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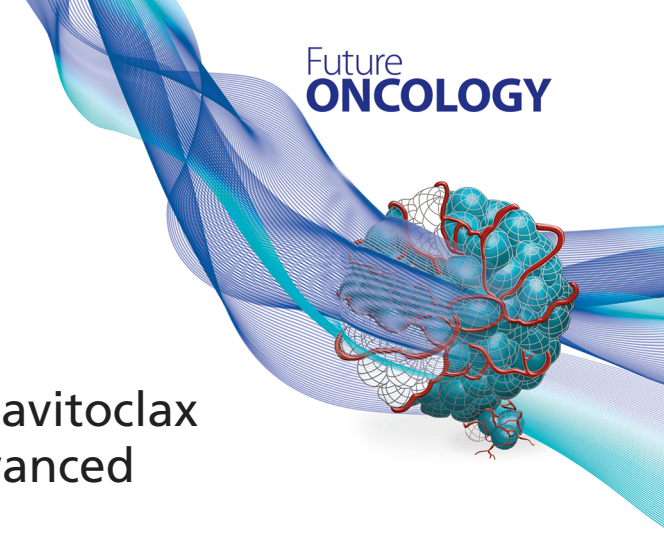

A Phase I study of the safety, pharmacokinetics and efficacy of navitoclax plus docetaxel in patients with advanced solid tumors

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Aim: This Phase I study investigated safety of navitoclax and docetaxel in patients (n = 41) with advanced solid tumors. **Patients & methods:** Two navitoclax plus docetaxel dosing schedules (21 and 28 days) were evaluated. Maximum tolerated dose, dose-limiting toxicities and preliminary antitumor activity were assessed. **Results:** Ten (24%) patients experienced dose-limiting toxicities; dose-escalation cohorts: n = 7 (21-day schedule: n = 5; 28-day schedule: n = 2) and 21-day expanded safety cohort: n = 3. Navitoclax 150-mg days 1–5 every 21 days with docetaxel 75 mg/m^2 day 1 was the maximum tolerated dose and optimal schedule. Adverse events included thrombocytopenia (63%), fatigue (61%), nausea (59%) and neutropenia (51%). Four confirmed partial responses occurred. **Conclusion:** Navitoclax 150-mg orally once/day was safely administered with docetaxel. Myelosuppression limited dose escalation; antitumor activity was observed.

Clinical trial registration: NCT00888108 (ClinicalTrials.gov)

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Apoptosis (programmed cell death) is a gene-directed and normally efficient process through which damaged, aged or redundant cells are eliminated. The BCL-2 protein family plays a key role in regulating mitochondrial or intrinsic apoptosis [1]. However, dysregulation of BCL-2 signaling pathways is central to tumor growth, allowing cancer cells to circumvent apoptosis and maintain a microenvironment that supports tumor survival [2,3]. Whereas the efficacy of chemotherapeutic agents and radiotherapy is dependent on the activation of intrinsic apoptosis after inducing DNA damage, the BCL-2 family may act to prevent efficient apoptosis and instead facilitate tumor development and resistance to anticancer therapy [1,4].

Dysregulation of apoptosis in cancer is associated with disequilibrium between pro- and anti-apoptotic BCL-2 proteins [1]. Anti-apoptotic signaling via the BCL-2 protein family (e.g., BCL-2, BCL-X_L, BCL-W and MCL-1) acts against pro-apoptotic proteins including BAX, BIM, BAK, BAD and PUMA to disrupt apoptosis. BCL-X_L and MCL-1 bind BIM and BAX, resulting in their sequestration [5]. In solid tumors, a high mRNA *BCL-2*/*BAX* expression ratio is associated with blockade of *BAX* activation, with the *BAX* gene further regulated by the p53 protein [6]. Mutated p53 results in inactivation of *PUMA* transcription, whereas BAD, which normally acts as

an inhibitor of BCL-X_L, is inactivated by PI3K/protein kinase B signaling [5,7]. BCL-X_L is associated with drug resistance and progression both in solid and hematologic malignancies, and is also a primary survival protein for platelets [8]. Against this background, BCL-2 and other anti-apoptotic regulators have emerged as key targets for therapy in multiple hematologic malignancies and solid tumors where BCL-2 expression is known to be increased [2,9].

Navitoclax (ABT-263) is an orally (p.o.) bioavailable, potent and highly selective inhibitor of BCL-2, BCL-X_L and BCL-W [10]. It is an analogue of ABT-737 [10], previously shown to cause mechanism-based killing of multiple small-cell lung cancer (SCLC) cell lines and regression of tumor xenografts [11,12]. Like ABT-737 and venetoclax (ABT-199), navitoclax mimics the pro-death BCL-2 homology-3 domain-only proteins such as BIM and PUMA, to promote apoptosis [13]. BCL-2, BCL-X_L and BCL-W are not equivalent targets of these drugs. For example, navitoclax more readily disrupts BCL-X_L/BIM or BCL-W/BIM complexes than ABT-737, with increasing levels of BCL-X_L and BCL-W conferring resistance to ABT-737 [14]. In contrast, elevated MCL-1 expression confers resistance to navitoclax [15]. Preclinical work with navitoclax showed complete tumor regression in xenograft models of SCLC and acute lymphoblastic leukemia [10], and paved the way for its clinical development. Phase I studies of navitoclax monotherapy in patients with solid tumors and hematologic malignancies defined a maximum tolerated dose (MTD) of 325 mg/day on a continuous 21-day schedule, with thrombocytopenia a key mechanism-based dose-limiting toxicity (DLT) associated with BCL-X_L inhibition [16,17]. These and other studies demonstrated a limited role for navitoclax as monotherapy in solid tumors [16–19].

