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Phase I Dose-Escalation Study of the Dual PI3K-mTORC1/2 Inhibitor Gedatolisib in Combination with Paclitaxel and Carboplatin in Patients with Advanced Solid Tumors

Ilaria Colombo[1], Sofia Genta[1], Federica Martorana[1], Monia Guidi[2,3], Milo Frattini[4], Eleftherios Pierre Samartzis[5], Simone Brandt[6], Sheila Gaggetta[1], Laura Moser[1], Mariarosa Pascale[7], Tatiana Terrot[7], Cristiana Sessa[1], and Anastasios Stathis[1,8]

ABSTRACT

Purpose: This phase I study evaluated safety, tolerability, pharmacokinetics, and preliminary activity of the PI3K/mTORC1/2 dual inhibitor gedatolisib combined with carboplatin and paclitaxel.

Patients and Methods: Patients with advanced solid tumors treated with ≤ 2 prior chemotherapies received intravenous gedatolisib on days 1, 8, 15, and 22 (95, 110, or 130 mg according to dose level); carboplatin (AUC5) on day 8 (day 1 following protocol amendment); and paclitaxel at 80 mg/m^2 on days 8, 15, and 22 (1, 8, and 15 after amendment), every 28 days. Patients without progressive disease after cycle 6 received maintenance gedatolisib until progression.

Results: Seventeen patients were enrolled [11 ovarian (10 clear cell ovarian cancer, CCOC), 4 endometrial, 2 lung cancers]. Median number of prior chemotherapies was 1 (range, 0–2). Median number of administered cycles was 6 (range, 2–16). Dose-limiting toxicities occurred in 4 patients: 2 (cycle 2 delay due to G2–G3 neutropenia) at 110 mg leading to a change in the treatment schedule, 2 at 130 mg (G2 mucositis causing failure to deliver ≥ 75% of gedatolisib at cycle 1). The recommended phase II dose is gedatolisib 110 mg on days 1, 8, 15, and 22 with carboplatin AUC5 on day 1 and paclitaxel 80 mg/m^2 on days 1, 8, and 15. The most frequent ≥G3 treatment-related adverse events were neutropenia (35%), anemia (18%), and mucositis (12%). The overall response rate was 65% (80% in CCOC). Pharmacokinetic parameters of gedatolisib were consistent with single-agent results.

Conclusions: Gedatolisib combined with carboplatin and paclitaxel is tolerable, and preliminary efficacy was observed especially in CCOC.

Introduction

The PI3K pathway is involved in different physiologic cellular processes and is frequently deregulated in cancer cells (1–3). Molecular alterations in components of this pathway are frequent and may predict response to pharmacologic inhibition in selected solid tumor types (4, 5). Over the last years, several agents targeting the PI3K/AKT/mTOR axis at different levels [including pan-PI3K (6, 7), isoform specific PI3K (5, 8), AKT (9, 10) and the mTOR complex (mTORC) inhibitors (11, 12)] have been developed.

Recently, the α-specific PI3K inhibitor alpelisib was approved in combination with fulvestrant in patients with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative advanced breast cancer previously treated with endocrine therapy previously (5).

Downstream of PI3K, the inhibition of mTORC1 with everolimus or temsirolimus induces activation of mTORC2 resulting in adaptive feedback activation of PI3K/AKT signaling (13) that may be overcome using dual PI3K and mTOR inhibitors.

Gedatolisib (PF-05212384) is an intravenous potent, ATP-competitive dual inhibitor of both PI3K (pan class I isoform) and mTORC1/2 that reduces AKT/mTOR signaling and induces antitumor activity in cell lines and tumor xenografts models (14). The safety profile of single-agent gedatolisib was assessed in a first-in-human trial that enrolled 78 patients with advanced solid tumors (15). The MTD was 154 mg of gedatolisib administered intravenously once a week. The most common treatment-related adverse events (AE) were mucositis and stomatitis (58.4%), nausea (42.9%), hyperglycemia (26%), decrease appetite (24.7%), fatigue (24.7%), and vomiting (24.7%). Three patients achieved a partial response (2 confirmed and 1 unconfirmed) and 8 had stable disease (SD) > 6 months (15). A phase II study in patients with recurrent/progressive endometrial cancer investigated the efficacy and safety of weekly intravenous gedatolisib compared with another oral dual PI3K/mTOR inhibitor (PF-05212384) administered daily. This study confirmed the previously reported safety profile of gedatolisib and its limited activity when administered as single agent. The PF-05212384 arm was prematurely discontinued because of unacceptable toxicity (pulmonary and skin toxicity; ref. 16).

