2022 ASCO® ANNUAL MEETING

KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Advanced/Metastatic Non-Small Cell Lung Cancer Harboring a $KRAS^{G12C}$ Mutation

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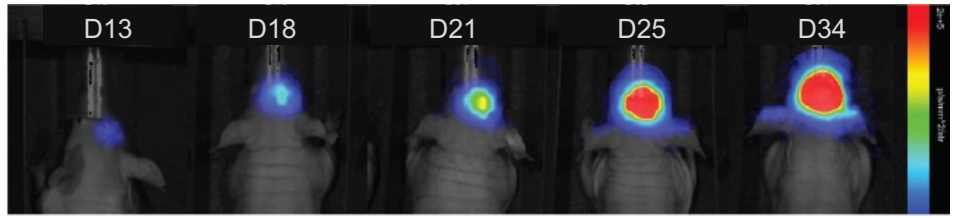
Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

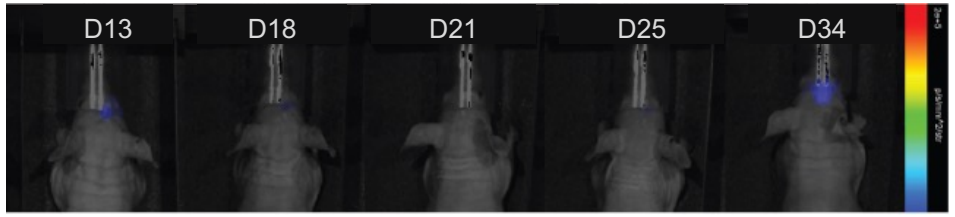
- KRAS^{G12C} mutations act as oncogenic drivers and occur in ~14% of patients with NSCLC (adenocarcinoma)[1]
  - Approximately 27–42% of patients with KRAS^{G12C}-mutated NSCLC have CNS metastases at diagnosis[2,3]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, was optimized for desired properties of a KRAS^{G12C} inhibitor, including a long half-life (23 hours), dose-dependent PK and CNS penetration[4,5]
- In the FIH Phase 1/1b trial of adagrasib in patients with KRAS^{G12C}-mutated NSCLC (n=15), the ORR was 53.3%, median DOR was 16.4 months, and median PFS was 11.1 months[6]
- Adagrasib demonstrated CNS penetration and CNS tumor regressions in preclinical models.[7] In a preliminary analysis in a Phase 1b cohort evaluating adagrasib in patients with NSCLC and active, untreated CNS metastases (n=2):[7]
  - Mean $K_{p,uu}$ value was 0.47
  - Regression of CNS metastases was observed in both patients

LU99Luc KRAS^{G12C} Brain Metastases Model[7]

Vehicle



Adagrasib (100 mg/kg BID)



- Clinical activity with adagrasib has been shown in patients with various KRAS^{G12C}-mutated solid tumors, including NSCLC, CRC, PDAC, ovarian and endometrial cancers, and other GI cancers[5,8–10]

KRYSTAL-1 (849-001) Phase 2 Cohort A Study Design

Phase 2
NSCLC Monotherapy Treatment

Key Eligibility Criteria

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

Adagrasib 600 mg BID (Capsule, Fasted)

Study Objectives

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

Here we report data from a registrational Phase 2 cohort evaluating adagrasib 600 mg BID in previously treated patients with NSCLC harboring a KRAS^{G12C} mutation (N=116)

Enrollment period, January 2020 to December 2020

[a]KRAS^{G12C} mutation detected in tumor tissue by sponsor-approved local laboratory testing
ClinicalTrials.gov. NCT03785249

Demographics and Baseline Characteristics

	Adagrasib Monotherapy (N=116)[a]
Median age (range), years	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%)
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]Among the enrolled patients, 113 (97%) had adenocarcinoma and 3 (3%) had squamous histology; 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

