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REVIEW ARTICLE

A Review on Pharmacology and Resistance Mechanisms for Sunvozertinib in EGFR Exon 20 Insertion–Mutant Non-Small Cell Lung Cancer

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Abstract: Epidermal growth factor receptor exon 20 insertion mutations is a genetically and structurally distinct class of oncogenic drivers in non-small cell lung cancer, historically characterized by marked insensitivity to classical first-, second-, and third-generation tyrosine kinase inhibitors. The clinical management of this disease has radically changed following the introduction of targeted modalities specifically engineered to overcome the steric hindrance imposed by αC-helix and loop insertions within the ATP-binding cleft. Sunvozertinib is an orally bioavailable, irreversible, rationalized small-molecule tyrosine kinase inhibitor exhibiting selective, nanomolar potency against a wide spectrum of exon 20 insertion variants while preserving wild-type receptor margins. Clinical trial evaluations across the multi-cohort WU-KONG program have established confirmed objective response rates ranging from 46% to 62% in platinum-pretreated advanced disease, alongside robust intracranial activity and prolonged response duration. Regulatory approvals in China and the United States validate its role as a pivotal oral targeted option in second-line settings. Nevertheless, clinical utility is eventually challenged by acquired resistance pathways, including secondary receptor alterations such as the C797S covalent binding site disruption, MET and ERBB2 bypass amplification, downstream pathway reactivation, and histological lineage plasticity. Ongoing phase III investigations explore frontline positioning against systemic chemo-immunotherapy combinations, while companion biomarker discovery aims to define individualized treatment sequencing. Sunvozertinib provides a compelling pharmacological option that bridges long-standing unmet needs in precision thoracic oncology.

Keywords: EGFR exon 20 insertion; Non-small cell lung cancer; Sunvozertinib; Tyrosine kinase inhibitor; Targeted oncotherapy.

1. Introduction

Primary pulmonary carcinoma is the predominant cause of malignancy-associated mortality internationally, responsible for approximately 1.8 million deaths each year [1]. Non-small cell lung cancer (NSCLC) accounts for roughly 85% of all pulmonary malignant neoplasms [2]. Over the preceding two decades, empirical cytotoxic chemotherapeutic regimens have been substantially superseded by molecularly targeted strategies guided by oncogenic driver alterations [3]. Somatic activating mutations within the epidermal growth factor receptor (*EGFR*) gene represent critical oncogenic drivers, detected in approximately 15% to 35% of lung adenocarcinomas globally, with marked enrichment observed among Asian cohorts and individuals without prior tobacco exposure [4].

The vast majority (85% to 90%) of *EGFR*-mutated NSCLC cases are driven by classical sensitizing alterations: in-frame deletions within exon 19 (predominantly delE746-A750) and the missense substitution L858R within exon 21 [5]. These canonical mutations perturb the inactive auto-inhibited configuration of the kinase domain, rendering the catalytic cleft exceptionally susceptible to successive generations of EGFR tyrosine kinase inhibitors (TKIs), ranging from reversible quinazolines (gefitinib, erlotinib) and irreversible pan-HER inhibitors (afatinib, dacomitinib) to mutant-selective, third-generation covalent inhibitors such as osimertinib [6]. These agents have markedly prolonged progression-free intervals and overall survival in clinical trials [7].

In marked contrast to these classic variants, in-frame insertions and duplications within exon 20 constitute the third most prevalent category of *EGFR* mutations, comprising approximately 4% to 10% of all *EGFR*-altered NSCLC cases [8, 9]. Unlike exon 19 deletions or L858R substitutions that promote an open, drug-accessible active kinase pocket, the introduction of supplementary

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amino acid sequences within the αC-β4 loop region of exon 20 preserves an active kinase conformation while sterically crowding the adjacent ATP-binding cleft [10, 11]. Consequently, earlier generations of EGFR TKIs, as well as standard dosing regimens of osimertinib, show minimal therapeutic activity against the vast majority of exon 20 insertions, yielding objective response rates (ORR) consistently beneath 10% [12].

Historically, patients harboring *EGFR* exon 20 insertions were managed primarily with platinum-based doublet chemotherapy [13]. Cytotoxic regimens provide limited clinical benefit, demonstrating objective response rates between 20% and 30%, modest median progression-free survival (PFS) of approximately 4 to 6 months, and median overall survival (OS) of 16 to 18 months, outcomes markedly inferior to those seen in classic sensitizing *EGFR* mutations treated with targeted agents [14].

A substantial therapeutic shift began with the accelerated regulatory approval of the bispecific EGFR-MET monoclonal antibody amivantamab and the small-molecule irreversible EGFR/HER2 inhibitor mobocertinib for platinum-pretreated advanced disease [15, 16]. However, the therapeutic regimen was destabilized by prominent off-target toxicity and the voluntary global withdrawal of mobocertinib in late 2023 following its failure to show superior progression-free survival against platinum-based chemotherapy in the confirmatory frontline EXCLAIM-2 trial [17].

Sunvozertinib (DZD9008) emerged as a rational, third-generation, structurally optimized oral EGFR TKI developed specifically to address the geometric constraints of the exon 20 insertion kinase domain [18]. Sunvozertinib achieves irreversible covalent target engagement with preserved selectivity over wild-type EGFR by exploiting an aminopyrimidine scaffold coupled to an electrophilic warhead, [19]. The clinical validation across the international WU-KONG trial enterprise revealed objective response rates between 46% and 62% in platinum-pretreated disease, prompting conditional marketing authorization by China's National Medical Products Administration (NMPA) in August 2023, followed by accelerated approval from the U.S. Food and Drug Administration (FDA) [20, 21, 22].

2. Molecular Biology of EGFR Exon 20 Insertions

2.1. Receptor Architecture and Physiological Activation

The epidermal growth factor receptor (EGFR, ErbB1, HER1) is a 170-kDa transmembrane glycoprotein receptor tyrosine kinase belonging to the ErbB family of receptors, which includes HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [23]. The structural anatomy of EGFR comprises an extracellular ligand-binding domain (subdomains I–IV), a single-pass hydrophobic transmembrane α-helix, an intracellular juxtamembrane segment, a conserved catalytic kinase core, and an unstructured C-terminal regulatory tail harboring critical tyrosine autophosphorylation sites [24].

Under basal physiologic conditions, the monomeric receptor exists in an auto-inhibited, tethered conformation. Engagement of canonical extracellular ligands—such as epidermal growth factor, transforming growth factor-alpha, or amphiregulin—induces an untethering rearrangement of domain II, promoting receptor homodimerization or heterodimerization with partner ErbB family members [24]. This interaction drives an asymmetric dimerization of the intracellular kinase domain, wherein the C-terminal lobe of the "activator" kinase interacts with the N-terminal lobe of the "receiver" kinase [24, 25].

The catalytic core spans residues 712 to 979, adopting a canonical kinase bilobal geometry separated by an ATP-binding cleft and a flexible hinge region [26]. The smaller N-terminal lobe consists predominantly of antiparallel β-sheets alongside the regulatory αC-helix, while the larger C-terminal lobe is primarily α-helical [26]. Enzymatic transition to the active state requires inward rotation of the αC-helix (the "αC-in" orientation), which facilitates the formation of a critical catalytic salt bridge between Lys745 within β-strand 3 and Glu762 within the αC-helix [27]. Similarly, the activation loop adopts an extended, non-inhibitory configuration that allows ATP binding, transfer of the γ-phosphate to peptide substrates, and extensive trans-autophosphorylation across C-terminal tyrosine residues [25, 27]. These phosphorylated tyrosines serve as high-affinity docking sites for SH2- and PTB-domain-containing adaptor proteins, subsequently initiating signaling along the RAS-RAF-MEK-ERK, PI3K-AKT-mTOR, and JAK-STAT pathways [25]. Figure 1 shows the displacement of the αC-helix and steric congestion within the ATP-binding cleft preserving an active kinase state.

