Risk and Management of Intracranial Progression on Amivantamab in Epidermal Growth Factor Receptor (EGFR) Exon 20 Insertion (ex20ins)–mutated Non–Small Cell Lung Cancer (NSCLC)

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BACKGROUND

- Amivantamab is a fully human epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell–directing activity that targets activating and resistance EGFR mutations and MET mutations and amplifications[1-3]
- Amivantamab shows robust clinical efficacy and durable responses in non–small cell lung cancer (NSCLC) with EGFR exon 20 insertion (ex20ins) mutations[4] and is approved for the treatment of advanced EGFR ex20ins NSCLC in patients who have progressed on platinum-based chemotherapy

OBJECTIVE

- In this exploratory analysis, we investigated the patterns of progression on amivantamab therapy among patients with advanced EGFR ex20ins NSCLC enrolled in the CHRYSALIS study (ClinicalTrials.gov Identifier: NCT02609776)

METHODS

- The CHRYSALIS study enrolled patients with advanced NSCLC and allowed the inclusion of patients with treated stable brain metastases
  - Results reported here are from the cohort of patients with EGFR ex20ins NSCLC
- Baseline brain magnetic resonance imaging (MRI) was required at screening in the dose-expansion phase of the study
  - Post-baseline surveillance MRIs were performed according to local practice and were not required per protocol
- Sites of target, non-target, and new lesion progression were reported by the investigator and were evaluated for occurrence of progressive disease in the brain only and/or other sites
  - Patient subgroups with or without brain metastases present at study baseline were analyzed; those with brain/central nervous system (CNS) lesions present at baseline included patients who had brain/CNS metastasis history or brain/CNS lesions as target or non-target lesions at baseline.
  - The feasibility and tolerability of stereotactic radiosurgery (SRS) in patients receiving amivantamab were of particular interest

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RESULTS

- The analysis includes 114 patients who received amivantamab on or before 4 June 2020; 38 had brain metastases at study baseline (**Table 1**)

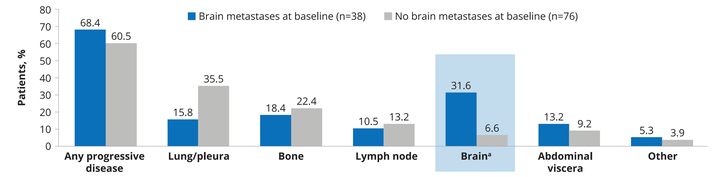
Table 1. Demographic and Baseline Characteristics[a]

Characteristic, n (%)	Brain metastases at baseline[b] (n=38)	No brain metastases at baseline (n=76)
Median age (range), years	59.5 (36-84)	63.0 (41-84)
Male/female	18 (47)/20 (53)	26 (34)/50 (66)
Race		
Asian	23 (61)	36 (47)
White	10 (26)	32 (42)
Black	1 (3)	2 (3)
Not reported	4 (11)	6 (8)
Median weight (range), kg	60 (38-94)	62 (35-115)
Median number of prior lines (range)	2.0 (1-7)	2.0 (1-6)
Prior therapies		
Platinum-based chemotherapy	38 (100)	76 (100)
Immunotherapy	16 (42)	34 (45)
EGFR TKI	7 (18)	18 (24)
Any prior radiotherapy	33 (87)	5 (7)
Radiotherapy within past 6 months	26 (68)	3 (4)
Radiotherapy within past 3 months	20 (53)	3 (4)

CNS, central nervous system; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
[a]Patients who received amivantamab on or before 4 June 2020.
[b]Patients with brain/CNS lesions present at baseline included those who had brain/CNS metastasis history or brain/CNS lesions as target or non-target lesions at baseline.

