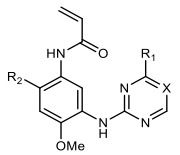
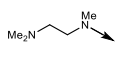
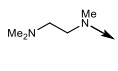
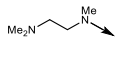
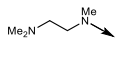
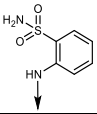
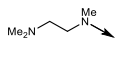
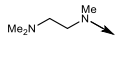
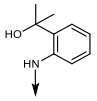
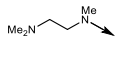
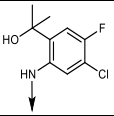
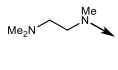
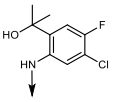
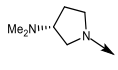
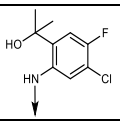
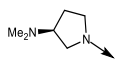
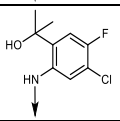
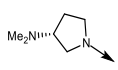
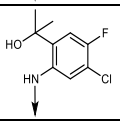
Supplementary Materials

Supplementary Table S1. A brief SAR summary for the discovery of sunvozertinib

	R_2 =	R_1 =	X =	pEGFR IC_{50} (nM)				Selected in vitro DMPK		
				H1975	Ba/F_3		A431	Kinetic solubility @ pH = 7.4 (μM)	Human Heps Clint [(μL/min)/(10^6 cells)]	Human plasma protein binding (% free)
				L858R /T790M	ASV	NPH	Wild-type			
AZD9291 (osimertinib)			CH	1.9	128	165	230	7.0*	3.9*	3.4*
Cpd-1			N	3.9	38	54	17	-	-	-
Cpd-2			N	13	130	97	75	-	-	-
Cpd-3			N	0.61	16	64	46	-	<1	71.1
Cpd-4			N	2.0	-	8.9	3.9	1.9	27.7	14.8
Cpd-5			N	0.32	6.8	15	6.3	90	34	33.6
Cpd-6			N	0.3	6.9	9.7	7.6	869	7.1	22.9
Cpd-7			CH	0.9	12	14	14	>1000	10.3	13.3
Cpd-8			N	0.6	6.9	14	12	471	2.8	19.6
Cpd-9 (Enantiomer of DZD9008)			CH	1.0	52	51	362	862	<1	11.1
DZD9008 (Sunvozertinib)			CH	1.1	20	20	80	616	3.3	8.5

*Data from Finlay et al (21)

Supplementary Table S2. Summary of nonclinical DMPK properties of sunvozertinib

Parameters	Values
Intrinsic permeability in Caco2 cell pH6.5/7.4	15.2 × 10^-6 cm/s (apical to basolateral)
Rat PK: IV route, Dose, CL, V_{ss}, $t_{1/2}$,	3 mg/kg, 30.8 mL/min/kg, 13.6 L/kg, 6.37 hr
Oral route, Dose, %F	3 mg/kg, 39.6%
Dog PK: IV route, Dose, CL, V_{ss}, $t_{1/2}$,	1 mg/kg, 30.9 mL/min/kg, 29.5 L/kg, 13.9 hr
Oral route, Dose, %F	1 mg/kg, 48.8%
CYP reversible inhibition (IC_{50}, nM)	> 30 μM (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2E1), 6.3 μM (CYP2D6), 18.2 μM (CYP3A4)
Time dependent inhibition (%inhibition at 10 μM)	< 20% (CYPs 1A2, 2C9, 2C19, and 2D6), 24.3% (CYP3A4)

Supplementary Table S3. Kinase panel screening at single-concentration of 1 μM sunvozertinib