Navitoclax has been shown to act synergistically with several cytotoxic agents, and generated preclinical results of interest in both hematologic and solid tumor models [20–22]. In particular, navitoclax significantly enhanced the antitumor activity of docetaxel both in *in vitro* and *in vivo* models [21]. Docetaxel is a cytotoxic agent that binds and stabilizes tubulin, inducing cell cycle arrest, and is approved for the treatment of breast, lung, prostate, head and neck, and gastric cancers. In addition, docetaxel can neutralize MCL-1 function [21].

On the basis of these preclinical observations, and limited single-agent activity in solid tumors, we hypothesized that targeting BCL-2 with navitoclax in combination with docetaxel could effectively overcome resistance to chemotherapy-induced apoptosis of cancer cells. We performed a multicenter Phase I, dose-escalation study to evaluate the safety, pharmacokinetics (PK), MTD and optimal schedule of navitoclax in combination with docetaxel in patients with relapsed or refractory solid tumors. Additionally, we assessed the preliminary efficacy of the combination and evaluated the relationship between BCL-2 family protein expression and response.

Patients & methods

Patient selection

This was an open-label, multicenter, Phase I dose-escalation study with an MTD expansion cohort (ClinicalTrials.gov: NCT00888108) conducted at five study centers. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation, and was approved by regulatory and independent ethics committees/institutional review boards at each site. All patients provided written informed consent before any study procedures were performed.

Patients with histologically or cytologically documented advanced solid tumors for which docetaxel was considered an appropriate therapy were enrolled. Key inclusion criteria included: age ≥18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1, measurable disease by Response Evaluation Criteria In Solid Tumors (version 1.0) [23], and adequate bone marrow (absolute neutrophil count ≥1500/μl; platelets ≥150,000/mm^3; hemoglobin ≥9.0 g/dl), renal (serum creatinine ≤2.0 mg/dl or calculated creatinine clearance ≥50 ml/min) and hepatic function (aspartate aminotransferase and alanine aminotransferase ≤1.5× the upper limit of normal [ULN] of institution's normal range; alkaline phosphatase ≤2.5× ULN or ≤5.0× ULN for patients with bone metastasis; and bilirubin ≤ULN). Patients with brain metastases could enroll if they had radiologically stable disease (SD) with stable neurologic function for ≥28 days following definitive therapy.

Because of the known antiplatelet effect of navitoclax, patients were excluded if they had an underlying predisposition to or active bleeding, active peptic ulcer disease or other potentially hemorrhagic conditions including esophagitis/gastritis, recent history of thrombocytopenia-associated bleeding, active immune thrombocytopenic purpura, autoimmune hemolytic anemia, peptic ulcer disease or refractoriness to platelet transfusions within 1 year. Patients requiring full-dose anticoagulation therapy, aspirin or any other antiplatelet drugs were also excluded.

Study design

This study evaluated two dosing schedules of navitoclax in combination with docetaxel: a 21-day schedule and a 28-day schedule. In the 21-day schedule, navitoclax (150 or 200 mg) was administered p.o. once daily (q.d.) as a liquid formulation via syringe on days 1–5 or 1–3 every 21 days, in combination with docetaxel 75 mg/m^2 administered via intravenous (iv.) infusion over 1 h immediately following navitoclax administration on day 1. To allow for single-agent PK analysis, navitoclax was administered starting on day 3 of cycle 2 only in the dose-escalation part of the study. In the 28-day schedule, navitoclax (150 or 200 mg) was administered p.o. q.d. on days 1–3, 8–10 and 15–17 every 28 days, in combination with iv. docetaxel 30 mg/m^2 on days 1, 8 and 15. Dose escalation in the 28-day schedule occurred in parallel with MTD expansion in the 21-day schedule.

For the 21-day schedule, the 150-mg starting dose of navitoclax was chosen for combination with docetaxel on the basis of safety data from an ongoing Phase I/II single-agent study [16]. Thrombocytopenia was the primary DLT of single-agent navitoclax. A dose of 150-mg q.d. resulted in an average maximal platelet drop of approximately 60% from baseline in Phase I studies [16,17]. Docetaxel alone causes thrombocytopenia in approximately 8% of patients with non-SCLC (NSCLC; ~3% of which is grade 3/4), although it is not the major DLT [24]. Navitoclax and docetaxel induce thrombocytopenia via different mechanisms; therefore, the combination was expected to significantly lower the platelet nadir and prolong the duration of thrombocytopenia caused by either docetaxel or navitoclax alone. Thrombocytopenia was predicted to be the main DLT. Monotherapy experience and simulations projecting an estimated reduction in platelets given the combined thrombocytopenia guided the starting dose.

Dose increments of 25–40% were planned at each subsequent dose level in the absence of DLT. The study followed a 3 + 3 design, with dose escalation only if zero of three or one or fewer of six patients experienced a DLT. If one out of three patients experienced a DLT, a cohort was expanded to six patients; if a further DLT was observed, dose de-escalation occurred to assess lower dose levels. The MTD was defined as the highest dose level at which one or fewer of six patients experienced a DLT. Once the MTD of navitoclax in combination with docetaxel was determined in both dosing schedules, additional patients were to be enrolled for further safety and PK analysis at the MTD.

