Lung Cancer: Targets and Therapy

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COMMENTARY

Spotlight on Patritumab Deruxtecan (HER3-DXd) from HERTHENA Lung01. Is a Median PFS of 5.5 Months Enough in Light of FLAURA-2 and MARIPOSA?

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Abstract: On December 22, 2023, the US Food and Drug Administration (FDA) approved the biologics license application for patritumab deruxtecan (HER3-DXd) for priority review. This treatment is aimed at adult patients with locally advanced or metastatic NSCLC with EGFR mutations, who have received at least two prior systemic therapies. Approval of patritumab deruxtecan would mark it as the first HER3 targeted therapy in the United States. This prioritization by the FDA is grounded in compelling results from the global Phase II HERTHENA-Lung01 trial, wherein HER3-DXd exhibited clinically meaningful efficacy, achieving a median progression-free survival (mPFS) of 5.5 months in patients with heavily treated EGFR-mutated NSCLC. A pivotal question remains: Is a mPFS of 5.5 months sufficient in the context of the evolving first-line landscape observed in the FLAURA-2 and MARIPOSA trials?

Keywords: EGFR, NSCLC, post-osimertinib, targeted therapy

Background

Treatment landscape for NSCLC with EGFR mutations and resistance to EGFR TKIs

Significant progress has been made in NSCLC management through the development of targeted therapeutic approaches, particularly in the context of patients harboring EGFR mutations. These mutations are present in a significant percentage of NSCLC cases, varying by population and demographic factors. As a third-generation EGFR tyrosine kinase inhibitor (TKI), osimertinib has transformed the first-line treatment landscape for patients with NSCLC. However, despite initial great responses, a majority of tumors ultimately become resistant to osimertinib, necessitating the exploration of subsequent therapeutic strategies. This resistance can emerge through multiple pathways, such as EGFR-dependent and EGFR-independent routes. Salvage treatments following disease advancement on EGFR TKs and platinum-based chemotherapy (PBC) reported mPFS in the range of 2.8–3.3 months.[1]

To effectively manage progression following osimertinib treatment, a comprehensive and multifaceted strategy is essential. This includes proactively delaying resistance through intensified initial treatments. Choices involve pairing an EGFR TKI (such as osimertinib) with chemotherapy, as seen in the FLAURA2 trial,[2] or integrating an EGFR-MET bispecific agent, as explored in the MARIPOSA study.[3,4] Additionally, directly addressing specific resistance mechanisms is crucial. For instance, if a patient acquires a C797S mutation causing resistance to osimertinib, considering a novel fourth-generation EGFR inhibitor being tested in clinical trials might be a practical choice. Alternatively, broader approaches like chemotherapy, antibody-drug conjugates (ADCs), or a combination of chemotherapy and immunotherapy, potentially augmented with a VEGF inhibitor, may be employed.

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Treatment approaches incorporating both chemotherapy and immune checkpoint inhibitors (ICI) were tested against PBC in the Phase 3 KEYNOTE-789 and CheckMate 722 trials. However, these investigations failed to show any notable disparities in survival results among patients unresponsive to previous EGFR TKI therapy.[5,6] The ORIENT-31 and IMpower150 trials enhanced their regimen by including an anti-VEGF monoclonal antibody (either bevacizumab or its biosimilar) to the existing combination of ICIs and chemotherapy. ORIENT-31, however, failed to reveal a beneficial effect on overall survival (OS), and its study was specifically confined to China.[7] The final results from the IMpower151 trial demonstrated that the inclusion of bevacizumab to the combined therapy of chemotherapy and immunotherapy did not yield any statistically significant therapeutic advantage for patients with EGFR mutated NSCLC.[8]

HER3 ADC

The human epidermal growth factor receptor 3 (HER3), also called receptor tyrosine-protein kinase ErbB3, belongs to the ErbB receptor family, encompassing EGFR (ErbB1), Human Epidermal Growth Factor Receptor (HER)-2 (ErbB2), and HER4 (ErbB4). HER3 activation contributes to the enhanced growth and advancement of cancer cells due to its role in activating the PI3K/AKT/mTOR and JAK–STAT signaling pathways. HER3 has been reported to be expressed in 83% of NSCLC tumors[9] and in 85%–100% of tumors with a concurrent activating EGFR mutation.[10,11] It is vital in the development of resistance to EGFR TKIs in EGFR-mutated NSCLC. For instance, aberrant mechanisms, such as MET amplification, can interact with HER3 to activate the PI3K/AKT/mTOR signaling pathway in tumor cells during EGFR TKI therapy.[11] Furthermore, the ligand for HER3, heregulin, can induce the coupling and signaling of HER2/HER3, promoting cancer cell survival independently of EGFR.[12] This independent pathway underscores the importance of HER3 as a target for oncological therapy, especially in EGFR-mutated NSCLC.[13,14] It is reported that HER3 levels are elevated in patient tumor samples following progression from initial EGFR TKIs.[11,15]

