- Extensive volume of distribution predicted based on nonclinical studies

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)
- 7.3% of TRAEs led to discontinuation

[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 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.

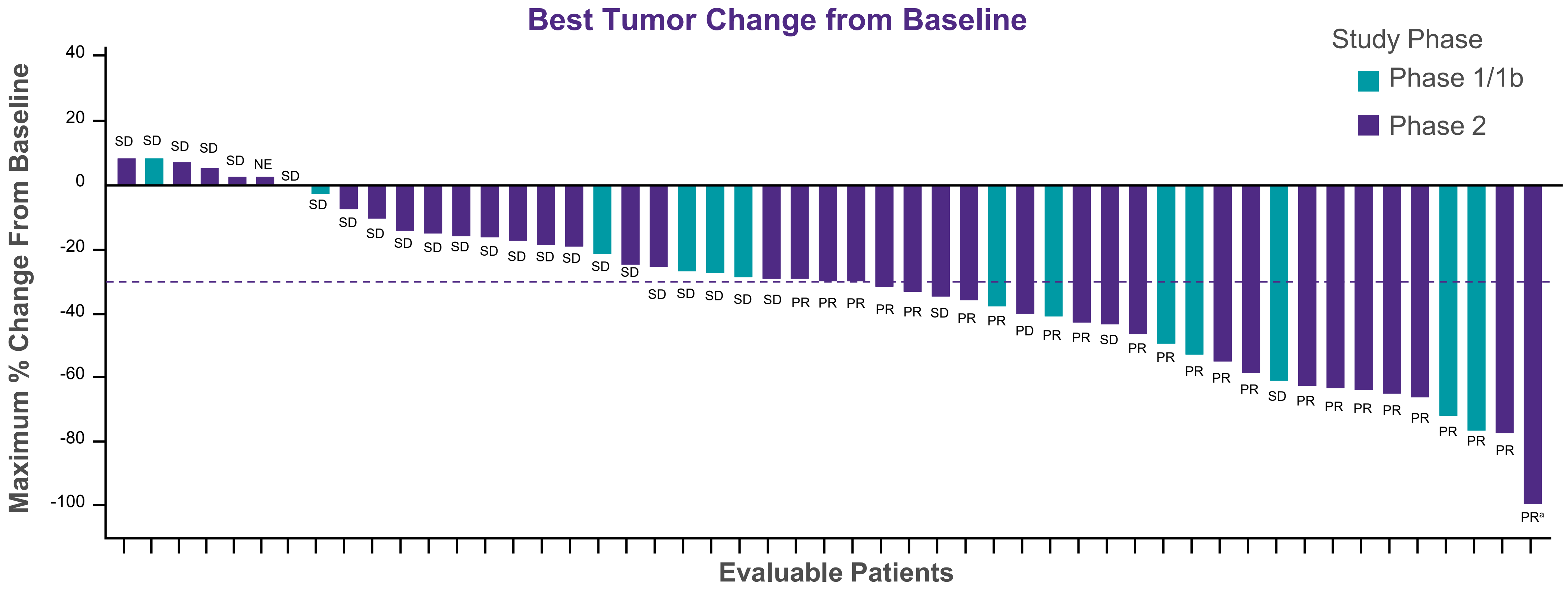
Adagrasib in Patients With NSCLC: ORR in Pooled Dataset

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 cut off, 5 patients had unconfirmed PRs. All 5 were confirmed by scans that were performed after the 30 August 2020 data cut off. [c]One patient had tumor reimaging too early for response assessment.

Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

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



- Clinical benefit (DCR) observed in 96.1% (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 two consecutive scans (1 after August 30 data cutoff) demonstrated 100% tumor regression in target and non-target lesions after resuming treatment.

Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

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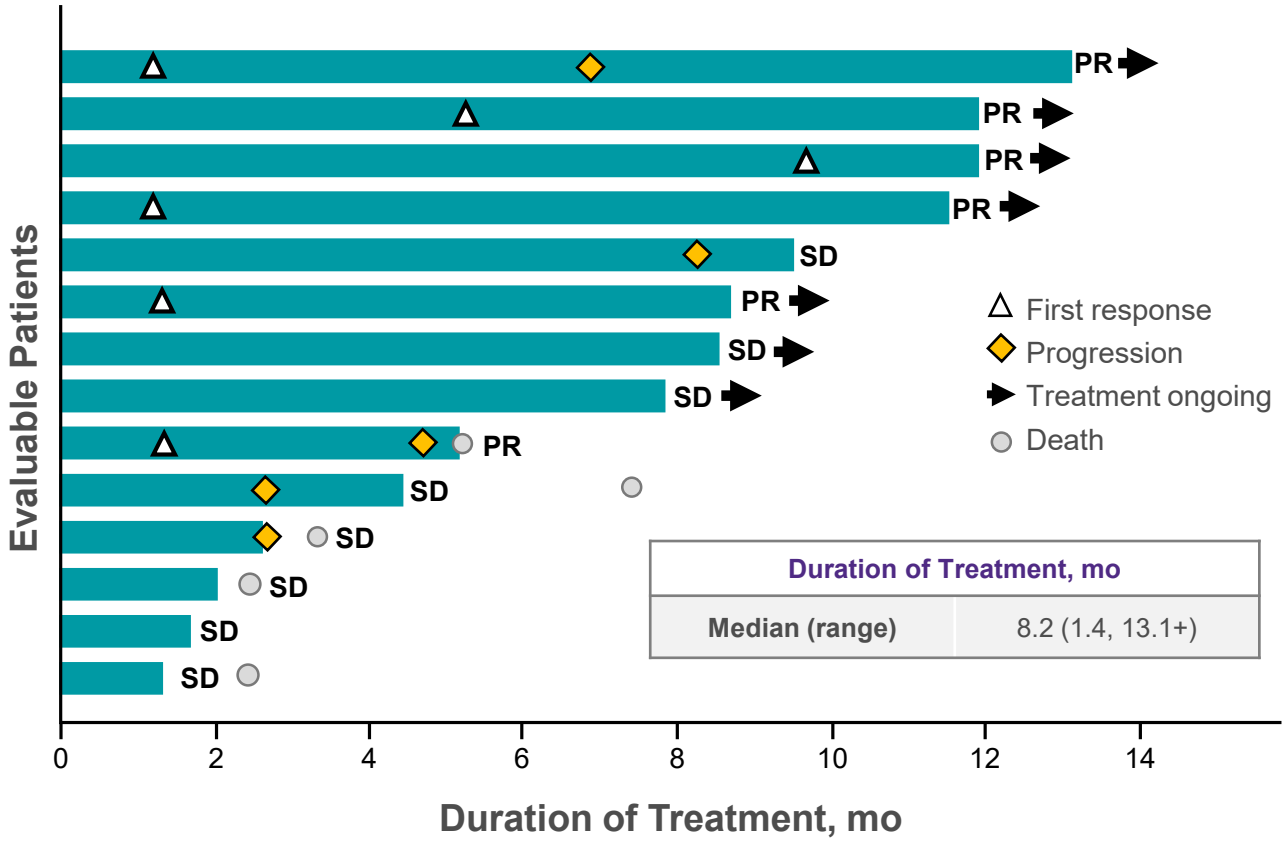
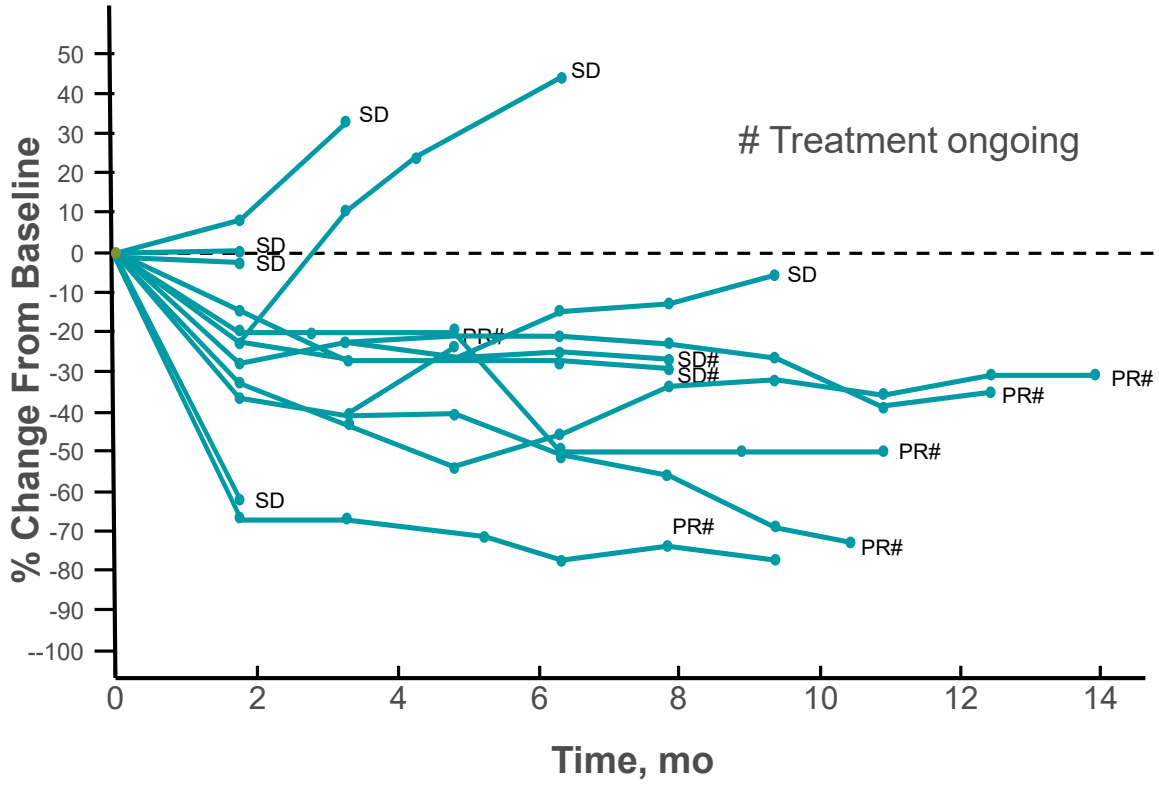
Adagrasib 600 mg BID in Patients With NSCLC: Treatment Duration and Change in Tumor Burden

