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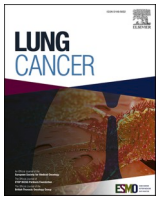

Intracranial and systemic progression on amivantamab in platinum-treated epidermal growth factor receptor exon 20 insertion-mutated advanced non-small cell lung cancer

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A R T I C L E I N F O

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A B S T R A C T

Background: Amivantamab, an epidermal growth factor receptor (EGFR)-MET bispecific antibody, is approved as monotherapy and as combination therapy for patients with advanced non-small cell lung cancer (NSCLC) harboring various *EGFR* mutations in first-line and refractory settings. Sites of progressive disease on amivantamab monotherapy are not well understood and could be instructive for treatment management.
Methods: CHRYSALIS (NCT02609776) enrolled participants with NSCLC, including those with treated brain metastases. Brain magnetic resonance imaging was required at screening but performed per local practice after enrollment (conducted postbaseline every 6 [±1] weeks after Cycle 1 Day 1). Sites of target, non-target, and new lesion progression were reported. This analysis includes 114 participants with *EGFR* exon 20 insertion (Ex20ins) NSCLC after disease progression on platinum-based chemotherapy who received amivantamab monotherapy on or before June 4, 2020.
Results: As of March 30, 2021, the median follow-up was 12.5 months (range, 0.2–30.5). Among 114 participants, the objective response rate by blinded independent central review was 43 %; median duration of response was 10.8 months, and median progression-free survival was 6.7 months. RECIST-defined progressive disease occurred in 72/114 participants (63 %); 25/72 (35 %) continued amivantamab after progression (4.2 median additional months; range, 1.0–12.5). The most common first sites of progression were the lungs/pleura (29 %), followed by bone (21 %), brain (15 %), and lymph node (12 %). Thirteen participants (11 %) had intracranial-only first progression. Six of these 13 participants underwent stereotactic radiosurgery (SRS) while continuing amivantamab. The median duration of amivantamab treatment post-progression in these 6 participants was 4.0 months (range, 2.3–6.0). SRS was well tolerated, with 2 adverse events reported (nausea and fatigue, n = 1 each).
Conclusions: Amivantamab monotherapy in post-platinum Ex20ins NSCLC demonstrated meaningful antitumor activity in participants, and intracranial-only progression was infrequent. Treatment of brain progression with SRS while continuing amivantamab appears feasible and tolerable.

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1. Introduction

Epidermal growth factor receptor (*EGFR*) exon 20 insertion (Ex20ins) mutations are detected in up to 4 % of all patients with non-small cell lung cancer (NSCLC) [1]. *EGFR* Ex20ins NSCLC has been associated with a poor prognosis, with an estimated 5-year real-world overall survival (OS) rate of 8 % compared to 19 % for common *EGFR* mutations (eg, exon 19 deletions [Ex19del], exon 21 L858R mutations) [2]. The real-world median OS among patients with *EGFR* Ex20ins NSCLC after disease progression on platinum-based chemotherapy is 11.5 months [3]. Due to mutation-induced steric hinderance at the tyrosine kinase inhibitor (TKI) binding site, the majority of *EGFR* Ex20ins are insensitive to treatment with first-, second-, and third-generation EGFR TKIs indicated for classical Ex19del or L858R mutations [4].

Amivantamab is a fully human EGFR-MET bispecific antibody with immune cell–directing activity [5]. It is approved for patients with *EGFR* Ex20ins locally advanced or metastatic NSCLC in the first-line setting in combination with chemotherapy and as a monotherapy for those with disease progression on or after platinum-based chemotherapy. Additionally, amivantamab is approved for patients with *EGFR* Ex19del or exon 21 L858R locally advanced or metastatic NSCLC in combination with the third-generation TKI lazertinib in the first-line setting and in combination with chemotherapy for those with disease progression on or after EGFR TKI therapy [6].