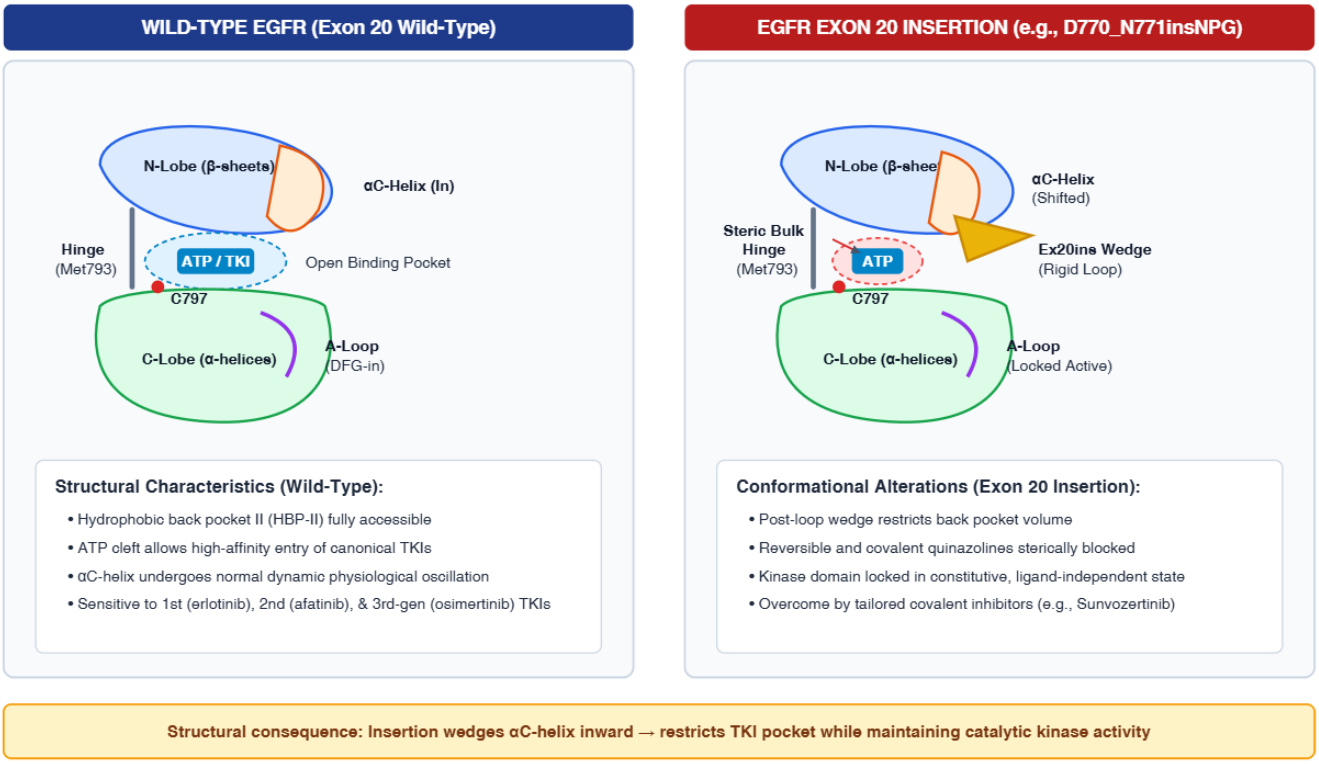

Figure 1. Structural comparison of the wild-type EGFR catalytic pocket and the exon 20 insertion configuration.

2.2. Mutational Heterogeneity and Structural Consequences

Exon 20 of *EGFR* encodes residues 762 to 823, encompassing the C-terminal turn of the regulatory αC-helix, the contiguous αC-β4 loop (residues 767–774), and the beginning of the β4 strand [28]. Exon 20 insertions represent an intensely heterogeneous spectrum of in-frame additions, duplications, or complex insertion-deletions spanning 1 to 7 amino acids (3 to 21 base pairs) [29]. More than 80 discrete structural variants have been documented in clinical oncology databases [30].

Structurally, insertions can be classified into two distinct topographic groups:

1. Near-loop or αC-helix insertions: A minority subset (comprising roughly 5% to 10% of exon 20 alterations), characterized by insertions occurring within the αC-helix proper or at the immediate junction between the helix and loop (such as A763_Y764insFQEA and A767_S768insTLA) [31, 32]. These mutations alter the flexible hinge without compressing the back-pocket volume, maintaining an open ATP-binding pocket that retains relative nanomolar sensitivity to third-generation TKIs like osimertinib [33, 34].
2. Post-loop insertions: Representing approximately 90% of all exon 20 insertion events, these alterations occur throughout the αC-β4 loop region between residues 769 and 775 [31, 32]. The most prevalent recurring variants include D770_N771insNPG (accounting for 15% to 20%), H773_V774insNPH, A767_V769dupASV, and N771_P772insH [32].

Post-loop insertions introduce conformational rigidification into the loop architecture, effectively acting as an intramolecular "wedge" [10]. This insertion exerts continuous mechanical pressure against the C-terminal segment of the αC-helix, stabilizing the helix in a constitutively active "in" position and preventing the kinase from reverting to the inactive "out" conformation [10, 35]. Crucially, unlike classical sensitizing mutations that create an enlarged drug-docking volume, post-loop insertions displace the αC-helix laterally into the internal kinase vestibule, directly constricting the hydrophobic back pocket II [10, 35].

This structural reorganization creates severe steric hindrance against first- and second-generation anilinoquinazoline inhibitors, preventing standard hydrophobic anchoring while preserving sufficient open cleft volume to accommodate endogenous ATP [10, 35]. Consequently, standard reversible and irreversible TKIs fail to achieve sufficient competitive binding affinity at clinically tolerable systemic drug exposures, establishing an intrinsic resistance profile distinct from secondary acquired resistance mutations [36]. Table 1 summarizes the structural classification, conformational impact, and the corresponding TKI sensitivity patterns across representative *EGFR* exon 20 insertion variants.

Table 1. Structural, Molecular, and Pharmacological Types of EGFR Exon 20 Insertion Variants

Insertion Variant Class	Mutations	Structural Impact on Kinase Architecture	Intrinsic Sensitivity to 1st/2nd/3rd Gen TKIs	Sensitivity to Sunvozertinib
Near-loop / αC-helix Tip	A763_Y764insFQEA, A767_S768insTLA	Leaves hydrophobic back-pocket volume preserved; shifts hinge flexibility	Sensitive to osimertinib, erlotinib, and afatinib at standard dosing	Nanomolar activity observed; active across preclinical models
Post-loop (αC-β4 loop cluster 1: Residues 769–771)	D770_N771insNPG, D770_N771insSVD, N771_P772insH	Displaces αC-helix laterally; compresses hydrophobic back pocket II (HBP-II)	Resistant to erlotinib, gefitinib, afatinib, and standard-dose osimertinib	High potency (IC_{50} 2.4–5.8 nM); robust clinical response
Post-loop (αC-β4 loop cluster 2: Residues 772–775)	H773_V774insNPH, P772_H773insYNP, H773_V774insH	Introduces rigid steric wedge; locks kinase domain in constitutive active conformation	Highly refractory to classical reversible and covalent quinazoline TKIs	High potency (IC_{50} 4.1–9.5 nM); consistent clinical disease control
Complex In-frame Duplications	A767_V769dupASV, S768_D770dupSVD	Duplication of structural loop residues altering hinge-loop transition	Refractory to early-generation inhibitors due to steric hindrance	Active in both in vitro enzymatic panels and clinical trial cohorts

2.3. Epidemiology and Clinicopathologic Attributes

The epidemiological distribution of *EGFR* exon 20 insertion mutations exhibits unique characteristics when compared to classical *EGFR* sensitizing alterations. While classical del19 and L858R mutations show marked enrichment in East Asian populations, *EGFR* exon 20 insertions display a comparatively uniform global prevalence across diverse ethnic groups, accounting for approximately 1% to 2% of all NSCLC cases and 4% to 10% of the *EGFR*-mutated subset [8, 37].