Duration of Treatment, n=14



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

Change in Tumor Burden Over Time, n=14



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

Data as of 30 August 2020

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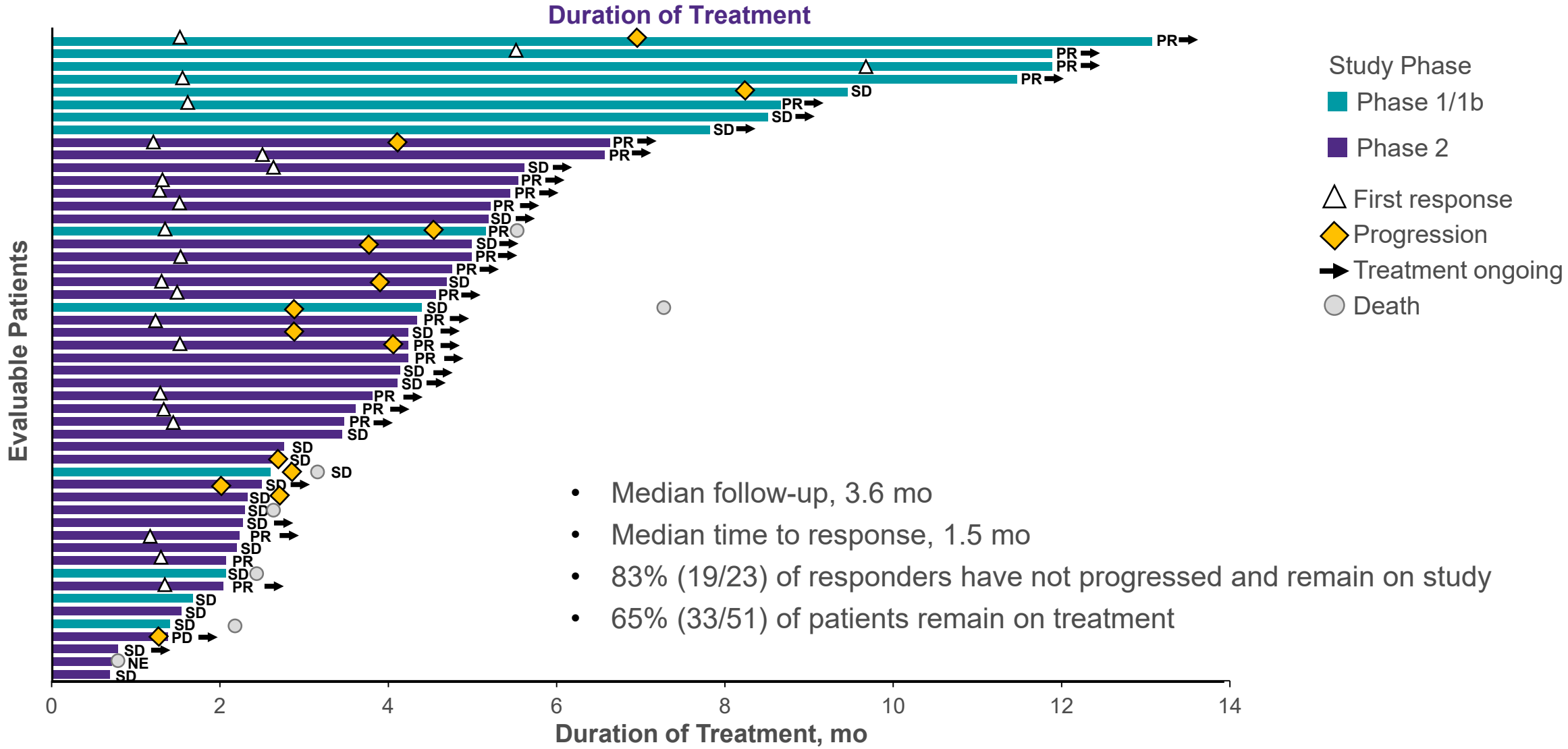
Duration of Treatment in Patients With NSCLC Treated With Adagrasib 600 mg BID in Pooled Dataset



