PI3Kα-Selective Inhibition With Alpelisib (BYL719) in PIK3CAAltered Solid Tumors: Results From the First-in-Human Study

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METHODS

Pharmacokinetic profiling

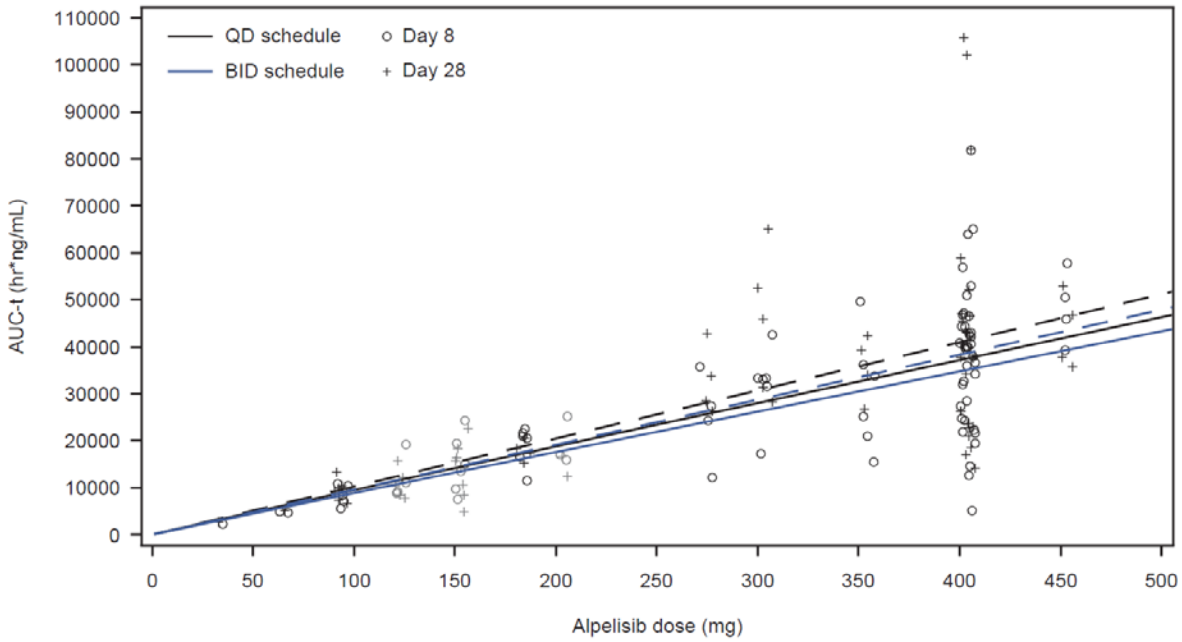
For the once-daily dosing schedule, blood samples for full PK profiling were collected during Cycle 1 on Days 1 and 8 and during Cycle 2 on Day 1 at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post-dose. In subsequent cycles, samples were collected on Day 1 at pre-dose. For the twice-daily dosing schedule, blood samples for full PK profiling were collected during Cycle 1 on Day 1 and Day 8 and during Cycle 2 on Day 1 at pre-morning dose and 0.5, 1, 1. .5, 2, 3, 4, and 6 hours post-dose, and at pre-evening dose. On Day 2 and Day 9 of Cycle 1, and Day 2 of Cycle 2, samples were also collected at pre-morning dose. In subsequent cycles, samples were collected on Day 1 at pre-morning dose.

Next-generation sequencing

Tumor DNA was extracted from fresh frozen or formalin-fixed, paraffin-embedded tumor tissue blocks or sections. Comprehensive cancer genomic profiling was performed using the FoundationOne assay. The assay laboratory procedures (preparation of tumor DNA, library construction, and hybrid capture) and computational methods involved in subsequent data analysis have been described previously: Frampton *et al.* Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing (*Nature Biotechnology* 2013;31:1023–31).

