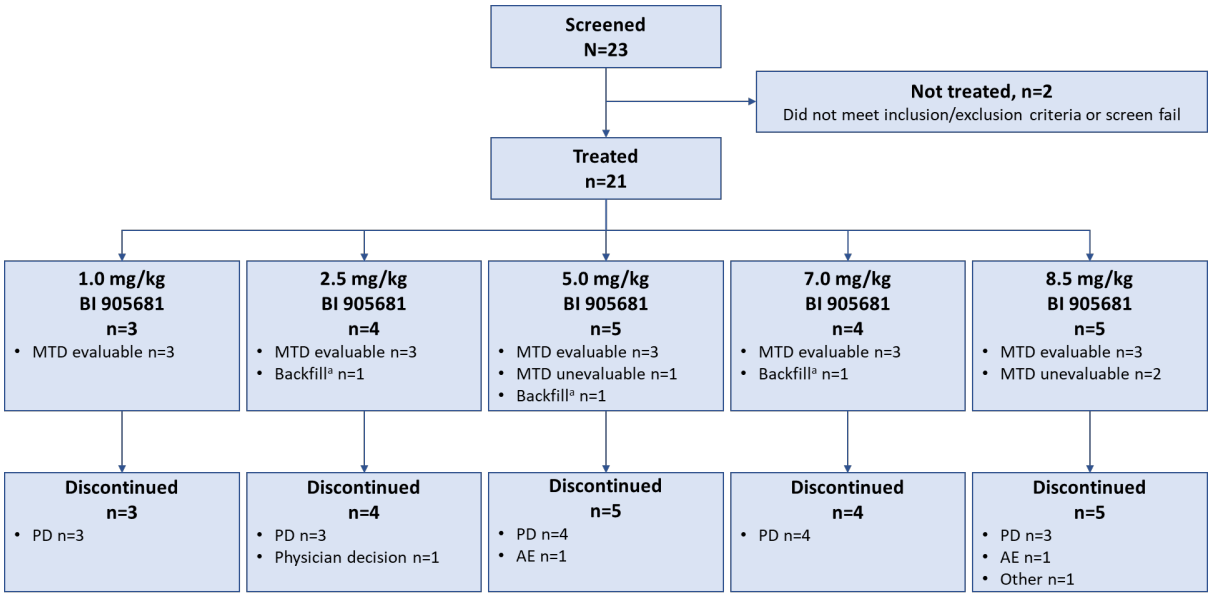
Supplementary Material

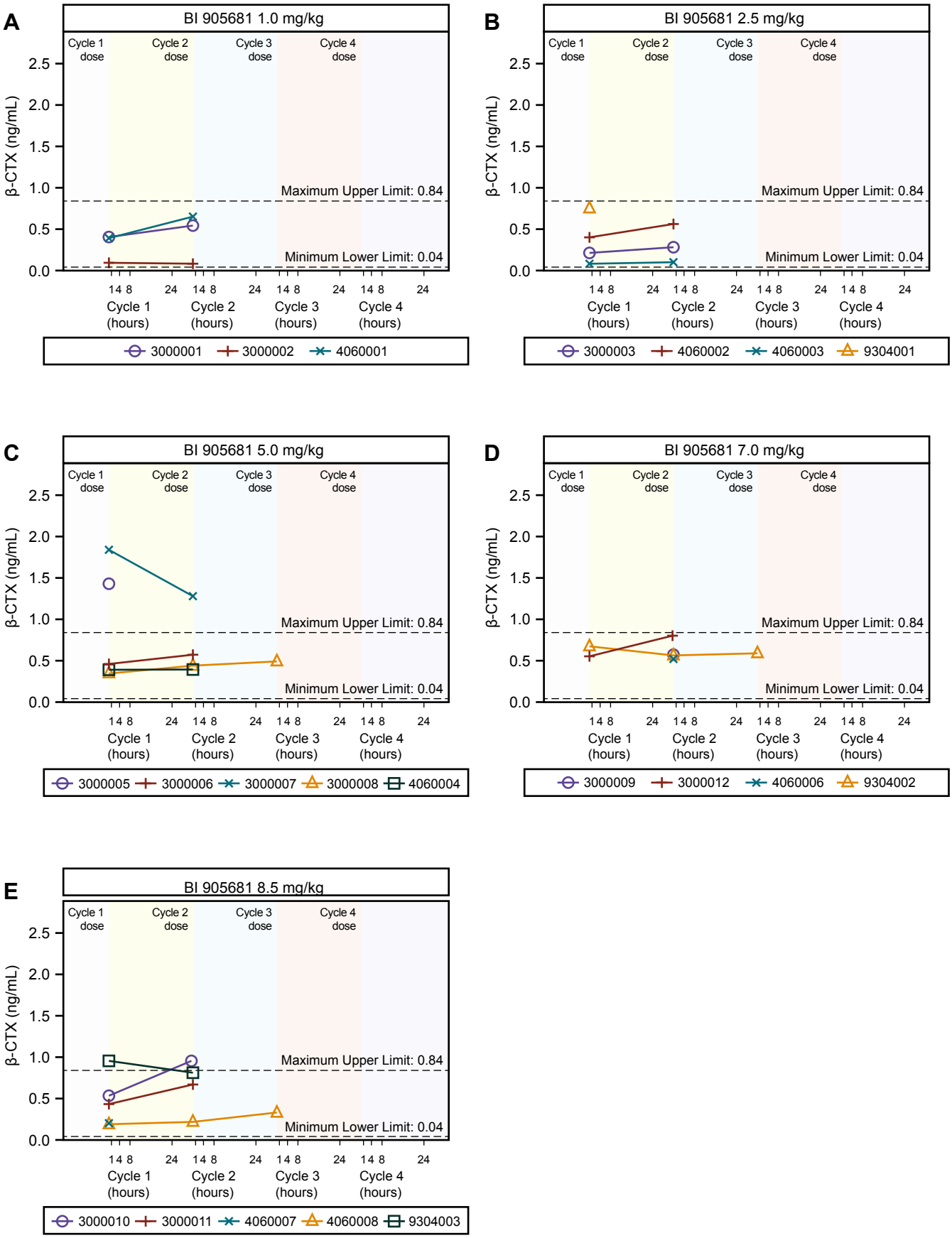
Supplementary Figure 1. *Patient disposition*



