Clinical Cancer Research

POSEIDON Trial Phase 1b Results: Safety, Efficacy and Circulating Tumor DNA Response of the Beta Isoform-Sparing PI3K Inhibitor Taselisib (GDC-0032) Combined with Tamoxifen in Hormone Receptor Positive Metastatic Breast Cancer Patients

Richard D. Baird[1], Annelot G.J. van Rossum[2], Mafalda Oliveira[3], Karin Beelen[2,4], Meiling Gao[1], Mariette Schrier[2], Ingrid A.M. Mandjes[2], Javier Garcia-Corbacho[1], Anne-Laure Vallier[1], Greig Dougall[1], Erik van Werkhoven[2], Constanza Linossi[1], Sanjeev Kumar[1], Harm van Tinteren[2], Maurizio Callari[1], Emma Beddowes[1], José-Manuel Perez-Garcia[3,5], Hilde Rosing[2], Else Platte[2], Petra Nederlof[2], Margaret Schot[2], Aurelia de Vries Schultink[2], René Bernards[2], Cristina Saura[3], William Gallagher[6], Javier Cortès[3,5], Carlos Caldas[1], and Sabine C. Linn[2,7]

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Abstract

Purpose: The strategy of combining endocrine therapy with PI3K-mTOR inhibition has shown promise in estrogen receptor (ER)–positive breast cancer, but new agents and combinations with a better therapeutic index are urgently needed. Taselisib is a potent, selective, beta-isoform–sparing PI3 kinase inhibitor.

Patients and Methods: 30 patients with ER-positive, metastatic breast cancer who had failed prior endocrine therapy were treated with escalating doses of taselisib (2 or 4 mg in an intermittent or continuous schedule) combined with tamoxifen 20 mg once daily in this phase 1b study using a "rolling six" design.

Results: Taselisib combined with tamoxifen was generally well tolerated, with treatment-emergent adverse events as expected for this class of drugs, including diarrhea (13 patients, 43%), mucositis (10 patients, 33%), and hyperglycemia (8 patients, 27%). No dose-limiting toxicities were observed. Objective responses were seen in 6 of 25 patients with RECIST-measurable disease (ORR 24%). Median time to disease progression was 3.7 months. Twelve of 30 patients (40%) had disease control for 6 months or more. Circulating tumor (ct)DNA studies using next-generation tagged amplicon sequencing identified early indications of treatment response and mechanistically relevant correlates of clinical drug resistance (e.g., mutations in *KRAS*, *ERBB2*) in some patients.

Conclusions: Taselisib can be safely combined with tamoxifen at the recommended phase 2 dose of 4 mg given once daily on a continuous schedule. Preliminary evidence of antitumor activity was seen in both *PIK3CA* mutant and wild-type cancers. The randomized phase 2 part of POSEIDON (testing tamoxifen plus taselisib or placebo) is currently recruiting.

Introduction

The strategy of combining endocrine therapy with inhibitors of the PI3K/AKT/mTOR pathway has shown promise in estrogen receptor (ER)–positive breast cancer (1, 2), where there is a high prevalence of pathway alterations. However, the modest improvement in treatment efficacy when adding these agents has frequently been offset by significant increased toxicity (3).

Taselisib (GDC-0032) is an oral, potent, isoform-selective inhibitor of PI3K alpha, delta and gamma isoforms, with 30-fold less inhibition of PI3K beta relative to alpha ($K_i = 0.29$ nmol/L; ref. 4). In taselisib early clinical development, anti-tumor activity was observed in patients with ER-positive breast cancer, with proportionately more responses in *PIK3CA*-mutant compared with *PIK3CA* wild-type tumors, consistent with preclinical

[1]Cancer Research UK Cambridge Centre, Cambridge, United Kingdom. [2]Netherlands Cancer Institute, Amsterdam, the Netherlands. [3]Vall d'Hebron University Hospital and Institute of Oncology, Barcelona, Spain. [4]Reinier de Graaf Gasthuis, Delft, the Netherlands. [5]Ramon y Cajal University Hospital, Madrid, Spain. [6]University College Dublin, Dublin, Ireland. [7]University Medical Center Utrecht, Utrecht, the Netherlands.

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

R.D. Baird, A.G.J. van Rossum, M. Oliveira, J. Cortès, C. Caldas, and S.C. Linn contributed equally to this article.

Prior Presentation: The Annual Meeting of the American Society of Clinical Oncology 2016, Abstract #2520.

Corresponding Author: Richard D. Baird, Cancer Research UK Cambridge Center, Addenbrookes Hospital Box 97, Cambridge, CB2 0QQ, United Kingdom. Phone: 44-12-2376-9463; Fax: 44-12-2325-7219; E-mail: rdb39@cam.ac.uk

Clin Cancer Res 2019;25:6598–605

doi: 10.1158/1078-0432.CCR-19-0508

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Translational Relevance

The strategy of combining endocrine therapy with PI3K-mTOR inhibition has shown promise in estrogen receptor (ER)–positive breast cancer, but new agents and combinations with a better therapeutic index are urgently needed. Taselisib is a potent, selective, PI3 kinase inhibitor. In this phase 1b trial, 30 patients with ER-positive, metastatic breast cancer who had failed prior endocrine therapy were treated with escalating doses of taselisib combined with tamoxifen. The combination was generally well tolerated, with adverse events as expected for this class of drugs, including diarrhea, mucositis, and hyperglycemia. No dose-limiting toxicities were observed. Objective responses were seen in 6 of 25 patients with RECIST-measurable disease (ORR 24%). Twelve of 30 patients (40%) had disease control for 6 months or more. Circulating tumor DNA studies using next-generation tagged amplicon sequencing identified early indications of treatment response and mechanistically relevant correlates of clinical drug resistance (e.g., mutations in *KRAS*, *ERBB2*) in some patients.

data (5). This was true both for taselisib as a single agent, and also for taselisib in combination with other anti-estrogens fulvestrant and letrozole (6, 7).

