Adavosertib in Combination with Olaparib in Patients with Refractory Solid Tumors: An Open-Label, Dose-Finding and Dose-Expansion Phase Ib Trial

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Supplementary Table 1: Demographics and baseline characteristics by cohort

	Cohort														
	1 (n=3)	**2 (n=3)**	**3.1 (n=4)**	**3.2 (n=7)**	**4.1 (n=7)**	**4.2 (n=14)**	**4.3 (n=14)**	**5 (n=5)**	**6.1 (n=8)**	**6.2 (n=7)**	**7.1 (n=16)**	**7.2 (n=4)**	**7.3 (n=3)**	**7.4 (n=13)**	**8.1 (n=11)**
Age															
Mean, years	66.3	57.3	53.5	59.0	58.6	56.1	54.0	60.4	59.9	60.3	61.9	53.0	58.0	60.7	62.5
(SD)	(8.6)	(2.1)	(13.7)	(10.0)	(8.5)	(12.4)	(11.4)	(11.1)	(14.2)	(6.5)	(11.4)	(7.3)	(9.5)	(11.6)	(7.8)
Median, years (range)	68 (57–74)	58 (55–59)	60 (33–62)	61 (44–76)	58 (50–72)	57 (26–77)	56 (33–75)	63 (41–69)	62 (38–80)	63 (51–69)	64 (36–76)	55 (44–59)	59 (48–67)	62 (29–76)	65 (50–72)
≥65 years, %	66.7	0	0	14.3	28.6	28.6	14.3	40.0	50.0	14.3	50.0	0	33.3	38.5	54.5
Female, %	100	66.7	50.0	85.7	100	71.4	57.1	80.0	62.5	71.4	81.3	50.0	100	53.8	63.6
Race, n (%)															
White	3 (100)	3 (100)	4 (100)	7 (100)	6 (85.7)	10 (71.4)	13 (92.9)	5 (100)	6 (75.0)	7 (100)	15 (93.8)	3 (75.0)	3 (100)	10 (76.9)	10 (90.9)
Black/African American	0	0	0	0	1 (14.3)	2 (14.3)	0	0	0	0	1 (6.3)	0	0	1 (7.7)	1 (9.1)
Asian	0	0	0	0	0	1 (7.1)	1 (7.1)	0	1 (12.5)	0	0	1 (25.0)	0	1 (7.7)	0
Other	0	0	0	0	0	1 (7.1)	0	0	1 (12.5)	0	0	0	0	1 (7.7)	0
Mean BMI, kg/m^2 (SD)	23.9 (3.2)	30.7 (10.3)	28.7 (2.5)	26.6 (6.6)	23.7 (1.7)	27.0 (7.8)	28.4 (5.9)	28.4 (6.9)	27.3 (4.4)	24.6 (5.4)	30.7 (10.5)	27.1 (6.9)	29.8 (4.1)	26.3 (4.9)	25.2 (5.2)
ECOG PS, n (%)															
0 (normal activity)	0	1 (33.3)	1 (25.0)	1 (14.3)	3 (42.9)	4 (28.6)	5 (35.7)	2 (40.0)	1 (12.5)	3 (42.9)	6 (37.5)	2 (50.0)	2 (66.7)	2 (15.4)	3 (27.3)

