A Phase I Study of Nilotinib in Combination with Paclitaxel in Patients with Advanced Solid Tumors

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ABSTRACT

Purpose: We assessed the safety, maximum tolerated dose, and recommended phase 2 dose (RP2D), efficacy, pharmacokinetics, and pharmacodynamics of the nilotinib–paclitaxel combination in 44 patients with solid tumors.

Patients and Methods: Paclitaxel was administered intravenously (days 1, 8, and 15), and nilotinib was administered twice daily orally beginning on cycle 1 day 2 (C1D2; escalation) or C1D3 (expansion) in 28-day cycles using a 3 + 3 dose escalation design. Pharmacodynamic biomarkers of drug action were assessed in paired tumor biopsies and circulating tumor cells at the RP2D.

Results: The RP2D was 300 mg nilotinib twice daily with 80 mg/m^2 paclitaxel. Grade 4 (Gr4) neutropenia and Gr3 rash, photosensitivity, and transaminase elevation were dose-limiting. The most common Gr3-4 toxicities were hematologic and hypophosphatemia; one patient (2%) experienced Gr3 peripheral neuropathy. Three patients [two with adult ovarian granulosa cell tumors (AOGCT) and one with endometrial carcinoma] had confirmed partial responses (cPR); the patients with AOGCT remained on study for 5 and 6+ years, and mesenchymal-like circulating tumor cells were measured prior to progression or during treatment holiday (patients 12 and 10, respectively).

Conclusions: This study determined the maximum tolerated dose of this combination, demonstrated sustained cPRs in patients with AOGCT, and profiled molecular pharmacodynamic responses that will inform further mechanism-of-action studies. The rate of peripheral neuropathy suggests enhanced tolerability of this combination.

Introduction

Combination oncology therapies often confer enhanced clinical benefit over the respective monotherapies at patient population levels and for certain individual patients (1). The NCI-ALMANAC (A Large Matrix of Anti-neoplastic Agent Combinations) preclinical study screened pairwise combinations of >100 FDA-approved anticancer drugs for greater-than-additive *in vitro* activity in the NCI-60 human tumor cell line panel (2). This screen identified greater-than-additive cytotoxic activity for the BCR-Abl tyrosine kinase inhibitor nilotinib when combined with the microtubule-stabilizing drug paclitaxel in multiple cell lines. *In vivo* studies confirmed that this combination yielded greater-than-single-agent antitumor activity in several human tumor xenograft models, including ovarian, renal cell, and triple-negative breast cancer models (2).

In the NCI-ALMANAC study, the greater-than-additive *in vitro* activity of the nilotinib–paclitaxel combination was not associated with the expression of known nilotinib targets (2) or the expression of ATP-binding cassette (ABC) transporter proteins that were previously shown to inhibit paclitaxel efflux (3, 4). Indeed, nilotinib did not significantly modulate intracellular paclitaxel concentrations *in vitro* in several breast cancer cell lines (5) nor intratumoral concentrations of paclitaxel *in vivo* in responsive human tumor xenograft models (2). Interestingly, the combination induced a nonapoptotic form of cell death independent of caspase-3 cleavage (2). The molecular basis for the antitumor activity of the nilotinib–paclitaxel combination remains an area of active research interest.

Recent preclinical data demonstrated that nilotinib attenuates paclitaxel-induced peripheral neuropathy (PIPN) via inhibition of the murine organic anion transporter OATP1B2 (a homolog of the human transporter OATP1B1) in dorsal root ganglia cells (5). These findings led to an ongoing phase 1b/2 study (NCT04205903) of the impact of nilotinib on PIPN in patients with breast cancer (6). However, this mechanism does not account for the greater-than-additive activity of the combination, and additional molecular pathways underlying combination activity have yet to be elucidated. Based on promising preclinical activity, we conducted a phase 1 clinical trial of the nilotinib–paclitaxel combination that assessed its safety, antitumor activity, pharmacokinetics (PK), and pharmacodynamic effects

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Translational Relevance

Clinical testing of combinations of FDA-approved oncology drugs with greater-than-additive preclinical activity is an important component of the development of novel, effective combination therapies for patients with cancer. In this study, we present phase 1 clinical safety, response, pharmacokinetic, and pharmacodynamic data for the combination of two such FDA-approved small-molecule oncology agents: the tyrosine kinase inhibitor nilotinib and the anti-tubulin agent paclitaxel. The tolerability and promising antitumor activity of this combination in patients with some advanced solid tumors, particularly in patients who did not respond to prior paclitaxel regimens, demonstrate the success of this "bench-to-bedside" approach to identify and evaluate combination therapies. This study provides a framework for similar analyses of other such combinations in the future and underscores the importance of preclinical combination screening of approved drugs for the discovery of unexpected yet effective new regimens for treating cancer.

in patients with advanced solid tumors. This trial incorporated exploratory endpoints that tested plausible hypotheses of the drugs' mechanism of action.