DLTs (as well as all adverse events [AEs]) were defined in cycle 1 on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; however, events that occurred after the first cycle of dosing were also evaluated and assessed for dose-escalation decisions. A DLT was defined as any of the following events considered 'possibly' or 'probably' related to navitoclax: unexpected grade 2 toxicity requiring dose modification or treatment delay of >1 week, grade ≥2 bleeding associated with thrombocytopenia of any grade, grade 3 or 4 nonhematologic toxicity (excluding grade 3 nausea, vomiting and/or diarrhea responsive to treatment within 48 h; and grade 3 docetaxel infusion-related events [e.g., hypotension, anaphylaxis, rash]) and grade 3 or 4 hematologic toxicity (excluding grade 3 thrombocytopenia, grade 3 afebrile neutropenia [unless it delayed the start of cycle 2], grade 4 afebrile neutropenia lasting less than 7 days, grade 3/4 leukopenia and grade 3/4 lymphopenia).

Treatment could continue until disease progression, withdrawal of consent or unacceptable toxicity. Patients could continue with navitoclax monotherapy after discontinuation of docetaxel treatment, provided they had completed docetaxel dosing in cycle 1. In this setting, navitoclax monotherapy was administered using a 325-mg q.d. dose with a 150-mg lead-in period, on the basis of the recommended Phase II dose from a single-agent solid tumor study [16,17].

Safety assessments

Patients were evaluated for safety at baseline, weekly throughout the study, and at end of study by full medical history, vital signs, physical examination, ECOG PS assessment, laboratory studies (full blood count with differential, coagulation profile, serum biochemistry, urinalysis), ECGs and echocardiograms. In addition to weekly testing, platelet count was checked on days 2, 3 and 5 of cycle 1 and days 3, 4 and 6 of cycle 2 in the dose-escalation portion of the 21-day schedule. At MTD expansion, counts were checked at days 2, 3 and 5 of cycles 1 and 2. In the 28-day schedule, counts were checked on days 3, 10 and 17 of cycle 1. During monotherapy, platelet counts were checked on days 2, 3, 5 and 8 during lead-in and cycle 1.

PK analysis

Venous blood samples (4 ml) were collected in the 21-day dose-escalation schedule to determine plasma concentrations of navitoclax and docetaxel. For navitoclax PK assays, blood samples were collected on cycle 1 day 1 and cycle 2 day 3 (pre dose and 2, 4, 6, 8 and 24 h post dose). For docetaxel PK assays, blood samples were

collected on cycles 1 and 2, days 1 and 2 (before infusion; at 55, 75 and 90 min, then 3, 5, 8, 24 and 48 h from the start of infusion). Plasma concentrations of navitoclax and docetaxel were determined using validated liquid chromatography methods with tandem mass spectrometric detection.

Values for the PK parameters of navitoclax including maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}) and area under the plasma concentration–time curve (AUC) from time 0 to 24 h, were determined for each navitoclax dose. Values for the PK parameters of docetaxel including C_{max}, T_{max}, the terminal phase elimination rate constant (β), the terminal phase half-life, the AUC from time zero to the time of last measurable concentration, the AUC from time zero to infinity (AUC_{inf}) and clearance were determined for each docetaxel dose. PK parameters of navitoclax and docetaxel were estimated using noncompartmental methods with Phoenix WinNonlin-Professional™, Version 6.2 (Pharsight Corporation, CA, USA).

A repeated-measures analysis was performed using SAS version 9.2 (SAS Institute, Inc., NC, USA) on PK variables including T_{max}, β and the natural-log–transformed, dose-normalized C_{max} and AUC (when applicable), to compare the exposures of navitoclax or docetaxel between the combination regimen (assessed on cycle 1, day 1) and the single-drug regimen (cycle 2, day 3 for navitoclax; cycle 2, day 1 for docetaxel). A point estimate and 90% CIs for the ratios of the central values of C_{max} and AUC of the combination to the single-drug regimen were calculated.

Response evaluation

Radiologic assessment (CT and/or MRI scans) for tumor response was performed at baseline and at the end of every two cycles. Response was measured using Response Evaluation Criteria In Solid Tumors version 1.0 [23].

Results

Patient characteristics

A total of 41 patients enrolled in the study. Patient characteristics are summarized in Table 1; 31 and ten patients were treated in the 21-day and 28-day schedules, respectively. All but two patients had previously received chemotherapy or targeted therapies for their malignancy. A total of 35 patients were assessed for efficacy. The median number of treatment cycles received for all patients was 2.0 (range: 1–19 for the 21-day schedule and 1–8 for the 28-day schedule). Five patients continued with single-agent navitoclax after completing combination therapy. Common reasons for combination therapy treatment discontinuation included disease progression (n = 23 patients [56%]), AEs (n = 13 [32%]), withdrawal of consent (n = 2 [5%]), decline in ECOG PS (n = 5 [12%]), death (n = 1 [2.4%]) and continuation to monotherapy with navitoclax (n = 5 [12%]).

