SUPPLEMENTARY INFORMATION

A Multi-Arm Phase I Study of the PI3K/mTOR Inhibitors PF-04691502 and Gedatolisib (PF-05212384) plus Irinotecan or the MEK Inhibitor PD-0325901 in Advanced Cancer

Zev A. Wainberg, Maria Alsina, Heloisa P. Soares, Irene Braña, Carolyn D. Britten, Gianluca Del Conte, Patrick Ezeh, Brett Houk, Kenneth A. Kern, Stephen Leong, Nuzhat Pathan, Kristen J. Pierce, Lillian L. Siu, Jennifer Vermette, Josep Tabernero

[1]David Geffen School of Medicine at UCLA, 2020 Santa Monica Blvd, Suite 600, Los Angeles, CA 90404, USA; [2]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Vall d'Hebron 119-129, Barcelona 08035, Spain; [3]Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA; [4]Princess Margaret Cancer Centre, 610 University Avenue, Toronto M5G 2M9, Canada; [5]Medical University of South Carolina, 39 Sabin St., MSC 635, Charleston, SC 29425, USA; [6]IRCCS Ospedale S. Raffaele, via Olgettina 60, Milano 20132, Italy; [7]Pfizer Oncology, 300 Technology Square, Cambridge, MA 02139, USA; [8]Pfizer Oncology, 10646 Science Center Drive, San Diego, CA 92121, USA; [9]University of Colorado Denver School of Medicine, 13001 E 17th Place, Aurora, CO 80045, USA; [10]Pfizer Oncology, 558 Eastern Point Road, Groton, CT 06340, USA.

Methods

Treatment schedules for arms A and B

In arm A, PF-04691502 was administered orally in a continuous daily-dosing regimen, with doses starting at 4 mg, to be escalated to 6 and 8 mg daily until the maximum tolerated dose (MTD) or the maximum dose of 8 mg were reached. PD-0325901 was administered orally twice daily in a 3-weeks-on/1-week-off regimen, at 8 or 5 mg twice daily.

In arm B, PF-04691502 was dosed daily on days 2–12 and days 16–26 of each cycle, with doses starting at 4 mg, to be escalated to 6 and 8 mg daily until the MTD or the maximum dose of 8 mg was reached. Irinotecan was administered at 180 mg/m^2 biweekly on days 1 and 15 of each treatment cycle.

Supplementary Tables

Supplementary Table S1 Dose-limiting toxicities, by treatment arm

Arm A: PF-04691502 + PD-0325901 (*n* = 7)		Arm B: PF-04691502 +irinotecan (*n* = 14)		Arm C (Stage 1): Gedatolisib + irinotecan (*n* = 13)		Arm D: Gedatolisib + PD-0325901 (*n* = 37)	
DLT-evaluable = 7		DLT-evaluable = 12		DLT-evaluable = 13		DLT-evaluable = 35	
Group	Nature of DLT	Group	Nature of DLT	Group	Nature of DLT	Group	Nature of DLT
A1	Grade 3 diarrhea, grade 3 nausea and grade 3 vomiting	B1	Grade 2 neutropenia[a]	C3	Grade 4 febrile neutropenia	D0	Grade 2 mucosal inflammation[a]
A1	Grade 4 mucosal inflammation	B2	Grade 2 fatigue[a]	C3	Grade 3 fatigue	D1	Grade 3 hypophosphatemia
A4	Grade 3 increased blood alkaline phosphatase	B2	Grade 3 febrile neutropenia			D1A	Grade 3 stomatitis
Total	3		3		2		3

[a]Persistent, intolerable adverse events resulting in failure to deliver at least 75% of doses during the first cycle or in a delay >2 weeks in starting cycle 2 were considered DLTs.

DLT dose-limiting toxicity

Supplementary Table S2 Safety summary and treatment discontinuations/dose reductions due to adverse events, by treatment arm

