2022 ASCO® ANNUAL MEETING

Activity of Adagrasib (MRTX849) in Patients with KRAS^{G12C}-Mutated NSCLC and Active, Untreated CNS Metastases in the KRYSTAL-1 Trial

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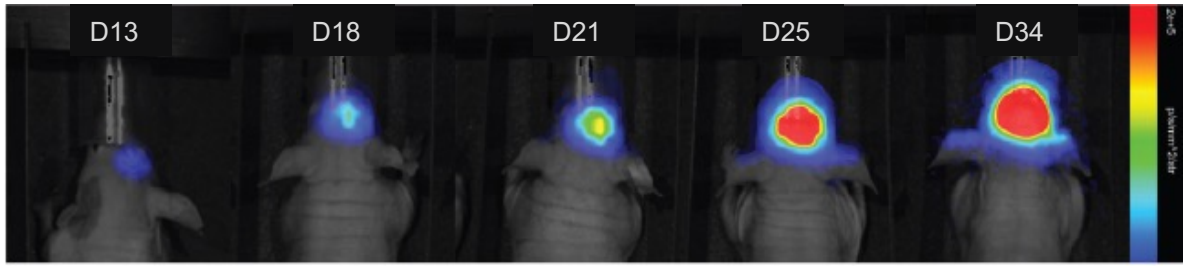
Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

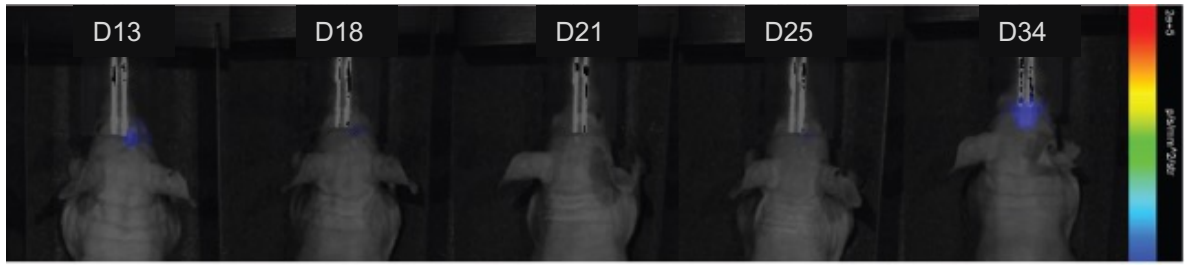
- Approximately 27–42% of patients with KRAS^{G12C}-mutated NSCLC have CNS metastases at diagnosis[1–4]
- Patients with active, untreated CNS metastases have a poor prognosis, median OS ~5 months[5]
- CNS-penetrant targeted therapies improve outcomes for patients with NSCLC complicated by CNS metastases[a,6–8]
- Adagrasib has demonstrated CNS exposure, tumor regressions in animal models, and clinical activity in treated, stable CNS metastases (IC ORR 33%, IC DCR 85%)[9,10]

LU99Luc KRAS^{G12C} CNS Metastases Model

Vehicle



Adagrasib (100 mg/kg BID)



Adagrasib has penetration in the CNS with $K_{p,uu}$ of 0.4 (1 hour)

[a]$K_{p,uu}$ measurements: osimertinib 0.39, alectinib 0.63–0.94, lorlatinib 0.75

KRYSTAL-1 (849-001) Phase 1b: Active, Untreated CNS Metastases Cohort

KRYSTAL-1: Multi-cohort Phase 1/2 Study
Phase 1b

Key Eligibility Criteria

- Solid tumors with KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- Active, untreated CNS metastases[b]
  - Asymptomatic, neurologically stable brain lesions, including focal leptomeningeal disease, and cerebellar metastases, but excluding brainstem (midbrain, pons, and medulla) metastases

Adagrasib 600 mg BID
(Capsule, Fasted)

Study Objectives

- Safety
- Intracranial and systemic activity via BICR (mRANO-BM,[c] RECIST 1.1)
- Adagrasib concentration in CSF (measured when feasible)

Here we report the first data for a KRAS^{G12C} inhibitor in patients with NSCLC harboring a KRAS^{G12C} mutation and active, untreated CNS metastases at baseline (N=25)

[a]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA per protocol; [b]Previously irradiated lesions were only considered as target lesions if there was unequivocal progression post-radiation; [c]Modifications: ≥5 mm lesions, corticosteroid use monitored per concomitant medications, ECOG PS (rather than Karnofsky Performance Scale)
ClinicalTrials.gov. NCT03785249