Tamoxifen is well-established endocrine therapy frequently used for the treatment of ER-positive breast cancer, increasingly in patients who have failed prior endocrine therapies, including aromatase inhibitors and/or fulvestrant. To overcome endocrine resistance, CDK4/6 inhibitors have shown to be of added value (8), and are increasingly being used in the first or second-line setting. However, not all patients derive benefit from a combination with CDK4/6 inhibitors. Inhibition of the PI3K pathway in combination with tamoxifen may be beneficial for a significant proportion of ER-positive patients, most likely in the second- or third-line setting.

We undertook a phase 1b trial to establish the safety, tolerability, and recommended phase 2 dose (RP2D) of taselisib in combination with tamoxifen, for patients with hormone receptor (HR)–positive metastatic breast cancer with progression after prior endocrine therapy. Secondary and exploratory objectives included assessment of pharmacokinetics (PK) and (preliminary) antitumor efficacy. Correlative translational studies were performed to identify biomarkers with potential clinical utility, including intensive plasma sampling for circulating tumor (ct)DNA analysis using next generation tagged amplicon sequencing. ctDNA monitoring in early-phase clinical trials may have value in drug development (9) for the assessment of biomarkers which can: Predict response to therapy (10); provide an early indication of treatment response (11); and shed light on potential mechanisms of acquired drug resistance (12).

Patients and Methods

Patients

This phase 1b, multi-center, dose–escalation study was conducted in Amsterdam, Barcelona, and Cambridge, UK. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by regulatory authorities, ethics committees and institutional review boards at each site. All patients had HR-positive breast cancer and provided written informed consent before taking part. Other key inclusion criteria: Measurable or non-measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; age $\geq$18 years; life expectancy $\geq$12 weeks; fasting glucose $\leq$120 mg/dL and HbA1c below the upper limit of normal (ULN). Key exclusion criteria: More than 5 prior chemotherapeutic regimens for metastatic breast cancer; presence of untreated, symptomatic or progressive brain metastases; diabetes mellitus requiring anti-hyperglycemic medication; history of thrombo-embolic or inflammatory bowel disease.

Study design and drug administration

The phase 1b part of the POSEIDON trial reported here used a rolling 6 design to test 3 doses/schedules of taselisib tablets in combination with 20 mg tamoxifen daily (QD). Cohort 1 tested tamoxifen plus 2 mg taselisib QD in a 21 day on/7 day off intermittent schedule; Cohort 2 tested tamoxifen plus 4 mg taselisib QD in a 21 day on/7 day off intermittent schedule; and Cohort 3 tested tamoxifen plus 4 mg taselisib QD in a 28 day continuous schedule. Planned cohort expansions were undertaken in cohorts 2 and 3 to gain additional preliminary data regarding safety, tolerability and efficacy. On cycle 1 day 1, only taselisib was administered for single-agent PK studies. Tamoxifen was administered in combination with taselisib from cycle 1 day 2 onwards.

Safety and dose intensity

Data on Adverse Events (AEs) was collected according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All AEs were collected regardless of causality until 30-days after the last study drug administration. Dose-limiting toxicities (DLT) were those treatment-emergent AEs occurring during cycle 1 (days 1–28) that warranted a dose-reduction or that were $\geq$ grade 3 with exceptions listed in Supplementary Methods. Relative dose intensity of both taselisib and tamoxifen was defined as the actual received dose intensity divided by the intended dose intensity.

Plasma pharmacokinetic and circulating tumor (ct)DNA studies

Details of plasma taselisib (13) and tamoxifen (14) pharmacokinetic assays, and ctDNA assays (11, 12, 15) are provided in Supplementary Methods.

Tumor response

Tumor response to treatment was evaluated clinically and also by CT scan assessments every 8 weeks (2 cycles of treatment), with confirmation of objective responses performed $\geq$4 weeks later. Time to progression (TTP) was calculated from start of treatment until progressive disease. All patients had progressed at the time of analysis and therefore no censoring was necessary.

