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ARTICLE

Clinical Studies

A Phase 1B open-label study of gedatolisib (PF-05212384) in combination with other anti-tumour agents for patients with advanced solid tumours and triple-negative breast cancer

Giuseppe Curigliano[1,18]✉, Geoffrey I. Shapiro[2,18], Rebecca S. Kristeleit[3], Albiruni R. Abdul Razak[4], Stephen Leong[5], Maria Alsina[6], Antonio Giordano[7], Karen A. Gelmon[8], Erica Stringer-Reasor[9], Ulka N. Vaishampayan[10], Mark Middleton[11], Anthony J. Olszanski[12], Hope S. Rugo[13], Kenneth A. Kern[14], Nuzhat Pathan[14], Rachelle Perea[14], Kristen J. Pierce[15], Sarah C. Mutka[16] and Zev A. Wainberg[17]

BACKGROUND: This Phase 1b study (B2151002) evaluated the PI3K/mTOR inhibitor gedatolisib (PF-05212384) in combination with other anti-tumour agents in advanced solid tumours.

METHODS: Patients with various malignancies were administered gedatolisib (90–310 mg intravenously every week [QW]) plus docetaxel (arm A) or cisplatin (arm B) (each 75 mg/m^2 intravenously Q3W) or dacomitinib (30 or 45 mg/day orally). The safety and tolerability of combination therapies were assessed during dose escalation; objective response (OR) and safety were assessed during dose expansion.

RESULTS: Of 110 patients enrolled, 107 received gedatolisib combination treatment. Seven of 70 (10.0%) evaluable patients had dose-limiting toxicities; the most common was grade 3 oral mucositis ($n = 3$). Based upon reprioritisation of the sponsor's portfolio, dose expansion focused on arm B, gedatolisib (180 mg QW) plus cisplatin in patients ($N = 22$) with triple-negative breast cancer (TNBC). OR (95% CI) was achieved in four of ten patients in first-line (overall response rate 40.0% [12.2–73.8%]) and four of 12 in second/third-line (33.3% [9.9–65.1%]) settings. One patient in each TNBC arm (10%, first-line; 8.3%, second/third-line) achieved a complete response.

CONCLUSIONS: Gedatolisib combination therapy showed an acceptable tolerability profile, with clinical activity at the recommended Phase 2 dose in patients with TNBC.

CLINICAL TRIAL: ClinicalTrial.gov: NCT01920061.

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BACKGROUND

The hyperactivation of intracellular signalling of phosphatidylinositol-3-kinase (PI3K), AKT and downstream mechanistic target of rapamycin (mTOR) may promote tumour cell proliferation, sustain progression and induce resistance to chemotherapy, hormonal therapy, or other targeted agents in a variety of cancer types [1, 2]. Gedatolisib is a dual inhibitor of PI3K/mTOR that may reverse therapy resistance by reducing cell proliferation and survival dependent on the pathway [1, 3]. Gedatolisib has demonstrated broad anti-tumour activity in preclinical studies and in clinical trials of heavily pre-treated patients with advanced solid tumours [3–5].

Although PI3K/mTOR blockade from single-agent therapy has been associated with the inhibition of tumour growth, these agents may be very useful in combination with chemotherapy or other targeted drugs [6]. Combining chemotherapy with gedatolisib may improve anti-tumour responses in malignancies associated with upregulated PI3K/mTOR or associated pathways, including prostate cancer when combined with docetaxel and triple-negative breast cancer (TNBC) when combined with cisplatin [1, 7, 8]. In addition, combining gedatolisib with dacomitinib in the treatment of head and neck cancer may augment responses and prevent adaptation that may occur in response to epidermal growth factor receptor inhibition.

[1]Istituto Europeo di Oncologia, IRCCS and University of Milan, Milano, Italy. [2]Dana-Farber Cancer Institute, Boston, MA, USA. [3]University College London, Cancer Institute, London, UK. [4]Phase 1 Program, Princess Margaret Cancer Centre, Toronto, ON, Canada. [5]University of Colorado Cancer Center, Aurora, CO, USA. [6]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [7]Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA. [8]BC Cancer, Vancouver, BC, Canada. [9]University of Alabama at Birmingham O'Neal Comprehensive Cancer Center, Birmingham, AL, USA. [10]University of Michigan/Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA. [11]University of Oxford, Oxford, UK. [12]Fox Chase Cancer Center, Philadelphia, PA, USA. [13]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA. [14]Pfizer, San Diego, CA, USA. [15]Pfizer, Groton, CT, USA. [16]Celcuity, Minneapolis, MD, USA. [17]David Geffen School of Medicine at University of California, Los Angeles, CA, USA. [18]These authors contributed equally: Giuseppe Curigliano, Geoffrey I. Shapiro. ✉email: giuseppe.curigliano@ieo.it

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We conducted a two-part Phase 1b study to investigate the safety, tolerability, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of gedatolisib in combination with selected doses of other anti-tumour agents in a variety of advanced cancers. In Part 1 (dose escalation), we estimated the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) for gedatolisib in combination with another agent. Tumour types were mostly exclusive to one arm of the study unless otherwise indicated. In Part 2 (dose expansion), we tested the RP2D and assessed additional safety for gedatolisib in combination with cisplatin in women with metastatic or locally recurrent/advanced TNBC.

METHODS

Study design

Study B2151002 (NCT01920061) was a Phase 1b, multi-arm, open-label, non-randomised, multicentre study of gedatolisib in combination with other anti-tumour agents. During dose escalation, gedatolisib 90 to 310 mg intravenously (IV) every week (QW) was to be administered in combination with either docetaxel 75 mg/m^2 IV every 3 weeks (Q3W) (arm A: prostate cancer, non-small cell lung cancer [NSCLC] and advanced breast cancer), cisplatin 75 mg/m^2 IV Q3W (arm B: TNBC, urothelial transitional cell carcinoma, NSCLC and ovarian cancer) or dacomitinib 30 or 45 mg orally daily (arm C: head and neck cancer, NSCLC, oesophageal cancer [HER2-positive oesophagogastric cancer; and breast cancer [HER2-positive breast cancer refractory to prior trastuzumab or lapatinib]). After the MTD/RP2D for gedatolisib was defined, patients with metastatic TNBC in the first-line (1L) and second/third-line (2L/3L) settings were enrolled in dose-expansion arms and treated with gedatolisib in combination with cisplatin. The overall study design, including tumour types and treatments received in each arm, is depicted in Supplementary Fig. S1.

A modified toxicity probability interval (mTPI) design was used for arms A and B [9]. Gedatolisib dose levels were escalated until the MTD of gedatolisib for each drug combination was reached. In arm C, a zone-based method (modified 3 + 3 design) was used to evaluate the MTD of gedatolisib in combination with two different doses of dacomitinib (30 or 45 mg/day), using two separate but concurrent gedatolisib dose levels [10].

Treatments

Part 1 (dose escalation). During a lead-in period (cycle 0 day −7 [day −14 for arm C]), a single IV infusion of gedatolisib was administered to assess PK in the absence of a combinatorial agent. The gedatolisib starting dose with combination therapy was 90 mg IV QW, which was 58% of the MTD (154 mg) of gedatolisib for single-agent administration estimated in a previous trial [5]. The dose of gedatolisib was escalated (i.e., 110, 130, 150, 180, 215, 260 and 310 mg/week) independent of the co-administered agent, which was either considered standard-of-care or an agent (i.e., dacomitinib) deemed sensitive for the indication.

For cycle 1 only, the combinatorial agent (docetaxel, cisplatin or dacomitinib) was administered alone on day 1 and gedatolisib was dosed on days 2, 8 and 15. In each subsequent cycle, both agents were administered concurrently on day 1. Docetaxel and cisplatin doses were administered using prophylactic pre-medication(s) and/or pre- and/or post-hydration procedures. Patients in arm C self-administered oral dacomitinib according to standard dosing starting with cycle 0 on day −14.