Kinase (Human)	% Kinase Activity Inhibition	Kinase (Human)	% Kinase Activity Inhibition	Kinase (Human)	% Kinase Activity Inhibition
EGFR (T790M, L858R)	99	CK1γ1	15	MARK1	4
BTK	96	ROCK2	15	PI3 Kinase (p110d/p85α)	4
BLK	90	CDK7/cyclinH/MAT1	14	FGFR1	3
ErbB4	88	Syk	14	CaMKI	2
ALK	86	Fms	13	cKit	2
BMX	80	PKCα	13	FGFR4	2
EGFR	76	AMPKα2	12	JAK2	2
FAK	74	SGK	12	PKCε	2
ErbB2	73	DMPK	11	SRPK1	2
Mnk2	67	eEF-2K	11	DDR2	1
Fes	65	IRAK1	11	DRAK1	1
BRK	63	PI3 Kinase (p120g)	11	FGFR1(V561M)	1
Ros	51	Plk1	11	Ret	1
TrkA	51	Aurora-B	10	TBK1	1
Yes	51	CDK9/cyclin T1	10	FLT1	0
TNIK	47	c-RAF	10	GSK3α	0
Lyn	44	FGFR2	10	PI3 Kinase (p110a/p85α)	0
TGFBR1	42	MAPK1	10	ROCK1	0
LCK	37	CaMKII	9	DNA-PK	-1
IGF-1R	35	CHK1	9	PI3 Kinase (p110b/p85α)	-1
MLK1	33	GSK3β	9	PDGFRβ	-2
MET	30	Rsk1	9	PDK1	-2
MSK1	26	Fer	8	PI3KC2α	-2
EphB1	24	Ret (V804L)	8	ULK2	-2
IRAK4	24	Ron	8	JNK1α1	-3
JAK3	24	EphB4	7	MINK	-3
Fyn	23	PKA	7	p70S6K	-3
MEK1	21	ABL	6	PI3KC2g	-3
TAK1	21	Aurora-C	6	IKKβ	-5
PRAK	19	JAK1	6	PKBα	-5
ABL(T315I)	18	mTOR	6	AMPKα1	-6
ARG	18	Lck, activated	5	CK2α2	-6
cSRC	18	NEK2	5	Ret(V804M)	-6
ARK5	17	PAK2	5	PRKG2	-8
EphA5	17	PAK4	5	MLCK	-9
PKCθ	17	Rse	5	PAK1	-9
AXL	16	b-RAF	4	PKBβ	-10
FLT3	16	FGFR3	4	CDK1/cyclinB	-13
Pim-2	16	MAPKAP-K2	4	CDK2/cyclinA	-13

Supplementary Table S4. *In vitro* inhibitory activity (IC_{50}s, nM) of sunvozertinib against 15 kinases which were inhibited > 50% at 1 uM of sunvozertinib

Kinase (Human)	IC_{50}
EGFR (T790M, L858R)	13
BTK	213
EGFR	226
FAK	255
ErbB2	392
BRK	529
ErbB4	704
Ros	937
Mnk2	1032
BLK	1036
ALK	1172
Fes	1764
BMX	2289
Yes	2895
TrkA	>10,000

Supplementary Table S5. Common (> 10%) TEAEs by MedDRA preferred term

MedDRA Preferred Term	50 mg (n = 6) n (%)	100 mg (n = 9) n (%)	200 mg (n = 16) n (%)	300 mg (n = 51) n (%)	400 mg (n = 20) n (%)	All (n = 102) n (%)
Diarrhoea	1 (16.7)	1 (11.1)	10 (62.5)	29 (56.9)	17 (85.0)	58 (56.9)
Rash	3 (50.0)	2 (22.2)	3 (18.8)	23 (45.1)	14 (70.0)	45 (44.1)
Anaemia	2 (33.3)	3 (33.3)	4 (25.0)	16 (31.4)	11 (55.0)	36 (35.3)
Nausea	1 (16.7)	3 (33.3)	3 (18.8)	19 (37.3)	8 (40.0)	34 (33.3)
Vomiting	1 (16.7)	2 (22.2)	3 (18.8)	13 (25.5)	13 (65.0)	32 (31.4)
Decreased appetite	1 (16.7)	3 (33.3)	2 (12.5)	17 (33.3)	9 (45.0)	32 (31.4)
Paronychia	1 (16.7)	1 (11.1)	4 (25.0)	15 (29.4)	8 (40.0)	29 (28.4)
Blood creatine phosphokinase increased	0 (0.0)	2 (22.2)	3 (18.8)	9 (17.6)	12 (60.0)	26 (25.5)
Fatigue	2 (33.3)	1 (11.1)	1 (6.3)	11 (21.6)	7 (35.0)	22 (21.6)
Blood creatinine increased	0 (0.0)	1 (11.1)	1 (6.3)	9 (17.6)	8 (40.0)	19 (18.6)
Mouth ulceration	0 (0.0)	1 (11.1)	2 (12.5)	11 (21.6)	4 (20.0)	18 (17.6)
Weight decreased	0 (0.0)	3 (33.3)	0 (0.0)	6 (11.8)	6 (30.0)	15 (14.7)
Amylase increased	0 (0.0)	2 (22.2)	2 (12.5)	8 (15.7)	2 (10.0)	14 (13.7)
Lipase increased	0 (0.0)	0 (0.0)	1 (6.3)	8 (15.7)	4 (20.0)	13 (12.7)
Hypokalaemia	0 (0.0)	1 (11.1)	0 (0.0)	5 (9.8)	7 (35.0)	13 (12.7)
Aspartate aminotransferase increased	1 (16.7)	1 (11.1)	1 (6.3)	5 (9.8)	4 (20.0)	12 (11.8)
Dizziness	0 (0.0)	2 (22.2)	1 (6.3)	5 (9.8)	4 (20.0)	12 (11.8)
Pneumonia	0 (0.0)	1 (11.1)	1 (6.3)	5 (9.8)	4 (20.0)	11 (10.8)