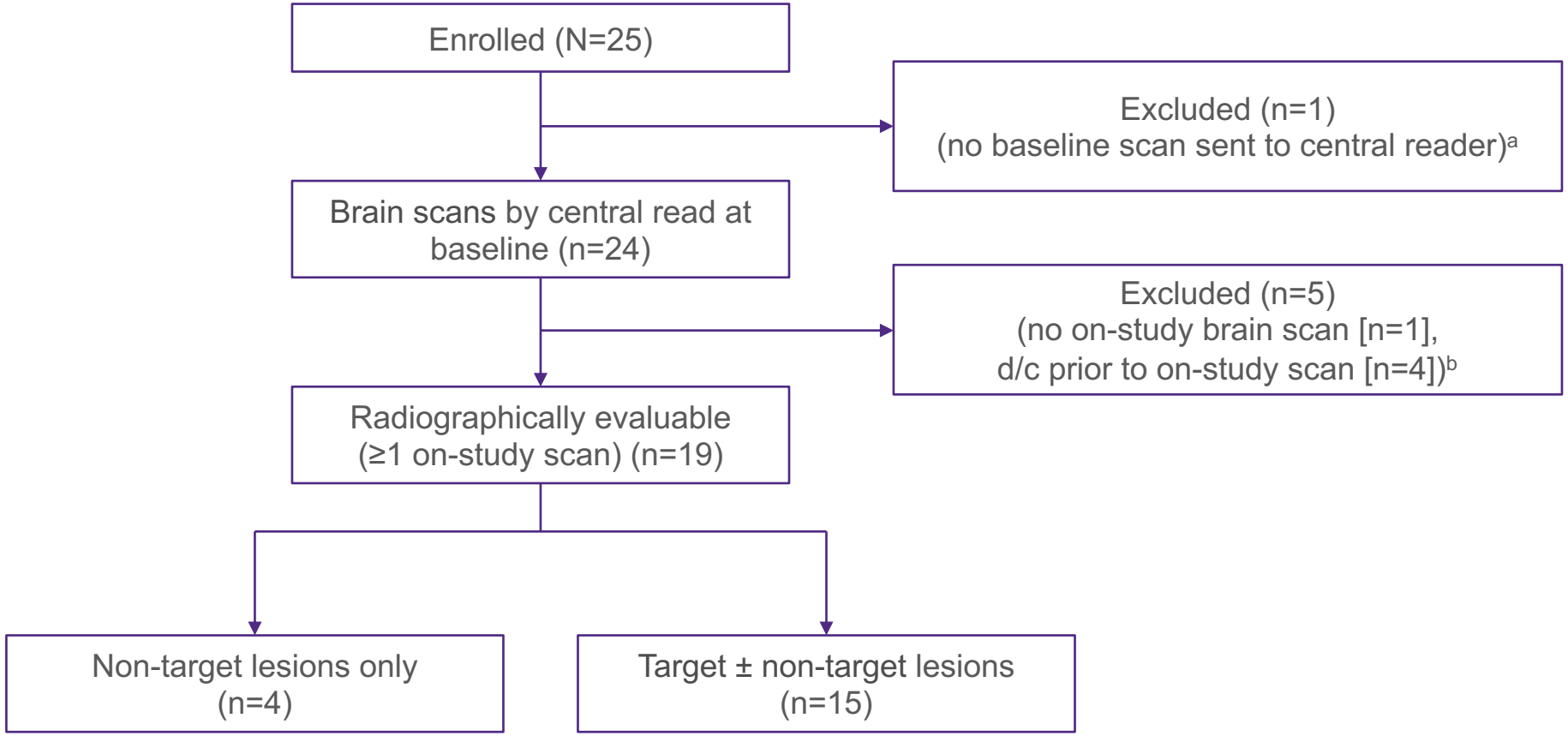
Demographics and Baseline Characteristics

	Adagrasib Monotherapy (N=25)
Median age (range), years	66 (47–89)
Female sex, n (%)	13 (52%)
Race, n (%)	
White	21 (84%)
Black or African American	1 (4%)
Asian / Other	1 (4%) / 2 (8%)
ECOG PS, n (%)	
0 / 1	7 (28%) / 18 (72%)
Smoking history, n (%)	
Never smoker / Current or former smoker	1 (4%) / 24 (96%)
Number of baseline CNS lesions,[a] n (%)	
Target: 0 / 1 / 2–5 / >5	5 (20%) / 12 (48%) / 7 (28%) / 0
Non-target: 0 / 1 / 2–5 / >5	6 (24%) / 7 (28%) / 10 (40%) / 1 (4%)
Prior lines of systemic therapy,[a] n (%)	
0	3 (12%)
1	12 (48%)
2	5 (20%)
3+	4 (16%)

[a]Missing baseline data, n=1

Data as of December 31, 2021 (median follow-up: 6.6 months)

Patient Disposition



Target lesions: all measurable lesions (size ≥5 mm) with ≤5 lesions in total, and representative of all involved organs; non-target lesions: all evaluable lesions and measurable lesions not identified as target lesions

[a]Patient new to study so no scan completed before cut-off; [b]Due to reasons of: AEs (n=2), patient withdrawal (n=1), death (n=1)

Data as of December 31, 2021 (median follow-up: 6.6 months)