Part 2 (dose expansion). To assess both safety and anti-tumour activity of gedatolisib in combination with cisplatin in patients with TNBC, two expansion arms (arm 1 and arm 2) were enrolled, including patients receiving 1L or 2L/3L treatment in the metastatic setting, respectively. Dosing continued until disease progression, uncontrollable toxicity, termination of the study or the patient or the investigator decided to discontinue treatment.

Objectives

The primary objective of Part 1 was to assess the safety and tolerability of the three gedatolisib combinations and to estimate the MTD of gedatolisib for each combination in patients with advanced solid tumours. The primary objective of Part 2 was to evaluate the anti-tumour activity of gedatolisib in combination with cisplatin in patients with TNBC.

In both parts of this study, key secondary objectives included an evaluation or continued evaluation of the overall safety profile of combination treatment, assessments of single- and multiple-dose PK, and PD parameters (PD in Part 1 only) and efficacy evaluations of anti-tumour activity. Exploratory objectives included evaluations of both tumour and blood biomarkers with potential relevance to the mechanism of action or resistance to combination therapy.

Patients

Eligible patients aged ≥18 years had a histologically or cytologically proven diagnosis of advanced solid tumours (Part 1; as previously described) or TNBC (Part 2). Key inclusion criteria included the following: measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, provision of archival or fresh tumour biopsy specimens, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, adequate organ function and a fasting serum glucose ≤126 mg/dL. Patients were excluded if they had known symptomatic brain metastases, uncontrolled or significant cardiovascular disease, prior radiation therapy to >25% of bone marrow or more than two prior regimens containing cytotoxic chemotherapy in the metastatic setting (all dose escalation cohorts). Prior treatment with platinum therapy (carboplatin or cisplatin) excluded patients with TNBC from participating in Part 2 of the study.

Study endpoints and assessments

Safety and tolerability. The primary endpoint for Part 1 of the study was the number of dose-limiting toxicities (DLTs) evaluated from the lead-in period through to cycle 2 day 1. DLTs included both haematologic and non-haematologic adverse events (AEs) potentially attributable to the drug combination. Haematologic DLTs were defined as grade 4 neutropenia >7 days, grade ≥3 febrile neutropenia/neutropenia with infection and grade 3 (with bleeding) or 4 thrombocytopenia. Non-haematologic DLTs were defined as grade ≥2 pneumonitis, grade ≥3 toxicities besides pneumonitis and toxicities not maximally treated, persistent grade 3 mean corrected QT ≥ 501 msec, persistent intolerable toxicities that precluded delivery of ≥75% of the gedatolisib (or dacomitinib in arm C) doses during cycle 1 or caused more than a 2-week delay of cycle 2.

AEs were characterised by type, frequency and relatedness, and graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 at screening (within 28 days prior to study treatment), continuously during the study and at follow-up (28–35 days after treatment discontinuation). AEs included laboratory abnormalities, significant vital sign alterations and corrected QT evaluation.

Anti-tumour activity. Objective tumour response was assessed by the investigator using RECIST v1.1. Tumour assessments (chest, abdomen and pelvis computed tomography or magnetic resonance imaging scans) were performed at baseline, every 6 weeks ±5 days from cycles 2 through 12 and every 9 weeks ±5 days thereafter until the end of the study, as defined as a secondary endpoint in Part 1, and as a primary endpoint in Part 2. Confirmation of a complete (CR) or partial (PR) response was required ≥4 weeks after an initial response was observed (Part 2 only). Additional efficacy endpoints in Part 2 included: clinical benefit response (CBR; i.e., CR + PR + stable disease [SD] ≥ 24 weeks), duration of response (DoR) and progression-free survival (PFS). DoR was calculated from the first date of PR or CR to the date of progression or death due to any cause; in the absence of progression or death, the last tumour assessment date without progression will apply. PFS was defined as the time from first dose of the study drug to the date of first documented disease progression or death due to any cause.

Pharmacokinetics. In Part 1, PK parameters were assessed for single-dose PK for gedatolisib and the combination agents individually. Following the lead-in period, multiple-dose PK parameters were evaluated for combination therapy. In Part 2, gedatolisib single- and multiple-dose PK parameters in both 1L and 2L/3L arms were collected. Key PK parameters included maximum observed plasma concentration (C_{max}) and time to reach maximum observed plasma concentration (T_{max}) for the first two doses of gedatolisib (first dose: 7 days prior to cycle 1 in arms A and B, 14 days prior in arm C, and on day 1 of cycle 1 in the expansion cohort; second dose: day 1 of cycle 2 in all cohorts). Area under the plasma concentration curve from time zero to the last quantifiable concentration (AUC_{last}) was assessed according to the first dose schedule only. PK parameters were calculated using an internally validated software system (eNCA version 2.2.4).

Pharmacodynamics. In Part 1, serum biomarkers of glucose, insulin and haemoglobin (Hb)A1c and molecular biomarkers were assessed for each tumour type, and by treatment cohort. In Part 2, exploratory genomic analyses were conducted using tumour tissue and peripheral blood biomarkers from the cohort of patients with TNBC.

Tissue and plasma next-generation sequencing (NGS). Fresh biopsies were only collected in the absence of a baseline archival tumour tissue biopsy. Samples were analysed using a FoundationOne-targeted NGS assay (Foundation Medicine, Inc., Cambridge, MA). This validated assay provides information about clinically relevant biomarkers and genomic alterations. When available, plasma circulating tumour DNA (ctDNA) was extracted from plasma samples collected at baseline (cycle 1 day 1), on treatment (cycle 5 day 1) and at the end of treatment, and analysed using the Guardant360 panel (Guardant Health, Redwood City, CA).

Statistical analysis

Descriptive statistics were used throughout the study for demographic PK, biomarkers, and safety data. Approximately 124 patients were planned for study enrolment, including up to 94 patients for Part 1 and 30 response-evaluable patients (15 per arm) for Part 2.

Part 1. The mTPI design was used for arms A and B; the target DLT rate at the MTD was 25%, and an equivalence interval of 20–32% was used to estimate the MTD. Dose assignment recommendations were based on the posterior distribution of the DLT rate, and the unit probability mass was used to facilitate decision-making.

Part 2. Confirmed objective response rate (ORR) and CBR were summarised with exact two-sided 95% confidence intervals (CIs) calculated using an exact method based on the binomial distribution. For patients with an objective response (OR), the median DoR was estimated using the Kaplan–Meier method and the 95% CI was obtained using the Brookmeyer–Crowley method. PFS was analysed using the Kaplan–Meier method.

All enrolled patients represented the full analysis set. Enrolled patients who received at least one dose of study medication were included in the safety analysis set, and among them, those without major treatment dosing deviations during cycle 1 (i.e., <75% or >125% of the planned dose of either treatment) were considered DLT-evaluable and comprised the per protocol analysis set. Enrolled and treated patients who had the disease under study and an adequate baseline tumour assessment were in the response analysis set. Enrolled and treated patients in the PK concentration and parameter analysis sets had a PK concentration measurement at one or more time points and sufficient data to estimate at least one PK parameter of interest, respectively. The serum PD analysis set comprised all enrolled and treated patients with a baseline and at least one post-baseline serum PD biomarker measurement.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

RESULTS

Patients

Between September 10, 2013, and January 8, 2020, 110 patients were screened and enrolled at 16 sites across five countries (Canada, Spain, Italy, the United Kingdom and United States). In Part 1, 88 patients were assigned to treatment (arm A: $n = 21$; arm B: $n = 34$; and arm C: $n = 33$), and 85 were treated and evaluated for safety, efficacy and PK ($n = 20$, $n = 33$ and $n = 32$, respectively). In Part 2, 22 patients were assigned to treatment, treated and assessed for safety, efficacy and PK (1L arm: $n = 10$, 2L/3L arm: $n = 12$). Patient disposition and dose administration data are summarised in Supplementary Tables S1 and S2, respectively.