Pooled analysis of WU-KONG1 and WU-KONG2 studies. Data cut-off date: 3 April 2021. TEAE: treatment emergent adverse event. MedDRA: Medical Dictionary for Regulatory Activities.

Supplementary Table S6. Summary of multiple-dose sunvozertinib pharmacokinetic parameters geometric mean [%CV] after daily administration on day 1 of Cycle 2.

	50 mg N = 5	**100 mg** N = 7	**200 mg** N = 9	**300 mg** N = 11	**400 mg** N = 10
AUC_{tau} (hr*ng/mL)	1271 [32.73]	4371 [51.80]	6817 [50.57]	9131 [50.82]	16730 [47.69]
$C_{ss,max}$ (ng/mL)	68.42 [36.93]	252.1 [46.65]	402.3 [50.27]	521.4 [48.38]	976.2 [52.27]

Data are preliminary, unvalidated and subject to change. AUC_{tau}, area under the concentration-time curve within dosing interval; C_{max}, maximum plasma concentration.

Supplementary Table S7. Antitumor activity of sunvozertinib in EGFR exon20ins subtypes

Mutation subtypes	**ORR*, n (%)**	**DCR, n (%)**
V769_D770insASV (N = 20)	8 (40.0)	19 (90.0)
D770_N771insSVD (N = 10)	6 (60.0)	9 (90.0)
Other subtypes[#] (N = 18)	7 (38.9)	15 (83.3)
Unknown subtypes (N = 5)	0 (0.0)	4 (80.0)
All (N = 53)	21 (39.6)	46 (86.8)

Pooled analysis of WU-KONG1 and WU-KOKNG2 studies at dose levels ≥ 100 mg. Data cut-off date: 3 April 2021. ORR: objective response rate; DCR: disease control rate. [*]: Confirmed ORR; [#]: Other subtypes of EGFR exon20ins include: V774_C775insHV, D770delinsDV, V769_D770insASV, H773_V774insH, H773_V774insAH, D770_N771insG, H773_V774insPHPH and N771_P772insSVDN.

Supplementary Table S8. Antitumor activity of sunvozertinib in EGFR or HER2 mutations beyond EGFR exon20ins in the phase 1 study

Mutation Types	Number of PR (n)	Number of SD (n)
EGFR sensitizing mutation (n=4)	1	2
EGFR double mutation (n=6)	1	3
HER2 exon20ins (n=26)	3	7
EGFR uncommon mutation (n=1)	0	1

Note:

EGFR sensitizing mutation includes L858R and 19del. EGFR double mutation include L8585R/T790M or 19del/T790M.

In 4 patients with EGFR sensitizing mutation who received median 5 lines of prior systemic therapy, including 100% post EGFR TKI treatment, 1 showed PR.

In 6 patients with EGFR sensitizing /T790M double mutation who received median 3 lines of prior systemic therapy, including 100% post EGFR TKI treatment, 1 showed PR (50 mg, post icotinib treatment, but not osimertinib).

In 26 patients with HER2 Exon20ins who received median 3 lines of prior systemic therapy including 3 received HER2 targeted therapy, 3 showed PR (2 cases, 300 mg; 1 case, 400 mg) with 1 confirmed.