Results

Baseline patient demographics and disease characteristics

From November 2014 to January 2016, 30 patients were enrolled. The cutoff for data analysis was 2018, 8 February. Median treatment duration was 4 months (range, 1–17). Patients had a median of 2 lines of prior endocrine therapy

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Table 1. Patient baseline characteristics

	Cohort 1 ($N = 6$) 2 mg Taselisib QD 21d, 7d off + 20 mg tamoxifen	Cohort 2 ($N = 13$) 4 mg Taselisib QD 21d, 7d off + 20 mg tamoxifen	Cohort 3 ($N = 11$) 4 mg Taselisib continuous + 20 mg tamoxifen	All patients ($N = 30$)
Age in years, median (range)	51 (41–68)	54 (45–72)	54 (35–81)	53 (35–81)
ECOG performance status				
0	3 (50%)	3 (23%)	5 (45%)	11 (37%)
1	3 (50%)	10 (77%)	6 (55%)	19 (63%)
Histologic subtype				
Ductal	4 (67%)	12 (92%)	8 (73%)	24 (80%)
Lobular	2 (33%)	1 (8%)	2 (18%)	5 (17%)
Unknown	0	0	1 (9%)	1 (3%)
PIK3CA mutational status				
Wild type	5 (83%)	13 (100%)	8 (73%)	26 (87%)
H1047R mutation	1 (17%)	0	2 (18%)	3 (10%)
E545K mutation	0	0	1 (9%)	1 (3%)
Number of prior metastatic therapies, median (range)				
Endocrine	2 (1–2)	2 (1–3)	2 (0–3)	2 (0–3)
Cytotoxic	2 (0–7[a])	1 (0–5)	2 (0–5)	2 (0–7[a])
Prior endocrine therapies for metastatic disease				
Tamoxifen	1 (17%)	4 (31%)	1 (9%)	6 (20%)
Aromatase inhibitor				
- Anastrozole	0	3 (23%)	4 (36%)	7 (23%)
- Letrozole	2 (33%)	6 (46%)	4 (36%)	12 (40%)
- Exemestane	3 (50%)	4 (31%)	2 (18%)	8 (27%)
Fulvestrant	2 (33%)	2 (15%)	2 (18%)	6 (20%)
Megestrol acetate	0	1 (8%)	0	1 (3%)

[a]After data cleaning it was found that 1 patient had received more than 5 prior lines of cytotoxic chemotherapy.

(range, 0–3) and 2 lines of prior cytotoxic chemotherapy (range, 0–7) for metastatic disease. Overall 25 out of 30 patients (83%) had received a prior aromatase inhibitor for the treatment of metastatic disease, and 6/30 (20%) prior fulvestrant (Table 1).

Safety and tolerability

No DLTs were observed. However, shortly after finishing the DLT window, one patient in cohort 1 developed diarrhea grade 3 due to colitis, therefore the cohort was expanded. As predefined, cohorts 2 and 3 were expanded to confirm safety of these dose levels. Following independent data monitoring committee review, the RP2D of taselisib in combination with tamoxifen was set at 4 mg in a continuous schedule.

The most common treatment-emergent AEs of any grade were elevated liver enzymes (13 out of 30 patients, 43%), diarrhea (43%), anemia (40%) and oral mucositis (33%, Table 2). The majority of these AEs first occurred during the DLT window, persisted during study treatment, but reversed after treatment discontinuation. AEs of special interest occurred in 6 patients (20%): 3 patients had diarrhea grade 3 due to colitis, 2 patients had rash grade 3 and 1 patient developed pneumonitis grade 4.

Table 2. Most frequently observed treatment-emergent adverse events[a]

	Cohort 1 ($N = 6$) 2 mg Taselisib QD 21d, 7d off + 20 mg tamoxifen		Cohort 2 ($N = 13$) 4 mg Taselisib QD 21d, 7d off + 20 mg tamoxifen		Cohort 3 ($N = 11$) 4 mg Taselisib continuous + 20 mg tamoxifen		All patients ($N = 30$)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
AST/ALT/GGT increase	1 (17%)	0	5 (38%)	3 (23%)	4 (36%)	0	10 (33%)	3 (10%)
Diarrhea/colitis	2 (33%)	1 (17%)	5 (38%)	1 (8%)	3 (27%)	1 (9%)	10 (33%)	3 (10%)
Anemia	3 (50%)	0	3 (23%)	0	6 (54%)	0	12 (40%)	0
Mucositis, oral	2 (33%)	0	2 (15%)	2 (15%)	4 (36%)	0	8 (27%)	2 (7%)
Nausea	2 (33%)	0	5 (38%)	0	2 (18%)	0	9 (30%)	0
Hyperglycemia	0	0	3 (23%)	0	4 (36%)	1 (9%)	7 (23%)	1 (3%)
Lipase/amylase increase	1 (17%)	0	2 (15%)	2 (15%)	1 (9%)	2 (18%)	4 (13%)	4 (13%)
Fatigue	0	0	3 (23%)	0	4 (36%)	0	7 (23%)	0
Headache	1 (17%)	0	5 (38%)	0	1 (9%)	0	7 (23%)	0
Thrombocytopenia	1 (17%)	0	3 (23%)	1 (8%)	1 (9%)	0	5 (17%)	1 (9%)
Alopecia	0	0	4 (31%)	0	1 (9%)	0	5 (17%)	0
Weight loss	1 (17%)	0	1 (8%)	0	3 (27%)	0	5 (17%)	0
Abdominal pain	1 (17%)	0	1 (8%)	0	2 (18%)	0	4 (13%)	0
Creatinine increase	0	0	3 (23%)	0	1 (9%)	0	4 (13%)	0
Triglyceride increase	0	0	2 (15%)	0	1 (9%)	1 (9%)	3 (10%)	1 (3%)
Pneumonitis	0	0	0	1 (8%)	0	0	0	1 (3%)
Any AE	**4 (67%)**	**1 (17%)**	**5 (38%)**	**8 (62%)**	**6 (54%)**	**5 (45%)**	**15 (50%)**	**14 (47%)**

Abbreviations: AE, adverse event; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyltransaminase; QD, once daily.
[a]Highest grade of AEs occurring at any time point, in at least 10% of patients, and thought to be at least possibly study–drug related.