	Arm A: PF-04691502 + PD-0325901 (*n* = 7)		Arm B: PF-04691502 + irinotecan (*n* = 14)		Arm C: Gedatolisib + irinotecan (*n* = 44)		Arm D: Gedatolisib + PD-0325901 (*n* = 37)	
Patients, *n* (%)	All	Related	All	Related	All	Related	All	Related
Adverse events								
AEs	7 (100)	7 (100)	14 (100)	14 (100)	44 (100)	43 (97.7)	37 (100)	36 (97.3)
Serious AEs	4 (57.1)	4 (57.1)	7 (50)	2 (14.3)	7 (15.9)	2 (4.5)	12 (32.4)	0
Grade 3-4 AEs	5 (71.4)	5 (71.4)	7 (50)	4 (28.6)	17 (38.6)	11 (25.0)	19 (51.4)	8 (21.6)
Grade 5 AEs	0	0	0	0	0	0	3 (8.1)	0
Permanent discontinuation								
PI3K inhibitor	2 (28.6)	2 (28.6)	3 (21.4)	2 (14.3)	4 (9.1)	0	6 (16.2)	1 (2.7)
Irinotecan	–	–	3 (21.4)	2 (14.3)	5 (11.4)	0	–	–
PD-0325901	2 (28.6)	2 (28.6)	–	–	–	–	6 (16.2)	1 (2.7)
Temporary discontinuation								
PI3K inhibitor	5 (71.4)	5 (71.4)	8 (57.1)	5 (35.7)	10 (22.7)	3 (6.8)	18 (48.6)	15 (40.5)
Irinotecan	–	–	7 (50.0)	4 (28.6)	8 (18.2)	2 (4.5)	–	–
PD-0325901	5 (71.4)	5 (71.4)	–	–	–	–	17 (45.9)	12 (32.4)
Dose reduction								
PI3K inhibitor	1 (14.3)	1 (14.3)	1 (7.1)	1 (7.1)	1 (2.3)	1 (2.3)	3 (8.1)	3 (8.1)
Irinotecan	–	–	1 (7.1)	0	11 (25.0)	10 (22.7)	–	–
PD-0325901	1 (14.3)	1 (14.3)	–	–	–	–	2 (5.4)	2 (5.4)

AE adverse event, related treatment-related

Supplementary Table S3 Treatment-related adverse events reported in >15% of patients in arm A (*n* = 7)

Adverse event, n (%)	Grade 1	Grade 2	Grade 3[a]	Grade 4	Grade 5	Total
Any	1 (14.3)	1 (14.3)	4 (57.1)	1 (14.3)	0	7 (100.0)
Diarrhea	1 (14.3)	0	3 (42.9)	0	0	4 (57.1)
Nausea	3 (42.9)	1 (14.3)	0	0	0	4 (57.1)
Acneiform dermatitis	1 (14.3)	1 (14.3)	1 (14.3)	0	0	3 (42.9)
Rash	2 (28.6)	1 (14.3)	0	0	0	3 (42.9)
Chills	2 (28.6)	0	0	0	0	2 (28.6)
Dry eye	2 (28.6)	0	0	0	0	2 (28.6)
Fatigue	2 (28.6)	0	0	0	0	2 (28.6)
Hypokalemia	0	1 (14.3)	1 (14.3)	0	0	2 (28.6)
Mucosal inflammation	1 (14.3)	0	0	1 (14.3)	0	2 (28.6)
Pruritus	2 (28.6)	0	0	0	0	2 (28.6)
Maculopapular rash	0	2 (28.6)	0	0	0	2 (28.6)
Vomiting	1 (14.3)	1 (14.3)	0	0	0	2 (28.6)

[a]One patient each experienced grade 3 arrhythmia, pruritic rash, and increased alkaline phosphatase.

Supplementary Table S4 Treatment-related adverse events reported in ≥14% of patients in arm B (*n* = 14)

Adverse event, *n* (%)	Grade 1	Grade 2	Grade 3[a]	Grade 4	Grade 5	Total
Any	1 (7.1)	9 (64.3)	4 (28.6)	0	0	14 (100.0)
Vomiting	9 (64.3)	1 (7.1)	0	0	0	10 (71.4)
Nausea	5 (35.7)	3 (21.4)	1 (7.1)	0	0	9 (64.3)
Diarrhea	1 (7.1)	4 (28.6)	0	0	0	5 (35.7)
Fatigue	2 (14.3)	2 (14.3)	1 (7.1)	0	0	5 (35.7)
Decreased appetite	3 (21.4)	1 (7.1)	0	0	0	4 (28.6)
Alopecia	2 (14.3)	0	1 (7.1)	0	0	3 (21.4)
Hyperglycemia	0	2 (14.3)	0	0	0	2 (14.3)
Neutropenia	0	2 (14.3)	0	0	0	2 (14.3)
Rash	2 (14.3)	0	0	0	0	2 (14.3)

[a]One patient each experienced grade 3 cholestasis, febrile neutropenia, and increased transaminases.

Supplementary Table S5 Gene mutations detected in responders in arms C and D

	Individual patients					
	Arm C		Arm D			
Best response	PR	PR	PR	PR	PR	PR
Tumor type	CRC	CRC	ovarian	ovarian	ovarian	endometrial
PTEN (tumor tissue)	n. a.	1+	2+	2+	2+	2+
PTEN (stromal tissue)	n. a.	1+	3+	2+	3+	n. a.
KRAS mutation	n. a.	negative	G12A	G13D	G12V	G12D
BRAF mutation	n. a.	n. a.	negative	negative	n. a.	negative
PIK3CA mutation	n. a.	n. a	negative	n. a.	n. a.	H1047R