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

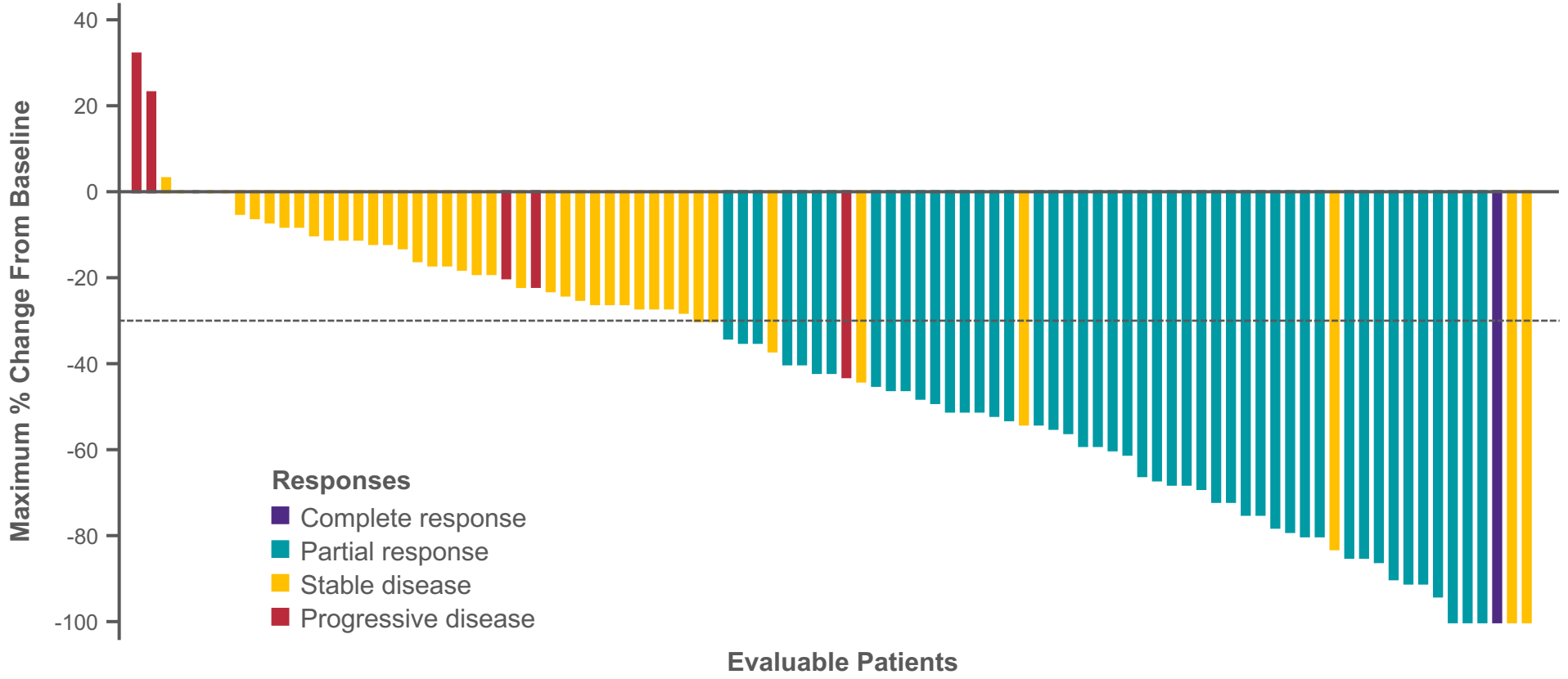
Efficacy Outcome	Adagrasib Monotherapy (n=112)[a]
Objective response rate, n (%)	48 (43%)
Best overall response, n (%)	
Complete response	1 (1%)
Partial response	47 (42%)
Stable disease	41 (37%)
Progressive disease	6 (5%)
Not evaluable	17 (15%)
Disease control rate, n (%)	89 (80%)

- 17 patients were not evaluable due to having received post-baseline scans too early (n=3) or study withdrawal prior to first scheduled assessment (n=14)[b]
- For evaluable patients (on treatment and who had a scan at ~6 weeks[c]), ORR was 51% (48/95)

[a]Full analysis set as per BICR excludes 4 patients who did not have measurable disease at baseline; [b]Due to reasons of: withdrawal by patient (n=5), AEs (n=3; 2 patients experienced AEs not related to treatment, 1 patient experienced a TRAE), global deterioration of health (n=3), death (n=2), non-compliance (n=1); [c]6 weeks ± 10 days

Data as of October 15, 2021 (median follow-up: 12.9 months)