The demographics for all patients are shown in Table 1. The mean age (range) of patients across treatment arms was 57.1 (22–74) years in Part 1 and 53.7 (29–73) years in Part 2. Females comprised 60% and 100% of the patients, respectively. All 22 patients in Part 2 had measurable disease.

Safety

DLTs. In Part 1, DLTs were reported in seven (10%) of the 70 patients evaluable for DLTs across all gedatolisib dose levels, and the three combination arms (Table 2).

AEs in Part 1. Treatment-related AEs (TRAEs) were reported for all (100%) patients (Table 3). Grade 3 or 4 TRAEs were reported as follows: arm A: $n = 20$ (100%), arm B: $n = 25$ (75.8%), and arm C: $n = 12$ (37.5%). There were no treatment-related grade 5 AEs. The most frequent grade 4 event in patients was neutropenia (arm A: $n = 12$ [60.0%], arm B: $n = 2$ [6.1%]) and leukopenia (arm A: $n = 2$ [10%]). The most commonly reported all-grade TRAEs in patients were neutropenia (90.0%), mucositis (60.0%) and alopecia (55.0%) in arm A; nausea (78.8%), mucositis and anaemia (57.6% each) in arm B; and mucositis (84.4%), diarrhoea (68.8%) and nausea (56.3%) in arm C.

The most frequently reported all-causality treatment-emergent AEs (TEAEs) of any grade were neutropenia (90.0%), mucositis (60.0%) and alopecia (55.0%) in arm A; nausea (78.8%), anaemia and vomiting (60.6% each) and mucositis (57.6%) in arm B; and mucositis (84.4%), diarrhoea (71.9%) and nausea (62.5%) in arm C (Supplementary Table S3). Notably, for laboratory results, across all treatment arms and cycles, the majority of haematologic and chemistry parameters were CTCAE grade 0–2.

Definition of MTD and RP2D. Based on portfolio prioritisation by the Sponsor, enrolment on April 1, 2015 was discontinued in arms A and C in Part 1 of the study. Early closure precluded an estimation of the MTD of gedatolisib in combination with either docetaxel or dacomitinib.

Although the single-agent MTD of gedatolisib was previously estimated at 154 mg/week [5], an analysis of estimated exposures required for pathway inhibition along with improved management of mucositis caused us to evaluate higher doses of gedatolisib (180, 215 and 260 mg) in combination with cisplatin. However, when co-administered with cisplatin, both the 215 and 260 mg doses of gedatolisib produced an increased frequency of high-grade AEs (including grade 3 rash). Therefore, the 180-mg dose of gedatolisib in combination with cisplatin became the estimated MTD/RP2D for this regimen.

AEs in Part 2. TRAEs were reported for all (100%) patients with TNBC (Supplementary Table S4). Grade 3/4 TRAEs were reported for 14 of 22 (63.6%) patients, including six (60.0%) and eight (66.7%) in the 1L and 2L/3L arms, respectively. Grade 4 events were reported for two of 22 (9.1%) patients, one each with hyperuricemia or decreased platelet count. There were no grade 5 TRAEs. The most commonly reported all-grade TRAEs were largely consistent with those reported in Part 1 of the study for arm B and included anaemia (81.8%), nausea (72.7%) and fatigue (68.2%). The most frequently reported all-causality TEAEs of any grade were anaemia (86.4%), fatigue and nausea (72.7% each) (Supplementary Table S5).

Anti-tumour activity

Part 1. The maximal change in tumour size for each response-evaluable patient is shown by treatment arm in Fig. 1. Best overall response (BOR) by dose level in each arm is summarised in Supplementary Fig. S2 and BORs, ORR and CBRs are summarised by tumour type in each arm in Supplemental Table S6. Across all gedatolisib dose levels, five patients in arm A achieved PR (ORR 25.0%; 95% CI 8.7–49.1%), ten patients in arm B achieved a PR (ORR 30.3%, 95% CI 15.6–48.7%) and six patients in arm C achieved CR/PR (ORR 18.8%; 95% CI 7.2–36.4), including one (3.1%) patient who achieved CR and five (15.6%) who achieved PR.

Part 2. Four patients of the 10 enrolled in the 1L TNBC arm achieved confirmed CR/PR (ORR 40.0%; 95% CI 12.2–73.8%), one

Table 1. Patient demographic and baseline characteristics (safety analysis set[a])—Parts 1 and 2.

	Dose escalation			Dose expansion	
	Gedatolisib + Docetaxel	Gedatolisib + Cisplatin	Gedatolisib + Dacomitinib	Gedatolisib (RP2D) + Cisplatin	
	Arm A[b]	Arm B[c]	Arm C[d]	1L Arm	2L/3L Arm
n	20	33	32	10	12
Male:female	10:10	7:26	17:15	0:10	0:12
Age, median (range)	65 (40–72)	58 (37–74)	57.5 (22–73)	51.5 (29–71)	54.5 (37–73)
Race					
White	18 (90.0)	30 (90.9)	29 (90.6)	9 (90.0)	11 (91.7)
Black	1 (5.0)	1 (3.0)	2 (6.3)	1 (10.0)	0
Asian	1 (5.0)	2 (6.1)	1 (3.1)	0	1 (8.3)
BMI, median (range), kg/m^2	28.0 (19.2–39.4)	24.8 (18.6–37.5)	24.8 (15.3–39.9)	22.2 (17.8–34.2)	23.3 (19.5–34.7)
ECOG PS					
0	9 (45.0)	12 (36.4)	11 (34.4)	5 (50.0)	8 (66.7)
1	11 (55.0)	21 (63.6)	21 (65.6)	5 (50.0)	4 (33.3)
Primary cancer					
Breast cancer	5 (25.0)	NA	5 (15.6)	NA	NA
Prostate cancer	5 (25.0)	NA	NA	NA	NA
Non-small-cell lung cancer	10 (50.0)	6 (18.2)	8 (25.0)	NA	NA
Ovarian cancer	NA	2 (6.1)	NA	NA	NA
Transitional cell carcinoma	NA	7 (21.2)	NA	NA	NA
Triple-negative breast cancer	NA	18 (54.5)	NA	10 (100.0)	12 (100.0)
Oesophageal carcinoma	NA	NA	7 (21.9)	NA	NA
Head and neck cancer	NA	NA	12 (37.5)	NA	NA
Prior systemic therapies					
No	0	1 (3.0)	0	0	0
Yes	20 (100)	32 (97.0)	32 (100.0)	10 (100.0)	12 (100.0)
Number of regimens					
1	8 (40.0)	12 (36.4)	9 (28.1)	6 (60.0)	4 (33.3)
2	4 (20.0)	9 (27.3)	12 (37.5)	4 (40.0)	5 (41.7)
3	4 (20.0)	7 (21.2)	9 (28.1)	0	1 (8.3)
>3	4 (20.0)	4 (12.1)	2 (6.3)	0	2 (16.7)
Prior radiation therapies					
No	10 (50.0)	11 (33.3)	7 (21.9)	3 (30.0)	4 (33.3)
Yes	10 (50.0)	22 (66.7)	25 (78.1)	7 (70.0)	8 (66.7)
Prior surgeries					
No	2 (10.0)	0	2 (6.3)	0	1 (8.3)
Yes	18 (90.0)	33 (100.0)	30 (93.8)	10 (100.0)	11 (91.7)

NA no data available, *1L* first-line treatment, *2L/3L* second-line/third-line treatment, *BMI* body mass index (weight [kg]//<height [cm] × 0.01>^{2}), *RP2D* recommended Phase 2 dose of gedatolisib, *SD* standard deviation.