Safety & tolerability

In the 21-day schedule, one DLT (grade 3 febrile neutropenia) was observed at the first navitoclax dose level (150 mg); the cohort was therefore expanded to a total of six patients, and no further DLTs were observed (Table 2). At the second navitoclax dose level (200 mg), the first two patients experienced DLTs (grade 4 thrombocytopenia and grade 3 febrile neutropenia in one patient; grade 3 febrile neutropenia in the second patient). In order to maintain navitoclax at the higher dose of 200-mg q.d., an alternate dosing schedule with navitoclax 200 mg on days 1–3 was explored. However, two DLTs were observed at this dose level (grade 4 febrile neutropenia in one patient; grade 3 febrile neutropenia, grade 3 fatigue and grade 4 neutropenia in the other patient). Therefore, the MTD was determined to be navitoclax 150 mg on days 1–5 with 75-mg/m^2 docetaxel on day 1, every 21 days. An additional 17 patients were enrolled in an expanded safety cohort, for a total of 23 patients who were included in this dosing schedule; DLTs were observed in three patients in the safety cohort, for a total of four out of 23 (17%).

In the 28-day dose-escalation schedule, no DLTs were observed at the first navitoclax dose level (150 mg; Table 2). At the second (200 mg) dose level, two patients experienced DLTs (grade 4 thrombocytopenia in one patient; grade 5 demyelination and grade 5 peripheral neuropathy in the other patient). Because of limited dose escalation and limited observed efficacy (see 'Response' section), the 28-day schedule was not continued to MTD expansion and the MTD was not determined.

Common AEs included thrombocytopenia (63% [grade 1/2: 29%; grade ≥3: 34%]), fatigue (61% [44%; 17%]), nausea (59% [56%; 2%]), neutropenia (51% [2%; 49%]) and diarrhea (44% [39%; 5%]). A higher proportion of patients experienced treatment-related toxicities in the 21-day compared with the 28-day schedule. Thrombocytopenia was attributed to navitoclax in 63% of cases and to docetaxel in 37%. Alopecia, febrile neutropenia and vomiting were attributed to docetaxel alone. Grade 3 or higher AEs observed in ≥10% of

Table 1. Patient characteristics.

Characteristic	n = 41
Median (range) age, year	58 (30–83)
Male, n (%)	26 (63.4)
ECOG PS	
– 0	14
– 1	27
Tumor type, n	
– NSCLC	8
– Breast	5
– CRPC	4
– Bladder	3
– Esophageal	3†
– Melanoma	3‡
– SCLC	3
– Head and neck	2
– Pancreas	2
– Ovary	2
– Cholangiocarcinoma	2
– Mesothelioma	1
– Skin	1
– Sarcoma	1
– Thymoma	1
Prior systemic therapies, median (range), n	2 (1–8)
Prior systemic therapies, patients, n	
– 0–1	10
– 2	12
– ≥3	17

†Includes one gastroesophageal cancer.
‡Includes one choroidal melanoma.
CRPC: Castration-resistant prostate cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer.

Table 2. Dose escalation and dose-limiting toxicities per dose level.

Dose level	Navitoclax dose, mg	Navitoclax administration, days	Cohort, n	DLT, n	DLT
21-day schedule					
1	150	1–5	6	1	Grade 3 febrile neutropenia (n = 1)
2	200	1–5	2	2	Grade 4 thrombocytopenia, grade 3 febrile neutropenia (n = 1) Grade 3 febrile neutropenia (n = 1)
2	200	1–3	6	2	Grade 4 febrile neutropenia (n = 1) Grade 3 febrile neutropenia, grade 3 fatigue and grade 4 neutropenia (n = 1)
MTD expansion	150	1–5	17	3	Grade 3 febrile neutropenia (n = 1) Grade 3 febrile neutropenia (n = 1) tumor hemorrhage thrombocytopenia (n = 1) Grade 4 thrombocytopenia (n = 1)
28-day schedule					
1	150	1–3, 8–10, 15–17	4	0	
2	200	1–3, 8–10, 15–17	6	2	Grade 4 thrombocytopenia (n = 1) Grade 5 demyelination and grade 5 peripheral neuropathy (n = 1)

DLT: Dose-limiting toxicity; MTD: Maximum tolerated dose.

