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COMMENTARY

Sunvozertinib in EGFR Exon 20 Insertion NSCLC: Approved but Not Available – Practical Dose Selection Considerations and Real-World Access Challenges

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Abstract: Sunvozertinib has emerged as one of the most promising tyrosine kinase inhibitors (TKIs) for previously treated non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) exon 20 insertion (exon20ins) mutations, a molecular subset with limited sensitivity to conventional EGFR TKIs and a persistent unmet need especially in the second-line setting. Regulatory approvals have occurred at different doses – 300 mg daily in China based on WU-KONG6 and 200mg daily in the United States based on WU-KONG1B – raising an important question regarding optimal dose selection in clinical practice. In this editorial, we outline the preclinical and clinical evidence supporting sunvozertinib's approval, compare the efficacy and tolerability at 200mg versus 300mg, and discuss other emerging TKIs in this evolving treatment landscape. Finally, we highlight a critical paradox: despite FDA approval, sunvozertinib remains largely inaccessible to patients in the United States.

Keywords: sunvozertinib, TKI, NSCLC, exon20insertion, exon20ins, access challenges, WUKONG

Introduction

Epidermal growth factor receptor (EGFR) mutations are among the most clinically actionable drivers in non–small cell lung cancer (NSCLC), second to KRAS in prevalence.[1] Classical EGFR sensitizing mutations, namely exon 19 deletions and L858R point mutations, are highly responsive to EGFR tyrosine kinase inhibitors (TKIs).[2,3] In contrast, exon 20 insertions (exon20ins), which account for roughly 2% of NSCLC and 12% of EGFR mutations,[1] have limited sensitivity to conventional TKIs and are associated with inferior clinical outcomes.[4] Resistance stems from the unique spatial configuration of exon20ins mutations, including a modified kinase domain structure, a sterically hindered ATP-binding pocket, and considerable heterogeneity (>60 subtypes) of exon20ins.[5]

Therapeutic progress has been modest. Amivantamab, an EGFR and mesenchymal–epithelial transition factor (MET) bispecific antibody, is now approved as first line in combination with platinum-based chemotherapy for EGFR exon20ins NSCLC, with an overall response rate (ORR) of 73%,[6] while ORR is 40% with amivantamab monotherapy in the second-line setting.[7] However, its use is limited by significant skin toxicities[6] and treatment options remain limited in the second-line setting. Sunvozertinib was purposely developed to address this gap. An earlier effort with the EGFR TKI mobocertinib, which received accelerated approval for platinum-pretreated NSCLC with EGFR exon20ins, was later withdrawn after EXCLAIM-2 trial failed to demonstrate superior PFS compared to chemotherapy.[8]

Sunvozertinib is a selective EGFR TKI that preferentially bind to different EGFR exon20ins (along with EGFR classical, T790M, and uncommon mutations) over wild-type inhibition. Its clinical trial program was named "WUKONG", which may be viewed as symbolizing agility and innovation from the mythical monkey with supernatural

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powers, perhaps reflecting the developers' ambition for sunvozertinib in this molecular subset. Sunvozertinib was first approved in China in 2023 (based on WU-KONG6 study) at a 300mg daily dose. It recently gained accelerated approval in the United States in July 2025 (based on WUKONG 1B study) at a 200mg daily dose for platinum pre-treated patients with locally advanced or metastatic NSCLC with exon20ins mutations. As sunvozertinib advances into the global Phase III evaluation in the first-line setting (WUKONG-28), the difference in approved dosing – 200mg in the United States and 300mg in China – makes it important to carefully examine the efficacy and safety profiles of both regimens to help define the most appropriate clinical use. Moreover, because sunvozertinib remains of limited real-world availability in the United States, discussion of other emerging TKIs in this setting is also relevant.