PI3K pathway also plays a role in inducing resistance to chemotherapy and there is preclinical evidence that PI3K/AKT/mTOR pathway activation promotes resistance to cisplatin and therefore its inhibition can sensitize cancer cells to chemotherapy (17–19). Phase I trials have recently demonstrated the feasibility of combining PI3K

[1]Service of Medical Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland. [2]Service of Clinical Pharmacology, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland. [3]Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. [4]Molecular Pathology Laboratory, Cantonal Institute of Pathology, Locarno, Switzerland. [5]Department of Gynecology and Gynecological Cancer Center, University Hospital Zurich, Zurich, Switzerland. [6]Institute of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland. [7]Clinical Trial Unit, Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland. [8]Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Anastasios Stathis, Service of Medical Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona 6500, Switzerland. Phone: 0041-(0)91-811-8931; Fax: 0041-(0)91-811-8047; E-mail: anastasios.stathis@eoc.ch

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Translational Relevance

The PI3K/AKT/mTOR pathway is activated in a wide variety of malignancies and may promote resistance to chemotherapy, including platinum compounds. Inhibition of mTOR induces co-stimulatory loops that activate PI3K and AKT and are responsible for drug resistance. The dual PI3K/mTORC1/2 inhibitor gedatolisib (PF-05212384) has a good safety profile but limited single-agent activity. Thus, the combination of gedatolisib and platinum-based chemotherapy might exert synergistic activity and overcome such resistance. This phase I dose-escalation study evaluated the safety, recommended phase II dose (RP2D), pharmacokinetics, and preliminary antitumor activity of increasing doses of gedatolisib in combination with carboplatin and weekly paclitaxel in patients with advanced solid tumor. The combination showed a manageable safety profile, and an RP2D of gedatolisib 110 mg on days 1, 8, 15, and 22 with carboplatin AUC5 on day 1 and paclitaxel 80 mg/m^2 on days 1, 8, and 15 in 28-day cycles was determined. The pharmacokinetic profile of gedatolisib was consistent with previous results. Signs of activity have been observed, particularly in patients with clear cell ovarian cancer. These findings provide preliminary evidence of the safety and activity of combining gedatolisib with platinum-based chemotherapy.

inhibitors with chemotherapy agents (20–22). The PI3K inhibitor pilaralisib was tested in combination with carboplatin and paclitaxel in a phase I trial showing an acceptable toxicity profile without improving chemotherapy efficacy in patients with pretreated advanced solid tumors (20). The pan-PI3K inhibitor pictilisib was administered in combination with standard first-line platinum-based chemotherapy in a phase Ib trial in patients with non–small cell lung cancer (NSCLC) showing an acceptable tolerability and preliminary sign of activities (21).

We conducted a phase I dose-escalation study to assess the safety and preliminary activity of gedatolisib in combination with carboplatin and weekly paclitaxel in patients with advanced solid tumors (clinicaltrials.gov identifier: NCT02069158).

Patients and Methods

Study design and treatment

This was an open-label, single centre, dose-escalation phase Ib clinical trial of gedatolisib in combination with carboplatin and weekly paclitaxel in patients with selected advanced solid tumors. The primary objective was to assess the safety and tolerability of the combination and to define the MTD and recommended phase II dose (RP2D). Secondary objectives were the evaluation of the pharmacokinetic profile of gedatolisib in combination with carboplatin and paclitaxel and the preliminary antitumor activity.

Gedatolisib was administered as a 30-minute intravenous infusion at increasing doses (95, 110, and 130 mg) on days 1, 8, 15, and 22. Given the administration of gedatolisib in combination with chemotherapy in this trial, the starting dose of 95 mg was selected to be approximately 60% of the single-agent MTD (154 mg; ref. 15). During cycle 1, carboplatin (AUC5) was administered on day 8 and paclitaxel 80 mg/m^2 on days 8, 15, and 22 in 28-day cycles, to adequately assess gedatolisib pharmacokinetic profile. From cycle 2 onward, chemotherapy was started on day 1 (carboplatin on day 1 and paclitaxel on days 1, 8, and 15). Treatment was administered up to six cycles. Patients without evidence of progressive disease (PD) could continue single-agent gedatolisib as maintenance treatment until PD or unacceptable toxicity. Primary prophylactic use of GMCSFs was not permitted by protocol and particularly during cycle 1 to allow for a correct dose-limiting toxicity (DLT) assessment.

Following the first 9 patients treated with the above mentioned schedule, the study was amended and all drugs were started on day 1 of cycle 1, due to the occurrence of DLTs consisting in the delay of the start of cycle 2 due to neutropenia (see below). Patients received standard antiemetic prophylaxis for carboplatin (dexamethasone 10 mg i.v. and granisetron 1 mg i.v. before each infusion) and premedication for paclitaxel with steroids, antihistamines and H1 antagonists as per standard practice. No premedication was required, when gedatolisib was administered as single agent.