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After withholding the study drugs, and treatment with high dose corticosteroids, all recovered to ≤ grade 1.

Pharmacokinetics

The concentration–time curves for taselisib in combination with tamoxifen at cycle 1 day 15 are shown in [Supplementary Fig. S1]. Samples from POSEIDON trial are displayed as individual data points against the backdrop of a population PK model from the broader taselisib clinical development program provided by Genentech. At the taselisib 4 mg daily dose level, combining patients on intermittent and continuous schedules, the cycle 1 day 15 median C_{max} for taselisib in combination with tamoxifen was 68.7 ng/mL and median AUC 1070 ng·h/mL, compared with an expected median C_{max} of 59.2 ng/mL (range, 33.6–111) and

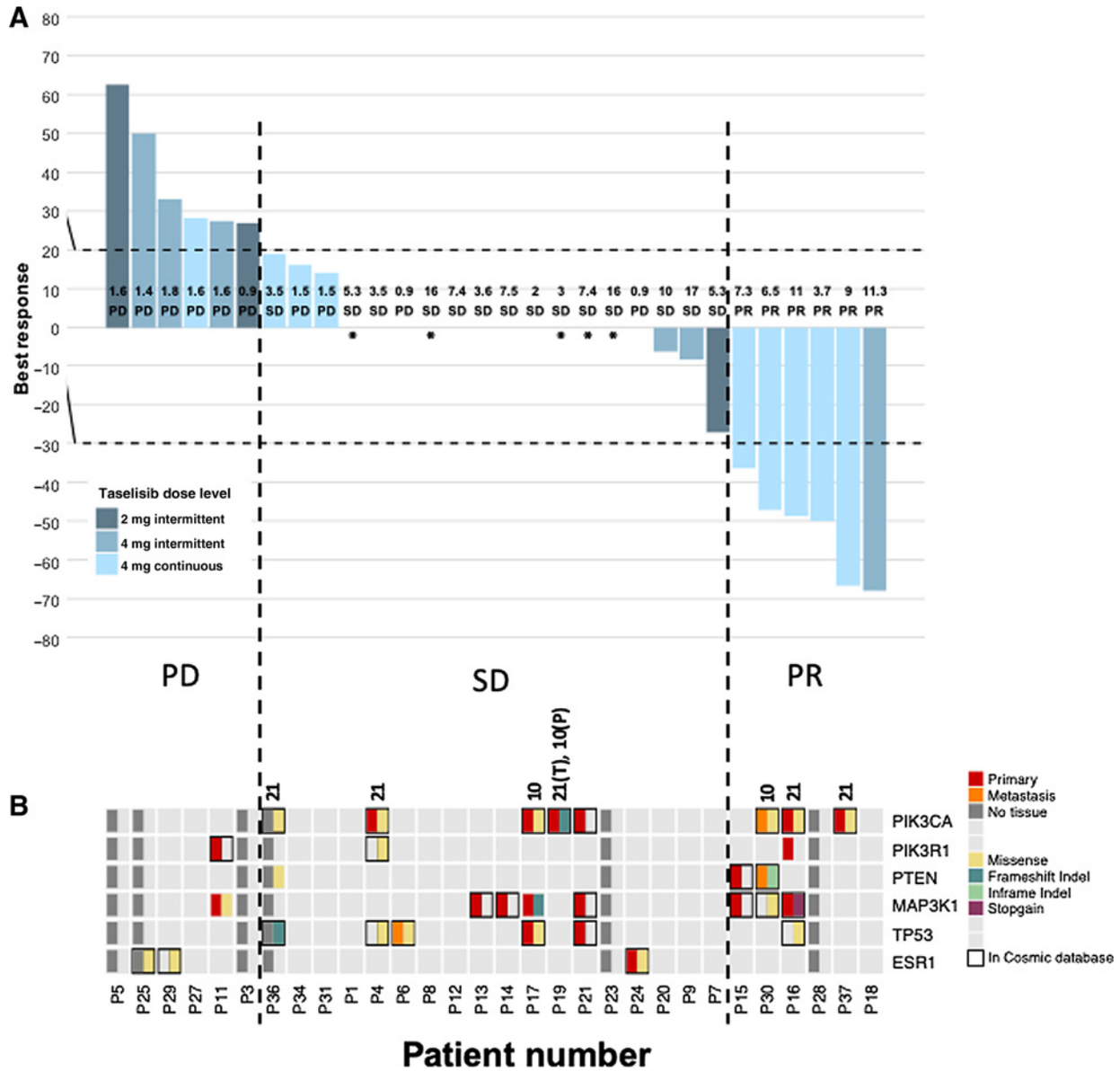

Figure 1.

