A New Frontier in the Treatment of Epidermal Growth Factor Receptor-mutated Non–Small-Cell Lung Cancer: Amivantamab-vmjw and Chemotherapy

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Until recently, chemotherapy had been the standard of care for patients with advanced non–small-cell lung cancer (NSCLC) with classical epidermal growth factor receptor (EGFR) mutations progressing on osimertinib. It also remained as the first-line treatment for patients with advanced NSCLC harbouring EGFR exon 20 insertions. The recent results from the MARIPOSA-2 and PAPILLON phase III clinical trials demonstrate that the addition of amivantamab-vmjw, a bispecific antibody targeting the EGFR and mesenchymal–epithelial transition factor pathways, to chemotherapy offers improved clinical benefits in both settings when compared with chemotherapy alone.

Keywords

Amivantamab, chemotherapy, clinical trials, epidermal growth factor receptor, lung cancer, non–small-cell lung cancer, precision medicine, targeted therapy

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Unmet clinical needs for patients with advanced epidermal growth factor receptor-mutated non–small-cell lung cancer

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) have become the standard first-line therapy for patients with advanced non–small-cell lung cancer (NSCLC) harbouring a classical activating EGFR mutation (exon 19 deletion or exon 21 L858R). Osimertinib, a third-generation EGFR-TKI, is the preferred option. However, resistance inevitably occurs. For these patients, chemotherapy remains the standard of care, with limited benefits.[1]

Following exon 19 deletions and exon 21 L858R mutations, EGFR exon 20 insertions represent the third most common type of EGFR mutations, accounting for 4–10% of all EGFR mutations.[2] In contrast to the classical activating EGFR mutations, EGFR exon 20 insertions are consistently associated with *de novo* resistance to clinically approved EGFR-TKIs, including osimertinib.[3] Therefore, the recommended first-line treatment is platinum-doublet chemotherapy in spite of poor outcomes; the overall response rate (ORR) is 19%, and the median progression-free survival (mPFS) remains under 6 months.[4] Based on the phase I CHRYSALIS study (A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer; ClinicalTrials.gov identifier: NCT02609776), amivantamab-vmjw is now approved in pretreated patients with NSCLC harbouring EGFR exon 20 insertion mutations.[1,5]

Amivantamab-vmjw is a bispecific monoclonal antibody with immune cell-directing activity and high-affinity binding to both EGFR and mesenchymal–epithelial transition (MET) factor.[6] As amivantamab targets the extracellular domains of EGFR and MET, it can inhibit both pathways independently of their intracellular driver mutations or any resistance mutations acquired during the treatment.[7] As opposed to EGFR-TKIs, it is administered intravenously. Its unique mechanisms of action positioned amivantamab as an innovative therapeutic agent for the treatment of patients with EGFR-mutated NSCLC.[1]

Amivantamab for patients with advanced non–small-cell lung cancer harbouring epidermal growth factor receptor exon 20 insertions

In May 2021, amivantamab was granted accelerated approval by the Food and Drug Administration (FDA).[8] In January 2023, it was also approved by the European Medicines Agency for the treatment of patients with locally advanced or metastatic NSCLC carrying EGFR exon 20 insertion mutations after progression to platinum-based chemotherapy.[9] The approval was based on the preliminary results of the phase I CHRYSALIS study; updated results of 114 patients were presented at the European Lung Cancer Congress 2023.[5,10] After a median follow-up of 19.2 months, the median overall survival was 23 months. The ORR was 37%, the median duration of response (mDoR) was 12.5 months and the mPFS was 6.9 months. Toxicity was usually of low grade; the most common side effects were rash, paronychia and stomatitis. In addition, infusion-related reactions (IRRs)

Table 1: Clinical efficacy of amivantamab in different scenarios[5,12–15]

	EGFR exon 20 insertion		EGFR ex19del/L858R			
Treatment	Amivantamab	Amivantamab + chemotherapy	Amivantamab + lazertinib	Amivantamab + lazertinib + chemotherapy	Amivantamab + chemotherapy	Amivantamab + lazertinib + chemotherapy
Trial name	CHRYSALIS[5]	PAPILLON[12]	CHRYSALIS-2[13]	CHRYSALIS-2[14]	MARIPOSA-2[15]	MARIPOSA-2[15]
Phase	I	III	I	I	III	III
Previous lines of therapy	≥2	0	2 (osimertinib and platinum-based chemotherapy)	≥1 (EGFR-TKI most recent line)	1 (osimertinib)	1 (osimertinib)
Number of patients	81	308 (randomized 1:1 versus chemotherapy alone)	50	20	657 (randomized 2:2:1 to amivantamab-chemotherapy, chemotherapy and amivantamab-lazertinib-chemotherapy)	657 (randomized 2:2:1 to amivantamab-chemotherapy, chemotherapy and amivantamab-lazertinib-chemotherapy)
ORR (%)	40	73 (versus 47 with chemotherapy alone)	36	50	64 (versus 36 with chemotherapy)	63 (versus 36 with chemotherapy)
mDoR (months)	12.5	9.7 (versus 4.4 with chemotherapy alone)	NE	NE	6.9 (versus 5.6 with chemotherapy)	9.4 (versus 5.6 with chemotherapy)
mPFS (months)	8.3	11.4 (versus 6.7 with chemotherapy alone)	NE	14	6.3 (versus 4.2 with chemotherapy)	8.3 (versus 4.2 with chemotherapy)