Data as of 30 August 2020. Pooled includes NSCLC Phase 1/1b and Phase 2 600 mg BID.

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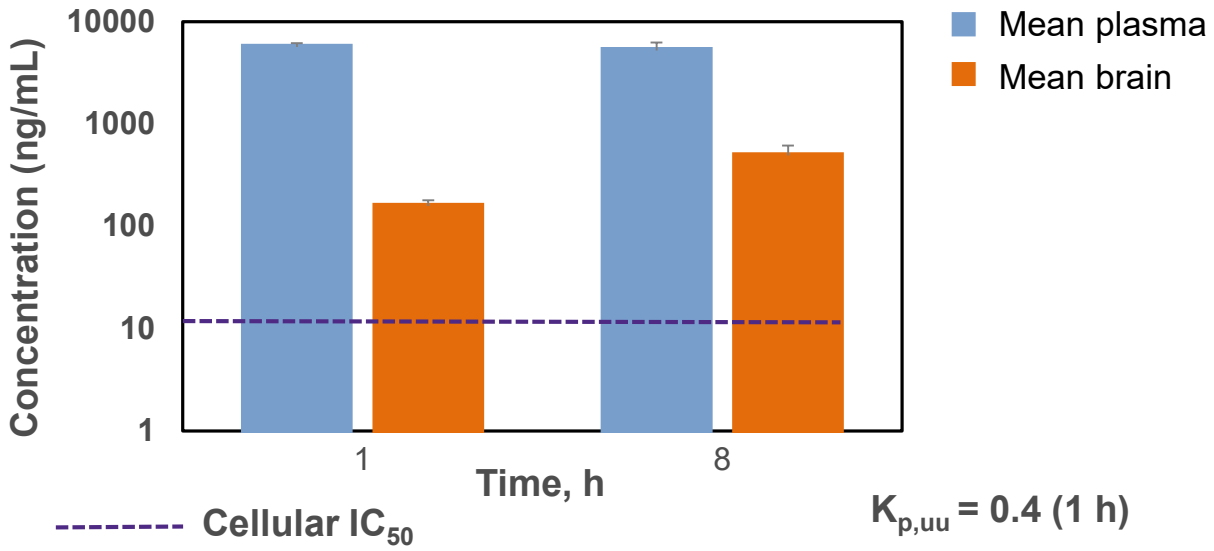
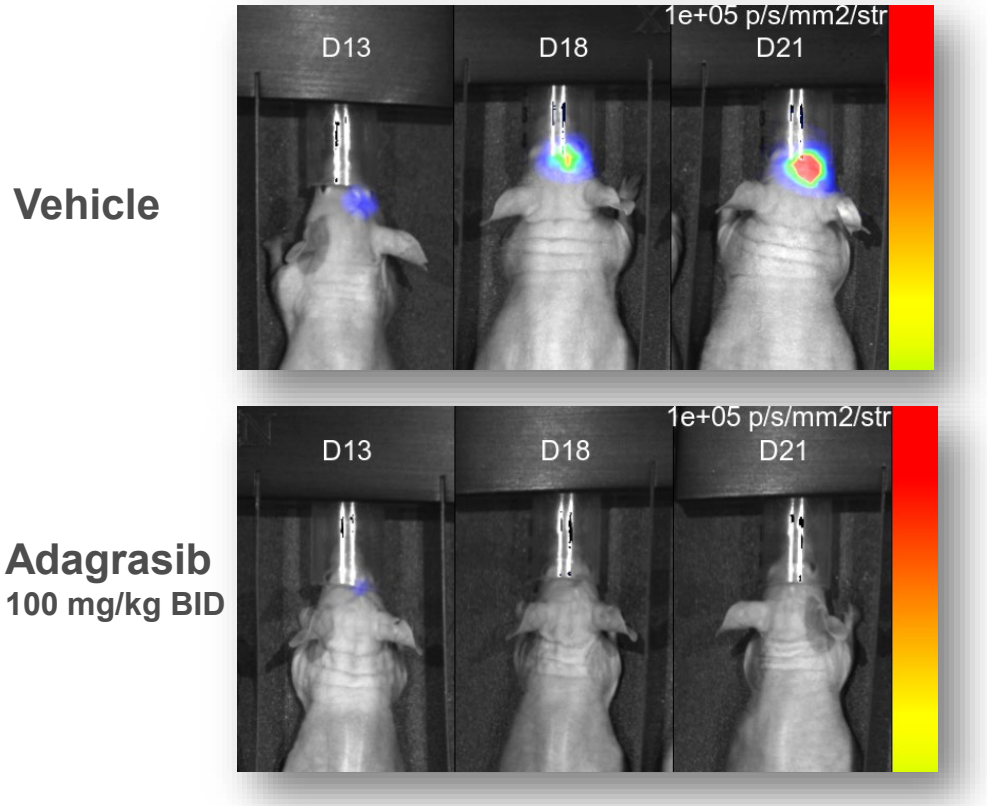
Adagrasib Penetrates the Brain/CSF and Results in Tumor Regression in a Preclinical Model[a]