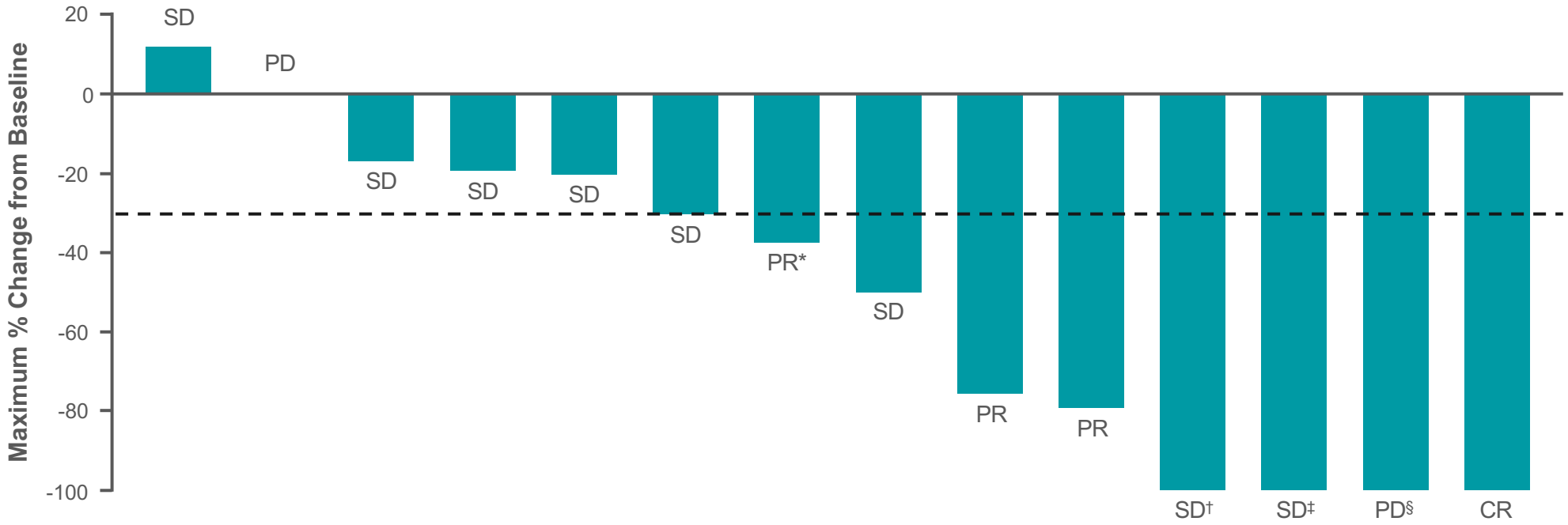
Adagrasib in Patients with Active, Untreated CNS Metastases: Intracranial Response by BICR

Efficacy Outcome	Patients with Non-target Lesions Only (n=4)	Patients with Target Lesions (n=15)[a]	Overall (n=19)[b]
Objective response rate, n (%)	**2 (50%)**	**4 (27%)**	**6 (32%)**
Best overall response, n (%)			
Complete response (CR)	2 (50%)	1 (7%)	3 (16%)
Partial response (PR)	0	3 (20%)[c]	3 (16%)[c]
Stable disease (SD)	2 (50%)	8 (53%)	10 (53%)
Progressive disease (PD)	0	2 (13%)	2 (11%)
Not evaluable	0	1 (7%)[d]	1 (5%)[d]
Disease control rate, n (%)	**4 (100%)**	**12 (80%)**	**16 (84%)**

All results are based on BICR (mRANO-BM)
[a]Includes patients with target ± non-target lesions; [b]Includes patients in clinically evaluable population with ≥1 post-baseline assessment;
[c]Unconfirmed (n=1), confirmed CR after data cut-off; [d]Not evaluable (n=1) due to scans being too early (100% regression in target lesions)

Data as of December 31, 2021 (median follow-up: 6.6 months)

Adagrasib in Patients with Active, Untreated CNS Metastases: Intracranial Best Tumor Change From Baseline



- Objective IC responses were observed in 32% (95% CI, 12.6–56.6)[a]
- IC DCR was 84% (95% CI, 60.4–96.6)

All results are based on BICR (mRANO-BM criteria). Only patients with target lesions and ≥1 post-baseline scans are shown; 1 patient not evaluable for best overall response due to scans being too early (100% regression in target lesions)
*Unconfirmed at data cut-off, confirmed CR after data cut-off; †SD due to non-target lesion progression; ‡Unconfirmed CR due to no subsequent scan; §PD due to new lesions
[a]Includes patients with target and non-target lesions

Data as of December 31, 2021 (median follow-up: 6.6 months)

Adagrasib in Patients with Active, Untreated CNS Metastases: Concordance of Intracranial and Systemic Disease Control

Efficacy Outcome	Intracranial BOR	Systemic BOR
Patient 1	PR	PR[a]
Patient 2	SD	PR[a]
Patient 3	SD	SD
Patient 4	SD	SD
Patient 5	SD	PR
Patient 6	PD	SD
Patient 7	SD	PR
Patient 8	PR	SD
Patient 9	PD	PD
Patient 10	CR	SD