Antitumor activity and pretreatment tumor genetics (all patients, $N = 30$). **A,** Waterfall plot showing best treatment response for all 30 patients—25 with RECIST-measurable disease and 5 with nonmeasurable disease (the latter marked by an asterisk*). Best RECIST response and time on treatment in months are indicated for each patient. PR, partial response; SD, stable disease; PD, progressive disease. **B,** Oncoprint plot showing pretreatment mutation status of PIK3CA, PIK3R, PTEN, MAP3K1, and TP53 genes. In each square, detection of a mutation in the tissue (primary or metastatic) is shown on the left side, whereas detection on plasma (at baseline) is shown on the right. Cases in which tissue was not available are indicated in dark gray; for all the others, both tissue and plasma were tested. The black outline indicates that the mutation is present in Cosmic database. The white star indicates mutations in tissue and plasma are not in the same position. Numbers on the top indicate the exon of PIK3CA mutations (9 or 20); T, tumor; P, plasma.

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median AUC 1190 ng·h/mL (range, 630–2,273) from the single-agent taselisib population PK model. Endoxifen levels are shown in [Supplementary Fig. S2].

Antitumor activity and *PIK3CA* mutational status

Six patients had a confirmed RECIST partial response, yielding an objective response rate (ORR) of 24% in the RECIST-measurable group ($n = 25$), or 20% in the overall intention-to-treat population ($n = 30$). Best responses according are shown as a waterfall plot in Fig. 1, alongside an oncoprint plot showing key gene mutations in baseline plasma or tumor tissue samples. Median TTP for the whole population was 4 months (interquartile range, 2–8), and 8 months for patients achieving a RECIST partial response. The time-course of responses to treatment are also visualized on a spider plot (Fig. 2) and a swimmers plot [Supplementary Fig. S3]. Twelve out of 30 patients had disease control for 6 months or more, thus a 6-month clinical benefit rate (CBR) of 40%.

PIK3CA mutation testing was done for all patients on baseline tumor tissue and on plasma ctDNA samples. *PIK3CA* mutations were found in 8/30 (27%) of patients (see Oncoprint Fig. 1 and mutation lollipop diagram; Supplementary Fig. S4). In this group of 8 patients with *PIK3CA* mutant tumors, 3 patients had a PR, and the other 5 stable disease as their best response. There was no statistically significant difference for PIK3CA mutant (exon 9, exon 20 or both) versus wild-type subgroups for either ORR (38% vs. 14%) or TTP (153 v. 113 days, respectively).

Circulating tumor (ct)DNA correlative studies

All patients had serial plasma sampling for ctDNA correlative studies. Here, we describe four patients in whom ctDNA results illustrate molecular correlates with treatment response (Fig. 3). ctDNA was not detected in all patients, and our dataset was not powered to detect overall correlations in the whole patient group.

In the first case, the patient had previously received weekly paclitaxel and anastrozole as treatment for her *PIK3CA*-mutant breast cancer metastatic to bone, lung, and subcutaneous tissues, and was treated with tamoxifen plus taselisib in the 4-mg QD continuous schedule. A rapid fall in plasma ctDNA $PIK3CA^{H1047R}$ fraction was observed just 1 week after starting therapy, 7 weeks before her first scheduled CT scan to assess treatment response.

In the second case, the patient had previously received epirubicin, exemestane and capecitabine as treatment for her *PIK3CA* mutant breast cancer metastatic to liver and bone and was treated with tamoxifen plus taselisib in the 4 mg QD continuous schedule. She did not respond to treatment and an increase in plasma ctDNA $PIK3CA^{H1047R}$ fraction was seen on cycle 1 day 15, six weeks before her end of cycle 2 restaging CT scan.

In the third case, the patient had previously received paclitaxel, anastrozole, everolimus–exemestane, capecitabine, vinorelbine–docetaxel and letrozole to treat her *PIK3CA* wild-type breast cancer metastatic to liver and bones and was treated in the tamoxifen plus taselisib 4-mg QD 21/7 intermittent cohort. She did not respond to treatment and increases in plasma ctDNA levels were found for *GATA3* and *KRAS* mutations two weeks ahead of cycle 2 CT scan.

In the fourth case, the patient had previously received paclitaxel, letrozole, docetaxel, capecitabine, exemestane, and eribulin to treat her *PIK3CA* wild-type breast cancer metastatic to liver and bones and was treated in the tamoxifen plus taselisib 4 mg QD continuous cohort. She did not respond to treatment and increases in plasma ctDNA levels were found for *ERBB2* and *CDH1* mutations 34 and 27 days, respectively, before she came off trial with disease progression.

