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PHASE I STUDIES

A phase Ib study of sonidegib (LDE225), an oral small molecule inhibitor of smoothened or Hedgehog pathway, in combination with docetaxel in triple negative advanced breast cancer patients: GEICAM/2012–12 (EDALINE) study

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Summary

Up-regulation of the Hedgehog (Hh) pathway is implicated in the genesis of a wide range of tumors including triple negative breast cancer (TNBC). Sonidegib is a potent and selective oral inhibitor of Smo, a key component of the Hh signaling pathway. We designed a phase I clinical study to explore the combination of sonidegib plus docetaxel (fixed dose at 75 mg/m^2) in advanced TNBC patients. The primary objective was to ascertain the combination's maximum tolerated dose and the recommended phase II dose (RP2D), based on dose limiting toxicities (DLTs) in the first 2 cycles. A standard "3 + 3" design was followed including three dose levels (DL) of sonidegib: 400 mg (DL1), 600 mg (DL2), and 800 mg (DL3). Twelve patients were included. Sonidegib 800 mg orally q.d. plus docetaxel 75 mg/m^2 given intravenously on day 1 of 21-day cycles was established as the RP2D. No DLTs were observed at any DL. The median number of administered cycles at DL3 was 8 (range: 6 to 9). Grade 3 adverse events (AEs) at DL3 were neutropenia (66.7%), CPK increase (33.3%), leukopenia (33.3%), and paresthesia (33.3%), grade 4 AEs were not reported at this DL. At the RP2D, the combination showed antitumor activity in three out of 10 patients with measurable disease. Median time to progression for the overall study was 42.5 days (95% Confidence Interval: 29–155), and 188 days at DL3. No drug-to-drug interactions between sonidegib and docetaxel were found in the PK assessment. Trial Registration: EudraCT study number: 2013–001750-96. Study GEICAM/2012–12. TRIAL REGISTRATION: EudraCT study number: 2013-001750-96. Study GEICAM/2012-12. ClinicalTrials.gov: NCT02027376

Keywords Triple negative · hormone receptor and HER2 negative · advanced breast cancer · sonidegib · Hedgehog · docetaxel

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Introduction

Outstanding breakthroughs in advanced breast cancer (ABC) control have been achieved by specific targeted drugs causing a therapeutic blockage of certain biologic events selectively critical for cancer cells survival. These novel targeted therapies base their efficacy in the parallel characterization and selection of tumors particularly sensitive to each therapy. The discovery of a particular oncogenic driver (i.e., HER2 or estrogen receptor (ER)) opens the possibility of using specific blockers that achieve prolonged disease control. Currently, the main challenge in breast cancer control resides in triple negative breast cancer (TNBC) [1] which is clinically defined by the lack of expression of the ER, progesterone receptor (PgR), and HER2 by immunohistochemistry and/or in situ hybridization (IHC/ISH). TNBC is a highly heterogeneous disease [2] with no effective targeted therapies available to date, except for PARP inhibitors for patients with germline BRCA mutations. Patients with recurrent TNBC present an ominous situation with a very poor prognosis given TNBC's aggressive nature and the lack of effective therapeutic options. Chemotherapy is the standard treatment for TNBC patients. Whereas it can produce short-lived responses, acquired resistance appears soon and the overall survival is poor, usually about one year. Given the clinical context, discovering novel therapeutic strategies is an unmet and urgent need. Any new effective therapy for TNBC should be accompanied by ancillary biomarkers to identify those patients who will benefit from the treatment.

Conventional taxanes play a central role in the treatment of metastatic breast cancer, based on the evidence of their benefit on clinical outcomes [3]. Docetaxel has been intensively investigated for the treatment of metastatic breast cancer, where it has proved to be one of the most active agents. As a single agent docetaxel is very active in the treatment of breast cancer patients with basal-like subtype. As a chemotherapy agent with an antimitotic mechanism of action [4], docetaxel has been used in breast cancer therapy in two dosing schedules, each with their own toxicity profiles. The approved outpatient regimen, the most common in clinical practice, is 60 to 100 mg/m^2, administered intravenously for 1 h every 3 weeks.

The Hedgehog (Hh) signaling pathway [5] has been shown to be activated in a subset of breast cancers [6–8], with increasing data emphasizing its contribution to TNBC pathophysiology growth. This pathway plays an important role in embryonic development and regulates stem cell renewal and tissue homeostasis. It is a highly conserved developmental signaling system essential for epithelial to mesenchymal signaling in development. The Hh ligands, Sonic (Shh), Indian (Ihh) and Desert (Dhh), bind to and inactivate the transmembrane receptor Patched (Ptch). Ptch is a constitutive inhibitor of Smothened (Smo), a transmembrane protein required for all Hh signaling. An inactive Smo allows for the formation of a multiprotein complex that constitutively processes the Gli proteins to short, transcriptionally repressive forms. Activation of Smo decouples this complex from microtubule domains and leads to stabilization of full length, trans-activating Gli proteins that initiate transcription of Hh target genes, including Gli1.