[a]Data are *n* (%), unless otherwise specified.

[b]Arm A subgroups included patients treated with gedatolisib (dosed at 90 mg [$n = 4$], 110 mg [$n = 5$], 130 mg [$n = 3$], 150 mg [$n = 3$] and 180 mg [$n = 5$]) + docetaxel.

[c]Arm B subgroups included patients treated with gedatolisib (dosed at 90 mg [$n = 4$], 110 mg [$n = 3$], 130 mg [$n = 3$], 150 mg [$n = 3$], 180 mg [$n = 3$], 215 mg [$n = 10$] or 260 mg [$n = 5$] and 310 mg [$n = 2$] + cisplatin.

[d]Arm C subgroups included patients treated with gedatolisib (dosed at 90 mg + 30 mg dacomitinib [$n = 15$], 90 mg + 45 mg dacomitinib [$n = 4$], 110 mg + 30 mg dacomitinib [$n = 7$], 130 mg + 30 mg dacomitinib [$n = 3$] and 150 mg + 30 mg dacomitinib [$n = 3$]).

patient (10.0%) achieved CR and three patients (30.0%) achieved PR (Table 4). In the 2L/3L TNBC arm, four patients achieved a confirmed CR/PR (ORR, 33.3%; 95% CI 9.9–65.1%), one (8.3%) patient achieved CR and three (25.0%) patients achieved PR. CBR (1L arm: 60% [95% CI 26.2-87.8]; 2L/3L arm: 50.0% [95% CI 21.1–78.9]), median DoR (1L arm: 6.9 months [95% CI 2.6–9.9]; 2 L/3L arm: not reached [NR] [7.4 months–not estimable <NE>]) and median PFS (1L arm: 4.8 months [95% CI 0.8–7.0]; 2L/3L arm: 8.5 months [1.2–NE]) are summarised in Table 4. BORs for patients are also shown in the context of treatment duration in Fig. 2a, and maximal changes in tumour size are depicted in Fig. 2b.

Pharmacokinetics

Part 1. Gedatolisib pharmacokinetic parameters are presented in Supplementary Tables S7, S9 and S11. Due to the small sample size of cohorts and heterogenous patient population, all

Table 2. Dose-limiting toxicities (per protocol analysis set[a])—Part 1.

Gedatolisib ascending dose levels, mg	DLT-evaluable patients/ patients treated, *n*	Patients with DLTs, *n* (%)	Gedatolisib dose during DLT, grade (Gr), period of onset of event(s), relation to treatment, and outcome[b]
Arm A, gedatolisib + docetaxel (75 mg/m^2, Q3W)			
90 mg	4/4	0	One patient with DLT at gedatolisib **180 mg**: - 56-year-old white female with treatment-emergent Gr 3 mucositis during cycle 1; event related to gedatolisib and docetaxel; doses of both drugs reduced; event resolved in 7 days
110 mg	3/5	0	
130 mg	3/3[c]	0	
150 mg	3/3	0	
180 mg	2/5	**1**	
Total	15/20[c]	1 (6.7%)	
Arm B, gedatolisib + cisplatin (75 mg/m^2 Q3W)			
90 mg	3/4	0	First patient with DLT at gedatolisib **310 mg**: - 50-year-old white female with treatment-emergent Gr 3 mucositis (SAE) during treatment lead-in period[d]; event related to gedatolisib dose, which was reduced, cisplatin dose unchanged; event resolved in 10 days Second patient with DLT at gedatolisib **310 mg**: - 69-year-old White female with treatment-emergent Gr 3 nausea (SAE) and Gr 3 stomatitis (SAE) during cycle 1; both events were related to treatment and gedatolisib and cisplatin doses were reduced; nausea resolved in 10 days and stomatitis resolved in 7 days
110 mg	3/3	0	
130 mg	3/3	0	
150 mg	3/3	0	
180 mg	3/3	0	
215 mg	8/10	0	
260 mg	3/5	0	
310 mg	2/2	**2**	
Total	28/33	2 (7.1%)	
Arm C, gedatolisib + dacomitinib (30 mg or 45 mg QD)			
90 mg	13/15	0	First patient with DLT at gedatolisib **90 mg** (+dacomitinib 45 mg): - 58-year-old White female with treatment-emergent Gr 3 rash maculopapular during cycle 1; event was treatment-related, gedatolisib and dacomitinib doses were stopped temporarily; event resolved in 12 days Second patient with DLT at gedatolisib **90 mg** (+ dacomitinib 45 mg): - 67-year-old Asian female with treatment-emergent Gr 3 mucositis during cycle 1; event related to dacomitinib, gedatolisib dose unchanged, dacomitinib dose reduced; event resolved in 2 days First patient with DLT at gedatolisib **110 mg** (+ dacomitinib 30 mg): - 64-year-old White male with treatment-emergent Gr 2 fatigue (SAE) during cycle 1; event was treatment-related, gedatolisib and docetaxel were stopped temporarily before being restarted at a reduced dose; event resolved in 9 days Second patient with DLT at gedatolisib **110 mg** (+ dacomitinib 30 mg): - 51-year-old White male with treatment-emergent Gr 3 pneumonitis during study lead-in period[f]; event considered related to gedatolisib and dacomitinib, gedatolisib permanently discontinued and dacomitinib dose reduced; event resolved in 4 days
90 mg[e]	2/4	**2**	
110 mg	7/7	**2**	
130 mg	3/3	0	
150 mg	2/3	0	
Total	27/32	4 (14.8%)	

DLT dose-limiting toxicity, *Gr* maximum grade, *MTD* maximum tolerated dose, *Q3W* every 3 weeks, *QD* every day on a continuous basis, *SAE* serious adverse event.

Bolded numbers for patients with DLTs indicate the dose of gedatolisib.

[a]All enrolled patients who received at least one dose of study medication and who did not have a major treatment deviation during cycle 1.

[b]Investigators assessed event severity and relatedness to study drug(s).

[c]One patient was classified as missing.

[d]Arm B lead-in treatment period refers to administration of a single dose of gedatolisib (cycle 0 day −7).

[e]Gedatolisib 90 mg received in combination with dacomitinib 45 mg.

[f]Arm C lead-in treatment period refers to administration of a single dose of gedatolisib (cycle 0 day −14).

Table 3. Treatment-related adverse events reported for ≥10% of patients overall by treatment arm and select grades, all cycles[a] (safety analysis set)—Part 1.