SUPPLEMENTARY FIGURES AND TABLES

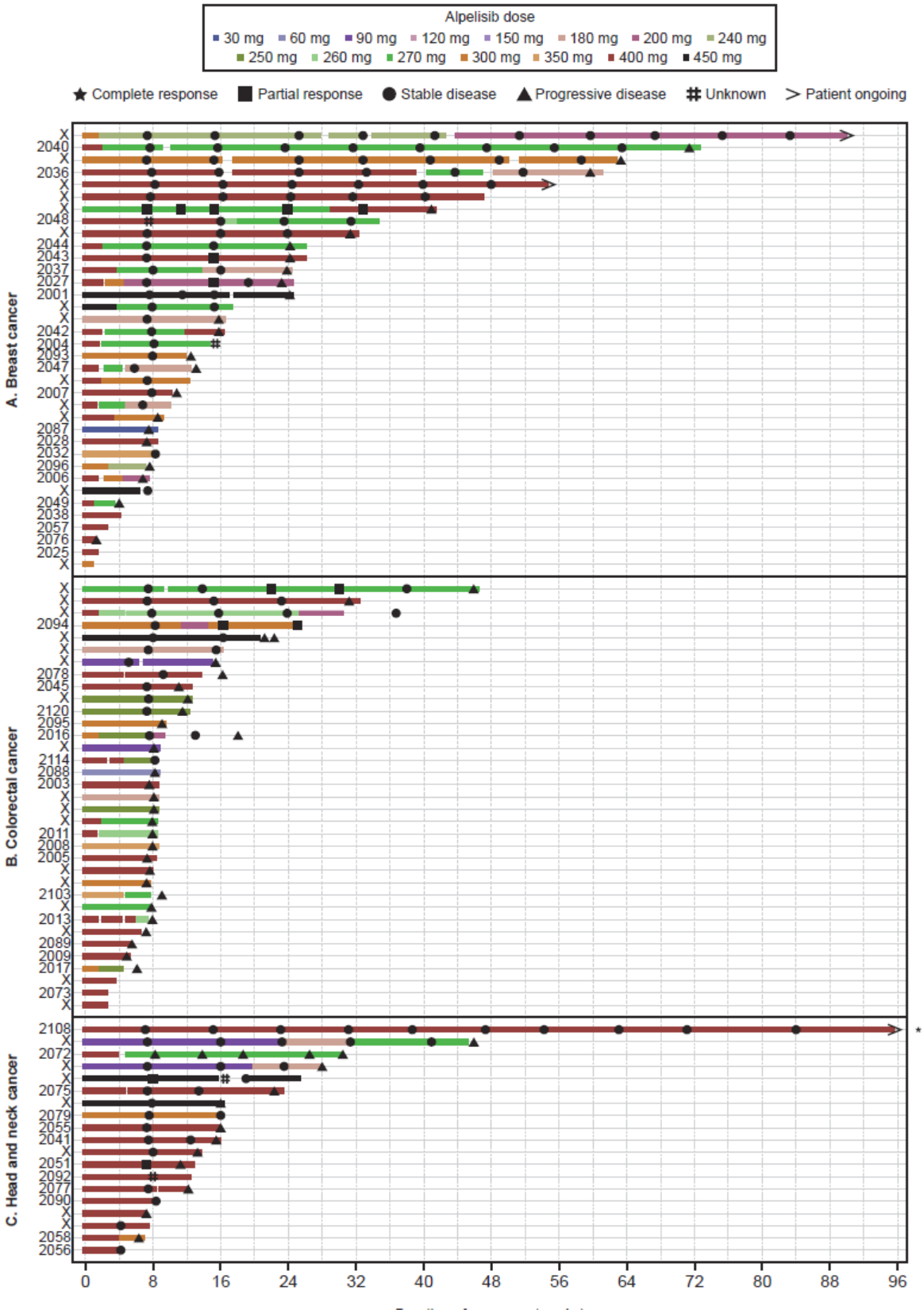
Supplementary Figure 1: Dose proportionality of alpelisib plasma exposure at steady state in patients receiving once-daily and twice-daily alpelisib

