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EDITORIAL

Will CHRYSALIS turn into a butterfly?

On 9 December 2021, the European Commission granted conditional marketing approval (CMA) of amivantamab for the treatment of adult patients with advanced non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) exon 20 insertion (Exon20ins) mutations, after failure of platinum-based therapy. The approval is mainly based on the findings of the single-arm, dose-escalation and dose-expansion phase I CHRYSALIS study.[1] The ongoing CHRYSALIS study is evaluating the efficacy—as determined by overall response rate (ORR)—and safety of amivantamab in advanced NSCLC patients with activating EGFR or mesenchymal–epithelial transition factor (c-MET) mutations or amplifications in six cohorts. The EGFR Exon20ins cohort consisted of 114 patients in the safety and efficacy population.

Initially, the results from the CHRYSALIS study were published by Park et al. with 9.7 (1.1-29.3) months' duration of follow-up. The CMA is based on a longer follow-up period (12.5 and 14.5 months) published in the summary of product characteristics and European public assessment report.[2,3]

An investigator-assessed ORR of 37% [95% confidence interval (CI) 28% to 46%] was reported. Responses were durable with a median duration of response (DoR) of 12.5 months (95% CI 6.5-16.1 months). Blinded independent central review (ICR) assessment showed an ORR of 43% (95% CI 34% to 53%) and a DoR of 10.8 months (95% CI 6.9-15.0 months). Additionally, 55% of patients had a DoR $\geq$6 months. The median progression-free survival (PFS) in the efficacy population (81 patients with a follow-up of 14.5 months) was 8.3 months (95% CI 5.5-12.3 months) by investigator assessment and by ICR 8.3 months (95% CI 5.5-11.1 months). In the total population (114 patients with a follow-up of 12.5 months), the PFS was 6.9 months (95% CI 5.6-8.6 months) by investigator assessment and 6.7 months (95% CI 5.5-9.7 months) by ICR.

The median overall survival (OS) for 81 patients and 14.5 months of follow-up and for 114 patients and 12.5 months of follow-up was 22.8 months (95% CI 17.5 months-not reached) in both populations.[1-3]

Amivantamab had a favorable toxicity profile: Rash, infusion-related reactions and nail toxicity reported in 76%, 67% and 47% of patients, respectively, were the most common adverse events. The most common grade 3-4 adverse events were rash (3%), hypoalbuminemia, diarrhea, liver toxicity, nail toxicity and infusion-related reactions (3%). Dose reductions due to adverse events occurred in 22 patients (14.4%) out of 151 subjects in the Exon20ins plus prior chemotherapy group. Treatment-related dose discontinuations were reported in 21 patients (4.3%).[3]

EGFR EXON 20 INSERTIONS IN NSCLC

Following classical activating EGFR mutations such as exon 19 deletions or L859R exon 21 mutations, Exon20ins mutations represent the third most common activating EGFR mutation subtype in NSCLC patients.[4,5] EGFR Exon20ins mutations are detected in ~0.1%-4% of the NSCLC cases.[6,7] While common EGFR mutations are more frequently diagnosed in Asian patients compared to Caucasian ones, no such distribution is found in EGFR Exon20ins patients.[8] Female gender and smoking status (never smoker) seem to be associated with EGFR Exon20ins mutations.[9]

First- to third-generation EGFR tyrosine kinase inhibitors (TKIs) approved in NSCLC patients harboring activating EGFR mutations demonstrated only limited efficacy with an ORR $<$10% in the EGFR Exon20ins population.[7,10,11] Additionally, those patients have a dismal prognosis and inferior PFS compared to classical EGFR-mutated NSCLC patients (14 versus 2 months, $P < 0.0001$).[11]

Platinum-based chemotherapy leads to superior PFS in EGFR Exon20ins patients compared to all-generation EGFR TKIs (6.4 months; 95% CI 5.7-7.1 months versus 2.9 months; 95% CI 1.5-4.3 months; $P < 0.001$)[12] and is considered as the standard-of-care first-line therapy in the daily clinical routine outside of clinical trials.

As for immunotherapy, data are still scarce: A retrospective analysis showed that patients with EGFR Exon20ins treated with immune checkpoint inhibitors had a PFS of 1.9 months, a median OS of 5.5 months and an ORR of 10.7%.[13] The prevalence of programmed death-ligand 1 positivity (tumor proportion score $\geq$1%) is low in such patients (45% of the patients) accompanied with a low tumor mutational burden.[14]

From this background, it is obvious that 'an unmet clinical need has to be addressed in NSCLC patients harboring EGFR Exon20ins mutations' paving the way for amivantamab's CMA by the European authorities.