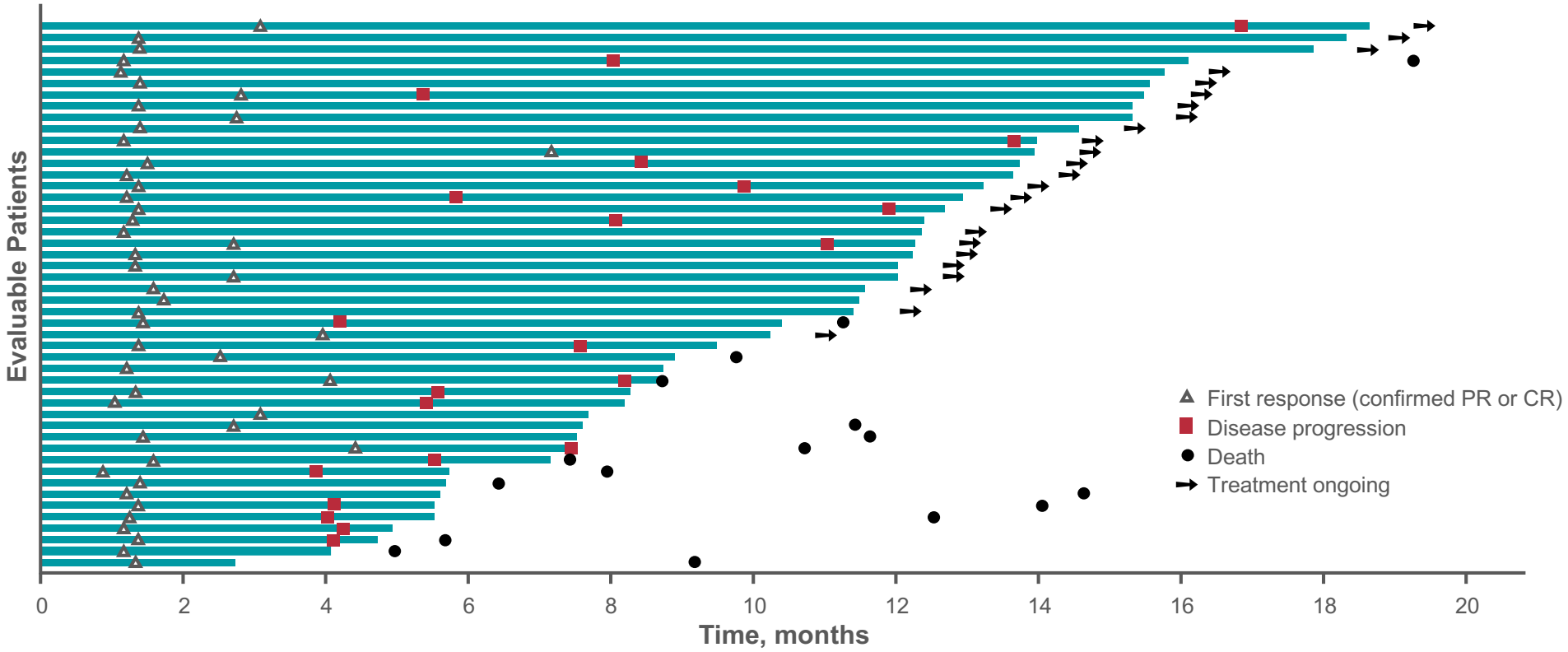
Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Best Tumor Change From Baseline



- Objective responses were observed in 43% (95% CI, 33.5–52.6); DCR was 80% (95% CI, 70.8–86.5)
- Responses were deep with 75% of responders achieving >50% tumor reduction

All results are based on BICR. Responses include target lesion tumor regression, as well as non-target lesion assessment
Data as of October 15, 2021 (median follow-up: 12.9 months)