Sunvozertinib Pre-Clinical Data

Sunvozertinib (developmental code DZD9008, marketed as Zegrovy) was developed by Dizal Pharmaceutical.[9] The compound was rationally designed from the osimertinib scaffold (Figure 1). Similar to osimertinib, it preserves its irreversible covalent interaction with the cysteine-797 residue of EGFR to retain potency against classical sensitizing EGFR mutations. Its structure differs by replacing the rigid methylindole group in osimertinib with a more flexible anilinophenyl group. This modification enables binding within the sterically restricted ATP-binding pocket unique to exon20ins mutations.[10]

Compared with osimertinib and other TKIs, sunvozertinib demonstrates 1.4 to 9.6 fold greater selectivity for ex20ins mutants than for wild-type EGFR.[10] This higher selectivity improves the therapeutic index and reduces the frequency of toxicities (such as rash and diarrhea) that are common with earlier generation ex20ins TKIs. Preclinical studies also confirm CNS penetration and intracranial tumor activity in xenograft models. However, the drug should be avoided during pregnancy due to preclinical studies that have shown maternal toxicity and teratogenic effects.[9–11]

Pharmacodynamic Data

Data from the prescribing information reports that increasing sunvozertinib from 200mg (the approved dose) to 300 mg (1.5 times the approved dose) showed no clinically significant improvement in exposure–response relationships for ORR. No clinically significant QTc interval prolongations were observed at 300mg compared to 200mg.

Pharmacokinetic Data

Sunvozertinib reaches peak plasma concentration (Tmax) approximately 6 hours after oral administration. The drug can be taken with or without food. Sunvozertinib is a CYP3A4 substrate and concomitant use with strong or moderate CYP3A4 inducers or inhibitors should be avoided as they may decrease or increase systemic exposure, respectively. No clinically significant pharmacokinetic differences were observed in specific populations based on age (19–96 years), sex, race, body weight (30 to 118 kg), mild-to-moderate renal impairment (creatinine clearance 30–89mL/min), or mild-to-moderate hepatic impairment (bilirubin ≤upper limit of normal with AST≥ upper limit of normal or bilirubin >1-3x ULN with any AST).[9]

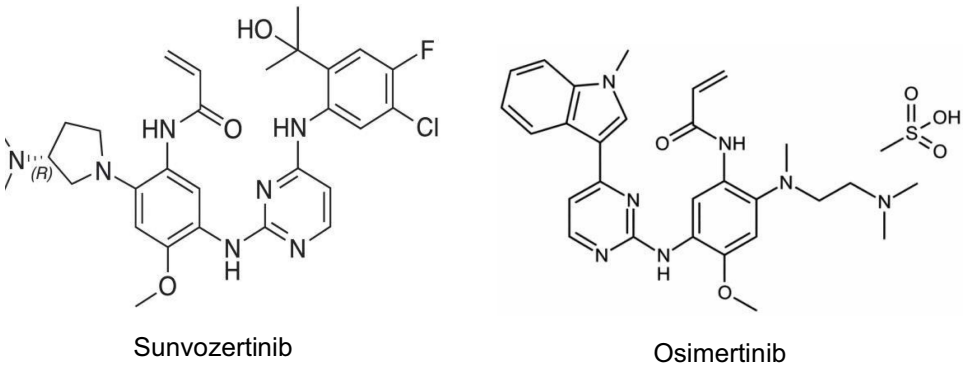

Figure 1 Structural comparison of sunvozertinib and osimertinib. Sunvozertinib, derived from the osimertinib scaffold, retains covalent binding to epidermal growth factor receptor (EGFR) cysteine-797 (Cys797) while incorporating a more flexible anilinophenyl group in place of the less flexible methylindole moiety of osimertinib, thereby facilitating accommodation within the sterically constrained ATP-binding pocket of exon 20 insertion mutations.

Clinical Studies

The clinical development program for sunvozertinib is named "WU-KONG".