Mean Plasma and Brain Concentrations of Adagrasib After a Single 100 mg/kg Oral Dose in Mice



LU99Luc KRAS^{G12C} Brain Metastases Model



- Adagrasib demonstrates dose-dependent brain and CSF exposure in preclinical studies
- A single 100 mg/kg oral dose in mice results in brain concentrations exceeding the cellular IC_{50} of adagrasib
- Plasma levels achieved at 100 mg/kg BID in mice are comparable to levels achieved at a 600 mg BID human dose and results in near complete tumor regression in LU99Luc KRAS^{G12C} tumors

[a]Data on file, Mirati Therapeutics, Inc.

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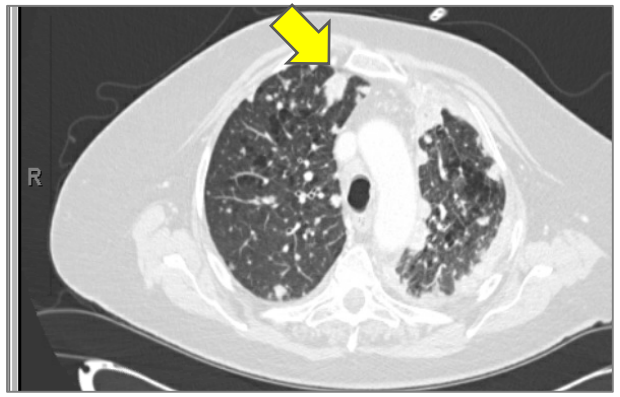
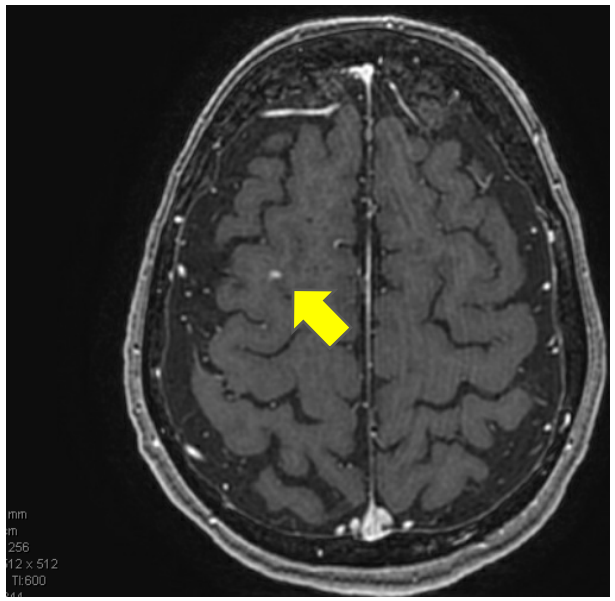
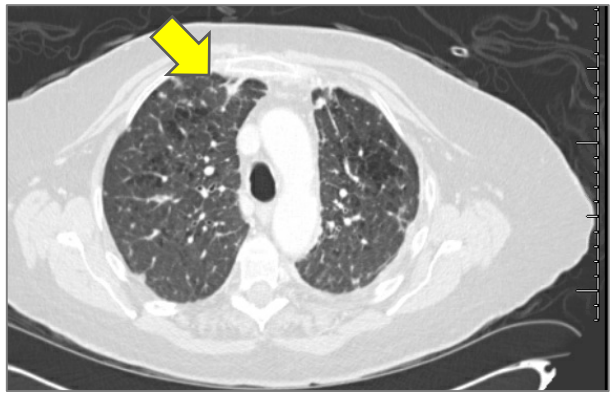
Patient Case: Patient With Brain Metastasis and KRAS^{G12C} Mutation

