WU-KONG28: Sunvozertinib as a Potential Chemotherapy-Sparing First-Line Option for EGFR Exon 20 Insertion-Mutant Advanced NSCLC

Dear Editor,

We read with great interest the phase III WU-KONG28 trial reported by Zhou et al.[1], which compared first-line sunvozertinib with platinum-based chemotherapy in patients with advanced non-squamous non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) exon 20 insertion mutations. Historically, this molecular subgroup has been difficult to treat with conventional EGFR tyrosine kinase inhibitors (TKIs), and platinum-based chemotherapy has therefore remained a common first-line option. WU-KONG28 provides important phase III evidence that sunvozertinib may offer a chemotherapy-sparing first-line option for selected patients. This interpretation should remain conditional on the absence of a demonstrated overall survival advantage and on patient-specific considerations, including intracranial disease, toxicity, treatment access, and subsequent therapy.

EGFR exon 20 insertion mutations were detected in 33 of 1,500 lung adenocarcinomas (2.2%) and represent a clinically distinct and molecularly heterogeneous subset of EGFR-mutant disease[2]. Because uncommon variants may be missed by limited hotspot assays, comprehensive next-generation sequencing is particularly important in routine practice[3]. Real-world studies further underscore variations in subtype distribution and outcomes[4], and the negative EXCLAIM-2 trial cautions that efficacy cannot be generalized across exon 20-targeted TKIs[5]. WU-KONG28 enrolled 324 treatment-naive patients with 54 distinct insertion variants across 154 sites in 15 countries. Patients were randomly assigned to sunvozertinib 300 mg once daily (n = 163) or carboplatin-pemetrexed followed by pemetrexed maintenance (n = 161)[1]. Blinded independent central review (BICR)-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was the primary endpoint, and randomization was stratified by baseline brain metastases. Eligibility was restricted to an Eastern Cooperative Oncology Group performance-status score of 0 or 1 and adequate organ function. Patients with brain metastases had to be clinically stable after local therapy. The protocol allowed patients assigned to chemotherapy to cross over to sunvozertinib after BICR-confirmed progression, which improved treatment access but complicated interpretation of overall survival.

At the primary analysis, sunvozertinib prolonged median PFS by 2.8 months compared with chemotherapy (10.3 vs. 7.5 months; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.50–0.85; $P < 0.001$)[1]. The separation persisted at landmark analyses: the 12-, 18-, and 24-month PFS rates were 46.1%, 33.2%, and 23.0% with sunvozertinib and 26.7%, 17.1%, and 10.3% with chemotherapy, respectively. Objective response rate and duration of response also favored sunvozertinib (Table 1). These findings establish better disease control, but they do not support an unconditional claim of overall clinical superiority because overall survival was immature and patient-reported outcomes were not reported.

Safety requires equally careful interpretation. The safety population included 163 patients treated with sunvozertinib and 150 treated with chemotherapy. Grade 3 or higher adverse events occurred in 75.5% and 56.7% of patients, respectively, and serious adverse events occurred in 45.4% and 26.7%. The most common grade 3 or higher

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Table 1: Key efficacy outcomes reported for WU-KONG28

Outcome	Sunvozertinib ($N = 163$)	Chemotherapy ($N = 161$)	Treatment effect (95% CI)	P value
Median PFS	10.3 months	7.5 months	HR, 0.65 (0.50–0.85)	< 0.001
12-month PFS rate	46.1%	26.7%	NA	NA
18-month PFS rate	33.2%	17.1%	NA	NA
24-month PFS rate	23.0%	10.3%	NA	NA
ORR	58.9%	31.1%	Odds ratio, 3.2 (2.0–5.0)	NA
Median DoR	11.2 months	7.1 months	NA	NA
Median OS	29.8 months	28.8 months	HR, 0.99 (0.70–1.40)	0.48

BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; HR, hazard ratio; NA, not reported in the primary publication; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. PFS, ORR, and DoR were assessed by BICR. OS was a secondary endpoint, and the OS data were 38.9% mature at the primary analysis.

events with sunvozertinib were increased serum creatine kinase (20.9%), diarrhea (14.1%), and anemia (9.2%); the predominant severe events with chemotherapy were decreased neutrophil count (18.7%) and anemia (11.3%)[1]. Treatment-related adverse events led to dose interruption in 45.4% versus 27.3%, dose reduction in 40.5% versus 24.0%, and permanent discontinuation in 7.4% versus 11.3%, respectively. No treatment-related fatal event occurred with sunvozertinib; one treatment-related fatal pneumonia occurred with chemotherapy. Interstitial lung disease and pneumonitis led to sunvozertinib discontinuation in 1.8% and 1.2% of patients, respectively.

Oral administration should not be equated with a low treatment burden. Management should follow the locally approved dose and prescribing information. The July 2025 US prescribing information for post-platinum sunvozertinib recommends prompt antidiarrheal therapy, such as loperamide, and fluid replacement; grade 2 or 3 diarrhea warrants treatment interruption until recovery to grade 1 or lower, with dose reduction after recurrence. After a first episode of grade 4 diarrhea, treatment may be resumed at the next lower dose only after recovery to grade 1 or lower within 3 weeks; otherwise, treatment must be permanently discontinued. Recurrent grade 4 diarrhea also requires permanent discontinuation[6]. Creatine kinase levels and muscle symptoms should be monitored; grade 3 or 4 abnormalities warrant treatment interruption and resumption at the same or a lower dose only after recovery to grade 1 or lower within 3 weeks. Suspected interstitial lung disease or pneumonitis requires immediate interruption and confirmed disease requires permanent discontinuation[6]. Long-term surveillance should also address dermatologic, ocular, gastrointestinal, pulmonary, and muscular toxicities during continuous treatment.

Overall survival must be interpreted in the context of extensive treatment switching. At the interim analysis, median overall survival was 29.8 months with sunvozertinib and 28.8 months with chemotherapy (HR, 0.99; 95% CI, 0.70–1.40; $P = 0.48$), with 126 deaths observed among 324 patients[1]. Among 112 chemotherapy-group patients with BICR-confirmed progression, 101 (90.2%) crossed over to sunvozertinib. The intention-to-treat analysis appropriately preserves randomization but estimates the effect of the assigned treatment policy, including crossover; an HR near 1.0 should therefore not be interpreted as proof of no benefit from initial sunvozertinib. Rank-preserving structural failure time models, inverse probability-of-censoring weighting, and two-stage methods could provide complementary estimates, provided their assumptions and sensitivity analyses are reported transparently. Future updates should distinguish assigned treatment, eligibility for crossover, actual on-study crossover, and off-trial subsequent therapy.

The available data do not yet establish intracranial efficacy. Only 41 of 324 patients (12.7%) had brain metastases at baseline, and the exploratory PFS estimate in this subgroup was imprecise (HR, 0.96; 95% CI, 0.44–2.08)[1]. Because enrolled patients with brain metastases had to be stable after local therapy, the study did not directly address untreated active central

nervous system disease. The primary publication did not report the proportion with measurable intracranial lesions, intracranial response, intracranial PFS, central nervous system progression patterns, or the timing and type of brain-directed therapy. Dedicated prospective central nervous system analyses are therefore needed before assuming that systemic response translates into intracranial control. Molecular heterogeneity also remains relevant. The 769_ASV and 770_SVD insertions accounted for 103 and 53 patients, respectively. Exploratory PFS results favored sunvozertinib for 769_ASV (HR, 0.46; 95% CI, 0.29–0.73) and near-loop insertions (HR, 0.59; 95% CI, 0.43–0.82), whereas estimates for other or unknown variants and far-loop insertions were less precise. Efficacy by *TP53* or other co-occurring alterations was not reported, making aggregate molecular reporting an important limitation.