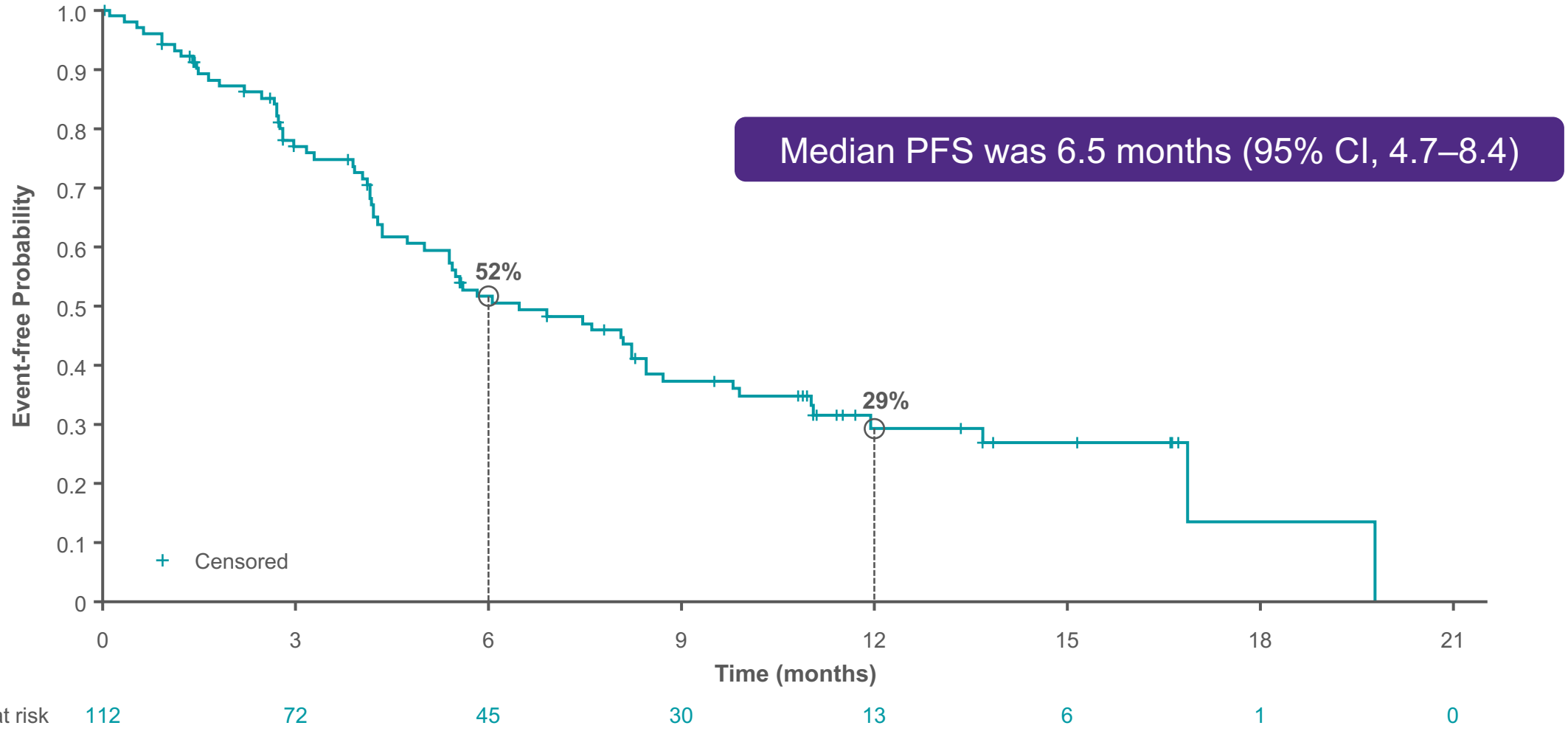
Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Duration of Response



- Median TTR was 1.4 months (range, 0.9–7.2)
- Median DOR was 8.5 months (95% CI, 6.2–13.8)
- Treatment is ongoing in 50% (24/48) of patients who experienced a response, and 33% (16/48) are still in response

All results are based on BICR. The median duration of treatment was 5.7 months (range, 0.03–19.6)
Data as of October 15, 2021 (median follow-up: 12.9 months)

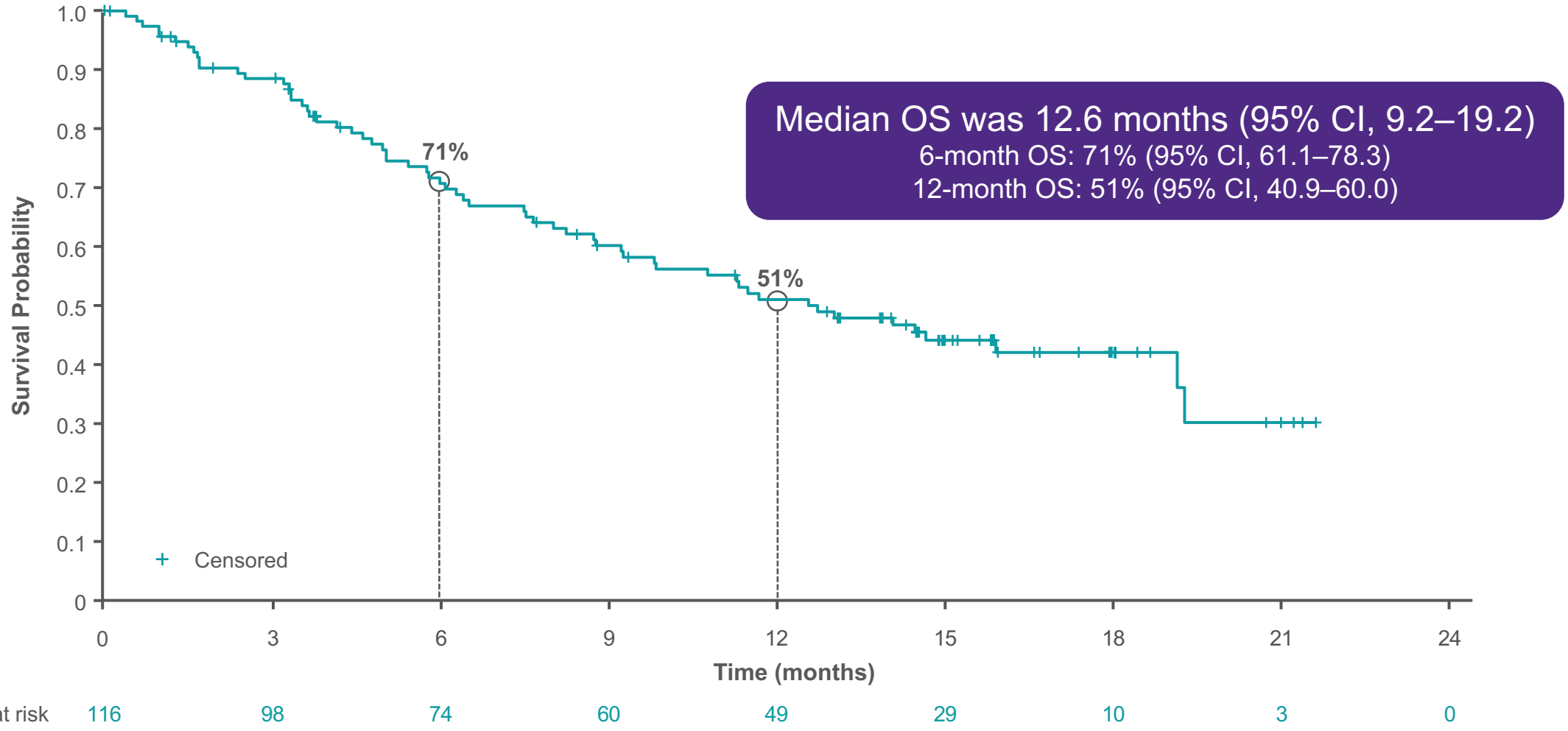
Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Progression-Free Survival