[a] Once each dose-level was cleared, backfilled patients with tumors harboring *RNF43* mutations or RSPO fusions were to be added.

AE, adverse event; MTD, maximum tolerated dose; PD, progressive disease; RNF43, ring finger protein 43; RSPO, R-spondin.

Supplementary Figure 2. *B-CTX levels over time per BI 905681 dose level (A: 1.0 mg/kg; B: 2.5 mg/kg; C: 5.0 mg/kg; D: 7.0 mg/kg; E: 8.5 mg/kg)*



Actual times are represented relative to dosing in each cycle. End of Treatment results are not included. β-CTX is a form of C-telopeptide used as a marker of bone resorption.

Supplementary Table 1. *Definition of dose-limiting toxicities*

Dose-limiting toxicity	**Grade**
Non-hematologic	
Bone mineral density change of >5% from baseline, confirmed ≥2 months after initial observation	-
β-CTX increase of at least two-fold from baseline	-
Osteoporosis	3
Retinopathy and clinically meaningful changes in fundus photography and spectral domain optical coherence tomography	≥2
Any fracture without a history of trauma or as a result of a fall from standing height or less	-
Vomiting or diarrhea (irrespective of whether adequately treated)	4
Any non-hematologic toxicity[a]	≥3
Hematologic	
Anemia	4
Anemia requiring blood transfusion	3
Neutropenia present for >7 days	4
Febrile neutropenia	≥ 3
Neutropenia with documented infection	3
Any thrombocytopenia with bleeding or a requirement for platelet transfusions	3
Thrombocytopenia (platelets <25,000/μL)	4

AEs were coded using the Medical Dictionary for Drug Regulatory Activities.
β-CTX is a form of C-telopeptide used as a marker of bone resorption.

[a] With the following exceptions: inadequately treated grade 3 vomiting or diarrhea persisting for <48 hours after start of adequate treatment, grade 3 vomiting or diarrhea that persists for <48 hours after start of adequate treatment, inadequately treated nausea, grade 3 fatigue that persists <7 days, and any grade 3 laboratory abnormality that is not considered clinically relevant by the investigator, resolves spontaneously or responds to conventional medical intervention.

AE, adverse event; β-CTX, beta-carboxy-terminal telopeptide.