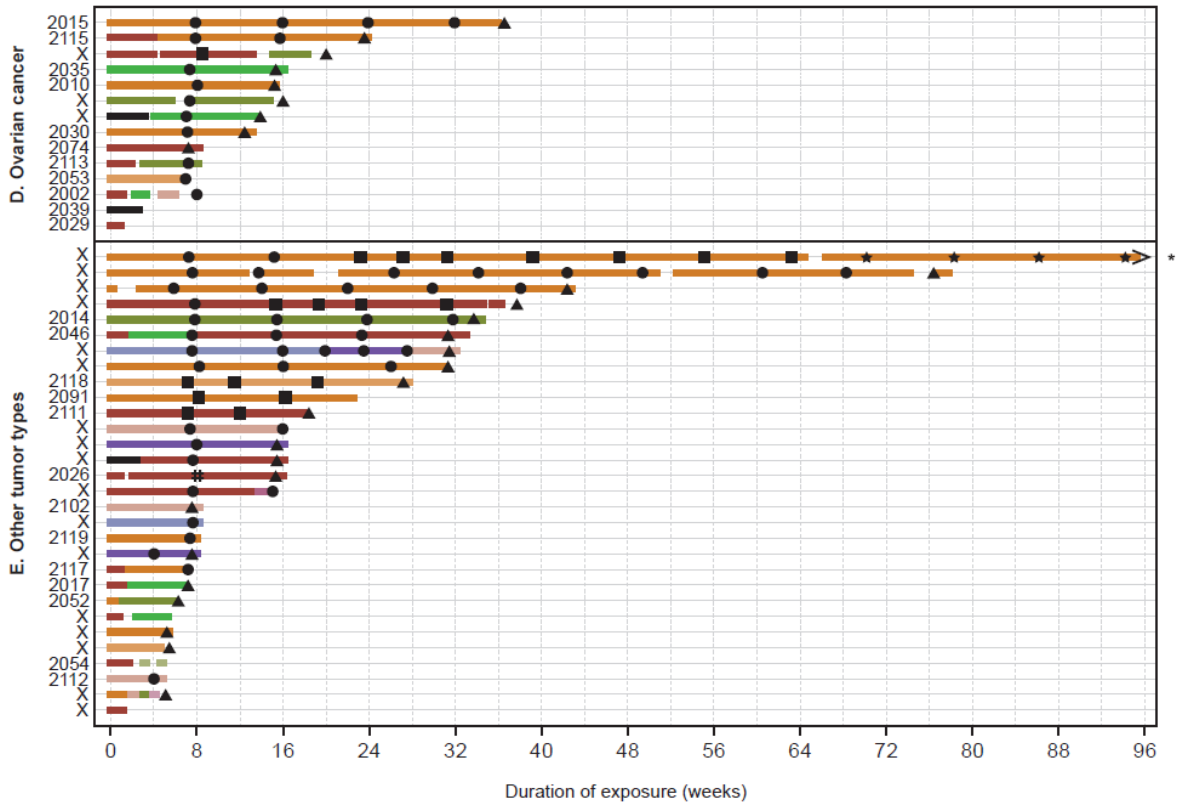


Dashed lines represent reference values derived from the model, with slope set to 1.

AUC=area under the curve. BID=twice-daily. QD=once-daily.

Supplementary Figure 2: Swimmers plots of duration of exposure and overall response (per RECIST v1.0) in patients with breast (A), colorectal (B), head and neck (C), ovarian (D), and other cancers (E).