Patritumab deruxtecan is a conjugate that combines patritumab, a monoclonal antibody targeting HER3, with deruxtecan - A payload of topoisomerase I inhibitor connected through a tetrapeptide-based cleavable linker. This design enables the targeted delivery of the chemotherapeutic agent directly to cancer cells, thus enhancing efficacy while minimizing systemic toxicity. A Phase I study (U31402-A-U102) demonstrated that 39% of heavily pretreated patients with EGFR-mutated NSCLC achieved an objective response to HER3-DXd.[10] The mPFS reached 8.2 months (Table 1). HER3-DXd demonstrated anticancer effects across different resistance mechanisms to EGFR TKI, such as EGFR C797S mutation and MET. These encouraging results from the phase I trial prompted the start of the phase II HERTHENA-Lung01 trial.

HERTHENA-Lung01 Trial

In this global phase II trial,[16] 225 patients who had previously undergone at least one EGFR TKI and one PBC were treated with patritumab deruxtecan. At 18.9 months, the ORR was observed to be 29.8%, and the median duration of response was 6.4 months.[16] The trial reported a mPFS of 5.5 months and a median overall survival (OS) of 11.9 months.[16] Anticancer effects were noted across various subgroups as well. Notably, the outcomes for patients with central nervous system (CNS) metastases (N = 115) were comparable to those without CNS involvement. Tumor tissue analysis from 197 patients showed no significant variations in ORR based on HER3 expression. Specifically, 2 out of 7 patients (28.6%) with undetectable HER3 expression experienced confirmed partial responses. Sustained responses to HER3-DXd were evident in patients whose tumors exhibited EGFR C797X or MET amplification, representing the predominant resistance mechanisms to third-generation EGFR TKIs.[17] The occurrence of treatment-related adverse events (TRAEs) of Grade 3 or higher was 64.9%, and 28.9% of patients encountered at least one Grade 4 TRAE (Table 1).

Discussion

Results from this phase II trial highlight the promising safety profile and effectiveness of the HER3-targeted ADC, patritumab deruxtecan, in EGFR-mutated NSCLC population who failed TKIs and PBCs. Both the HERTHENA-Lung01 and U102 Phase I study[10] demonstrated clinical benefits across various subgroups, regardless of tumor HER3 expression, different resistance mechanisms to EGFR TKIs, and whether or not there were brain metastases. Despite these similarities, notable variations in the ORR and PFS were noted between the two studies (Table 1). The investigators suspect that these variations might be attributed to several factors, such as the smaller number of patients in the phase I study, differences in the

