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COMPOUND NUMBER: PF-04691502

PROTOCOL NO.: B1271003

PROTOCOL TITLE: An Open-Label, Randomised Phase 1b/2 Study of PF-04691502 in Combination With Letrozole Compared With Letrozole Alone in Patients With Estrogen Receptor Positive, HER-2 Negative Early Breast Cancer

Study Centers: A total of 5 centers took part in study and enrolled subjects; 2 in Sweden, 1 each in Italy, Belgium and Spain.

Study Initiation and Final Completion Dates: 21 March 2012 to 05 December 2012
The study was terminated prematurely.

Phase of Development: Phase 1b/2

Study Objectives:

Phase 1b (Lead-in Portion):

Primary Objective:

- To assess the tolerability of PF-04691502 combined with letrozole in postmenopausal subjects with estrogen-receptor (ER) positive, human-epidermal-growth-factor receptor 2 (HER-2) negative advanced breast cancer (ABC).

Secondary Objectives:

- To evaluate the safety profile of PF-04691502 in combination with letrozole;
- To evaluate the pharmacokinetics (PK) of PF-0461502 and letrozole when administered alone and in combination;
- To characterize the effects, if any, of PF-0461502 combined with letrozole on QTc interval;
- To explore preliminary anti-tumor activity of PF-04691502 combined with letrozole.

Phase 2:

Primary Objective:

- To compare the change in Ki-67 value from Baseline to Week 6 in matched tumor biopsies from subjects with ER positive, HER-2 negative early breast cancer treated with PF-04691502 in combination with letrozole or letrozole alone.

Secondary Objectives:

- To evaluate the overall safety profile of the 2 regimens;
- To explore tumor response in subjects treated with the 2 regimens;
- To evaluate the PK of PF-0461502 when given alone and in combination with letrozole;
- To explore the pharmacodynamic (PD) effect of the 2 regimens in tumor tissue at the 2-week time-point and at the 6-week time-point as compared to baseline;
- To evaluate genetic alterations and/or protein changes at Baseline and after treatment with the 2 regimens, with a focus on the Phosphoinositide 3-kinase (PI3K) pathway, to explore novel subject selection biomarkers in ER positive, HER-2 negative early breast cancers.

METHODS

Study Design: This was an open label, multicenter, randomized Phase 1b/2 clinical trial in postmenopausal women with breast cancer. The study was to be conducted in 2 phases, a Phase 1b lead-in stage and a randomized Phase 2 stage. The lead-in portion assessed the tolerability of PF-04691502 and letrozole when administered to women with ER positive, HER-2 negative ABC. The planned randomized Phase 2 portion of the study was to compare the PD effects and safety of PF-04691502 combined with letrozole versus letrozole alone in subjects with ER positive, HER-2 negative early breast cancer. The schedule of activities is summarized in Table 1.

Table 1. Schedule of Activities in the Phase 1b (Lead-In Portion)

Protocol Activity	Screen / Baseline[a]	Study Treatment / Visits[b]								Post Treatment	
	≤28 Days Prior to First Dose of Study Drug	First 2 Weeks			Weeks 3-8			Visits From Week 9 Until Week 52	Visits Beyond Week 52	End of Treatment[c]	Follow-Up[d]
		Day 1	Day 2	Day 12	Week 3	Week 5	Week 7	Every 4 Weeks	As per SOC at Institution		
Baseline documentation											
Informed consent[e]	X										
Registration[f]	To be completed prior to first dose of study drug										
General medical history[g]	X										
Physical examination (including vital signs and ECOG performance status)[h]	X	X			X	X	X	X	As per SOC at institution	X	X
Tumor history[i]	X										
Baseline signs and symptoms[j]		X									
Laboratory studies											
Hematology[k]	X	X			X	X	X	X	As per SOC at institution	X	
Blood chemistry[l]	X	X			X	X	X	X	X	X	
Urinalysis[m]	X	X			X			X	As per SOC at institution	X	
Other clinical assessments											
12-lead ECG[n]	X within 21 days prior to first dose	X	X	X						X	
AEs[o]	Continuous monitoring and assessment										
Concomitant medication[p]	Continuous monitoring and assessment										
Tumor assessments											
CT or MRI scan or equivalent[q]	X							X At Week 12 and Week 36	As per SOC at institution	X	
Study drug administration[r]											
Letrozole		X		CDD from Day 12 on							
PF-04691502			CDD from Day 2 on								

Hematology and blood chemistry were done up to 4 days prior to scheduled visit to facilitate availability of results to investigator at the time of clinic visit.
Tumor assessments were done up to 14 days prior to scheduled visit.

