BRIEF REPORT

Preventing Infusion-Related Reactions With Intravenous Amivantamab—Results From SKIPPirr, a Phase 2 Study: A Brief Report

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ABSTRACT

Introduction: Amivantamab, an EGFR-MET bispecific antibody, is approved for multiple indications in *EGFR*-mutated advanced NSCLC as monotherapy or combined with other agents. Intravenous amivantamab is associated with a 67% infusion-related reaction (IRR) rate.

Methods: The phase 2 SKIPPirr study (NCT05663866) enrolled participants with *EGFR*-mutated (exon 19 deletion or exon 21 L858R) advanced NSCLC after progression on osimertinib and platinum-based chemotherapy who received intravenous amivantamab plus oral lazertinib (amivantamab-lazertinib), a third-generation tyrosine kinase inhibitor. Aiming to mitigate IRRs, four independent prophylactic approaches were evaluated using Simon's two-stage design with an expansion stage if a cohort passed both stages: oral dexamethasone 4 mg twice daily given on cycle (C) 1 day (D) −1 (two doses); oral dexamethasone 8 mg twice daily given on C1D−2, C1D−1, and the morning of C1D1 (five doses); oral montelukast 10 mg once daily given on C1D−4, C1D−3, C1D−2, C1D−1, and C1D1 (five doses); subcutaneous methotrexate 25 mg (one dose) given anytime between C1D−7 and C1D−3. The primary end point was C1D1 IRR incidence.

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Results: As of June 24, 2024, 68 participants were treated across all cohorts. The dexamethasone 8 mg cohort passed stages 1 and 2 proceeding to the expansion stage, with 24 additional participants treated. At C1D1, nine of 40 participants (22.5%) experienced IRRs, resulting in an approximately threefold decrease versus historical data (67.4%). By the end of C3, 10 of 41 participants (24.4%) in the dexamethasone 8 mg cohort experienced IRRs (grades 1–2, except one grade 3 on C2D1). Amivantamab-lazertinib's safety and efficacy were consistent with previous reports.

Conclusions: Prophylaxis with 8 mg oral dexamethasone meaningfully reduced IRRs and can be readily implemented in clinical practice.

Keywords: Amivantamab; Dexamethasone; Infusion-related reactions; NSCLC; Prophylaxis

Introduction

Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity.[1–3] Intravenous amivantamab has shown significant clinical efficacy and received regulatory approval in combination with lazertinib for first-line treatment of common *EGFR*-mutated advanced NSCLC, in combination with chemotherapy for second-line treatment after disease progression on EGFR tyrosine kinase inhibitors, and in combination with chemotherapy for first-line treatment or as monotherapy after progression on platinum-based chemotherapy for NSCLC with *EGFR* exon 20 insertion mutations.[4,5]

Like other anticancer therapies, intravenous amivantamab is associated with infusion-related reactions (IRRs; 67%).[6] Historically, approaches to manage IRRs associated with intravenous amivantamab in clinical trials included splitting the first dose over two days and premedication with antihistamines, antipyretics, and glucocorticoids.[6] Subcutaneous amivantamab reported a lower incidence of IRRs compared with intravenous amivantamab and is under review by several health authorities.[7]

Emerging data suggested that adding montelukast to premedication regimens or the use of methotrexate can reduce IRRs associated with monoclonal antibodies.[8,9] A case series also used dexamethasone to reduce the incidence of IRRs with encouraging results.[10]

On the basis of these data, the phase 2 SKIPPirr study (NCT05663866) evaluated four independent prophylactic strategies to reduce the incidence and severity of IRRs in participants with *EGFR* exon 19 deletion or exon 21 L858R-mutated advanced or metastatic NSCLC treated with the combination of intravenous amivantamab plus oral lazertinib (amivantamab-lazertinib). Here, we present safety and efficacy results from SKIPPirr.

Materials and Methods

Participants

Eligible participants were aged 18 years or older with advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutations and an Eastern Cooperative Oncology Group performance status score of 0 to 1. Participants had disease that had progressed on or after prior treatment with osimertinib and platinum-based chemotherapy. Prior use of first- or second-generation tyrosine kinase inhibitors was allowed if administered before osimertinib.

