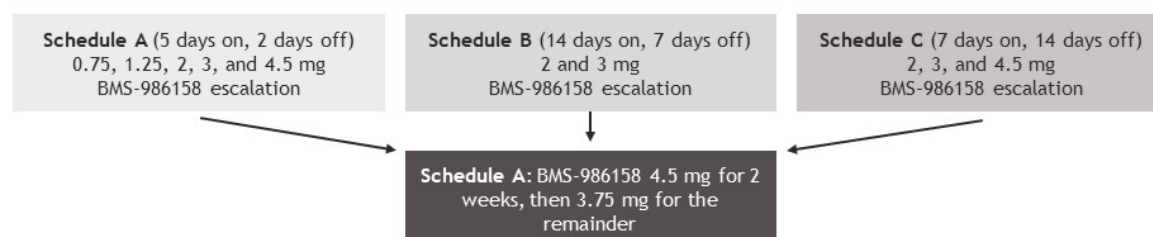# Supplemental Materials

Title: BMS-986158, a Small Molecule Inhibitor of the Bromodomain and Extraterminal Domain Proteins, in Patients With Selected Advanced Solid Tumors: Results From a Phase 1/2a Trial
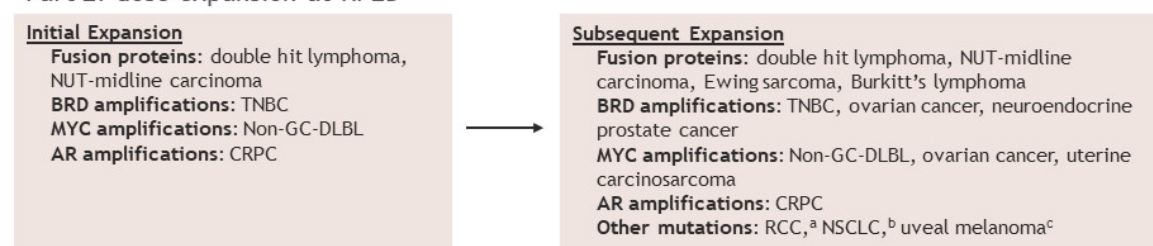
John Hilton,[1] Mihaela Cristea,[2] Sophie Postel-Vinay,[3] Capucine Baldini,[3] Mark Voskoboynik,[4,5] William Edenfield,[6] Geoffrey I. Shapiro,[7] Michael L. Cheng,[7] Jacqueline Vuky,[8] Bradley Corr,[9] Sharmila Das,[10] Abraham Apfel,[10] Ke Xu,[10] Martin Kozicki,[10] Keziban Ünsal-Kaçmaz,[10] Amy Hammell,[10] Guan Wang,[10] Palanikumar Ravindran,[10] Georgia Kollia,[10] Oriana Esposito,[10] Shodeinde Coker,[10] Jennifer R. Diamond[9]

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Part 1: dose escalation in patients with TNBC, ovarian cancer, SCLC, or other selected solid tumors

Schedule A (5 days on, 2 days off)
0.75, 1.25, 2, 3, and 4.5 mg
BMS-986158 escalation

Schedule B (14 days on, 7 days off)
2 and 3 mg
BMS-986158 escalation

Schedule C (7 days on, 14 days off)
2, 3, and 4.5 mg
BMS-986158 escalation

Schedule A: BMS-986158 4.5 mg for 2 weeks, then 3.75 mg for the remainder

Part 2: dose expansion at RP2D

Initial Expansion
   Fusion proteins: double hit lymphoma, NUT-midline carcinoma
   BRD amplifications: TNBC
   MYC amplifications: Non-GC-DLBL
   AR amplifications: CRPC