Table 1. Schedule of Activities in the Phase 1b (Lead-In Portion)

Protocol Activity	Screen / Baseline[a]	Study Treatment / Visits[b]								Post Treatment	
	≤28 Days Prior to First Dose of Study Drug	First 2 Weeks			Weeks 3-8			Visits From Week 9 Until Week 52	Visits Beyond Week 52	End of Treatment[c]	Follow-Up[d]
		Day 1	Day 2	Day 12	Week 3	Week 5	Week 7	Every 4 Weeks	As per SOC at Institution		

AEs = adverse events; CDD = cell death and Differentiation; CRF = case report form; CT = computer-tomographic; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; MRI = medical resonance imaging; NCI CTC AE = National Institute of Cancer (Common Terminology Criteria for Adverse Events); SOC = standard of care.

a. Screening / baseline assessments were completed within 28 days of beginning study treatment as shown in the schedule of events above.
b. Clinical visits were conducted every 2 weeks until Week 8 (ie, Weeks 1, 3, 5 and 7), and every 4 weeks thereafter starting from Week 9 until Week 52 (1 year). The allowable window for clinical visits until Week 52 is ±3 days. After Week 52, subjects may receive clinical visits and assessments as per standard of care (SOC) at the institution where subjects are treated.
c. Obtained these assessments if not completed in the last week (last 12 weeks for tumor assessments).
d. Subjects were evaluated up to 28 days after last dose of study treatment or until a new anti-tumor agent was administered. Review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity were conducted.
e. Informed consent were obtained prior to undergoing any study specific procedures.
f. Subject enrollment number assigned by Sponsor.
g. Medical history were collected within 28 days prior to first dose of study medication. Includes history of disease process other than oncology (active or resolved), and concomitant illnesses. Includes prior treatments as well as concurrent medications.
h. Physical examination included height (baseline only), body weight, vital signs (blood pressure and heart rate to be recorded in reclining position), and ECOG performance status. If procedures already conducted within 7 days prior to the first dose of study treatment, then it was not to be repeated at Day 1 (ie, first day of treatment). These procedures were conducted by the Investigator or his / her designee.
i. Tumor history were collected within 28 days prior to first dose of study medication. Includes history of oncology disease including details of primary diagnosis and treatment history (systemic treatment and radiotherapy).
j. At Day 1 (ie, first day of treatment) prior administration of study treatment subjects were asked about any signs and symptoms experienced within the past 14 days of starting treatment. During trial treatment (following informed consent) any new or worsened conditions since baseline was reported on the Adverse Event CRF.
k. Blood samples were collected prior administration of study treatment. If already conducted within 7 days prior to the first dose of study treatment, then it was not repeated at Day 1 (ie, first day of treatment).
l. Blood samples were collected prior administration of study treatment. If already conducted within 7 days prior to the first dose of study treatment then it was not repeated at Day 1 (ie, first day of treatment).
m. Urinalysis performed by dipstick at Baseline, Day 1 (ie, first day of treatment) and every 4 weeks thereafter until Week 52, and at End of Treatment. After Week 52, it was performed as per standard of care at the institution where subjects were treated. Additional tests were performed in the event of AEs. Microscopic analyses were done (per Investigator discretion) if dipstick deemed abnormal.
n. ECGs were collected within 21 days prior to the first dose of study drug, at Day 1, Day 2, Day 12 and at the End of Treatment Visit.
o. AEs were documented and recorded at each visit using NCI CTC AE version 4.0.
p. All concomitant medications were recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat AEs or chronic diseases.
q. Tumor assessments were performed at screening, at Week 12, Week 36, and as per standard of care at each institution thereafter and at the End of Treatment Visit if >12

Table 1. Schedule of Activities in the Phase 1b (Lead-In Portion)

Protocol Activity	Screen / Baseline[a]	Study Treatment / Visits[b]								Post Treatment	
	≤28 Days Prior to First Dose of Study Drug	First 2 Weeks			Weeks 3-8			Visits From Week 9 Until Week 52	Visits Beyond Week 52	End of Treatment[c]	Follow-Up[d]
		Day 1	Day 2	Day 12	Week 3	Week 5	Week 7	Every 4 Weeks	As per SOC at Institution		

weeks had passed since the last evaluation. Tumor assessments were done up to 14 days prior to scheduled visit.

r. Subjects received single agent letrozole on Day 1, single agent PF-04691502 from Day 2 until Day 11 (10 days) and the combination of PF-04691502 and letrozole from Day 12 on.