Generalizability and patient experience should also temper clinical interpretation. Asian patients comprised 204 of 324 participants (63.0%), and 142 patients (43.8%) were 65 years of age or older. The exploratory PFS HR was 0.56 (95% CI, 0.41–0.77) in Asian patients and 0.93 (95% CI, 0.58–1.48) in non-Asian patients; these subgroup estimates are hypothesis-generating rather than evidence of a treatment-by-race interaction[1]. Patients with performance-status scores of 2 or higher, major uncontrolled comorbidities, or inadequate organ function were not represented. Access to comprehensive molecular testing, locally approved first-line options, and supportive care also varies across regions. In addition, WU-KONG28 did not report global health status, physical functioning, symptom burden, time to deterioration, hospitalization burden, or other health-related quality-of-life outcomes. Oral administration may reduce the need for infusion, but continuous daily treatment and frequent dose modifications may offset some of that convenience. Validated patient-reported outcome data are needed to establish a net quality-of-life advantage over intravenous chemotherapy.

The first-line treatment landscape also argues for cautious, quantitative comparison. In WU-KONG28, sunvozertinib improved median PFS from 7.5 to 10.3 months (HR, 0.65) and objective response rate (ORR) from 31.1% to 58.9%[1]. In the separate PAPILLON trial, amivantamab plus chemotherapy improved median PFS from 6.7 to 11.4 months (HR, 0.40; 95% CI, 0.30–0.53) and ORR from 47% to 73%[7]. By contrast, EXCLAIM-2 showed no PFS advantage for first-line mobocertinib over chemotherapy (9.6 vs. 9.6 months; HR, 1.04; 95% CI, 0.77–1.39), with ORRs of 32% and 30%[5]. Differences in eligibility, control-arm performance, follow-up, crossover, and toxicity preclude treatment ranking from these cross-trial comparisons. After progression in WU-KONG28, 46.6% of patients assigned to sunvozertinib received subsequent therapy, most commonly chemotherapy, whereas 72.0% of patients assigned to chemotherapy received subsequent therapy, predominantly sunvozertinib[1]. Acquired resistance mechanisms were not characterized, and the trial did not prospectively evaluate post-sunvozertinib bispecific antibodies, targeted rechallenge, or an optimal sequence. Platinum-pemetrexed, an approved amivantamab-based regimen, and clinical trials may each be considered after progression according to prior exposure, disease distribution, toxicity, access, and regional standards, but their efficacy specifically after first-line sunvozertinib remains uncertain.

In conclusion, WU-KONG28 provides phase III evidence that first-line sunvozertinib improves median PFS by 2.8 months and increases response rate and response duration compared with platinum-based chemotherapy in advanced EGFR exon 20 insertion-mutant NSCLC. The results support sunvozertinib as a potential chemotherapy-sparing first-line option for selected patients, but they do not yet establish an overall survival or intracranial advantage. Treatment selection should account for baseline central nervous system disease, the substantial burden of grade 3 or higher toxicity and dose modification, access, and available subsequent options. Crossover-adjusted survival analyses, dedicated intracranial and molecular subgroup results, patient-reported outcomes, resistance data, and prospective sequencing studies remain priorities.

Author contributions

Runliang Ni drafted the manuscript. Yuwei Ding critically revised the manuscript. Both authors approved the final version of the manuscript.

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Ethics statement

Not applicable.

Data availability statement

No datasets were generated or analyzed for this work.

AI statement

During pre-publication revision, the authors used OpenAI Codex (GPT-6) as a language-editing tool to improve grammar, clarity, and readability. No generative AI was used in preparing the original manuscript. The tool was not used for data analysis, data generation, image processing, or scientific content creation. The authors are responsible for reviewing and verifying all AI-assisted edits and take full responsibility for the accuracy and integrity of the final content.

Conflicts of interest

The authors declare no conflicts of interest.

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