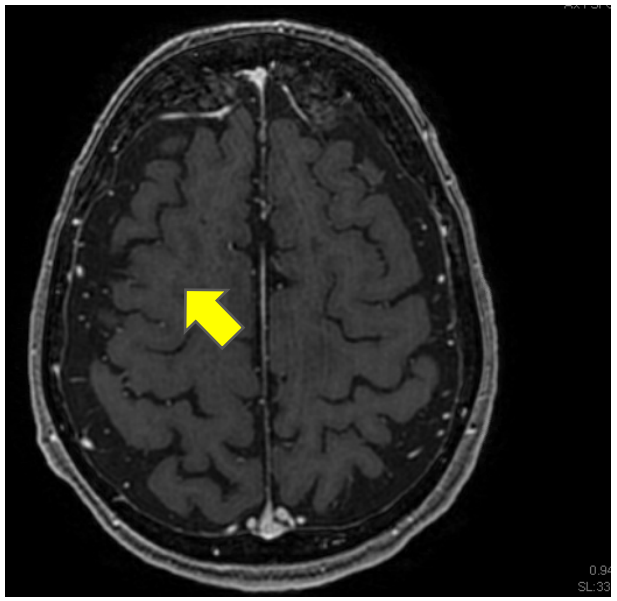
Baseline





Adagrasib 600 mg BID, Cycle 7
PR, (-67%)



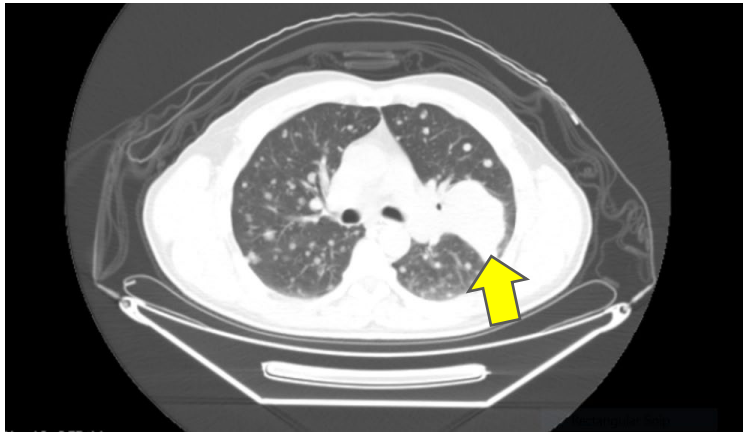


- **77-year-old female previous smoker**
- **NSCLC diagnosed, April 2019**
- **Only mutation identified by NGS panel: KRAS^{G12C}**
- **Treatment history**
  - Carboplatin, pemetrexed, pembrolizumab, May-July 2019
  - Pemetrexed maintenance, August-December 2019
  - Left frontal brain met radiation, November 2019
  - Pembrolizumab maintenance, January-February 2020
  - Pemetrexed, March 2020
  - Left and right cerebellar radiation, March 2020
- **Patient started adagrasib 600 mg BID, May 2020**
- **Metastases were in the lung and liver and an unirradiated brain lesion in the right middle frontal gyrus**
- **TRAEs**
  - Grade 1 nausea, vomiting, diarrhea, dysphagia, anemia, rash, and thigh discomfort
- **Currently in cycle 7**

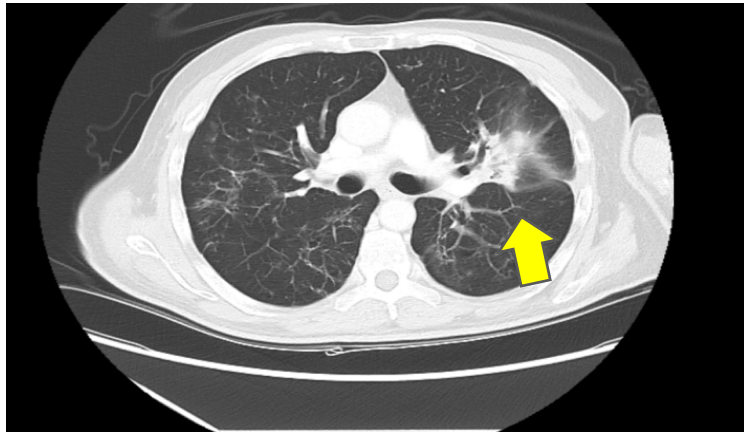
Data as of 25 September 2020.