Clinically, patients harboring *EGFR* exon 20 insertions share demographic similarities with classical *EGFR*-mutated populations: a higher incidence in females, an association with non-smoking or light-smoking history, and a predominance of adenocarcinoma histology [8, 38]. Disease presentation is frequently characterized by advanced stage at initial diagnosis and an aggressive clinical trajectory [38, 39]. Central nervous system (CNS) metastases are documented in approximately 20% to 30% of patients at baseline, with cumulative incidence exceeding 45% during the course of metastatic progression [40, 41].

Co-occurring genomic alterations, such as *TP53* mutations and cell-cycle pathway disruptions, frequently compound clinical risk [42]. The identification of exon 20 insertions requires comprehensive genomic profiling via next-generation sequencing (NGS) platforms [43]. Standard allele-specific polymerase chain reaction (PCR) panels typically target only a limited number of recurring insertion variants, leading to high false-negative rates [44]. Targeted hybrid-capture DNA or RNA sequencing provides the sensitivity and broad coverage necessary to identify rare and non-canonical in-frame insertions, preventing the inappropriate assignment of these patients to empirical non-targeted regimens [43, 44].

2.4. Downstream Oncogenic Signaling Pathways

Constitutive, ligand-independent autophosphorylation of the *EGFR* exon 20 insertion kinase core triggers continuous hyperactivation of classical downstream signaling cascades [10, 25, 45]. Signal transduction along the RAS-RAF-MEK-ERK mitogenic pathway accelerates cell cycle progression and unscheduled entry into the S-phase via cyclin D1 transcription [25, 45]. Similarly, recruitment of the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K) catalyzes the generation of phosphatidylinositol (3,4,5)-trisphosphate, facilitating the phosphorylation and activation of AKT at Thr308 and Ser473 [45, 46]. The downstream activation of the mechanistic target of rapamycin (mTOR) pathway suppresses pro-apoptotic signals while upregulating glycolytic metabolic programming [46]. Furthermore, phosphorylation of signal transducer and activator of transcription 3 (STAT3) supports immune evasion mechanisms and metastatic survival [25, 45].

In terms of tumor immunogenicity, *EGFR* exon 20 insertion-positive tumors reflect the broader immunologically "cold" microenvironment typical of oncogene-addicted lung adenocarcinomas [47]. These malignancies routinely show low tumor mutational burden (TMB) and variable, frequently minimal, programmed death-ligand 1 (PD-L1) surface expression [47, 48]. As a direct functional consequence of this low neoantigen burden and suppressed immune infiltration, immune checkpoint inhibitor monotherapies have shown very low objective response rates (below 10%) and negligible progression-free survival benefits in this patient demographic [47, 49]. This biology highlights the need for potent, mutation-directed kinase inhibition as the primary systemic

treatment approach [49]. Figure 2 shows ligand-independent receptor activation and downstream signaling cascades (RAS-RAF-MEK-ERK, PI3K-AKT-mTOR, and JAK-STAT3)

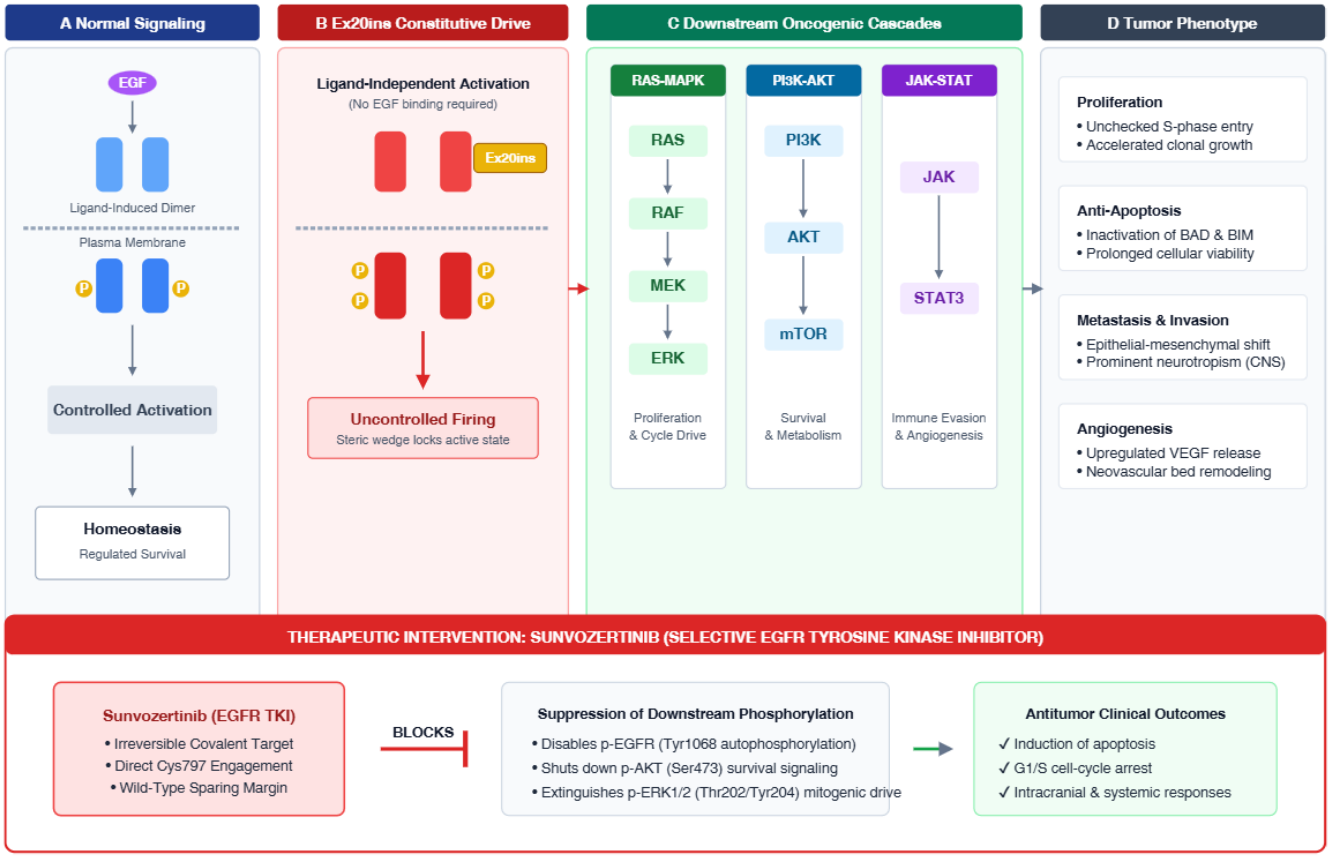

Figure 2. Pathophysiology and signaling pathways in EGFR exon 20 insertion non-small cell lung cancer

3. Structural Pharmacology and Mechanism of Action of Sunvozertinib

3.1. Structure-Guided Rational Drug Design

Sunvozertinib (development code DZD9008) was developed using structure-guided drug design to circumvent the steric clashes characteristic of the altered exon 20 insertion catalytic cleft [18]. Structural analysis revealed that while the post-loop insertion displaces the αC-helix inward to narrow the hydrophobic back pocket, the spatial volume adjacent to the kinase hinge region and the solvent-exposed outer channel remains open [18, 50]. Classical quinazoline TKIs fail because their planar aromatic cores depend on penetrating deeply into this compressed back pocket [50].