1 (symptoms but ambulatory)	3 (100)	2 (66.7)	3 (75.0)	6 (85.7)	4 (57.1)	10 (71.4)	9 (64.3)	3 (60.0)	7 (87.5)	4 (57.1)	10 (62.5)	2 (50.0)	1 (33.3)	11 (84.6)	8 (72.7)
Primary diagnosis, n (%)															
Ovary	1 (33.3)	1 (33.3)	2 (50.0)	3 (42.9)	2 (28.6)	3 (21.4)	0	2 (40.0)	0	1 (14.3)	4 (25.0)	1 (25.0)	0	3 (23.1)	3 (27.3)
Breast	0	0	0	2 (28.6)	1 (14.3)	3 (21.4)	3 (21.4)	1 (20.0)	2 (25.0)	1 (14.3)	5 (31.3)	0	1 (33.3)	0	0
Lung	0	0	0	0	0	2 (14.3)	0	0	1 (12.5)	2 (28.6)	4 (25.0)	1 (25.0)	0	5 (38.5)	0
Prostate	0	0	1 (25.0)	1 (14.3)	0	2 (14.3)	1 (7.1)	1 (20.0)	1 (12.5)	0	1 (6.3)	0	0	0	1 (9.1)
Uterus	0	0	0	0	2 (28.6)	0	0	1 (20.0)	2 (25.0)	1 (14.3)	1 (6.3)	0	1 (33.3)	1 (7.7)	0
Colon	1 (33.3)	1 (33.3)	0	0	0	0	0	0	0	0	0	0	1 (33.3)	2 (15.4)	1 (9.1)
Pancreas	0	0	0	0	0	0	4 (28.6)	0	0	0	0	0	0	0	2 (18.2)
Rectal	0	1 (33.3)	0	1 (14.3)	0	0	1 (7.1)	0	0	1 (14.3)	0	0	0	0	0
Soft tissue	0	0	0	0	1 (14.3)	1 (7.1)	0	0	0	0	0	1 (25.0)	0	0	0
Central nervous system	0	0	0	0	0	0	0	0	1 (12.5)	0	0	0	0	0	0
Fallopian tube	0	0	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0	0

Liver	0	0	0	0	0	0	1 (7.1)	0	0	0	0	0	0	0	0
Gallbladder	0	0	0	0	0	0	0	0	0	1 (14.3)	0	0	0	0	0
Other	1 (33.3)	0	1 (25.0)	0	1 (14.3)	2 (14.3)	4 (28.6)	0	1 (12.5)	0	1 (6.3)	1 (25.0)	0	2 (15.4)	4 (36.4)
Median number of previous therapy regimens															
Systemic	3.0	8.0	3.5	2.0	3.0	3.0	3.0	7.0	4.5	4.0	4.0	3.5	3.0	4.0	3.0
Radiotherapy	0	0	0	1.0	0	1.0	1.0	1.0	1.0	1.0	1.0	1.5	0	1.0	0

BMI body mass index, *ECOG PS*, Eastern Cooperative Oncology Group performance status, *SD* standard deviation

Supplementary Table 2: Summary of clinical response by cohort (parts A and B)

Cohort	Patients, n	Evaluable for ORR, n[a]	ORR, n (%)	Median PFS, months (95% CI)	Evaluable for DCR, n[a]	DCR,[b] n (%)
1	3	3	0	5.6 (2.8–5.6)	3	3 (100)
2	4	3	1 (33.3)	4.4 (1.5–4.4)	3	2 (66.7)
3.1	4	3	0	6.0 (0.8–11.1)	4	3 (75.0)
3.2	7	7	1 (14.3)	10.9 (1.3–10.9)	7	5 (71.4)
4.1	7	7	1 (14.3)	2.6 (0.8–6.4)	7	4 (57.1)
4.2	14	13	4 (30.8)	7.4 (1.2–15.8)	13	10 (76.9)
4.3	14	13	1 (7.7)	2.7 (1.3–3.5)	14	7 (50.0)
5	5	4	2 (50.0)	9.8 (4.7–NC)	4	4 (100)
6.1	7	6	1 (16.7)	1.4 (0.6–NC)	7	1 (14.3)
6.2	7	7	0	1.3 (0.6–5.5)	7	1 (14.3)
7.1	16	15	0	4.0 (1.4–10.0)	16	10 (62.5)
7.2	4	4	1 (25.0)	5.9 (1.2–7.7)	4	3 (75.0)
7.3	3	3	0	1.4 (1.1–1.7)	3	0
7.4	13	11	1 (9.1)	4.0 (1.4–10.6)	13	8 (61.5)
8.1	11	9	3 (33.3)	1.4 (1.2–10.0)	10	4 (40.0)
SCLC	9	9	1 (11.1)	1.5 (1.3–4.2)	9	2 (22.2)