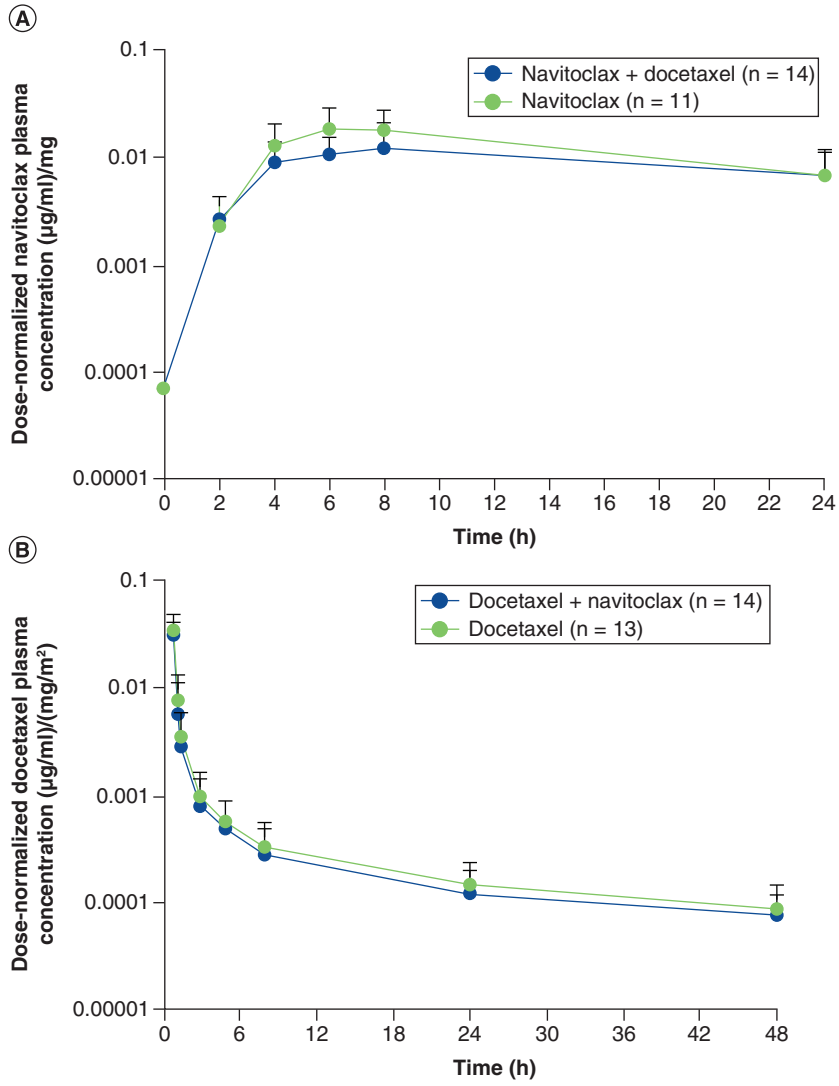

Figure 1. Mean (+ standard deviation) dose-normalized navitoclax (A) and docetaxel (B) plasma concentration–time profiles (21-day dose-escalation cohort).

patients were neutropenia (49%), thrombocytopenia (34%), febrile neutropenia (27%), leukopenia (24%), fatigue (17%) and hyponatremia (15%).

There were four on-study deaths; two deaths were attributed to progressive disease (PD). A third patient, treated at the 200-mg dose level on the 28-day schedule, experienced an event of grade 5 demyelination and peripheral neuropathy on day 5, possibly related to both navitoclax and docetaxel. A fourth patient, treated at the 150-mg dose level on the 21-day schedule, experienced an event of fatal tumor hemorrhage 8 days after the last treatment dose, possibly related to both navitoclax and docetaxel.

Pharmacokinetics

PK analysis was possible for 11, 13 and 14 patients administered navitoclax alone, docetaxel alone and both drugs together, respectively. Plasma concentration profiles of navitoclax and docetaxel administered alone or in combination are presented in Figure 1. Dose-normalized values are used because some patients received reduced doses of navitoclax or docetaxel.

Co-administration of navitoclax and docetaxel appeared to slightly reduce the exposure of each drug (Table 3). The central values of the dose-normalized navitoclax C_{max} and AUC from time 0 to 24 h in the presence of docetaxel were 68% (90% CI: 57–80) and 78% (90% CI: 65–94), respectively, of those in the absence of docetaxel. The

Table 3. Mean ± standard deviation pharmacokinetic parameters of navitoclax (21-day dose-escalation cohort).

Parameter, unit	Navitoclax alone† (n = 11‡)	Navitoclax + docetaxel§ (n = 14)	Geometric mean ratio (90% CI), combination§/single-drug† regimen¶
T_{max}, h	9.5 ± 7.2	8.7 ± 6.3	
C_{max}/dose, (μg/ml)/mg	0.021 ± 0.009	0.014 ± 0.008#	0.676 (0.571–0.801)
AUC_{0-24}/dose, (μg·h/ml)/mg	0.279 ± 0.113	0.203 ± 0.118#	0.780 (0.648–0.939)
Mean ± standard deviation PK parameters for docetaxel (21-day dose-escalation cohort)			
Parameter, unit	**Docetaxel alone†† (n = 13)**	**Docetaxel + navitoclax‡‡ (n = 14)**	**Geometric mean ratio (90% CI), combination‡‡/single-drug†† regimen§§**
C_{max}/dose, (μg/ml)/(mg/m²)	0.035 ± 0.013	0.031 ± 0.011¶¶	0.826 (0.723–0.944)
AUC_t/dose, (μg·h/ml)/(mg/m²)	0.038 ± 0.017	0.032 ± 0.016¶¶	
AUC_{inf}/dose, (μg·h/ml)/(mg/m²)	0.040 ± 0.018	0.034 ± 0.017¶¶	0.812 (0.733–0.901)
$t_{1/2}$,## h	17.5 ± 6.0	20.1 ± 5.5	
CL,††† l/h/m²	29.5 ± 12.7	33.4 ± 9.6	

