Supplementary Materials and Methods

The sources, application and dilution of the antibodies used for Western blotting (WB) or immunohistochemical (IHC) analyses in this study are listed below.

Antibody	Source	Application	Dilution
Phospho-Akt	Cell Signaling Technologies #2965	WB	1:1000
Phospho-Erk1/2	Cell Signaling Technologies #9101	WB	1:1000
Phospho-IGF1Rβ/INSRβ	Cell Signaling Technologies #3024	WB	1:1000
Phospho-S6	Cell Signaling Technologies #2211	WB	1:2000
Akt	Cell Signaling Technologies #9272	WB	1:1000
β-Actin	Sigma-Aldrich #A2066	WB	1:5000
Erk1/2	Cell Signaling Technologies #2965	WB	1:1000
IGF1Rβ	Cell Signaling Technologies #3027	WB	1:1000
S6	Cell Signaling Technologies #2217	WB	1:2000
BrdU	AbD Serotec #OBT0030CX	IHC	1:1000
Cleaved Caspase 3	Cell Signaling Technologies #9664	IHC	1:200
Phospho-Erk1/2	Cell Signaling Technologies #4376	IHC	1:40
Phospho-S6	Cell Signaling Technologies #4858	IHC	1:200

Statistics of data collection and processing	
Ligand	BI 885578
X-ray source	SLS BEAMLINE X06SA
Wavelength [Å]	1.0000
Detector	Pilatus 6M
Temperature [K]	100
Space group	P212121
Cell: a; b; c [Å]	56.6; 70.4; 87.9
α; β; γ [°]	90.0; 90.0; 90.0
Resolution [Å] [1]	2.27 (2.27-2.26)
Unique reflections [1]	16,922 (175)
Completeness [%] [1]	100.0 (100.0)
Multiplicity [1]	6.4 (6.6)
R_{sym}[%] [1]	6.4 (33.6)
R_{meas} [%] [1, 2]	9.3 (69.1)
Mean(I)/sigma [1,2]	14.3 (3.0)

Supplementary Table S1: Statistics of x-ray data collection and processing.

[1] Numbers in brackets correspond to the resolution bin with highest resolution.

[2] Calculated from independent reflections

Refinement statistics[1]

Ligand	BI 885578
Resolution [Å]	37.26-2.26
Number of reflections (working / test)	41,861 / 2140
R_{cryst}[2] [%]	21.26
R_{free}[2] [%]	26.20
Total number of atoms:	
Protein	2,269
Water	137
Ligand	39
Deviation from ideal geometry: [3]	
Bond lengths [Å]	0.008
Bond angles [°]	0.98
Ramachandran Plot: [4]	
Most favored regions	93.4%
Additional allowed regions	6.6%
Generously allowed regions	0.0%
Disallowed regions	0.0%

Supplementary Table S2: X-ray refinement statistics.

[1] Values as defined in AutoBUSTER

[2] Test-set contains 5.04 % of measured reflections

[3] Root mean square deviations from geometric target values

[4] Calculated with program PROCHECK

Kinase	IC_{50} (nM)*
IGF1R	1
INSR	1
CLK2	33
FER	33
IRAK1	44
PRKCN	50
FES	55
PTK2	58
PRKD2	58
PRKD1	60
NTRK1	74
CLK1	106
FLT3	119
NTRK3	123
PTK2B	164
MELK	211
CSNK1D	236
NTRK2	248
MAP3K9	285
EPHA2	298
NUAK1	411
MST1R	489
MERTK	597
EGFR	623
LCK	717
CDK2	890
EPHB2	911
174 other kinases†	>1000

Supplementary Table S3: *In vitro* human kinase inhibition profile of BI 885578.

*Each kinase was tested in the presence of an ATP concentration corresponding to the respective Km.

†In the presence of 1000 nM BI 885578, the activity of the following kinases was greater than 50% control: ABL1/2, ACVR1B, ADRBK2, AKT1/2/3, AURKB/C, BLK, BRAF, BRSK1, CAMK1A/1D/2A/2B/2D/K4, CDC42BPA, CDK1/5/7, CHEK1/2, CLK3, CSF1R, CSK, CSNK1A1/1G1/1G2/1G3/2A1/2A2, DAPK1/3, DCAMKL2, DNA-PK, DYRK1A/1B, DYRK3/4, EEF2K, EPHA1/8, EPHB3/4, ERBB2/4, FGFR1/2/3/4, FLT1/4, FYN, GRK4/5/6/7, GSK3A/B, HCK, HIPK1/3/4, IKBKB/E, ITK, JAK1/2/3, KDR, KIT, MAP2K1/6, MAP3K8, MAP4K2/4/5, MAPK1/3/8/9/10/11/12/13/14, MAPKAPK2/3/5, MARK1/2/3/4, MATK, MET, MINK1, MKNK1, MST4, MTOR, MYLK2, NEK1/2/4/6/7/9, PAK1/2/3/4/6/7, PASK, PDGFRA/B, PDK1, PHKG1, PI4KB, PIK3C2A/2B/C3/CG, PIM1/2, PKN1, PLK1/2/3, PRKACA, PRKCA/B1/B2/D/E/G/H/I/Q/Z, PRKG1/2, PRKX, PTK6, RAF1, ROCK1/2, ROS1, RPS6KA4/A5/B1, SGK, SGK2, SGKL, NF1LK2, SPHK1/2, SRMS, SRPK1/2, STK3/4/6/22B/23/24/25, TAOK2, TBK1, TEK, TYK2, TYRO3, ZAP70.