CRC colorectal cancer, *BRAF* v-Raf murine sarcoma viral oncogene homolog B, *KRAS* v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, n. a. not available, *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, PR partial response, PTEN phosphatase and tensin homolog

Supplementary Table S6 Pharmacokinetic parameters for gedatolisib in arm C

Parameter[a]	Arm C: gedatolisib + irinotecan			
	C1 (stage 1)	C2 (stage 1)	C3 (stage 1)	C2 (stage 2)
Gedatolisib dose	95 mg	110 mg	130 mg	110 mg
Cycle 1/day 2				
N, *n*	2, 1	6, 5	4, 3	30, 25
AUC_{inf} (ng·hr/mL)	NR	7968 (41)	9277 (48)	10070 (42)
AUC_{last} (ng·hr/mL)	NR	7487 (41)	10530 (44)	9485 (43)
AUC_{τ} (ng·hr/mL)	NR	7510 (41)	10560 (44)	9503 (43)
C_{max} (ng/mL)	NR	3404 (82)	4759 (25)	5221 (61)
T_{max} (hr)	NR	1.02 (0.500–1.67)	0.992 (0.500–1.00)	0.500 (0.467–1.07)
$t_{½}$ (hr)	NR	32.14 ± 1.33	29.23 ± 7.11	32.16 ± 4.52
CL (L/hr)	NR	13.95 (52)	14.18 (38)	11.06 (39)
V_z (L)	NR	646.6 (53)	586.4 (45)	508.4 (35)
Cycle 1/day 16				
N, *n*	3, 1	6, 5	4, 3	28, 20
AUC_{τ} (ng·hr/mL)	8816 (71)	8240 (25)	11050 (48)	10850 (38)
C_{max} (ng/mL)	2201 (16)	2814 (50)	4656 (32)	5728 (56)
T_{max} (hr)	1.00 (1.00–1.08)	0.992 (0.583–1.05)	0.734 (0.500–1.00)	0.525 (0.333–2.92)
C_{min} (ng/mL)	NR	4.746 (71)	5.661 (111)	NR
$t_{½}$ (hr)	NR	37.98 ± 5.56	34.50 ± 8.43	35.10 ± 3.31

CL (L/hr)	NR	13.05 (29)	14.43 (17)	10.55 (35)
V_z (L)	NR	709.9 (38)	704.9 (15)	532.0 (35)
R_{ac}	1.061 (49)	1.097 (40)	1.049 (31)	1.124 (26)

[a]Geometric mean (arithmetic %CV) for all except median (range) for T_{max} and arithmetic mean ± SD for $t_{½}$. Summary statistics not presented for *n* <3; geometric means not presented for C_{min} when individual values included zero.

%CV percent coefficient of variation, AUC area under the curve, CL clearance, C_{max} maximum concentration, C_{min} minimum concentration, N number of subjects contributing to the summary statistics, n number of subjects for $t_{½}$, AUC_{inf}, V_z and CL, NR not reported, R_{ac} accumulation ratio, $t_{½}$ half-life, T_{max} time to maximum concentration, V_z volume of distribution

Supplementary Table S7 Pharmacokinetic parameters for gedatolisib in arm D

Parameter[a]	Arm D: gedatolisib + PD-0325901							
	D0	D0A	D0B	D1	D1A	D1B	D2	D2A
Gedatolisib dose	110 mg	130 mg	154 mg	110 mg	130 mg	154 mg	110 mg	130 mg
Cycle 0/day –14								
N, *n*	7, 5	3, 3	4, 3	7, 6	6, 6	3, 3	4, 4	2, 2
AUC_{inf} (ng·hr/mL)	6353 (40)	10460 (20)	14880 (39)	12600 (29)	14620 (23)	14230 (46)	9766 (22)	NR
AUC_{last} (ng·hr/mL)	7627 (46)	10250 (21)	14850 (31)	12590 (27)	14280 (24)	13840 (47)	9619 (22)	NR
C_{max} (ng/mL)	3625 (62)	5937 (32)	11170 (16)	8476 (32)	8586 (36)	6279 (70)	7239 (39)	NR
T_{max} (hr)	0.500 (0.500–1.00)	0.500 (0.500–0.983)	0.500 (0.500–0.500)	0.500 (0.500–3.22)	0.509 (0.500–0.583)	1.00 (0.500–3.08)	0.500 (0.500–0.600)	NR
$t_{½}$ (hr)	24.62 ± 3.23	27.37 ± 6.47	30.77 ± 6.49	25.85 ± 4.15	29.35 ± 5.51	29.63 ± 3.71	27.05 ± 4.67	NR
CL (L/hr)	15.63 (33)	12.44 (22)	10.36 (34)	8.725 (30)	8.893 (24)	10.83 (55)	11.28 (20)	NR
V_z (L)	551.3 (24)	480.4 (33)	454.0 (17)	321.8 (16)	371.2 (37)	460.9 (67)	435.6 (21)	NR
Cycle 1/day 15								
N, *n*	5, 3	3, 3	4, 4	6, 6	5, 3	1, 1	4, 3	1, 1
AUC_{T} (ng·hr/mL)	12530 (32)	12130 (1)	19990 (25)	13590 (20)	21200 (36)	NR	12680 (25)	NR
C_{max} (ng/mL)	8621 (18)	6153 (34)	12440 (32)	8717 (50)	8913 (54)	NR	7989 (45)	NR
T_{max} (hr)	0.500 (0.500-0.500)	0.500 (0.500-1.00)	0.500 (0.500-0.517)	0.509 (0500-0.567)	0.517 (0.500-0.583)	NR	0.500 (0.500-3.92)	NR
C_{min} (ng/mL)	4.638 (33)	5.991 (32)	8.037 (25)	5.205 (45)	11.12 (40)	NR	4.435 (43)	NR
$t_{½}$ (hr)	35.90±4.88	39.30 ± 10.68	41.25 ± 6.23	34.43 ± 8.54	40.20 ± 5.86	NR	33.30 ± 0.96	NR