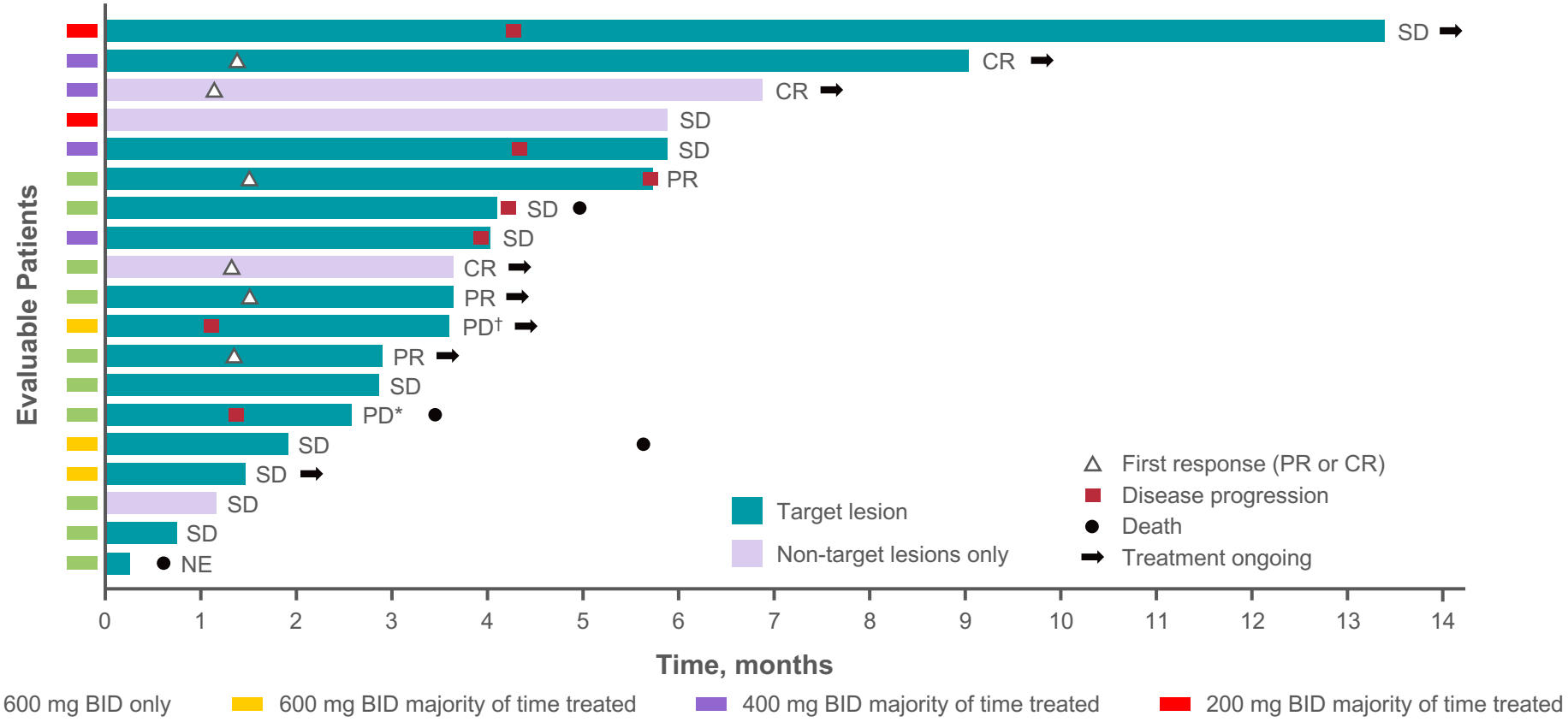
Efficacy Outcome	Intracranial BOR	Systemic BOR
Patient 11	SD	SD
Patient 12	SD	PR
Patient 13	CR	SD
Patient 14	SD	SD
Patient 15	PR[b]	PR[c]
Patient 16	SD	PD
Patient 17	CR	PR
Patient 18	NE	NE
Patient 19	SD	NE

Concordant disease control Discordant disease control

- Concordance between systemic and intracranial disease control was 88% (14/16)
- Systemic ORR by RECIST v1.1 was 37% (95% CI, 16.3–61.6); systemic DCR 79% (95% CI, 54.4–93.9)

All results are based on BICR (mRANO-BM, RECIST 1.1)
Systemic responses in clinically evaluable population with ≥1 post-baseline assessment (n=19)
[a]Confirmed after data cut-off; [b]Unconfirmed at data cut-off, confirmed CR after data cut-off; [c]Unconfirmed at data cut-off, BOR of SD after data cut-off
Data as of December 31, 2021 (median follow-up: 6.6 months)

Adagrasib in Patients With Active, Untreated CNS Metastases: Duration of Treatment