The trial was conducted according to a 3+3 design and no intrapatient dose escalation was permitted. DLTs were defined as clinically significant AEs at least possibly related to study treatment occurring during cycle 1 and included: grade 4 neutropenia lasting >7 days; febrile neutropenia; grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding; grade ≥ 3 non-haematologic AEs (with the exception of nausea, vomiting, diarrhea, and hyperglycemia if not adequately treated with supportive measures); persistent, intolerable toxicities with failure to deliver at least 75% of doses at cycle 1 and persistent, intolerable toxicities resulting in delay of start of cycle 2 by more than 2 weeks.

This study was conducted in accordance with the protocol, International Conference on Harmonization, Good Clinical Practice guidelines, applicable regulations, and ethical principles according to Declaration of Helsinki. The protocol was approved by the local Ethical Committee. All patients provided written informed consent.

Patients

Patients were eligible if they were ≥18 years of age and had histologically or cytologically confirmed advanced/metastatic breast, NSCLC, ovarian, endometrial, small cell lung or head and neck squamous cell cancer and had received no more than two prior lines of chemotherapy for advanced disease. Other criteria included: measurable or evaluable disease as per RECIST 1.1; Eastern Oncology Cooperative Group (ECOG) performance status (PS) 0 to 1; adequate bone marrow (hemoglobin ≥ 9 g/dL, absolute neutrophil count > 1.5 × 10^9/L, platelets >100 × 10^9/L), renal [serum creatine ≤ 1.5 × upper limit of normal (ULN) or estimated creatinine clearance ≥ 60 mL/minute] and hepatic function [total bilirubin ≤ 1.0 mg/dL, aspartate (AST) and alanine (ALT) aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN in case of liver metastasis, alkaline phosphatase ≤ 2.5 × ULN or ≤ 5 × ULN in case of bone metastasis] and adequate blood glucose control [no history of diabetes mellitus or glycosylate hemoglobin (HbA1c) <7%]. Exclusion criteria included: no PD during or within 3 months of prior platinum agents, prior treatment with weekly paclitaxel with tumor progression, active brain metastases (patients with previously diagnosed brain metastases were eligible if treatment was completed, steroids treatment discontinued for at least 4 weeks and were neurologically stable).

Safety and antitumor activity assessment

Screening tests were performed within 14 days from cycle 1 day 1 and included laboratory analyses (complete blood count, AST, ALT, alkaline phosphatase, sodium, potassium, calcium, direct/indirect bilirubin, total bilirubin, creatinine, uric acid, glucose, albumin, total protein, HbA1c, partial thromboplastin time, prothrombin time, urine dipstick, serum or urine pregnancy test when indicated), triplicate

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ECG, radiological tumor assessment, and physical examination. During treatment, laboratory analyses were performed weekly before drugs administration. ECG monitoring was performed on day 1 of cycles 1 and 2, at the end of gedatolisb infusion and at the end of treatment visit. Treatment-emergent AEs (TEAE) were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03.

Tumor assessment was performed every two cycles. Objective response rate [ORR: complete response (CR) or partial response (PR)] was assessed by the investigator according to RECIST version 1.1. Progression-free survival (PFS) was defined as the time from the date of treatment start to the date of earliest disease progression (PD) or death from any cause. Duration of response (DOR) was defined as the time from the date of the first CR or PR to the earliest documentation of radiographic PD or death due to any cause.

Pharmacokinetic analysis

Blood samples for gedatolisb pharmacokinetic analysis were collected on day 1 of cycles 1 and 2 at 0 (pre-dose), 0.5, 1, 2, 4, 6, 24, and 72 hours; on days 8, 15, and 22 of cycle 1 (pre-dose) and on day 1 of cycles 3, 4, 5, and 6 at 0 hours (pre-dose).

Gedatolisib plasma concentrations were measured using a validated method with a lower limit of quantification of 2 ng/mL (at inVentiv Health Clinical Lab, Inc., a Syneos Health company).

The following pharmacokinetic parameters were calculated for each patient using noncompartmental method as implemented in the R package PKNCA (23): maximum (C_{max}) and last (C_{last}) observed plasma concentration, time to C_{max} (t_{max}), time of C_{last} (t_{last}), elimination half-life ($t_{1/2}$), area under the plasma concentration–time curve (AUC) from time 0 to last observed concentration ($AUC_{0\text{-}last}$), AUC from time 0 to infinity ($AUC_{0\text{-}inf}$), elimination rate constant (λ_z), clearance and the volume of distribution during the terminal elimination phase (V_z). Only a reduced set of pharmacokinetic parameters ($AUC_{0\text{-}last}$, C_{max}, C_{last}, t_{last}, and t_{max} with last being day 4) could be computed in cycle 2 because of the shorter scheduled sampling time compared with cycle 1. Calculation of these parameters also for cycle 1 allowed comparison between the two cycles' exposures.

Pharmacokinetic analysis was done at the Service of Clinical Pharmacology, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland.