Medicinal chemistry efforts focused on assembling a flexible aminopyrimidine scaffold that forms hydrogen bonds with the hinge region without demanding extensive back-pocket clearance [18, 51]. To secure potent and long-lasting target engagement despite the altered binding pocket geometry, an electrophilic acrylamide warhead was installed, positioned to form an irreversible covalent bond with the side-chain thiol of Cys797 at the margin of the ATP cleft [18, 52]. The optimization of solvent-exposed substituents further conferred high biochemical selectivity for the insertion-altered enzyme over wild-type EGFR [18, 19].

3.2. Chemical Structure and Covalent Target Engagement

Sunvozertinib is chemically *N*-(5-((4-(4-((dimethylamino)methyl)-3-fluorophenoxy)pyrimidin-2-yl)amino)-4-methoxy-2-morpholinophenyl)acrylamide, with a molecular formula of $C_{29}H_{35}ClFN_7O_3$ and a formula weight of 586.06 g/mol [18, 51].

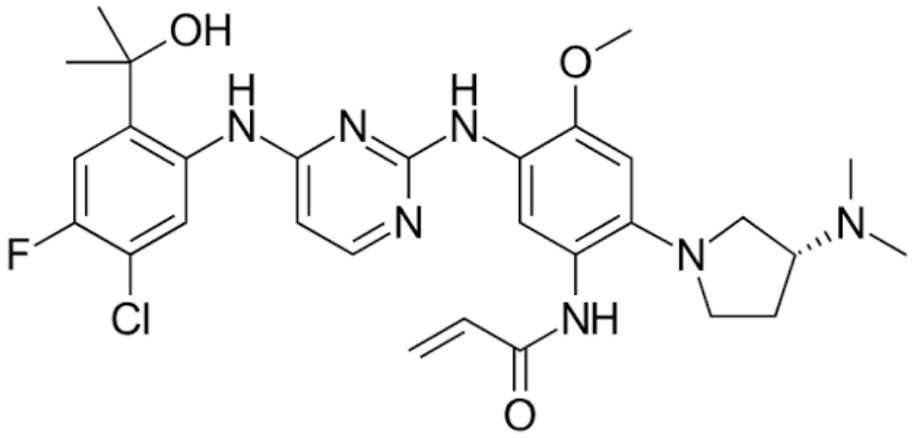

Figure 3. Structure of Sunvozertinib

The chemical structure is organized around three functional domains:

1. The Aminopyrimidine Hinge-Binding Core: Forms critical bidentate donor-acceptor hydrogen-bonding contacts with the backbone amide of Met793 within the kinase hinge region, precisely orienting the molecule inside the ATP-binding cleft [18].
2. The Electrophilic Acrylamide Warhead: Oriented toward the solvent-accessible margin where it participates in a Michael-addition reaction with the nucleophilic sulfhydryl group of the non-catalytic cysteine residue at position 797 (Cys797). This covalent interaction forms an irreversible carbon-sulfur bond [18, 52].
3. The Substituted Piperazine/Morpholino Side Chains: Extend outward into the solvent front, avoiding steric clashes with the displaced αC-helix, enhancing aqueous solubility, and conferring preferential selectivity over the unmutated kinase [18, 19].

The pharmacological kinetics of covalent inhibition rely on both initial reversible affinity (K_i) and the rate of subsequent covalent bond formation (k_{inact}) [52]. The covalent efficiency metric (k_{inact}/K_i) of sunvozertinib allows sustained pharmacological inhibition that continues after unbound systemic concentrations decline, maintaining pharmacodynamic suppression of receptor autophosphorylation throughout the clinical once-daily dosing interval [18, 52].

In biochemical kinase assays, sunvozertinib shows potent inhibitory activity across diverse exon 20 insertion variants, with half-maximal inhibitory concentrations (IC_{50}) ranging from 2.4 nM to 9.5 nM against D770_N771insNPG, H773_V774insNPH, and A767_V769dupASV [18]. Against unmutated wild-type EGFR, the enzymatic IC_{50} is roughly 100 nM to 500 nM, establishing a 20- to 100-fold margin of mutant selectivity [18, 19]. This wild-type-sparing selectivity reduces the gastrointestinal and dermatologic toxicities commonly associated with non-selective, first- and second-generation pan-ErbB TKIs [18, 19].

3.3. Kinome Selectivity Profiling and Preclinical Efficacy

Broader kinomic screening across panels of more than 300 non-target serine/threonine and tyrosine kinases indicates that sunvozertinib maintains an exceptionally clean selectivity profile [18]. The drug does not inhibit off-target kinases such as BTK, ALK, ROS1, or VEGFR family members at physiologically relevant therapeutic concentrations [18]. Moderate, nanomolar-range cross-reactivity is observed against HER2 (ERBB2), driven by sequence homology within the catalytic cleft and the presence of the homologous nucleophilic cysteine residue (Cys805 in HER2) [18, 53]. This dual activity provides a mechanistic rationale for evaluating sunvozertinib in *HER2* exon 20 insertion-mutated pulmonary adenocarcinomas [54].

Preclinical evaluation using transformed Ba/F3 murine pro-B cells expressing various human *EGFR* exon 20 insertion constructs indicated potent suppression of cell proliferation and downstream phosphorylation of EGFR (Tyr1068), AKT (Ser473), and ERK1/2 (Thr202/Tyr204) [18]. In vivo studies utilizing patient-derived xenograft (PDX) models and cell line-derived xenografts (CDX) carrying diverse insertion variants confirmed dose-dependent, sustained tumor regression [18, 55]. Notably, intracranial PDX models showed that sunvozertinib penetrates the blood-brain barrier, reducing intracranial tumor burden and prolonging survival in mice bearing brain metastases [18, 56].

4. Pharmacokinetics and Clinical Pharmacodynamics

4.1. Absorption, Distribution, Metabolism, and Elimination

Sunvozertinib is administered as an oral tablet formulation. Phase I pharmacokinetics indicate that following oral administration, peak plasma concentrations (T_{max}) are achieved within a median of 2 to 4 hours [22, 57].

Co-administration with food exerts a meaningful impact on bioavailability: ingestion of a high-fat or standard-fat meal increases the area under the plasma concentration-time curve (AUC) by approximately 30% to 60% and maximum concentration (C_{max}) by 20% to 40% compared to fasted administration [22, 57]. This food effect helped establish the clinical dosing recommendation that sunvozertinib be taken with meals in the international registration cohort, maximizing bioavailability while optimizing gastrointestinal tolerability [21, 57].

The apparent volume of distribution at steady state (V_{ss}/F) exceeds 500 liters, reflecting extensive tissue penetration and lipophilicity [57, 58]. Binding to human plasma proteins is high (approximately 90% to 95%), primarily to albumin and alpha-1-acid glycoprotein [57]. Sunvozertinib exhibits an effective terminal half-life ($t_{1/2}$) of approximately 14 to 20 hours, supporting a once-daily dosing regimen and reaching steady-state plasma concentrations within 5 to 7 days of continuous administration [22, 57].