Brain metastases are frequent in NSCLC and can have a negative impact on clinical outcomes. Intracranial progression can manifest in patients with NSCLC as growth of existing or development of new lesions [7]. Due to its molecular weight, amivantamab was initially thought to be unlikely to have central nervous system (CNS) protective or treatment properties. However, in the phase 3 MARIPOSA-2 study (ClinicalTrials.gov Identifier: NCT04988295), amivantamab plus chemotherapy reduced the risk of intracranial disease progression or death by 45 % versus chemotherapy alone (median, 12.5 versus 8.3 months; hazard ratio, 0.55; 95 % CI, 0.38–0.79) [8].

There are several hypotheses that may provide explanations as to why amivantamab could have intracranial activity, such as blood brain barrier (BBB) penetrance and better systemic disease control resulting in better intracranial disease control. Patients with advanced lung cancer experience higher levels of BBB leakage or permeability than those with early lung cancer, increasing permeability and allowing drugs, such as amivantamab, to reach the CNS more easily [9]. As amivantamab displays immune cell–directing activity via engagement of macrophages, monocytes, and natural killer cells and induces trogocytosis [5], amivantamab may possibly induce an activated immune response against intracranial lesions. Other large molecular weight drugs with immune cell–directed activity, such as pembrolizumab and nivolumab, have demonstrated intracranial antitumor activity [10].

We investigated patterns of intracranial and systemic progression in the CHRYSALIS study (ClinicalTrials.gov Identifier: NCT02609776) to explore whether amivantamab monotherapy may have intracranial antitumor activity. We also explored the feasibility of concurrent stereotactic radiosurgery (SRS) in participants receiving amivantamab.

2. Methods

2.1. Participants and study design

Data from CHRYSALIS (a single-arm, dose-escalation, dose-expansion study) Cohort D were used in this analysis [11]. Cohort D enrolled participants with *EGFR* Ex20ins advanced or metastatic NSCLC with disease progression on or after platinum-based chemotherapy (ie, the population consistent with the amivantamab monotherapy label). The clinical cutoff was March 30, 2021. This analysis included participants who received their first dose of amivantamab monotherapy at the recommended phase 2 dose on or before June 4, 2020.

2.2. Assessments

The efficacy response was assessed by blinded independent central review (BICR) using RECIST v1.1. Computed tomography (CT) with contrast and/or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis, and all active disease sites was performed at screening, 6 weeks (+1 week) after Cycle 1 Day 1 for the first assessment, then every 6 (±1 week) relative to Cycle 1 Day 1 if post-baseline assessments were conducted. Baseline brain MRI (or CT scan if MRI was contraindicated) was required at screening for all participants in the dose-expansion phase of the study. Post-baseline brain imaging was performed according to local practice and was not required per protocol. Sites of target, non-target, and new lesion disease progression were reported by the investigator.

2.3. Statistical analysis

Participant subgroups with or without brain metastases present at study baseline were analyzed. Participants in the brain metastases subgroup included individuals with a history of brain metastases and those with active target or non-target intracranial lesions at baseline. Participants with definitively, locally treated metastases that were clinically stable and asymptomatic for $\geq$ 2 weeks and who were off or receiving low-dose corticosteroid treatment ($\leq$ 10 mg prednisone or equivalent) for $\geq$ 2 weeks prior to study treatment were eligible to participate. Cumulative incidence curves of intracranial/non-intracranial recurrences were estimated through survival analysis.

3. Results

3.1. Participant disposition

Overall, 114 participants with *EGFR* Ex20ins advanced NSCLC were included in the analysis. Demographics and baseline characteristics are

Table 1
Demographics and Baseline Disease Characteristics.

Characteristic, n (%)	Brain metastases at baseline (n = 43)[a]	No brain metastases at baseline (n = 71)	Total (N = 114)[b]
Median age (range), years	60.0 (36–84)	63.0 (44–84)	62.0 (36–84)
Male / Female	20 (47) / 23 (53)	24 (34) / 47 (66)	44 (39) / 70 (61)
Race			
Asian	27 (63)	32 (45)	59 (52)
White	11 (26)	31 (44)	42 (37)
Black	1 (2)	2 (3)	3 (3)
Not reported	4 (9)	6 (8)	10 (9)
Median weight (range), kg	59 (38–94)	62 (35–115)	62 (35–115)
Median number of prior lines (range)	2.0 (1–7)	2.0 (1–5)	2.0 (1–7)
Prior therapies			
Platinum-based chemotherapy	43 (100)	71 (100)	114 (100)
Immunotherapy	20 (47)	30 (42)	50 (44)
EGFR TKI	9 (21)	16 (23)	25 (22)
Any prior brain radiotherapy	38 (88)	0	38 (33)
Radiotherapy within past 6 months	29 (67)	0	29 (25)
Radiotherapy within past 3 months	23 (53)	0	23 (20)

CNS, central nervous system; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

[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.

