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KRYSTAL-7: Efficacy and Safety of Adagrasib With Pembrolizumab in Patients With Treatment-Naïve, Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a KRAS^{G12C} Mutation

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DECLARATION OF INTERESTS

Personal Financial Interests: AstraZeneca, Abion, MSD International GmbH, Bayer, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Incyte, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati Therapeutics, Daiichi Sankyo, Regeneron, Merck, Blueprint, Janssen, Sanofi, AbbVie, BeiGeneius, OncoHost, Medscape

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Background

- KRAS is one of the most common mutations in lung cancer, with KRAS^{G12C} being the most frequent mutation, occurring in ~14% of lung adenocarcinomas[1]
- Pembrolizumab monotherapy is a standard-of-care in patients with treatment-naïve advanced NSCLC with PD-L1 ≥50% (5-year OS rate 32% and ORR 39–45%);[2–4] however, there is an unmet need for optimized combinations that may lead to increased response rates and durability
- Severe hepatotoxicity compromises the ability to administer sotorasib concurrently with CPI in treatment-naïve NSCLC, and has also been observed when sotorasib is administered sequentially following prior CPI, particularly within 30 days[5–10]

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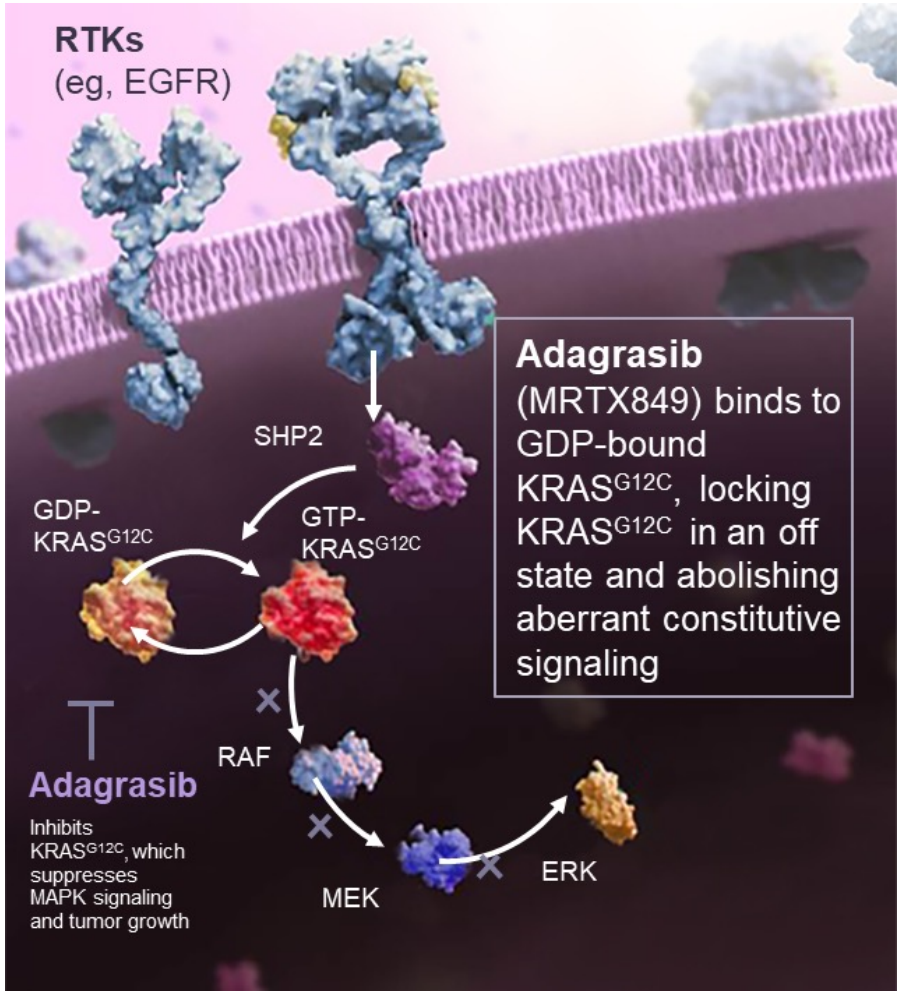
Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- Adagrasib, a KRAS^{G12C} inhibitor, was selected for favorable properties, including:[11–13]
  - Long half-life (23 hours) and dose-dependent PK
  - CNS penetration
  - Non-covalent binding affinity and minimized cysteine reactivity
- The steady-state PK of adagrasib with a low peak-to-trough ratio, and minimized cysteine reactivity, are hypothesized to limit off-target effects in the liver and other organs[11–13]
- Administration of adagrasib sequentially or in combination with pembrolizumab is not limited by hepatotoxicity[14,15]
  - No patients had grade ≥3 hepatotoxicity of those who received anti-PD-(L)1 <30 days before adagrasib[14]
  - <10% of patients had grade ≥3 ALT/AST increase from initial data evaluating concurrent adagrasib plus pembrolizumab[15]