The highlighted rows indicate the MTD for bid and qd dosing; the RP2D (cohort 7.4, adavosertib 200 mg qd + olaparib 200 mg bid) was carried forward into the dose-expansion part of this study. [a]For ORR and DCR, evaluable patients have measurable disease and received >75% of the planned dose of adavosertib and olaparib; [b]Defined as the proportion of patients achieving CR, PR, or stable disease over the entirety of the study. *bid* twice daily, *CI* confidence interval, *CR* complete response, *DCR* disease control rate, *MTD* maximum tolerated dose, *ORR* objective response rate, *PFS* progression-free survival, *PR* partial response, *qd* once daily, *RP2D* recommended phase II dose

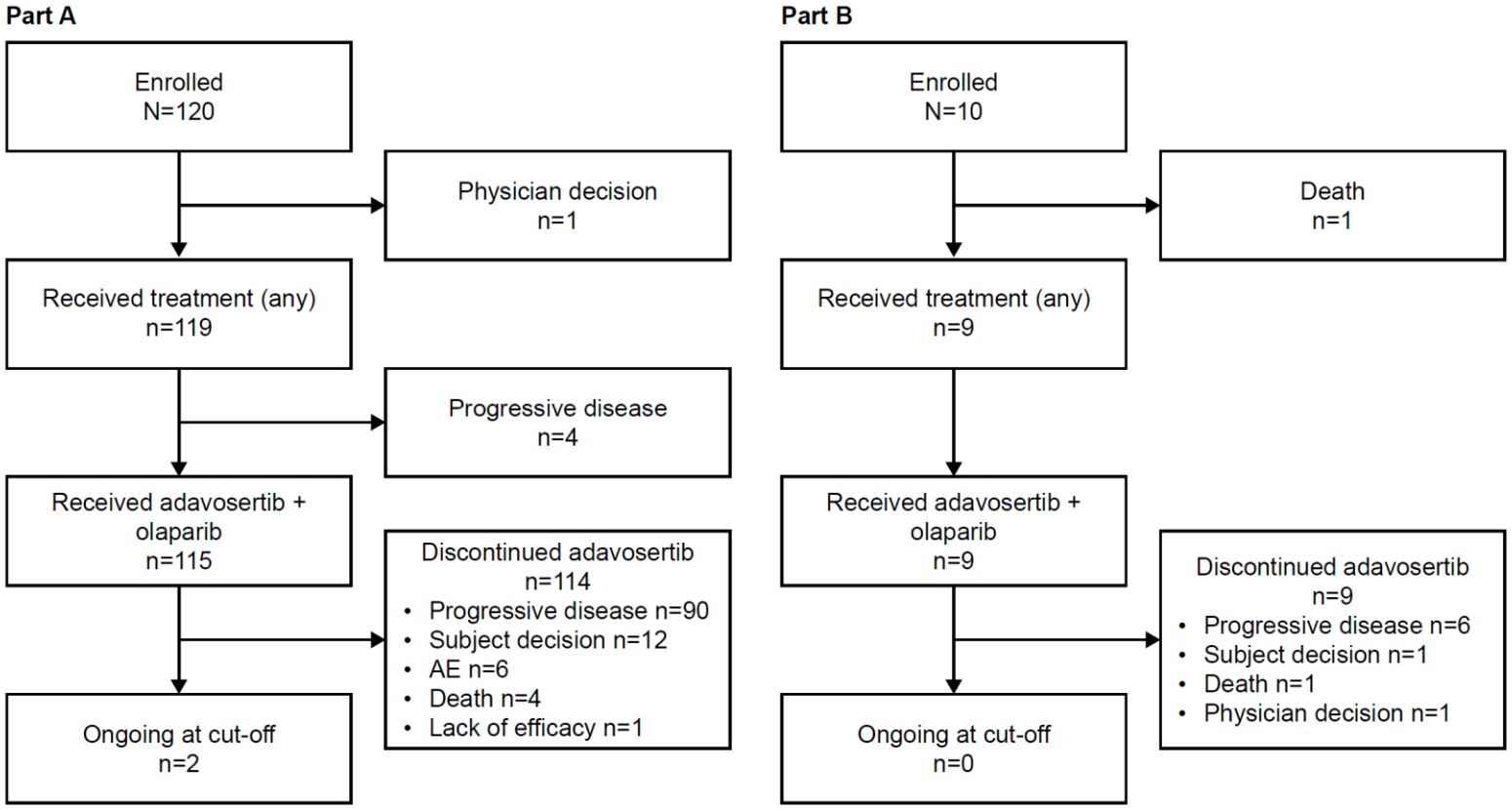
Supplementary Table 3: Changes in olaparib pharmacokinetics following combination with adavosertib (part A)