[b] Patients who received amivantamab on or before June 4, 2020.

Table 2
Efficacy Endpoints per BICR/INV.

Outcome	Brain metastases at baseline (n = 43)[a]		No brain metastases at baseline (n = 71)		Total (N = 114)	
	BICR	INV	BICR	INV	BICR	INV
Objective response rate, n (%)	19 (44)	15 (35)	30 (42)	27 (38)	49 (43)	42 (37)
Median duration of response (95 % CI), months	8.7 (4.9, NE)	12.7 (4.1, NE)	11.0 (8.2, NE)	11.2 (5.2, NE)	10.8 (6.9, 15.0)	12.5 (6.5, 16.1)
Duration of response ≥ 6 months, n (%)	10/19 (53)	10/15 (67)	17/30 (57)	17/27 (63)	27/49 (55)	27/42 (64)
Median progression-free survival (95 % CI), months	6.7 (5.3, 10.8)	6.7 (3.9, 8.3)	6.9 (5.4, 10.8)	7.7 (5.6, 10.6)	6.7 (5.5, 9.7)	6.9 (5.6, 8.6)
Median overall survival (95 % CI), months	17.5 (14.0, 23.0)		NE (18.5, NE)		22.8 (17.5, NE)	

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; INV, investigator; NE, not evaluable.
[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.

presented in Table 1. Among all participants in this analysis, the median age was 62.0 years (range, 36–84), 70 (61 %) participants were women, 59 (52 %) were Asian, and all participants had received one or more prior lines of therapy. Baseline brain metastases (historical or active but controlled metastases) were reported in 43 of 114 participants.

3.2. Efficacy

As of the March 30, 2021 cutoff, the median duration of follow-up was 12.5 months (range, 0.2–30.5). Among all 114 participants, the objective response rate (ORR) by BICR was 43 %, median duration of response (DoR) was 10.8 months, and median progression-free survival (PFS) was 6.7 months. These endpoints, whether determined by BICR or investigator, were similar between those with or without brain metastases at baseline and consistent with the overall population (Table 2). For participants with versus without brain metastases at baseline, respectively, ORR by BICR was 44 % versus 42 %, median DoR by BICR was 8.7 months versus 11.0 months, and median PFS by BICR was 6.7 months versus 6.9 months.

In total, 72 participants (63 %) experienced disease progression; of these 72 participants, 25 (35 %) continued amivantamab post-progression for a median of 4.2 additional months of therapy (range, 1.0–12.5). In the overall population (n = 114), the most common first site of progression was the lungs/pleura (29 %), followed by the bone (21 %), brain (15 %), and lymph node (12 %; Fig. 1).

Among all participants (n = 114), 13 (11 %) had intracranial disease as the first site of progression (Fig. 2). Another 4 participants (4 %) had progression in both the brain and extracranial sites, while 55 (48 %) had extracranial-only progression, most commonly in the lung, bone, lymph node, and liver. Nine of the 13 participants with intracranial-only progression had baseline brain metastases, while 4 did not. Median time to progression for participants with intracranial-only progression was 4.5 months (range, 1.4–16.6) versus 5.5 months (range, 0.6–24.1) among participants with systemic progression.

Six of the 13 participants with intracranial-only progression underwent SRS while continuing amivantamab. Of these 6 participants, the median duration of amivantamab treatment after progression was 4.0 months (range, 2.3–6.0). Adverse events temporally associated with SRS were nausea (10 days after SRS) and fatigue, reported in one participant each. The time between SRS and next amivantamab dose ranged from 6 to 13 days.