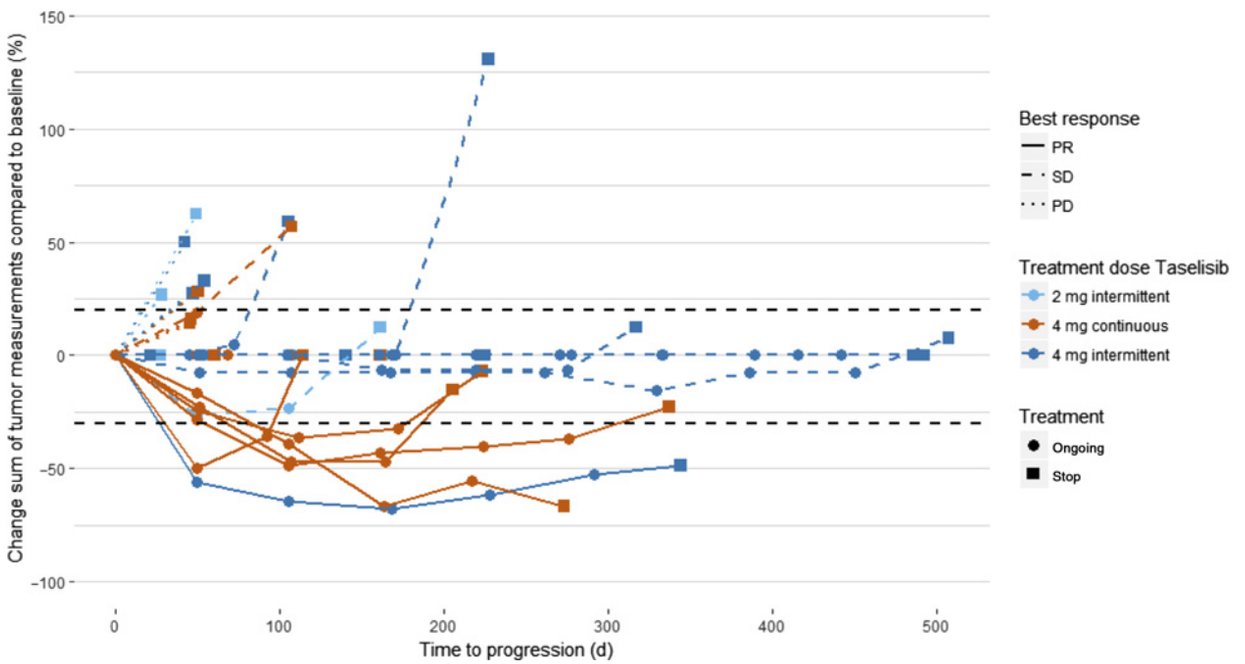

Figure 2.
Spider plot showing change in tumor size over time for individual patients with RECIST-measurable disease ($N = 25$).

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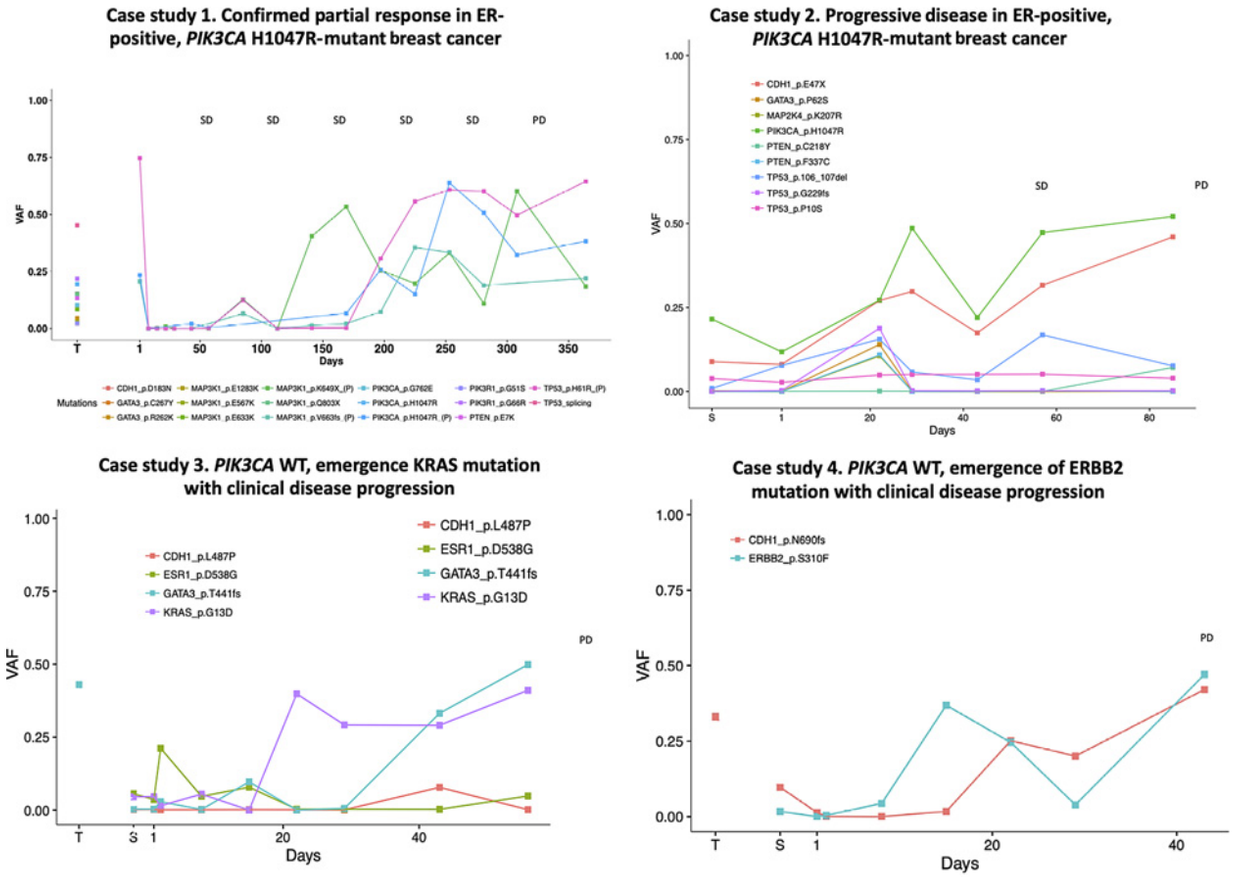