Supplementary Figures Legends

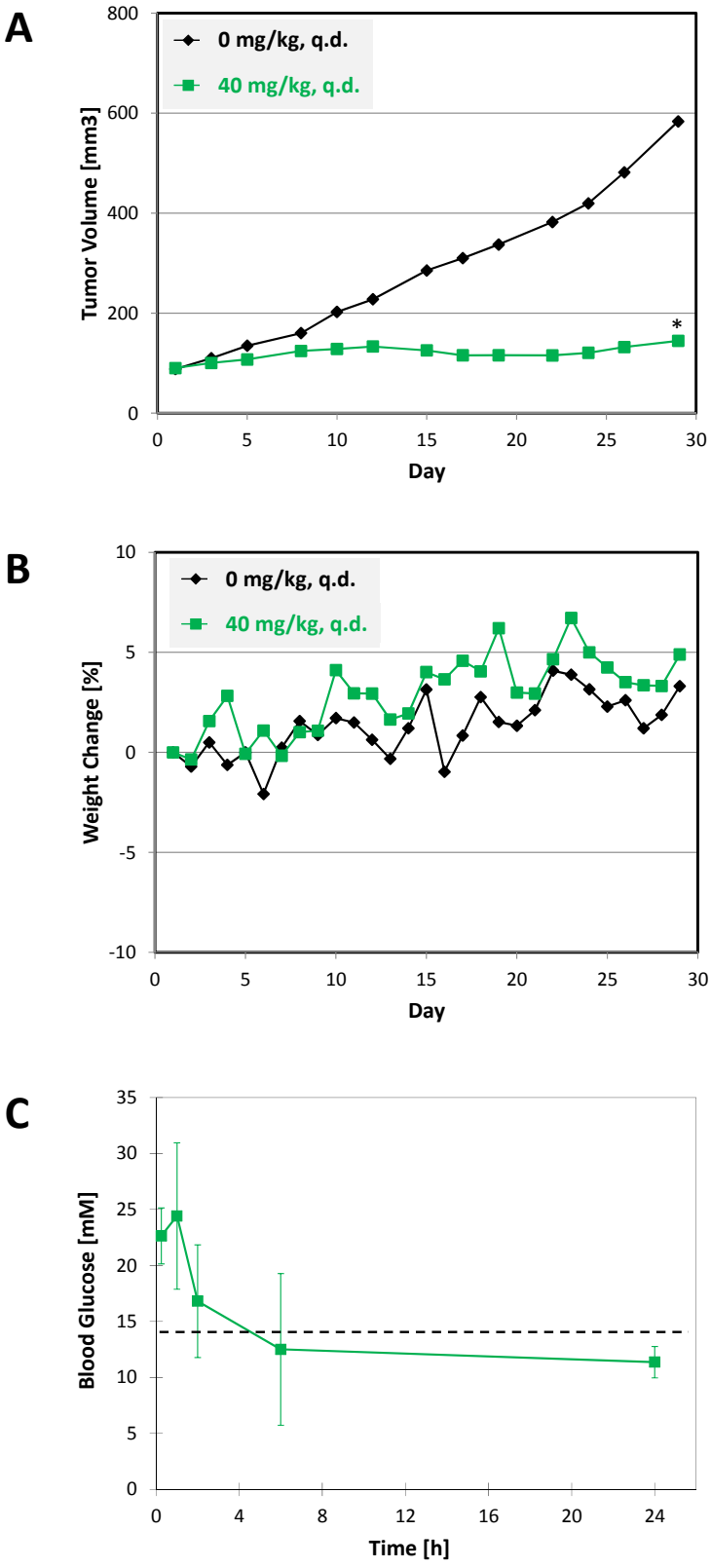
Supplementary Figure S1: Efficacy and tolerability of BI 885578 in the CL-14 xenograft model. CL-14 tumor-bearing mice (7 per group) were treated orally with vehicle control (0 mg/kg q.d.) or BI 885578 (40 mg/kg q.d.). (*A*) Median tumor volumes were monitored on the days indicated by a data point. (*B*) Median changes in mouse body weight were monitored every day. (*C*) Following the final BI 885578 treatment, blood glucose levels were measured at the indicated time points. The upper limit of normal (ULN) blood glucose levels in untreated mice is indicated by the dashed line.

* $p < 0.05$ for treated versus control group.

Supplementary Figure S2: Effects of BI 885578 on IGF1R and INSR phosphorylation in GEO tumors. GEO tumor-bearing mice were treated once orally with BI 885578 (40 mg/kg) and tumors sampled at 0, 6, 24, 48 and 72 h after administration (3 animals per time point). The phosphorylation of the IGF1R and INSR was measured in tumor protein extracts.

* $p < 0.05$ for treated versus control group.

Supplementary Figure S1



Supplementary Figure S2