Patients and Methods

Patient eligibility criteria

This study enrolled patients with histologically confirmed solid tumors who had progressed on at least one standard therapy or for which no standard treatment options existed. Patients were required to have a life expectancy of >3 months, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and adequate marrow and organ function, including a platelet count ≥100,000/μL, an absolute neutrophil count ≥1,500/μL, total bilirubin ≤1.5× the institutional upper limit of normal (ULN) or ≤3×ULN for patients with Gilbert syndrome, alanine aminotransferase and/or aspartate aminotransferase ≤3×ULN or ≤5×ULN for patients with liver metastases, and creatinine ≤1.5×ULN (or, for patients with levels >1.5×ULN, creatinine clearance of ≥60 mL/minute/1.73 m^2). Patients must have recovered to eligibility levels from toxicities or adverse events due to prior therapy, and prior therapies were required to be completed ≥3 weeks or ≥5 half-lives, whichever was shorter, prior to enrollment. Patients enrolled in the expansion cohort were required to be willing to undergo biopsies and have tumors amenable to biopsy. Patients with the following conditions were excluded from this study: Fredericia's formula-corrected QT (QTcF) interval of >450 ms at study entry or history of congenital long QT syndrome, sensory/motor neuropathy grade ≥2 (≥Gr2), receiving combination antiretroviral therapy for human immunodeficiency virus, pregnancy, uncontrolled intercurrent illness, active brain metastases, or carcinomatous meningitis (patients with treated brain metastases, whose brain metastatic disease had remained stable for ≥4 weeks without requiring steroids and antiseizure medication, were eligible).

Trial design

This study (NCT02379416) was conducted at the NIH Clinical Center (Bethesda, Maryland). All participants provided written informed consent. The study was approved by the NIH Institutional Review Board and performed in accordance with the U.S. Common Rule. This study met the criteria for Investigational New Drug (IND) exemption per Code of Federal Regulations part 21 CFR 312 guidelines. Dose escalation followed a standard 3 + 3 design, with both agents administered in 28-day cycles. The starting dose level (DL1) was 300 mg nilotinib administered orally twice daily and 60 mg/m^2 paclitaxel administered intravenously on days 1, 8, and 15 of each cycle; dose levels are listed in Supplementary Table S1. During dose escalation, nilotinib administration began on cycle 1 day 2 (C1D2) to collect single-agent paclitaxel PK data on C1D1. During dose expansion, nilotinib administration began on C1D3 to enable the collection of tumor biopsy specimens on C1D2 to evaluate single-agent paclitaxel pharmacodynamics.

Toxicity grades were assigned according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The criteria for dose-limiting toxicities (DLT), dose reductions, and planned treatment breaks (i.e., treatment holidays) are listed in the Supplementary Methods. Histories and physical examinations were done weekly during cycle 1 and at the start of each subsequent cycle; laboratory evaluations were performed weekly during cycle 1 and then prior to every paclitaxel infusion. Tumor size was measured radiographically prior to treatment and every two cycles for the first year, every three cycles for patients on study for more than 1 year, and every four cycles for patients on study for more than 3 years. Responses were classified according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (7).

Pharmacokinetic analyses

In the dose escalation cohort, blood specimens for PK analysis were collected on C1D1 and C1D8 prior to drug administration and at 90 and 150 minutes and 5, 9, and 24 hours following the administration of paclitaxel (C1D1) or paclitaxel and nilotinib (C1D8). PK samples were analyzed by validated LC/MS or LC/MS-MS methods. Briefly, 100 μL of plasma was extracted with 3 mL of methyl tert-butyl ether containing 5 nmol/L docetaxel, which was used as an internal standard. The samples were vortexed for 3 minutes and centrifuged at 1,000 × *g* for 10 minutes, and the organic layer was recovered and evaporated under a stream of N_2 to dryness. The samples were reconstituted in 100 μL of a 4:1 acetonitrile/water solution, and 10 μL was injected into the LC/MS-MS. Extraction efficiency was greater than 90%. Analytes were separated on a 2.1 × 150 mm Xterra C18 column using a gradient of acetonitrile and 0.1% formic acid with 0.001% sodium formate (35%–90%). The precursor ions used were M + Na species, and the mass spectral (mass-to-charge ratio) transitions were 876 to 591 for paclitaxel, 892 to 607 for both 6-hydroxy paclitaxel and 3′-hydroxy paclitaxel, and 830 to 549 for docetaxel. Comparison of peak areas of the product ions of paclitaxel and its metabolites with the peak area of the product ion of docetaxel was used for quantitation. Standard curves constructed from spiked plasma samples showed linearity from 0.005 to 2 μmol/L. The limit of quantitation was determined to be 0.005 μmol/L for paclitaxel and its metabolites.

