Editorial Commentary

Will "Sun"-WUKONG, the monkey king, conquer EGFR exon 20 insertion mutation positive non-small cell lung cancer?

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In the classical Chinese novel *Journey to the West*, the monkey king Sun Wukong safeguarded his master on a formidable journey from China to India to collect the Buddhist scriptures. Throughout their 16-year pilgrimage, the fellowship encountered 81 challenges, each tougher than the previous. This long and challenging quest resembles the history of drug development in treating epidermal growth factor receptor (*EGFR*) mutated non-small cell lung cancer (NSCLC), which began 20 years ago when the pathogenic mutation was discovered (1). Significant advances have been achieved in the development of EGFR tyrosine kinase inhibitor (TKI) over the years, and third-generation TKI is now the standard treatment for NSCLC harbouring sensitizing *EGFR* mutations, both in early and late stage disease. However, *EGFR* exon 20 insertion mutations (*EGFR* ex20ins) are resistant to conventional TKIs, and there are no approved TKIs available at present for this difficult-to-treat population (2).

NSCLC harbouring sensitizing *EGFR* mutations such as exon 19 deletion and exon 21 L858R mutation are sensitive to EGFR TKI as the mutant-EGFR exhibits lower affinity for ATP but higher affinity for EGFR TKI compared to its wild-type (WT) counterpart (3). This allows a therapeutic window for EGFR TKI to target tumour cells harbouring mutant EGFR at the cost of low-grade skin and gastrointestinal toxicity related to wild-type EGFR inhibition. In contrast to sensitizing *EGFR* mutations, *EGFR* ex20ins exhibits a unique steric configuration that results in an affinity for conventional TKIs similar to that of WT-EGFR, and therefore it is not feasible to inhibit EGFR ex20ins at a clinically tolerable dose (4). Consequently, patients with *EGFR* ex20ins NSCLC treated with conventional TKIs achieve poor tumour responses and survival outcomes, except for some rare variants such as A763_Y764insFQEA and D770delinsGY which are sensitive to conventional EGFR TKIs (5,6).

The phase III randomized PAPILLON trial compared the combination of amivantamab, an EGFR-MET bispecific antibody, with chemotherapy against chemotherapy alone in patients with treatment-naïve, advanced *EGFR* ex20ins NSCLC. This trial demonstrated superiority of amivantamab-chemotherapy over chemotherapy alone in terms of both progression-free survival (PFS) (median PFS 11.4 *vs.* 6.7 months) and tumour response rates (73% *vs.* 47%) (*Table 1*) (7). While amivantamab plus chemotherapy is now established as the standard first-

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Table 1 Summary of key clinical trials in NSCLC harbouring EGFR exon 20 insertions

Agent	Trial	Comparator	Phase	Median PFS (months)	ORR (%)	Grade ≥3 adverse events (%)
Mobocertinib	EXCLAIM-2	Chemotherapy	III	9.6	32	62
Amivantamab plus chemotherapy	PAPILLON	Chemotherapy	III	11.4	73	75
Sunvozertinib	WU-KONG6	N/A	II	NR	61	45

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; N/A, not applicable; NR, not reached; PFS, progression-free survival; ORR, objective response rate.

line treatment, this regimen is associated with a higher frequency of skin and haematological toxicities and requires parenteral administration (7). More than 50% of patients in the PAPILLON arm developed rash and paronychia, with about 10% being grade 3 or above. Patients treated with amivantamab plus chemotherapy also commonly experienced neutropenia (59% all grade, 33% ≥ grade 3) and infusion-related reactions (42% all grade) (7). Recently, the PALOMA-3 phase III study demonstrated that subcutaneous amivantamab was non-inferior to intravenous amivantamab in terms of pharmacokinetics and treatment efficacies, while associated with significantly less infusion-related reactions and enhanced patient convenience (8). Nonetheless, a "chemotherapy-free" option is not yet available for treatment *EGFR* ex20ins NSCLC. Development of an EGFR ex20ins targeted TKI remains a significant unmet need.