All results are based on BICR

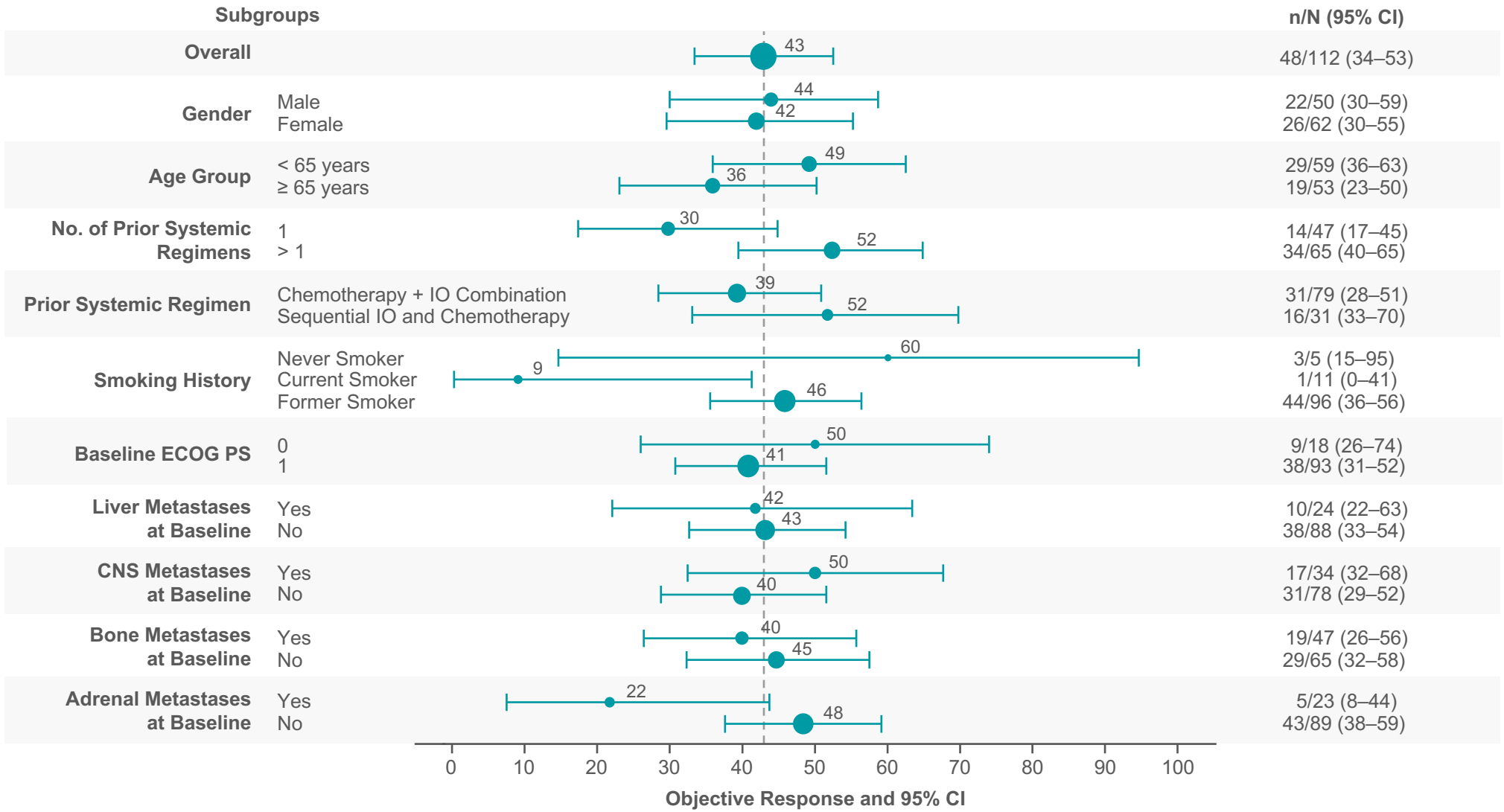
Data as of October 15, 2021 (median follow-up: 12.9 months)