Deregulation of Hh signaling has been associated to the pathogenesis of cancer through, in part, the promotion of epithelial–stromal interactions. Such deregulation has been identified as a relevant event driving tumorigenesis in breast cancer stem cells (BCSC). It has been hypothesized that tumor growth and heterogeneity are driven by subpopulations BCSCs. Enrichment for BCSC phenotype and genetic signature in TNBC has been associated with higher incidence of recurrence and metastases [9].

Sonidegib (LDE225) (Odomzo® Capsules, Novartis Pharmaceuticals Corp., USA) is a selective, potent, and orally available Smo antagonist [10]. Its *in vivo* efficacy was defined in medulloblastoma models, where sonidegib caused tumor regression, and its activity was correlated with Hh signaling activation measured by *GLI1* mRNA [11]. In vivo PK/PD models showed a good correlation among the given dose, the measured blood and tissue levels, the effects on the Hh pathway as determined by *GLI1* mRNA expression, and the anti-tumor activity. Sonidegib was approved by the Food and Drug Administration (FDA) [12] in July 2015 at a dose of 200 mg p.o. daily for the treatment of adult patients with metastatic or locally advanced basal cell carcinoma (BCC).

The emerging role of the Hh signaling pathway in the preservation and progression of different human cancers underscores the relevance of its inhibition, in combination with standard therapies as a promising anticancer therapeutic approach. In fact, preclinical data on ovarian cancer showed that combining sonidegib with taxanes reduces tumor burden in xenografts models [13].

Based on these data GEICAM, the Spanish Breast Cancer Group, designed a phase Ib trial to evaluate the safety and potential clinical activity of the sonidegib and docetaxel combination. Specifically, our primary objective was to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of the combination based on dose limiting toxicities (DLTs) in the first 2 cycles. Here we report the safety, efficacy, and pharmacokinetics (PK) data from this study.

Material and methods

Eligibility

Female patients with histologically confirmed (by local laboratory) advanced TNBC were eligible to participate in the study if they met the following criteria: age ≥ 18 years; World Health Organization (WHO) performance status ≤1; life expectancy ≥12 weeks; TNBC defined as <1% positive

cells by IHC [14] for both estrogen receptor (ER) and progesterone receptor (PgR) and HER2 negative [15] defined as IHC 0 or 1+ or ISH negative by local laboratory. Participants should also have: no more than three previous chemotherapy regimens for advanced disease; no measurable or non-measurable disease according to Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 [16], adequate bone marrow, liver, and renal functions, normal plasma creatine phosphokinase (CPK), normal cardiac function and no concomitant medical condition that may increase the risk of toxicity. Patients with brain metastases were allowed if already treated and clinically stable without medication. Due to the administration of sonidegib, patients with impair gastrointestinal (GI) function or on any medication known to be a potent inhibitor or inducer of CYP3A4/5 or a substrate of CYP2B6 or CYP2C9 were excluded. Written informed consent from all participants was obtained and documented before performing any protocol-specific procedure. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws. The protocol was approved by the Institutional Review Board and the Ethics Committee of the participating sites, according to the requirements of the Spanish regulations. The trial was an investigator-initiated study sponsored and coordinated by GEICAM (study code GEICAM/2012–12; clinicaltrials.gov identifier: NCT02027376).

Study design and treatment

This is a single-arm, open-label, phase Ib study, with dose escalations performed in cohorts of three patients according to a standard 3 + 3 algorithm. Patients were treated with oral sonidegib on a daily basis and docetaxel on Day 1 of 21-day cycles. to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of the combination. The MTD was defined as the highest dose tested in which a dose limiting toxicity (DLT) was experienced by 0 out of 3 or 1 out of 6 patients among the dose levels. Once the MTD was reached the RP2D was established. Three dose levels were explored, from level 1 to 3, with increasing doses of sonidegib at 400, 600, or 800 mg, and docetaxel at 75 mg/m^2, respectively. A dose level with sonidegib 400 mg and docetaxel 60 mg/m^2 was included in the study protocol just in case level 1 was not tolerable. All patients at each dose level were required to complete at least the first two cycles of therapy before the enrolment in the next dose level was started. Patients who did not complete those two cycles for a reason other than toxicity were replaced. Intra-patient escalation was not allowed. DLT was defined as the occurrence of any adverse events (AE) or abnormal laboratory values, related to study drugs, occurring within the first two cycles of treatment. AEs considered as DLTs included neutropenia of grade 4 lasting more than one week, febrile neutropenia, thrombocytopenia of grade 3/4 or with bleeding more than grade 2, and any non-hematologic toxicity of grade 3/4, except nausea and vomiting of grade 3, GI toxicity (except nausea and vomiting) of grade 2 lasting more than 2 weeks, and inability to resume dosing for cycles 2 or 3 at the current dose level within 14 days due to treatment-related toxicity.

The secondary objectives included the combination's effects on corrected QT interval (QTc) and their correlation with systemic drug exposure, safety and tolerability; efficacy in terms of time-to-progression (TTP) and objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and the pharmacokinetics (PK) of the combination.