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KRYSTAL-7 (849-007) Phase 2 Cohorts

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with KRAS^{G12C} mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease[b]
- Stable brain metastases allowed
- Known PD-L1 TPS score[c]

Cohorts 1a and 2[c]
Adagrasib 400 mg BID +
Pembrolizumab 200 mg Q3W
N=148

Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study evaluating adagrasib[e] + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a KRAS^{G12C} mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

[a]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA by sponsor-approved local laboratory testing. [b]Prior systemic therapy or chemoradiation in the (neo)adjuvant setting were allowed if >1 year prior to the first dose of study treatment, and no TRAE of grade ≥2 while on (neo)adjuvant CPI (exceptions for clinically stable vitiligo and psoriasis regardless of grade, and hyper- or hypothyroidism that was adequately controlled). [c]Cohort 1a enrolled patients with PD-L1 TPS <1%; Cohort 2 enrolled patients with PD-L1 TPS ≥1%. Molecular testing for PD-L1 TPS was performed locally or centrally, with a sponsor-approved laboratory test (PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx or Ventana PD-L1 [SP142] assay). An additional cohort (1b) is enrolling patients with PD-L1 TPS <1% to receive adagrasib monotherapy, 600 mg BID. [d]Three patients excluded due to protocol deviations, including one each of atrial fibrillation, stroke within 6 months of enrollment, and presence of KRAS^{G13C} mutation. [e]KRYSTAL-7 was initiated using the capsule (fasted) form of adagrasib but switched to the tablet (fed or fasted) form during study conduct

Demographics and Baseline Characteristics

	Concurrent 400 mg BID Adagrasib + Pembrolizumab	
	All Patients (N=148)	PD-L1 TPS ≥50% (n=54)
Median age (range), years	67 (40–90)	66 (40–80)
Female, n (%)	71 (48)	28 (52)
Race, n (%)		
White	113 (76)	42 (78)
Black or African American	5 (3)	3 (6)
Asian / Other[a]	26 (18)	9 (17)
ECOG PS, n (%)		
0 / 1	57 (39) / 91 (61)	18 (33) / 36 (67)
Smoking history, n (%)		
Never smoker	2 (1)	0
Current smoker / former smoker	32 (22) / 114 (77)	12 (22) / 42 (78)
Baseline metastases, n (%)		
Bone	46 (31)	17 (31)
CNS	21 (14)	9 (17)
Adrenal	28 (19)	9 (17)
Liver	24 (16)	10 (19)

[a]Race information missing for two patients

Data as of 19 June 2023. Median follow-up for all patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

Treatment-Related Adverse Events

Most Frequent TRAEs[a], %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase increased	24	3	9	10	1