Number of Subjects (Planned and Analyzed): The Phase 1b portion of the study was designed to enroll 10 evaluable subjects to assess the safety of PF-04691502 with starting dose of 8 mg in combination with letrozole. A total of 14 subjects were enrolled and treated. The Phase 2 portion of the study was not conducted.

Diagnosis and Main Criteria for Inclusion: Postmenopausal female subjects with histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic disease or locally advanced disease, not amenable to resection or radiation therapy with curative intent; ER positive and HER-2 negative breast cancer (ie, immunohistochemistry [IHC] 0 or 1+; if IHC 2+, fluorescent in situ hybridization or chromogenic in situ hybridization negative); subjects must be candidates to receive letrozole as standard of care.

Main Criteria for Exclusion: Clinical presentation of inflammatory carcinoma; Subjects unwilling to undergo core biopsies after 2 and 6 weeks of treatment; presence of active brain metastases, presence of spinal cord compression, or carcinomatous meningitis, or leptomeningeal disease; subjects with previously diagnosed brain metastases are eligible if they have completed their central nervous system treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable; prior therapy with an agent that is known or proposed to be active by action on PI3K and/or mammalian target of rapamycin were excluded from the study.

Study Treatment: Subjects received PF-04691502 tablets 1 and 5 mg and letrozole tablets 2.5 mg orally. On Day 1, subjects received single agent letrozole (2.5 mg). From Day 2 until Day 11, subjects received single agent PF-04691502 (8 mg/day). From Day 12 onwards, subjects received PF-04691502 in combination with letrozole as a continuous daily dose until progression of disease, unacceptable toxicity, or withdrawal of subject consent. The median duration of treatment with PF-04691502 was 5.64 weeks (range 1.86 to 30.43 weeks) and with letrozole was 8.00 weeks (range 2.29 to 33.71 weeks).

Efficacy Pharmacokinetic, Pharmacodynamic, and Safety Endpoints:

Phase 1b (Lead-in portion):

Primary Endpoint:

- Adverse Events (AEs) as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.0 [NCI CTCAE v 4.0]) timing, seriousness and relationship to study therapy.

Secondary Endpoints:

- Laboratory test abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.0) and timing;
- Vital Signs;
- QTc Interval;

- PK parameters of PF-04691502 and letrozole when administered alone and in combination;
- Objective tumor response.

Phase 2:

Primary Endpoint:

- Ki-67 (% positive tumor cells) as tested by IHC (central lab).

Secondary Endpoints:

- AEs as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.0) timing, seriousness and relationship to study therapy;
- Laboratory test abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v. 4.0) and timing;
- Vital Signs;
- Objective tumor response;
- PK parameters of PF-04691502 when administered alone and in combination with letrozole;
- Expression levels of PI3K pathway proteins (eg, pAKT, pS6, stathmin) and markers of cellular proliferation and survival (eg, Ki-67, apoptosis assays) in biopsied tumor tissue;
- Genetic alteration, RNA and protein expression data in biopsied tumor tissue relating to PI3K pathway signaling (eg, PIK3CA, AKT mutations, PIK3CA amplification, PTEN protein levels) and other pathways relevant to the biology of ER positive, HER-2 negative early breast cancer.

Safety Evaluations: AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) system and graded according to NCI CTCAE v 4.0 whenever possible. AEs were presented according to treatment group and frequency and relatedness to treatment was indicated. AEs leading to death or discontinuation of treatment, AEs of ≥Grade 3 severity, treatment-related AEs, and serious adverse events (SAEs) were given particular attention.

Statistical Methods: The following population sets were analyzed:

Full Analysis Set:

- Phase 1b: All enrolled subjects;
- Phase 2: All randomized subjects.

