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SUPPLEMENTAL INFORMATION

Supplemental Table 1. Incidence and severity of treatment-related adverse events in ≥2 patients treated at the 10-, 21-, 43-, 89-mg dose levels

10 mg ***N = 4***			**21 mg** ***N = 4***			**43 mg** ***N = 4***			**89 mg** ***N = 4***		
AE^	**All Grades *n* (%)**	**G3 *n* (%)**	**AE^**	**All Grades *n* (%)**	**G3 *n* (%)**	**AE^**	**All Grades *n* (%)**	**G3 *n* (%)**	**AE^**	**All Grades *n* (%)**	**G3 *n* (%)**
Any AE	3 (75.0)	1 (25.0)	Any AE	3 (75.0)	0	Any AE	4 (100)	0	Any AE	4 (100)	0
Blood alkaline phosphatase increased	2 (50.0)	0	Nausea	2 (50.0)	0	Decreased appetite	2 (50.0)	0	Diarrhea	2 (50.0)	0
Fatigue	2 (50.0)	0							Rash	2 (50.0)	0

^ No grade 4 and grade 5 treatment-related AEs were reported. AE, adverse event; G3, grade 3.

Supplemental Table 2. Incidence and severity of treatment-related adverse events in ≥2 patients treated at the 222-, 266-, and 319-mg dose levels

222 mg ***N = 7***			**266 mg** ***N = 8***			**319 mg** ***N = 4***		
AE^	**All Grades** ***n* (%)**	**G3** ***n* (%)**	**AE^**	**All Grades** ***n* (%)**	**G3** ***n* (%)**	**AE^**	**All Grades** ***n* (%)**	**G3** ***n* (%)**
Any AE	7 (100)	4 (57.1)	Any AE	8 (100)	4 (50.0)	Any AE	4 (100)	3 (75.0)
Mucosal inflammation and stomatitis	7 (100)	3 (42.9)	Mucosal inflammation and stomatitis	8 (100)	1 (12.5)	Mucosal inflammation and stomatitis	4 (100)	1 (25.0)
Nausea	3 (42.9)	0	Rash	6 (75.0)	1 (12.5)	Hyperglycemia	3 (75.0)	0
Abdominal pain upper	2 (28.6)	0	Nausea	5 (62.5)	0	Nausea	3 (75.0)	0
Constipation	2 (28.6)	0	Hyperglycemia	4 (50.0)	2 (25.0)	Anemia	2 (50.0)	0
Decreased appetite	2 (28.6)	0	Vomiting	4 (50.0)	0	Diarrhea	2 (50.0)	1 (25.0)
Dysgeusia	2 (28.6)	0	Fatigue	3 (37.5)	0	Fatigue	2 (50.0)	0
Fatigue	2 (28.6)	0	Pruritus	3 (37.5)	0	Paresthesia oral	2 (50.0)	0
Paresthesia oral	2 (28.6)	0	Arthralgia	2 (25.0)	0	Rash	2 (50.0)	1 (25.0)
Vomiting	2 (28.6)	0	Asthenia	2 (25.0)	0			
			Decreased appetite	2 (25.0)	0			
			Glycosylated hemoglobin increased	2 (25.0)	0			

^ No grade 4 and grade 5 treatment-related AEs were reported. AE, adverse event; G3, grade 3.

Supplemental Table 3. Pharmacokinetic parameters for single-dose administration of PF-05212384 at the maximum tolerated dose

Parameter	**Cycle 1** ***N* = 42**	
	n	**154 mg**
AUC_{inf} (ng.hr/mL)*	39	16,250 (28)
AUC_{last} (ng.hr/mL)*	42	15,780 (28)
AUC_{tau} (ng.hr/mL)*	42	15,810 (28)
C_{max} (ng/mL)*	42	9988 (28)
T_{max} (hr)**	42	0.467 (0.417, 0.667)
$t_{1/2}$^ (hr)	39	35.84 (±6.25)
CL (L/hr)*	39	9.475 (28)
V_{ss} (L)*	39	167.2 (35)

*Geometric mean (%CV); **median (range); ^arithmetic mean (±SD). AUC, area under the curve; CL, systemic clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; SD, standard deviation; T_{max}, time to maximum plasma concentration; $T_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady state.