†Measured on day 3 of cycle 2.
‡N = 12 for T_{max}.
§Measured on day 1 of cycle 1.
¶Only patients who completed PK collection in both regimens were included in analysis (n = 10).
#Statistically significant difference from navitoclax alone ($p < 0.05$, ANOVA).
††Measured on day 1 of cycle 2.
‡‡Measured on day 1 of cycle 1.
§§Only patients who completed PK collection in both regimens were included in analysis (n = 12).
¶¶Statistically significant difference from docetaxel alone ($p < 0.05$, ANOVA).
##Harmonic mean ± pseudo-standard deviation; evaluations of $t_{\frac{1}{2}}$ were based on statistical tests for the terminal phase elimination constant (β).
†††Parameter was not tested statistically.
AUC: Area under the plasma concentration–time curve; AUC_{0-24}/dose: Dose-normalized AUC from time 0 to 24 h; AUC_{inf}/dose: Dose-normalized AUC from time zero to infinity; AUC_t/dose: Dose-normalized AUC from time zero to the time of the last measurable concentration; CL: Clearance; C_{max}: Maximum plasma concentration; C_{max}/dose: Dose-normalized C_{max}; PK: Pharmacokinetic; $t_{\frac{1}{2}}$: Half-life; T_{max}: Time to C_{max}.

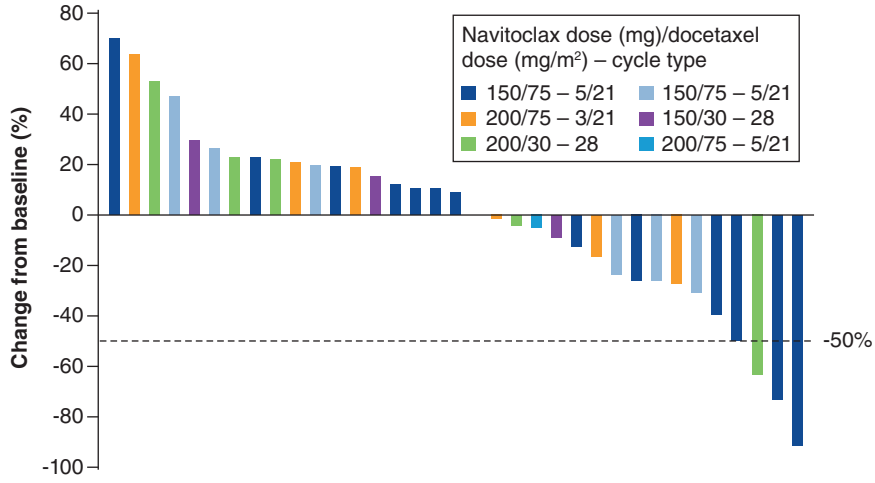

Figure 2. Per-patient display of best percentage change from baseline in tumor size.

central values of the dose-normalized docetaxel C_{max} and AUC_{inf} in the presence of navitoclax were 83% (90% CI: 72–94) and 81% (90% CI: 73–90), respectively, of those in the absence of navitoclax.

Response

Thirty-five patients were assessed for response (Figure 2). Four confirmed partial responses (PRs) and one unconfirmed PR were observed. A male patient with metastatic thymoma to the pleura who had received three lines of previous treatment demonstrated a confirmed PR lasting 358 days (Figure 3). The response was first seen after six cycles of combination treatment and maintained for a further four cycles before the patient opted to stop docetaxel for lifestyle reasons. He then completed nine cycles (5 months) of navitoclax monotherapy before a