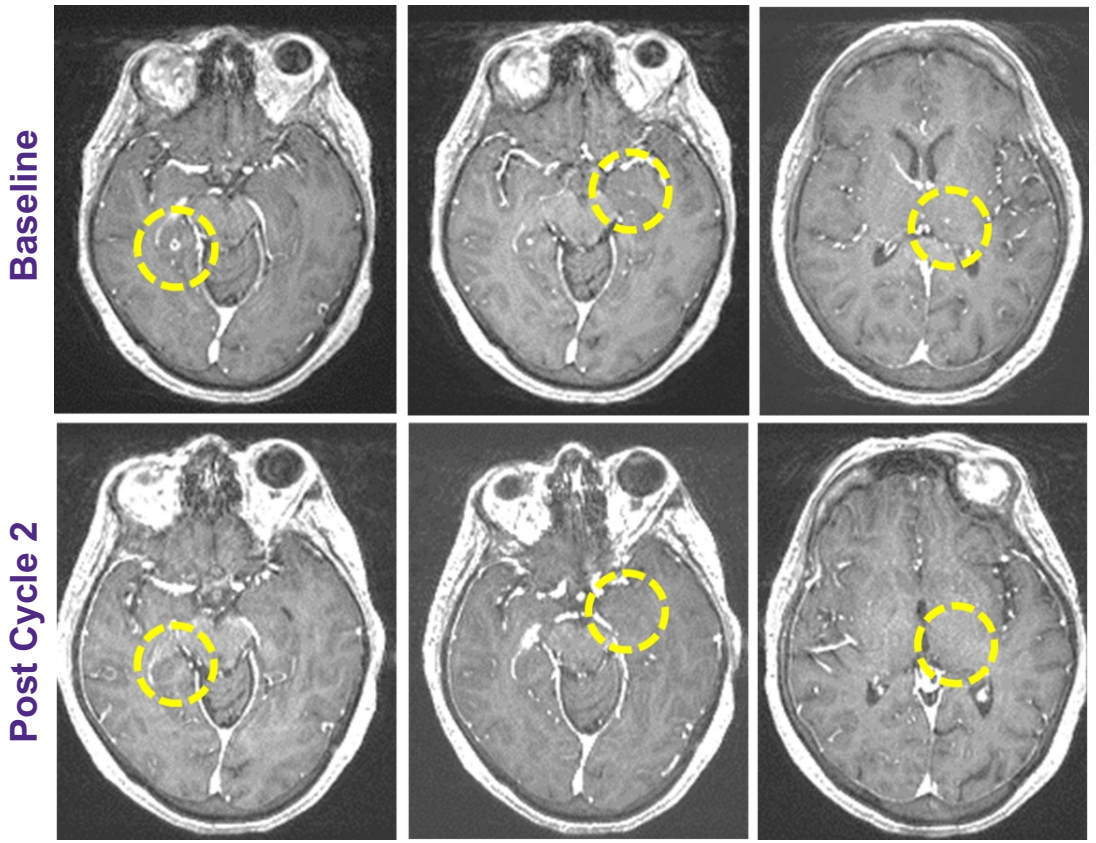


- Median IC DOR was not reached (95% CI, 4.1–NE)[a]
- Median IC PFS was 4.2 months (95% CI, 3.8–NE)[b]; median OS had not been reached

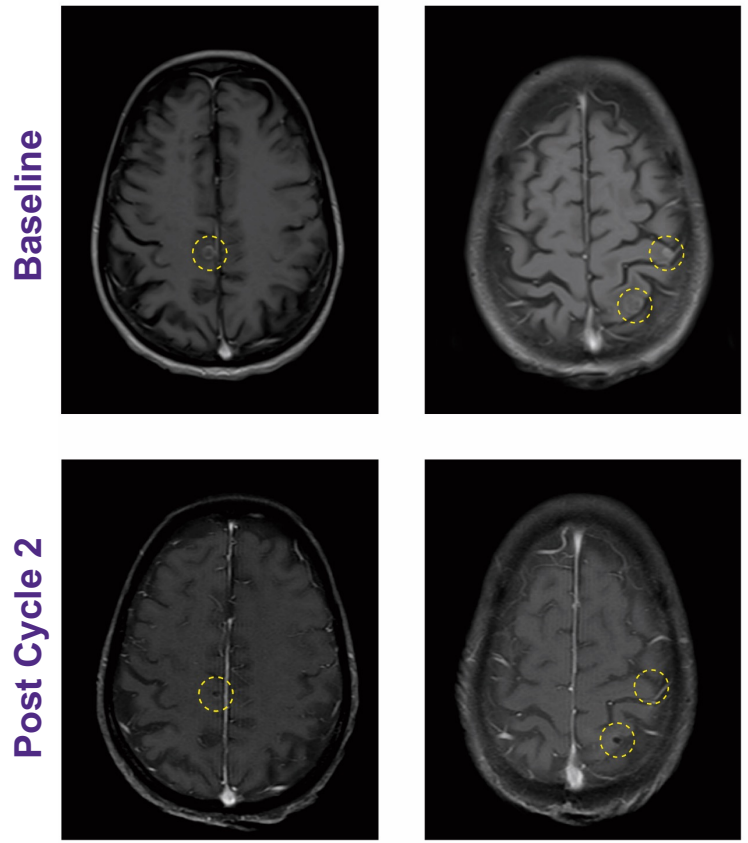
All results are based on BICR (mRANO-BM criteria)
*IC BOR of PD, systemic BOR of PD; †IC BOR of PD, systemic BOR of SD; [a]Systemic mDOR of confirmed responses was 9.6 months (95% CI, 2.7–9.6); [b]Median systemic PFS was 5.6 months (95% CI, 3.8–11.0)

Data as of December 31, 2021 (median follow-up: 6.6 months)

Adagrasib in Patients with Active, Untreated CNS Metastases



- **Cerebrospinal fluid**
  - 34.6 nM (20.9 ng/mL)
  - $K_{p,uu}$ = 0.42



- **Cerebrospinal fluid**
  - 24.2 nM (14.6 ng/mL)
  - $K_{p,uu}$ = 0.51

- Two patients had CSF collected, with an average $K_{p,uu}$ of 0.47; this exceeds values for TKIs for which both CNS penetration and antitumor activity in CNS metastases has been demonstrated[9]