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Overall Survival



As of October 15, 2021, median OS was 11.7 months (95% CI, 9.2–NE); median follow-up: 12.9 months
Data as of January 15, 2022 (median follow-up: 15.6 months)

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Exploratory Subgroup Analyses

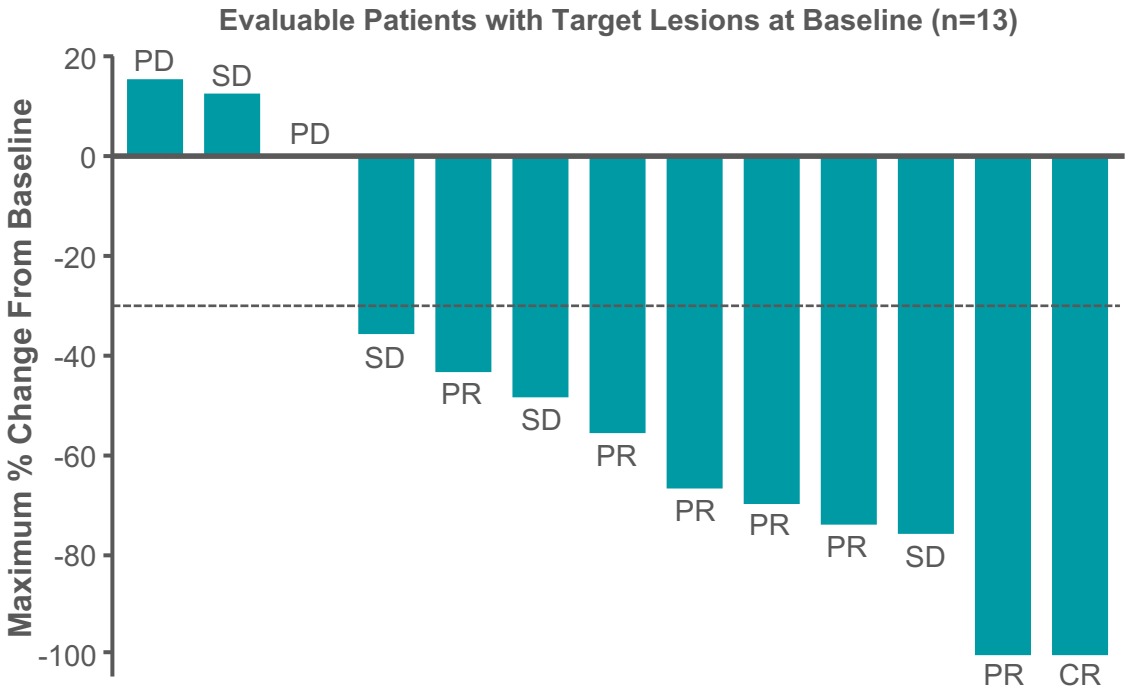


All results are based on BICR. Dot size indicates sample size. Note that for the 3 patients with squamous NSCLC: 1 patient had a BOR of PR, 2 patients had a BOR of SD

Data as of October 15, 2021 (median follow-up: 12.9 months)

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Intracranial Response in Patients with Treated, Stable CNS Metastases[a]

Best Overall Response	Overall (n=33)[b]	Patients with Non-target Lesions Only (n=19)	Patients with Target Lesions (n=13)[c]
IC ORR, n (%)	**11 (33%)**	**4 (21%)**	**7 (54%)**
Complete response	5 (15%)	4 (21%)	1 (8%)
Partial response	6 (18%)	-	6 (46%)
Stable disease	17 (52%)	13 (68%)	4 (31%)
IC DCR, n (%)	**28 (85%)**	**17 (89%)**	**11 (85%)**