Pharmacodynamic analyses

Core needle (18-gauge) tumor biopsies were collected at baseline, on C1D2, and on C1D28 as previously described (8). Biopsy specimens were snap-frozen at the point of collection, thawed under neutral buffered formalin fixative to preserve labile phosphoproteins (9, 10), and embedded in paraffin blocks for sectioning slides at 5-micron thickness (https://dctd.cancer.gov/ResearchResources/biomarkers/DDR3/SOP340550_Biopsy_Section_Testis_Jejunum_Controls.pdf). Biopsy specimens were evaluated by quantitative

immunofluorescence microscopy (IFA) for serine 10-phosphorylated histone H3 (pHH3), a nuclear marker of mitotic arrest (11), and for tumor cell expression of E-cadherin, vimentin, and their co-localization (12, 13) to assess epithelial–mesenchymal transition (EMT; https://dctd.cancer.gov/ResearchResources/biomarkers/emt.htm). For the EMT analysis, we calculated $\log_{10}$ ratios of tumor areas positive for vimentin versus those positive for E-cadherin [$\log_{10}$(V/E)] across two biopsy cores per time point and several regions of interest for each biopsy core. Pharmacodynamic biomarker measurements were obtained using analytically validated, clinically fit-for-purpose assays as described previously (11–13). For each patient, mean biomarker values were compared across biopsy time points using unpaired *t* tests, assuming unequal variances. Circulating tumor cell (CTC) specimens were assessed for EMT phenotype as described previously (14, 15).

Data availability

Deidentified clinical data will be posted on ClinicalTrials.gov (Identifier: NCT02379416) and will be available prior to being posted on ClinicalTrials.gov upon request to the corresponding author. Requests for pharmacodynamic and PK data, as well as raw data for any figure or table, may be made to the corresponding author.

Results

Patient population and disposition

From April 2015 to August 2021, 45 patients were enrolled (25 females and 20 males; **Table 1**; Supplementary Table S2). One patient did not begin study treatment and is not included in these analyses. The median patient age was 63 years (range: 24–81), and the median number of prior systemic therapies was 3 (range: 0–9; **Table 1**). A total of 11 patients had received prior paclitaxel-based therapy (seven in combination, two both in combination and as monotherapy, and two as paclitaxel only; Supplementary Table S3). One patient (patient 20) previously received paclitaxel monotherapy, docetaxel in combination, and nab-paclitaxel monotherapy. Ten patients received therapy with other taxane-based regimens (nine with docetaxel and one with nab-paclitaxel) but not with paclitaxel (Supplementary Table S3). The most common tumor types (**Table 1**) were sarcoma/carcinosarcoma (10 patients; 23%), followed by ovarian/uterine carcinomas (seven patients: five ovarian and two uterine; 16%), lung cancers (four patients; 9%), and neuroendocrine tumors/carcinomas (four patients; 9%). The data cutoff (DCO) was August 5, 2022.

Table 1. Patient characteristics.

Characteristics	Number of patients
Number of patients (female, male)	44 (25, 19)
Median age, *y* (range)	63 (24–81)
ECOG score	
0	3
1	40
2	1
Median number of prior therapies (range)	3 (0–9)
Tumor type	
Ovarian carcinoma[a]	5
Neuroendocrine tumor/carcinoma[b]	4
Non–small cell lung cancer	4
Bladder carcinoma	3
Breast carcinoma	3
Carcinoma of unknown primary origin	3
Leiomyosarcoma[c]	3
Endometrial/uterine carcinoma	2
Endometrial/uterine carcinosarcoma	2
Anal carcinoma	1
Cholangiocarcinoma	1
Chondrosarcoma	1
Colon adenocarcinoma	1
Endometrial stromal sarcoma	1
Gastrointestinal stromal tumor	1
Liposarcoma	1
Melanoma	1
Mesothelioma	1
Pancreatic adenocarcinoma	1
Pancreaticobiliary carcinoma	1
Sclerosing epithelioid sarcoma	1
Small bowel adenocarcinoma	1
Small cell carcinoma of unknown primary origin	1
Thyroid carcinoma	1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]2 adult granulosa cells, 1 juvenile granulosa cell, 2 serous.
[b]1 pancreatic, 1 nasopharyngeal, 1 small intestine, 1 prostate.
[c]2 uterine, 1 nonuterine.

Maximum tolerated dose determination and adverse events

All 44 patients evaluable for toxicity experienced ≥1 treatment-related adverse event (trAE). Gr4 neutropenia and Gr3 rash, photosensitivity, and transaminase elevation were dose-limiting (Supplementary Table S4). The maximum tolerated dose/recommended phase 2 dose was nilotinib 300 mg orally twice daily and paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of each cycle (i.e., DL2, Supplementary Table S1). Across all dose levels, lymphopenia (82% any grade, 36 patients) was the most common trAE; anemia (75% any grade, 33 patients), leukopenia (75% any grade, 33 patients), hypophosphatemia (64% any grade, 28 patients), and fatigue (57% any grade, 25 patients) also occurred (**Table 2**; Supplementary Table S5). Lymphopenia was the most common Gr3/4 trAE (39%, 17 patients) but was not dose-limiting. Despite its relatively low overall prevalence (32%, 14 patients), neutropenia was among the most prevalent Gr3/4 trAEs (20%, nine patients) and was the most prevalent Gr4 trAE (9%, four patients). No patients experienced neutropenic fever.