Table 1 Efficacy and Safety of HER3-DXd Treating EGFR Mutated NSCLC Patients

Trial Name	U31402-A-U102	Herthena-Lung 01
Phase	I	II
Patient selection	Metastatic EGFR-mutated NSCLC	Metastatic EGFR-mutated NSCLC
Number of lines of previous treatment	Median of 4 (range, 1–9) prior lines of systemic therapy. 89% received prior osimertinib and 80% received prior PBC	Median of 3 (range, 1–11) prior lines of systemic therapy. Previously treated with EGFR TKI and PBC. 92.9% received osimertinib
Sample size	Dose escalation: 36 patients Dose expansion: 45 patients	Fixed dose arm: 225 patients Uptitration arm: 51 patients
Sites	Global	Global
Design	Dose escalation: HER3-DXd (once every 3 weeks): 3.2 mg/kg (n = 4), 4.8 mg/kg (n = 15), 5.6 mg/kg (n = 12), and 6.4 mg/kg (n = 5) Dose expansion: 5.6 mg/kg (n=45)	Arm 1: a fixed-dose regimen of HER3-DXd 5.6 mg/kg (n=225) Arm 2: an uptitration regimen: cycle 1 day 1, 3.2 mg/kg; cycle 2 day 1, 4.8 mg/kg; cycle 3 day 1; and subsequent cycles, 6.4 mg/kg (n=51)
ORR	39% (Pooled HER3-DXd 5.6 mg/kg) (n = 57)	29.8% (Fix dose of HER3-DXd 5.6 mg/kg) (n = 225)
DOR (Months)	6.9 (Pooled HER3-DXd 5.6 mg/kg) (n = 57)	6.4 (Fix dose of HER3-DXd 5.6 mg/kg) (n = 225)
PFS (Months)	8.2 (Pooled HER3-DXd 5.6 mg/kg) (n = 57)	5.5 (Fix dose of HER3-DXd 5.6 mg/kg) (n = 225)
OS (Months)	NE (Pooled HER3-DXd 5.6 mg/kg) (n = 57)	11.9 (Fix dose of HER3-DXd 5.6 mg/kg) (n = 225)
Grade 3–4 AE Rate	74% (Pooled HER3-DXd 5.6 mg/kg) (n = 57)	64.9% (Fix dose of HER3-DXd 5.6 mg/kg) (n = 225)
TEAE Associated Death Rate	7% (Pooled HER3-DXd 5.6 mg/kg) (n = 57)	1.8% (Fix dose of HER3-DXd 5.6 mg/kg) (n = 225)

Abbreviations: AE, adverse effect; DOR, duration of response; EGFR, Epidermal Growth Factor Receptor; NE, not estimable; NSCLC, Non-Small Cell Lung Cancer; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitors.

demographic distribution of Asian versus non-Asian patients, and the number of previous treatment lines administered to the patients.[16] CNS metastases are observed in approximately 70% of patients with advanced EGFR-mutated NSCLC.[18] In this context, HER3-DXd has been effective, showing clinically meaningful responses in treating NSCLC with brain metastases. Increasing evidence is highlighting the potential for intracranial responses with large-molecule therapies.[19]

Ongoing Trials for HER3-DXd

The Phase 3 HERTHENALung02 trial is currently in progress, enrolling approximately 560 patients with locally advanced or metastatic non-squamous NSCLC harboring an EGFR-activating mutation. These patients, having undergone one or two lines of approved EGFR TKI treatment (including a third-generation EGFR TKI), are being randomized in a 1:1 ratio to receive either HER3-DXd or PBC. The primary endpoint is PFS, and the main secondary endpoint is OS. The trial commenced enrollment in August 2022, is expected to be completed by August 2026.[20]

Preclinical studies indicate that while resistance mechanisms to EGFR TKIs may not result in changes to HER3, the inhibition of EGFR can provoke a compensatory increase in HER3 membrane expression. Consequently, targeting HER3 could potentially enhance the efficacy of EGFR TKI therapy.[21] A Phase 1 trial is currently exploring the combination of HER3-DXd and osimertinib as a first-line therapy for NSCLC patients with EGFR mutations.[22]

FLAURA-2, MARIPOSA, and MARIPOSA-2

The treatment landscape for EGFR-mutated NSCLC has significantly evolved over recent decades. Initially, standard chemotherapy provided a PFS of 4–6 months. The introduction of first- and second-generation EGFR TKIs extended PFS to 10–15 months.[23,24] The latest advancement, the third-generation EGFR TKI osimertinib, further improved PFS to 18.9 months.[25]

Current clinical trials, including HERTHENA-Lung01 and HERTHENA-Lung02 studies, primarily focus on overcoming EGFR resistance after first-line treatment failure. In contrast, trials like FLAURA-2 and MARIPOSA aim to enhance first-line therapy to improve initial PFS (Table 2). The FLAURA-2 trial[2] (a global Phase III trial) has shown that first-line therapy combining osimertinib with chemotherapy significantly extends PFS compared to osimertinib monotherapy in advanced NSCLC patients with EGFR mutations (29.4 vs 19.9 months, hazard ratio [HR] = 0.62). The regimen involves four cycles of chemotherapy (pemetrexed and either cisplatin or carboplatin) with osimertinib followed by maintenance therapy with pemetrexed and osimertinib, which suggests that early integration and consistent administration of chemotherapy enhance clinical outcomes by delaying disease progression and improving overall response rates. The FLAURA-2 regimen has subsequently been FDA approved in February 2024. MARIPOSA is another global phase III study, where EGFR mutated NSCLC patients were randomized in a 2:2:1 ratio, to receive a combination of amivantamab + lazertinib, osimertinib, or lazertinib.[4] Lazertinib, an integral part of this trial, is a highly selective, third-