CL (L/hr)	10.14 (27)	10.70 (1)	7.706 (34)	8.085 (24)	5.642 (50)	NR	8.342 (32)	NR
V_z (L)	521.2 (15)	592.7 (26)	454.6 (23)	389.8 (37)	324.9 (53)	NR	401.3 (34)	NR
R_{ac}	1.235 (33)	0.9724 (12)	1.281 (24)	1.063 (44)	1.158 (21)	NR	1.299 (29)	NR

[a]Geometric mean (arithmetic %CV) for all except median (range) for T_{max} and arithmetic mean ± SD for $t_{½}$. Summary statistics not presented for *n* <3; geometric means not presented for C_{min} when individual values included zero.

%CV percent coefficient of variation, AUC area under the curve, CL clearance, C_{max} maximum concentration, C_{min} minimum concentration, N number of subjects contributing to the summary statistics, n number of subjects for $t_{½}$, AUC_{inf}, V_z and CL, NR not reported, R_{ac} accumulation ratio, $t_{½}$ half-life, T_{max} time to maximum concentration, V_z volume of distribution at steady state

Supplementary Table S8 Pharmacokinetic parameters for PD-0325901 in arm D

Parameter[a]	Arm D: gedatolisib + PD-0325901							
	D0	D0A	D0B	D1	D1A	D1B	D2	D2A
PD-0325901 dose	2 mg BID	2 mg BID	2 mg BID	4 mg BID	4 mg BID	4 mg BID	6 mg BID	6 mg BID
Cycle 0/day –1								
n	7	3	3	7	7	3	3	2
AUC_8 (ng·hr/mL)	342.0 (30)	347.4 (27)	376.0 (44)	729.3 (28)	831.2 (34)	563.9 (36)	848.0 (17)	NR
C_{max} (ng/mL)	85.28 (27)	63.80 (14)	87.99 (51)	180.6 (28)	191.9 (44)	115.8 (70)	231.3 (69)	NR
T_{max} (hr)	1.00 (1.00–6.02)	2.00 (2.00–3.00)	1.03 (1.0–2.33)	1.97 (0.917–4.00)	1.07 (1.00–2.00)	1.00 (0.333–4.00)	2.00 (1.00–4.00)	NR
C_{min} (ng/mL)	20.53 (42)	23.22 (47)	28.04 (34)	42.56 (43)	49.04 (44)	40.80 (33)	26.73 (87)	NR
Cycle 1/day 1								
N	5	3	3	6	6	3	4	2
AUC_8 (ng·hr/mL)	375.4 (27)	356.5 (20)	346.5 (36)	656.8 (26)	824.6 (26)	572.0 (51)	768.3 (34)	NR
C_{max} (ng/mL)	91.69 (31)	74.23 (43)	64.99 (56)	138.7 (23)	183.6 (29)	114.6 (50)	211.9 (44)	NR
T_{max} (hr)	1.00 (1.00–2.00)	2.00 (1.00–4.00)	1.00 (1.00–4.00)	2.00 (1.00–4.00)	1.00 (1.00–2.02)	2.00 (2.00–4.05)	1.50 (1.00–6.00)	NR
C_{min} (ng/mL)	23.74 (39)	22.71 (38)	24.03 (35)	40.52 (27)	55.21 (31)	34.39 (53)	NR	NR

[a]Geometric mean (arithmetic %CV) for all except median (range) for T_{max}. Summary statistics not presented for *n* <3; geometric means not presented for C_{min} when individual values included zero.

%CV percent coefficient of variation, AUC area under the curve, BID twice a day, C_{max} maximum concentration, C_{min}=minimum concentration, N number of subjects contributing to the summary statistics, NR not reported, T_{max} time to maximum concentration