Preferred term[b], *n* (%)	Gedatolisib + Docetaxel (*n* = 20)— Arm A				Gedatolisib + Cisplatin (*n* = 33)— Arm B				Gedatolisib + Dacomitinib (*n* = 32) —Arm C			
	Gr 1–2	Gr 3	Gr 4	All Gr[c]	Gr 1–2	Gr 3	Gr 4	All Gr[c]	Gr 1–2	Gr 3	Gr 4	All Gr[c]
Any TRAE	0	8 (40)	12 (60.0)	20 (100)	8 (24.2)	22 (66.7)	3 (9.1)	33 (100)	20 (62.5)	11 (34.4)	1 (3.1)	32 (100)
Neutropenia	0	6 (30.0)	12 (60.0)	18 (90.0)	6 (18.2)	2 (6.1)	2 (6.1)	10 (30.3)	NA	NA	NA	NA
Mucosal inflammation	9 (45.0)	3 (15.0)	0	12 (60.0)	13 (39.4)	6 (18.2)	0	19 (57.6)	23 (71.9)	4 (12.5)	0	27 (84.4)
Nausea	8 (40.0)	0	0	8 (40.0)	22 (66.7)	4 (12.1)	0	26 (78.8)	18 (56.3)	0	0	18 (56.3)
Diarrhoea	6 (30.0)	0	0	6 (30.0)	8 (24.2)	0	0	8 (24.2)	21 (65.6)	1 (3.1)	0	22 (68.8)
Anaemia	5 (25.0)	0	0	5 (25.0)	14 (42.4)	5 (15.2)	0	19 (57.6)	NA	NA	NA	NA
Alopecia	11 (55.0)	0	0	11 (55.0)	NA	NA	NA	NA	4 (12.5)	0	0	4 (12.5)
Vomiting	4 (20.0)	0	0	4 (20.0)	18 (54.5)	0	0	18 (54.5)	9 (28.1)	0	0	9 (28.1)
Fatigue	4 (20.0)	1 (5.0)	0	5 (25.0)	16 (48.5)	0	0	16 (48.5)	12 (37.5)	0	0	12 (37.5)
Dermatitis acneiform	NA	NA	NA	NA	NA	NA	NA	NA	13 (40.6)	1 (3.1)	0	14 (43.8)[d]
Paronychia	NA	NA	NA	NA	NA	NA	NA	NA	11 (34.4)	1 (3.1)	0	12 (37.5)
Rash	4 (20.0)	0	0	4 (20.0)	10 (30.3)	2 (6.1)	0	12 (36.4)	6 (18.8)	1 (3.1)	0	7 (21.9)
Hypomagnesemia	NA	NA	NA	NA	9 (27.3)	3 (9.1)	0	12 (36.4)	NA	NA	NA	NA
Dysgeusia	7 (35.0)	0	0	7 (35.0)	7 (21.2)	0	0	7 (21.2)	NA	NA	NA	NA
Asthenia	2 (10.0)	1 (5.0)	0	3 (15.0)	10 (30.3)	1 (3.0)	0	11 (33.3)	1 (3.1)	3 (9.4)	0	4 (12.5)
Decreased appetite	4 (20.0)	0	0	4 (20.0)	9 (27.3)	1 (3.0)	0	10 (30.3)	10 (31.3)	0	0	10 (31.3)
Dry skin	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	10 (31.3)	0	0	10 (31.3)
Leukopenia	1 (5.0)	3 (15.0)	2 (10.0)	6 (30.0)	6 (18.2)	2 (6.1)	0	8 (24.2)[d]	NA	NA	NA	NA
Hyperglycaemia	6 (30.0)	0	0	6 (30.0)	4 (12.1)	3 (9.1)	0	7 (21.2)	NA	NA	NA	NA
Rash maculopapular	NA	NA	NA	NA	5 (15.2)	0	0	5 (15.2)	8 (25.0)	1 (3.1)	0	9 (28.1)
Stomatitis	3 (15.0)	0	0	3 (15.0)	6 (18.2)	3 (9.1)	0	9 (27.3)	4 (12.5)	0	0	4 (12.5)
Tinnitus	NA	NA	NA	NA	8 (24.2)	0	0	8 (24.2)	NA	NA	NA	NA
Weight decreased	NA	NA	NA	NA	4 (12.1)	0	0	4 (12.1)	6 (18.8)	0	0	6 (18.8)
Lymphocyte count decreased	0	2 (10.0)	0	2 (10.0)	3 (9.1)	3 (9.1)	0	6 (18.2)	NA	NA	NA	NA
Blood creatinine increased	NA	NA	NA	NA	6 (18.2)	0	0	6 (18.2)	NA	NA	NA	NA
Pruritus	NA	NA	NA	NA	4 (12.1)	1 (3.0)	0	5 (15.2)	7 (21.9)	0	0	7 (21.9)
Skin fissures	NA	NA	NA	NA	NA	NA	NA	NA	5 (15.6)	0	0	5 (15.6)
Constipation	2 (10.0)	0	0	2 (10.0)	5 (15.2)	0	0	5 (15.2)	NA	NA	NA	NA
Neuropathy peripheral	2 (10.0)	0	0	2 (10.0)	5 (15.2)	0	0	5 (15.2)	NA	NA	NA	NA
Deafness	NA	NA	NA	NA	5 (15.2)	0	0	5 (15.2)	NA	NA	NA	NA
Dehydration	3 (15.0)	0	0	3 (15.0)	NA	NA	NA	NA	4 (12.5)	1 (3.1)	0	5 (15.6)
Myalgia	3 (15.0)	0	0	3 (15.0)	NA	NA	NA	NA	NA	NA	NA	NA
Pyrexia	3 (15.0)	0	0	3 (15.0)	3 (9.1)	1 (3.0)	0	4 (12.1)	NA	NA	NA	NA
Rash papular	NA	NA	NA	NA	NA	NA	NA	NA	4 (12.5)	0	0	4 (12.5)
Paraesthesia	2 (10.0)	0	0	2 (10.0)	3 (9.1)	1 (3.0)	0	4 (12.1)	NA	NA	NA	NA
Hypokalaemia	NA	NA	NA	NA	1 (3.0)	3 (9.1)	0	4 (12.1)	NA	NA	NA	NA
Headache	NA	NA	NA	NA	4 (12.1)	0	0	4 (12.1)	NA	NA	NA	NA

Table 3. continued

Preferred term[b], *n* (%)	Gedatolisib + Docetaxel (*n* = 20)— Arm A				Gedatolisib + Cisplatin (*n* = 33)— Arm B				Gedatolisib + Dacomitinib (*n* = 32) —Arm C			
	Gr 1–2	Gr 3	Gr 4	All Gr[c]	Gr 1–2	Gr 3	Gr 4	All Gr[c]	Gr 1–2	Gr 3	Gr 4	All Gr[c]
Febrile neutropenia	0	1 (5.0)	1 (5.0)	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Neutrophil count decreased	0	1 (5.0)	1 (5.0)	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
White blood cell count decreased	0	2 (10.0)	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Hyponatraemia	1 (5.0)	1 (5.0)	0	2 (10.0)	3 (9.1)	1 (3.0)	0	4 (12.1)	NA	NA	NA	NA
Arthralgia	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Bone pain	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Conjunctivitis	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Dyspnoea	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Dyspnoea exertional	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Erythema	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Feeling cold	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Oedema peripheral	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA
Pneumonia	2 (10.0)	0	0	2 (10.0)	NA	NA	NA	NA	NA	NA	NA	NA

NA not applicable, *CTCAE* Common Terminology Criteria for Adverse Events, *Gr* maximum CTCAE grade, *MedDRA* Medical Dictionary for Regulatory Activities, *TRAE* treatment-related adverse events.
[a]Included data up to 28 days after last dose of study drug.
[b]MedDRA (version 22.1) coding dictionary applied.
[c]No grade 5 treatment-related AEs were observed during the dose escalation phase of the study in any treatment arm.
[d]Rounding resulted in a lower/higher total for the treatment arm.