Study Design

A Simon's two-stage design with an expansion stage was used to evaluate four independent prophylactic regimens (cohorts): oral dexamethasone 4 mg twice daily given on cycle (C) 1 day (D) −1 (two doses); oral dexamethasone 8 mg twice daily given on C1D−2 and C1D−1 and another dose an hour before infusion of amivantamab on C1D1 (five doses); oral montelukast 10 mg once daily given on C1D−4, C1D−3, C1D−2, C1D−1, and C1D1 (five doses); or a single dose of subcutaneous methotrexate 25 mg given anytime between C1D−7 and C1D−3 (Supplementary Fig. 1). All participants received intravenous amivantamab 1050 mg (1400 mg if $\geq$80 kg) once weekly for four weeks and then every two weeks thereafter, and oral lazertinib 240 mg daily. The initial amivantamab dose was administered as a split dose over two days (C1D1 [350 mg] and C1D2 [remainder of dose]). All participants received standard premedication with antihistamines, antipyretics, and intravenous dexamethasone 10 mg. Adequate oral hydration was encouraged with prophylactic oral dexamethasone. Each cohort initially enrolled up to six participants in stage 1, and if three or fewer participants had IRRs, this cohort would move to stage 2. In stage 2, up to 10 additional participants would be enrolled. If eight or fewer of 16 participants in stages 1 and 2 had IRRs, this cohort would move to an expansion stage, where 24 more participants would be enrolled.[11]

Study End Points and Assessments

The primary end point was the rate of IRRs occurring on C1D1 within 24 hours of the start of amivantamab administration. Each prophylactic approach was evaluated individually. Secondary end points included rates and severity of IRRs in subsequent Cs, incidence and severity of other adverse events (AEs), amivantamab

Table 1. Demographic and Baseline Characteristics

Characteristics	Dexamethasone 4 mg (n = 6)	Dexamethasone 8 mg (n = 41)	Montelukast (n = 15)	Methotrexate (n = 6)	All Cohorts (N = 68)
Median age (range), y	56 (44-77)	62 (32-82)	66 (47-78)	66 (48-82)	63.5 (32-82)
Female, n (%)	3 (50)	26 (63)	10 (67)	5 (83)	44 (65)
Race, n (%)					
Asian	2 (33)	24 (59)	10 (67)	6 (100)	42 (62)
White	4 (67)	10 (24)	4 (27)	0	18 (26)
Black or African American	0	1 (2)	0	0	1 (1)
Not reported	0	6 (15)	1 (7)	0	7 (10)
ECOG PS score of 1, n (%)	4 (67)	32 (78)	12 (80)	3 (50)	51 (75)
Brain metastases, n (%)	3 (50)	15 (37)	10 (67)	2 (33)	30 (44)
EGFR mutation type, n (%)					
Exon 19 deletion	5 (83)	29 (71)	9 (60)	2 (33)	45 (66)
Exon 21 L858R	1 (17)	12 (29)	6 (40)	4 (67)	23 (34)
Median prior lines of therapy (range)	3 (2-4)	3 (2-9)	4 (2-9)	4 (3-9)	3 (2-9)

ECOG PS, Eastern Cooperative Oncology Group performance status.

infusion duration, health care utilization, objective response rate (ORR), and duration of response. The response was assessed by the investigator according to Response Criteria in Solid Tumors version 1.1. Additional methods are included in the Supplementary Materials.

Statistical Analysis

Categorical values were summarized using the number of events and percentages. Where appropriate, two-sided exact 95% confidence intervals (CIs) were included. Continuous variables were summarized using the number of events, median, and range. The primary end point was assessed on the basis of the per-protocol analysis set, defined as participants who received all prophylaxis treatment as scheduled and received amivantamab-lazertinib on C1D1.

ORR was defined as the proportion of participants who achieved either a complete response or partial response as defined by investigator assessment using the Response Criteria in Solid Tumors version 1.1. Owing to the limited number of participants and the nature of this study, all antitumor analyses were considered descriptive.