Treatment was repeated until radiographic or symptomatic disease progression, unacceptable toxicity or withdrawal of the informed consent. Patients with permanent discontinuation of any of the study drugs were discontinued from the study.

Safety and efficacy assessments

Safety was assessed by standard clinical (including physical examination, vital signs, and triplicate 12-lead electrocardiograms [ECGs]) and laboratory tests (hematology and serum chemistry). AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [17]. We performed efficacy assessments at baseline and every 9 weeks (three cycles), using the same method of measurement than at baseline, according to the RECIST version 1.1.

PK assessments

PK sampling of sonidegib was performed pre-dose on Day 1 of each cycle until Cycle 5 for trough concentrations measurements. PK sampling of docetaxel was performed on Day 1 of Cycle 1 and 2 and docetaxel plasma concentrations were determined at 0 and 30 min after the start of the infusion, at 5–10 min before the end of the infusion, and at 0.5, 1.5, 4, 8, and 24 h post-infusion. Docetaxel plasma concentrations were determined by validated high-performance liquid chromatography with ultraviolet-light detection (HPLC-UV). Trough sonidegib concentrations were determined according to an analytical method previously validated at SGS Cephac Europe for the determination of sonidegib in human plasma under SGS Cephac Europe Study Reference No. CP125349 /Novartis Pharma AG Report No. DMPK R1300055 [18].

To evaluate the effect of sonidegib on the docetaxel PK, main docetaxel PK parameters were estimated on two different days, on Day 1 of Cycles 1 and 2, and compared. PK parameters were estimated by non-compartmental approach using Phoenix® WinNonlin® software (version 7.0). To

evaluate the effect of docetaxel on the sonidegib PK and given that patients were always on both drugs simultaneously in all PK profile assessments, this study's trough sonidegib concentrations were compared with those simulated from a previous developed PK model from sonidegib given as monotherapy. Therefore, a population PK model of sonidegib reported in the literature [19] and developed in healthy subjects and patients with advanced solid tumors was implemented in NONMEN version 7.3 program and we performed Monte-Carlo simulations of sonidegib concentrations after administration of the same doses than those used in our study.

Statistical considerations

We used standard descriptive statistics, such as the mean, median, range and proportion, to summarize the patient sample characteristics. Parameters of interest and corresponding 95% Confidence Intervals (CI) were estimated. The ORR and 95% CI were reported. We used Kaplan-Meier techniques to assess the TTP. A Kaplan-Meier curve was generated and quartiles and appropriate point probabilities were calculated. Safety analyses included summaries of adverse events incidence by maximum NCI-CTCAE grade version 4.0 occurring during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality and according to the relationship to study drug as assessed by the investigator.

Results

Patient characteristics

Twelve patients were included in five Spanish sites between May 2014 and Jun 2015. Patients' characteristics are described by dose level in Table 1. Median age was 49.5 years (range, 26–76) and 58.3% ($n = 7$) were postmenopausal. All tumors were diagnosed as invasive ductal breast carcinomas, most of them were of high grade ($n = 9$) and the median Ki-67 index was 65% (range, 20–90). Regarding previous anticancer therapy, eleven (91.7%) patients were previously treated with neoadjuvant and/or adjuvant therapy. Eight (66.7%) patients did not receive any previous therapy for advanced disease, including the three patients enrolled at dose level (DL) 3. All patients were previously treated with taxanes as part of their prior therapy for early stage and/or advanced disease.

Dose escalation and determination of RP2D

Five patients were treated at DL1 (400 mg), four at DL2 (600 mg) and three at DL3 (800 mg). Two patients at DL1 and one at DL2 were replaced as they did not complete the first two cycles because of progressive disease (Fig. 1).

The median number of cycles was 2 for DL1 and DL2 (range, from 2 to 4 and from 1 to 3, respectively) and 8 for DL3 (range, from 6 to 9) (Table 2). The median relative dose intensity (RDI) of sonidegib and docetaxel was similar between dose levels; the RDI for sonidegib was of 100% at DL1 and DL2 and of 99.5% at DL3, and for docetaxel was of 100.3% at DL1, 99.8% at DL2 and 99.9% at DL3. One patient at DL2 took 800 mg of sonidegib on one day instead of 600 mg by mistake (on Cycle 3); this patient did not suffer any adverse event (AE) in relation to the overdose. The reason for treatment discontinuation for eleven patients was progressive disease. A twelfth patient discontinued treatment due to investigator's judgment as this patient experienced persistent grade 2 fatigue and grade 2 arthralgias due to cumulative toxicity associated with docetaxel. As per protocol indications, the administration of any of the study drugs as a single agent was not allowed.

No DLTs were reported at any of the DLs evaluated within the first two cycles of treatment. No additional DLs with sonidegib dose above 800 mg daily were explored, as per the study protocol, based on the efficacy and safety data reported on previous clinical studies that evaluated sonidegib doses equal or higher than 800 mg per day. DL 3 (sonidegib 800 mg daily plus docetaxel 75 mg/m^2 on Day 1, on 21-day cycles) was established as the RP2D.