Biomarker analysis

An exploratory analysis of potential biomarkers correlated with PI3K/AKT/mTOR pathway inhibition was retrospectively conducted on the available archival tissue. Formalin-fixed paraffin-embedded archival tumor samples were used for retrospective analysis of *PIK3CA* and *KRAS* aberrations and ARID1A expression. The presence of *PIK3CA* (exons 9 or 20) and *KRAS* mutations were assessed by Sanger sequencing or real-time PCR, respectively, at the Molecular Pathology Laboratory of the Cantonal Institute of Pathology, Locarno, Switzerland (24). Information from patients with available molecular data from a next-generation sequencing analysis performed prior to enrollment was used for the purpose of this study. ARID1A expression (retain or loss) was assessed on available archival tissue on IHC at the Institute of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland. The slides were stained with a polyclonal anti-ARID1A antibody produced in rabbit (Sigma-Aldrich, HPA005456, dilution 1:200; ref. 25). Nuclear expression was scored as retained nuclear expression (positive, score 1) or loss of nuclear expression (negative, score 0).

Statistical analyses

The total sample size was dependent on the number of patients treated at each gedatolisib dose level (DL) and the DLTs observed. To be evaluable for safety, patients should have received at least one dose of gedatolisib. To be evaluable for antitumor activity, patients should have undergone at least one post-baseline tumor measurement.

Descriptive statistics were used for demographic, safety, efficacy, and pharmacokinetic assessments. The Kaplan–Meier method was used to estimate PFS and DOR.

Results

Patient characteristics

Between May 2014 and June 2018, 17 patients were enrolled. Primary tumor types were ovarian [$n = 11$; 10 clear cell ovarian cancer (CCOC) and 1 low-grade serous], endometrial ($n = 4$; all high-grade histology), and NSCLC ($n = 2$). Median age was 52 (range, 34–71). Main patients' characteristics are summarized in **Table 1**. The median number of prior systemic chemotherapies was 1 (range, 0–2). Nine patients had received prior treatment with platinum-based chemotherapy and 8 (47%) were systemic treatment naïve (1 patient with endometrial and 7 with CCOC).

Treatment

Median number of administered cycles was 6 (range, 2–16) and the total number 118. Seven patients received maintenance treatment with gedatolisib after six cycles of combination (median number of cycles of

Table 1. Patient characteristics.

Characteristics	($n = 17$)
Age (year)	
Age	52
Range	34–71
Gender	
Female	15 (88%)
Male	2 (12%)
ECOG PS	
0	14 (83%)
1	3 (17%)
Tumor type	
Ovary	11 (65%)
Endometrium	4 (23%)
Lung	2 (12%)
Histology by tumor type	
Ovary	
Clear cell	10 (59%)
Low-grade serous	1 (6%)
Endometrium	
High-grade serous	3 (17%)
High-grade endometrioid	1 (6%)
Lung	
Adenocarcinoma	2 (12%)
Previous surgery	
Yes	16 (94%)
No	1 (6%)
No. of previous lines of systemic chemotherapy	
0	8 (47%)
1	6 (35%)
2	3 (18%)

Abbreviations: ECOG, Eastern Oncology Cooperative Group; PS, performance status.

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Table 2. DLTs by DL.

Dose level	Gedatolisib dose (mg)	Total no. of pts	No. pts evaluable for DLT	No. of DLTs	Type of DLT
1	95	4	4	0	NA
2	110	5	4	2	Neutropenia G2 (1 patient) and G3 (1 patient) with delay > 2 weeks in starting cycle 2
2	110 amended schedule	3	3	0	NA
3	130 amended schedule	5	5	2	G2 mucositis with failure to deliver ≥ 75% of gedatolisib in both patients

Abbreviations: DLT, dose-limiting toxicity; G, grade; NA, not applicable.

gedatolisib maintenance was 4; range, 2–10). Reasons for treatment discontinuation were PD (13 patients), toxicity (2 patients: 1 pneumonitis and 1 oral mucositis), investigator decision (1 patient due to not drug-related infectious pneumonia), and patient decision (1 patient).

Among 17 enrolled patients, 16 were evaluable for DLT. One patient at DL2 was not evaluable because cycle 1 was not administered as per protocol. Four DLTs were observed over the three DLs studied (**Table 2**). At DL2 (110 mg), 2 patients experienced a DLT consisting in delay in starting cycle 2 by more than 2 weeks of scheduled day due to G2 and G3 neutropenia. Consequently, further 3 patients were enrolled at DL2 and received treatment according to the new schedule and no DLTs occurred. Thus, gedatolisib was further escalated to 130 mg (DL3). At DL3, 2 of 5 patients experienced a DLT: G2 mucositis resulting in failure to deliver at lest 75% of the planned gedatolisib dose at cycle 1 in both patients. Notably no delay in starting cycle 2 due to neutropenia fulfilling the DLT criteria occurred with the amended schedule. Gedatolisib 110 mg on days 1, 8, 15, and 22 with carboplatin AUC5 on day 1 and paclitaxel 80 mg/m^2 on days 1, 8, and 15 in 28-day cycle was defined as the RP2D.