Subsequent Expansion
   Fusion proteins: double hit lymphoma, NUT-midline carcinoma, Ewing sarcoma, Burkitt's lymphoma
   BRD amplifications: TNBC, ovarian cancer, neuroendocrine prostate cancer
   MYC amplifications: Non-GC-DLBL, ovarian cancer, uterine carcinosarcoma
   AR amplifications: CRPC
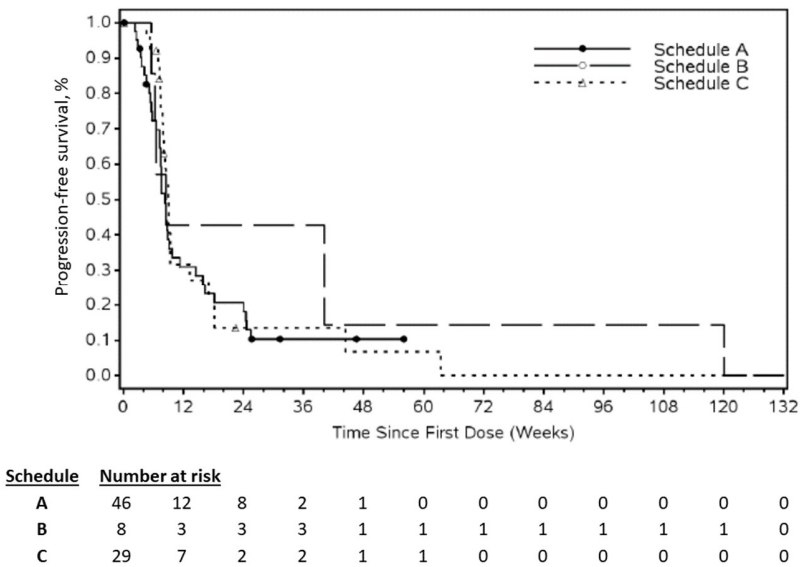   **Other mutations:** RCC,[a] NSCLC,[b] uveal melanoma[c]