Safety

The most common AEs reported related to the study treatment (Table 3) at DL1 ($n = 5$) were anemia of grade 1 (80%), nausea and vomiting of grade 1 (60% for each AE), AST increaseof grade 2, and ALT increase, alkaline phosphatase increase, arthralgia, myalgia, and fatigue, all of grade 1 (40% for each AE); two AEs of neutropenia were reported, one of grade 1 and the other of grade 3 (20% for each AE). The most common related AEs per patient at DL2 ($n = 4$) were white blood cell (WBC) count decreaseand fatigue, both of grade 1 (50% for each AE). Again, two AEs of neutropenia were observed at this DL, one of grade 1 and the other one of grade 4 (25% for each AE). Finally, the most common related AEs at DL3 ($n = 3$) were neutropenia of grade 3 (66.7%), nausea of grade 2 (66.7%), and oral mucositis, fatigue, maculopapular rash, arthralgia, and myalgia of grade 1 (66.7% for each AE). Other relevant AEs included paresthesia, creatine phosphokinase (CPK) increase and WBC count decreaseof grade 3 (33.3% for each AE).

At DL2 there was only a report of one AE grade 4 at Cycle 1, an uncomplicated neutropenia lasting under seven days. One patient at DL3 experienced a grade 3 increase of CPK on Cycle 3 lasting eight days, not associated with renal function impairment. This event was not considered a DLT. There were no dose reductions in Cycles 1 and 2.

Table 1 Baseline characteristics

	Dose Level 1 $n = 5$	Dose Level 2 $n = 4$	Dose Level 3 $n = 3$	Total $n = 12$
Age, years (range)				
Median	48.0 (26–64)	45.0 (35–76)	54.0 (51–57)	49.5 (26–76)
Race, n (%)				
Caucasian	5 (100.0%)	4 (100.0%)	3 (100.0%)	12 (100.0%)
Menopausal status, n (%)				
Postmenopausal	3 (60.0%)	1 (25.0%)	3 (100.0%)	7 (58.3%)
Premenopausal	2 (40.0%)	3 (75.0%)	–	5 (41.7%)
WHO performance status, n (%)				
0	2 (40.0%)	2 (50.0%)	3 (100.0%)	7 (58.3%)
1	3 (60.0%)	2 (50.0%)	–	5 (41.7%)
Histological tumor type, n (%)				
Invasive ductal carcinoma	5 (100.0%)	4 (100.0%)	3 (100.0%)	12 (100.0%)
Histological tumor grade, n (%)				
Grade 3, poorly differentiated	4 (80.0%)	4 (100.0%)	1 (33.3%)	9 (75.0%)
Grade 2, moderately differentiated	1 (20.0%)	–	1 (33.3%)	2 (16.7%)
Grade X, unknown	–	–	1 (33.3%)	1 (8.3%)
Ki-67 Index (cut-off 20%), n (%)				
≥ 20%	4 (80.0%)	4 (100.0%)	3 (100.0%)	11 (91.7%)
Unknown	1 (20.0%)	–	–	1 (8.3%)
Number of metastatic locations, n (%)				
1	–	3 (75.0%)	2 (66.7%)	5 (42.0%)
2	2 (40.0%)	1 (25.0%)	1 (33.3%)	4 (33.0%)
≥ 3	3 (60.0%)	–	–	3 (25.0%)
Metastatic locations, n (%)				
Visceral	2 (40.0%)	–	3 (100.0%)	5 (42.0%)
Non-visceral	3 (60.0%)	4 (100.0%)	–	7 (58.0%)
Prior therapeutic lines for advanced breast cancer, n (%)				
1st line	1 (20.0%)	1 (25.0%)	–	2 (16.7%)
2nd line	–	1 (25.0%)	–	1 (8.3%)
3rd line	1 (20.0%)	–	–	1 (8.3%)
No previous therapy	3 (60.0%)	2 (50.0%)	3 (100.0%)	8 (66.7%)
Previous chemotherapy, n (%)				
Anthracyclines	4 (80.0%)	4 (100.0%)	2 (66.7%)	10 (83.3%)
Taxanes*	5 (100.0%)	4 (100.0%)	3 (100.0%)	12 (100.0%)
Neoadjuvant				7 (58.0%)
Adjuvant				4 (33.0%)
1st line				2 (16.7%)
Platinum agents	4 (80.0%)	1 (25.0%)	1 (33.33%)	6 (50.0%)
Capecitabine	3 (60.0%)	–	–	3 (25.0%)
Gemcitabine	3 (60.0%)	–	–	3 (25.0%)
Bevacizumab	1 (20.0%)	1 (25.0%)	–	2 (16.67%)
Cyclophosphamide	4 (80.0%)	3 (75.0%)	2 (66.67%)	9 (75.00%)
5-Fluorouracil	4 (80.0%)	1 (25.0%)	–	5 (41.67%)
Vinorelbine	1 (20.0%)	–	–	1 (8.33%)