AMIVANTAMAB

Amivantamab is a first-in-class fully humanized EGFR-MET bispecific antibody. Amivantamab exerts its activity by (i) inhibition of epidermal growth factor and hepatocyte growth factor ligand binding, (ii) EGFR and MET internalization and degradation and (iii) immune cell directing activity such as antibody-dependent cellular cytotoxicity or trogocytosis.[15,16]

Table 1. Key studies of amivantamab conducted in advanced/metastatic NSCLC including the PALOMA trial conducted in solid tumors

Identifier	Drug	Indication	Phase
NCT02609776 **CHRYSALIS**	Amivantamab plus/minus lazertinib or plus carboplatin/ pemetrexed	Activating EGFR or MET mutations or amplifications and progressed on previous therapy	I
NCT04077463 **CHRYSALIS-2**	Lazertinib plus/minus amivantamab or plus amivantamab plus chemotherapy	Activating EGFR mutations including EGFR Exon20ins, uncommon mutations or after osimertinib failure	I
NCT04606381 **PALOMA**	Subcutaneous amivantamab plus/minus recombinant human hyaluronidase	Advanced solid tumors	I
NCT04965090	Amivantamab plus lazertinib	Activating EGFR mutations with new or progressing CNS metastases or leptomeningeal disease	II
NCT04538664 **PAPILLON**	Amivantamab plus carboplatin/pemetrexed versus carboplatin/pemetrexed		III
NCT04487080 **MARIPOSA**	Amivantamab plus lazertinib versus osimertinib versus lazertinib	Exon 19del or exon 21 L858R EGFR mutation in the first-line setting	III
NCT04988295 **MARIPOSA-2**	Amivantamab plus lazertinib plus carboplatin/pemetrexed versus carboplatin/pemetrexed versus amivantamab plus carboplatin/pemetrexed	Exon 19del or exon 21 L858R EGFR mutation and progressed on or after osimertinib	III

CNS, central nervous system; EGFR, epidermal growth factor receptor; MET, mesenchymal—epithelial transition; NSCLC, non-small-cell lung cancer.

Given its broad activity profile, amivantamab is developed not only in EGFR Exon20ins-mutated NSCLC, but also in common EGFR-mutated NSCLC as monotherapy or in combination with lazertinib or chemotherapy, after osimertinib failure and in MET-amplified or MET exon 14 skipping mutated tumors (Table 1).

Although the results of the CHRYSALIS trial are impressive in the EGFR Exon20ins cohort and the CMA seems to be well deserved given the high medical need in this setting, there are still a couple of unresolved questions, which have to be answered to define amivantamab's role in this population:

Besides amivantamab, TKIs such as mobocertinib or poziotinib are developed for the treatment of EGFR Exon20ins-mutated NSCLC. The Food and Drug Administration-approved oral TKI mobocertinib demonstrated in a single-arm phase I/II study in 114 platinum-pretreated patients an ICR-assessed ORR of 28% (95% CI 20% to 37%) and a median DoR of 17.5 months (95% CI 7.4-20.3 months). The median PFS was 7.3 months (95% CI 5.5-9.2 months), while the OS was 24.0 months (95% CI 14.6-28.8 months).[17] Diarrhea and skin rash were the most common treatment-related adverse events.[17]

Given the limitations of cross-trial comparisons, the activity of mobocertinib seems to be partially comparable to amivantamab, although the ORR was numerically lower. Thus, the optimal approach after platinum failure in EGFR Exon20ins-mutated NSCLC patients remains a matter of debate and is currently guided by the regional approval status of both substances, costs and the differential toxicity profile.

Apart from that, it is unclear if the distinct Exon20ins location (helical region versus near loop or far loop) is associated with response. If yes, the question arises whether combinations with TKIs such as mobocertinib could improve the efficacy of amivantamab.

The optimal combination partner of amivantamab is currently explored in the studies outlined above. There is a sound rationale that full EGFR pathway suppression by amivantamab in combination with lazertinib might further enhance the activity compared to amivantamab monotherapy. Given the immune cell directing activity of amivantamab, it is tempting to speculate that adding (novel) immunotherapies might be effective as well, although no such trials are currently ongoing in this setting.

Most importantly, the randomized phase III PAPILLON trial will evaluate the efficacy as measured by PFS of amivantamab plus chemotherapy versus chemotherapy alone in previously untreated EGFR Exon20ins-mutated stage IV NSCLC patients and has the potential to define a new standard of care in this setting. Since patients with untreated brain metastases will be excluded from this trial (similar to CHRYSALIS), the unknown (but questionable) capability of amivantamab to cross the blood—brain barrier and exert intracranial responses will remain elusive.

Fortunately, an investigator-sponsored study (NCT04965090) conducted at the Memorial Sloan Kettering Cancer Center will evaluate the efficacy of amivantamab plus lazertinib in EGFR-mutated NSCLC with progressive or new central nervous system metastases on previous treatment generating evidence in this setting.

Finally, novel and more convenient subcutaneous amivantamab formulations as tested in the PALOMA trial might circumvent frequent (but mild) infusion reactions.

The CMA of amivantamab in Europe is a huge step forward in the treatment landscape of EGFR Exon20ins-mutated NSCLC. However, for full market approval, CHRYSALIS is not sufficient and amivantamab has to show its beauty as a PAPILLON as well.

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