EGFR = epidermal growth factor receptor; mDoR = median duration of response; mPFS = median progression-free survival; NE = not estimated; ORR = objective response rate; TKI = tyrosine kinase inhibitor.

are commonly reported (67% of overall and 2–7% of grade 3 reactions), particularly with the first and second cycles. Mitigation strategies include, among others, the administration of a first dose of amivantamab in a 'split manner' in two consecutive days.[11]

The phase III PAPILLON study (A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared With Carboplatin-Pemetrexed, in Patients With EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer; ClinicalTrials.gov identifier: NCT04538664) is a confirmatory randomized study exploring the benefit of amivantamab in combination with carboplatin–pemetrexed chemotherapy compared with chemotherapy alone in the first-line treatment setting. The results were presented at the European Society for Medical Oncology (ESMO) 2023 Annual Congress, with simultaneous publication of the manuscript.[12] Overall, 308 patients with EGFR exon 20 insertion advanced NSCLC were randomized to receive either chemotherapy alone or combination with amivantamab, with a clinically significant benefit in progression-free survival (PFS) favouring the amivantamab–chemotherapy group and a longer median duration of treatment. The mPFS was 11.4 versus 6.7 months; the hazard ratio (HR) was 0.40. Adverse events (AEs) related to EGFR and MET inhibition were increased with the amivantamab combination, which were mostly grades 1–2. Serious AEs and rates of discontinuation were comparable between arms. Based on these results, amivantamab plus chemotherapy emerges as a potential new frontline standard of care for patients with advanced EGFR exon 20 insertion mutation NSCLC (*Table 1*).[5,12–15]

So far, there are no other targeted therapies approved for EGFR exon 20 insertion mutations. Mobocertinib, an EGFR-TKI, was initially approved by the FDA in pretreated patients based on the results of a single-arm phase I–II trial, which confirmed its clinical activity in this population, with an objective response rate of 43%, mDoR of 14 months and mPFS of 7.3 months.[16,17] In the first-line setting, the phase III EXCLAIM-2 trial (A Randomized Phase 3 Multicenter Open-Label Study to Compare the Efficacy of TAK-788 as First-Line Treatment Versus Platinum-Based Chemotherapy in Patients With Non-Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations; ClinicalTrials.gov identifier: NCT04129502) explored the role of mobocertinib for untreated patients with advanced NSCLC harbouring EGFR exon 20 insertion mutations. Patients were randomized to mobocertinib 160 mg daily versus platinum–pemetrexed chemotherapy. The efficacy of mobocertinib was similar but not superior to platinum-based chemotherapy. Objective response rates were 32 and 30% for mobocertinib and chemotherapy, respectively; and the mPFS was also similar between arms (mobocertinib 9.59 months and chemotherapy 9.63 months). The study met the prespecified futility criteria (PFS HR >1).[18] Based on these results, the company decided to voluntarily withdraw mobocertinib from use in the USA.[19]

Other agents, such as sunvozertinib (A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer [NSCLC] With EGFR or HER2 Mutation; ClinicalTrials.gov identifier: NCT03974022), furmonertinib (A Phase Ib, Randomized, Open-label, Multi-center Study to Evaluate the Preliminary Efficacy and Safety of Furmonertinib Mesilate in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer Harboring EGFR Exon 20 Insertion Mutation; ClinicalTrials.gov identifier: NCT04858958) and zipalertinib (A Phase 1/2, Open-Label, Multi-Center Trial to Assess Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of CLN-081 in Patients With Locally-Advanced or Metastatic Non-Small Cell Lung Cancer Harboring EGFR Exon 20 Insertion Mutations Who Have Previously Received Platinum-Based Systemic Chemotherapy; ClinicalTrials.gov identifier: NCT04036682), are currently under investigation in clinical trials.[3,20–22]

Amivantamab in patients with advanced non–small-cell lung cancer harbouring classical epidermal growth factor receptor mutations after progression on osimertinib

Despite the efficacy of osimertinib in patients harbouring tumours with classical EGFR mutations, progression inevitably occurs.