Safety

All enrolled patients were evaluable for safety. TEAEs of any grade were reported in all patients. The most common TEAEs of any grade

Table 3. TEAEs by grade and gedatolisib DL (any grade TEAE occurring ≥ 15% patients and ≥G3 in all patients).

	95 mg *n* = 4		110 mg *n* = 5		110 mg amended *n* = 3		130 mg amended *n* = 5		Total *n* = 17	
n (%)	Any G	G3/4	Any G	G3/4	Any G	G3/4	Any G	G3/4	Any G	G3/4
Oral mucositis	3	—	5	—	3	1	5	1	16 (94%)	2
Fatigue	3	—	5	—	2	—	5	1	15 (88%)	1
Nausea	3	—	5	—	2	1	3	—	13 (76%)	1
Alopecia	3	—	4	—	3	—	2	—	12 (71%)	—
Anorexia	1	—	3	—	2	—	4	—	10 (59%)	—
Diarrhea	2	—	4	—	1	—	3	—	10 (59%)	—
Rash[a]	2	—	5	—	1	—	1	—	9 (53%)	—
Peripheral sensory neuropathy[b]	3	1	1	—	3	—	2	—	9 (53%)	1
Neutropenia	2	—	3	3	1	1	3	2	9 (53%)	6
Anemia	2	1	1	—	2	1	3	1	8 (47%)	3
Vomiting	2	—	2	—	1	—	2	—	7 (41%)	—
Constipation	1	—	3	—	1	—	1	—	6 (35%)	—
Dysgeusia	2	—	2	—	1	—	1	—	6 (35%)	—
Arthralgia	1	—	3	—	1	—	—	—	5 (29%)	—
Epistaxis	2	—	1	—	—	—	1	—	4 (24%)	—
Lip infection	2	—	1	—	1	—	—	—	4 (24%)	—
Infusion-related reaction	—	—	1	—	2	—	—	—	3 (18%)	—
Platelet count decrease	—	—	2	—	1	1	—	—	3 (18%)	1
Hypokalemia	—	—	—	—	—	—	3	1	3 (18%)	1
Weight loss	1	—	—	—	—	—	2	—	3 (18%)	—
Myalgia	2	—	1	—	—	—	3	—	3 (18%)	—
Abdominal pain	—	—	2	—	1	—	—	—	3 (18%)	—
Aortic intramural hematoma	1	1	—	—	—	—	—	—	1 (6%)	1
Enterocolitis infectious	—	—	1	1	—	—	—	—	1 (6%)	1
Hypomagnesemia	—	—	—	—	—	—	1	1	1 (6%)	1

Abbreviations: ALT, alanine aminotransferase; G, grade; TEAE, treatment-emergent adverse events.
[a]Including rash maculopapular and acneiform.
[b]Including paresthesia.

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Table 4. Best response according to RECIST 1.1.

N (%)	All patients (*n* = 17)	Clear cell ovarian cancer (*n* = 10)
Complete response	3 (18%)	3 (30%)
Partial response	8 (47%)	5 (50%)
Stable disease	3 (18%)	1 (10%)
Progressive disease	3 (18%)	1 (10%)

were oral mucositis (94%), fatigue (88%), nausea (76%), alopecia (71%), anorexia (59%), diarrhea (59%), rash (53%), peripheral sensory neuropathy (53%), and neutropenia (53%). The most frequent G ≥ 3 TEAEs were neutropenia (35%), anemia (18%), and mucositis (12%; **Table 3**; Supplementary Table S1).

Six patients (3 treated at DL2 at the original schedule and 1 at DL2 and 2 at DL3 according to the amended schedule) had their gedatolisib dose reduced as a consequence of a TEAE.

Serious AEs (SAE) occurred in 7 patients (41.2%) for a total of 12 SAEs, with 4 considered related to the study treatment: G3 aortic intramural hematoma, G3 enterocolitis infectious, G2 infusion-related reaction, and G2 pneumonitis. One patient died after treatment discontinuation due to malignant bowel obstruction as consequence of disease progression. No treatment-related deaths occurred.