Secondary end points and safety data were assessed on the basis of the safety analyses set.

Results

Participants

At the clinical cutoff date, June 24, 2024, 68 participants were treated across all cohorts (median follow-up: 4.2 mo; Table 1). The median age was 63.5 years (range: 32–82 y), 65% were female participants, and 62% were Asian participants, with a median of three prior lines of treatment (range: 2–9). Owing to small sample sizes in all but the dexamethasone 8 mg cohort and sequential enrollment, some demographic and baseline characteristic imbalances existed between cohorts.

Incidence and Severity of IRRs

The dexamethasone 4 mg and methotrexate cohorts both had five of six participants (83.3%) who experienced IRRs and did not pass stage 1. The montelukast cohort had 10 of 15 participants (66.7%) who experienced IRRs and did not pass stage 2. The dexamethasone 8 mg twice daily cohort passed stages 1 and 2 and proceeded to the expansion stage, where 24 additional participants were enrolled and treated. One participant did not receive an amivantamab infusion on C1D1 per protocol and was excluded from the primary end point analysis, but did not experience an IRR in the study.

On C1D1, nine of 40 participants (22.5%) in the dexamethasone 8 mg cohort reported an IRR (Fig. 1*A*). For the dexamethasone 8 mg cohort, all IRRs on C1D1 were grades 1 to 2 and none were serious. The most frequent IRR-related symptoms were nausea (8%), dyspnea (5%), and hypotension (5%); all were grades 1 to 2 (Fig. 1*B*).

By the end of C3, 10 of 41 participants (24.4%) in the dexamethasone 8 mg cohort experienced IRRs. Nine participants had IRRs on C1D1 (one of these participants also had an IRR on C1D2); one participant had an IRR on C2D1. All IRRs were grades 1 to 2 except for the one grade 3 IRR that occurred on C2D1.

Safety

The most frequent AEs in the overall population by preferred term were rash (44%), paronychia (44%), and hypoalbuminemia (35%; Table 2). AEs occurring in the