Early development in *EGFR* ex20ins targeted TKI was unsuccessful mainly due to high-incidence of gastrointestinal and dermatological toxicities related to WT-EGFR inhibition. The first reported *EGFR* ex20ins targeted TKI was mobocertinib. In patients with advanced, chemotherapy pre-treated, *EGFR* ex20ins NSCLC enrolled in the phase I/II EXCLAIM study, mobocertinib achieved a response rate of 25% and median PFS of 7.3 months (9). However, 93% of patients suffered from diarrhoea, with 16% being grade 3 or above (9). In the subsequent phase III randomized clinical trial (EXCLAIM-2), mobocertinib failed to demonstrate superiority over platinum-based chemotherapy as first-line treatment. The median PFS was 9.6 months for both mobocertinib and chemotherapy treatment arms (*Table 1*). Importantly, dose intensity was low in the mobocertinib arm, with 70%, 45% and 18% of patients experiencing dose interruption, reduction and discontinuation, respectively, due to side effects. These factors likely contributed to the inferior efficacy observed (10). As a result, Takeda announced to withdraw mobocertinib globally in October 2023. Poziotinib, another EGFR TKI, exhibited moderate response rates and a high incidence of diarrhoea and skin toxicities (11).

Sunvozertinib, also named DZD9008, differs from osimertinib by replacing the methylindole with an anilinophenyl group, which occupies an EGFR ex20ins specific pocket next to the C-helix (12). Preclinical data suggested that sunvozertinib has improved selectivity on EGFR ex20ins over WT-EGFR compared to osimertinib and mobocertinib. The half maximal inhibitory concentration (IC_{50}) values of sunvozertinib for EGFR ex20ins_ASV, EGFR ex20ins_NPH and WT-EGFR were 20, 20 and 80 nM respectively, corresponding to a 4-fold selectivity (12). In comparison, the IC_{50} of mobocertinib on EGFR ex20ins_ASV, EGFR ex20ins_NPH and WT-EGFR were 10.9, 22.5 and 34.5 nM respectively, which only corresponded to a 1.5–3-fold selectivity (13). In the phase I dose-escalation study, the incidence of grade 3 or above diarrhoea was only 5%, and no patients experienced grade 3 or above rash. Treatment efficacy was seen across 100 to 400 mg daily cohorts (12). Sunvozertinib 300 mg daily was chosen for further development.

Recently, Wang *et al.* reported the results of the WU-KONG6 study, a single-arm, multicentre, phase II trial that evaluated sunvozertinib in patients with advanced *EGFR* ex20ins NSCLC (14). This study was conducted exclusively in China. In this study, patients with metastatic *EGFR* ex20ins NSCLC previously treated with platinum-based chemotherapy were enrolled and treated with sunvozertinib 300 mg daily. Patients with prior exposure to EGFR ex20ins targeted TKI or untreated brain metastases were excluded. The primary endpoint was objective response rate (ORR) assessed by independent radiology review among patients with centrally confirmed *EGFR* ex20ins.

A total of 104 patients were enrolled in the study and

of the 97 evaluated patients, 3% had prior amivantamab therapy and 32% had brain metastases at the time of enrolment. At data cut-off, median follow-up time was 7.6 months. In the efficacy analysis, the confirmed ORR was 61% and disease control rate was 88%. Median time to first documented response was 43 days. ORRs were similar among patients with EGFR 769_ASV (63%), 770_SVD (59%), and other mutations (60%). Two out of 3 patients who had previously been treated with amivantamab achieved partial response. Median PFS and OS were not mature at data cut-off (*Table 1*).

Despite the short follow up, tumour response with sunvozertinib was comparable to those of conventional TKI in treating NSCLC harbouring sensitizing *EGFR* mutations, and was clearly superior to mobocertinib and amivantamab monotherapy in the context of *EGFR* ex20ins. Encouragingly, clinical benefit was observed across different subtypes of *EGFR* ex20ins. This is an important feature, as different *EGFR* ex20ins subtypes may be associated with varying sensitivity to TKIs. For example, with poziotinib, ORR was 46% versus 0% in patients with near- and far-loop insertions, respectively (11).