Table 2 Efficacy and Safety Comparison Among FLAURA2 and MARIPOSA

Trial Name	FLAURA-2	MARIPOSA
Phase	III	III
Patient selection	EGFR-mutated NSCLC	EGFR-mutated NSCLC
Line of therapy	First line	First line
Sample size	557 patients	1074 patients
Sites	Global	Global
Design	Arm A: Osimertinib + chemo (n=279) Arm B: Osimertinib (n=278)	Arm A: Amivantamab + Lazertinib (n=429) Arm B: Osimertinib (n=429) Arm C: Lazertinib (n=216)
Stratification factors	Race (Chinese-Asian/ non-Chinese Asian/ non-Asian), EGFR mutation (local/ central test), WHO PS 0/1	EGFR mutation types (Ex19del or L858R), Asian race, CNS metastases
ORR	A: 83% B: 76%	A: 86% B: 85%
DOR (Months)	A: 24 B: 15.3	A: 25.8 B: 16.8
PFS (months)	A: 29.4 B: 19.9	A: 23.7 B: 16.6 C: 18.5
OS (Months)	Immature	Immature
Grade 3–4 AE Rate	A: 64% B: 27%	A: 75% B: 43%
TEAE Associated Death Rate	A: 1.8% B: 0.4%	A: 8% B: 7%

Abbreviations: AE, adverse effect; CNS, Central Nervous System; DOR, duration of response; EGFR, Epidermal Growth Factor Receptor; NSCLC, Non-Small Cell Lung Cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, Performance Status; TEAE, Treatment-Emergent Adverse Event; WHO, World Health Organization.

generation TKI with strong CNS penetration, known for its effectiveness in addressing activating EGFR mutations and overcoming T790M resistance.[26,27] Meanwhile, amivantamab, a bispecific antibody targeting EGFR and MET with activity directed at immune cells,[28–30] has been approved for treating patients with EGFR exon 20 insertion mutations. PFS was substantially extended with amivantamab + lazertinib versus osimertinib (23.7 vs 16.6 months). The combination of amivantamab and lazertinib was associated with a higher incidence of treatment-emergent adverse events compared to osimertinib alone. For instance, 15% of patients in the combination group experienced grade 3 or higher rash, while only 1% of patients in the osimertinib group faced the same severity. Additionally, treatment-related adverse events leading to discontinuation occurred in 10% of patients treated with amivantamab and lazertinib, compared to 3% with osimertinib. These findings underscore the importance of carefully managing and understanding adverse reactions in combination therapies to optimize patient outcomes. FLAURA-2 and MARIPOSA trials affirm the effectiveness of augmenting initial therapy to delay EGFR-TKI resistance in NSCLC. Data show that incorporating agents like amivantamab or chemotherapy with third-generation EGFR TKIs extends the pre-resistance period by 8.8–9.5 months in FLAURA-2 and 7.1 months in MARIPOSA, highlighting a significant enhancement in disease management.

Not to be confused with MARIPOSA is the MARIPOSA-2[31] trial, a study focusing on second-line treatment for advanced NSCLC with EGFR mutation post-osimertinib, revealed that PFS was significantly longer for amivantamab + chemotherapy and amivantamab + lazertinib+ chemotherapy versus chemotherapy (median of 6.3 and 8.3 versus 4.2 months, respectively). Patients with a history of brain metastasis who had not previously undergone brain radiation also experienced comparable improvements. The augmentation in intracranial PFS observed with amivantamab treatment might be ascribed to its direct antitumor effects or, alternatively, to its ability to modulate the immune system, thereby exerting an indirect therapeutic impact.

Is a Median PFS of 5.5 Months in HERTHENA-LUNG 01 Sufficient in Light of FLAURA-2 and MARIPOSA Studies?