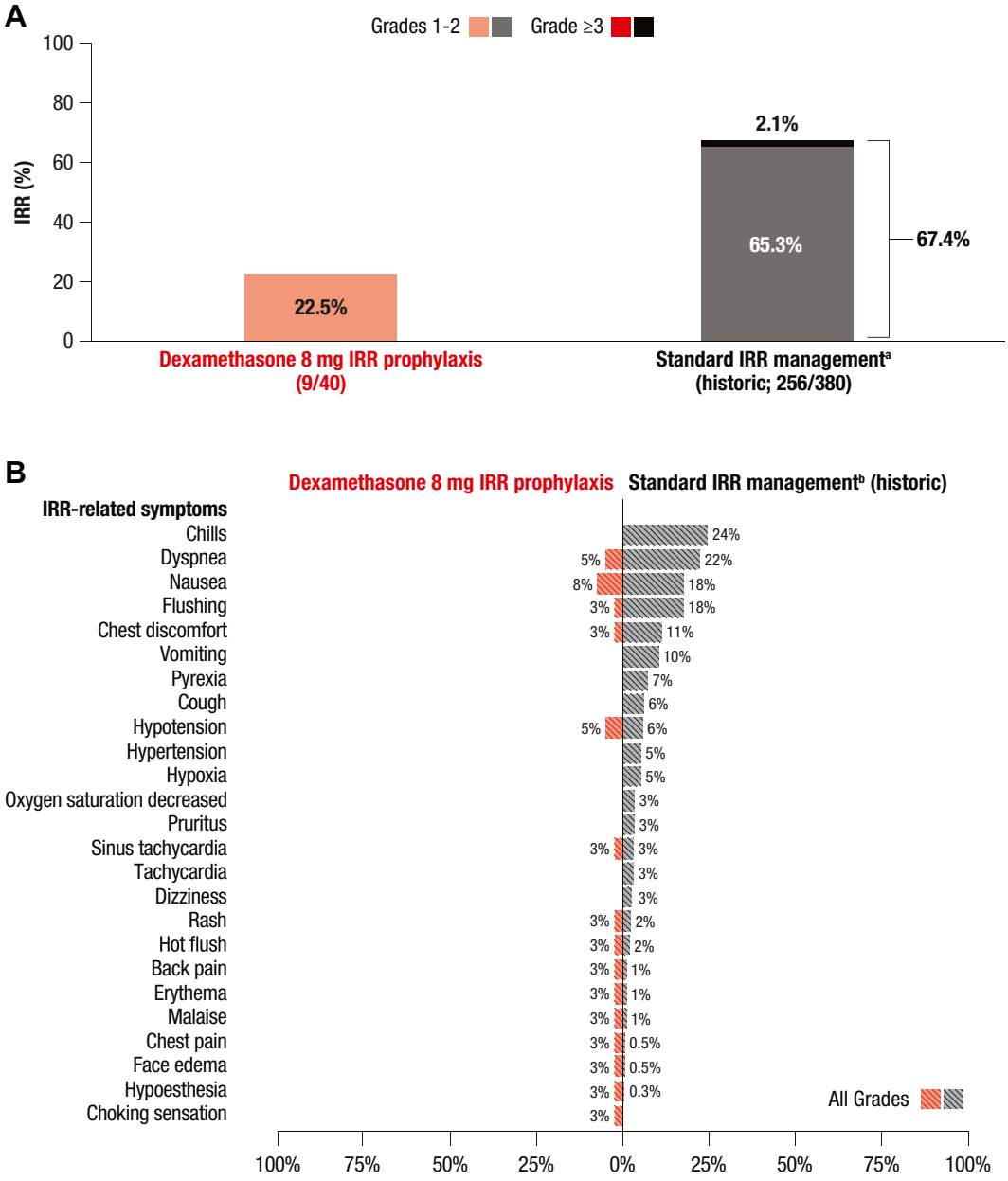

Figure 1. Incidence of *(A)* IRRs and *(B)* IRR-related Symptoms on C1D1. Clinical cutoff: C1D2. Participants from historical data in the standard IRR management group received standard premedications (antihistamines, antipyretics, and glucocorticoids). [a]Includes IRRs from 380 participants treated at the RP2D in the CHRYSALIS study on the basis of a March 30, 2021, data cutoff for the entire study period. Most (98.4%) IRRs occurred on C1D1 with an IRR rate of 66.3%, of which 1.8% were grade 3 or higher. [b]IRR symptoms on C1D1 with IV amivantamab monotherapy are reported in the 380 participants treated at the RP2D in the CHRYSALIS study on the basis of a March 30, 2021, data cutoff. C, Cycle; D, Day; IRR, infusion-related reaction; RP2D, recommended phase 2 dose.

dexamethasone 8 mg cohort were similar to the overall population and consistent with prior reports,[4,5,7,12] where rash (41%), hypoalbuminemia (41%), and paronychia (39%) were the most frequently reported events. AEs reported by the investigator as potentially related to dexamethasone prophylaxis occurred in three participants receiving dexamethasone 8 mg (one event each: gastroesophageal reflux disease, muscle atrophy, somnolence) and were all grades 1 to 2.

Efficacy

Investigator-assessed ORR in the dexamethasone 8 mg cohort was 33% (95% CI: 19–49), and the confirmed response rate was 28% (95% CI: 15–44; Supplementary Table 1), which are consistent with results from prior studies in similar populations.[7,12] The median follow-up for this cohort was 4.2 months. The median duration of response among confirmed responders was not estimable (not