Regarding safety of sunvozertinib, 45% of patients reported grade 3 or worse treatment-related adverse events (TRAEs) (14). The most common grade 3 or worse TRAE was increased blood creatine phosphokinase (17%). Regarding on-target toxicities, 8% of patients experienced grade 3 or worse diarrhoea and 3% of patients experienced grade 3 or worse stomatitis. Dose interruption, reduction and discontinuation rates occurred in 38%, 29% and 10% of patients, respectively. Overall, the toxicity profile compared favourably to that of mobocertinib in the EXCLAIM-2 study (10).

Based on WUKONG-6, sunvozertinib was approved in China for patients with advanced, platinum-pretreated, *EGFR* ex20ins NSCLC in August 2024. Recently, Yang *et al.* reported the primary analysis of the WU-KONG1 study, a global study that evaluated sunvozertinib in the same setting as WUKONG-6 (15). The outcomes were similar to those of WUKONG-6: among 107 patients treated, confirmed ORR was 45% and the 9-month duration of response was 57%. 17% of patients reported grade 3 or worse diarrhoea. Currently, a global phase 3 study is ongoing (WU-KONG28) to compare sunvozertinib with platinum-based chemotherapy as first-line treatment for patients with advanced *EGFR* ex20ins NSCLC. About 320 patients will be enrolled into this study and randomized 1:1 to receive sunvozertinib monotherapy or platinum-pemetrexed chemotherapy. The primary endpoint is PFS.

If WU-KONG28 is positive, this could definitively establish the role of TKI in treating *EGFR* ex20ins NSCLC. Aside sunvozertinib, several EGFR ex20ins targeted TKIs, such as furmonertinib and zipalertinib, have also demonstrated promising efficacies. In a phase Ib study, furmonertinib achieved an ORR of 69% and median PFS of 10.7 months in patients with treatment-naïve advanced *EGFR* ex20ins NSCLC (n=30) (16). Zipalertinib achieved an ORR of 38% and median PFS of 10 months among 73 patients with heavily pretreated advanced disease, including those who had been treated with EGFR ex20ins targeted TKI (17). Both agents are now tested in the first-line setting. In the FURVENT study, patients are randomized to furmonertinib monotherapy or platinum-based chemotherapy (NCT05607550). In the REZILIENT3 study, patients are randomized to zipalertinib plus chemotherapy, versus chemotherapy alone (NCT05973773).

Although the WUKONG-6 study represented a major leap in treatment for *EGFR* ex20ins NSCLC, several important questions remain unanswered. Firstly, it is unclear whether sunvozertinib is superior to amivantamab plus chemotherapy, which is currently the standard first-line treatment for *EGFR* ex20ins NSCLC. From patients' perspectives, a "chemotherapy-free" option with low toxicity and high convenience is often preferred (18). In addition, oral treatment improves healthcare resource utilization by reducing the need for hospital visits and dedicated clinical staff for chemotherapy administration. Secondly, the clinical activity of *EGFR* ex20ins TKI after amivantamab failure, or vice versa, is unclear. In a study of zipalertinib in patients post-amivantamab, the ORR was 40%, the duration of response was not estimable and the median PFS was 9.7 months (19). Further research is needed to investigate the resistance mechanisms of EGFR ex20ins TKI and amivantamab, and the optimal treatment sequence for *EGFR* ex20ins NSCLC. Thirdly, as patients with *EGFR* ex20ins NSCLC are at high risk of developing brain metastases, the intracranial efficacy of sunvozertinib and other EGFR ex20ins TKIs require further investigations.

In summary, the WU-KONG6 study reported a high response rate of 60% with sunvozertinib in patients with advanced *EGFR* ex20ins NSCLC who had previously been treated with chemotherapy. After a long quest of twenty years combatting *EGFR* mutated NSCLC, we now see hope

in conquering *EGFR* exon 20 insertion mutations.

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