CDH1 – cadherin 1; CT – computed tomography; ERBB2 – Erb-B2 Receptor Tyrosine Kinase 2; GATA3 – GATA Binding Protein 3; KRAS – Kirsten ras oncogene homolog; PIK3CA – Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; VAF – variant allele fraction; WT – wild type.
S = screening. T = pre-treatment tumour sample.

Figure 3.
Circulating tumor (ct)DNA correlative case studies. In four individual patients, each having different clinical outcomes, the variant allele fraction is shown over time for gene mutations in plasma while on study treatment.

Discussion

Taselisib in combination with tamoxifen is generally well tolerated, with a side effect profile that was manageable, and consistent with taselisib given as a single agent and in combination with other endocrine agents. In keeping with other PI3K inhibitors, the commonest side effects were diarrhea, anemia, nausea, mucositis, and hyperglycemia. Three out of 30 patients had grade 3 colitis, one patient was found to have grade 4 pneumonitis, all of which were reversible. The RP2D of taselisib in combination with tamoxifen was determined to be 4 mg on a daily continuous schedule.

Tamoxifen is a pro-drug that is converted to its active metabolites by cytochrome (CYP) P450 enzymes, including CYP2D6, CYP3A4, CYP2B6, and CYP2C19. Taselisib is a weak inhibitor of CYP3A4 and does not inhibit any other CYPs *in vitro*, and did not alter the PK of midazolam, a CYP3A4 substrate, in the first-in-man study of taselisib (PMT4979g). Therefore, no change in taselisib PK was expected when given in combination with tamoxifen. Indeed, the observed taselisib concentrations at day 15 of cycle 1 were in the same range as those of a previously treated single-agent taselisib cohort. Also, cycle 2 day 1 Z-endoxifen levels were on average above the laboratory threshold of 5.9 ng/mL (16) in all dose levels.

Preliminary evidence of antitumor activity was observed, with confirmed partial responses seen in 6 of 25 patients with RECIST-measurable disease (ORR 24%). Responses were seen in patients with *PIK3CA*^{H1047R} mutant, *PIK3CA*^{E545K} mutant and *PIK3CA*^{WT} tumors.

A strong rationale exists to explore the combination of PI3K inhibitors with endocrine therapy for the treatment of ER+ breast cancer. The combination of tamoxifen with everolimus improved the median time to progression from 4.5 to 8.6 months in the TAMRAD trial (1), and it is an important research question to test whether or not isoform-selective PI3K inhibitors have therapeutic advantages over TORC inhibitors in this setting. In addition to the POSEIDON trial combination with tamoxifen, taselisib is given in clinical trials together with fulvestrant (NCT02340221; ref. 17) and letrozole (NCT02273973; ref. 7). Although *PIK3CA* mutations have been implicated in primary endocrine resistance and their prevalence is relatively high (20%–25% in ductal breast cancer and 40% in lobular breast cancer), results are conflicting (18, 19) and the

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outcome might depend on the specific mutation that is studied (20).

In the SANDPIPER randomized phase 3 trial (NCT02340221; ref. 17), patients with or without a *PIK3CA* mutation were randomized between taselisib plus fulvestrant and placebo plus fulvestrant. Taselisib dose and schedule were the same as recommended for phase 2 of the POSEIDON study (i.e., taselisib 4 mg daily continuous). Median PFS with taselisib plus fulvestrant in patients with a *PIK3CA* mutation was significantly longer (7.4 months) than with placebo plus fulvestrant (5.4 months; HR, 0.70). No significant PFS difference was observed in patients who had a *PIK3CA* wildtype tumor (median PFS 5.6 months vs. 4.0 months). However, information about a test for interaction is lacking. Adverse events grade 3 or higher were observed in almost half of the patients. The toxicity profile seen in POSEIDON is consistent to that reported in previous trials testing taselisib plus endocrine therapy in the metastatic setting. In addition, in the SOLAR-1 randomized phase 3 trial (NCT02437318; ref. 21) patients with HR-positive, HER2-negative advanced breast cancer were randomized to receive fulvestrant plus the alpha-isoform–selective PI3K inhibitor alpelisib, or placebo. The addition of alpelisib to fulvestrant improved PFS in patients with PIK3CA mutations but not PIK3CA wild-type patients (median PFS 20 vs. 11 months).