Figure S1. Study design. [a]Renal cell carcinoma with *SWI*/*SNF* mutations; [b]Non-small cell lung cancer with *SWI*/*SNF* or *KRAS*/wt*TK11*; [c]Uveal melanoma with *Gnaq*/*11*. AR, androgen receptor; BRD, bromodomain; CRPC, castration-resistant prostate cancer; Non-GC-DLBL, non-germinal center diffuse large B-cell lymphoma; NSCLC, non-small cell lung cancer; NUT, nuclear protein in testis; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.
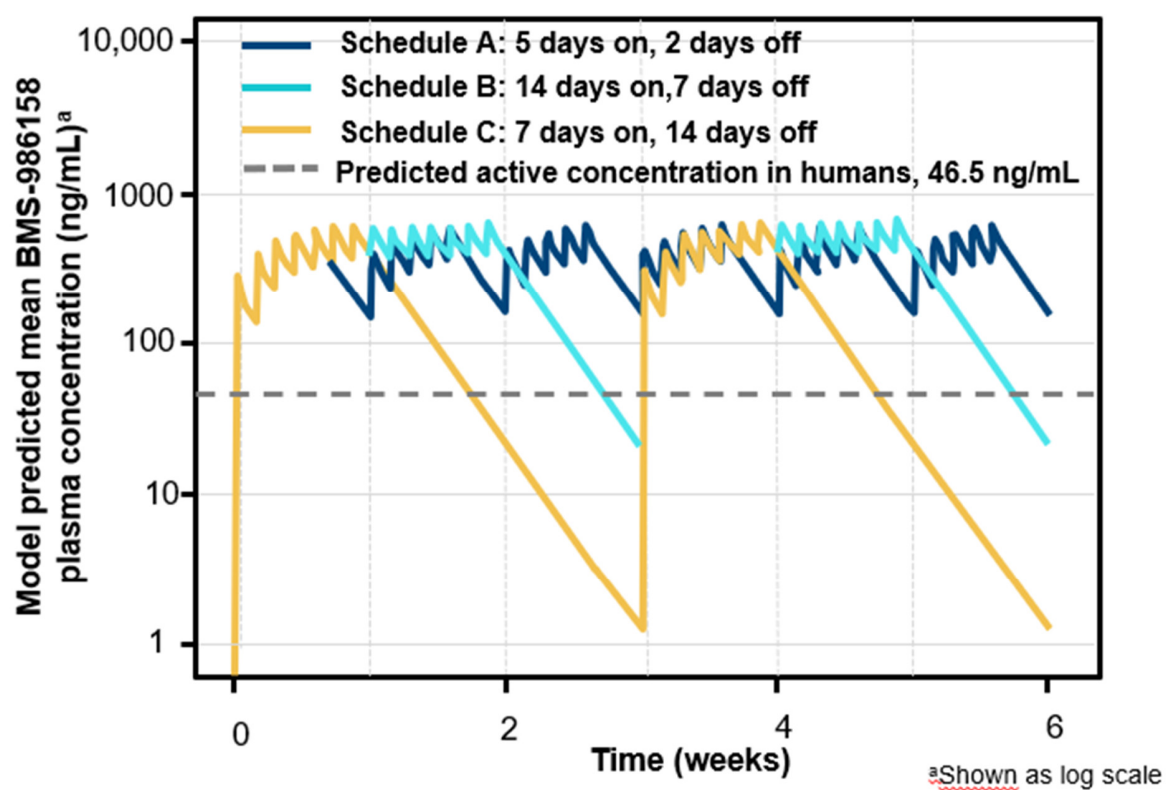
Figure S2. Predicted pharmacokinetic profile at BMS-986158 3-mg dose for each treatment schedule.
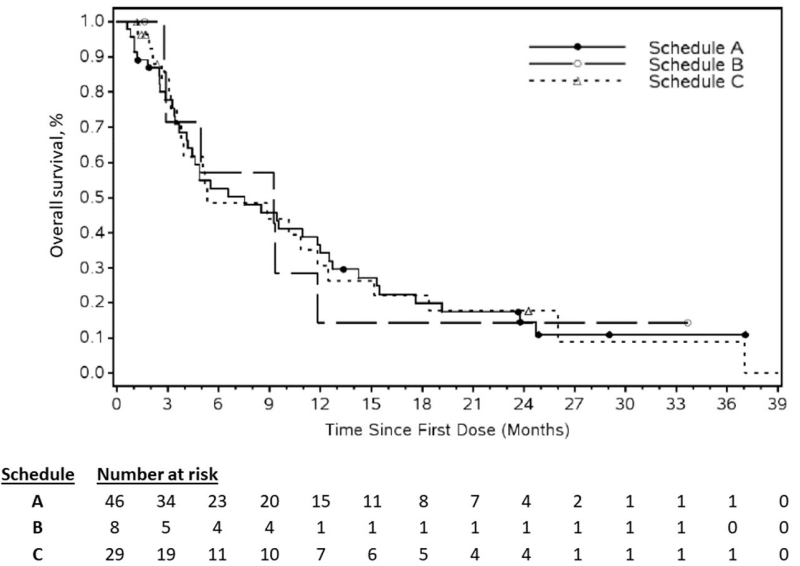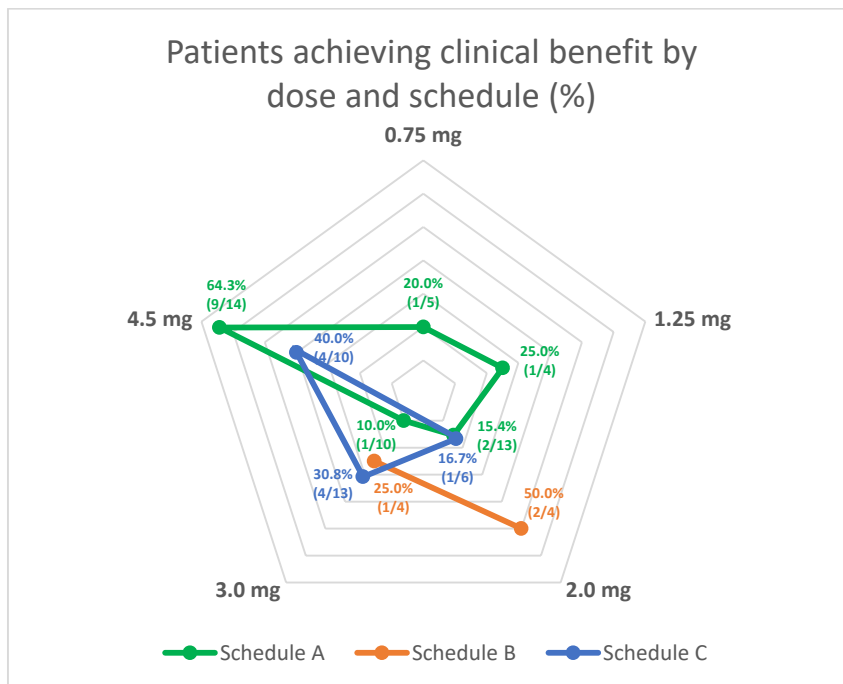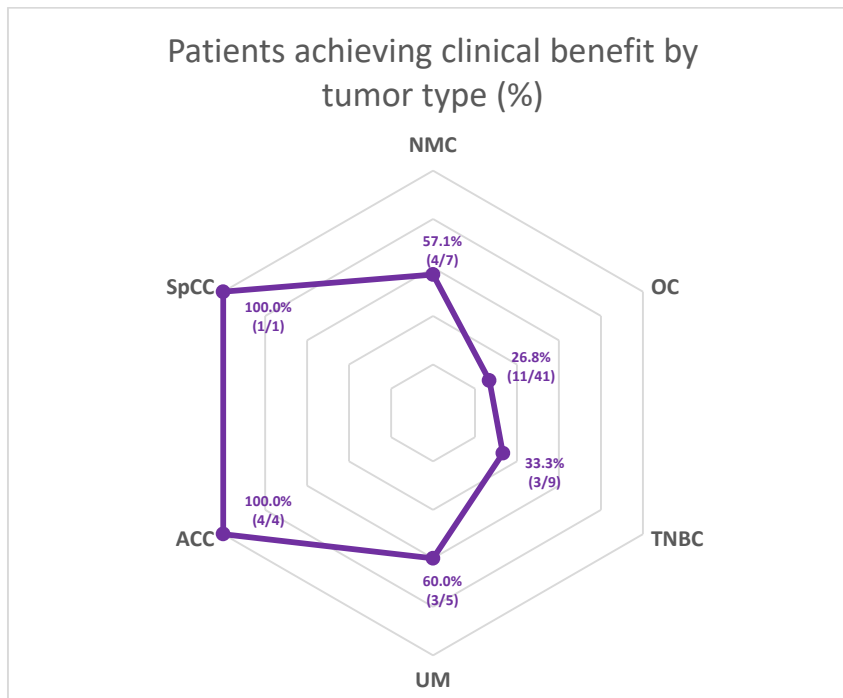
A)