From Sabari JK, et al. *Clin Cancer Res.* 2022

Adagrasib: Patient Case with Active, Untreated CNS Metastases

62-year-old male, former smoker with metastatic KRAS^{G12C}-mutant NSCLC

August 2019	Stage IIIA KRAS^{G12C}-mutant NSCLC diagnosis
September 2019	Neoadjuvant cisplatin and pemetrexed +/- pembrolizumab (blinded clinical trial)
December 2019	R1 resection; right upper lobectomy ypT1cN2, 70% viable tumor, positive margins
March 2020	PORT and concurrent carboplatin/paclitaxel
November 2020	Recurrent metastatic disease to pelvis and brain, s/p XRT to pelvis and GK SRS to 4 brain metastases
February 2021	New brain metastases, not previously radiated
March 2021	Adagrasib 600 mg BID (C1D1), Reduced to 400 mg BID (C2D1)
April 2021	Intracranial PR (-38%) at first on-study scan
August 2021	Intracranial CR (-100%)
May 2022	Best overall response of intracranial confirmed CR Currently in Cycle 22

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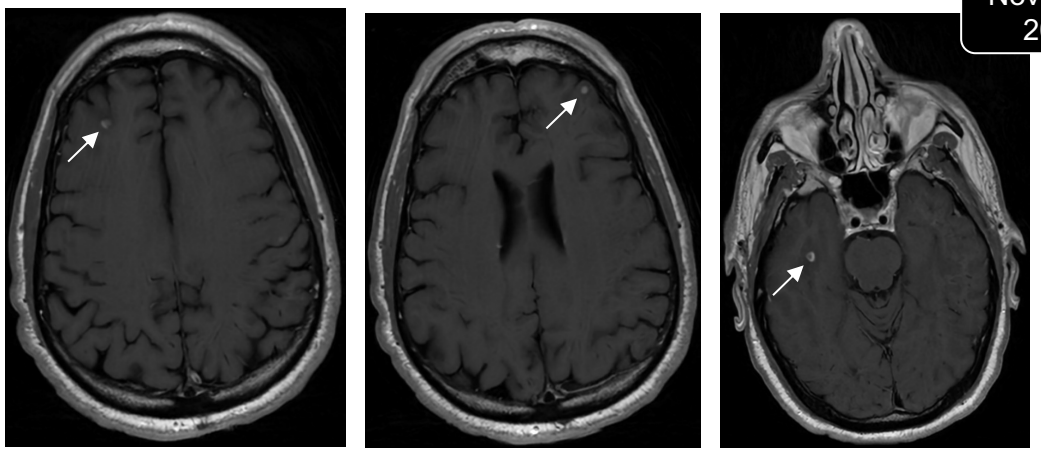
Baseline and post-treatment scans



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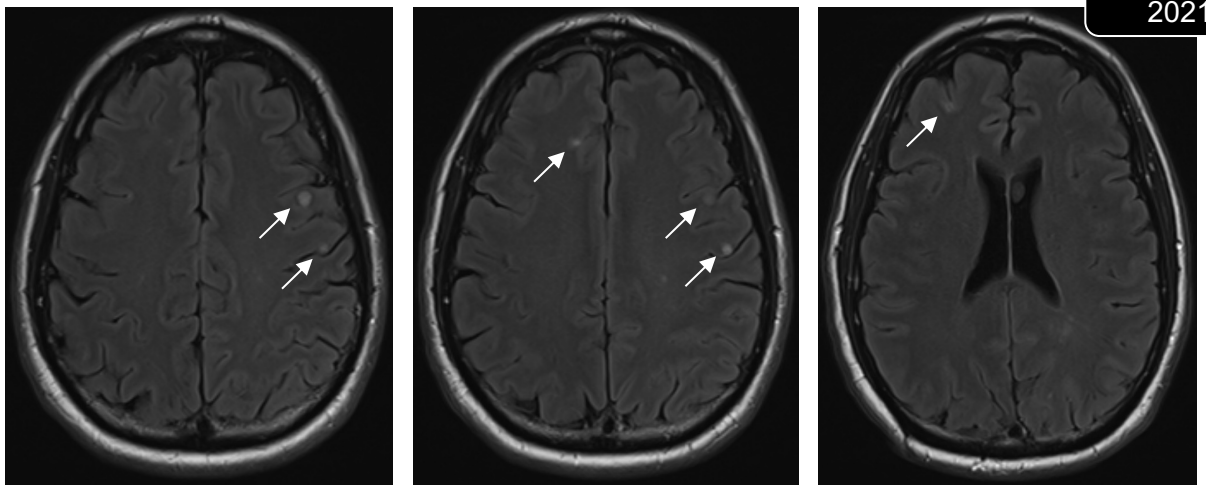