- There were two Grade 5 TRAEs, one each of pneumonitis and pneumonia
- Immune-related TRAEs[b] of any grade occurred in 18% of patients (26/148) and grade ≥3 occurred in 5% (8/148)
- TRAEs led to adagrasib dose reduction in 46% of patients (68/148) and temporary dose interruption in 59% of patients (88/148)
- TRAEs led to permanent discontinuation of adagrasib only in 6% of patients (9/148) and pembrolizumab only in 11% of patients (16/148); 4% of patients (6/148) discontinued both drugs due to TRAEs

[a]Any grade TRAEs occurring in ≥20% of patients. [b]Includes all TRAEs of colitis, hepatitis, adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, nephritis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and pneumonitis
Data as of 19 June 2023. Median follow-up 8.7 months

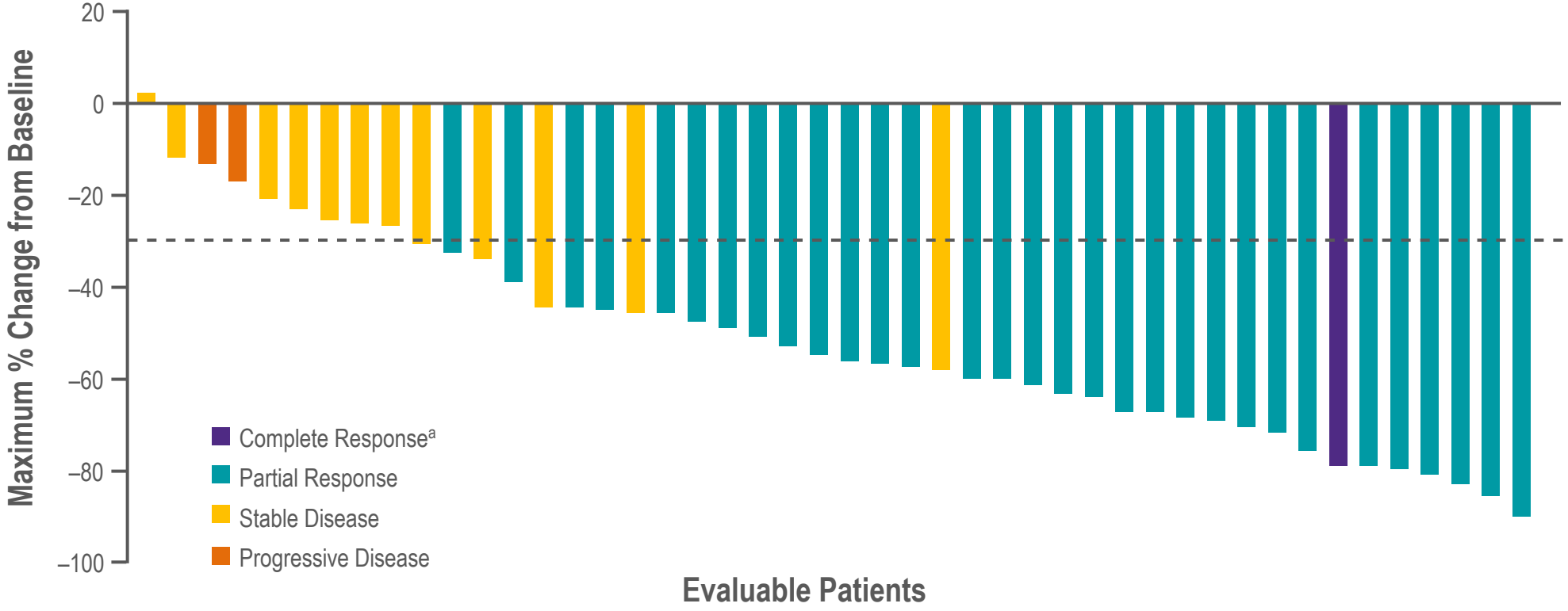
Liver Treatment-Related Adverse Events

Most Frequent Liver TRAEs, %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicity[a]	1	0	1	1	0
Liver injury	1	0	1	0	0
Drug-induced liver injury	1	1	0	0	0
Hepatic failure	1	0	0	1	0
Acute hepatitis	1	0	1	0	0
Immune-mediated hepatitis	1	0	0	1	0