Cohort	Adavosertib dose (schedule)	Olaparib dose	N	$AUC_{0–10h}$ ratio (95% CI)	C_{max} ratio (95% CI)
4.1	175 mg bid (3/4)	200 mg bid	7	1.62 (1.33–1.97)	1.29 (1.08–1.56)
4.2	175 mg bid (3/4)	200 mg bid	13	1.15 (0.93–1.43)	1.01 (0.79–1.30)
4.3	175 mg bid (3/4)	200 mg bid	14	1.10 (0.92–1.32)	0.98 (0.86–1.12)
3.2	150 mg bid (3/4)	200 mg bid	7	0.73 (0.47–1.13)	0.83 (0.51–1.35)
7.4	200 mg qd (3/4)	200 mg bid	13	1.10 (0.94–1.28)[a]	1.01 (0.87–1.17)
5	175 mg bid (3/4)	300 mg bid	4	1.08 (0.43–2.73)	0.99 (0.54–1.83)
8.1	200 mg qd (3/4)	300 mg bid	10	0.95 (0.76–1.18)	0.79 (0.62–1.00)

[a]Data only available for N=12 patients

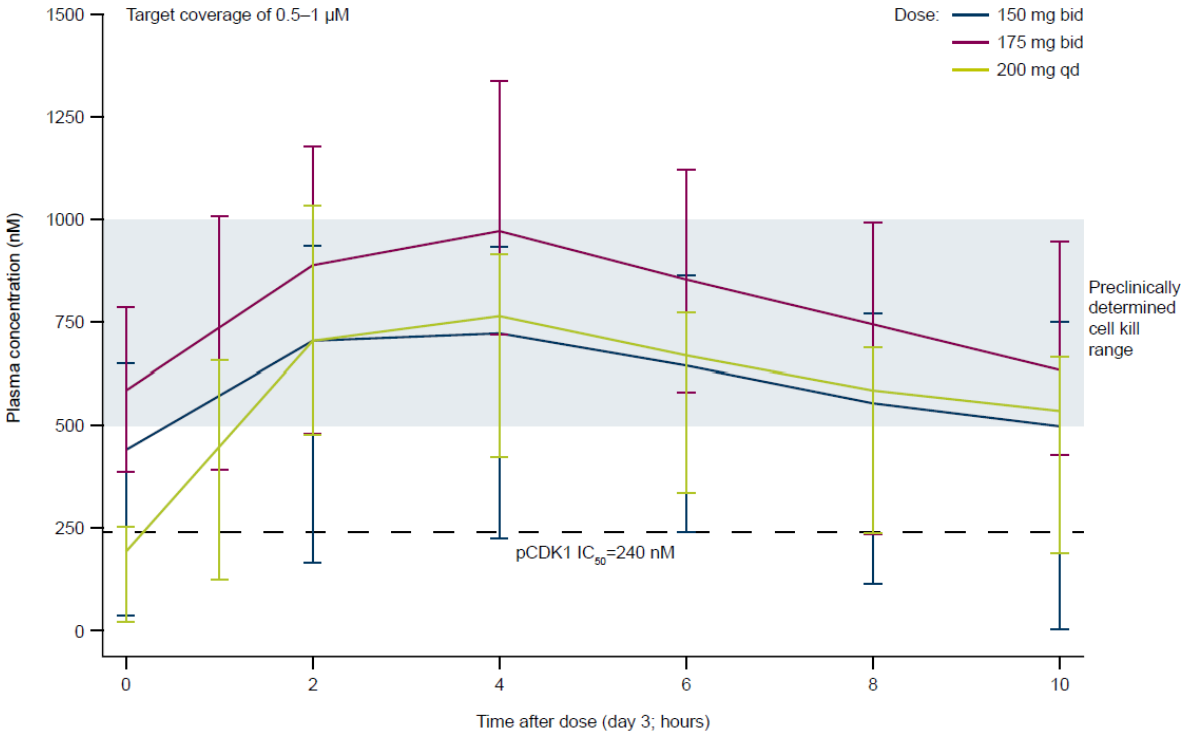
AUC_{0-10h} area under the plasma concentration–time curve from time zero to 10 hours, *bid* twice daily, *CI* confidence interval, *C_{max}* maximum plasma drug concentration, *qd* once daily