Patient Case: Response in NSCLC Harboring KRAS^{G12C} and STK11 Co-Mutations

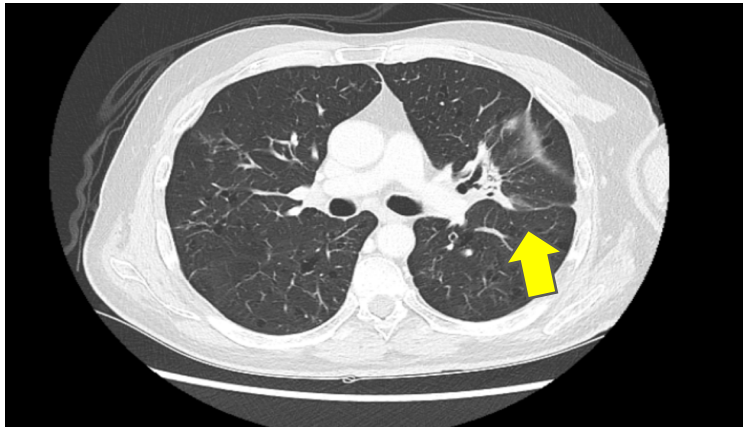
Baseline



Adagrasib 600 mg BID, Cycle 6
PR (-56%)



Adagrasib 600 mg BID, Cycle 10
PR (-59%)



- **53-year-old male former smoker; NSCLC diagnosed, December 2018**
- **KRAS^{G12C} and STK11^{N41*} mutations detected by NGS**
- **Treatment history**
  - Radiotherapy to brain, December 2018
  - Carboplatin, pemetrexed, pembrolizumab, January-April 2019 with BOR of SD
  - Radiotherapy to brain, March-April 2019
  - Pemetrexed with pembrolizumab as continuation maintenance through September 2019
  - LMB-100 (investigational agent) with pembrolizumab, October-December 2019
- **Patient started adagrasib 600 mg BID in February 2020**
- **No TRAEs**
- **Patient remains on study**

Data as of 05 October 2020.