- Despite elevations in ALT/AST, treatment-related hepatic events occurred in <10% of patients
- No patient discontinued both adagrasib and pembrolizumab due to ALT/AST increase or hepatic TRAEs[b]
- The median time to first resolution of increased ALT/AST was 22 days and resolution occurred in ~80% of cases[c,d]
- 24 (16%) patients had grade ≥3 treatment-related ALT/AST increase:
  - 10 received concomitant steroids
  - Most resumed the combination; 4 resumed adagrasib only, and no patients resumed pembrolizumab only[e]
  - 1 patient has not yet resumed therapy due to ALT/AST increase at data cut-off, but may resume with longer follow-up
  - 3 patients had recurrence of any grade treatment-related ALT/AST increase after resuming therapy

[a]Listed as preferred term. [b]One patient discontinued adagrasib due to ALT increase and three discontinued pembrolizumab due to ALT/AST increase. [c]Resolution rate at data cut-off; five patients remain on adagrasib treatment and ALT/AST increase may resolve with longer follow-up. [d]Median time to any grade treatment-related increased ALT/AST onset was 40 and 42 days, respectively. [e]Adagrasib was interrupted and resumed at a lower dose following resolution of grade ≥3 ALT/AST increase in 17/18 patients; pembrolizumab was interrupted and resumed at approved dosing following resolution of grade ≥3 ALT/AST increase. Five patients discontinued both drugs due to reasons other than ALT/AST increase and 18 resumed therapy
Data as of 19 June 2023. Median follow-up 8.7 months

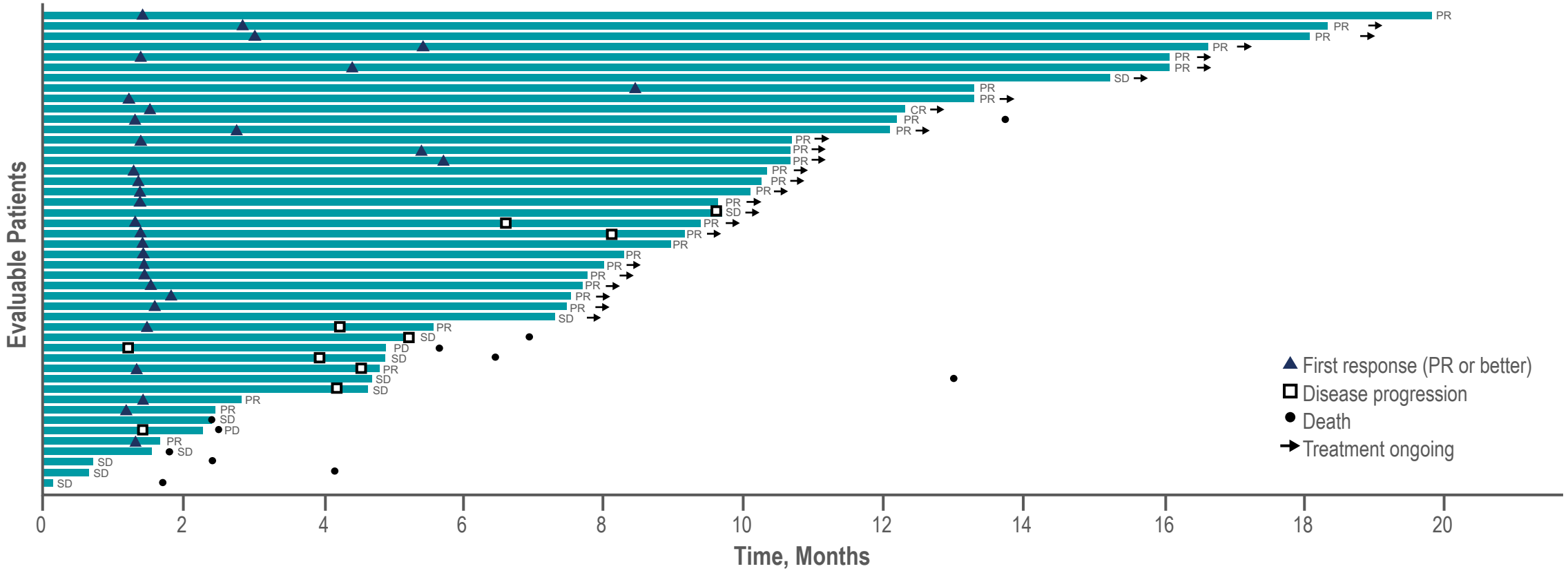
ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50%