Supplementary Table 2. *Treatment exposure*

	BI 905681, mg/kg					
	1.0 n=3	**2.5 n=4**	**5.0 n=5**	**7.0 n=4**	**8.5 n=5**	**Total N=21**
Number of treatment cycles, n (%)						
1	0	1 (25.0)	1 (20.0)	0	1 (20.0)	3 (14.3)
2	3 (100)	3 (75.0)	3 (60.0)	3 (75.0)	3 (60.0)	15 (71.4)
3	0	0	0	0	0	0
4	0	0	1 (20.0)	1 (25.0)	1 (20.0)	3 (14.3)
≥5	0	0	0	0	0	0
Median number of treatment cycles, n (range)	2.0 (2–2)	2.0 (1–2)	2.0 (1–4)	2.0 (2–4)	2.0 (1–4)	2.0 (1–4)
Number of patients with dose reductions, n (%)	0	0	0	0	1 (20.0)	1 (4.8)
Median dose intensity, % (range)	99.9 (100–100)	100.5 (99–102)	100.0 (100–102)	100.9 (99–10.2)	100.7 (91–102)	100.3 (91–102)

Supplementary Table 3. *BI 905681 pharmacokinetics at Cycle 1*

	BI 905681, mg/kg				
	1.0 n=3	**2.5 n=4**	**5.0 n=4**	**7.0 n=4**	**8.5 n=3**
gMean (gCV [%])					
C_{max}, µg/mL	NA[a]	49.6 (19.7)	157 (18.0)[b]	185 (23.1)	201 (21.4)[c]
$C_{max,norm}$, (µg/mL)/mg	NA[a]	0.272 (13.8)	0.397 (19.0)[b]	0.297 (11.7)	0.264 (36.1)[c]
$AUC_{0–tz}$, µg·h/mL	4260 (27.8)	7640 (10.6)	18200 (53.2)[b]	30000 (23.8)	18900 (217)[c]
$AUC_{0–tz,norm}$, (µg·h/mL)/mg	56.3 (7.27)	41.8 (20.3)	46.0 (44.0)[b]	48.1 (9.63)	24.9 (257)[c]
$AUC_{0–504}$, µg·h/mL	4270 (27.8)	7820 (12.2)	22600 (20.6)	30100 (23.3)	36300 (28.7)
$AUC_{0–504,norm}$, (µg·h/mL)/mg	56.3 (7.28)	42.8 (20.2)	54.9 (19.3)	48.3 (10.1)	50.8 (5.12)
$AUC_{0–\infty}$, µg·h/mL	4910 (32.8)	9530 (14.1)	26800 (17.7)	37600 (17.7)	49300 (35.6)
$AUC_{0–\infty,norm}$, (µg·h/mL)/mg	64.9 (11.4)	52.2 (27.7)	65.2 (18.9)	60.3 (15.7)	69.0 (24.8)
$\%AUC_{tz–\infty}$, %	12.5 (39.1)	19.0 (33.0)	16.0 (12.7)	19.6 (28.5)	22.8 (62.9)
$T_{1/2}$, day	7.31 (20.1)	8.48 (27.4)	8.11 (9.88)	9.23 (18.4)	10.6 (50.6)
MRT, hours	242 (19.5)	282 (26.3)	268 (9.28)	307 (13.7)	366 (43.1)
CL, mL/min	0.257 (11.4)	0.320 (27.7)	0.256 (18.9)	0.276 (15.7)	0.241 (24.8)
V_z, L	3.90 (13.0)	5.63 (17.4)	4.31 (21.1)	5.30 (3.86)	5.32 (23.7)
V_{ss}, L	3.72 (12.0)	5.41 (15.6)	4.12 (21.4)	5.09 (2.91)	5.30 (17.6)
Median (range)					
t_{max}, hours	NA[a]	2.56 (1.03–7.53)	1.60 (10.2–8.00)[b]	1.95 (1.08–3.98)	3.99 (1.08–4.10)[c]
t_z, hours	504 (503–504)	504 (388–504)	504 (71.5–505)[b]	503 (480–505)	493 (24.2–528)[c]

[a] N=2 (one patient had missing data due to prolonged infusion); [b] N=5; [c] N=4.

AUC, area under the curve; CL, clearance; C_{max}, maximum measured concentration; gCV, geometric coefficient of variation; IV, intravenous; MRT, mean residence time; NA, not applicable; PK, pharmacokinetics; PKS, pharmacokinetic set; Q3W, once every 3 weeks; $t_{1/2}$, terminal half-life; t_{max}, time to reach maximal plasma concentration; t_z, last measured time; V_{ss}, volume of distribution after intravenous infusion; V_Z, apparent volume of distribution during the terminal phase.