Despite these encouraging results, *PIK3CA* mutational status may not on its own be sufficient to optimally identify which patients with ER-positive breast cancer will benefit most from the addition of a PI3K inhibitor to endocrine therapy. Individual patients with *PIK3CA* wild-type tumors can respond, and some patients with *PIK3CA* mutant tumors do not. Further studies are required to identify the optimal biomarker profile for PI3K combination therapy, and how best to use the results of real-time plasma ctDNA monitoring for the management of individual patients. These questions are being addressed in the randomized phase 2 part of POSEIDON which is ongoing.

To conclude, the RP2D of taselisib in combination with tamoxifen 20 mg daily is 4 mg QD in a continuous schedule. Phase 2 of POSEIDON (NCT02301988) is currently recruiting and randomizes patients ($N = 280$ in total) to receive tamoxifen 20 mg daily with either taselisib 4 mg or placebo once daily; including a specific focus on patients with lobular breast cancer ($N = 110$); and a major translational effort to identify predictive biomarkers to help select which patients are most likely to benefit from the addition of a PI3K inhibitor to their endocrine therapy.

Disclosure of Potential Conflicts of Interest

R.D. Baird reports receiving speakers bureau honoraria from Novartis and Roche/Genentech; commercial research grants from Genentech, AstraZeneca, and Boehringer-Ingelheim; and commercial research support from AstraZeneca. M. Oliveira reports receiving speakers bureau honoraria from Roche, and is a consultant/advisory board member for Roche, GlaxoSmithKline, and PUMA Biotechnology. C. Saura is a consultant/advisory board member for AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Roche, Genomic Health, Novartis, Pierre Fabre, Piqur Therapeutics, Puma, and Synthon. W. Gallagher is an employee of and has ownership interests (including patents) at OncoMark Limited, and is a consultant/advisory board member for Carrick Therapeutics. J. Cortès is an employee of and has ownership interests (including patents) at MedSIR; is a consultant/advisory board member for Roche, Celgene, Cellestia, AstraZeneca, Biothera, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Servier, and Merck Sharp & Dohme; and reports receiving honoraria for lectures. C. Caldas reports receiving speakers bureau honoraria from Illumina, is a consultant/advisory board member for AstraZeneca, and reports receiving commercial research grants from AstraZeneca, Servier, Genentech, and Roche. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: R.D. Baird, M. Oliveira, K. Beelen, H. van Tinteren, R. Bernards, J. Cortès, C. Caldas, S.C. Linn

Development of methodology: R.D. Baird, A.G.J. van Rossum, M. Oliveira, K. Beelen, M. Gao, H. van Tinteren, M. Callari, H. Rosing, J. Cortès, C. Caldas

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.D. Baird, A.G.J. van Rossum, M. Oliveira, M. Gao, M. Schrier, I.A.M. Mandjes, J. Garcia-Corbacho, C. Linossi, S. Kumar, E. Beddowes, J.-M. Perez-Garcia, H. Rosing, P. Nederlof, M. Schot, C. Saura, J. Cortès, C. Caldas, S.C. Linn

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.D. Baird, A.G.J. van Rossum, M. Oliveira, M. Gao, E. van Werkhoven, H. van Tinteren, M. Callari, E. Beddowes, J.-M. Perez-Garcia, J. Cortès, C. Caldas, S.C. Linn

Writing, review, and/or revision of the manuscript: R.D. Baird, A.G.J. van Rossum, M. Oliveira, K. Beelen, M. Schrier, I.A.M. Mandjes, J. Garcia-Corbacho, E. van Werkhoven, S. Kumar, H. van Tinteren, M. Callari, J.-M. Perez-Garcia, H. Rosing, P. Nederlof, A. de Vries Schultink, C. Saura, W. Gallagher, J. Cortès, C. Caldas, S.C. Linn

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.D. Baird, A.G.J. van Rossum, M. Gao, M. Schrier, I.A.M. Mandjes, A.-L. Vallier, G. Dougall, H. van Tinteren, E. Platte, P. Nederlof, W. Gallagher, C. Caldas

Study supervision: R.D. Baird, A.G.J. van Rossum, M. Oliveira, M. Schrier, I.A.M. Mandjes, G. Dougall, R. Bernards, C. Saura, J. Cortès, C. Caldas, S.C. Linn

Other (patient identification, consent, and caring for the patients during the study): J. Garcia-Corbacho

Other (care for patients): M. Schot

Acknowledgments

POSEIDON is a European investigator-initiated trial, funded by the EU FP7 RATHER consortium (project ID: 258967) and EurocanPlatform (project ID: 260791), with additional support from an unrestricted research grant from Genentech, and led by the Netherlands Cancer Institute (Amsterdam, the Netherlands), Cambridge Cancer Center (Cambridge, UK), and Vall d'Hebron Institute of Oncology (Barcelona, Spain). The investigators would like to thank the patients who took part in the study, and their families. Support is also acknowledged from the NKI Data Center, the NKI Core Facility Molecular Pathology and Biobanking (CFMPB), Cancer Research UK Cambridge Cancer Centre, and the Cambridge: Experimental Cancer Medicine Center (ECMC); Cancer Molecular Diagnostics Laboratory (CMDL); NIHR Biomedical Research Center (BRC); and Cambridge Clinical Research Center (CCRC).

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Received February 21, 2019; revised June 1, 2019; accepted August 2, 2019; published first August 22, 2019.

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