3.3. Risk analysis

The cumulative incidence function assessing the risk of CNS recurrence over time was calculated using a Fine and Gray model (Fig. 3). At a 12-month landmark, the cumulative probability of extracranial-only progression was 44.6 %, intracranial-only progression was 9.0 %, and simultaneous extracranial and intracranial progression was 3.7 %. At an 18-month landmark, cumulative probabilities were 53.8 %, 15.7 %, and 3.7 %, respectively.

4. Discussion

Amivantamab has demonstrated systemic antitumor activity leading to approvals in *EGFR* Ex20ins advanced NSCLC in combination with chemotherapy in the first-line setting and as monotherapy after disease progression on platinum-based chemotherapy. Amivantamab is also approved for patients with *EGFR* Ex19del or exon 21 L858R advanced NSCLC in combination with lazertinib in the first-line setting and in combination with chemotherapy after progression on or after EGFR TKI therapy [6]. The low incidence of intracranial disease progression seen

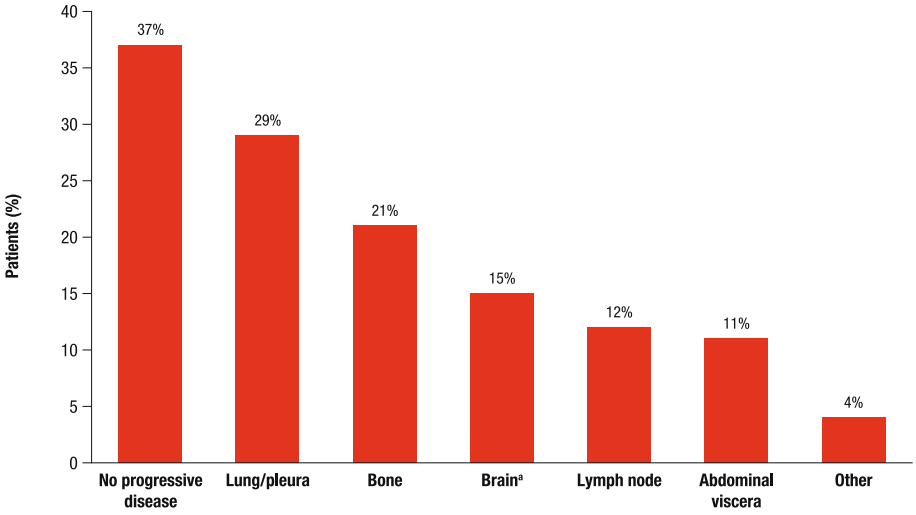

Fig. 1. Sites of first progressive disease recurrence. Safety population, n = 114. [a]Of 4 participants who had brain and extracranial sites of progression, all had brain metastases at baseline; the extracranial sites included lung and bone (n = 1), lung (n = 1), heart (n = 1), and lymph node (n = 1).