WU-KONG 1 (Phase 1/2, Global)

WU-KONG1 was initiated in 2019 as the first-in-human, open-label, multinational Phase I study of sunvozertinib as a second-line treatment in patients with EGFR exon20 insertion mutations. It was conducted globally across 17 centers in the United States, Australia, Taiwan, and Korea. The trial included two components: Part A (dose-escalation) and Part B (dose-expansion). A parallel phase I study, WU-KONG2, was conducted at 8 centers in China with a similar design. In the dose-escalation cohorts (Part A), patients received once-daily oral sunvozertinib at doses ranging from 50 mg to 400 mg. The drug was generally tolerated up to 400 mg, with dose-limiting toxicities observed at higher exposures, including grade 3 diarrhea at 300 mg and grade 3 cardiac arrhythmia at 400 mg.[10] In the expansion cohorts (Part B) with WUKONG 1B, sunvozertinib was further evaluated at 200 mg and 300 mg once daily[12] as discussed later in this article.

WU-KONG 6 (Phase 2, China)

A similar Phase II study, WU-KONG6, was conducted in 2021 as a single-arm, multicenter trial in China in which all enrolled patients received 300 mg daily. This trial reported an independent review committee (IRC)-assessed overall response rate (ORR) of 61% (median DOR 8.3 months) and provided the pivotal data leading to breakthrough therapy designations by both the United States FDA and the China National Medical Products Administration (NMPA) in 2022, with subsequent conditional approval in China in 2023.[11]

200mg vs 300mg: Efficacy and Tolerability

In July 2025, the FDA granted accelerated approval of sunvozertinib at 200 mg once daily for patients with EGFR exon20 insertion–mutant NSCLC previously treated with platinum chemotherapy, based on findings from the WU-KONG1B trial.[13] In China, approval was granted at 300 mg following results from WU-KONG6,[11] leading to differences in the approved dose across regions.

WU-KONG1B, a multinational phase II study, compared the efficacy and safety of 200 mg and 300 mg dosing. Confirmed ORRs were 45.9% at 200 mg and 47.2% at 300 mg (confirmed ORR 45.8% in the pooled 300 mg cohort), with no clinically meaningful difference between the two doses. Median PFS was also comparable (8.4 for 200mg vs 7.7 months for 300mg). DoR modestly favored 300mg (13.8 vs 11.1 months). Subgroup analyses indicated higher activity of 300 mg in patients with brain metastases (52.4% vs 28.6%) and in those previously exposed to amivantamab (41.7% vs 25%).[12]

Concurrently, the 300 mg dose was associated with substantially greater toxicity. Diarrhea was more frequent (82.9% vs 68.1%), with a higher incidence of grade ≥3 events (18% vs 2.2%). Rash occurred more often at 300 mg (47.7% vs 40.7%), although grade 3 cases were comparable across doses (4.5% vs 4.4%). Treatment modifications were more frequent with 300 mg – interruptions (49.5% vs 35.2%), reductions (38.7% vs 23.1%), and discontinuations (7.2% vs 4.4%). Discontinuations were mainly driven by interstitial lung disease (1.8% vs 0), pneumonitis (1.8% vs 0), and pneumonia (1.8% vs 0), while dose reductions were primarily due to diarrhea (9.9% vs 3.3%) and elevated CPK (7.2% vs 4.4%).[12]

Collectively, these data support the FDA's decision to approve 200 mg as the U.S. label dose, achieving comparable efficacy with improved tolerability. Although the 300 mg regimen may be considered in specific subgroups (such as patients with brain metastasis and prior exposure to amivantamab), its use is limited by increased toxicity. The minimal gain in ORR (absolute difference 1.3%) does not appear to justify the increased toxicity, particularly in patients whom quality of life and tolerability are important considerations.

An ongoing phase III global trial, WU-KONG28, is currently evaluating sunvozertinib as first-line therapy compared with platinum-based chemotherapy in patients with NSCLC and EGFR exon20 insertion mutations. If positive, this study could potentially move TKI into the frontline standard of care in treating EGFR exon20ins NSCLC.[14]

Beyond Clinical Data: The Prescriber's Experience

Despite FDA approval, sunvozertinib remains largely unavailable to clinicians and patients in the United States. Dizal, the developer of the drug, lacks commercial presence or distribution network in the United States. With manufacturing

based in China, distribution is further hindered by ongoing supply chain barriers and the current 2025 U.S.–China trade tariffs.[15] Establishing a U.S.-based manufacturing facility appears unlikely in the near term. Until a distribution or commercialization agreement is secured, sunvozertinib will not reach U.S. pharmacy shelves.