Supplemental Table 4. Pharmacokinetic parameters for multiple-dose administration of PF-05212384 at the maximum tolerated dose

Parameter	**Cycle 2 *N* = 31**	
	n	**154 mg**
AUC_{tau} (ng.hr/mL)*	23	47,130 (54)
C_{max} (ng/mL)*	31	8594 (64)
T_{max} (hr)**	31	0.467 (0.417, 0.917)
$t_{1/2}$^ (hr)	23	35.97 (±5.32)
CL (L/hr)*	23	3.109 (53)
V_{ss} (L)*	23	29.77 (90)
C_{avg} (ng/mL)*	23	280.5 (54)
C_{min} (ng/mL)*	31	7.810 (58)
R_{ac}*	23	2.930 (58)

*Geometric mean (%CV); **median (range); ^arithmetic mean (±SD). AUC, area under the curve; C_{avg}, average plasma concentration; CL, systemic clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV, coefficient of variation; R_{ac}, accumulation ratio; SD, standard deviation; T_{max}, time to maximum plasma concentration; $T_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady state.

Supplemental Table 5. Tumor responses to single-agent treatment with PF-05212384 in patients with advanced solid malignancies

Tumor Response	**PF-05212384 (*N* = 77)** ***n* (%)**
Complete response	0
Partial response	2 (2.6)
Stable/no response and time to failure ≥184 days	8 (10.4)
Stable/no response and time to failure <184 days	19 (24.7)
Objective progression	38 (49.4)
Symptomatic deterioration	3 (3.9)
Early death	1 (1.3)
Indeterminate	6 (7.8)
Clinical benefit response rate [95% exact CI]	10 (13.0) [6.4, 22.6]

CI, confidence interval.

Supplemental Table 6. Changes in glucose, insulin, and C-peptide levels from baseline in the maximum tolerated dose group

Changes in glucose levels from baseline	***N***	**Mean (SD)**
Baseline (mg/dL)	**42**	**97.2 (16.67)**
Cycle 1, day 2	40	13.7 (21.49)
Cycle 1, day 8	41	8.9 (34.04)
Cycle 1, day 15	38	11.0 (29.98)
Cycle 1, day 22	39	13.4 (36.43)
Cycle 2, day 1	33	2.8 (15.74)
Changes in insulin levels from baseline	***N***	
Baseline (mU/mL)	**38**	**13.6 (9.27)**
Cycle 1, day 2	37	22.8 (25.68)
Cycle 2, day 1	27	1.3 (8.66)
Cycle 3, day 1	14	–0.7 (11.66)
Cycle 4, day 1	8	2.9 (6.35)
Cycle 5, day 1	5	2.3 (5.24)
Changes in C-peptide levels from baseline	***N***	
Baseline (ng/mL)	**37**	**2.9 (1.80)**
Cycle 1, day 2	34	3.6 (2.23)
Cycle 2, day 1	26	0.4 (1.36)
Cycle 3, day 1	12	0.5 (1.15)
Cycle 4, day 1	7	0.9 (1.45)
Cycle 5, day 1	4	0.4 (0.86)

SD, standard deviation.

Supplemental Table 7. Changes in PI3K/mTOR activation biomarkers from baseline in tumor biopsies from patients treated in the maximum tolerated dose group

Biomarker	*N*	Mean (SD)
AKT S473		
At screening (NFC)	8	34.3 (26.82)
Cycle 1/day 22 change from baseline (NFC)	8	–10.6 (34.70)
AKT T308		
At screening (NFC)	7	38.5 (25.80)
Cycle 1/day 22 change from baseline (NFC)	7	–3.0 (23.61)
FKHR T24 FKHRL1 T32		
At screening (NFC)	8	145.1 (113.99)
Cycle 1/day 22 change from baseline (NFC)	8	–28.2 (83.50)
STAT3		
At screening (NFC)	7	231.4 (219.22)
Cycle 1/day 22 change from baseline (NFC)	7	–56.9 (135.40)

NFC, normalized to cytokeratin; SD, standard deviation.