Antitumor activity

All patients were evaluable for antitumor activity. The ORR was 65% (11/17 patients: 8 PR and 3 CR) and SD 17% (3/17; **Table 4**). Among patients with CCOC ($n = 10$, 7 of them chemo-naïve), the ORR was 80% (8/10), with 3 patients (all chemo-naïve) achieving CR. Among 9 previously platinum-treated patients, 4 had a PR (2 patients with CCOC, 1 low-grade serous ovarian cancer, and 1 NSCLC; **Fig. 1**). At data cutoff (March 3, 2020), the median follow-up was 7.9 months (range, 1.8–35.1). Median PFS was 6.35 months [95% confidence interval (CI), 4.6–11.11]. Two patients were still without evidence of PD at the time of data cutoff. Median DOR was 7.6 months (95% CI, 1.9–13.4). In patients with CCOC, the median DOR was 8 months (95% CI, 1.8–18.1).

Pharmacokinetics

Pharmacokinetic analysis of gedatolisib was performed on 16 patients (Supplementary Tables S2 and S3). One patient was not evaluable for pharmacokinetics because none of the concentrations of the full pharmacokinetic profile at day 1 cycle 1 were quantifiable. Median $t_{1/2}$ after single administration of gedatolisib on cycle 1 day 1 was of 35 hours (range, 17–66) across all DLs, as reported previously (15). A slower concentration decline from cycle 2 was observed, in line with previously reported gedatolisib single-agent data (**Fig. 2**; Supplementary Table S3; ref. 15).

Biomarkers

The presence of potential predictive biomarkers was assessed on available archival tissue (**Fig. 1**). ARID1A expression was assessed in 12 patients: 9 patients had ARID1A expression retained (6 responded to treatment, 2 had SD, and 1 PD) and 3 had ARID1A loss (2 with CR and 1 PD). The presence of *PI3K* and *KRAS* mutations could be assessed in 13 patients. Four patients had a mutation in one gene coding for a PI3K protein: 1 *PIK3CA* N345K exon 5 (serous endometrial cancer that achieved PR), 1 *PIK3CG* exon 2 P311A (NSCLC with PR), 1 *PIK3CA* R524K exon 9 (CCOC with PD), and 1 *PIK3CA* H1047R exon 20 (CCOC with PR). Four patients had a *KRAS* mutation: 1 *KRAS* G13D (serous endometrial cancer with PR, harbouring also a *PIK3CA* mutation), 1 *KRAS* G12V (endometrioid

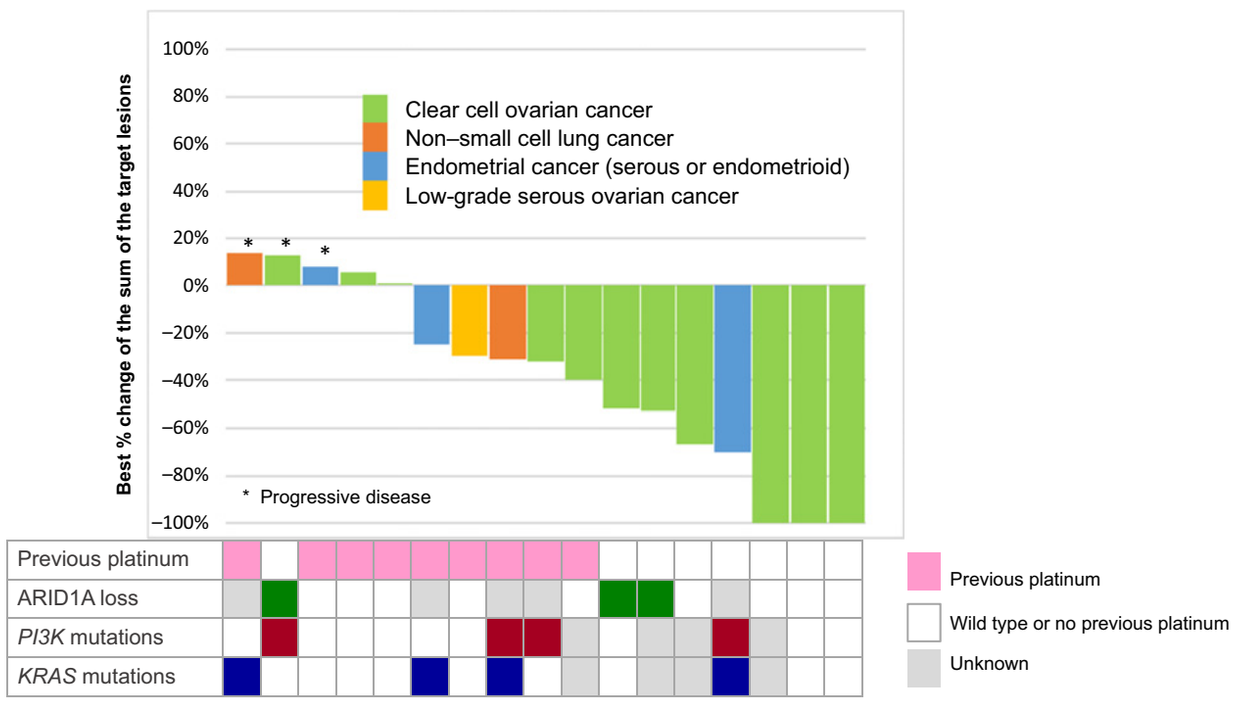

Figure 1.
Best percentage change of the sum of the target lesions and available biomarkers results.