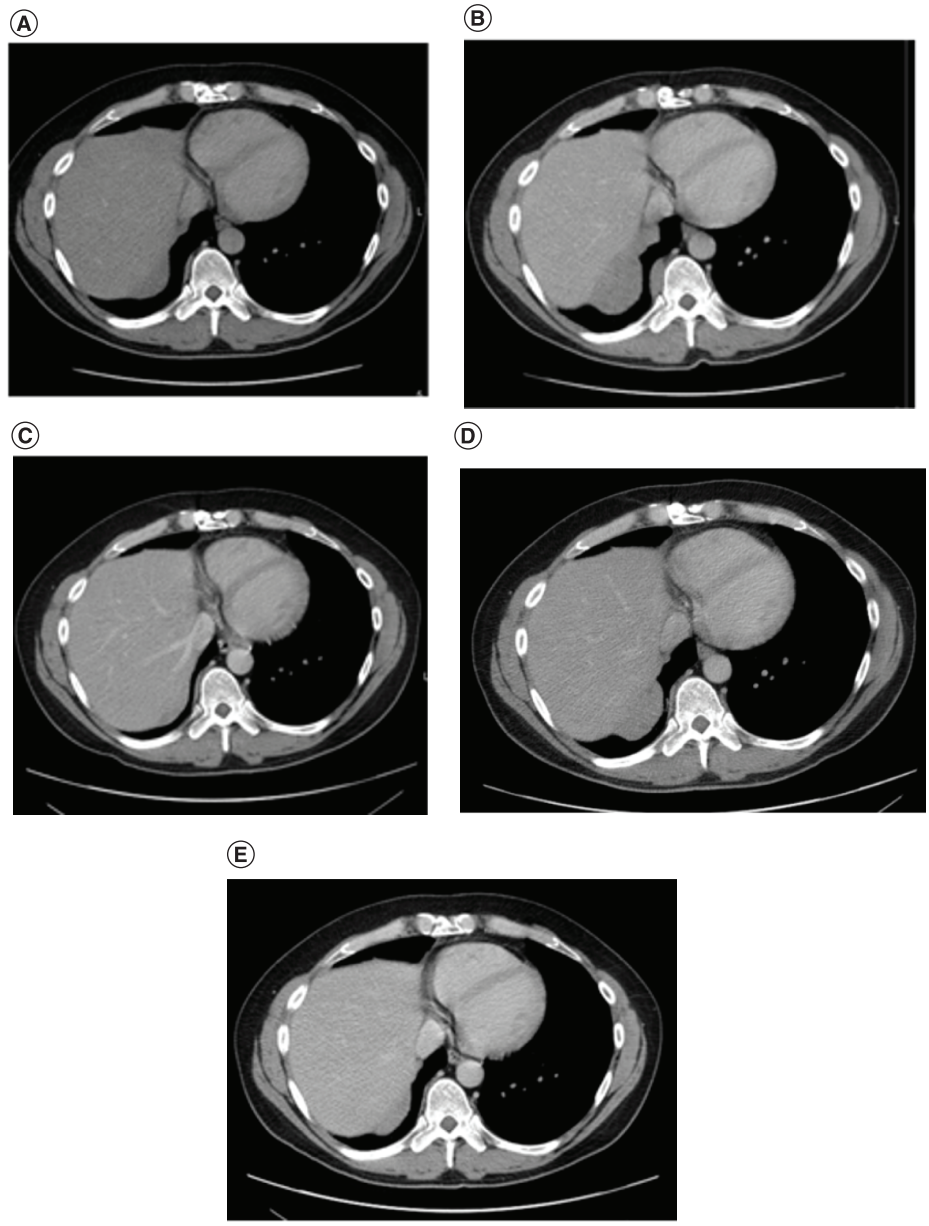

Figure 3. Computed tomography scan showing partial response in a patient with thymoma. (A) Eight months before study. **(B)** Study baseline. **(C)** Best response on combination therapy (7 months on study) and start of monotherapy. **(D)** Progressive disease while on monotherapy (14 months on study) and restart of combination therapy. **(E)** End of combination therapy and resumption of monotherapy (18.5 months on study).

CT scan demonstrated PD (though lesions did not return to baseline [study start] measurements). Combination therapy was resumed, with a PR observed after two cycles and maintained for six cycles, before the patient received monotherapy for a further four cycles, with slow PD. He was then taken off trial and received further systemic therapy and surgery.

The second confirmed PR was seen in a female patient with metastatic transitional cell carcinoma (TCC) of the bladder who had previously been treated with a neoadjuvant regimen of cisplatin-gemcitabine. She was treated with eight cycles of combination therapy (200-mg navitoclax; 30-mg/m^2 docetaxel). The PR occurred after four cycles and lasted 110 days. Another patient with metastatic TCC bladder and metastatic lung cancer, previously treated with gemcitabine and paclitaxel ± sunitinib, demonstrated a PR lasting 96 days; the patient progressed with brain metastases, though the response in extracranial disease was maintained.

The fourth confirmed PR occurred in a female patient with NSCLC previously treated with two lines of therapy (gemcitabine and cisplatin; erlotinib) who demonstrated a PR after six cycles of combination therapy.

The unconfirmed PR occurred in a male patient with NSCLC who demonstrated a PR after one cycle; he received monotherapy after cycle 2 because of a grade 3 hypersensitivity reaction to docetaxel, and had PD after a total of three cycles. Twelve patients demonstrated clinically meaningful SD.

Discussion

This Phase I study assessed the safety, PK interaction, and preliminary efficacy of the combination of the BCL-2, BCL-X_L and BCL-W inhibitor navitoclax with docetaxel. Dose escalation of navitoclax in combination with 75-mg/m^2 docetaxel was limited by thrombocytopenia and febrile neutropenia; co-administration appeared to prolong the duration of neutropenia (data not shown) and contribute to febrile neutropenia. Consequently, only two dosing schedules of navitoclax in combination with docetaxel (21 and 28 day) were explored in the reported study. In the 21-day schedule, navitoclax was administered on days 1–5 every 21 days, in combination with docetaxel administered immediately following navitoclax administration on day 1. In the 28-day schedule, navitoclax was administered on days 1–3, 8–10 and 15–17 every 28 days, in combination with docetaxel on days 1, 8 and 15. The 28-day schedule did not allow for further dose escalation due to observed toxicity and lack of evidence of clinical benefit. Thus, the 28-day schedule did not continue to MTD expansion and was subsequently abandoned. When administered together, navitoclax and docetaxel appeared to have a slightly lower exposure compared with either drug administered alone. The changes in drug exposure were about <20% for docetaxel C_{max} and AUC_{inf}, and 32 and 22% for navitoclax C_{max} and AUC_{inf}, respectively, and were not considered clinically meaningful. This conclusion may be partly attributed to the limited number of patient samples available. The MTD was defined as 150-mg q.d. on days 1–5 with docetaxel 75 mg/m^2 on day 1, every 21 days.

In an earlier Phase I study evaluating the combination of navitoclax and gemcitabine in 39 patients with solid tumors, the DLT of the combination was grade 3 transaminitis and the MTD was established on a 21-day dosing schedule as navitoclax 325 mg and gemcitabine 1000 mg/m^2 [25]. Twenty one of the 39 patients had a best objective tumor response of SD, with no complete responses or PRs observed. Another Phase I study assessing the combination of navitoclax (150 mg) with either paclitaxel (135 or 175 mg/m^2) or paclitaxel and carboplatin (175 mg/m^2 and AUC 4–6, respectively) in patients with solid tumors has been discontinued [26]. The significant hematologic and nonhematologic toxicity observed, together with modest efficacy, led to the decision to end the study [26].