The FLAURA 2 trial demonstrated a notable PFS of 29.4 months, whereas the combination therapy of osimertinib with lazertinib and PBC in the MARIPOSA 2 trial yielded an aggregated PFS of 27.2 months (calculated as 18.9 months for osimertinib monotherapy plus an additional 8.3 months from amivantamab + lazertinib +PBC). A significant consideration in this therapeutic landscape is the potential early exhaustion of PBC options. The FLAURA 2 and MARIPOSA 2 regimens, while effective, may deplete PBC as a viable treatment option in subsequent lines of therapy. In contrast, the strategy of employing osimertinib in combination with a HER3 Dxd offers a notable advantage by sparing patients from immediate PBC utilization. This approach is especially pertinent for patients ineligible for platinum therapy, or when the preference would be to preserve PBC for future lines of treatment (ie, low tumor burden) when resistance to other agents becomes predominant.

It is important to note that in this phase II trial (HERTHENA-LUNG 01), HER3-Dxd exhibited a PFS of 5.5 months in a cohort that had previously been treated with osimertinib and chemotherapy. Transitioning directly to HER3 Dxd following osimertinib treatment in a phase III setting (HERTHENA-Lung02) presents a substantial opportunity to surpass this PFS benchmark. Achieving a PFS exceeding 5.5 months with HER3 Dxd alone could potentially align with, or even exceed, outcomes observed in other trials. Specifically, to surpass the PFS outcomes of FLAURA 2, an extension of 9–10 months is required; for MARIPOSA, an improvement of 4–5 months; and for MARIPOSA 2, an increase of 8–9 months. Notably, even an incremental improvement in PFS over the FLAURA 2 or MARIPOSA-2 results could be clinically significant, offering a treatment option that conserves PBC for later use.

Optimizing Strategies During the Interim: Awaiting Further Data in Clinical Research

As oncologists, while awaiting for more comprehensive data, we can still make effective use of current research to guide our treatment approaches. Based on insights from the FLAURA-2 trial, integrating osimertinib with chemotherapy as a first-line treatment appears to enhance patient outcomes significantly. In cases where disease progression occurs, and specific resistance mutations such as the C797S mutations are identified, shifting to a 4th-generation EGFR inhibitor on a clinical trial could be a strategic choice. For other situations, considering combinations such as amivantamab+ lazertinib+ chemotherapy, or exploring the use of HER3-DXd, may offer viable alternatives. Nevertheless, a deeper

understanding and additional data, especially from the ongoing HERTHENA-Lung02 will be crucial in further refining these treatment strategies and ensuring the best possible care for our patients.

Conclusion

The evolving landscape of EGFR-mutated NSCLC treatment, particularly in the context of resistance to EGFR TKIs, is marked by significant advancements and challenges. Although osimertinib is very effective as an initial treatment, the eventual development of resistance necessitates innovative therapeutic strategies. The integration of intensified initial treatments, for instance, integrating a third-generation EGFR TKI with chemotherapy (FLAURA2) or using an EGFR-MET bispecific agent (MARIPOSA) has shown promise. Moreover, the exploration of broader approaches, including chemotherapy, ADCs, and combination therapies, continues to be vital.

The role of HER3 in EGFR-TKI resistance in EGFR-mutated NSCLC, highlighted by the increased HER3 expression following EGFR TKI progression, has opened new therapeutic avenues. Patritumab deruxtecan, an ADC targeting HER3, has exhibited notable efficacy in heavily pretreated EGFR-mutated NSCLC patients as demonstrated in HERTHENA-Lung01 trial. The ongoing HERTHENALung02 trial is set to provide further insights, particularly in assessing the potential of HER3-DXd in extending PFS compared to standard treatments. This study, along with others like FLAURA-2, MARIPOSA, and MARIPOSA 2, will help to refine and optimize treatment strategies for EGFR-mutated NSCLC.

Abbreviations

ADC, Antibody–Drug Conjugate; BLA, Biologics License Application; CI, Confidence Interval; CNS, Central Nervous System; EGFR, Epidermal Growth Factor Receptor; FDA, US Food and Drug Administration; HER, Human Epidermal Growth Factor Receptor; HR, Hazard Ratio; ICI, Immune Checkpoint Inhibitor; mPFS, Median Progression-Free Survival; NSCLC, Non-Small Cell Lung Cancer; ORR, Objective Response Rate; OS, Overall Survival; PBC, Platinum-Based Chemotherapy; TKI, Tyrosine Kinase Inhibitor; TRAE, Treatment-Related Adverse Event.

Ethics Statement

This commentary is based on publicly available, de-identified clinical trial data and does not require IRB approval.

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