Biotransformation occurs predominantly in the liver via cytochrome P450 3A4 (CYP3A4)-mediated oxidative pathways, with secondary contributions from CYP1A2 and CYP2D6 [57]. Circulating metabolite profiling has identified an active dealkylated derivative, designated M9, which shows comparable biochemical potency against exon 20 insertion mutations and contributes to overall clinical efficacy [58]. Fecal excretion represents the primary elimination route (accounting for roughly 72% of the total administered dose), while renal clearance is a minor pathway, responsible for approximately 20% of the dose recovered as parent drug and polar metabolites [57]. Table 2 outlines the fundamental physicochemical properties, systemic pharmacokinetic parameters, and metabolic pathways governing once-daily oral administration of sunvozertinib.

Table 2. Clinical Pharmacokinetic and Physicochemical Profile of Sunvozertinib

Pharmacokinetic Parameter	Characteristic	Clinical Relevance
Chemical Formula & Molecular Weight	$C_{29}H_{35}ClFN_7O_3$ (586.06 g/mol)	Lipophilic, small-molecule irreversible covalent kinase inhibitor
Time to Peak Concentration (T_{max})	2.0 to 4.0 hours (median)	Rapid gastrointestinal absorption following oral administration
Elimination Half-Life ($t_{1/2}$)	14 to 20 hours	Supports convenient once-daily (QD) oral maintenance dosing
Time to Steady State	5 to 7 days	Rapid attainment of therapeutic systemic concentrations
Food Effect	AUC increases by 30%–60%; C_{max} increases by 20%–40%	Recommends taking the 200 mg dose with food in international protocols
Apparent Volume of Distribution (V_{ss}/F)	>500 L	Broad peripheral tissue distribution and central nervous system penetration
Plasma Protein Binding	90% to 95%	Binds predominantly to serum albumin and alpha-1-acid glycoprotein
Primary Metabolic Route	Hepatic CYP3A4 oxidation (minor CYP1A2, CYP2D6)	Primary clearance mechanism; subject to CYP3A modulators
Major Circulating Metabolite	M9 (dealkylated derivative)	Pharmacologically active, contributing to anti-tumor efficacy
Excretion Pathways	Feces (~72%), Urine (~20%)	Fecal elimination predominates; renal clearance plays a secondary role

4.2. Drug Interaction Vulnerabilities

Because CYP3A4 is the primary clearance pathway, systemic exposure of sunvozertinib is sensitive to co-administration with strong CYP3A modulators [57]. Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, itraconazole) increases sunvozertinib exposure by roughly two-fold, increasing the risk of adverse reactions [57, 59]. Conversely, co-administration with potent CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's Wort) reduces systemic exposure by more than 50%, which can compromise therapeutic efficacy [57, 59]. Concomitant use with strong CYP3A inducers should be avoided, and cautious dose

modification is warranted when strong inhibitors are required [57]. *In vitro* evaluations indicate that sunvozertinib does not meaningfully inhibit or induce major CYP isoforms at therapeutic concentrations, suggesting a low potential for perpetrator-type pharmacokinetic drug-drug interactions [57].

4.3. Pharmacodynamic and Exposure-Response Relationships

Pharmacodynamic assessments in early-phase clinical studies incorporated serial assessments of circulating tumor DNA (ctDNA) and paired baseline and on-treatment tumor biopsies [22]. Liquid biopsy analyses indicated rapid, dose-dependent reductions in the variant allele frequency (VAF) of *EGFR* exon 20 insertions within the first cycle of treatment at doses of 100 mg daily and higher [22, 60]. Paired tumor biopsies confirmed target engagement, showing substantial reductions in phosphorylated EGFR, AKT, and ERK [18, 22]. Early molecular clearance of ctDNA by the conclusion of cycle 2 correlated with radiographic tumor regression and prolonged progression-free survival [60]. Exposure-response and exposure-safety analyses across the WU-KONG studies indicated that higher drug exposure (AUC) correlated with improved objective response rates, while simultaneously increasing the frequency of grade 3 or higher treatment-related adverse events [22, 57]. These findings supported the use of two distinct clinical dosing regimens: 300 mg once daily under fasted conditions in the Chinese development cohort (WU-KONG6) and 200 mg once daily administered with food in the international global cohort (WU-KONG1B) [20, 21, 22]. This 200 mg with-food regimen achieves comparable systemic therapeutic exposure while maintaining a more favorable overall tolerability profile [21, 22].

5. Clinical Trial Development

The clinical development program for sunvozertinib, designated the WU-KONG enterprise, encompasses a coordinated sequence of phase I through phase III clinical trials designed to assess pharmacokinetics, safety, efficacy, and direct comparative outcomes in both pretreated and treatment-naïve settings. Table 3 provides the structural design, clinical trial phases, evaluated dosing schedules, and benchmark efficacy of the multi-cohort WU-KONG clinical development program.

Table 3. Consolidated Design and Primary Outcomes Across the Sunvozertinib WU-KONG Clinical Enterprise

Study Name (Identifier)	Phase	Target Population	Dosing Regimen & Administration	Efficacy Endpoints	Current Development Status
WU-KONG1 (NCT04148898)	I/II	Advanced *EGFR*-mutated NSCLC; ≥ 1 prior line of systemic therapy	50–400 mg QD (dose-escalation); 200 mg QD with food (cohort 1B)	MTD established at 300 mg (fasted); global RP2D defined at 200 mg with food; verified target engagement	Completed; served as basis for regulatory review
WU-KONG2 (NCT04029792)	I/II	Advanced *EGFR* Ex20ins NSCLC; pretreated Western populations	200–400 mg QD dose-escalation	Evaluated international safety and PK; confirmed clinical partial responses	Completed
WU-KONG6 (NCT05141591)	II	Platinum-pretreated *EGFR* Ex20ins NSCLC; China multicenter cohort	300 mg QD under fasted conditions ($n = 97$ evaluable)	Confirmed IRC-assessed ORR: 61.9%; DCR: 88.7%; median PFS: 10.3 months; intracranial ORR: 60.0%	Published; basis for China NMPA conditional approval (2023)
WU-KONG1B (NCT04148898)	II	Platinum-pretreated *EGFR* Ex20ins NSCLC; international cohort	200 mg QD with meals ($n = 85$ evaluable)	Confirmed IRC-assessed ORR: 45.9%; median DoR: 11.1 months; median PFS: 12.2 months	Basis for U.S. FDA accelerated approval (2025)
WU-KONG8 (NCT05607550)	III	Treatment-naïve metastatic *EGFR* Ex20ins NSCLC; randomized global trial	Sunvozertinib (200 mg QD with food) vs. Platinum-Pemetrexed Doublet	Primary: PFS by BICR; Secondary: OS, ORR, DoR, intracranial control, safety	Active enrollment ongoing
WU-KONG15	II	Treatment-naïve *EGFR* Ex20ins NSCLC; single-arm first-line study	200 mg QD with food	Primary: ORR; preliminary readouts demonstrate frontline ORR >70%	Active investigation ongoing

5.1. First-in-Human Phase I Studies: WU-KONG1 and WU-KONG2

The clinical profile of sunvozertinib was first evaluated in two parallel phase I/II studies: WU-KONG1 (NCT04148898), conducted across Asian clinical sites, and WU-KONG2 (NCT04029792), conducted in the United States and Europe [22, 61]. These open-label, dose-escalation and expansion trials enrolled patients with advanced *EGFR*-mutated NSCLC whose disease had progressed following standard systemic therapies, including platinum chemotherapy and prior EGFR TKIs [22, 61].