'Per Protocol' Analysis Set:

- Phase 1b: Enrolled subjects treated with study treatment for at least 2 months who received at least 2 months of treatment unless it was interrupted due to toxicity;
- Phase 2: Randomized subjects treated on the assigned arm who had evaluable baseline and Week 6 Ki-67 levels. Evaluable is defined as having lab results for the Ki-67 time points.

Safety Analysis Set:

- Phase 1b: All enrolled who started treatment;
- Phase 2: All subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

The primary objective of Phase 1b was to assess the safety of PF-04691502 in combination with letrozole. AEs were classified using the MedDRA system and graded according to NCI CTCAE v 4.0 whenever possible.
Tumor responses were summarized using subject data listings that included, but were not limited to, starting dose, tumor response at each visit, dates of response, and best overall response.

RESULTS

Subject Disposition and Demography: From 21 March 2012 to 25 June 2012, 14 postmenopausal subjects with ER positive, HER-2 negative ABC were enrolled in the Phase 1b portion of the study. The subject evaluation group is summarized in Table 2. In the Phase 1b portion of this study, Grade 3 skin toxicity was observed in 7/14 subjects (50%) receiving PF-04691502 in combination with letrozole; this toxicity was not rapidly reversible following dose interruption or reduction and led to discontinuation of PF-04691502 treatment in 6/14 subjects (43%). Based on these findings the clinical development of PF-04691502 was discontinued. Therefore, the Phase 2 portion of the study was not conducted.

Table 2. (Phase 1b): Subject Evaluation Groups - Full Analysis Population

	PF-04691502 (8 mg) + Letrozole
Number of subjects	14
Assigned to study treatment	
Treated	14
Completed	0
Discontinued	14 (100%)
Analyzed for safety	
Adverse events	14 (100%)
PK analysis set	
PK concentration	14 (100%)

PK = pharmacokinetic.

Table 3 presents a summary of the discontinuations from study treatment.

Table 3. Summary of Discontinuation From Treatment

	Number of Subjects (%)
Discontinuations from treatment - PF-04691502	14 (100.0%)
Withdrew consent	-
Completed	-
Objective progression or relapse	1 (7.1%)
Global deterioration of health status	-
AE	9 (64.3%)
Subject died	1 (7.1%)
Protocol violation	-
Lost to follow-up	-
Subject refused continued treatment for reason other than AE	2 (14.3%)
Study Terminated by Sponsor	-
Other[a]	1 (7.1%)
Discontinuations from treatment - letrozole	14 (100.0%)
Withdrew consent	-
Completed	-
Objective progression or relapse	2 (14.3%)
Global deterioration of health status	-
AE	5 (35.7%)
Subject died	2 (14.3%)
Protocol violation	-
Lost to follow-up	-
Subject refused continued treatment for reason other than AE	1 (7.1%)
Study terminated by Sponsor	2 (14.3%)
Other[b]	2 (14.3%)

AE = adverse event.
a. Subject refused to continue treatment due to AE.
b. Investigator's decision.

Table 4 presents a summary of the demographic characteristics of subjects enrolled in the study.

Table 4. Summary of Demographic Characteristics

Age(years)	
N	14
<18	-
18–44	-
45–64	8 (57.1%)[a]
≥65	6 (42.9%)[a]
Mean	63.1
Standard deviation	11.5
Median	60.5
Range	51–86
Race	
N	14
White	14 (100.0%)[a]
Black	-
Asian	-
Other	-
Weight (kg)	
N	12
Mean	66.02
Standard deviation	11.13
Median	62.25
Range	52.00–86.00
Height (cm)	
N	11
Mean	160.36
Standard deviation	7.51
Median	162.00
Range	144.00–171.00

N = number of subjects; n = number of subjects with specified criteria.
a. Numbers presented as number of subjects and percentage: n (%).

Efficacy, Pharmacokinetic, and Pharmacodynamic Results:

Anti-Tumor Activity: Out of a total of 7 subjects for whom Investigator tumor assessments were reported, 1 subject had a partial response, 5 subjects had stable disease, and 1 subject had progressive disease. The 7 remaining subjects did not have on-study tumor assessments reported; 1 subject died due to progression of disease prior to on-study tumor assessment and the remaining 6 subjects discontinued the study prior to on-study tumor assessment.