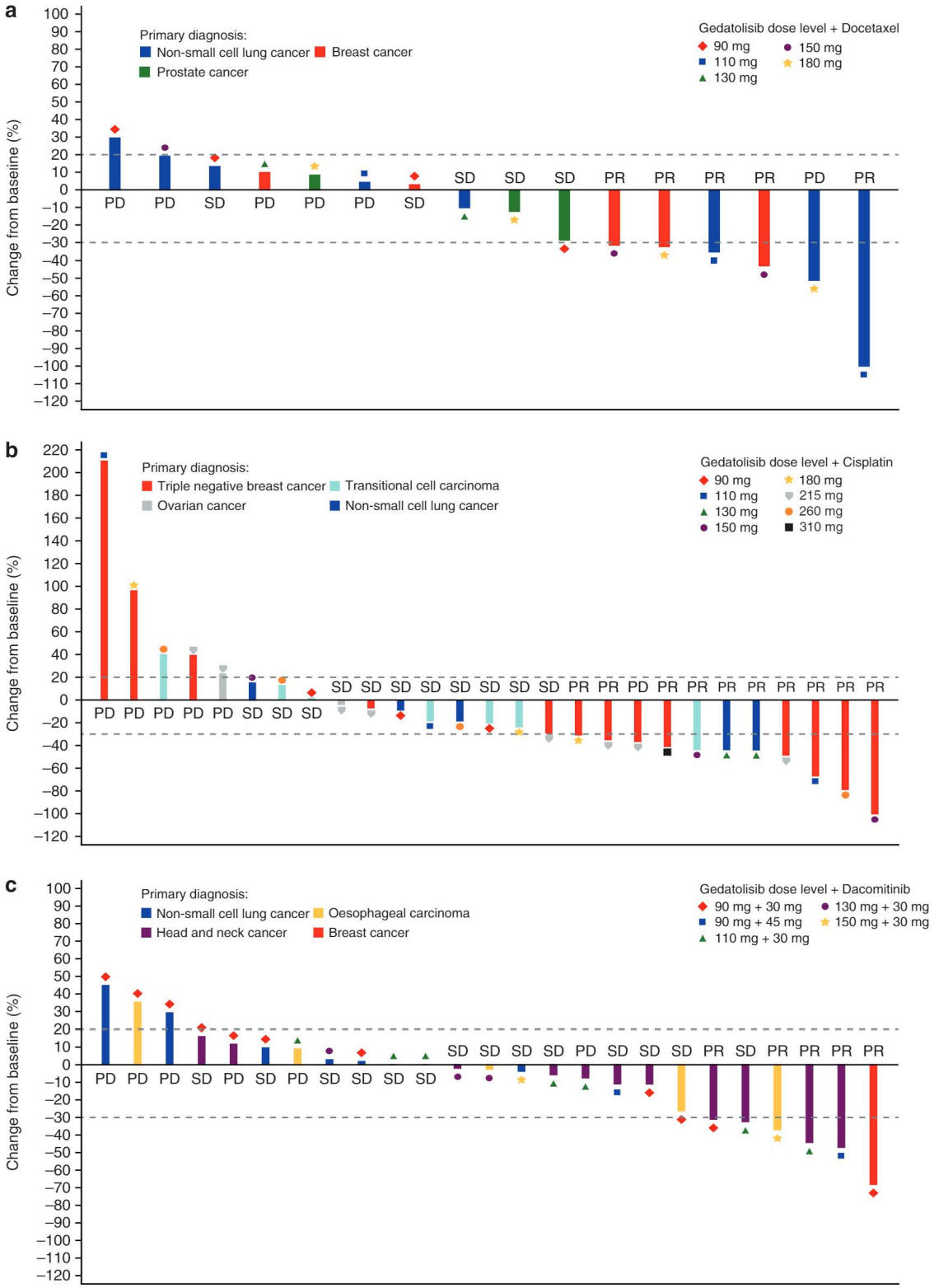

Fig. 1 Waterfall plots of best changes (%) in target lesions in patients with measurable disease in response-evaluable set during Part 1 of the study. Results for (**a**) arm A, $n = 16$; (**b**) arm B, $n = 27$; and (**c**) arm C, $n = 25$ depicted by tumour type.

comparisons and interpretations should be done with caution. Comparison of gedatolisib pharmacokinetic parameters in the lead-in period (cycle 0, day −7) indicated generally dose-proportional increase in gedatolisib exposures in the dose range evaluated. In all three treatment arms, relative to gedatolisib alone in the lead-in period, no clinically relevant changes in gedatolisib exposures were apparent following co-administration with combination agents docetaxel, cisplatin or dacomitinib on cycle 2 day 1. Any increase or decrease in gedatolisib exposures when co-administered with each of the combination agents were not

Table 4. Summary of antitumor activity in patients with triple-negative breast cancer (response analysis set)—Part 2.

	Gedatolisib 180 mg + Cisplatin	
	1L arm, *n* = 10	2L/3L arm, *n* = 12
Best overall response, n *(%)*		
CR	1 (10.0)	1 (8.3)
PR	3 (30.0)	3 (25.0)
SD	3 (30.0)	6 (50.0)
Objective progression	3 (30.0)	2 (16.7)
ORR (CR + PR), *n* (%) [95% CI[a]]	4 (40.0) [12.2–73.8]	4 (33.3) [9.9–65.1]
CBR (CR + PR + SD ≥ 24 weeks), *n* (%) [95% CI[a]]	6 (60.0) [26.2–87.8)	6 (50.0) [21.1–78.9]
Duration of objective response, months		
Median [95% CI[b]]	6.9 [2.6–9.9]	NR [7.4–NE]
Events		
Objective progression, *n* (%)	4 (100)	2 (50.0)
Censored, *n* (%)	0	2 (50.0)
Progression-free survival, months		
Median [95% CI[b]]	4.8 [0.8–7.0]	8.5 [1.2–NE]
Events		
Objective progression, *n* (%)	10 (100)	7 (58.3)[c]

1L first-line metastatic setting, *2L/3L* second-/third-line metastatic setting, *CBR* clinical benefit response, *CI* confidence interval, *CR* complete response, *NR* not reached, *NE* not estimable, *ORR* objective response rate, *PR* partial response, *SD* stable disease (included non-CR/non-PD for patients without measurable disease and SD for patients with measurable disease).
[a]Using exact two-sided method based on binomial distribution.
[b]Using Brookmeyer and Crowley Method.
[c]Five patients were censored for PFS.

consistent across dose levels within each arm indicating that the observed differences may be due, in part, to variability in gedatolisib pharmacokinetics.

Comparison of docetaxel, cisplatin and dacomitinib pharmacokinetic parameters without gedatolisib (cycle 1 day 1) and with gedatolisib (cycle 2 day 1) showed no clinically relevant effect of gedatolisib on the pharmacokinetics of the three combination drugs (Supplementary Tables S8, S10 and S12). Overall, pharmacokinetic evaluations indicate no drug interactions in the three arms.

Part 2. Gedatolisib pharmacokinetics was characterised in 22 subjects at the RP2D dose of 180 mg (Supplementary Table S13). Comparison of average gedatolisib exposures without and with cisplatin and comparison of average gedatolisib exposures in 1L and 2L/3L patients showed difference of ~30% or less suggesting no clinically relevant effect of cisplatin on gedatolisib pharmacokinetics and no remarkable differences in the disposition of gedatolisib in the two patient populations.

Pharmacodynamics and biomarker analyses

Although HbA1c routinely increased across arms, there were no marked trends in changes in circulating glucose, and insulin was only consistently elevated in arm C (gedatolisib in combination with dacomitinib).

In the patients with TNBC in Part 2 of the study, genomic analyses were performed whenever available, resulting in the profiling of 21 (95.5%) baseline plasma samples among 22 patients and 17 (77.3%) archival tumour samples (Fig. 2b). On-treatment and end-of-treatment samples for ctDNA were available from 11 and 14 patients, respectively.

Although the baseline status of PI3K pathway genes *(PIK3CA* and *PTEN)* assessed in archival tumour did not appear to be predictive of clinical response (Supplementary Fig. S3A), an unsupervised panel-wide search revealed novel candidates whose genetic alterations in tumour were associated with differential tumour size change from gedatolisib treatment, including *Notch3* for resistance and *DNMT3A* for sensitivity (Supplementary Fig. S3B).