Dose escalation tested cohorts receiving 50 mg to 400 mg once daily [22]. Dose-limiting toxicities, consisting primarily of grade 3 diarrhea and skin rash, were documented at the 400 mg dose level [22]. Based on safety and pharmacokinetic modeling, 300 mg once daily (fasted) was established as the maximum tolerated dose and recommended phase II dose (RP2D) for the Chinese cohort, whereas 200 mg once daily administered with meals was chosen as the international RP2D [22]. Antitumor responses were observed across multiple dose levels (≥ 100 mg), including in patients with prior exposure to amivantamab, demonstrating the activity of this irreversible small molecule following bispecific antibody failure [22].

5.2. Pivotal Phase II Trial in China: WU-KONG6

The pivotal Chinese registration study, WU-KONG6 (NCT05141591), was a multicenter, open-label, single-arm phase II trial evaluating sunvozertinib monotherapy at 300 mg once daily in patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 20 insertions who had progressed on or following platinum doublet chemotherapy [20]. The primary endpoint was confirmed objective response rate assessed by an independent review committee (IRC) using RECIST v1.1 criteria [20].

Among 97 evaluable patients in the primary efficacy population, the confirmed objective response rate reached 61.9% (95% CI: 51.5%–71.5%) [20]. All documented responses were partial responses; the overall disease control rate (DCR) reached 88.7% [20]. Antitumor activity was observed rapidly, with a median time to response of 1.4 months [20]. At a median follow-up of 7.6 months, the median duration of response (DoR) had not been reached, with 63% of responding patients maintaining response beyond 6 months [20]. The median progression-free survival was 10.3 months (95% CI: 7.3 months–not reached) [20]. Subgroup evaluations confirmed that clinical benefit was maintained regardless of patient age, smoking status, number of prior systemic therapies, or specific exon 20 insertion variant [20].

Among patients presenting with baseline central nervous system metastases, the intracranial ORR was 60.0%, demonstrating the compound's blood-brain barrier penetration [20]. These findings formed the basis for the conditional marketing approval granted by China's NMPA in August 2023 [62].

5.3. Phase II Trial: WU-KONG1B

The multinational registration cohort WU-KONG1B (NCT04148898 expansion) evaluated sunvozertinib monotherapy at the international RP2D of 200 mg once daily taken with food in platinum-pretreated advanced NSCLC harboring *EGFR* exon 20 insertions [21].

In the primary efficacy population ($n = 85$), the confirmed objective response rate as assessed by blinded independent central review was 45.9% (95% CI: 34.9%–57.2%) [21]. The median duration of response reached 11.1 months (95% CI: 8.2 months–not estimable), and median progression-free survival was 12.2 months [21]. The difference in ORR between WU-KONG6 (61.9% at 300 mg) and WU-KONG1B (45.9% at 200 mg with food) reflects differences in dose intensity, pharmacokinetic exposures, and patient baseline characteristics across cohorts, while both show durable disease control [20, 21]. The U.S. FDA subsequently granted accelerated approval to sunvozertinib for adult patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 20 insertion mutations whose disease progressed on or after platinum-based chemotherapy [21].

5.4. Phase III Trial: WU-KONG8 and WU-KONG15

To evaluate the potential of sunvozertinib in treatment-naïve disease, the global, randomized phase III WU-KONG8 trial (NCT05607550) was initiated [63]. This study directly compares sunvozertinib monotherapy (200 mg once daily with food) against investigator's choice platinum doublet chemotherapy (carboplatin or cisplatin plus pemetrexed) in treatment-naïve patients with locally advanced or metastatic *EGFR* exon 20 insertion NSCLC [63]. The primary endpoint is progression-free survival assessed by blinded independent central review, with overall survival serving as a secondary endpoint [63].

Preliminary data from the single-arm frontline Phase II trial WU-KONG15 have shown encouraging initial results, with objective response rates exceeding 70% in treatment-naïve patients [64]. Clinical response has been maintained across diverse molecular insertion variants [65]. These data reflect the improved efficacy observed when mutation-selective TKIs are moved into earlier lines

of treatment, mirroring the therapeutic shifts previously established with third-generation inhibitors in classical *EGFR*-mutated NSCLC [6, 64].

6. Clinical Safety and Tolerability Profile

6.1. Class-Associated Toxicities and Tolerability

The safety profile of sunvozertinib has been characterized across more than 400 clinical trial participants enrolled in the WU-KONG studies [19, 20, 21, 22]. The observed adverse event profile consists primarily of low-grade toxicities typical of the EGFR TKI drug class, alongside manageable laboratory abnormalities [20, 21].

Adverse events are predominantly mild to moderate (grade 1 or 2) and resolve with supportive care or standard dose adjustments [20, 21]. The incidence of high-grade dermatological and gastrointestinal toxicities is considerably lower than that reported with mobocertinib, consistent with sunvozertinib's greater selectivity for mutant over wild-type EGFR [16, 20]. Table 4 presents the comparative frequencies of treatment-emergent adverse events across dose cohorts alongside practical clinical intervention algorithms for optimal toxicity management.

Table 4. Incidence and Spectrum of Treatment-Emergent Adverse Events Documented with Sunvozertinib

Treatment-Emergent Adverse Event	WU-KONG1B (200 mg QD with Food) Any Grade (%)	WU-KONG1B (200 mg QD with Food) Grade ≥3 (%)	WU-KONG6 (300 mg QD Fasted) Any Grade (%)	WU-KONG6 (300 mg QD Fasted) Grade ≥3 (%)	Primary Clinical Management Protocol
Diarrhea	33%	4%	51%	8%	Early loperamide administration, oral rehydration, and dose reduction if persistent
Rash / Dermatitis Acneiform	27%	<2%	35%	<2%	Topical corticosteroids, emollients, and oral low-dose tetracycline antibiotics
CPK Elevation (Asymptomatic)	14%	5%	30%	17%	Routine clinical monitoring; temporary dose interruption until recovery to Grade ≤ 1
Nausea	18%	<1%	22%	1%	Prophylactic or reactive 5-HT_3 receptor antagonists and dietary modification
Fatigue	15%	1%	17%	1%	Supportive clinical care, rest, and monitoring for secondary anemia
Anemia	12%	4%	18%	6%	Monitoring hematologic panels; supportive iron supplementation or transfusions
Decreased Appetite	13%	<1%	16%	1%	Nutritional counseling and supportive dietary interventions
Paronychia	12%	0%	15%	0%	Antiseptic soaks, topical antibiotics, and avoidance of local nail trauma
Stomatitis / Mucositis	9%	0%	12%	<1%	Non-alcoholic antiseptic mouth rinses and mucosal coating agents
Interstitial Lung Disease (ILD)	2%	1%	5%	3%	Immediate drug discontinuation, HRCT scan, and systemic corticosteroid therapy

6.2. Creatine Phosphokinase Elevation

Elevation of serum creatine phosphokinase (CPK) represents a distinctive laboratory finding observed with sunvozertinib, occurring in approximately 14% of patients receiving the 200 mg dose and 30% of patients receiving the 300 mg dose [20, 21]. Grade 3 or greater CPK elevations were documented in 5% and 17% of patients across these respective cohorts [20, 21].

Importantly, these CPK elevations were predominantly asymptomatic laboratory findings, rarely accompanied by muscle pain, tenderness, clinical weakness, or signs of rhabdomyolysis [20, 66]. Serum elevations typically emerged within the first two treatment cycles and resolved promptly following temporary dose interruption or dose reduction, without permanent clinical sequelae [20, 66]. While the precise molecular mechanism remains under evaluation, regular monitoring of baseline and periodic serum CPK levels is recommended during active treatment [57, 66].