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

Response per investigator assessment (n=51; modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). [a]One patient had CR without –100% change from baseline due to lymph node as target lesion. [b]Includes AST increase, ALT increase, mixed liver injury and liver function test increase; no grade 4 hepatotoxicity was observed in patients with PD-L1 TPS ≥50%
Data as of 19 June 2023. Median follow-up 10.1 months

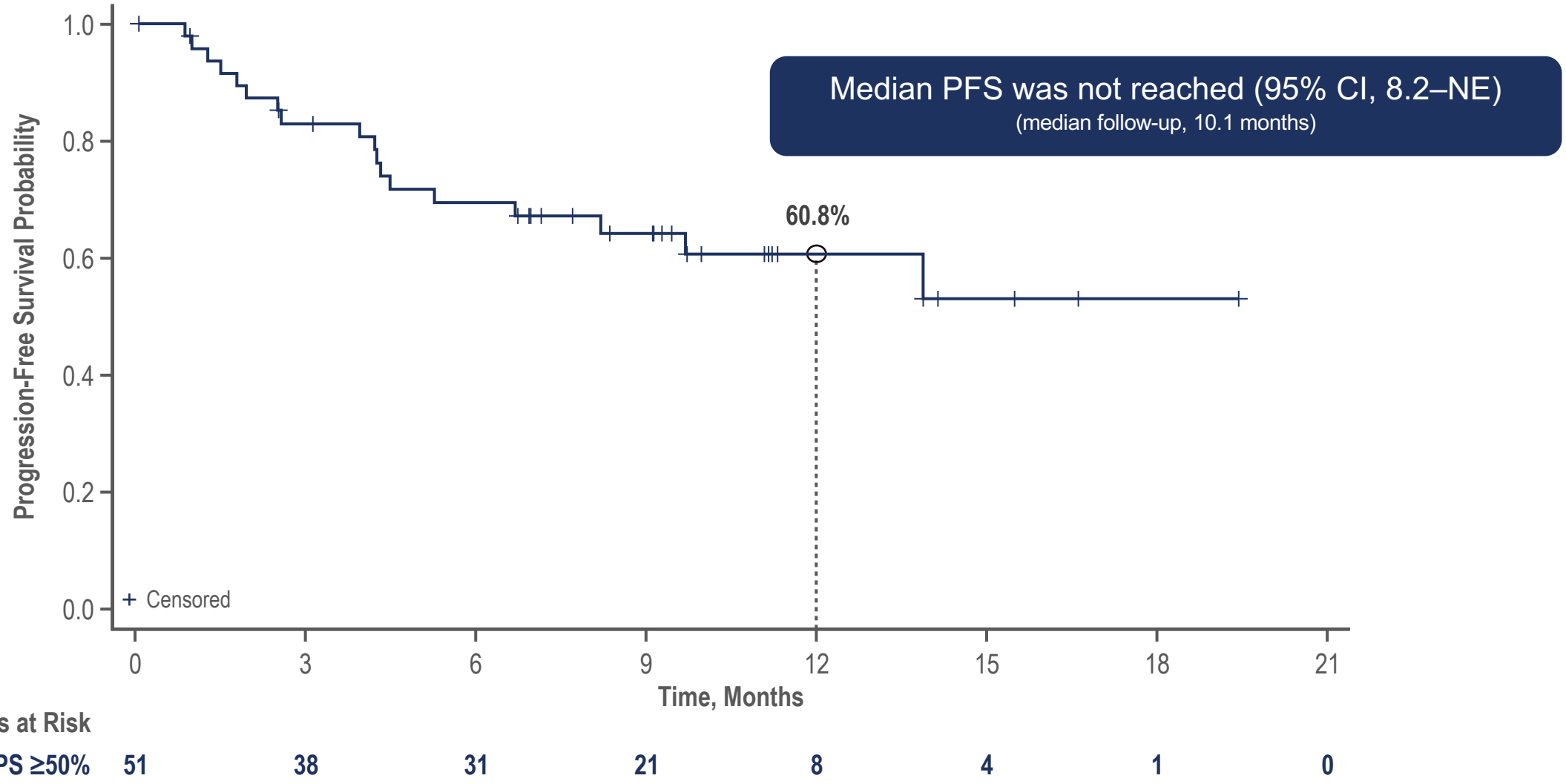
Duration of Treatment in Patients With PD-L1 TPS ≥50%