Previous studies have reported that up to 70% of patients receiving paclitaxel therapy experience PIPN (16). PIPN incidence and severity depend on the paclitaxel dose, frequency, and duration of treatment and may be influenced by comorbidities and/or supportive management (17, 18). In this study, PIPN occurred in 9 of 44 patients (20%; **Table 2**; Supplementary Table S6). Although dose intensity was not a DLT criterion in this study, the mean paclitaxel dose intensity delivered during the DLT evaluation period was comparable with the protocol-specified dose intensity at each paclitaxel dose level, and no patients missed a dose due to PIPN (Supplementary Table S7). With regard to cumulative PIPN, one patient (patient 43, 80 mg/m^2 paclitaxel) experienced Gr2 PIPN beginning at C5 that progressed to Gr3 PIPN at C12 and DL1A (60 mg/m^2 paclitaxel); Gr3 PIPN improved to Gr2 after a treatment hold of 14 days and subsequently remained at Gr2 with supportive measures for three additional cycles at DCO. Gr2 PIPN during C6 resolved in patient 8 after 17 days, and the patient completed four additional cycles without worsening of PIPN before disease progression. Patient 10 first experienced Gr1 PIPN during C4 that

Table 2. Most common adverse events attributed to nilotinib–paclitaxel therapy.

Adverse event	All grades *n* (%)	Gr1 and Gr2 *n* (%)	Gr3 *n* (%)	Gr4 *n* (%)
Hematologic				
Lymphopenia	36 (82)	19 (43)	15 (34)	2 (5)
Anemia	33 (75)	25 (57)	8 (18)	—
Leukopenia	33 (75)	22 (50)	9 (20)	2 (5)
Neutropenia	14 (32)	5 (11)	5 (11)	4 (9)
Thrombocytopenia	6 (14)	6 (14)	—	—
Gastrointestinal				
Nausea	21 (48)	21 (48)	—	—
Diarrhea	20 (45)	20 (45)	—	—
Vomiting	15 (34)	15 (34)	—	—
Anorexia	8 (18)	8 (18)	—	—
Electrolyte				
Hypophosphatemia	28 (64)	16 (36)	12 (27)	—
Hyponatremia	11 (25)	10 (23)	1 (2)	—
Hypomagnesemia	10 (23)	9 (20)	1 (2)	—
Hypoalbuminemia	7 (16)	7 (16)	—	—
Hypocalcemia	5 (11)	5 (11)	—	—
Hyperkalemia	5 (11)	5 (11)	—	—
Laboratory assessments				
Blood bilirubin increased	17 (39)	16 (36)	1 (2)	—
AST increased	17 (39)	15 (34)	2 (5)	—
ALT increased	16 (36)	14 (32)	2 (5)	—
Alkaline phosphatase increased	11 (25)	9 (20)	2 (5)	—
Creatinine increased	9 (20)	9 (20)	—	—
Nervous system				
Peripheral sensory neuropathy	9 (20)	8 (18)	1 (2)	—
Dysgeusia	6 (14)	6 (14)	—	—
Photosensitivity	2 (5)	1 (2)	1 (2)	—
Other				
Fatigue	25 (57)	21 (48)	4 (9)	—
Alopecia	13 (30)	13 (30)	—	—
Hypertension	7 (16)	6 (14)	1 (2)	—
Edema (limbs)	5 (11)	5 (11)	—	—
Rash (maculopapular)	3 (7)	2 (5)	1 (2)	—

Highest-grade adverse events per patient occurring in at least 10% of patients (or, for Gr3–4 events, in at least one patient) and at least possibly attributed to the study drugs are shown.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

lasted for nearly 3.5 years, followed by Gr1 paresthesia, Gr1 pain in fingertips, and Gr1 toe tingling/sensitivity, which were attributed to PIPN; this patient remained on study and had completed 80 cycles at DCO. Six patients experiencing PIPN went off study before any improvement or resolution of this toxicity.

Two patients who experienced durable PRs went on treatment holidays due to persistent toxicities. During treatment holidays, 28-day increments were counted as cycles despite no treatment being administered; treatment resumed with signs of disease progression, as determined by the principal investigator. Patient 10 went on treatment holiday from C33 through C66 due to persistent Gr2–3 neutropenia and continued on study after having completed 80 cycles at the DCO. Patient 12 experienced persistent Gr1–2 fatigue that interfered with quality of life and went on treatment holiday from C44 through C52 before ultimately experiencing progressive disease (PD) after cycle 64.

Clinical outcomes

Thirty-seven patients were evaluable for objective response (**Fig. 1**). Seven patients did not complete reimaging on study and were not evaluable for response by RECIST 1.1 (off treatment by patient choice: $n = 3$; clinical progression: $n = 2$; death unrelated to study treatment: $n = 2$, 1 due to cardiac arrest and 1 due to disease progression); one patient enrolled but died prior to the start of treatment. Confirmed partial responses (cPR) were measured in 3 of 37 evaluable patients (8% overall response rate; 90% confidence interval, 2%–17%; **Fig. 1**): two patients with adult ovarian granulosa cell tumor (AOGCT; patient 10, enrolled at DL2, and patient 12, enrolled at DL3) and one patient with endometrial cancer (patient 8, enrolled at DL2). Patient 3 (anal cancer) enrolled at DL1 and experienced an unconfirmed PR at early restaging but refused further treatment, coming off the study before a confirmatory scan was performed. These data suggest that this combination may confer clinical benefit at several different dose levels.