Schedule	Number at risk											
A	46	12	8	2	1	0	0	0	0	0	0	0
B	8	3	3	3	1	1	1	1	1	1	1	0
C	29	7	2	2	1	1	0	0	0	0	0	0

B)

Schedule	Number at risk												
A	46	34	23	20	15	11	8	7	4	2	1	1	1	0
B	8	5	4	4	1	1	1	1	1	1	1	1	0	0
C	29	19	11	10	7	6	5	4	4	1	1	1	1	0

Figure S3. Kaplan-Meier survival curves by treatment schedule for A) PFS and B) OS.

A)

B)

Figure S4. Patients who achieved clinical benefit (SD or better) by A) dose and schedule and B) tumor type.

Table S1. Pharmacokinetics of BMS-986158 and its metabolite at single dose by treatment schedule.

Pharmacokinetic parameter	Assigned to the cohort receiving:									
	Schedule A					Schedule B		Schedule C		
	0.75 mg n = 5	1.25 mg n = 3	2.0 mg n = 9	3.0 mg n = 10	4.5 mg n = 10	2.0 mg n = 1	3.0 mg n = 4	2.0 mg n = 6	3.0 mg n = 11	4.5 mg n = 7
	BMS-986158									
C_{max} (ng/mL), GM (%CV)	68.8 (23)	175 (36)	260 (20)	328 (36)	478 (24)	207	481 (25)	295 (29)	370 (22)	567 (24)
T_{max} (h), median (range)	4.00 (2.00–4.02)	1.00 (1.00–2.00)	2.00 (1.00–4.03)	2.00 (0.98–6.15)	2.04 (1.00–4.03)	1.00	1.03 (1.00–4.03)	1.00 (0.50–2.03)	1.00 (0.50–2.02)	2.02 (1.00–4.00)
$AUC_{(0–24)}$ (h×ng/mL), GM (%CV)	1027 (16)	2309 (13)	3610 (22)	4942 (43)	6786 (24)	2358	6921 (28)	3660 (27)	4468 (29)	7418 (43)
$AUC_{(0–T)}$ (h×ng/mL), GM (%CV)	2150 (15)	6372 (14)	8564 (48)	10,452 (50)	19,124 (46)	5202	28,852 (41)	10,931 (43)	11,493 (54)	17,220 (84)
Effective $T_{1/2}$ (h), mean (SD)	33.7 (1.4)[a]	48.7 (6.7)	41.4 (18.2)[a]	33.3 (7.6)[b]	48.3 (13.4)[c]	44.2	54.0[d]	64.6 (17.5)	48.2 (23.8)[e]	35.7 (17.8)[f]
V_z/F (L), GM (%CV)	14.7 (21)[a]	12.5 (18)	14.6 (15)[a]	12.8 (25)[b]	15.7 (29)[c]	23.2	15.3[d]	13.9 (29)	15.6 (28)[e]	11.6 (17)[f]
	Metabolite of BMS-986158									
C_{max} (ng/mL), GM (%CV)	5.0 (30)	10.0 (29)	16.9 (32)[g]	22.5 (38)[c]	30.0 (41)	13.6	26.3 (63)	21.1 (35)	19.4 (44)	45.5 (32)
MR C_{max}, GM (%CV)	0.07 (14)	0.06 (9)	0.07 (30)[g]	0.07 (34)[c]	0.06 (45)	0.07	0.06 (42)	0.07 (48)	0.05 (34)	0.08 (25)
T_{max} (h), median (range)	24.0 (2.6–24.2)	2.0 (2.0–24.0)	5.1 (2.0–72.0)[g]	23.9 (1.0–48.0)[c]	15.1 (1.0–48.0)	1.00	1.52 (1.0–47.4)	14.9 (1.0–71.5)	2.02 (1.0–48.0)	6.27 (1.0–45.6)
MR $AUC_{(0–24)}$ (h×ng/mL), GM (%CV)	0.10 (29)	0.08 (7)	0.08 (24)[g]	0.09 (44)[c]	0.08 (40)	0.08	0.06 (33)	0.10 (18)	0.08 (35)	0.10 (41)
MR $AUC_{(0–T)}$ (h×ng/mL), GM (%CV)	0.15 (33)	0.12 (29)	0.12 (21)[g]	0.14 (38)[c]	0.14 (37)	0.08	0.10 (28)	0.17 (35)	0.11 (41)	0.15 (48)

[a]n = 4; [b]n = 7; [c]n = 9; [d]n = 1; [e]n = 10; [f]n = 5; [g]n = 8.

$AUC_{(0–24)}$, area under the plasma concentration-time curve from time 0 to time 24 hours post dose; $AUC_{(0–T)}$, area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration; CL/F, apparent total body clearance; C_{max},

maximum observed plasma concentration; %CV, coefficient of variation; GM, geometric mean; MR, metabolite-to-parent; N/A, not available; $T_{1/2}$, half-life; T_{max}, time to C_{max}; Vz/F, apparent volume of distribution.

Table S2. Baseline treatment assignments for BMS-986158 monotherapy and tumor type [a].

Characteristic	Patients who achieved clinical benefit, n/N (%)[a]
All safety population	26/83 (31.3)
Schedule A, all doses	14/46 (30.4)
0.75 mg	1/5 (20.0)
1.25 mg	1/4 (25.0)
2.0 mg	2/13 (15.4)
3.0 mg	1/10 (10.0)
4.5 mg	9/14 (64.3)
Schedule B, all doses	3/8 (37.5)
2.0 mg	2/4 (50.0)
3.0 mg	1/4 (25.0)
Schedule C, all doses	9/29 (31.0)
2.0 mg	1/6 (16.7)
3.0 mg	4/13 (30.8)
4.5 mg	4/10 (40.0)
Tumor type, n (%)	
NUT carcinoma	4/7 (57.1)
Ovarian cancer	11/41 (26.8)
TNBC	3/9 (33.3)
UM	3/5 (60.0)
ACC	4/4 (100.0)
SpCC	1/1 (100.0)

[a]Percentage of patients with SD or better calculated as number of patients with SD or better divided by number of patients in the safety population with the same characteristic multiplied by 100.

ACC, adenoid cystic carcinoma; NUT, nuclear protein in testis; QD, once daily; SpCC, spindle cell carcinoma; TNBC, triple-negative breast cancer, UM, uveal melanoma.