In our study, the combination of navitoclax and docetaxel resulted in four confirmed PRs in patients with thymoma, TCC bladder and NSCLC, and one unconfirmed PR in a patient with NSCLC. Additionally, 12 patients demonstrated clinically meaningful SD. The most prominent response was in a taxane-naive patient with thymoma who responded initially with the combination and single-agent navitoclax. After progression, he was rechallenged with the combination and demonstrated a further response that was maintained, albeit for a shorter duration, on monotherapy. Because the tumor types in which response was shown are known to be sensitive to docetaxel, it is difficult to determine the effect of adding navitoclax.

In addition to the encouraging antitumor activity of navitoclax in combination with docetaxel in the present study, navitoclax has also shown promise in other combination regimens. In patients with previously untreated chronic lymphocytic leukemia or relapsed/refractory CD20-positive lymphoid malignancies, the combination of navitoclax and rituximab was well tolerated and yielded higher response rates than rituximab alone [27,28]. Navitoclax has also been evaluated in two Phase I studies in combination with erlotinib or irinotecan in patients with advanced solid tumors. The combination with erlotinib did not result in any objective responses, but disease control occurred in 27% of treated patients [29]. In the second study, navitoclax 150 mg/day was administered in either a once-weekly or every 3 weeks irinotecan schedule, with one patient in each group achieving a PR (objective response rate: 7 and 6%) [30]. A Phase I trial of the Mek inhibitor trametinib in combination with navitoclax is underway (NCT02079740). Finally, the use of predictive biomarkers including levels of BCL-2, BCL-X_L and MCL-1 may help determine both mechanisms of response and resistance.

Thrombocytopenia is a BCL-X_L inhibition-dependent on-target effect of navitoclax [31]. Venetoclax, a potent, p.o. available and highly selective BCL-2 inhibitor with a lower binding affinity to BCL-X_L and thus relatively platelet-sparing, was developed to address tumors more dependent on BCL-2 than BCL-X_L [32]. To date, venetoclax has been approved in the first-line and relapsed/refractory chronic lymphocytic leukemia and acute myeloid leukemia

settings [33]. However, to address tumors with BCL-X_L dependence, exploring navitoclax rather than selective BCL-2 inhibitors such as venetoclax may be a beneficial approach [34].

Conclusion

In summary, this Phase I study demonstrated that dose escalation of navitoclax in combination with docetaxel at 75 mg/m^2 every 21 days or 30 mg/m^2 weekly for 3 of 4 weeks was limited by myelosuppression, particularly thrombocytopenia. An MTD of navitoclax 150-mg p.o. q.d. on days 1–5 with docetaxel iv. 75 mg/m^2 day 1 every 21 days was established. Future combination strategies should include other targeted agents and use predictive biomarkers for patient selection and elucidation of mechanism of efficacy or treatment resistance.

Summary points

- BCL-2 and other anti-apoptotic members of the BCL-2 protein family have emerged as key targets for therapy in hematologic malignancies and solid tumors with increased BCL-2 expression.
- Navitoclax (ABT-263), a highly selective inhibitor of BCL-2, BCL-X_L and BCL-W, has been shown to significantly enhance antitumor activity of the cytotoxic agent docetaxel *in vitro* and *in vivo*.
- This Phase I dose-escalation study evaluated the safety, pharmacokinetics (PK), maximum tolerated dose (MTD), optimal schedule and preliminary efficacy of navitoclax combined with docetaxel in patients with advanced solid tumors.
- Based on dose-limiting toxicities (hematologic), that occurred in patients on the 21-day schedule, the MTD and optimal schedule was determined to be navitoclax 150 mg on days 1–5 every 21 days with docetaxel 75 mg/m^2 on day 1. The 28-day schedule did not continue to MTD expansion due to toxicity and lack of preliminary efficacy.
- Common adverse events included thrombocytopenia (63%), fatigue (61%), nausea (59%) and neutropenia (51%). Neutropenia (49%), thrombocytopenia (34%), febrile neutropenia (27%), leukopenia (24%), fatigue (17%) and hyponatremia (15%) were the most common grade ≥3 adverse events present in ≥10% of patients.
- Although not considered to be clinically meaningful, co-administration of navitoclax and docetaxel led to a slightly lower exposure of each drug compared with the exposure from either drug administered alone.
- Four out of 35 patients had a confirmed partial response to treatment, and 12 patients demonstrated clinically meaningful stable disease.
- While myelosuppression limited dose escalation, the optimal schedule and MTD of navitoclax and docetaxel described in this study allowed for safe administration of these therapeutic agents in patients with advanced solid tumors.

Author contributions

M Puglisi, LR Molife, MJA de Jonge, KH Khan, L van Doorn, MD Forster, M Blanco, M Gutierrez and Ferry ALM Eskens participated in the investigation of the study. All the authors participated in writing-reviewing and editing of the manuscript. T Busman contributed to data curation.

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Ethical conduct of research

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation, and was approved by regulatory and independent ethics committees/institutional review boards at each site. All patients provided written informed consent before any study procedures were performed.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data from: NCT00888108. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis datasets), as well as other information (e.g., protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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