Supplementary Table 4. *BI 905681 pharmacokinetics at Cycle 2*

	BI 905681				
	1.0 mg/kg n=3	**2.5 mg/kg n=4**	**5.0 mg/kg n=4**	**7.0 mg/kg n=4**	**8.5 mg/kg n=3**
gMean (gCV [%])					
C_{max}, µg/mL	33.7 (13.4)	55.6 (26.1)	152 (11.0)[a]	227 (22.5)	292 (3.43)
$C_{max,norm}$, (µg/mL)/mg	0.445 (7.33)	0.310 (18.5)	0.369 (13.7)[a]	0.364 (32.5)	0.409 (29.7)
$AUC_{0–tz}$, µg·h/mL	5010 (28.5)	10700 (32.5)	23700 (47.4)[a]	36800 (14.6)	53900 (8.68)
$AUC_{0–tz,norm}$, (µg·h/mL)/mg	66.1 (8.56)	59.9 (54.2)	57.8 (42.6)[a]	59.0 (20.2)	75.5 (34.6)
$AUC_{0–504}$, µg·h/mL	4960 (30.1)	9540 (13.0)	26800 (15.9)	36100 (16.1)	50200 (17.6)
$AUC_{0–504,norm}$, (µg·h/mL)/mg	65.5 (10.1)	53.3 (27.5)	65.8 (10.1)	57.9 (18.1)	70.4 (26.5)
$AUC_{0–\infty}$, µg·h/mL	5830 (39.7)	12400 (22.3)	33100 (17.1)	44700 (11.7)	64200 (18.6)
$AUC_{0–\infty,norm}$, (µg·h/mL)/mg	77.0 (18.8)	69.0 (39.4)	81.1 (8.65)	71.7 (23.3)	89.9 (20.9)
$\%AUC_{tz–\infty}$, %	10.5 (135)	5.88 (636)	6.92 (375)	17.2 (25.1)	6.45 (1060)
$T_{1/2}$, day	7.48 (34.9)	9.06 (26.6)	8.72 (6.18)	9.06 (15.8)	9.37 (15.2)
MRT, hours	242 (35.5)	334 (30.6)	303 (5.96)	298 (11.5)	327 (11.2)
CL, mL/min	0.254 (10.1)	0.313 (27.5)	0.253 (10.1)	0.288 (18.1)	0.237 (26.5)
V_{ss}, L	3.69 (25.3)	6.27 (3.28)	4.61 (15.7)	5.15 (7.05)	4.65 (38.5)
LI	1.01 (7.06)	1.00 (5.92)	0.939 (5.64)	0.960 (6.30)	1.02 (17.9)
PTF, %	296 (23.0)	234 (28.1)	218 (18.4)	268 (31.8)	239 (20.8)
$R_{A,Cmax}$	NA[b]	1.16 (3.80)	1.00 (9.95)	1.22 (25.6)	1.34 (17.7)
$R_{A,AUC0–504}$	1.16 (3.02)	1.26 (2.95)	1.11 (5.46)	1.20 (9.44)	1.39 (21.2)
Median (range)					
t_{max}, hours	1.57 (1.48–3.98)	1.55 (1.07–4.02)	1.13 (1.03–1.55)[a]	1.33 (1.10–1.52)	1.50 (1.02–4.12)
t_z, hours	504 (504–601)	819 (340–1640)	503 (171–1460)[a]	503 (502–623)	504 (502–1510)

[a] N=4; [b] N=2 (one patient had a missing C_{max} at Cycle 1 due to prolonged infusion).

AUC, area under the curve; CL, clearance; C_{max}, maximum measured concentration; gCV, geometric coefficient of variation; IV, intravenous; LI, linearity index; MRT, mean residence time; NA, not applicable; PK, pharmacokinetics; PKS, pharmacokinetic set; PTF, peak-trough fluctuation; Q3W, once every 3 weeks; R_A, accumulation ratio; $t_{1/2}$, terminal half-life; t_{max}, time to reach maximal plasma concentration; t_z, last measured time; V_{ss}, volume of distribution after intravenous infusion.

Supplementary Table 5. *Disease control*

	BI 905681, mg/kg					
	1.0 n=3	**2.5 n=4**	**5.0 n=5**	**7.0 n=4**	**8.5 n=5**	**Total N=21**
Number of patients with disease control, n (%)	1 (33.3)	1 (25.0)	1 (20.0)	1 (25.0)	1 (20.0)	5 (23.8)
Median duration of disease control, days (range)	35.0 (35–35)	41.0 (41–41)	80.0 (80–80)	89.0 (89–89)	80.0 (80–80)	80.0 (35–89)

[a] Median, Q1 and Q3 calculated from Kaplan-Meier curve.

Q, quartile.