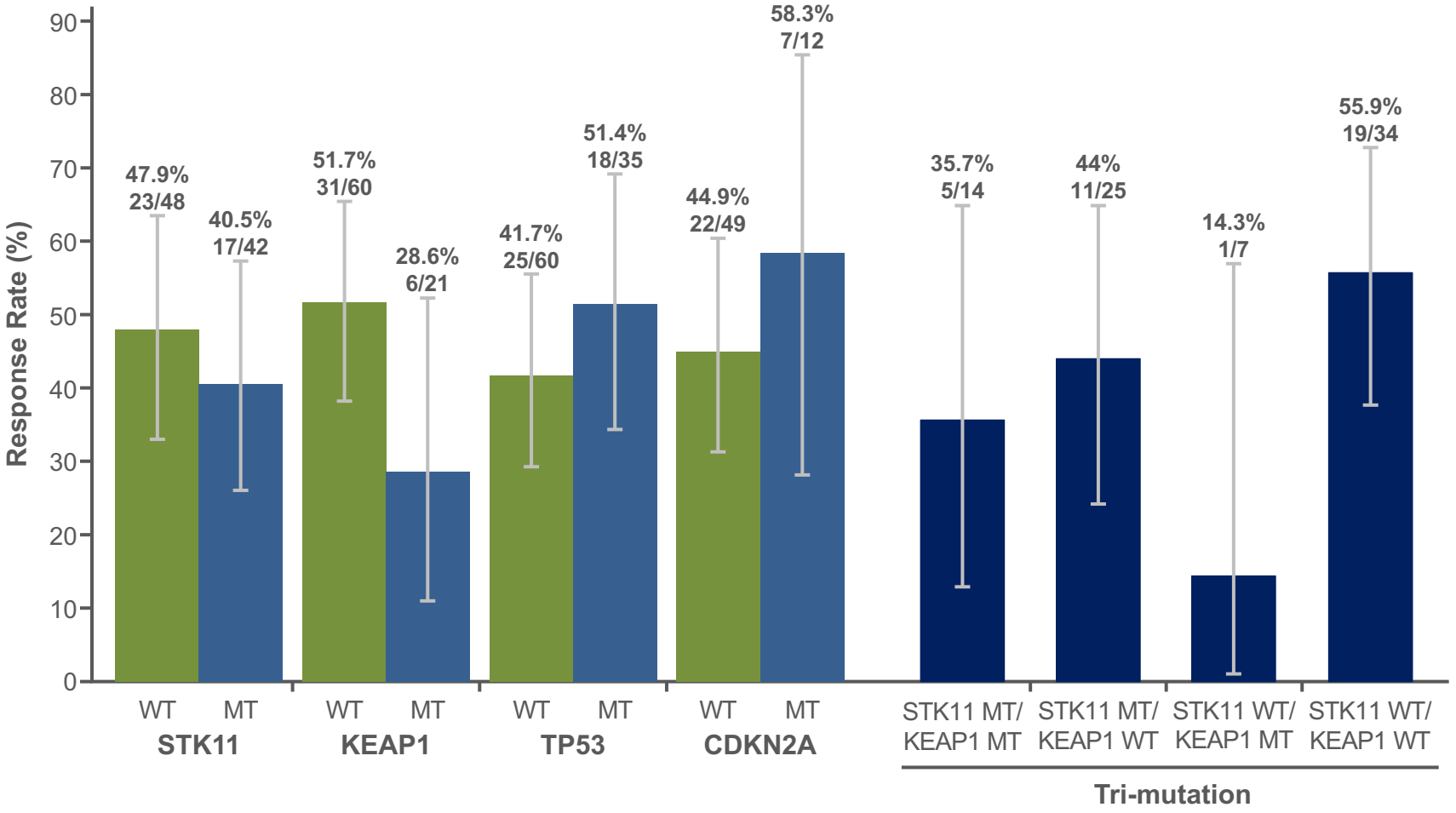
- IC ORR by modified RANO-BM was 33% (95% CI, 18–52); median IC DOR was 11.2 months (95% CI, 3.0–NE)
- IC DCR was 85% (95% CI, 68–95); median IC PFS was 5.4 months (95% CI, 3.3–11.6)

Target lesions: all measurable lesions (size ≥5 mm) with ≤5 lesions in total, and representative of all involved organs; non-target lesions: all non-measurable lesions and measurable lesions not identified as target lesions
[a]Among patients with adequately treated, stable CNS metastases, 33 patients were radiographically evaluable (i.e., had a baseline and on-treatment brain scan for evaluation), of whom 27 (82%) received radiation prior to adagrasib treatment (59% <3 months before study entry and 37% ≥6 months before study entry); [b]One patient with tumor shrinkage of 8% was deemed to be 'not evaluable' as the post-baseline scan was performed too early for evaluation; [c]Patients with target lesions may have also had non-target lesions