Analysis of ctDNA revealed additional preliminary insights. Although all samples had a low tumour mutation burden (<5), the on-treatment (cycle 5 day 1) tumour mutation burden was found to be inversely correlated with the best percentage change in tumour size (Supplementary Fig. S3C), and the on-treatment loss of *BRCA1/2* mutations were associated with greater reduction in tumour size (Supplementary Fig. S3D). Unpaired frequency change in genes, from day 1 of cycle 1 to day 1 of cycle 5, were most different between responders and non-responders for mutant *TP53*, *BRCA1* and *PIK3CA* (Supplementary Fig. S4). Furthermore, the end-of-treatment genetic status of *PTEN* was significantly associated with a lower level of clinical response, with similar marginal trends also observed for *CCNE1* and *CCND1* and marginal sensitivity for *AKT1* (Supplementary Fig. S5).

DISCUSSION

In this two-part Phase 1b study, we evaluated the safety, tolerability, preliminary clinical activity and PK/PD of gedatolisib IV administered QW in combination with standard anti-tumour therapies in patients with advanced solid malignancies. The estimated MTD/RP2D of gedatolisib was 180 mg QW in combination with cisplatin 75 mg/m^2 IV Q3W. Collectively, across all dose escalation arms, oral mucositis was the most common DLT. No notable drug–drug interactions between gedatolisib and the other anti-tumour agents were observed during gedatolisib dose escalations. Overall exposure to gedatolisib did not consistently increase following a single dose or multiple doses of either docetaxel, cisplatin or dacomitinib in a clinically relevant manner.

In general, intravenous administration of PI3K and PI3K-mTOR inhibitors has improved pharmacokinetic properties and therapeutic index. For example, the PI3K inhibitor copanlisib, with predominant activity against the p110α and δ isoforms, has been associated with decreased incidence and severity of adverse events when compared to orally administered therapeutics of this class. Similarly, gedatolisib, with a unique chemical structure affording high C_{max} and overall plasma exposure after intravenous administration, has demonstrated decreased incidence and severity of adverse events compared to all other oral or infusion-administered PI3K-mTOR inhibitors, while maintaining promising efficacy.

To date, other trials combining chemotherapy with PI3K pathway inhibitors have primarily focused on taxane-based combinations in breast cancers and other solid tumours. The safety and activity of alpelisib, an oral, selective PI3K p110α inhibitor, plus paclitaxel was assessed in patients with advanced solid tumours [11]. However, the safety profile of this combination presented challenges, and after completion of the dose-finding phase, the study was closed [11]. Another study assessed the safety and activity of alpelisib plus nab-paclitaxel in patients with HER2-negative metastatic breast cancer, the majority of whom had visceral disease and prior taxane exposure [12]. Among 42 evaluable patients, ORR was 59%, with 21% achieving response lasting >12 months. Median PFS was 8.7 months. Tumour and/or ctDNA *PIK3CA* mutations were observed in 40% of these patients, who also demonstrated better PFS compared with those without a mutation (11.9 vs. 7.5 months, hazard ratio 0.44, $P = 0.027$). A prospective, randomised, Phase 3 trial (NCT04251533) is currently

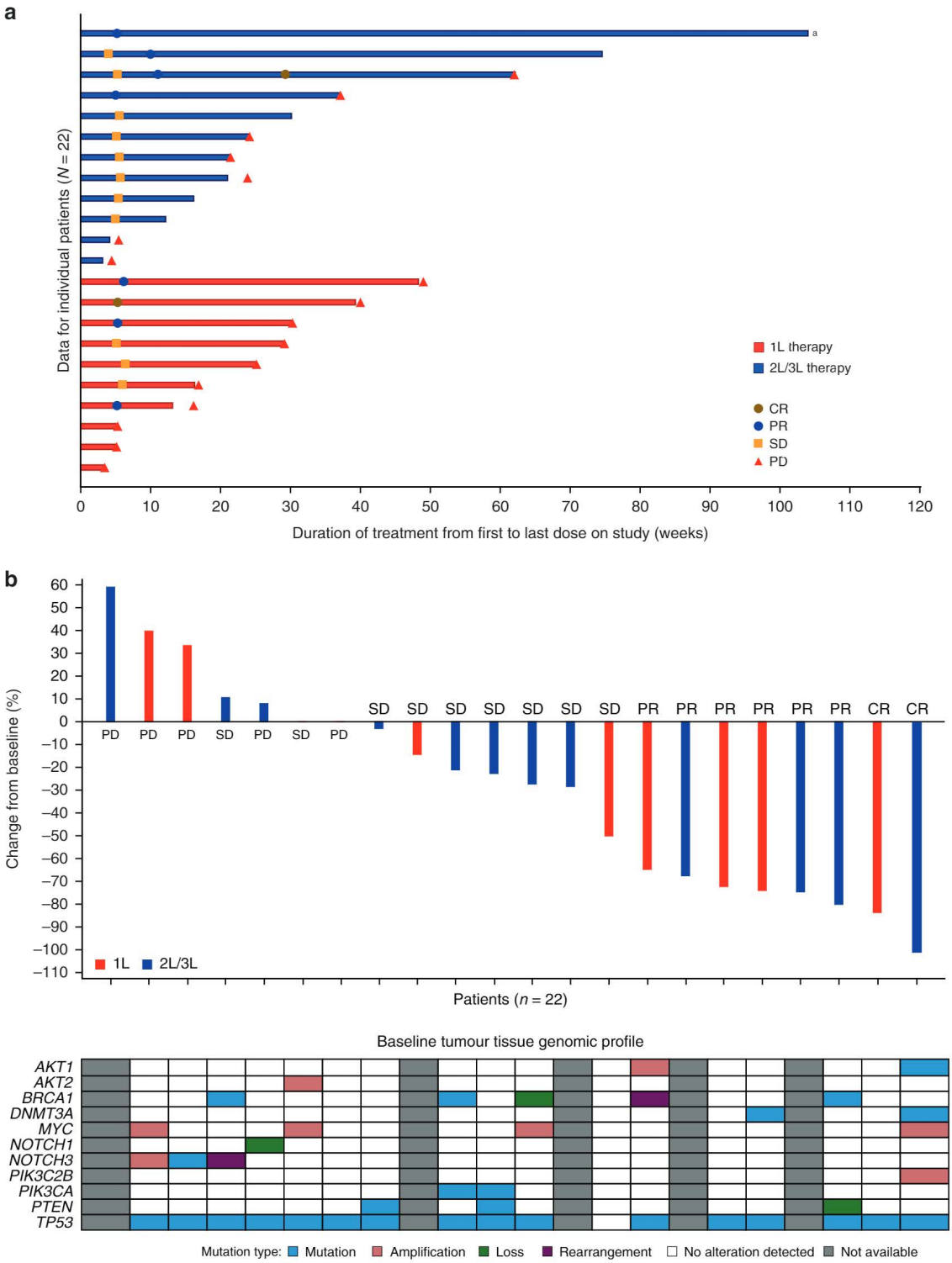

Fig. 2 Response to treatment in patients with triple-negative breast cancer participating in Part 2 of the study **a** Swimmer plot with solid bars representing the duration of treatment and symbols showing the timing of best overall response.[a] **b** Waterfall plot illustrating best change (%) in target lesions for patients with measurable disease and a corresponding baseline tumour genomic profile (molecular profiling tumour analysis set[b]). [a]Of note, a 66-year-old White woman in the 2L/3L arm received gedatolisib 180 mg + cisplatin over 104 weeks (728 days) in this study. Prior to her enrolment in December 2017, she had received a primary diagnosis of Stage III (TNM) ductal carcinoma in December 2015 and a diagnosis of metastatic disease in February 2016. In January 2020 she discontinued from the study when it ended and continued on compassionate use gedatolisib alone for the treatment of Stage IV disease. [b]Tumour analysis set was defined as all enrolled patients who start treatment and have a baseline archived tumour biopsy FFPE (or fresh FFPE if archived sample is not available) and were analysed for at least one of the selected biomarkers. 1L first-line treatment, 2L/3L second/third-line treatment, CR complete response, ctDNA circulating DNA, FFPE formalin-fixed paraffin-embedded, PR partial response, SD stable disease, TNM tumour, node, metastasis.

ongoing in patients with advanced (loco-regionally recurrent or metastatic) TNBC harbouring a *PIK3CA* mutation or *PTEN* loss (without *PIK3CA* mutation) to evaluate the efficacy and safety of alpelisib in combination with nab-paclitaxel as 1L/2L therapy. In addition to gedatolisib, other dual PI3K-mTOR inhibitors have also been studied previously in breast cancer, such as apitolisib. However, the development of apitolisib has been discontinued, and, to our knowledge, there are no other active trials of dual PI3K-mTOR inhibitors for breast cancer.