6.3. Interstitial Lung Disease and Pulmonary Toxicities

Drug-induced interstitial lung disease (ILD) and pneumonitis are known, class-specific toxicities of EGFR tyrosine kinase inhibitors [67]. In the sunvozertinib clinical development program, ILD/pneumonitis occurred in approximately 2% to 5% of patients across cohorts, with high-grade (grade ≥ 3) presentations documented in 1% to 3% [20, 21].

Clinical management requires proactive vigilance: patients presenting with new or worsening acute respiratory symptoms (such as cough, dyspnea, and fever) require immediate drug interruption and prompt evaluation by high-resolution computed tomography (HRCT) [57]. If non-infectious drug-related pneumonitis is confirmed, systemic corticosteroid therapy should be initiated [57]. Sunvozertinib should be permanently discontinued in all patients who develop grade 3 or 4 drug-induced ILD, as well as those with recurrent pneumonitis [57].

6.4. Dose Management and Treatment Discontinuation

Treatment-related toxicities were effectively managed through structured dose modification protocols [20, 21]. In the WU-KONG1B trial, dose reductions (most commonly from 200 mg down to 150 mg once daily) occurred in 36% of patients, primarily driven by grade 2 or 3 gastrointestinal symptoms or asymptomatic CPK elevations [21]. Permanent treatment discontinuation due to adverse events occurred in 6% of participants, indicating that the majority of patients tolerate long-term therapy when supported by dose adjustments [21].

7. Comparison of Treatments Available for EGFR exon 20 insertion-mutant NSCLC

The treatment for *EGFR* exon 20 insertion-mutant NSCLC has expanded beyond traditional platinum-based chemotherapy to encompass bispecific monoclonal antibodies, targeted small-molecule TKIs, and emerging antibody-drug conjugates [11, 45].

7.1. Sunvozertinib versus Amivantamab

Amivantamab is a fully human bispecific antibody targeting both EGFR and MET extracellular domains, demonstrating an ORR of 40% and a median PFS of 8.3 months as monotherapy in platinum-pretreated exon 20 insertion disease within the CHRYSALIS study [15]. More recently, the phase III PAPILLON trial established amivantamab in combination with carboplatin and pemetrexed as a standard frontline option, reporting an ORR of 73% and a median PFS of 11.4 months compared to 6.7 months for chemotherapy alone [68].

When comparing sunvozertinib with amivantamab in the post-platinum setting, several therapeutic distinctions emerge:

1. Response and Progression-Free Survival: Sunvozertinib monotherapy shows an ORR of 46% to 62% and a median PFS of 10.3 to 12.2 months, comparing favorably to amivantamab monotherapy (ORR 40%, median PFS 8.3 months) [15, 20, 21].
2. Route of Administration and Patient Tolerability: Sunvozertinib is taken orally once daily at home, eliminating the clinical burden and infusion-related reactions (IRRs) associated with amivantamab [15, 21]. Amivantamab requires prolonged intravenous infusions and produces IRRs in approximately 66% of patients, necessitating routine premedication and continuous infusion monitoring [15, 69].
3. Central Nervous System Disease: Due to its high molecular weight (~148 kDa), intact amivantamab exhibits poor penetration through the blood-brain barrier, offering limited protection or therapeutic response against active intracranial lesions [40, 69]. In contrast, sunvozertinib readily crosses into the CNS, demonstrating intracranial ORRs of 55% to 65% in patients with active brain metastases [20, 56].

4. Target Specificity: Amivantamab's simultaneous inhibition of the MET pathway offers a theoretical advantage against tumors with pre-existing MET dependencies [15, 70].

Table 5 lists out the comparative clinical efficacy endpoints, administration characteristics, intracranial responsiveness, and distinct toxicity profiles across current and emerging systemic therapies in *EGFR* exon 20 insertion-mutated NSCLC.

Table 5. Head-to-Head Comparison of Targeted Treatments Available for EGFR Exon 20 Insertion NSCLC

Therapeutic Modality	Mechanism of Action & Target	Administration Route	Confirmed ORR (%)	Median PFS (Months)	CNS Metastasis Activity	Defining Toxicities & Clinical Considerations
Sunvozertinib (*Zegfrovy*)	3rd-generation irreversible mutant-selective EGFR TKI	Oral (Once Daily)	46%–62%	10.3–12.2	High (intracranial ORR: ~55%–65%)	Asymptomatic CPK elevation; low-grade diarrhea and rash; ILD (2%–5%)
Amivantamab (*Rybrevant*)	Bispecific monoclonal antibody targeting EGFR and MET	Intravenous Infusion	40% (monotherapy)	8.3 (monotherapy)	Poor blood-brain barrier penetration (~148 kDa)	Infusion-related reactions (66%); severe rash and paronychia; MET-driven edema
Amivantamab + Chemo (*PAPILLON*)	Bispecific antibody + Carboplatin-Pemetrexed chemotherapy	IV Infusion + IV Chemotherapy	73% (frontline)	11.4 (frontline)	Modest systemic control; primarily restricted by antibody CNS exclusion	Additive hematologic cytopenias from chemotherapy; high clinical infusion burden
Mobocertinib (*Exkivity*)	Irreversible covalent EGFR/HER2 small-molecule TKI	Oral (Once Daily)	28% (withdrawn)	7.3 (withdrawn)	Limited intracranial response data	Severe diarrhea (21% Grade ≥ 3); QTc prolongation; high rate of dose reductions
Zipalertinib (*CLN-081*)	Irreversible mutant-selective oral EGFR TKI	Oral (Twice Daily)	38%–41%	8.0–10.0	Preliminary intracranial disease control reported	Manageable diarrhea and rash; favorable wild-type sparing profile
Furmonertinib (*Alflutinib*)	Third-generation EGFR TKI administered at high dose (240 mg)	Oral (Once Daily)	39%–46%	~7.0–9.7	Active against central nervous system lesions	Increased risk of EGFR wild-type off-target toxicities at escalated doses

7.2. Comparison with Mobocertinib and Investigational Kinase Inhibitors

Mobocertinib was the first oral EGFR/HER2 TKI to secure accelerated approval for platinum-pretreated *EGFR* exon 20 insertion NSCLC, reporting an ORR of 28% and a median PFS of 7.3 months [16]. However, mobocertinib's lack of selectivity over wild-type EGFR resulted in prominent gastrointestinal toxicities, including a 21% incidence of grade ≥ 3 diarrhea and frequent treatment discontinuations [16, 71]. Its failure to improve progression-free survival over chemotherapy in the first-line EXCLAIM-2 trial led to its voluntary market withdrawal in late 2023 [17, 71]. Sunvozertinib improved upon this profile through structure-guided design, achieving higher response rates (46% to 62%) with lower rates of grade ≥ 3 diarrhea (4% to 8%) [20, 21].

Among other investigational agents, zipalertinib (CLN-081) is an oral, irreversible, mutant-selective EGFR inhibitor designed to spare wild-type receptor signaling [72]. In phase I/II studies, zipalertinib achieved an ORR of 38% to 41% with a median PFS of approximately 8 to 10 months and a manageable safety profile, supporting its continuing development in pretreated cohorts [72]. High-dose furmonertinib (160 mg to 240 mg daily), an approved third-generation TKI in China for canonical *EGFR* mutations,

demonstrated an ORR of roughly 39% to 46% in the phase Ib FAVOUR trial [73]. However, the higher doses needed to inhibit exon 20 insertions raise concerns regarding cumulative long-term wild-type toxicity [73]. Poziotinib, a second-generation non-selective inhibitor, produced response rates of 14% to 32% but was limited by dose reductions exceeding 70% due to severe rash and gastrointestinal toxicities, preventing regulatory authorization [74].