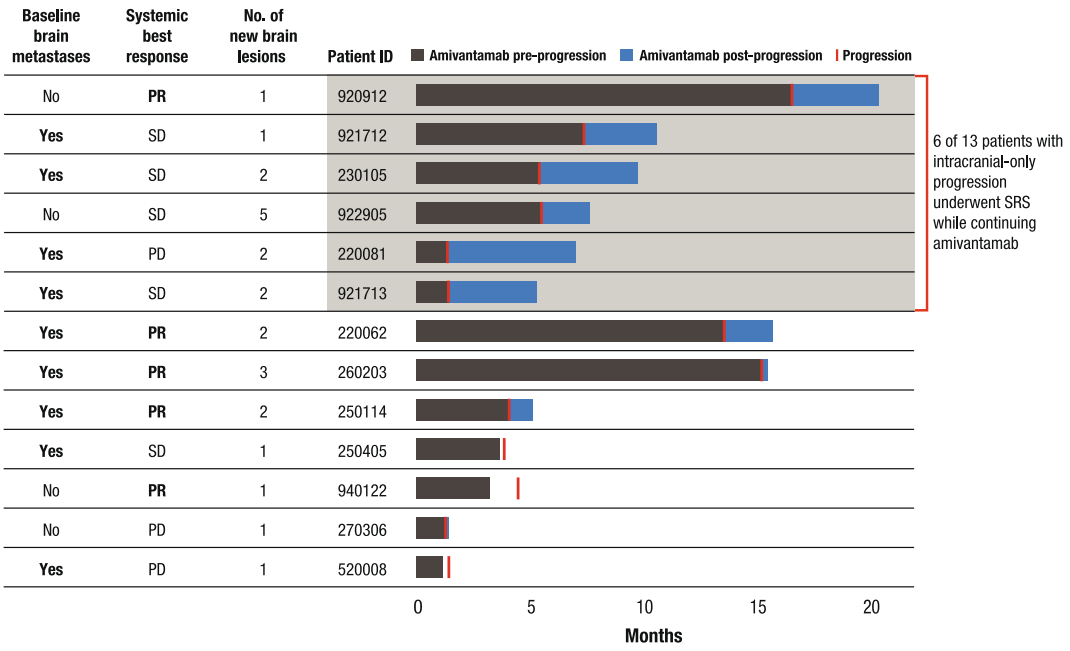

Fig. 2. Swimmer plot of management of intracranial progression in 13 participants with intracranial-only progressive disease. PD, progressive disease; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery.

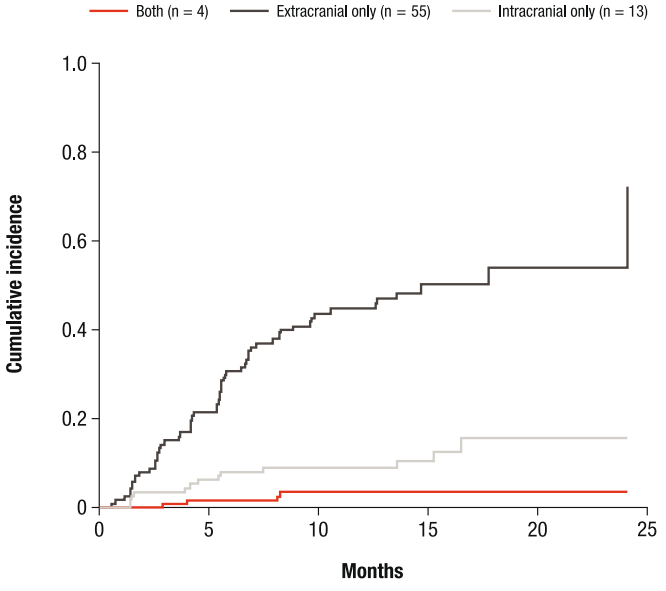

Fig. 3. Risk of central nervous system recurrence over time.

in CHRYSALIS may indicate that amivantamab has both intracranial and extracranial antitumor coverage. These results build upon the intracranial PFS benefits previously observed with amivantamab plus chemotherapy in MARIPOSA-2.

In this study, all participants, regardless of brain metastasis status, received platinum-based chemotherapy prior to amivantamab treatment. Participants with brain metastases at baseline were more likely than those without to have received prior brain radiotherapy, including within the past 3 or 6 months. Efficacy outcomes were similar among those who had brain metastases and those who did not and were consistent with the overall population. Extracranial disease progression was the highest contributing factor to all cases of disease progression. The lungs/pleura was the most frequent first site of disease progression among all participants. Among participants who experienced any kind of disease progression, some (25/72) elected to continue amivantamab after disease progression.

The combination of SRS and amivantamab appears to have a tolerable safety profile, as only 2 patients who received SRS reported adverse events (nausea and fatigue). Among patients with intracranial-only progression, those who also underwent SRS were more likely to use amivantamab post-progression than those who did not undergo SRS.

Patients with intracranial-only progression had similar time to disease progression compared to participants with extracranial progression, which suggests that amivantamab controls the rate of disease progression similarly regardless of tumor location.

A potential study limitation was that serial brain imaging was not required in all participants. Therefore, intracranial outcomes such as intracranial ORR, DoR, and PFS could not be reliably estimated. Additionally, 33 % of participants received prior brain radiotherapy, which may also impact the interpretation of intracranial outcomes.