The phase I multicohort study CHRYSALIS-2 (An Open-label Phase 1/1b Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 [Lazertinib], a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer; ClinicalTrials.gov identifier: NCT04077463) is exploring the role of amivantamab in the post-osimertinib setting.[23] The results from the cohort combining amivantamab with lazertinib (a third-generation EGFR-TKI) and platinum-doublet chemotherapy were recently presented at the World Conference in Lung Cancer 2023.[24] Among the 20 patients enrolled, the ORR was 50%, with an mPFS of 14 months, and 80% of patients were alive at 1 year. No new safety signals were seen, except for the high rates of grade 3 cytopaenia.[14]

To confirm these results, a combination of amivantamab, lazertinib and platinum-doublet chemotherapy has been evaluated in the phase III, randomized MARIPOSA-2 trial (A Phase 3, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure; ClinicalTrials.gov identifier: NCT04988295).[15] In this study, patients with locally advanced or metastatic NSCLC with EGFR ex19del or L858R mutation progressing to first-line osimertinib were randomized to treatment with amivantamab plus platinum-based chemotherapy, amivantamab plus platinum-based chemotherapy with lazertinib or platinum-based chemotherapy alone. The results were presented at the ESMO 2023 Annual Congress; the trial met its dual primary endpoint, showing a statistically significant improvement in PFS for amivantamab plus chemotherapy in both arms (with or without lazertinib) versus chemotherapy alone.[15] Amivantamab in combination with chemotherapy improved PFS over chemotherapy, with an mPFS of 6.3 versus 4.2 months and an HR of 0.48. Interestingly, adding lazertinib to the regimen provided similar outcomes, with an HR of 0.44 but with more toxicity, including higher rates of thrombocytopaenia, neutropaenia and venous thromboembolism. Amivantamab plus chemotherapy after progression on osimertinib may represent a new standard of care for this patient population.

Current challenges and future directions

Understanding the central nervous system (CNS) activity of new agents is crucial, as brain metastases arise in about one-third of all patients with EGFR-mutant NSCLC, with comparable frequency between classical EGFR and EGFR exon 20 insertion-mutant subgroups. Importantly, the MARIPOSA-2 study showed an improved intracranial PFS with amivantamab + chemotherapy versus chemotherapy alone (HR 0.55 and median intracranial PFS 12.5 versus 8.3 months); adding lazertinib did not improve CNS outcomes. Specifically, in patients with brain metastases and no prior brain radiation, the intracranial PFS was also improved with amivantamab + chemotherapy (HR 0.36), suggesting intracranial activity of amivantamab.[15]

Biweekly intravenous administration of amivantamab, with IRRs arising in about 67% of patients in the first cycle and requiring splitting the first dose over 2 days, may be challenging. To facilitate the administration and tolerability in clinical practice, the safety and efficacy of amivantamab via subcutaneous administration are being explored in the PALOMA trials (An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Amivantamab, a Human Bispecific EGFR and cMet Antibody for the Treatment of Advanced Solid Malignancies, ClinicalTrials.gov identifier: NCT04606381; A Phase 2, Open-Label, Parallel Cohort Study of Subcutaneous Amivantamab in Multiple Regimens in Patients With Advanced or Metastatic Solid Tumors Including EGFR-mutated Non-Small Cell Lung Cancer, ClinicalTrials.gov identifier: NCT05498428; and A Phase 3, Open-label, Randomized Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Patients With EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy, ClinicalTrials.gov identifier: NCT05388669).[25] The preliminary results presented at the 2023 American Society of Clinical Oncology Annual Meeting showed improved tolerability and reduced administration time.[25]

Additionally, novel regimens combining amivantamab with other agents such as capmatinib (A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Capmatinib Combination Therapy in Unresectable Metastatic Non-small Cell Lung Cancer; ClinicalTrials.gov identifier: NCT05488314) or cetrelimab (A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Cetrelimab Combination Therapy in Metastatic Non-small Cell Lung Cancer; ClinicalTrials.gov identifier: NCT05908734) are under investigation in phase I/II clinical trials.[26,27]

On the other hand, the combination of amivantamab with platinum-based chemotherapy has a manageable safety profile, but it can be hard to tolerate in less-fit patients. Single-agent amivantamab demonstrated clinical activity in the CHRYSALIS phase I trial, in both EGFR exon 20 insertion mutation and common EGFR mutations post-osimertinib.[10,28] Based on these data, further studies exploring the role of amivantamab monotherapy in unfit patients are warranted, especially in patients ineligible for platinum-based chemotherapy.

Finally, the role of amivantamab in other clinical scenarios, such as the adjuvant setting in patients with EGFR+ resected NSCLC or for locally advanced unresectable NSCLC EGFR+, may warrant further investigation in the future.

Conclusion

Amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity, has been established as a new standard of care in the first line in combination with chemotherapy for patients with advanced NSCLC harbouring EGFR exon 20 insertions, following the results from the PAPILLON phase III study. Additionally, amivantamab is positioned as a promising therapeutic agent in the treatment of patients with advanced NSCLC harbouring classical EGFR mutations after osimertinib, with positive results in the PFS with platinum-based chemotherapy versus chemotherapy alone in the MARIPOSA-2 trial. Pending long-term follow-up to determine the magnitude of benefit in the overall survival and quality-of-life outcomes, it seems that a new era has begun for patients with advanced EGFR-mutated NSCLC. ❑

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