*Eleven patients received taxanes as part of their neoadjuvant and/or adjuvant therapy; six patients received docetaxel as part of the therapeutic regimen for early stage disease; n: number of patients

The most relevant dose modifications observed were one sonidegib dose omission by a patient on DL1 due to neutropenia of grade 3 during Cycle 4, and two sonidegib dose reductions due to neutropenia and CPK increased,

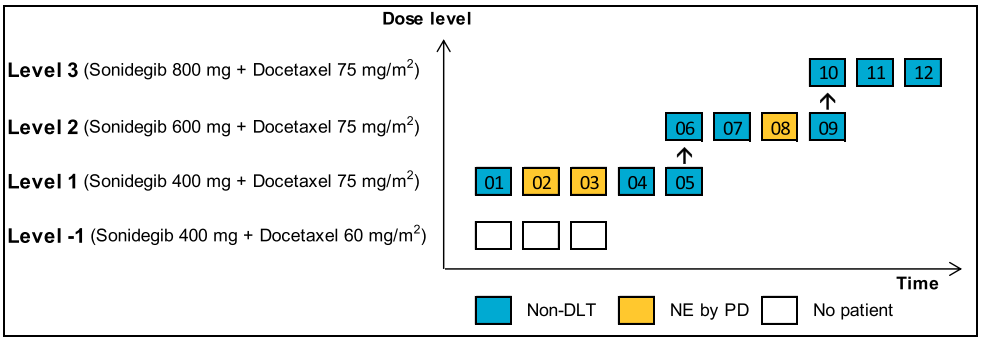

Fig. 1 Patients inclusion per dose level and their DLTs

DLT: dose limiting toxicity; NE: non-evaluable; PD: progressive disease; mg: milligram; m^2: square meter.

both of grade 3, on patients on DL3 during Cycles 3 and 4, respectively. Docetaxel was also delayed due to this AE of CPK increase of grade 3. Finally, patients on DL3 omitted sonidegibdue to CPK increase of grade 3 at Cycle 3, neutropenia of grade 3 at Cycle 2, and vomiting of grade 2 at Cycle 1.

According to our secondary objective, we evaluated the potential effects of sonidegib in combination with docetaxel on QTc intervals The comparison of the median QTc interval values measured in milliseconds (msec) by Fridericia's formula at baseline and at several time points on Cycle 3 (pre-dose and at 1, 2, 4, and 6 h post-dose), did not show statistically significant differences (Fig. 2).

At DL1 one AE of ECG QTc interval prolonged of grade 1 was reported at Cycle 3. This patient had a previous medical history of this alteration of grade 1 at baseline. A similar AE was reported at Cycle 3 for one patient enrolled at DL2. According to NCI-CTCAE classification, grade 1 severity corresponds to a QTc value between 450 and 480 msec. These patients did not meet the corresponding exclusion criteria (QTcF >470 msec on the screening ECG).

Efficacy

Ten of the twelve participating patients had measurable disease according to RECIST version 1.1. The ORR on these patients was 10% (95%CI 0.3–44.5). One patient at DL3 showed a complete response (CR) at Cycle 8, but was discontinued from the study treatment due to investigator's judgment based on cumulative toxicity related to docetaxel. This patient had received neoadjuvant chemotherapy (NAC) with doxorubicin plus cyclophosphamide followed by docetaxel. She experienced a disease-free survival (DFS) of 10.9 months from the end of NAC until disease recurrence with lung metastases.

In addition, stable disease was reported as the best tumor response on three patients, two enrolled at DL3 (with duration of 107 and 126 days, respectively) and the other one at DL1 (with duration of 32 days). The patient at DL3 with a duration of stable disease of 107 days had been previously treated with adjuvant chemotherapy (epirubicin plus cyclophosphamide followed by docetaxel). DFS from the end of adjuvant therapy until disease recurrence with liver and lung metastases was 36 months. The other patient with stable disease enrolled at DL3 had received NAC with carboplatin and docetaxel. DFS for this patient was 25 months from the end of NAC until disease recurrence with lung metastases. The patient at DL1 had received NAC with FEC regimen (5-fluorouracil, epirubicin, and cyclophosphamide) followed by paclitaxel. She developed metastatic disease in the lungs, liver, lymph nodes, and bone, but her DFS was unknown.