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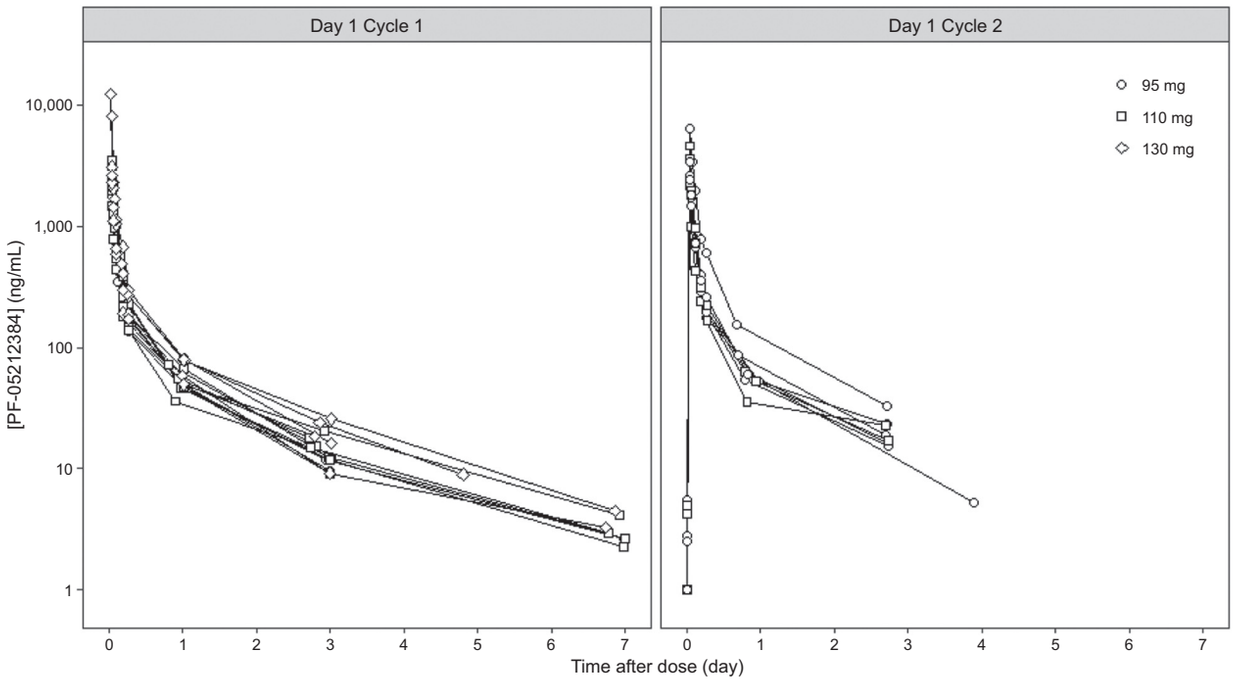

Figure 2.
Gedatolisib pharmacokinetic profile per DL on day 1 of cycles 1 and 2 (log-scale was used for *y*-axis)

endometrial cancer with SD), 1 *KRAS* G12D (NSCLC with PD), and 1 *KRAS* G12C (NSCLC with PR, harbouring also a *PIK3CG* mutation).

Discussion

Inhibition of the PI3K/AKT/mTOR pathway has been investigated in many tumor types but, except for selected indolent non-Hodgkin lymphomas, breast and kidney cancer, the clinical activity has been limited (5, 6, 8, 10, 11, 26). A possible mechanism of resistance to PI3K/AKT/mTOR inhibitors is the presence of co-stimulatory loops along the same pathway, which provided the rationale for the development of dual inhibitors to overcome it (13, 26). Gedatolisib (PF-05212384) is a potent intravenous ATP-competitive dual inhibitor of both PI3K (pan class I isoform) and mTORC1/2 and its safety and preliminary activity have been assessed in previous studies (15, 16, 22). The PI3K/AKT/mTOR pathway activation is also involved in chemotherapy resistance and its inhibition can promote sensitivity to platinum-based treatment (17, 18, 27). Previous studies reported the feasibility of combining platinum-based chemotherapy with PI3K pathway inhibitors supporting the rationale for investigating gedatolisib in similar combination regimens (20, 21).