No PK information was available at that time.

Safety Results:

Extent of Exposure: Table 5 presents a summary of study treatment duration.

Table 5. Summary of Treatment Duration

Treatment Duration[a]	Number and Percentage of Subjects Receiving Treatment	
	PF-04691502 + Letrozole (N=14)	Letrozole (N=14)
	n (%)	n (%)
Weeks		
Week 1 to Week <3	14 (100.0%)	14 (100.0%)
Week 3 to Week <5	13 (92.9%)	13 (92.9%)
Week 5 to Week <7	8 (57.1%)	10 (71.4%)
Week 7 to Week <9	4 (28.6%)	8 (57.1%)
Week 9 to Week <13	4 (28.6%)	5 (35.7%)
Week 13 to Week <17	4 (28.6%)	5 (35.7%)
Week 17 to Week <21	3 (21.4%)	5 (35.7%)
Week 21 to Week <25	1 (7.1%)	4 (28.6%)
Week 25 to Week <29	1 (7.1%)	2 (14.3%)
Week 29 to Week <33	1 (7.1%)	1 (7.1%)
Week 33 to Week <37	-	1 (7.1%)
N	14	14
Mean	9.16	12.65
Standard deviation	8.64	10.29
Median	5.64	8.00
Range	1.86–30.43	2.29–33.71

N = number of subjects; n = number of subjects with specified criteria.
a. Defined as the total number of weeks (rounded to integer) from first day of study treatment to, and including, the last day of study treatment.

Overall Summary of Adverse Events: Table 6 shows an overall summary of treatment-emergent all-causality AEs.

Table 6. Treatment-Emergent Adverse Events (All Causalities)

Subjects Evaluable for AEs	n (%)
	14
Number of AEs	187
Subjects with AEs	14 (100.0%)
Subjects with Serious AEs	7 (50.0%)
Subjects with Grade 3-4 AEs	10 (71.4%)
Subjects with Grade 5 AEs	2 (14.3%)
Subjects discontinued due to AEs	11 (78.6%)
Subjects with dose reduced due to AEs	2 (14.3%)
Subjects with dose temporarily discontinued due to AEs	7 (50.0%)

AEs = adverse events; n = number of subjects with specified criteria.

Table 7 presents a summary of all-causality AEs.

Table 7. Summary of Treatment-Emergent Adverse Events of Grade 3-5 by MedDRA Preferred Term and Maximum CTCAE Grade by Decreasing Order of Frequency (All Causalities, All Cycles) (N=14)

Preferred Term	Grade 3	Grade 4	Grade 5	Total
	n (%)	n (%)	n (%)	n (%)
Any AEs	8 (57.1)	1 (7.1)	2 (14.3)	11 (78.6)
Rash	4 (28.6)	-	-	4 (28.6)
Stomatitis	3 (21.4)	-	-	3 (21.4)
Diarrhea	2 (14.3)	-	-	2 (14.3)
General physical health deterioration	2 (14.3)	-	-	2 (14.3)
Hyperglycaemia	2 (14.3)	-	-	2 (14.3)
Pruritus	2 (14.3)	-	-	2 (14.3)
Rash maculopapular	2 (14.3)	-	-	2 (14.3)
Back pain	1 (7.1)	-	-	1 (7.1)
Blood insulin increased	1 (7.1)	-	-	1 (7.1)
Death	-	-	1 (7.1)	1 (7.1)
Decreased appetite	1 (7.1)	-	-	1 (7.1)
Dehydration	1 (7.1)	-	-	1 (7.1)
Diabetic ketoacidosis	1 (7.1)	-	-	1 (7.1)
Disease progression	-	-	1 (7.1)	1 (7.1)
Escherichia urinary tract infection	1 (7.1)	-	-	1 (7.1)
Fatigue	1 (7.1)	-	-	1 (7.1)
Hypoglycaemia	-	1 (7.1)	-	1 (7.1)
Hypokalaemia	-	1 (7.1)	-	1 (7.1)
Hyponatraemia	1 (7.1)	-	-	1 (7.1)
Lung infection	1 (7.1)	-	-	1 (7.1)
Lymphoedema	1 (7.1)	-	-	1 (7.1)
Neutropenia	1 (7.1)	-	-	1 (7.1)
Pneumocystis jiroveci pneumonia	1 (7.1)	-	-	1 (7.1)
Pulmonary embolism	1 (7.1)	-	-	1 (7.1)
Rash papular	1 (7.1)	-	-	1 (7.1)
Toxic skin eruption	1 (7.1)	-	-	1 (7.1)
Vomiting	1 (7.1)	-	-	1 (7.1)

AEs of Missing or Unknown severity were omitted as there were no cases in the source.
In case of multiple occurrence of the same event for the subject, only the highest grade is reported.
AEs = adverse events; CTCAE = Common terminology criteria for AE; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria.