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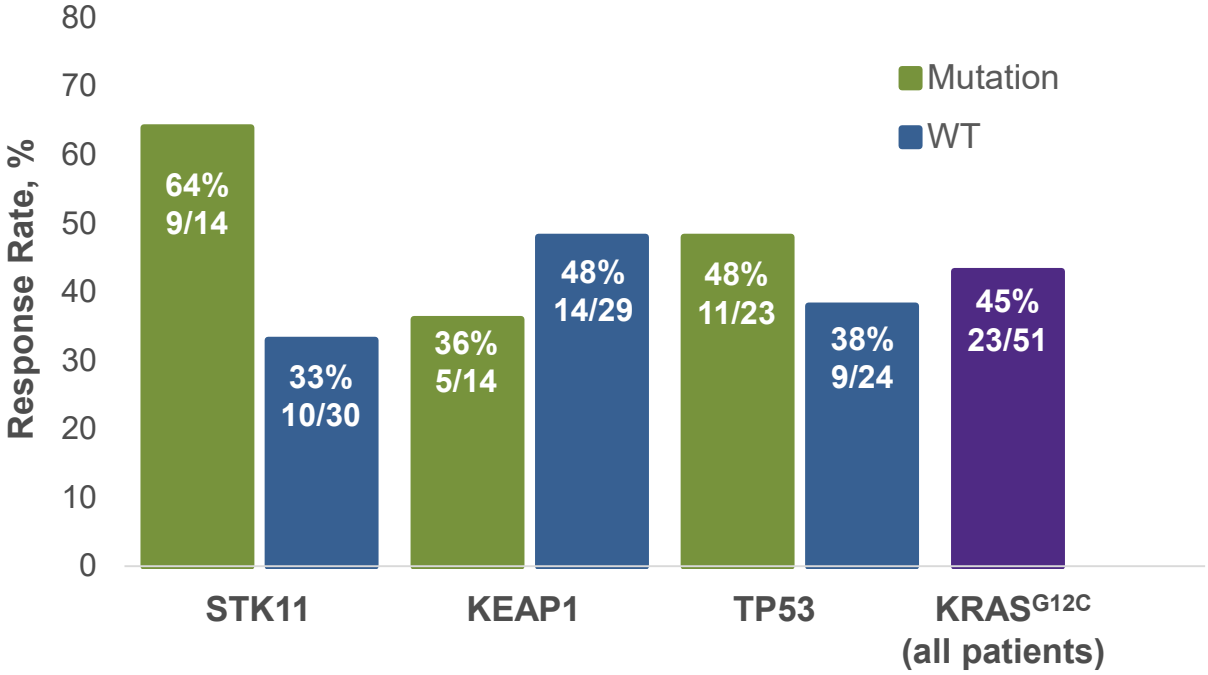
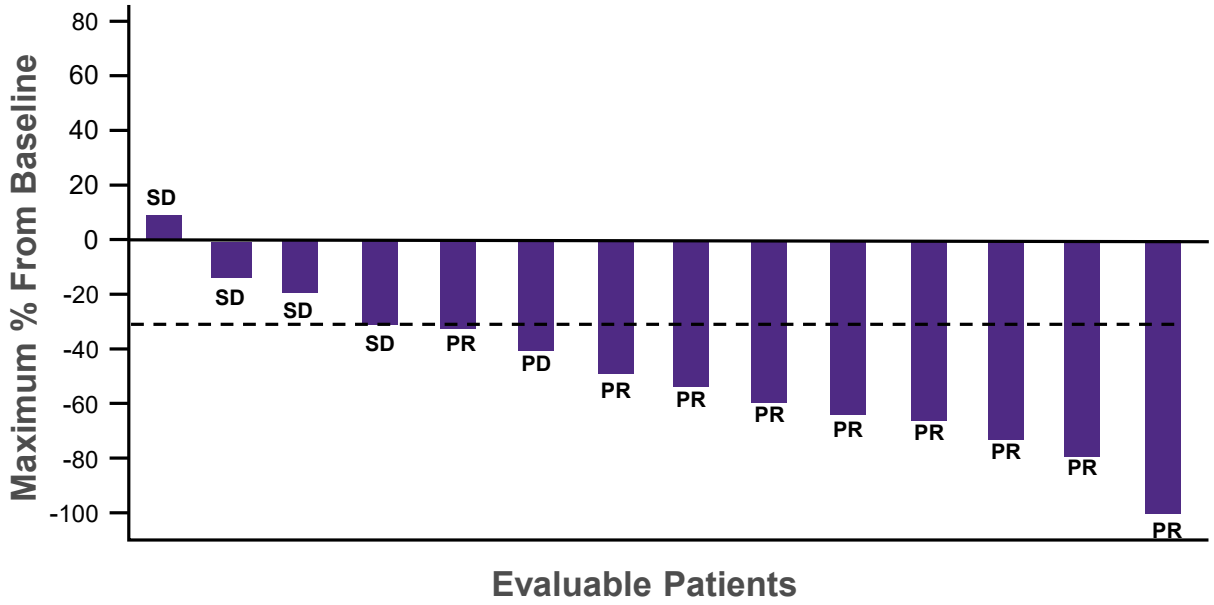
Preliminary Exploratory Correlative Analysis of Co-Mutations Including STK11 With KRAS^{G12C} and Response Rate in Patients with NSCLC Treated with Adagrasib

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 NSCLC patients with available mutation data[a]
- **64% ORR** in patients with tumors harboring STK11 and KRAS^{G12C} 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 VUS.
Data as of 30 August 2020. Based on unaudited data.

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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
- Adagrasib provides durable benefit to patients with NSCLC harboring KRAS^{G12C} mutations
  - Durable responses were observed
  - Broad disease control rate was observed
- In a preliminary exploratory genomic analysis, ORR was higher in patients with tumors harboring KRAS^{G12C} and STK11 co-mutations
- Pembrolizumab combination (NSCLC) arm has cleared the DLT observation period and enrollment in Phase 1b expansion at full dose of each agent is ongoing[a]
- Combination clinical trials are enrolling or planned in NSCLC with afatinib[a], TNO155[b] (SHP2-inhibitor), and palbociclib

Responses observed in CRC (n=3/18; 17%), and in patients with pancreatic, ovarian, and endometrial cancers, and cholangiocarcinoma
See Johnson ML et al., abstract LBA-04.

[a]ClinicalTrials.gov. NCT03785249. [b]ClinicalTrials.gov. NCT04330664.

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Abbreviations

BID = twice daily

C_{ave} = average drug plasma concentration

CBR = clinical benefit rate

CRC = colorectal cancer

CSF = cerebrospinal fluid

DCR = disease control rate

DLT = dose limiting toxicity

DOR = duration of response

ECOG = Eastern Cooperative Oncology Group

MTD = maximum tolerated dose

nM = nanomolar

NE = not evaluable

NGS = next-generation sequencing

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

uPR = unconfirmed partial response

VUS = variant of unknown significance