We conducted a phase I dose-escalation trial to assess safety, RP2D, pharmacokinetics, and preliminary antitumor activity of increasing doses of gedatolisib in combination with carboplatin (AUC5) and weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days) in patients with advanced solid tumors selected on the basis of known platinum sensitivity and frequent activation of the PI3K pathway. The combination was tolerable with a manageable safety profile. The observed DLTs were prolonged neutropenia with delay in the start of cycle 2 and mucositis with inability to receive ≥75% of gedatolisib. The RP2D was gedatolisib 110 mg on days 1, 8, 15, and 22 with carboplatin AUC5 on day 1 and paclitaxel 80 mg/m^2 on days 1, 8, and 15 every 28 days. Because of a slower than expected accrual rate, the study was discontinued without expansion at the RP2D.

The more frequent TEAEs were non-haematologic, and the most common G ≥ 3 TEAEs were neutropenia, anemia, and mucositis. No new safety signals emerged, and we did not observe significant liver toxicity or hyperglycemia. Gedatolisib, consistently with prior data and likely due to the intermittent intravenous administration, was well tolerated and could be safely combined with platinum-based chemotherapy.

The pharmacokinetic profile consistently with the ones already reported, showed a slower concentration decline at cycle 2 with no interaction with the administered chemotherapy agents (15). Antitumor activity was observed with an ORR of 65%, also in patients previously pretreated with platinum-based therapies. A high number of patients with CCOC were included on the basis of the reported relevance of the PI3K/AKT/mTOR pathway activation in this tumor type (28–30). A promising ORR of 80% with a median DOR of 8 months was observed in this tumor type which is frequently characterized by chemoresistance and poor prognosis (31–33). In advanced CCOC, the reported response rate to platinum-based chemotherapy is 20%–56% and is inferior to the one observed in the more common high-grade serous histologic subtype (32, 34, 35).

Despite signs of activity were observed both in the overall and in CCOC populations, no conclusions can be drawn on the value of the combination because of the small sample size of our study and the proportion of chemo-naïve patients. In addition, we retrospectively explored the role of possible biomarkers of activity, such ARID1A expression measured on IHC and the presence of *PIK3* and *KRAS* mutations on available archived tissue. Loss of ARID1A expression has been reported to be frequently associated with PI3K/AKT pathway alterations and to sensitize cancer cells to PI3K inhibitors (36, 37). PI3K and KRAS pathway mutations correlate with the activity of PI3K

pathway inhibition in selected solid tumors (5, 38–41). However, we observed signs of activity regardless the status of the selected biomarkers and this is likely due to the limited sample size and the number of archival tumor samples available. Thus, no correlation between potential predictive biomarkers and patients' outcome can be postulated in our patient population. Another limitation of our study is the lack of tissue pharmacodynamic markers to assess target engagement and DNA damage biomarkers.

In conclusion, we provided evidence that the dual PI3K/mTORC 1/2 inhibitor gedatolisib can be safely administered in combination with carboplatin and weekly paclitaxel in patients with advanced solid tumors. Antitumor activity was observed and future studies including biomarker assessment, may further evaluate the use of PI3K pathway inhibitors in combination with chemotherapy in different tumor types including CCOC.

Authors' Disclosures

I. Colombo reports grants and non-financial support from Pfizer during the conduct of the study, as well as other support from Tesaro and personal fees from AstraZeneca and GSK outside the submitted work. F. Martorana reports personal fees from Pfizer, Lilly, and Novartis outside the submitted work. E.P. Samartzis reports non-financial support from AstraZeneca and Roche outside the submitted work. A. Stathis reports grants from Pfizer during the conduct of the study, as well as grants from Pfizer, Roche, Bayer, Merck, Novartis, AbbVie, Cellestia, Philogen, ADC Therapeutics, and MEI Therapeutics and other support from Bayer, Debiopharm, Eli Lilly, Bayer, and Roche outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

I. Colombo: Data curation, formal analysis, supervision, investigation, writing–original draft, writing–review and editing. **S. Genta:** Data curation, formal analysis, investigation, writing–review and editing. **F. Martorana:** Data curation, formal analysis, investigation, writing–review and editing. **M. Guidi:** Formal analysis, investigation, writing–review and editing. **M. Frattini:** Formal analysis, investigation, writing–review and editing. **E.P. Samartzis:** Formal analysis, investigation, writing–review and editing. **S. Brandt:** Formal analysis, investigation, writing–review and editing. **S. Gaggetta:** Data curation, formal analysis, investigation, writing–review and editing. **L. Moser:** Data curation, investigation, writing–review and editing. **M. Pascale:** Data curation, formal analysis, writing–review and editing. **T. Terrot:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, project administration, writing–review and editing. **C. Sessa:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, project administration, writing–review and editing. **A. Stathis:** Conceptualization, data curation, formal analysis, supervision, methodology, writing–original draft, project administration, writing–review and editing.

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Phase I Dose-Escalation Study of the Dual PI3K-mTORC1/2 Inhibitor Gedatolisib in Combination with Paclitaxel and Carboplatin in Patients with Advanced Solid Tumors

Ilaria Colombo, Sofia Genta, Federica Martorana, et al.

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