In this study, we focused on the combination of gedatolisib plus cisplatin in patients with TNBC. Platinum-based chemotherapy was evaluated previously in this patient population in trials such as TNT and TBCRC009 [13, 14]. In TNT, the ORR for first-line carboplatin in the unselected population was 31.4% and similar to that of docetaxel. In TBCRC009, ORRs for cisplatin and carboplatin were 32.6% and 18.6%, respectively, among patients receiving 1L or 2L treatment. Overall, the results with combined gedatolisib/cisplatin were similar to those reported in these trials, and do not suggest a significantly improved response rate compared with cisplatin monotherapy. However, this result may be complicated by the small sample size and non-randomised study design. Further work will be necessary to conclude a true lack of benefit afforded by the addition of gedatolisib, not only in the 1L setting, but also in the 2L and 3L settings, where PI3K/mTOR inhibition could have great impact in overcoming chemotherapy resistance.

Additional study of the cisplatin/gedatolisib regimen in the TNBC population may benefit from a biomarker-driven approach. However, gedatolisib is not an alpha-isoform selective drug and is a dual pan-PI3K/mTOR inhibitor [5]. It remains to be determined if selection of patients with tumours harbouring PI3K pathway alterations will affect overall outcome [5]. Among the patients with TNBC enrolled, combined activating genomic alterations in PI3K pathway genes were common and were observed in ~25–30% of patients, as reported previously [15]. Although one patient with an activating *AKT1* mutation had a response, overall, a direct correlation of baseline PI3K pathway alterations with clinical responses was not observed in this study. Nonetheless, we observed a steep reduction of the *PIK3CA* mutation frequency, particularly among responders, in ctDNA on treatment, suggesting on-target action of gedatolisib to inhibit PI3K signalling in patients with TNBC.

A second potential biomarker approach relevant for platinum-based chemotherapy may be related to germline *BRCA1/2* (*gBRCA1/2*) status. In both the TNT and TBCRC009 trials, patients with TNBC with *gBRCA1/2* mutations achieved greater clinical benefit from platinum-based chemotherapy [13, 14]. In TNT, the ORR for carboplatin was double that of docetaxel (68% vs. 33%, respectively) among patients with *gBRCA* breast cancer, with a significant biomarker-treatment interaction [13]. Similarly, in TBCRC009, the response rate was 54.5% among patients with *gBRCA* mutations who received platinum agents, which was substantially higher than that of the unselected population (25.6%) [14]. In addition, in this trial, in patients without *BRCA1/2* mutations, an exploratory analysis showed that a *BRCA*-like genomic instability signature discriminated responders from non-responders. Notably, in our trial, a sharp reduction in the mutant *BRCA1* allele in ctDNA analysis on treatment was associated with response to gedatolisib/cisplatin. However, additional work will be required to determine whether the addition of gedatolisib could improve either the response or PFS rate compared with cisplatin alone in *BRCA*-associated disease.

Interestingly, in the archival tumour analysis, baseline alterations in *NOTCH3* and *DNMT3A* correlated with resistance and sensitivity to treatment, respectively. These results suggest that *NOTCH3* may activate other signalling pathways driving TNBC proliferation [16]. Conversely, *DNMT3A*-mutant cells may be highly dependent on PI3K pathway signalling for proliferation and survival, and dysregulated *DNMT3A* activity has been linked to PI3K pathway activation in breast cancer [17–19]. Such results will require confirmation in larger studies, but suggest predictive biomarkers that may facilitate patient selection in future trials.

Finally, several of our findings in ctDNA analyses on treatment and at end of treatment raise the possibility of the development of tumour cell adaptation and acquired resistance. Although the overall tumour mutation burden was low in this small sample set, there was a trend towards an inverse correlation between tumour mutational burden in ctDNA and tumour response. Larger sample size would be needed for confirmation, but the preliminary data are consistent with higher tumour mutational burden representing greater evolution toward drug resistance, characteristic of tumours with *TP53* mutation, as occurs in ~80% of TNBC cases [20]. In addition, the presence of *PTEN* mutation or *CCND1* or *CCNE1* amplification at the end of treatment, alterations associated with less tumour regression, may be suggestive of the emergence of resistant cells with elevated PI3K activity or proliferative capacity that may overcome gedatolisib [21, 22].

In summary, gedatolisib can be safely combined with a variety of agents and a dose of 180 mg QW showed an acceptable tolerability profile with cisplatin with anti-tumour activity in patients with TNBC. Further work will be necessary to confirm benefit from the addition of gedatolisib to cisplatin in this population, which may be easier to demonstrate in the 2L or 3L setting, where response rates to platinum-based chemotherapy are lower than in 1L, and where PI3K/mTOR inhibition may overcome drug resistance. Additional studies will also be required to develop a biomarker-driven approach to the development of this combination, with the evaluation of larger numbers of patients with tumours harbouring PI3K pathway alterations, *BRCA*-mutation or *DNMT3A* deficiency. Presently, the overall benefit-risk assessment for future studies of the gedatolisib/cisplatin doublet is challenging and the changing landscape of treatment options will need to be taken into consideration to assess subsequent development steps for patients with advanced TNBC. Currently, gedatolisib is being studied in combination with talazoparib in TNBC and *BRCA*-associated breast cancers (NCT03911973) and will soon enter a Phase 3 trial in combination with fulvestrant and palbociclib for patients with advanced HR +/HER2− breast cancer (NCT05501886). Further assessment of gedatolisib in combination with other therapeutics in breast cancer and other solid tumours is also under consideration, including with immune-checkpoint inhibitors.

DATA AVAILABILITY

On request, and subject to certain criteria, conditions and exceptions, Celcuity, Inc. will provide access to individual de-identified participant data from Celcuity sponsored interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) where development has been terminated. A brief research proposal will be assessed and form the basis of a data-sharing agreement. Data requests may be submitted by using the form provided at https://www.celcuity.com/contact/. https://www.nature.com/documents/aj-research-data-policy-type-3.pdf.

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AUTHOR CONTRIBUTIONS

GC, GIS, EC, KK, KJP and HSR contributed to the conception and design of the study. All authors contributed to the acquisition, analysis, or interpretation of data, and to drafting or revising the submitted manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. Dr. Curigliano (corresponding and co-first author) and Dr. Shapiro (co-first author) confirm they had full access to the data in the study and final responsibility for the decision to submit for publication.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol, its amendments, and informed consent documentation were reviewed and approved by the institutional review board(s) or independent ethics committee(s) at each site. Study procedures followed the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines and all local regulatory requirements. All patients provided informed consent before participating in any study-related procedure.

CONSENT TO PUBLISH

Not applicable.

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Correspondence and requests for materials should be addressed to Giuseppe Curigliano.

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