8. Mechanisms of Acquired Therapeutic Resistance

Despite high initial response rates with sunvozertinib, the emergence of acquired drug resistance remains the primary factor limiting long-term survival [75]. Acquired resistance develops through on-target secondary mutations, activation of bypass signaling pathways, and phenotypic lineage switching [75].

8.1. On-Target Secondary Mutations in the Kinase Domain

Secondary mutations that alter the drug-binding pocket represent a classic mechanism of acquired resistance to covalent kinase inhibitors [36, 75].

The most common on-target alteration is the acquired missense mutation at position 797, specifically the C797S substitution [76]. Sunvozertinib relies on the nucleophilic cysteine-797 residue to form its irreversible covalent bond [18, 52]. Substitution of this cysteine with a serine residue replaces the reactive thiol group with a hydroxyl group, preventing covalent bond formation and reducing the drug's binding affinity [76]. Analysis of post-progression plasma ctDNA and repeat tissue biopsies from sunvozertinib-treated patients has confirmed the emergence of C797S, mirroring the primary resistance pattern observed with third-generation inhibitors in classic *EGFR*-mutated NSCLC [36, 76, 77].

Other secondary gatekeeper mutations, including T790M and rare solvent-front alterations, have also been identified, emphasizing the need for comprehensive molecular profiling upon progression [77, 78].

8.2. Bypass Signaling Pathways and Genomic Amplifications

Tumor cells frequently circumvent EGFR inhibition by activating parallel receptor tyrosine kinases or downstream effectors, maintaining oncogenic signaling despite complete suppression of the primary driver [79, 80].

1. MET Amplification: High-level focal gene amplification of *MET* is an established bypass mechanism across multiple EGFR TKI generations [70, 79]. Hyperactivated MET recruits GAB1 and activates downstream PI3K-AKT and MAPK signaling independently of EGFR [70, 79]. Patients developing *MET* amplification following sunvozertinib progression represent candidates for combination regimens incorporating MET-targeted small molecules or the bispecific antibody amivantamab [70, 79].
2. HER2 (ERBB2) Amplification: Gene duplication or secondary kinase mutations within *ERBB2* reactivate heterodimeric signaling, bypassing EGFR blockade [53, 80].
3. Downstream Intracellular Alterations: Acquired activating mutations in downstream pathways, including *KRAS* point mutations (e.g., G12D, G12V), *BRAF* V600E substitutions, loss of *NF1*, and *PIK3CA* activating mutations (e.g., E545K, H1047R), uncouple downstream signaling from upstream receptor control, rendering tumors resistant to single-agent upstream inhibition [80, 81].

8.3. Lineage Plasticity and Phenotypic Transformations

Histological and phenotypic transformation indicates an important mechanism of resistance that cannot be identified through liquid biopsy alone [82].

1. Small Cell Neuroendocrine Transformation (SCLC): Transformation from lung adenocarcinoma to high-grade small cell neuroendocrine carcinoma is documented in roughly 3% to 10% of EGFR TKI-resistant cases [82]. This transition is typically accompanied by the functional loss of both retinoblastoma 1 (*RB1*) and tumor protein p53 (*TP53*) [82]. Transformed tumors show diminished EGFR dependency and become resistant to all EGFR-directed TKIs, requiring treatment with platinum-etoposide regimens [82].
2. Epithelial-to-Mesenchymal Transition (EMT): Resistant clones can undergo phenotypic transition toward a mesenchymal state, characterized by downregulation of E-cadherin, upregulation of vimentin and N-cadherin, and increased invasive and migratory potential [82].

9. Current Trends and Future Perspectives

9.1. First-Line Treatment Evolution

The ongoing phase III WU-KONG8 study will establish whether sunvozertinib monotherapy can show superior progression-free survival over standard platinum doublet chemotherapy in treatment-naïve patients [63]. In classical *EGFR*-mutated disease, the upfront use of third-generation TKIs improved survival outcomes and delayed the onset of resistance compared to cytotoxic therapy [6, 7].

A central question in the frontline setting is whether oral sunvozertinib monotherapy can provide clinical outcomes comparable to the intensive regimen of amivantamab plus carboplatin and pemetrexed established by the PAPILLON trial [68]. While the triplet combination achieved high response rates (ORR 73%, PFS 11.4 months), it carries significant cumulative toxicities and requires regular intravenous administration [68]. An effective oral monotherapy offers important practical advantages regarding patient convenience, quality of life, and healthcare resource utilization. Future investigations may explore combinations of sunvozertinib with anti-angiogenic agents to deepen initial responses and extend remission duration [83].

9.2. Central Nervous System Management

Given the neurotropism of *EGFR*-mutated NSCLC and the high lifetime risk of brain metastases, systemic agents with high intracranial efficacy are necessary to prevent intracranial progression and delay the neurocognitive toxicities associated with whole-brain radiotherapy [40, 84].

Clinical trials should prospectively assess intracranial response rates, intracranial PFS, and cumulative CNS recurrence in patients presenting with untreated, asymptomatic brain metastases [84, 85]. Paired pharmacokinetic studies of cerebrospinal fluid and plasma will help clarify blood-brain barrier transport kinetics and inform optimal dosing for intracranial disease control [56].

9.3. Liquid Biopsy Biomarkers and Dynamic Monitoring

Serial ctDNA monitoring using ultra-sensitive next-generation sequencing provides a non-invasive tool for assessing therapeutic response and tracking resistance evolution [60, 78].

Early reduction or complete clearance of the *EGFR* exon 20 insertion allele frequency in plasma during initial treatment cycles serves as an early surrogate marker of durable response [60]. Furthermore, persistent longitudinal ctDNA surveillance allows the early detection of subclonal resistance alterations—such as emerging C797S mutations or *MET* amplifications—months prior to radiographic progression by RECIST criteria [77, 78, 80]. This molecular monitoring will support the development of adaptive clinical trials exploring pre-emptive therapeutic switches or targeted combination therapies [77, 81].

9.4. Expansion to HER2 Exon 20 Alterations and Non-Canonical Mutations

The structural homology between the kinase domains of EGFR and HER2, combined with the presence of the conserved Cys805 residue, provides a biochemical rationale for evaluating sunvozertinib in *HER2* exon 20 insertion-positive NSCLC [53, 86]. Preliminary data from HER2 expansion cohorts in early-phase trials have shown antitumor activity [54, 87]. As the therapeutic landscape expands, sunvozertinib may emerge as an important oral targeted option alongside approved antibody-drug conjugates such as trastuzumab deruxtecan, helping clarify optimal treatment sequencing in *HER2*-altered thoracic malignancies [87, 88].

10. Conclusion

Sunvozertinib provides a targeted oral therapeutic option for patients with advanced *EGFR* exon 20 insertion-mutant non-small cell lung cancer, addressing a long-standing challenge in precision oncology. Through structure-guided drug design, it overcomes the steric constraints of post-loop insertions to achieve potent covalent inhibition while preserving wild-type receptor selectivity. The international WU-KONG clinical development program shows meaningful antitumor activity, robust central nervous system penetration, and a manageable safety profile in platinum-pretreated disease, supporting its regulatory approvals in China and the United States. While acquired resistance through secondary mutations, bypass signaling, and phenotypic transformation remains an inevitable clinical hurdle, ongoing frontline phase III trials, ctDNA-guided treatment monitoring, and rational combination techniques will continue to clarify its role across the spectrum of oncogene-addicted lung cancers.

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