Table 2. Safety Profile

Most Common Treatment-Emergent AEs (≥15%[a]), n (%)	Dexamethasone 4 mg (n = 6)		Dexamethasone 8 mg (n = 41)		Montelukast (n = 15)		Methotrexate (n = 6)		All Cohorts (N = 68)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Associated with EGFR inhibition										
Rash	2 (33)	0	17 (41)	0	8 (53)	3 (20)	3 (50)	1 (17)	30 (44)	4 (6)
Paronychia	2 (33)	0	16 (39)	0	10 (67)	0	2 (33)	0	30 (44)	0
Stomatitis	1 (17)	0	14 (34)	1 (2)	3 (20)	0	2 (33)	0	20 (29)	1 (1)
Pruritus	2 (33)	0	5 (12)	0	3 (20)	1 (7)	4 (67)	0	14 (21)	1 (1)
Dermatitis acneiform	2 (33)	0	7 (17)	0	3 (20)	0	0	0	12 (18)	0
Diarrhea	1 (17)	0	7 (17)	1 (2)	2 (13)	0	2 (33)	0	12 (18)	1 (1)
Associated with MET inhibition										
Hypoalbuminemia	1 (17)	1 (17)	17 (41)	0	4 (27)	0	2 (33)	0	24 (35)	1 (1)
Peripheral edema	0	0	9 (22)	0	5 (33)	0	0	0	14 (21)	0
Other										
IRR	5 (83)	0	10 (24)	1 (2)	11 (73)	1 (7)	5 (83)	0	31 (46)	2 (3)
Nausea	2 (33)	0	10 (24)	1 (2)	6 (40)	0	4 (67)	1 (17)	22 (32)	2 (3)
Epistaxis	0	0	9 (22)	0	3 (20)	0	1 (17)	0	13 (19)	0
Dyspnea	2 (33)	0	8 (20)	1 (2)	1 (7)	1 (7)	0	0	11 (16)	2 (3)
Hypoesthesia	1 (17)	0	8 (20)	0	4 (27)	0	1 (17)	0	14 (21)	0
Headache	0	0	8 (20)	0	1 (7)	0	1 (17)	0	10 (15)	0
Constipation	2 (33)	0	8 (20)	0	1 (7)	0	1 (17)	0	12 (18)	0
Hypotension	0	0	8 (20)	2 (5)	0	0	1 (17)	0	9 (13)	2 (3)
Asthenia	2 (33)	0	7 (17)	2 (5)	3 (20)	1 (7)	0	0	12 (18)	3 (4)
Dry skin	1 (17)	0	6 (15)	0	3 (20)	1 (7)	0	0	10 (15)	1 (1)
Pain in extremity	1 (17)	0	5 (12)	0	3 (20)	0	1 (17)	0	10 (15)	0
Decreased appetite	1 (17)	0	4 (10)	0	4 (27)	1 (7)	2 (33)	1 (17)	11 (16)	2 (3)
Chills	2 (33)	0	0	0	6 (40)	0	2 (33)	0	10 (15)	0

[a]Includes all AEs occurring in 15% or more participants from all cohorts or in the 8 mg dexamethasone cohort.
AE, adverse event; IRR, infusion-related reaction.

estimable; 95% CI: 4.2 mo–not estimable) owing to limited follow-up.

Health Care Utilization

The median (range) of amivantamab infusion times on C1D1 are shown in Supplementary Figure 2. By C1D15 and onward, the median duration of amivantamab infusion was approximately 2.3 hours for all cohorts. Median treatment room time, time in the infusion chair, and active health care provider time are shown in Supplementary Figure 3.

Discussion

In SKIPPirr, the addition of dexamethasone 8 mg twice daily to standard IRR prophylaxis with antihistamines, antipyretics, and intravenous dexamethasone 10 mg (Supplementary Fig. 4) effectively reduced the rate of first infusion IRRs for participants treated with intravenous amivantamab by approximately threefold versus historical intravenous amivantamab data (22.5% versus 67.4%). IRRs occurring through the end of C3 for participants in the dexamethasone 8 mg twice daily cohort were also reduced by approximately threefold compared with historical data, underscoring that most amivantamab-associated IRRs occurred on C1D1.

The confirmed ORR of amivantamab-lazertinib in participants receiving the dexamethasone 8 mg twice daily regimen (28%) was consistent with ORRs from similar participant populations in CHRYSALIS-2 Cohort A (28%) and PALOMA-3 (27%),[7,12] demonstrating that the addition of dexamethasone 8 mg did not impact the efficacy of amivantamab-lazertinib.