All patients treated with DL3 received the combination of sonidegib plus docetaxel as first line for their advanced

Table 2 Number of cycles administered per patient and per dose level

Treatment				
	Dose Level 1 n = 5	Dose Level 2 n = 4	Dose Level 3 n = 3	Total n = 12
Number of cycles				
1	–	1 (25.0%)	–	1 (8.3%)
2	4 (80.0%)	2 (50.0%)	–	6 (50.0%)
3	–	1 (25.0%)	–	1 (8.3%)
4	1 (20.0%)	–	–	1 (8.3%)
6	–	–	1 (33.3%)	1 (8.3%)
8	–	–	1 (33.3%)	1 (8.3%)
9	–	–	1 (33.3%)	1 (8.3%)

n number of patients

Table 3 Adverse events related to the study treatment per patient (NCI-CTCAE version 4.0)

AE, n (%)	Dose level 1 n = 5			Dose level 2 n = 4				Dose level 3 n = 3		
	G1	G2	G3	G1	G2	G3	G4	G1	G2	G3
Anemia	4 (80.0)	–	–	1 (25.0)	–	–	–	1 (33.3)	–	–
Neutropenia	1 (20.0)	–	1 (20.0)	1 (25.0)	–	–	1 (25.0)	–	–	2 (66.7)
WBC decreased	–	–	–	2 (50.0)	1 (25.0)	–	–	–	–	1 (33.3)
AST increased	–	2 (40.0)	–	1 (25.0)	–	–	–	–	–	–
ALT increased	2 (40.0)	–	–	1 (25.0)	–	–	–	1 (33.3)	–	–
AP increased	2 (40.0)	–	–	1 (25.0)	–	–	–	1 (33.3)	–	–
CPK increased	–	–	–	1 (25.0)	–	–	–	–	–	1 (33.3)
Creatinine increased	–	–	–	1 (25.0)	–	–	–	–	–	–
Fatigue	2 (40.0)	1 (20.0)	–	2 (50.0)	–	–	–	2 (66.7)	1 (33.3)	–
Anorexia	1 (20.0)	–	–	1 (25.0)	–	–	–	1 (33.3)	–	–
Alopecia	1 (20.0)	–	–	–	1 (25.0)	–	–	–	3 (100.0)	–
Headache	–	–	–	–	–	–	–	1 (33.3)	–	–
Arthralgia	2 (40.0)	–	–	–	–	–	–	2 (66.7)	–	–
Myalgia	2 (40.0)	–	–	–	–	–	–	2 (66.7)	–	–
Muscle spasms	–	–	–	–	–	–	–	1 (33.3)	–	–
Dysgeusia	–	–	–	–	1 (25.0)	–	–	1 (33.3)	1 (33.3)	–
Epistaxis	1 (20.0)	–	–	–	–	–	–	–	–	–
Paresthesia	–	–	–	–	–	–	–	1 (33.3)	–	1 (33.3)
Oral mucositis	1 (20.0)	–	–	1 (25.0)	1 (25.0)	–	–	2 (66.7)	–	–
Nausea	3 (60.0)	–	–	1 (25.0)	–	–	–	1 (33.3)	2 (66.7)	–
Vomiting	3 (60.0)	–	–	–	–	–	–	–	1 (33.3)	–
Diarrhea	1 (20.0)	–	–	–	–	–	–	1 (33.3)	–	–
Constipation	1 (20.0)	–	–	–	–	–	–	1 (33.3)	–	–
Abdominal pain	–	–	–	–	–	–	–	1 (33.3)	–	–
Dry mouth	–	–	–	–	–	–	–	1 (33.3)	–	–
Allergic reaction	1 (20.0)	–	–	–	–	–	–	–	–	–
Maculo-papular rash	–	–	–	–	–	–	–	2 (66.7)	–	–
Nail discoloration	–	–	–	–	–	–	–	3 (100.0)	–	–
Paronychia	–	–	–	1 (25.0)	–	–	–	–	–	–
Phlebitis	–	–	–	–	–	–	–	–	1 (33.3)	–
Eyelid function disorder	–	–	–	–	–	–	–	1 (33.3)	–	–
Photophobia	–	–	–	–	–	–	–	1 (33.3)	–	–
Watering eyes	–	–	–	–	–	–	–	1 (33.3)	–	–
Postnasal drip	–	–	–	–	–	–	–	1 (33.3)	–	–
Sore throat	–	–	–	–	–	–	–	1 (33.3)	–	–

NCI-CTCAE National Cancer Institute-Common Toxicity Criteria for Adverse Events, *AE* Adverse Event, *n* number of patients, *G* grade, *WBC* white blood cells, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AP* alkaline phosphatase, *CPK* creatine phosphokinase

disease. The patient treated with DL1 received the study treatment as the second line. Her first line therapy included the administration of carboplatin plus gemcitabine, and the progression-free interval was 36 days.

The median TTP for all 12 patients on the study was 42.5 days (range 20–203). At DL1 ($n = 5$) the median TTP was 42.0 days (range 29–84), at DL2 it was of 42.5 days (range 20–64), and at DL3 it was of 188 days (range 155–203+). The upper limit of the confident interval for DL3 was not defined as the TTP because the patient on CR was censored at the time of discontinuation before the PD was observed.