In conclusion, intracranial-only progression on amivantamab monotherapy was infrequent, which may reflect an inherent characteristic of *EGFR* Ex20ins NSCLC or that amivantamab could possess intracranial antitumor effects. Outcomes were similar regardless of presence or absence of brain metastases at baseline. For patients with advanced *EGFR* Ex20ins NSCLC who experience intracranial-only progression, brain lesions may be treatable with SRS while continuing amivantamab therapy.

Prior presentation

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Clinical trial information

NCT02609776 (CHRYSALIS).

Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

CRediT authorship contribution statement

Natasha B. Leighl: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Jose Trigo:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Keunchil Park:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Se-Hoon Lee:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Nicolas Girard:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Santiago Viteri:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Pilar Garrido:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Matthew G. Krebs:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Meena Thayu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization. **Roland E. Knoblauch:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization. **John Xie:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Joshua M. Bauml:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization. **Robert W. Schnepp:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization. **Anil Londhe:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Yichuan Xia:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Parthiv J. Mahadevia:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Data curation, Conceptualization. **Byoung Chul Cho:** Writing – review & editing, Writing – original draft, Investigation, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Natasha B. Leighl reports that financial support was provided by Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, EMD Serono, Guardant Health, Inivata, Janssen, MSD, Neogenomics, Novartis, Pfizer, Roche, Takeda, Eisai, and Sanofi. Jose Trigo reports that financial support was provided by Bristol Myers Squibb, Takeda, MSD, Boehringer Ingelheim, Roche, Merck, AstraZeneca, Bayer, and Pfizer. Keunchil Park reports that financial support was provided by AstraZeneca, Lilly, Ono Pharmaceutical, Bristol Myers Squibb, MSD, Blueprint Medicines, Amgen, Merck KGaA, LOXO, AbbVie, Daiichi Sankyo, Boehringer Ingelheim, Johnson & Johnson, Eisai, Puma Biotechnology, and MSD Oncology. Se-Hoon Lee reports that financial support was provided by AstraZeneca/MedImmune, Roche, Merck, Lilly, Amgen, and Pfizer. Nicolas Girard reports that financial support was provided by AstraZeneca, AbbVie, Amgen, Boehringer Ingelheim, Lilly, Hoffmann-La Roche, Janssen, Merck, MSD, Novartis, Pfizer, Sivan, Trizell, Bristol Myers Squibb, and Sanofi. Santiago Viteri reports that financial support was provided by AbbVie, Bristol Myers Squibb, Roche, Takeda, AstraZeneca, MSD, OSE Pharma, Merck, Merck Serono, Puma Biotechnology, and Janssen Cilag. Pilar Garrido reports that financial support was provided by AbbVie, Amgen, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, GSK, Johnson & Johnson, Lilly, MSD, Novartis, Pfizer, Roche, Regeneron, Sanofi, Takeda, Medscape, and Touch Medical. Matthew G. Krebs reports that financial support was provided by Roche, Novartis, Achilles Therapeutics, Janssen, Seattle Genetics, OM Pharma, Bayer, Zai Therapeutics, Bristol Myers Squibb, Eisai, AstraZeneca, BerGenBio, and Immutep. Meena Thayu reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Roland E. Knoblauch reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. John Xie reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Joshua M. Bauml reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Robert W. Schnepp reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Anil Londhe reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Yichuan Xia reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Parthiv J. Mahadevia reports that financial support was provided by Janssen Research & Development, LLC and Johnson & Johnson. Byoung Chul Cho reports that financial support was provided by Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono Pharmaceutical, Dizal Pharma, MSD, AbbVie, MedPacto, GI Innovation, Lilly, Blueprint Medicines, Interpark Bio Convergence Corp, Boehringer Ingelheim, Roche, Bristol Myers Squibb, Pfizer, Takeda, TheraCanVac Inc, Gencurix Inc, BridgeBio Therapeutics, KANAPH Therapeutics, Cyrus Therapeutics, Guardant Health, and Daan Biotherapeutics.

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