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Supplemental Table for:
Phase Ib Study of Combination Therapy with MEK Inhibitor Binimetinib and PI3K Inhibitor Buparlisib in Patients with Advanced Solid Tumors with RAS/RAF Alterations
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Table S1. Analysis set by treatment group

	BKM 50 mg + MEK 30 mg	BKM 50 mg + MEK 45 mg	BKM 60 mg + MEK 45 mg	BKM 70 mg + MEK 30 mg	BKM 80 mg + MEK 30 mg	BKM 80 mg + MEK 45 mg	BKM 90 mg + MEK 45 mg	All Patients *N* = 89
Analysis set								
Full analysis set	11	5	5	6	6	50	6	89
Safety set	11	5	5	6	6	49	7	89
Dose-determining set	8	4	4	3	6	33	6	64
Pharmacokinetic analysis set	11	5	5	6	6	48	6	87

Abbreviations: BKM, buparlisib; MEK, mitogen-activated protein kinase.

Table S2. Dose levels at which dose-limiting toxicities occurred

Dose of Combination Regimen	Dose-Limiting Toxicity
Dose-escalation phase	
Buparlisib (50 mg)/binimetinib (30 mg)	Grade 1 central serous retinopathy Grade 1 central serous retinopathy Grade 2 glossitis
Buparlisib (70 mg)/binimetinib (30 mg)	Grade 4 blood CPK elevation
Buparlisib (80 mg)/binimetinib (30 mg)	Grade 3 stomatitis
Buparlisib (80 mg)/binimetinib (45 mg)	Grade 3 maculopapular rash
Buparlisib (90 mg)/binimetinib (45 mg)	Grade 3 diarrhea Grade 3 anaphylactic reaction and grade 3 face swelling
Dose-expansion phase	
Buparlisib (80 mg)/binimetinib (45 mg)	Grade 2 diarrhea Grade 2 diarrhea Grade 3 lipase elevation and grade 3 amylase elevation Grade 3 diarrhea Grade 3 stomatitis

Abbreviation: CPK, creatine phosphokinase.

Table S3. Adverse events, regardless of study drug relationship, reported by ≥10% of patients (all grades) (safety set)