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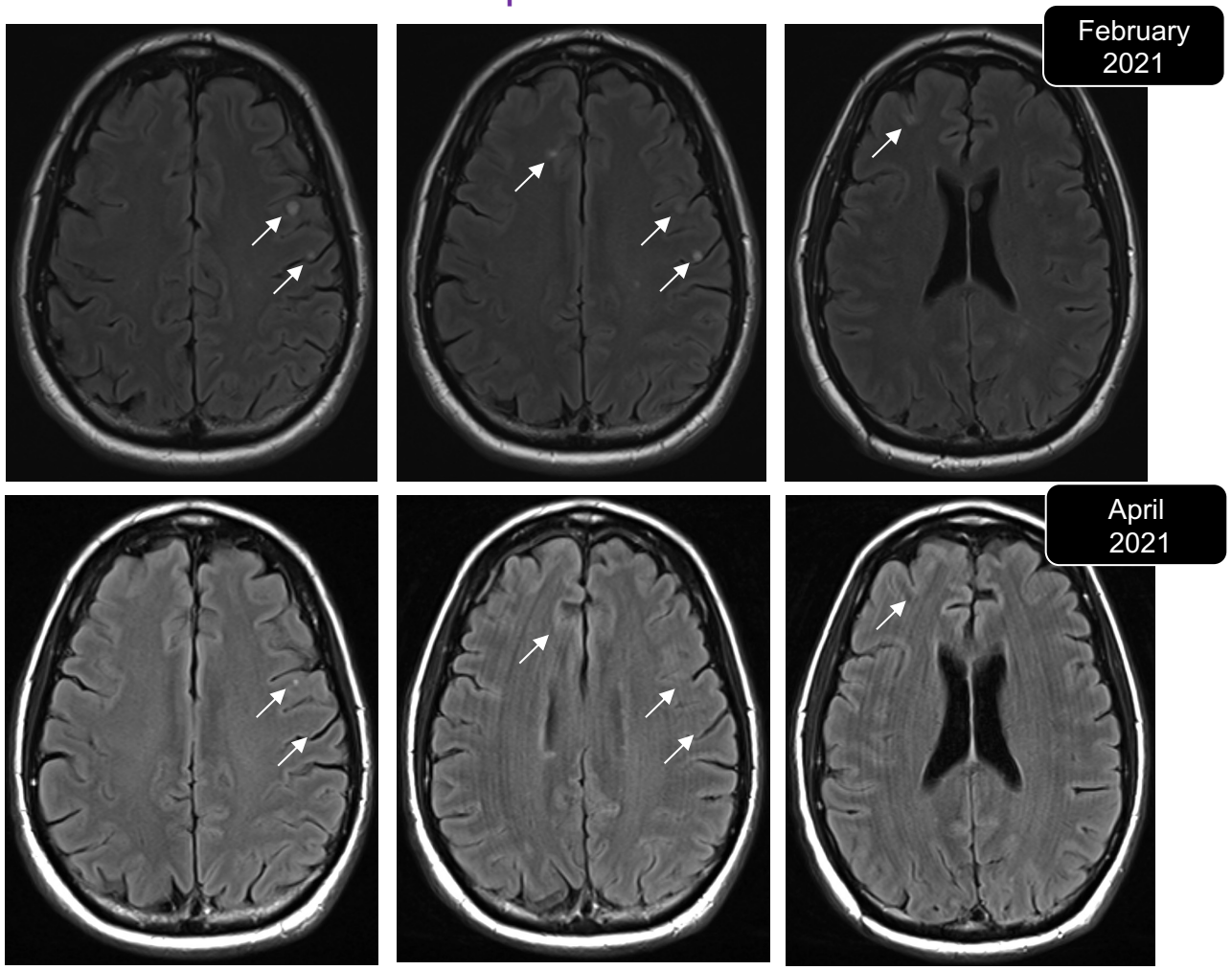

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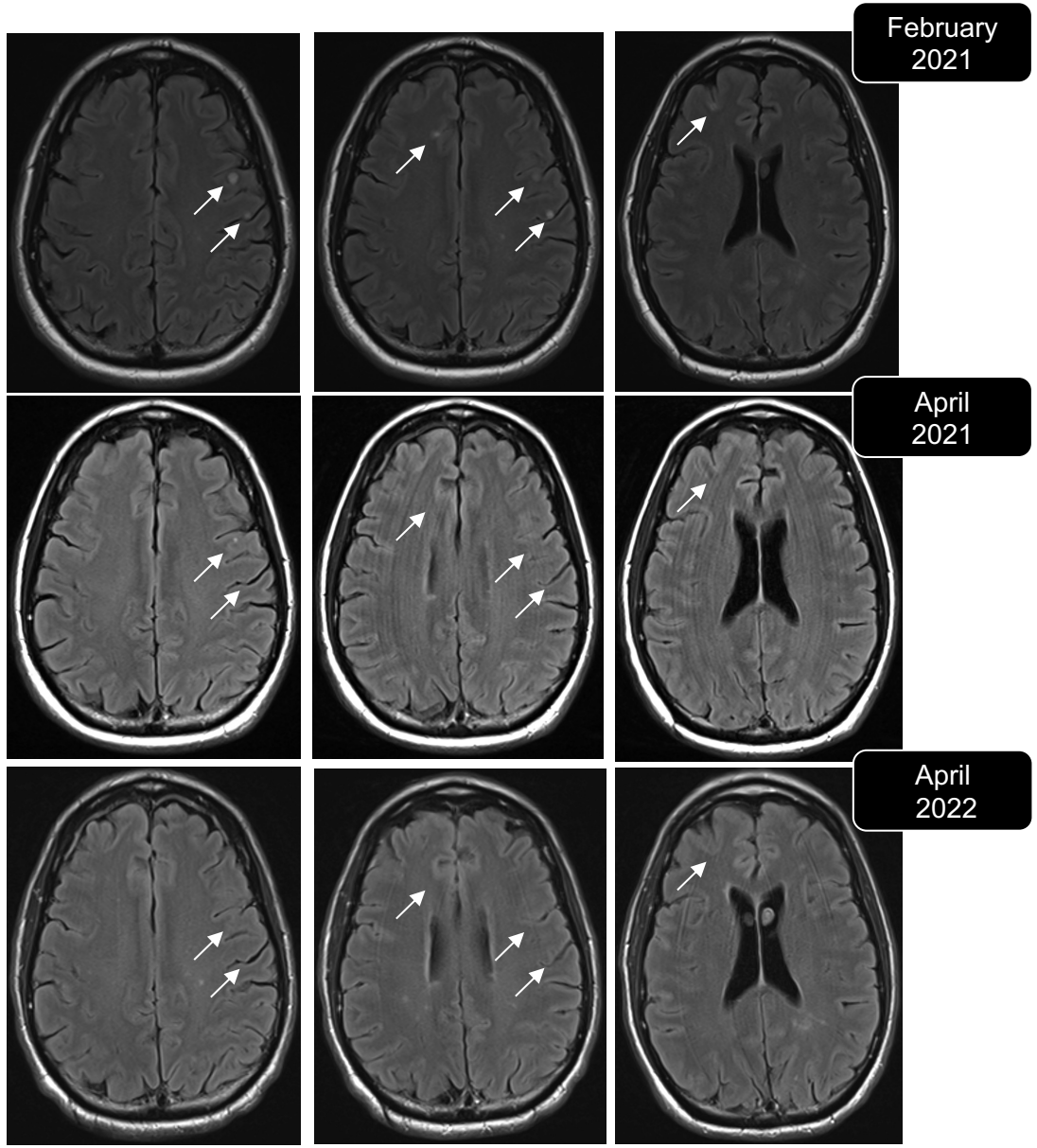