Table 8 presents a summary of treatment-related AEs.

Table 8. Incidence and Severity of Treatment-Emergent Adverse Events (Treatment-Related, All Cycles) (N=14)

System Organ Class Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	-	4 (28.6)	9 (64.3)	1 (7.1)	14 (100.0)
Gastrointestinal disorders	2 (14.3)	7 (50.0)	5 (35.7)	-	14 (100.0)
Diarrhea	3 (21.4)	3 (21.4)	2 (14.3)	-	8 (57.1)
Nausea	5 (35.7)	2 (14.3)	-	-	7 (50.0)
Stomatitis	2 (14.3)	2 (14.3)	3 (21.4)	-	7 (50.0)
Dyspepsia	4 (28.6)	-	-	-	4 (28.6)
Vomiting	3 (21.4)	-	1 (7.1)	-	4 (28.6)
Abdominal pain upper	1 (7.1)	-	-	-	1 (7.1)
Haemorrhoids	1 (7.1)	-	-	-	1 (7.1)
Oral discomfort	1 (7.1)	-	-	-	1 (7.1)
Oral pain	-	1 (7.1)	-	-	1 (7.1)
Skin and subcutaneous tissue disorders	2 (14.3)	2 (14.3)	8 (57.1)	-	12 (85.7)
Rash	1 (7.1)	1 (7.1)	4 (28.6)	-	6 (42.9)
Pruritus	-	3 (21.4)	2 (14.3)	-	5 (35.7)
Dry skin	1 (7.1)	2 (14.3)	-	-	3 (21.4)
Erythema	1 (7.1)	1 (7.1)	-	-	2 (14.3)
Rash maculopapular	-	-	2 (14.3)	-	2 (14.3)
Alopecia	1 (7.1)	-	-	-	1 (7.1)
Dermatitis acneiform	1 (7.1)	-	-	-	1 (7.1)
Hair texture abnormal	1 (7.1)	-	-	-	1 (7.1)
Onychoclasis	1 (7.1)	-	-	-	1 (7.1)
Rash papular	-	-	1 (7.1)	-	1 (7.1)
Skin exfoliation	-	1 (7.1)	-	-	1 (7.1)
Toxic skin eruption	-	-	1 (7.1)	-	1 (7.1)
Metabolism and nutrition disorders	2 (14.3)	5 (35.7)	3 (21.4)	1 (7.1)	11 (78.6)
Hyperglycaemia	2 (14.3)	4 (28.6)	2 (14.3)	-	8 (57.1)
Decreased appetite	3 (21.4)	4 (28.6)	-	-	7 (50.0)
Hypokalaemia	1 (7.1)	-	-	1 (7.1)	2 (14.3)
Dehydration	-	-	1 (7.1)	-	1 (7.1)
Diabetes mellitus	-	1 (7.1)	-	-	1 (7.1)
Diabetic ketoacidosis	-	-	1 (7.1)	-	1 (7.1)
Hyponatraemia	-	-	1 (7.1)	-	1 (7.1)
General disorders and administration site conditions	6 (42.9)	2 (14.3)	2 (14.3)	-	10 (71.4)
Fatigue	2 (14.3)	1 (7.1)	1 (7.1)	-	4 (28.6)
Asthenia	2 (14.3)	1 (7.1)	-	-	3 (21.4)
Chills	3 (21.4)	-	-	-	3 (21.4)
Mucosal inflammation	3 (21.4)	-	-	-	3 (21.4)
Early satiety	1 (7.1)	-	-	-	1 (7.1)
General physical health deterioration	-	-	1 (7.1)	-	1 (7.1)

Table 8. Incidence and Severity of Treatment-Emergent Adverse Events (Treatment-Related, All Cycles) (N=14)