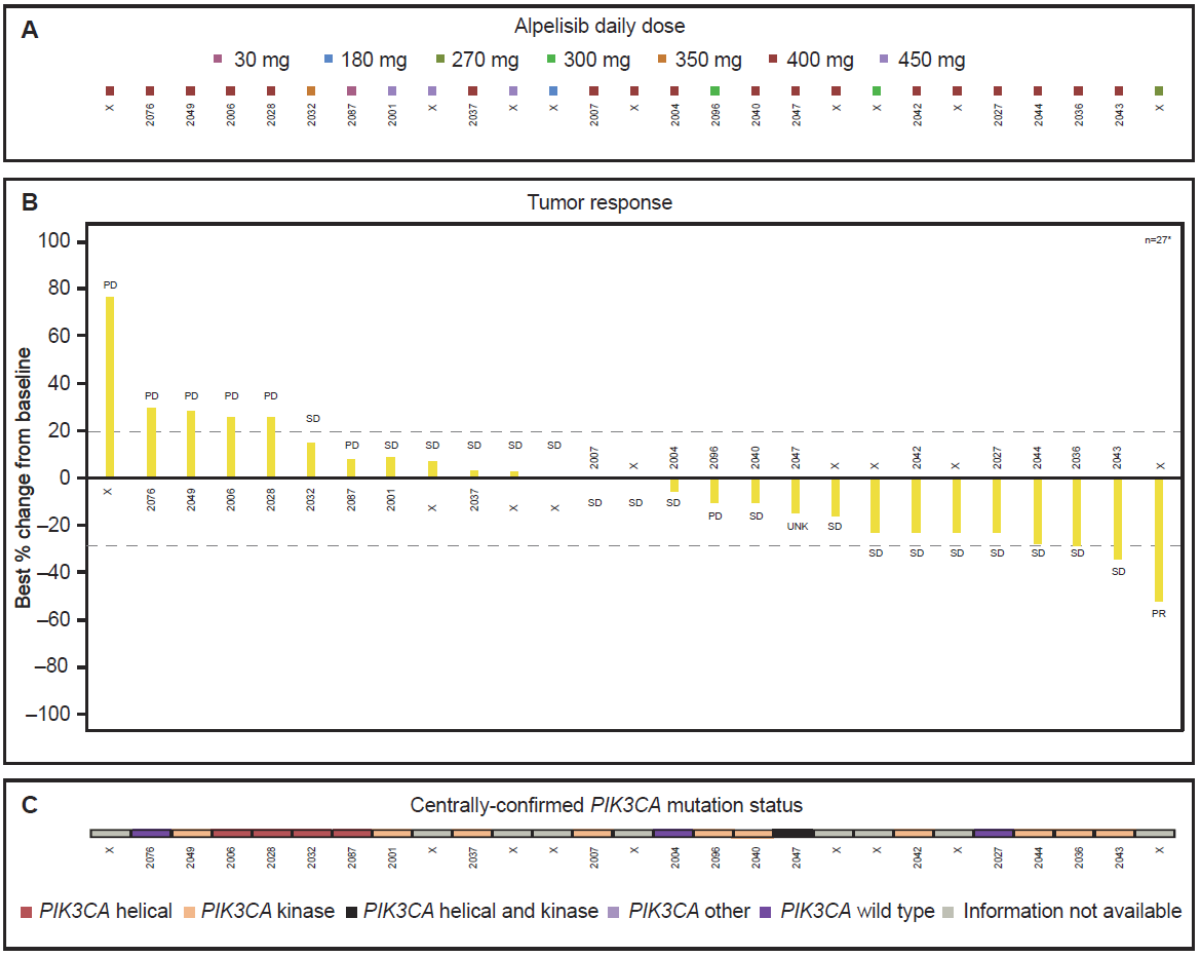




Dummy sample numbers for each patient correspond with the NGS results in Supplementary Tables 3–5.*One patient with head and neck cancer, and one patient with endometrial cancer had received treatment for >144 weeks and >108 weeks, respectively, and were ongoing at the time of data cut-off (February 5, 2015).

NGS=next-generation sequencing. RECIST=Response Evaluation Criteria In Solid Tumors.