Supplementary Fig. 1 Patient disposition



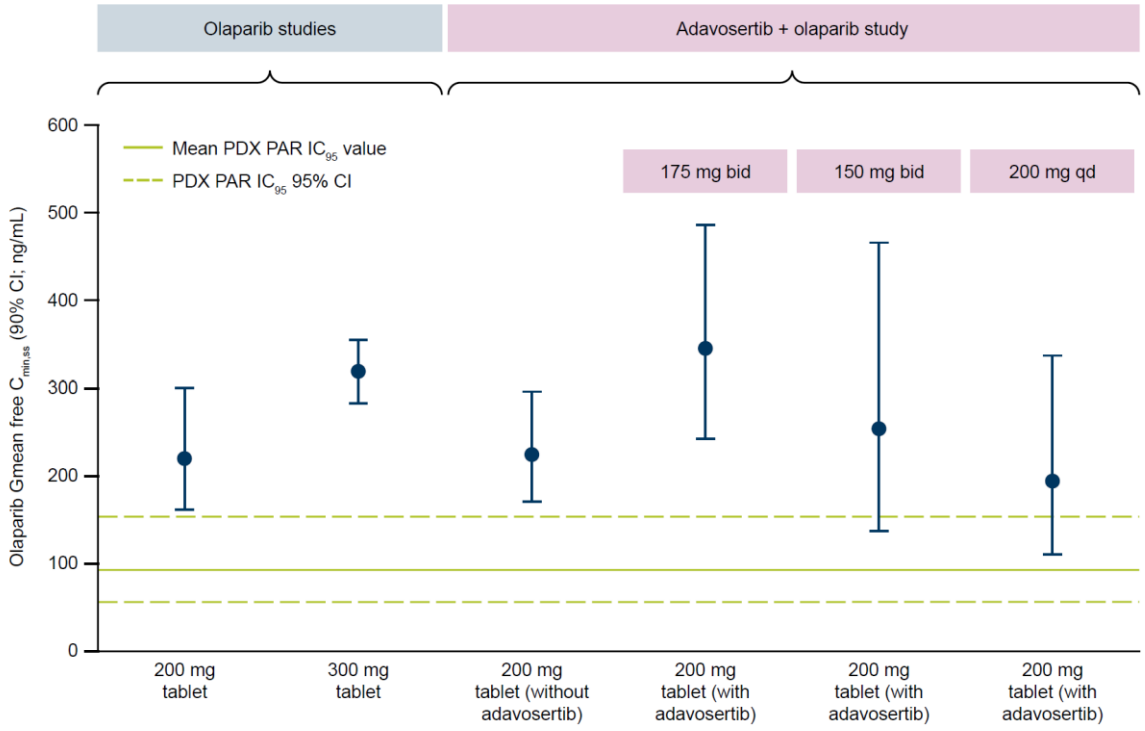
In part A, patients received adavosertib (qd or bid) for 3 consecutive days with 4 days off treatment (3/4), or for 5 consecutive days with 2 days off treatment (5/2; qd cohorts only), plus continuous oral olaparib (bid) for 14 or 21 days of a 21-day cycle. In part B (expansion cohort), patients received adavosertib 200 mg qd (3 days on, 4 days off treatment) for 2 of 3 weeks, plus olaparib 200 mg bid. *AE* adverse event, *bid* twice daily, *qd* once daily