- **Select TRAEs of relevance:**
  - Grade 2 increased ALT/AST
  - Grade 1 GI-related events (diarrhea, nausea, vomiting)
  - Intermittent grade 1 increased blood creatinine
  - Grade 3 lymphopenia

Treatment-Related Adverse Events

	Adagrasib Monotherapy (N=25) Capsule, Fasted	
TRAEs, n (%)	**Any Grade**	**Grade 3**
Any TRAEs	24 (96%)	9 (36%)
Most frequent TRAEs,[a] n (%)		
Nausea	20 (80%)	2 (8%)
Diarrhea	20 (80%)	0
Vomiting	11 (44%)	3 (12%)
AST increase	10 (40%)	1 (4%)
ALT increase	9 (36%)	2 (8%)
Fatigue	8 (32%)	0
Anemia	6 (24%)	0
Blood alkaline phosphatase increase	6 (24%)	1 (4%)
Blood creatinine increase	6 (24%)	0
Decreased appetite	6 (24%)	0
Dizziness	5 (20%)	2 (8%)
Dysgeusia	5 (20%)	0

- Grade 1–2 TRAEs occurred in 60% of patients
- No grade 4/5 TRAEs
- TRAEs led to dose reduction/interruption in 12 (48%) patients and discontinuation in 1 (4%) patient
- CNS-specific TRAEs included dizziness (20%, n=5) and grade 1/2 aphasia and insomnia (4%, n=1)

[a]Occurring in ≥20% of patients (any grade)

Data as of December 31, 2021 (median follow-up: 6.6 months)

Conclusions and Future Directions

- CNS metastases from KRAS-mutant NSCLC are common and associated with poor prognosis (median OS ~5 months with untreated CNS metastases)[5]
- Adagrasib demonstrated encouraging and durable CNS-specific activity in patients with KRAS^{G12C}-mutant NSCLC and active, untreated CNS metastases
  - Intracranial ORR 32%; median intracranial DOR not reached
  - Median OS not reached (median follow-up 6.6 months)
  - Mean $K_{p,uu}$ of 0.47, which is comparable to, or exceeds, values for known CNS-penetrant TKIs[9]
  - Manageable safety profile with few CNS-specific TRAEs[10–13]
- Adagrasib is the first KRAS^{G12C} inhibitor to demonstrate clinical activity in patients with KRAS^{G12C}-mutated NSCLC with treated and untreated CNS metastases
- Expanded Access Program is open and enrolling patients with KRAS^{G12C}-mutant solid tumors including patients with active, untreated CNS metastases

For further data describing the efficacy of adagrasib in patients with KRAS^{G12C}-mutated NSCLC, please see Spira et al, ASCO 2022 abstract 9002

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Abbreviations

ALK, anaplastic lymphoma kinase

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BICR, blinded independent central review

BID, twice daily

BOR, best overall response

C1, cycle 1

CI, confidence interval

CNS, central nervous system

CR, complete response

CSF, cerebrospinal fluid

ctDNA, circulating tumor deoxyribonucleic acid

D1, day 1

d/c, discontinuation

DCR, disease control rate

DOR, duration of response

ECOG PS, Eastern Cooperative Oncology Group Performance Status

EGFR, epidermal growth factor receptor

IC, intracranial

$K_{p,uu}$, unbound brain to unbound plasma concentration ratio

KRAS, Kirsten rat sarcoma virus

mRANO-BM, modified RANO-BM

NE, not evaluable

NR, not reached

NSCLC, non-small cell lung cancer

ORR, objective response rate

OS, overall survival

PD, progressive disease

PFS, progression-free survival

PORT, post-operative radiation therapy

PR, partial response

RANO-BM, Response Assessment in Neuro-Oncology-Brain Metastases

RECIST, Response Evaluation Criteria In Solid Tumors

SD, stable disease

TKI, tyrosine kinase inhibitor

TRAE, treatment-related adverse event