System Organ Class Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations	2 (14.3)	2 (14.3)	1 (7.1)	-	5 (35.7)
Blood insulin increased	1 (7.1)	-	1 (7.1)	-	2 (14.3)
Weight decreased	-	2 (14.3)	-	-	2 (14.3)
ALT increased	1 (7.1)	-	-	-	1 (7.1)
AST increased	1 (7.1)	-	-	-	1 (7.1)
Blood creatinine increased	-	1 (7.1)	-	-	1 (7.1)
LDH increased	1 (7.1)	-	-	-	1 (7.1)
Platelet count decreased	1 (7.1)	-	-	-	1 (7.1)
Musculoskeletal and connective tissue disorders	4 (28.6)	-	-	-	4 (28.6)
Arthralgia	2 (14.3)	-	-	-	2 (14.3)
Back pain	1 (7.1)	-	-	-	1 (7.1)
Myalgia	1 (7.1)	-	-	-	1 (7.1)
Infections and infestations	1 (7.1)	1 (7.1)	1 (7.1)	-	3 (21.4)
Escherichia urinary tract infection	-	-	1 (7.1)	-	1 (7.1)
Oesophageal candidiasis	1 (7.1)	-	-	-	1 (7.1)
Pneumocystis jiroveci pneumonia	-	-	1 (7.1)	-	1 (7.1)
Urinary tract infection	-	1 (7.1)	-	-	1 (7.1)
Nervous system disorders	2 (14.3)	1 (7.1)	-	-	3 (21.4)
Dizziness	1 (7.1)	1 (7.1)	-	-	2 (14.3)
Tremor	1 (7.1)	-	-	-	1 (7.1)

AEs of Grade 5 and missing or unknown severity were omitted as there were no cases in the source.
In case of multiple occurrence of the same event for the subject, only the highest grade is reported.
AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; N = number of subjects; n = number of subjects with specified criteria.

Serious Adverse Events: Table 9 presents a summary of treatment-related SAEs.

Table 9. Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum CTCAE Grade (Treatment-Related, All Cycles) (N=14)

System Organ Class Preferred Term	Grade 2	Grade 3	All Grades
	n (%)	n (%)	n (%)
Any AEs	1 (7.1)	6 (42.9)	7 (50.0)
Gastrointestinal disorders	1 (7.1)	2 (14.3)	3 (21.4)
Diarrhea	1 (7.1)	1 (7.1)	2 (14.3)
Stomatitis	-	1 (7.1)	1 (7.1)
Vomiting	-	1 (7.1)	1 (7.1)
Skin and subcutaneous tissue disorders	-	5 (35.7)	5 (35.7)
Rash	-	2 (14.3)	2 (14.3)
Rash maculopapular	-	2 (14.3)	2 (14.3)
Toxic skin eruption	-	1 (7.1)	1 (7.1)
Metabolism and nutrition disorders	-	2 (14.3)	2 (14.3)
Dehydration	-	1 (7.1)	1 (7.1)
Diabetic ketoacidosis	-	1 (7.1)	1 (7.1)
General disorders and administration site conditions	-	1 (7.1)	1 (7.1)
General physical health deterioration	-	1 (7.1)	1 (7.1)
Infections and infestations	-	1 (7.1)	1 (7.1)
Pneumocystis jiroveci pneumonia	-	1 (7.1)	1 (7.1)

SAEs of Grade 1, 4, 5 and Missing or Unknown severity were omitted as there were no cases in the source.
In case of multiple occurrence of the same event for the subject, only the highest grade is reported.
AEs = adverse events; CTCAE = Common terminology criteria for AE; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria; SAEs = serious adverse events.

Discontinuations due to AEs: Eleven (11/14) subjects (78.6%) discontinued treatment with PF-04691502 due to AEs.

Deaths: Two (2/14) subjects (14.3%) died; 1 subject died due to disease progression and 1 subject died due to natural causes.

CONCLUSIONS:

- Efficacy: The anti-tumor activity of PF-04691502 in combination with letrozole in subjects with ER positive, HER-2 negative, ABC cannot be determined due to the limited efficacy data collected.

- Safety: PF-04691502 (8 mg/ day) in combination with letrozole (2.5 mg/day) was poorly tolerated; in particular, skin reactions were unacceptably frequent and severe.