- Median time to response was 1.4 months; median duration of response was not reached (95% CI, 12.6–NE)

Response per investigator assessment (n=51; modified full analysis set). Swimmer plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days)
Data as of 19 June 2023. Median follow-up 10.1 months

Progression-Free Survival in Patients With PD-L1 TPS ≥50%



Response per investigator assessment (n=51; modified full analysis set)
Data as of 19 June 2023. Median follow-up 10.1 months

Conclusions

- With longer follow-up, concurrent adagrasib + pembrolizumab demonstrated encouraging preliminary activity in patients with PD-L1 TPS ≥50% and a manageable safety profile
- The safety profile of adagrasib + pembrolizumab was consistent with either agent as monotherapy, with a low rate of TRAEs leading to discontinuation of both drugs
- Liver-related TRAEs were predominantly low grade and manageable, with the majority being resolved and not leading to discontinuation of both drugs
- In patients with PD-L1 TPS ≥50%, adagrasib + pembrolizumab demonstrated a higher response rate (63%) than expected with pembrolizumab monotherapy (39–45%[3,4]) and promising early signs of durability
- These findings support the initiation of a Phase 3 trial evaluating concurrent adagrasib + pembrolizumab versus pembrolizumab in treatment-naïve KRAS^{G12C}-mutated NSCLC with PD-L1 TPS ≥50%

For more information contact Mirati Medical Information at medinfo@mirati.com

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Abbreviations

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BID, twice daily

CI, confidence interval

CNS, central nervous system

CPI, checkpoint inhibitor

CR, complete response

ctDNA, circulating tumor deoxyribonucleic acid

DCR, disease control rate

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

IHC, immunohistochemistry

IV, intravenous

KRAS, Kirsten rat sarcoma viral oncogene homolog

MAPK, mitogen-activated protein kinase

MEK, mitogen-activated protein kinase kinase

NE, not estimable

NSCLC, non-small cell lung cancer

ORR, objective response rate

OS, overall survival

PD, progressive disease

PD-(L)1, programmed cell death (ligand) 1

PFS, progression-free survival

PK, pharmacokinetics

PR, partial response

Q3W, every 3 weeks

RAF, rapidly activating fibrosarcoma

RECIST, Response Evaluation Criteria In Solid Tumors

RTK, receptor tyrosine kinase

SD, stable disease

SHP2, Src homology phosphatase 2

TPS, tumor proportion score

TRAE, treatment-related adverse event