Among patients with cPRs, times to response were 2, 4, and 19 cycles, and durations of time on study were 11, 80, and 64 cycles for patients 8, 10, and 12, respectively; patients 10 and 43 remain on treatment with cPR and SD, respectively, at DCO. Longitudinal tumor measurements demonstrate sustained tumor volume reductions in these patients (Supplementary Fig. S1). Both patients with AOGCT had a best response of progressive disease with prior

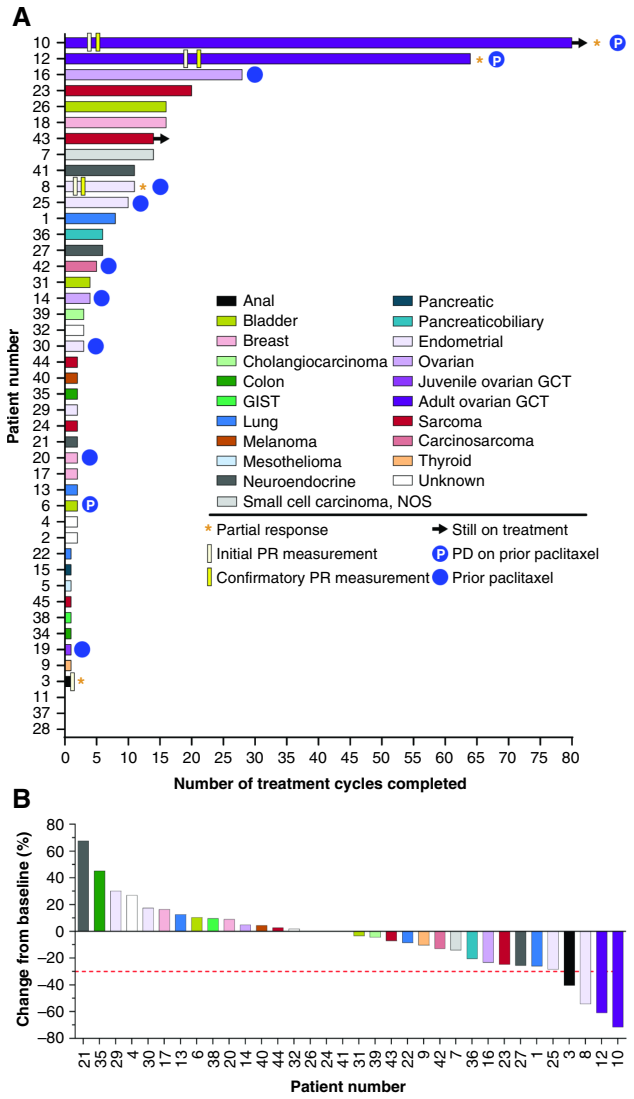

Figure 1.

Clinical response to nilotinib–paclitaxel combination therapy. **A,** Number of treatment cycles completed for patients on study for at least one cycle. Column colors indicate patient tumor types, as noted, and patients experiencing a partial response are denoted by gold asterisks. Blue circles indicate patients who have undergone prior paclitaxel therapy, whereas blue circles with a "P" indicate patients who had a documented best response of progressive disease on prior paclitaxel therapy. **B,** Best target lesion response for patients evaluable for objective response. The dashed horizontal red line indicates a target lesion size decrease of ≥30% relative to baseline. Colors represent the indicated tumor histologies as defined in **A**. GCT, granulosa cell tumor; GIST, gastrointestinal stromal tumor; NOS, not otherwise specified; PD, progressive disease; PR, partial response.

paclitaxel monotherapy. These two patients were designated as having exceptional responses (ER) to nilotinib–paclitaxel according to the criteria of the NCI's Exceptional Responder Initiative (https://www.cancer.gov/about-cancer/treatment/research/exceptional-responders-initiative-qa) by virtue of their protracted duration of response to nilotinib–paclitaxel as well as to a prior investigational combination therapy of temozolomide and the base excision repair-inhibiting agent TRC102 (19); both patients were also enrolled in the NCI Exceptional Responders study to explore the molecular determinants of ER to various therapies (19, 20). Prior to their enrollment in the present study and the preceding temozolomide-TRC102 trial, both patients had progressed rapidly on numerous lines of prior therapy (9 and 6 lines for patients 10 and 12, respectively), with median (interquartile range) times on treatment of 3 (2–4) months and 4 (2–7) months, respectively (Supplementary Table S8). Both patients enrolled in the escalation cohort of this trial and did not have biopsies.

In addition to these PRs, eight patients experienced stable disease for ≥10 cycles. These include one patient with serous ovarian carcinoma who was on study for 28 cycles, two patients with sarcomas (fibromyxoid sarcoma and uterine leiomyosarcoma; 20 and 14 cycles, respectively), one patient with bladder adenocarcinoma (16 cycles), one patient with hormone receptor–positive (HR^+)/$HER2^+$ breast adenocarcinoma (16 cycles), one patient with small cell carcinoma (not otherwise specified; 14 cycles), one patient with neuroendocrine carcinoma (11 cycles), and one patient with endometrial uterine adenocarcinoma (10 cycles).