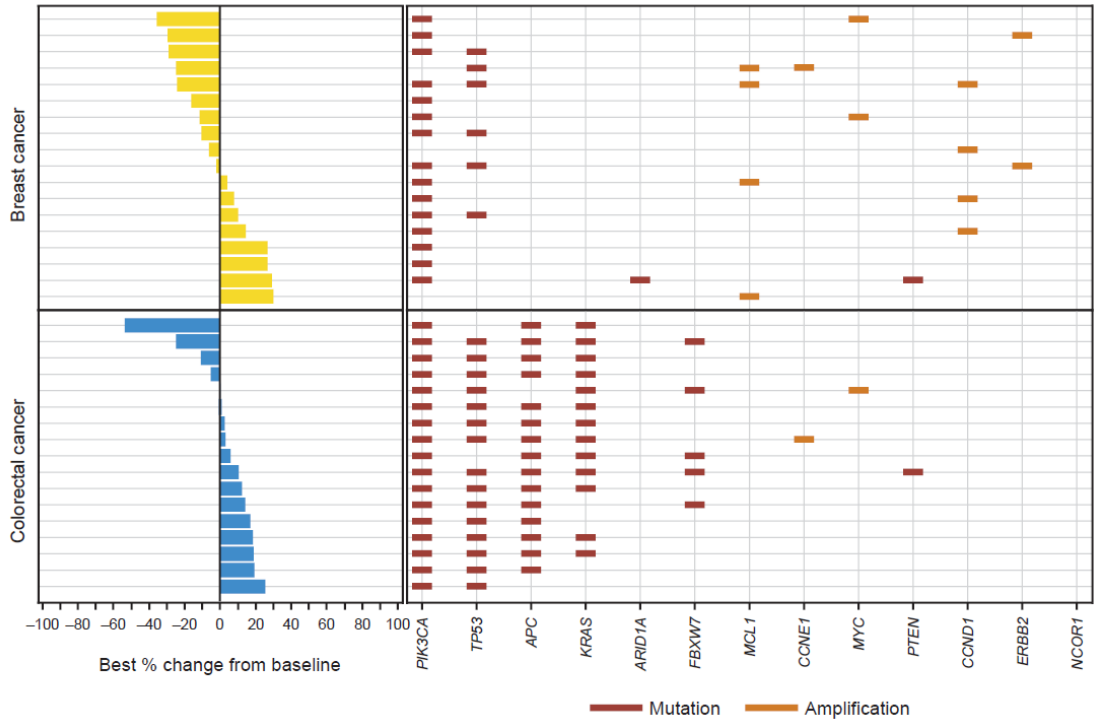
Supplementary Figure 3: Dose of study treatment received (A), best percentage change in sum of longest tumor diameters and best overall response in patients with ER+/HER2– advanced breast cancer (B), and centrally-obtained NGS results (C)



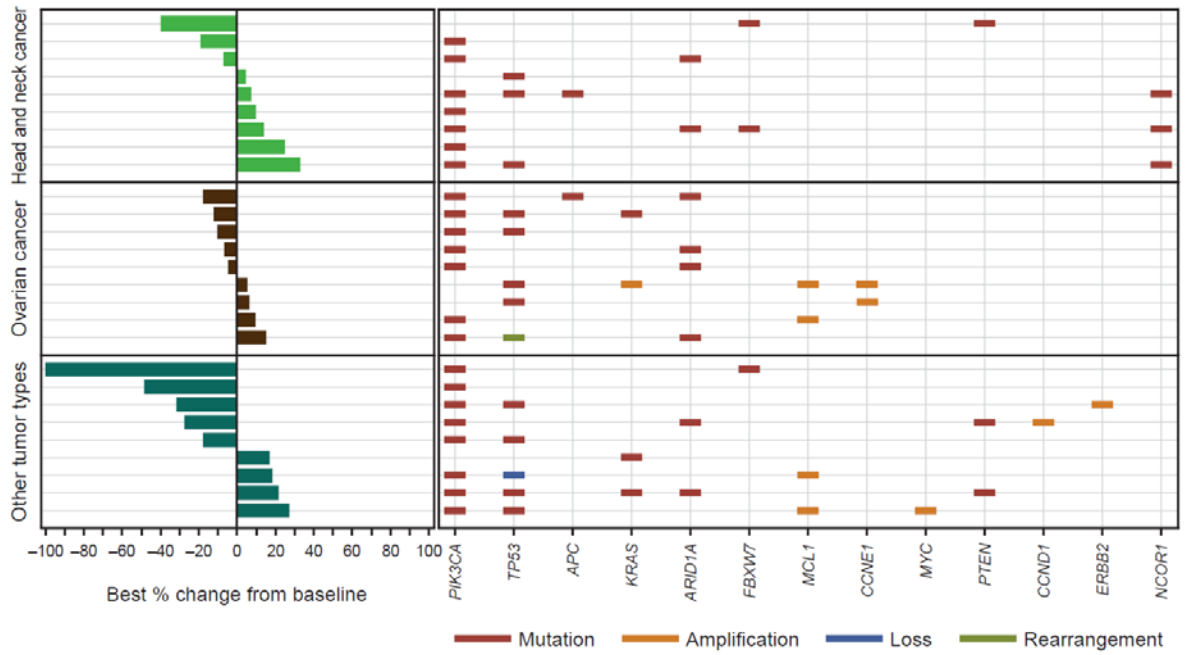
Dummy sample numbers for each patient correspond with the NGS results in Supplementary Tables 3–5.*Patients with no post-baseline assessment for target lesions or patients with only non-target lesions were excluded.