For patients considering access through China, additional barriers exist. The approved U.S. dose is 200 mg once daily, whereas in China the approved dose is 300 mg, with only the 150 mg tablets available to be dispensed. This discrepancy makes cross-border procurement impractical.

These challenges risk blunting the momentum of sunvozertinib's approval. If logistical barriers persist, there is a real possibility that competitor agents in development for exon20ins NSCLC may outpace sunvozertinib in adoption despite its solid clinical profile.

Emerging Contenders

Several novel TKIs are in development for EGFR exon20ins–mutant NSCLC and may represent potential competitors to sunvozertinib. Among these, furmonertinib and zipalertinib have also shown encouraging early results.

Furmonertinib is a third-generation small molecule EGFR TKI initially developed for EGFR T790M–mutant NSCLC and later repurposed at a higher daily dose (160mg, 240 mg) to target exon20ins, with minimal inhibitory activity against wild-type EGFR.[16] In the phase Ib FAVOUR study, furmonertinib 240mg daily has an ORR of 46.2% in previously treated patients (n=28, comparable to the ORR of sunvozertinib (ORR 45.9%). Diarrhea occurred in 73% of patients (no grade 3), slightly higher than with sunvozertinib (68.1% at 200mg; with grade ≥3 at 2.2%),[12,16] whereas rash was less frequent than sunvozertinib (23% vs 40.7% at 200mg). Hematologic adverse events were also more common with furmonertinib (43% vs. 30.8%); grade ≥3 were comparable (~4% in both groups).[12,16] Limitations of the FAVOUR study include the higher dose requirement for exon20ins NSCLC, a relatively small patient population, shorter follow-up, and single-region cohort design, in contrast to the larger, multinational studies of sunvozertinib.[12,16] Table 1 summarizes key differences among emerging tyrosine kinase inhibitors targeting EGFR exon20ins-mutated NSCLC. A phase III study (FURVENT) is ongoing to evaluate furmonertinib against platinum-based chemotherapy in the first-line setting (Table 2) [17]

Zipalertinib is another oral mutant-selective pyrimidine-based EGFR TKI similar to sunvozertinib. It demonstrates greater potency against exon20ins compared to wild-type EGFR, which reduces the frequency of EGFR-related toxicities.[18] In the phase I/II REZILIENT-1 trial, it demonstrated an ORR of 40% in platinum-only pretreated patients (median DOR 8.8 mos) and 30% after prior amivantamab (median DOR 14.7mos), as outlined in Table 1. For comparison, sunvozertinib has reported an ORR 46% with DOR of 11.1 mos at 200mg dose in platinum-pretreated patients. The safety profile of zipalertinib showed rash (30.3%) and acneiform dermatitis (24.6%) at lower frequencies than sunvozertinib (40.7% at 200mg). Diarrhea occurred in 21.7% of patients, with grade ≥3 events in 2.0%, also lower than with sunvozertinib (68.1% at 200mg, with grade ≥3 at 2.2%).[12,18,19] Treatment-related adverse events leading to discontinuation were almost similar between zipalertinib and sunvozertinib (8.2% vs 7.2% at 200mg), though treatment interruptions were higher with zipalertinib (39.3% vs. 23.1%).[12,19] Both agents have demonstrated activity in patients with brain metastases; zipalertinib achieved an intracranial ORR of 30.9% (median DOR 8.3 months), while sunvozertinib reported an intracranial ORR of 28.6% with DOR of 8.4 months at 200 mg and higher ORR 52.4% with DOR of 7.7 months at 300 mg.[12,19] Ongoing studies include the phase III REZILIENT-3 trial, evaluating zipalertinib in combination with platinum-based chemotherapy in the first-line setting for EGFR exon20ins NSCLC[20] (Table 2).