PK assessment

To evaluate a potential interaction between sonidegib and docetaxel PK, we observed the most relevant PK parameter, i.e., plasma clearance of docetaxel (Table 4). Mean plasma

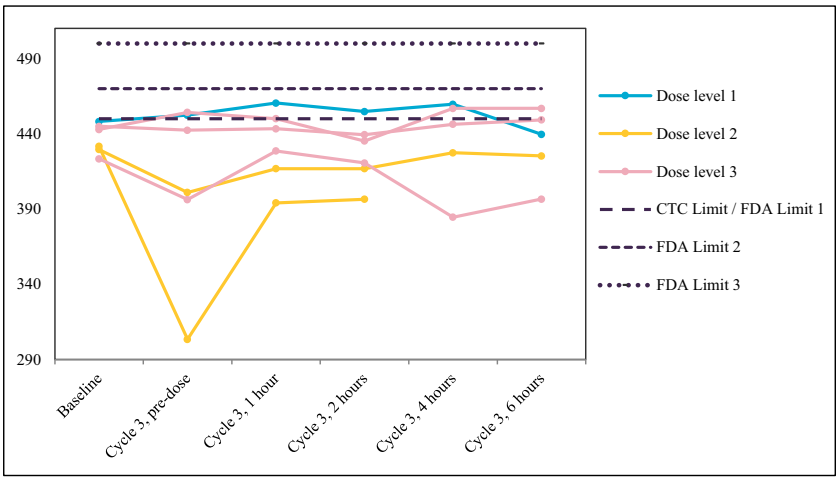

Fig. 2 QTc (Fridericia) measurements at baseline and cycle 3

**FDA Limits (absolute QTc interval prolongation). **Six patients received less than 3 cycles of study treatment and triplicate 12-lead ECGs were not performed as per study protocol requirements.*

clearance values on Day 1 of cycles 1 and 2 were similar (48.76 and 42.67 L/h, respectively); no changes were observed in the elimination process of docetaxel after repeated doses of sonidegib. Figure 3 displays the overlayed plasma concentrations versus time profiles of docetaxel for all patients on Cycles 1 and 2.

Concerning sonidegib PK, no statistical significant differences were found when normalized trough sonidegib concentrations were compared among the three dose levels (Table 5). However, median trough sonidegib concentration tended to decrease from dose of 400 to 800 mg.

The population pharmacokinetic model used for simulations of sonidegib concentrations consisted on a two compartment model with first order absorption and elimination processes. In combination with docetaxel, the observed trough sonidegib concentrations tended to be lower than the median of the corresponding simulated sonidegib concentrations from monotherapy, but the difference failed to achieve statistical significance.

Table 4 Mean values of PK parameters of docetaxel

Parameter	Mean	SD	CV%	Median	Min.	Max.
Day 1 Cycle 1						
Vss (L)	308.43	262.05	84.96	276.69	32.82	949.56
$T_{1/2lz}$ (h)	7.73	5.63	72.86	5.12	2.31	18.26
AUC(mg·h/L)	3.06	1.43	46.64	2.93	1.54	5.90
Cl (L/h)	48.76	19.55	40.09	49.45	21.48	85.06
Day 1 Cycle 2						
Vss (L)	241.57	224.97	93.13	155.50	33.27	676.44
$T_{1/2lz}$ (h)	12.18	10.74	88.16	5.29	1.62	28.05
AUC(mg·h/L)	4.89	3.76	76.86	4.44	1.44	13.13
Cl (L/h)	42.67	27.77	65.09	29.57	8.97	85.16

Vss: Steady-state distribution volume; $T_{1/2lz}$: elimination half-life

AUC area under the plasma concentration-time curve, *Cl* plasma clearance

Discussion

We report here the results from a phase I trial of the selective Smo antagonist sonidegib (LDE225) in combination with docetaxel in patients with locally advanced or metastatic TNBC.

We know that TNBC is a diverse entity that can encompass 4–5 several entities, each with a different sensitivity to chemotherapy and possibly with different potential targets [20]; however, over three-quarters of patients present with a tumor of the basal-like subtype. Docetaxel is a very active drug in metastatic breast cancer [4] with a well-known safety profile [21–23]. The Hh signaling pathway [24] is a promising therapeutic target to be explored, especially in TNBC, as new therapies are required to improve the clinical outcome of patients with this subset of breast cancer. Sonidegib is a selective inhibitor of SMO, structurally unrelated to cyclopamine [25]. Based on the discovery of the Hh signaling pathway and its role in the pathogenesis of basal cell carcinoma, smoothened (SMO) inhibitors have been developed with sonidegib being the second in class, after vismodegib. A Phase I [26] study accompanied by translational research, demonstrated a dose-dependent reduction in *GLI1* mRNA expression, with MTD = 800 mg once daily or 250 mg twice daily. Below the MTD, sonidegib was well tolerated with several low-grade (1 to 2) class-related AEs such as muscle spasm, myalgia, gastrointestinal toxicities, increased liver enzymes, fatigue, dysgeusia, and alopecia.