ER+=estrogen receptor-positive. HER2–=human epidermal growth factor receptor 2-negative. NGS=next-generation sequencing; PD=progressive disease. PR=partial response. SD=stable disease. UNK=unknown

. **Supplementary Figure 4: Genetic alterations detected by next-generation sequencing and best percentage change from baseline in sum of longest diameters**



Data cut-off: February 05, 2015.



Supplementary Table 1: Adverse events (≥10% of patients) suspected to be related to study treatment reported during treatment Cycle 1

Adverse event	Grade	Once-daily doses					Twice-daily doses			All patients (N=134)
		≤270 mg* (n=20)	300 mg (n=8)	350 mg (n=6)	400 mg (n=65)	450 mg (n=9)	120 mg (n=5)	150 mg (n=15)	200 mg (n=6)	
Total	All	13 (65.0%)	6 (75.0%)	6 (100%)	61 (93.8%)	9 (100%)	5 (100%)	14 (93.3%)	6 (100%)	120 (89.6%)
	3/4	1 (5.0%)	0	3 (50.0%)	27 (41.5%)	6 (66.7%)	0	6 (40.0%)	6 (100%)	49 (36.6%)
Hyperglycemia	All	2 (10.0%)	1 (12.5%)	1 (16.7%)	31 (47.7%)	5 (55.6%)	1 (20.0%)	7 (46.7%)	6 (100%)	54 (40.3%)
	3/4	0	0	0	16 (24.6%)	3 (33.3%)	0	5 (33.3%)	5 (83.3%)	29 (21.6%)
Nausea	All	4 (20.0%)	3 (37.5%)	4 (66.7%)	29 (44.6%)	6 (66.7%)	0	5 (33.3%)	3 (50.0%)	54 (40.3%)
	3/4	0	0	0	1 (1.5%)	2 (22.2%)	0	0	0	3 (2.2%)
Diarrhea	All	2 (10.0%)	1 (12.5%)	2 (33.3%)	26 (40.0%)	3 (33.3%)	2 (40.0%)	4 (26.7%)	2 (33.3%)	42 (31.3%)
	3/4	0	0	0	1 (1.5%)	0	0	0	1 (16.7%)	2 (1.5%)
Decreased appetite	All	2 (10.0%)	1 (12.5%)	3 (50.0%)	19 (29.2%)	3 (33.3%)	1 (20.0%)	2 (13.3%)	4 (66.7%)	35 (26.1%)
	3/4	0	0	1 (16.7%)	0	0	0	0	0	1 (0.7%)
Fatigue	All	1 (5.0%)	1 (12.5%)	1 (16.7%)	18 (27.7%)	2 (22.2%)	0	3 (20.0%)	1 (16.7%)	27 (20.1%)
	3/4	0	0	0	1 (1.5%)	0	0	0	0	1 (0.7%)
Vomiting	All	3 (15.0%)	1 (12.5%)	1 (16.7%)	18 (27.7%)	1 (11.1%)	0	0	2 (33.3%)	26 (19.4%)
	3/4	0	0	0	3 (4.6%)	0	0	0	0	3 (2.2%)
Stomatitis	All	0	2 (25.0%)	0	8 (12.3%)	2 (22.2%)	1 (20.0%)	3 (20.0%)	2 (33.3%)	18 (13.4%)
	3/4	0	0	0	1 (1.5%)	0	0	0	0	1 (0.7%)

*≤270 mg group includes patients treated with alpelisib 30, 60, 90, 180, and 270 mg once-daily.

All adverse events were characterized and graded per CTCAE v4.0, except for hyperglycemia, which was graded based on a modified version of the American Diabetes Association accepted criteria.