Summary and Perspective

Given the persistent unmet need in NSCLC harboring EGFR exon20ins mutations, the oral TKI sunvozertinib represents an important treatment option in the second-line setting. Current evidence suggests that the 200mg dose approved in the United States offers efficacy generally comparable to the 300mg dose approved in China, with a more favorable tolerability profile, although certain subgroups (eg. patients with brain metastasis and prior amivantamab exposure) may derive incremental benefit from the higher dose. Its clinical activity and tolerability support ongoing evaluation in the frontline setting, and phase III trials such as WU-KONG28 will be critical in defining its future role compared with platinum-based chemotherapy.

Table 1 Emerging Tyrosine Kinase Inhibitors for Epidermal Growth Factor Receptor (EGFR) Exon 20 Insertion-Mutated Non-Small Cell Lung Cancer (NSCLC)

	Trial	Dose	N	Phase	Median PFS/ mDOR/mOS (mos)	ORR (%) [95% CI] (Previously Treated)	Common Toxicities, All/ Grade ≥3 (%)	Dose Interruption/ Reduction/ Discontinuation (%)	Reference
Sunvozertinib	WUKONG-6 (China)	300mg once daily	97	II	NM/NM/NE	Prior platinum-based chemotherapy: 61% (50%, 71%); Prior EGFR TKIs: 54% (33%, 73%)	Diarrhea 67/8, rash 54/1, Anemia 49/6	38/29/10	[11]
	WUKONG-1B (Global)	200mg	85	II	8.4/11.1/NE	Prior platinum-based chemotherapy: 45.9% (33.6%, 58.5%)	200mg cohort: Diarrhea 68.1/2,2, increased creatine phosphokinase 35.2/6.6, rash 40.7/4.4, anemia 30.8/4.4	200mg cohort: 35.2/23.1/4.4	[12]
		300mg	89		7.7/13.8/NE	Prior platinum-based chemotherapy: 47.2% (35.1%, 59.5%)	300mg cohort: Diarrhea 82.9/18.0, increased creatine phosphokinase 52.3/12.6, rash 47.7/4.5, anemia 37.8/6.3	300mg cohort: 49.5/38.7/7.2	
Furmonertinib	FAVOUR	240mg; (previously treated)	26	1b	NR/13.1/NR;	Prior chemotherapy/ immunotherapy/ EGFR TKIs: 46.2% (26.59%, 66.63%)	Diarrhea 86/0, Anemia 25/4, Rash 21/0 (240mg cohort)	240mg: 32/18/4	[16]
		160mg (previously treated)	26	1b	NR/9.7/NR	38.5% (20.23%, 59.43%)	Diarrhea 32/7, Anemia 14/1, Rash14/0	160mg: 14/11/4	[16]
Zipalertinib	REZILIENT1	100mg twice daily	176 (primary efficacy population)	I/II	9.4/8.8/NM	Prior platinum-based chemotherapy: 40% (31.3, 49.1); Amivantamab only: 30% (14.7, 49.4); Amivantamab and other exon20ins-targeted agents: 14.3% (3.0, 36.3)	Paronychia 38.5/0, Rash 30.3/2.5, Dermatitis acneiform 24.6/0.4, Diarrhea 21.7/2.0, Anemia 19.7/7.0	39.3/14.3/8.2	[18, 19]

Abbreviations: NM, not mature; NE, not estimable; NR, not reached.

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Table 2 Ongoing Phase III Clinical Trials Comparing Sunvozertinib, Furmonertinib and Zipalertinib