Supplementary Fig. 2 Comparison of pharmacokinetics across adavosertib doses in combination with olaparib 200 mg bid (part A)



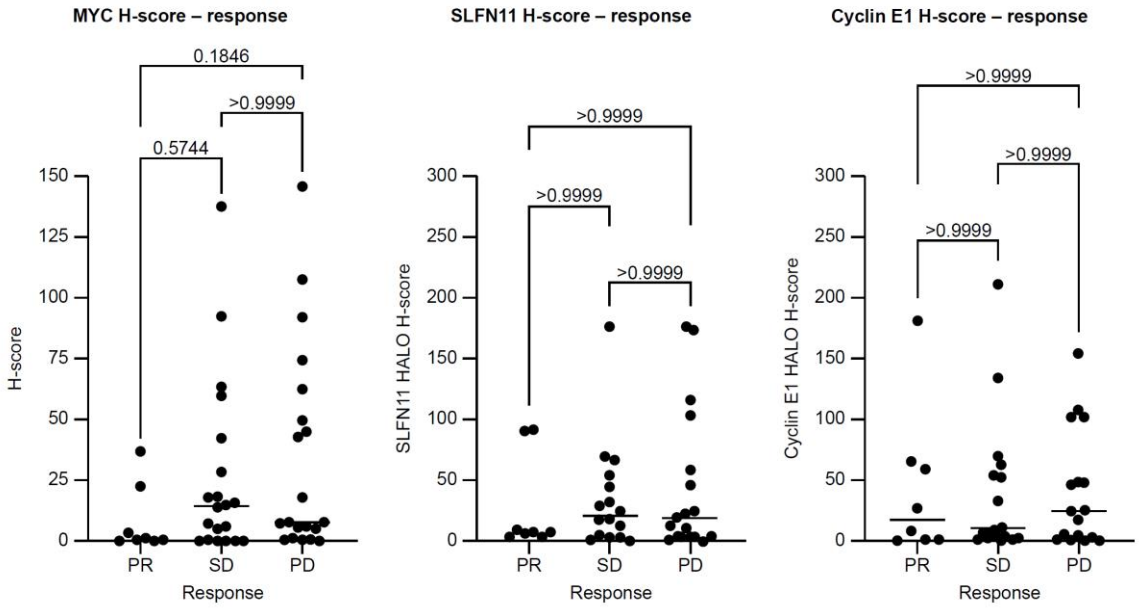
Data are shown as geometric mean ± SD. *bid* twice daily, *IC50* 50% inhibitory concentration, *pCDK1* phosphorylated CDK1, *qd* once daily

Supplementary Fig. 3 Olaparib clinical $C_{min,ss}$ compared with preclinical pharmacodynamics of the protease-activated receptor IC_{95} (part A)



Bid, twice daily, *CI* confidence interval, $C_{min,ss}$ clinical minimum steady-state plasma drug concentration, *PAR* protease-activated receptor, *PDX* pharmacodynamics, *qd* once daily

Supplementary Fig. 4 Best objective response of patients with available histology for MYC (n=63), cyclinE1 (n=58), and SLFN11 (n=61) expression



H-score: an ordinal score is assigned to the immunostaining intensity and multiplied by an estimate of the percentage of immunostained tissue for each intensity grade, yielding total scores between 0 and 300. *PD* progressive disease, *PR* partial response, *SD* stable disease