Pharmacokinetic analysis

Plasma concentrations of paclitaxel were dose-proportional across the two doses tested for each agent (**Fig. 2**; Supplementary Table S9). As CYP2C8 metabolizes paclitaxel to 6α-hydroxypaclitaxel (21) and nilotinib inhibits CYP2C8-mediated 6α-hydroxypaclitaxel formation (22), we assessed the effects of nilotinib coadministration on plasma levels of paclitaxel and 6α-hydroxypaclitaxel. Paclitaxel is also metabolized to 3′-p-hydroxypaclitaxel by CYP3A4, raising the possibility that standard prophylactic coadministration of a CYP3A4 inducer, dexamethasone, with paclitaxel may affect plasma paclitaxel levels. Comparison of paclitaxel AUC values on day 8 for DL2 and DL3 ($P = 0.567$, **Fig. 2**) demonstrated no significant modulation of paclitaxel concentration by different doses of nilotinib. On day 8, paclitaxel plasma AUC values in patients at DL2 (80 mg/m^2 paclitaxel dose) were significantly higher than in patients at DL1 (60 mg/m^2 paclitaxel dose, $P = 0.037$, **Fig. 2**; Supplementary Table S9). No significant changes were measured in 6α-hydroxypaclitaxel or 3′-p-hydroxypaclitaxel plasma concentrations between days or between dose levels. Although small sample sizes for DL1 and DL3 ($n = 4$ and 3 patients, respectively) precluded comparisons across dose levels, these data suggest that nilotinib does not modulate plasma paclitaxel exposures. Mean nilotinib $AUC_{(0-24hours)}$ values on day 8 were not significantly different between DL2 and DL3 (3,072 ± 2,175 and 5,425 ± 2,440 μmol/L × minutes, respectively, $P = 0.2982$ using an unpaired, two-sided t test). Neither DL2 nor DL3 $AUC_{(0-24hours)}$ values were significantly different from a published mean $AUC_{(0-24hours)}$ value for nilotinib monotherapy (3,848 ± 1,116 μmol/L × minutes, $P = 0.8771$ and 0.1802, respectively; ref. 23).

Pharmacodynamic analyses

In preclinical studies of the nilotinib–paclitaxel-responsive breast carcinoma xenograft model MDA-MB-468, the regimen employed in the present trial induced EMT, yielding a mesenchymal-like phenotype in surviving tumor cells from days 8 to 19 (13). At 5 weeks after the cessation of combination treatment, surviving cancer cells repopulated the tumor microenvironment according to their original mixture of epithelial and mesenchymal phenotypes (13). Based on these preclinical studies, we assessed tumor biopsies collected at baseline, after paclitaxel alone (C1D2), and after

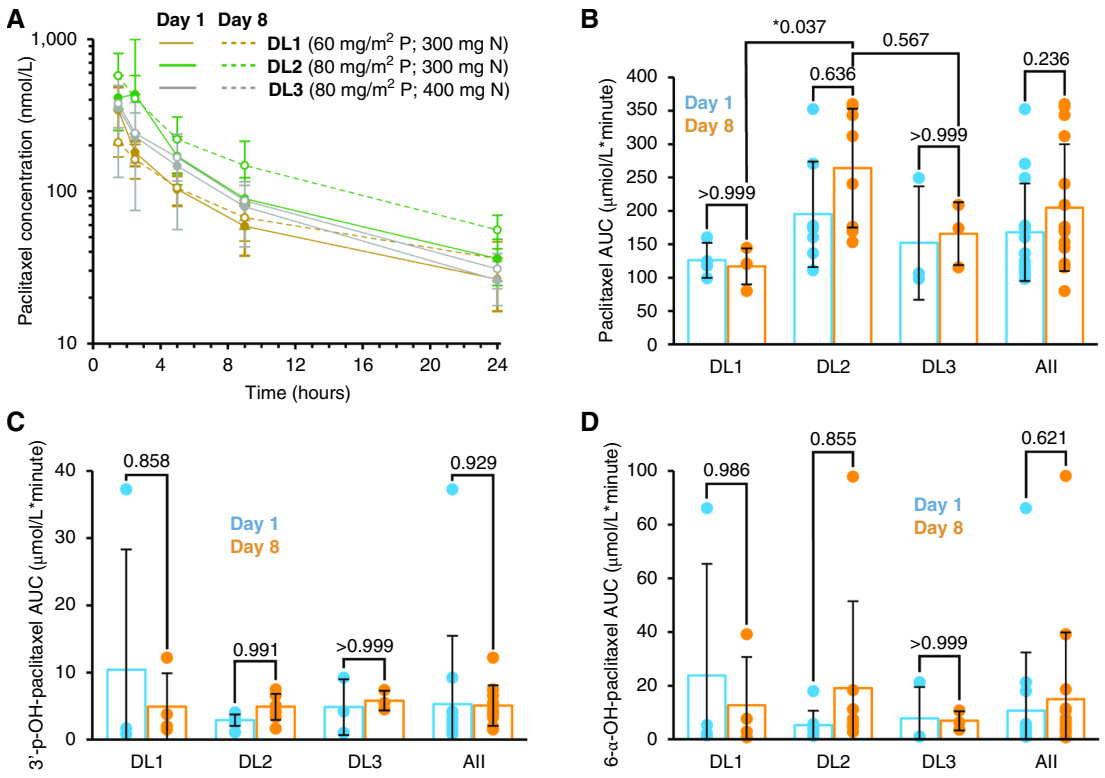

Figure 2.