Except for the reduced rate of IRRs, the safety profile of intravenous amivantamab-lazertinib was consistent with prior reports with no new safety signals identified.[7,12] The most frequently reported AEs were associated with inhibition of EGFR or MET. AEs often associated with steroid use were not observed in participants receiving the dexamethasone 8 mg twice daily regimen.[13]

Participants receiving the dexamethasone 8 mg twice daily regimen had numerically lower median amivantamab infusion times compared with a similar participant population receiving intravenous amivantamab with standard IRR management from PALOMA-3 (4.4 versus 5.0 h).[7] Decreased infusion times observed in all cohorts from C1D15 onward were consistent with historical data, reflecting the guidance for increased infusion rates owing to low incidences of IRRs after C1D1.

Intravenous amivantamab has received regulatory approvals around the world in multiple indications for *EGFR*-mutated advanced NSCLC as monotherapy or in combination with chemotherapy or lazertinib.[4,5] Timely adoption of the convenient dexamethasone 8 mg twice daily regimen to reduce IRRs and the prophylactic dermatologic AE management under evaluation in the COCOON study (NCT06120140)[14] could have an immediate clinical impact by enhancing safety and tolerability of intravenous amivantamab while allowing patients to initiate and remain on therapy.

CRediT Authorship Contribution Statement

Alexander I. Spira: Data curation, Investigation, Methodology, Writing - original draft, Writing - review & editing.

Luis Paz-Ares: Data curation, Investigation, Methodology, Writing - original draft, Writing - review & editing.

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Jin-Yuan Shih: Data curation, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing.

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Disclosure

Dr. Spira reports serving in a consulting or advisory role for Array Biopharma, Incyte, Amgen, Novartis, AstraZeneca, MedImmune, Mirati Therapeutics, Gritstone Bio, Jazz Pharmaceuticals, Merck, Bristol Myers Squibb, Janssen, Mersana, Blueprint Medicines, Daiichi Sankyo, Regeneron, Eli Lilly, Black Diamond Therapeutics, and Sanofi; serving in a leadership role for Next Oncology; owning stock or other ownership interest with Eli Lilly; receiving payment or honoraria from CytomX Therapeutics, AstraZeneca, Merck, Takeda, Amgen, Janssen, Novartis, Bristol Myers Squibb, and Bayer; receiving research funding from Roche, AstraZeneca, Boehringer Ingelheim, Astellas Pharma, MedImmune, Novartis, Incyte, AbbVie, Ignyta, Takeda, Macrogenics, CytomX Therapeutics, LAM Therapeutics, Astex Pharmaceuticals, Bristol Myers Squibb, Loxo Oncology, Arch Therapeutics, Gritstone Bio, Plexxikon, Amgen, Daiichi Sankyo, ADC Therapeutics, Janssen, Mirati Therapeutics, Rubius Therapeutics, Synthekine, Mersana, Blueprint Medicines, Regeneron, Alkermes, Revolution Medicines, Medikine, Black Diamond Therapeutics, BluPrint Oncology, Nalo Therapeutics, Scorpion Therapeutics, and ArriVent Biopharma. 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Dr. Nadal reports serving in a consulting or advisory role for Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Pfizer, Eli Lilly, Amgen, Janssen, Daiichi Sankyo, Boehringer Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, and Qiagen; receiving grants of contracts from Roche, Bristol Myers Squibb, and Pfizer; receiving payment or honoraria from Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Sanofi, Pfizer, Eli Lilly, Amgen, Janssen, Daiichi Sankyo, Boehringer Ingelheim, AstraZeneca, Takeda, Sanofi, Pierre Fabre, Qiagen, and Bayer; receiving support for attending meetings and/or travel from Johnson & Johnson, Merck Sharp & Dohme, Takeda, and Roche; serving on a Data Safety Monitoring Board or Advisory Board for Roche, Apollomics, Merck Sharp & Dohme, and Transgene; serving in a leadership role for the Steering Committee of the Spanish Group of Lung Cancer (GECP). Dr. Gil-Bazo reports serving in a consulting or advisory role for Johnson & Johnson, Eli Lilly, and Boehringer Ingelheim; receiving payment or honoraria from Johnson

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Data Availability 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 the Yale University Open Data Access Project site at http://yoda.yale.edu.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2025.01.018.

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