	Buparlisib/Binimetinib Dose, mg qd/bid (n)															
	50/30 (*n* = 11)		50/45 (*n* = 5)		60/45 (*n* = 5)		70/30 (*n* = 6)		80/30 (*n* = 6)		80/45 (*n* = 49)		90/45 (*n* = 7)		All Pts (*N* = 89)	
	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4
Preferred Term	*n* (%)	*n* (%)	*n* (%)	*n* (%)	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	11 (100)	11 (100)	5 (100)	5 (100)	5 (100)	5 (100)	6 (100)	6 (100)	6 (100)	6 (100)	49 (100)	43 (87.8)	7 (100)	7 (100)	89 (100)	83 (93.3)
Diarrhea	6 (54.5)	0	3 (60.0)	1 (20.0)	3 (60.0)	1 (20.0)	3 (50.0)	0	4 (66.7)	0	33 (67.3)	7 (14.3)	7 (100)	1 (14.3)	59 (66.3)	10 (11.2)
Blood CPK increased	5 (45.5)	2 (18.2)	4 (80.0)	2 (40.0)	3 (60.0)	2 (40.0)	3 (50.0)	2 (33.3)	3 (50.0)	0	33 (67.3)	15 (30.6)	3 (42.9)	2 (28.6)	54 (60.7)	25 (28.1)
AST increase	3 (27.3)	0	3 (60.0)	0	4 (80.0)	1 (20.0)	3 (50.0)	1 (16.7)	2 (33.3)	1 (16.7)	28 (57.1)	9 (18.4)	4 (57.1)	1 (14.3)	47 (52.8)	13 (14.6)
Nausea	3 (27.3)	0	2 (40.0)	0	3 (60.0)	0	3 (50.0)	0	3 (50.0)	0	28 (57.1)	1 (2.0)	4 (57.1)	1 (14.3)	46 (51.7)	2 (2.2)
Fatigue	4 (36.4)	0	1 (20.0)	0	2 (40.0)	0	3 (50.0)	0	3 (50.0)	0	24 (49.0)	3 (6.1)	2 (28.6)	0	39 (43.8)	3 (3.4)
ALT increase	2 (18.2)	0	1 (20.0)	0	2 (40.0)	1 (20.0)	2 (33.3)	0	1 (16.7)	1 (16.7)	23 (46.9)	11 (22.4)	4 (57.1)	1 (14.3)	35 (39.3)	14 (15.7)
Stomatitis	2 (18.2)	1 (9.1)	2 (40.0)	1 (20.0)	1 (20.0)	0	3 (50.0)	0	4 (66.7)	1 (16.7)	20 (40.8)	3 (6.1)	2 (28.6)	0	34 (38.2)	6 (6.7)
Decreased appetite	5 (45.5)	0	1 (20.0)	0	3 (60.0)	0	3 (50.0)	0	3 (50.0)	0	15 (30.6)	0	2 (28.6)	0	32 (36.0)	0
Vomiting	4 (36.4)	1 (9.1)	1 (20.0)	0	1 (20.0)	0	2 (33.3)	0	4 (66.7)	0	18 (36.7)	0	2 (28.6)	2 (28.6)	32 (36.0)	3 (3.4)
Peripheral edema	4 (36.4)	0	3 (60.0)	0	2 (40.0)	0	1 (16.7)	0	2 (33.3)	0	15 (30.6)	0	3 (42.9)	0	30 (33.7)	0
Maculopapular rash	1 (9.1)	0	1 (20.0)	1 (20.0)	2 (40.0)	1 (20.0)	2 (33.3)	1 (16.7)	4 (66.7)	2 (33.3)	17 (34.7)	4 (8.2)	3 (42.9)	2 (28.6)	30 (33.7)	11 (12.4)
Rash	4 (36.4)	0	3 (60.0)	0	1 (20.0)	1 (20.0)	1 (16.7)	0	4 (66.7)	0	14 (28.6)	3 (6.1)	1 (14.3)	0	28 (31.5)	4 (4.5)
Dermatitis acneiform	1 (9.1)	1 (9.1)	2 (40.0)	1 (20.0)	3 (60.0)	0	2 (33.3)	1 (16.7)	1 (16.7)	0	15 (30.6)	1 (2.0)	2 (28.6)	0	26 (29.2)	4 (4.5)
Hypokalemia	2 (18.2)	1 (9.1)	1 (20.0)	0	1 (20.0)	0	3 (50.0)	1 (16.7)	2 (33.3)	0	12 (24.5)	4 (8.2)	4 (57.1)	1 (14.3)	25 (28.1)	7 (7.9)
Anemia	2 (18.2)	1 (9.1)	1 (20.0)	0	0	0	0	0	4 (66.7)	1 (16.7)	14 (28.6)	2 (4.1)	2 (28.6)	0	23 (25.8)	4 (4.5)
Constipation	4 (36.4)	0	0	0	1 (20.0)	1 (20.0)	1 (16.7)	0	2 (33.3)	0	11 (22.4)	0	3 (42.9)	0	22 (24.7)	1 (1.1)
Hyperglycemia	3 (27.3)	0	1 (20.0)	0	2 (40.0)	0	0	0	1 (16.7)	0	12 (24.5)	1 (2.0)	2 (28.6)	0	21 (23.6)	1 (1.1)
Pyrexia	4 (36.4)	0	0	0	1 (20.0)	0	0	0	3 (50.0)	0	9 (18.4)	0	3 (42.9)	0	20 (22.5)	0
Hypertension	1 (9.1)	1 (9.1)	1 (20.0)	1 (20.0)	1 (20.0)	0	0	0	2 (33.3)	0	12 (24.5)	3 (6.1)	2 (28.6)	2 (28.6)	19 (21.3)	7 (7.9)
Dyspnea	3 (27.3)	1 (9.1)	2 (40.0)	1 (20.0)	1 (20.0)	0	0	0	1 (16.7)	0	11 (22.4)	1 (2.0)	0	0	18 (20.2)	3 (3.4)
Amylase increased	1 (9.1)	0	1 (20.0)	1 (20.0)	0	0	2 (33.3)	0	1 (16.7)	1 (16.7)	11 (22.4)	2 (4.1)	1 (14.3)	0	17 (19.1)	4 (4.5)
Lipase increased	2 (18.2)	1 (9.1)	0	0	1 (20.0)	0	1 (16.7)	0	1 (16.7)	1 (16.7)	11 (22.4)	7 (14.3)	1 (14.3)	0	17 (19.1)	9 (10.1)