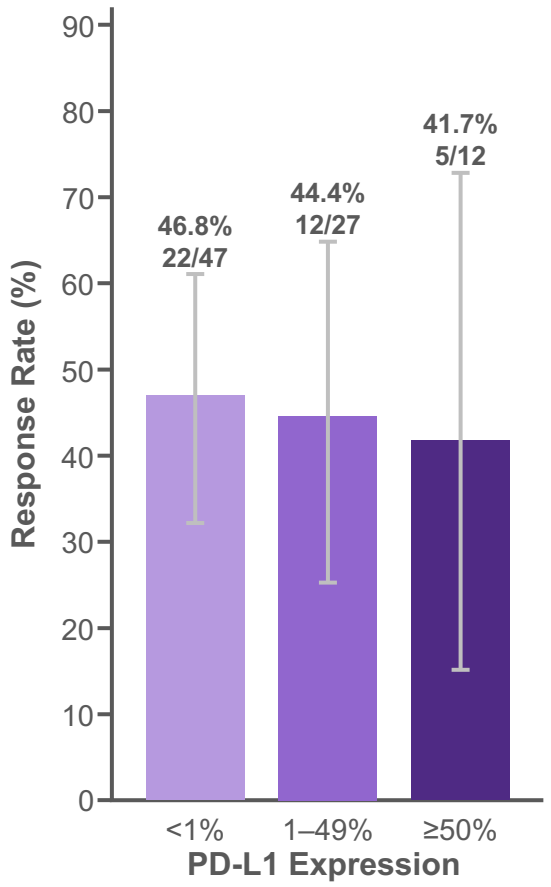
Data as of December 31, 2021 (median follow-up: 15.4 months)

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Pre-specified Correlative Analyses

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



ORR by PD-L1 Subgroups[a]



All results are based on BICR

[a]PD-L1 was centrally tested

Data as of October 15, 2021 (median follow-up: 12.9 months)

Treatment-Related Adverse Events

	Adagrasib Monotherapy (N=116) Capsule, Fasted	
TRAEs, n (%)	**Any Grade**	**Grades 3–4**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs[a], n (%)		
Diarrhea	73 (63%)	1 (<1%)
Nausea	72 (62%)	5 (4%)
Vomiting	55 (47%)	1 (<1%)
Fatigue	47 (41%)	5 (4%)
ALT increase	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
AST increase	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)

- Grade 1–2 TRAEs occurred in 53% of patients
- There were 2 grade 5 TRAEs (cardiac failure [n=1] and pulmonary hemorrhage [n=1])
- TRAEs led to dose reduction in 60/116 (52%) patients[b] and to dose interruption in 71/116 (61%) patients
- TRAEs led to discontinuation of study drug in 8/116 (7%) patients

[a]Occurring in >20% of patients (any grade), TRAEs occurring in >15% and <20% of patients were anemia (21 [18%]), amylase increase (20 [17%]) and QT prolongation (19 [16%]);
[b]Percentage of patients who experienced dose reductions: 400 mg BID (33%), 600 mg QD (11%), 200 mg BID/400 mg QD (14%)

Data as of October 15, 2021 (median follow-up: 12.9 months)

Conclusions and Future Directions

- In this registrational Phase 2 cohort, adagrasib demonstrated promising clinical activity (ORR, 43%; DCR, 80%; 1-year OS, 51%) as well as a manageable safety profile, in patients with previously treated NSCLC harboring a KRAS^{G12C} mutation
- Based on these data, the NDA for adagrasib has been accepted and under review for accelerated approval in the US and the MAA has been recently submitted to the European Medicines Agency
- A confirmatory Phase 3 study is evaluating adagrasib versus docetaxel in previously treated patients with KRAS^{G12C}-mutant NSCLC (KRYSTAL-12; NCT04685135)
- Adagrasib has demonstrated responses across 9 tumor types (NSCLC, CRC, PDAC, ovarian and endometrial cancers, and other GI cancers), across NSCLC-relevant molecular subsets, and patients with NSCLC with either stable/treated or untreated CNS metastases[5,8–10]

For further data describing the efficacy of adagrasib in patients with active, untreated CNS metastases, please see Sabari et al, ASCO 2022 abstract LBA9009

Monday, June 6, 2022, 4:30 PM–6:00 PM CDT

Session: Clinical Science Symposium/Including the Excluded: Advancing Care for All Patients With Lung Cancer

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ORIGINAL ARTICLE

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