In our study, following dose escalation of sonidegib administered on a daily basis with a fixed dose of docetaxel

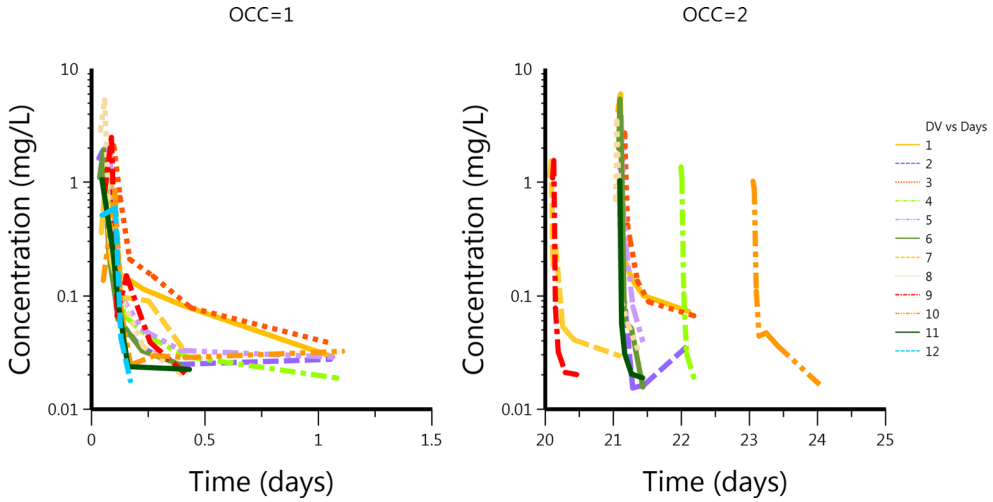

Fig. 3 Docetaxel plasma concentration-time profiles after intravenous infusion at fixed doses of 75 mg/m^2

administered every three weeks, sonidegib 800 mg QD and docetaxel 75 mg/m^2 were established as the RP2D for the combination in patients with advanced TNBC. It is the same dose of sonidegib recommended in a phase I trial in combination with paclitaxel [27].

The AEs of grade 3 reported for the combination at this dose level included paresthesia, WBC count decrease, and CPK increase. These were suffered by one patient each (33%), and neutropenia by two patients (67%). Grade 1 and 2 AEs reported for at least one patient included fatigue, anorexia, anemia, increased ALT or AP, nausea, vomiting, oral mucositis, diarrhea, constipation, abdominal pain, alopecia, arthralgia, myalgia, muscle spasms, paresthesia, or nail discoloration. There was only one AE in one patient treated at DL2 of grade 4, an uncomplicated neutropenia. No DLTs were observed at any of the dose levels evaluated. Additionally, no unexpected toxicities were observed compared to data reported from previous studies conducted with sonidegib or the known safety profile of docetaxel.

No effect was observed in this study on the pharmacokinetics of docetaxel when administered in combination with sonidegib. Median trough concentration of sonidegib showed a tendency to decrease from dose of 400 mg to 800 mg. This was in agreement with the decreasing bioavailability with increasing doses previously reported [19].

The small number of patients enrolled in this phase Ib study precludes any conclusion about the antitumor activity of the combination. However, patients on DL3 had the highest benefit from the study treatment with one patient experiencing a CR and the other two patients presented stable disease, with TTPs of 203+, 155 and 188 days, respectively. All of these patients had received docetaxel previously as part of their (neo-) adjuvant therapy, with a diverse disease-free interval between 10.9 and 36 months from the completion of the initial treatment for their early breast cancer. All of them had visceral involvement (lung and/or liver) and received the combination of sonidegib plus docetaxel as first line therapy for their metastatic disease.

Table 5 Trough concentration of sonidegib

	Units	400 mg		600 mg		800 mg	
		Ctrough	Ctrough/ Dose	Ctrough	Ctrough/ Dose	Ctrough	Ctrough/ Dose
Median	mg/L	0.333	0.00083	0.418	0.00070	0.509	0.00052
Mean	mg/L	0.398	0.00100	0.392	0.00065	0.727	0.00081
SD	mg/L	0.335	0.00084	0.086	0.00014	0.539	0.00064
Min	mg/L	0.141	0.00035	0.223	0.00037	0.201	0.00025
Max	mg/L	1.260	0.00315	0.461	0.00077	1.530	0.00191
CV	%	84.01	84.01	22.07	22.07	74.15	79.18

SD Standard deviation

CV%: coefficient of variation

Conclusions

The results of this phase Ib study on patients with advanced TNBC showed that the selective Smo antagonist sonidegib can be safely administered in combination with docetaxel. Sonidegib 800 mg q.d. and docetaxel 75 mg/m^2 on Day 1 of each 21-day cycle were declared as the RP2D. In the PK assessment, we failed to find any drug-to-drug interactions between sonidegib and docetaxel. The combination showed antitumor activity in three (all at the RP2D) out of 10 patients with measurable disease (one complete response and two long-lasting stabilizations).

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Compliance with ethical standards

Conflict of interest Federico Rojo: AES Program, grant PI15/00934 and grant PT17/0015/0006, ISCIII. Eva Carrasco's husband is Novartis advisor for onco-hematology products. Rest of the authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

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