- After a median follow-up of 12.5 months (range, 0.2-30.5), Response Evaluation Criteria in Solid Tumours (RECIST)–defined progressive disease as assessed by investigators was observed in 72 of 114 patients (63%)
- Of these 72 patients, 25 continued amivantamab post-progression for a median of 4.2 additional months (range, 1.0-12.5)
- Sites of first progressive disease are shown in **Figure 1**
  - 13/114 patients (11%) had intracranial disease as the sole site of progression and an additional 4 /114 patients (4%) had progression in the brain plus extracranial sites
  - Intracranial progression (with or without extracranial progression) occurred in 12/38 patients (32%) with brain metastases at study baseline and 5/76 patients (6.6%) who did not have brain metastases at study baseline

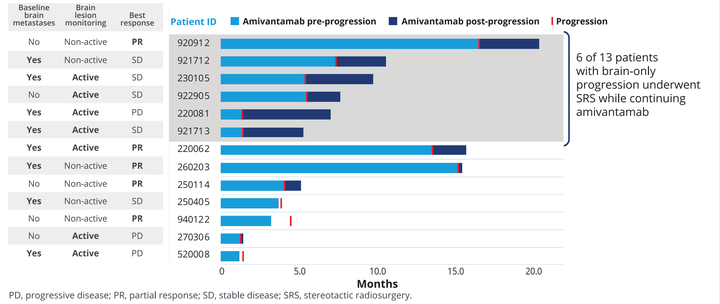
Figure 1. Investigator-assessed Sites of First Progressive Disease



[a]Of 4 patients who had brain and extracranial sites of progression, all had brain metastases at baseline; the extracranial sites included lung and bone (n=1), lung (n=1), heart (n=1), and lymph node (n=1).

- The median time to progression for patients with intracranial-only progression was 4.5 months (range, 1.4-16.6), as compared with 5.5 months (range, 0.6-24.1) for those patients with systemic progression
- **Figure 2** summarizes the management of patients with intracranial progression
  - Among the 13 patients with intracranial-only progression, the best responses were partial response (n=5), stable disease (n=5), and progressive disease (n=3), corresponding to median times to progression of 13.6, 5.5, and 1.4 months, respectively
  - 6 of the 13 patients with intracranial-only progression underwent SRS while continuing amivantamab
    - Adverse events temporally associated with SRS were nausea (10 days after SRS) and fatigue, reported in 1 patient each
    - For the 6 patients who underwent SRS, the median duration of amivantamab treatment after progression was 4.0 months (range, 2.3-6.0); the time between SRS and next amivantamab dose ranged from 6 to 13 days
  - 4 of 6 patients who had brain SRS, and 3 of 7 who did not have SRS, were actively monitored for brain lesions (eg, brain computed tomography [CT]/MRI scans throughout the study); non-active monitoring was defined as only receiving brain scans later in treatment, perhaps after the emergence of neurologic symptoms

Figure 2. Management of Intracranial Progression in 13 Patients With Intracranial-only Progressive Disease



PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery.

- Efficacy outcomes including response according to blinded independent central review are shown in **Table 2**

Table 2. Efficacy Outcomes

Outcome	Brain metastases at baseline[a] (n=38)	No brain metastases at baseline (n=76)	Total efficacy population (N=114)
Objective response rate by BICR, n (%)	17 (45)	32 (42)	49 (43)
Median duration of response (95% CI) by BICR, months	8.7 (4.9, NE)	11.0 (5.2, NE)	10.8 (6.9, 15.0)
Duration of response ≥6 months by BICR, n (%)	9/17 (53)	18/32 (52)	27/49 (55)
Median overall survival (95% CI), months	19.9 (14.0, NE)	NE (18.5, NE)	22.8 (17.5, NE)

BICR, blinded independent central review; CI, confidence interval; NE, not evaluable; CNS, central nervous system.
[a]Patients with brain/CNS lesions present at baseline included those who had brain/CNS metastasis history or brain/CNS lesions as target or non-target lesions at baseline.

KEY TAKEAWAY

- For patients with advanced EGFR ex20ins NSCLC who experience CNS progression, brain lesions can be treated with SRS while continuing amivantamab therapy

CONCLUSIONS

- Intracranial-only progression on amivantamab therapy occurred in 11% of patients
- Outcomes were similar regardless of presence or absence of brain metastases at baseline
- Treatment of brain progression with SRS while continuing amivantamab appears feasible and tolerable

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