Trial	Intervention	Comparison	Study Design	Key Inclusion Criteria	Sample Size	Primary Endpoint	Key Secondary Endpoints	Status	Reference:
WU-KONG 28	Sunvozertinib (300mg,once daily)	Platinum-based chemotherapy	Randomized, open-label, global, multi-center	1. Treatment-naïve 2. Locally advanced (Stage IIIb/IIIc)/ metastatic (Stage IV) NSCLC 3. EGFR exon 20 insertion mutation	324	PFS (by blinded independent central review)	OS	Active, not recruiting	[14]
FURVENT	Furmonertinib (160mg once daily, 240mg once daily)	Platinum-based chemotherapy	Randomized, open-label, global, multi-center	1. Treatment-naïve for locally advanced or metastatic NSCLC 2. Pre-treated for non-metastatic disease (Excluding EGFR-TKIs) with treatment free interval of at least 12 months 3. History of treated CNS metastasis or new asymptomatic CNS metastasis 4. EGFR exon 20 insertion mutation	375	PFS (by blinded independent central review)	OS, ORR, PFS (by investigator assessment), DOR, PFS2, PFS in patients with brain metastasis, time to CNS metastasis, CNS ORR, CNS DOR, CNS PFS, patient-reported outcomes (Quality of Life and Symptom Assessment Questionnaire), incidence and severity of adverse effects, pharmacokinetics	Active, not recruiting	[17]
REZILIENT-3	Zipalertinib in combination with platinum-based chemotherapy	Platinum-based chemotherapy	Randomized, open-label, global, multi-center	1. Treatment-naïve for locally advanced or metastatic non-squamous NSCLC 2. Pre-treated for early-stage with treatment-free interval >6months; prior monotherapy with an approved EGFR-TKI (ie, gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib) is allowed with additional criteria 3. Brain metastasis who previously received definitive local treatment for CNS disease; asymptomatic brain metastasis ≤2cm size and if immediate definitive treatment is not indicated 4. Part A: EGFR exon20ins mutation or other uncommon single or compound EGFR mutation Part B: EGFR exon20ins mutation	260	• Part A (safety lead-in to determine recommended dose) and Part B (safety and efficacy): rate and severity of treatment emergent adverse events • Part A and B: PFS (by blinded independent central review) • Part A: Rate and severity of dose-limiting toxicities	• Part A and B: ORR, DCR, DOR, intracranial ORR, intracranial duration of complete response, intracranial duration of response • Part B only: OS, pharmacokinetics, patient-reported outcomes (Quality of Life and Symptom Assessment Questionnaire)	Active, not recruiting	[20]

Abbreviations: NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; EGFR-TKIs, Epidermal growth factor receptor- tyrosine kinase inhibitors; CNS, central nervous system; ORR, overall response rate; DOR, duration of response; PFS2, time to second progression free survival; DCR, disease-control rate; DOR, duration of response.

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At the same time, the therapeutic landscape continues to evolve. Other emerging TKIs, such as furmonertinib and zipalertinib, have shown promising activity in EGFR exon20ins-positive NSCLC, although their Asia-based production similarly limits immediate access. Yet scientific progress alone is not sufficient. Despite FDA approval, sunvozertinib remains effectively out of reach for patients and clinicians in the United States. Ultimately, the future impact of these therapies will depend not only on efficacy and tolerability, but also on whether they can be delivered to patients in a timely and practical manner.

Cancer drugs are not a luxury; they are essential. Life-saving treatments should be on standby, ready for rapid deployment at the time of diagnosis, rather than delayed by regulatory or logistical hurdles. Oncology, perhaps more than any other field, sits at the crossroads of science, commerce, and international politics—where trade policy, nationalism, and global supply chains directly influence patient care. The case of sunvozertinib raises a broader question: how will current tariff structures affect the future availability of oncology therapeutics in the United States?

Disclosure

Zhaohui Liao Arter reports Advisory board from Jassen, from Rigel, from EMD Serono, from Taiho, from Catalyst, and from Boehringer Ingelheim., outside the submitted work. Sai-Hong Ignatius Ou reports personal fees from Pfizer, personal fees from Abbvie, personal fees from Bayer, stock ownership from MBrace Therapeutics, stock ownership from BlossomHIll Therapeutics, stock ownership from Lilly, stock ownership from Nuvalent, and stock options from Nuvation Bio, outside the submitted work; Misako Nagasaka reports personal fees from AstraZeneca, personal fees from Daiichi Sankyo, personal fees from Pfizer, personal fees from Lilly, personal fees from Genentech, personal fees from Regeneron, personal fees from Johnson and Johnson, personal fees from Mirati/BMS, personal fees from Takeda, personal fees, travel support from AnHeart/Nuvation Bio, personal fees from Caris Life Sciences, outside the submitted work. The authors report no other conflicts of interest in this work.

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