Pruritus	3 (27.3)	0	1 (20.0)	0	1 (20.0)	0	1 (16.7)	0	1 (16.7)	0	9 (18.4)	1 (2.0)	1 (14.3)	0	17 (19.1)	1 (1.1)
Chorioretinopathy	2 (18.2)	0	2 (40.0)	0	0	0	1 (16.7)	0	1 (16.7)	0	7 (14.3)	0	3 (42.9)	0	16 (18.0)	0
Anxiety	1 (9.1)	0	1 (20.0)	0	2 (40.0)	0	0	0	0	0	10 (20.4)	1 (2.0)	2 (28.6)	0	16 (18.0)	1 (1.1)
Urinary tract infection	1 (9.1)	1 (9.1)	2 (40.0)	0	2 (40.0)	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	8 (16.3)	1 (2.0)	0	0	15 (16.9)	4 (4.5)
Blood alkaline phosphatase increased	0	0	1 (20.0)	0	1 (20.0)	1 (20.0)	1 (16.7)	1 (16.7)	0	0	9 (18.4)	0	2 (28.6)	1 (14.3)	14 (15.7)	3 (3.4)
Depression	1 (9.1)	0	0	0	1 (20.0)	0	1 (16.7)	0	0	0	10 (20.4)	0	0	0	13 (14.6)	0
Hypoalbuminemia	1 (9.1)	0	2 (40.0)	0	0	0	0	0	0	0	8 (16.3)	2 (4.1)	1 (14.3)	0	12 (13.5)	2 (2.2)
Hypophosphatemia	0	0	1 (20.0)	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	9 (18.4)	5 (10.2)	0	0	12 (13.5)	7 (7.9)
Dehydration	0	0	1 (20.0)	1 (20.0)	1 (20.0)	0	2 (33.3)	0	0	0	8 (16.3)	1 (2.0)	0	0	12 (13.5)	2 (2.2)
Cough	2 (18.2)	0	0	0	0	0	0	0	1 (16.7)	0	8 (16.3)	0	1 (14.3)	0	12 (13.5)	0
Abdominal pain	2 (18.2)	1 (9.1)	0	0	1 (20.0)	1 (20.0)	1 (16.7)	0	0	0	5 (10.2)	1 (2.0)	2 (28.6)	0	11 (12.4)	3 (3.4)
Blood creatinine increased	2 (18.2)	0	0	0	0	0	1 (16.7)	0	1 (16.7)	0	6 (12.2)	0	0	0	10 (11.2)	0
Hypomagnesemia	0	0	0	0	0	0	0	0	1 (16.7)	0	8 (16.3)	0	1 (14.3)	0	10 (11.2)	0
Dry skin	0	0	2 (40.0)	1 (20.0)	1 (20.0)	0	1 (16.7)	0	1 (16.7)	0	3 (6.1)	0	2 (28.6)	0	10 (11.2)	1 (1.1)
Thrombocytopenia	1 (9.1)	0	1 (20.0)	0	1 (20.0)	0	3 (50.0)	0	1 (16.7)	0	2 (4.1)	0	1 (14.3)	0	10 (11.2)	0
Hypocalcemia	0	0	0	0	0	0	1 (16.7)	0	0	0	7 (14.3)	3 (6.1)	1 (14.3)	0	9 (10.1)	3 (3.4)
Dizziness	0	0	1 (20.0)	0	1 (20.0)	0	1 (16.7)	0	0	0	6 (12.2)	0	0	0	9 (10.1)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; CPK, creatine phosphokinase; G, grade; pt, patient; qd, once daily.

Table S4. Summary of best overall response per RECIST as per investigator assessment by patient group, patients at recommended phase II dose (RP2D; buparlisib 80 mg plus binimetinib 45 mg)

Parameter	Adv *EGFR*^{mut} NSCLC *N* = 13 *n* (%)	*RAS/BRAF*^{mut} Ovarian Cancer *N* = 18 *n* (%)	*KRAS*^{mut} NSCLC *N* = 11 *n* (%)
Complete response (CR)	0	0	0
Partial response (PR)	1 (7.7)	5 (27.8)[a]	0
Stable disease (SD)	4 (30.8)	6 (33.3)	6 (54.5)
Progressive disease (PD)	3 (23.1)	6 (33.3)	1 (9.1)
Unknown	5 (38.5)	1 (5.6)	4 (36.4)
Overall response rate (CR or PR), *n* (%)	1 (7.7)	5 (27.8)	0
95% CI	0.2-36.0	9.7-53.5	0.0-28.5
Disease control rate (CR or PR or SD), *n* (%)	5 (38.5)	11 (61.1)	6 (54.5)
95% CI	13.9-68.4	35.7-82.7	23.4-3.3

Abbreviations: Adv, advanced; CI, confidence interval; EGFR, epidermal growth factor receptor; mut, mutant; NSCLC, non-small cell lung cancer.

[a] *KRAS* mutation, *n* = 2; *NRAS* mutation, *n* = 1; *BRAF* mutation, *n* = 2

Table S5. Summary of selected pharmacokinetic parameters by treatment group (RP2D) at Day 15

	Binimetinib 45 mg + Buparlisib 80 mg				
Binimetinib (*N* = 47)	**$AUC_{(0\text{-}last)}$ (h•ng/mL) (*n* = 21)**	**AUC_{tau} (h•ng/mL) (*n* = 12)**	**C_{max} (ng/mL) (*n* = 21)**	**T_{max} (h) (*n* = 21)**	**R_{acc} (*n* = 12)**
Geo-mean	2,116.96	2,668.02	533.7		1.46
CV% geo-mean	46.19	46.71	54.6		31.46
Median	1,879.85	2,275.63	536.0	1.52	1.47
[min, max]	[832.41–4,477.25]	[1,542.99–5,230.23]	[132.0–1,180.0]	[0.45–5.00]	[0.87–2.42]
Buparlisib (*N*=47)	**(*n* = 22)**	**(*n* = 15)**	**(*n* = 22)**	**(*n* = 22)**	**(*n* = 14)**
Geo-mean	9,357.78	11,690.71	764.3		2.64
CV% geo-mean	53.15	36.44	36.6		38.23
Median	9,827.50	11586.13	731.5	2.94	2.64
[min, max]	[2,780.25–19,924.95]	[7321.74–23,531.58]	[461.0–1,310.0]	[0.50–7.13]	[1.27–4.66]

Abbreviations: AUC, area under the concentration curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; R_{acc}, relative accumulation ratio[a]; T_{max}, time to maximum plasma concentration.

[a] Calculated as $AUC_{\tau,ss}/AUC_{\tau}$, dose1.