CTCAE=Common Terminology Criteria for Adverse Event

Supplementary Table 2: Summary of alpelisib pharmacokinetic parameters on Cycle 1 Day 1 and Cycle 1 Day 8

		Cycle 1 Day 1				Cycle 1 Day 8			
		T_{max} hr (range)	C_{max} ng/mL (range)	$T_{1/2}$ hr (range)	AUC_{0-24h} hr•ng/mL (range)	T_{max} hr (range)	C_{max} ng/mL (range)	$T_{1/2}$ hr (range)	AUC_{0-24h} hr•ng/mL (range)
Once-daily doses	30 mg (n=1)	3 (3–3) n=1	284 (284–284) n=1	7 (7–7) n=1	2230 (2230–2230) n=1	2 (2–2) n=1	243 (243–243) n=1	7 (7–7) n=1	2210 (2210–2210) n=1
	60 mg (n=3)	6 (4–7) n=2	338 (297–378) n=2	6 (6–6) n=1	4010 (3540–4480) n=2	6 (4–6) n=3	475 (349–482) n=3	7 (7–7) n=1	4770 (4750–4790) n=2
	90 mg (n=6)	2 (1–2) n=6	725 (351–804) n=6	8 (6–12) n=6	5980 (4750–9010) n=6	3 (1–6) n=6	849 (547–1190) n=6	8 (7–16) n=5	8520 (5630–10900) n=5
	180 mg (n=6)	2 (1–3) n=6	1550 (855–2360) n=6	8 (6–15) n=6	16200 (6930–19400) n=6	3 (1–4) n=6	1740 (837–2540) n=6	9 (7–14) n=6	20600 (11400–22600) n=6
	270 mg (n=4)	4 (2–4) n=4	1950 (1190–3110) n=4	8 (5–13) n=4	21600 (10700–26800) n=4	2 (2–4) n=4	2880 (1080–3160) n=4	8 (4–8) n=3	25900 (12100–35600) n=4
	300 mg (n=8)	3 (1–7) n=8	2380 (735–3580) n=8	7 (6–12) n=6	25500 (9570–37700) n=6	4 (1–6) n=6	2970 (2060–3770) n=6	7 (6–10) n=5	33200 (17100–42600) n=6
	350 mg (n=6)	2 (1–4) n=6	2650 (1350–4280) n=6	7 (5–14) n=6	24400 (13000–38300) n=6	2 (1–3) n=6	3200 (1800–5440) n=6	7 (6–8) n=6	29500 (15400–49700) n=6

	400 mg (n=65)	2 (1–7) n=57	2760 (967–6670) n=57	8 (5–27) n=50	29000 (9930–68100) n=51	3 (1–8) n=48	3560 (501–7930) n=48	8 (5–14) n=33	39800 (5210–81700) n=37
	450 mg (n=9)	2 (1–4) n=9	2850 (1690–6440) n=9	8 (6–15) n=9	34800 (18900–54100) n=9	3 (2–6) n=7	3550 (2690–6440) n=7	7 (6–12) n=4	48200 (39200–57700) n=4
		T_{max} hr (range)	**C_{max} ng/mL (range)**	**$T_{1/2}$ hr (range)**	**$AUC_{0–12}$ hr•ng/mL (range)**	**T_{max} hr (range)**	**C_{max} ng/mL (range)**	**$T_{1/2}$ hr (range)**	**$AUC_{0–12}$ hr•ng/mL (range)**
Twice-daily doses	120 mg (n=5)	2 (2–3) n=5	1070 (991–1330) n=5	4 (3–5) n=4	6990 (5460–8060) n=5	3 (1–8) n=5	1480 (1110–2570) n=5	5 (5–6) n=3	10100 (8960–19200) n=4
	150 mg (n=15)	2 (1–6) n=14	1490 (809–2460) n=14	4 (3–14) n=9	8840 (5920–16100) n=11	2 (1–6) n=8	2410 (1090–3890) n=8	5 (3–8) n=7	15100 (7600–24200) n=7
	200 mg (n=6)	3 (1–3) n=5	2270 (855–2600) n=5	6 (3–7) n=5	11900 (7070–14200) n=5	2 (1–2) n=3	2350 (1640–4580) n=3	6 (5–7) n=2	16900 (15900–25100) n=3

$AUC_{0–24h}$=area under the curve from time 0 to 24 hours. C_{max}=maximum concentration. $T_{1/2}$=half-life. T_{max}=time of occurrence of C_{max}.