Plasma paclitaxel pharmacokinetics following nilotinib–paclitaxel combination therapy. **A,** Mean paclitaxel plasma concentrations following the single-agent paclitaxel run-in (day 1, solid lines) and nilotinib–paclitaxel combination therapy (day 8, dashed lines). Mean values (± standard deviation) are shown for each dose level (n = 4, 8, and 3 patients for DL1, DL2, and DL3, respectively). Doses of paclitaxel (P) and nilotinib (N) for each dose level are as noted. **B–D,** AUC values for paclitaxel and key metabolites. AUC values for each patient (circles), along with mean (bars) and standard deviation values, are shown on day 1 (blue) and day 8 (orange) for paclitaxel (**B**), 3′-p-hydroxypaclitaxel (**C**), and 6α-hydroxypaclitaxel (**D**). Brackets indicate P values for pairwise comparisons between AUC values from different days or DLs using ordinary one-way ANOVA and Šidák's multiple comparisons test in GraphPad Prism version 10.1.1; the only statistically significant difference (P < 0.05, paclitaxel AUC at DL1 vs. DL2 on day 8) is indicated by an asterisk in **B**.

multiple weeks of treatment (C1D28) for biomarkers of EMT (E-cadherin, vimentin, and their co-expression for epithelial, mesenchymal, and transitional phenotypes, respectively) using a clinically validated assay (13). As expected, five patients with sarcoma (patients 24, 29, 43, 44, and 45) and one patient with melanoma (patient 40) displayed tumor phenotypes with high $\log_{10}$(V/E) values at all time points, consistent with the known mesenchymal characteristics of these tumor types (Supplementary Fig. S2; ref. 24). Among seven patients with carcinomas, baseline EMT phenotypes were predominantly epithelial. Patient 30 (endometrial carcinosarcoma) had a mixed epithelial/mesenchymal (E/M) tumor phenotype at baseline, and patient 42 (uterine carcinosarcoma) had a mesenchymal baseline phenotype. Although statistically significant modulation of mean $\log_{10}$(V/E) values was noted, no obvious biologically relevant changes in EMT phenotype (e.g., conversion from a predominantly epithelial-like phenotype to a predominantly mesenchymal-like phenotype) were observed in response to single-agent paclitaxel (C1D2 biopsies) or the nilotinib–paclitaxel combination (C1D28 biopsies). A significant increase in the mitotic arrest marker pHH3 was measured in C1D2 biopsies relative to baseline biopsies (P = 0.0031; ANOVA P = 0.0010, F = 8.183; Supplementary Fig. S3), confirming the pharmacodynamic activity of paclitaxel. The lack of significant pHH3 modulation at C1D28 compared with baseline (P = 0.9955) is likely due to the timing of this biopsy (13 days after the last paclitaxel dose).

EMT was also assessed in CTCs in blood specimens using vimentin and cytokeratin markers for mesenchymal- and epithelial-like cells as previously described (14, 15). Longitudinal blood specimens for CTC EMT phenotype analysis collected from the three responding patients revealed increases in mesenchymal-like and E/M mixed-phenotype CTCs prior to progression in patients 8 and 12 and during the treatment holiday for patient 10 (**Fig. 3**). Baseline and early treatment cycles for patient 8 were not reportable due to the use of an earlier generation assay and analysis platform that did not include the vimentin biomarker. These results suggest CTC EMT measurements may be useful for longitudinal monitoring of patients responding to the nilotinib–paclitaxel combination and for clinical decision-making about the resumption of treatment following drug holidays. However, the lack of responding patients in the biopsy expansion cohort precluded analysis of tumor pharmacodynamic effects that might be associated with response.

Discussion

The nilotinib–paclitaxel combination demonstrated antitumor activity and acceptable tolerability. Rates of high-grade PIPN (Gr3:

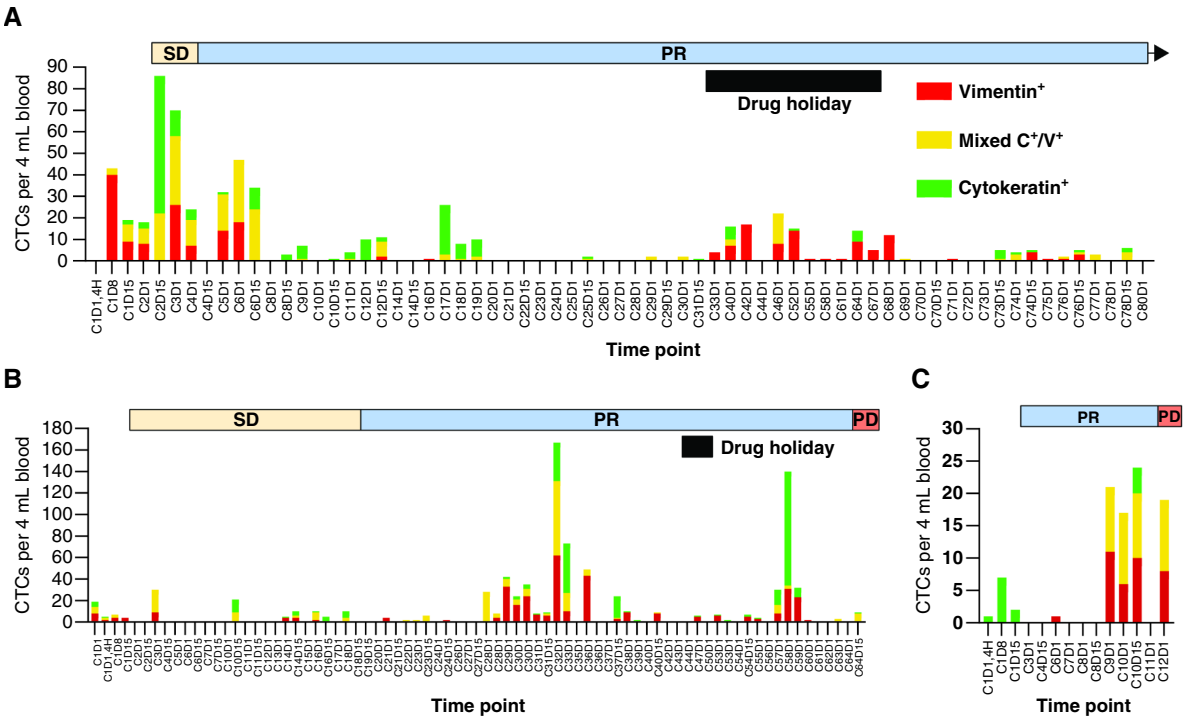

Figure 3.

Pharmacodynamic effects on the epithelial/mesenchymal phenotype of CTCs in patients with cPRs to nilotinib–paclitaxel. Longitudinal CTC enumeration and epithelial/mesenchymal phenotype quantitation are shown for patients 10 (**A**), 12 (**B**), and 8 (**C**) with cPRs. Bar heights indicate the number of CTCs of each epithelial/mesenchymal phenotype [C^+ (green), mixed C^+/V^+ (yellow), or V^+ (red)] and in aggregate (overall height of the stacked bars for each patient and time point). Sample availability limited analysis to one replicate per time point, precluding the determination of standard deviations or other statistical analyses. RECIST response (PD, progressive disease; PR, partial response; SD, stable disease) and drug holidays (black bars), as applicable, are shown above each graph.

2%; Gr4: 0%) were comparable with or lower than those reported in the literature for paclitaxel monotherapy administered on similar dosage regimens (Supplementary Table S6), and the overall frequency of PIPN (20%) was low relative to historical PIPN rates for paclitaxel monotherapy [e.g., 71% or 96% (after 12 or 16 weeks of treatment, respectively) for patients with breast cancer receiving 80 mg/m^2 paclitaxel weekly (25)]. However, given the relatively short median time on treatment for patients in this study (2 months), the observed frequency of PIPN may be due to the lower median cumulative dose delivered for this phase 1 trial relative to those reported for comparator studies of paclitaxel monotherapy (median time to progression: up to 14.7 months, Supplementary Table S6), many of which also utilized weekly paclitaxel administration rather than the intermittent 3 weeks on/1 week off schedule used in this study. Tolerability for the combination, together with RECIST responses recorded for patients across all DLs, is indicative of a promising therapeutic window for this combination in some tumor types.

The response rate in this tissue-agnostic phase 1 study was 8% (3 of 37 patients), with cPRs measured in both patients with AOGCT and one patient with endometrial carcinoma. Despite the limited literature about AOGCT's natural history (due to the relative rarity of this disease), the available case reports and retrospective analyses indicate that the ≥5-year duration of sustained tumor regression measured for both responding patients with AOGCT in the present study is well beyond tumor burden fluctuations typically observed in patients not undergoing treatment (26–28). Such sustained tumor regression is also exceptional relative to data from other early-phase treatment trials of pretreated patients with recurrent AOGCT, for which median progression-free survival times ranging from 8.6 to 12 months have been reported (28–30). Indeed, weekly paclitaxel monotherapy in a phase 2 study arm consisting of 32 patients with relapsed ovarian sex cord–stromal tumors (84% of which were AOGCT) yielded a progression-free survival of 14.7 months (31), which, along with the lack of response to prior paclitaxel monotherapy in the two heavily pretreated ER patients with AOGCT in the present study, underscores the impressive activity of the nilotinib–paclitaxel combination in this tumor type. Together with the cPR in one patient with endometrial carcinoma, these two ERs in patients with AOGCT suggest that further testing of the nilotinib–paclitaxel combination in patients with gynecologic cancers may be warranted.

Questions remain about whether nilotinib–paclitaxel offers improved clinical activity relative to the respective single agents and, if so, by what mechanism(s) this activity is achieved. Demonstrating greater-than-additive activity for a combination is challenging in human tumor xenograft models, let alone in patients, given the need for assessing multiple different combination doses. In practice, promising combination activity is typically identified by greater-than-single-agent activity, as previously demonstrated for the nilotinib–paclitaxel combination in xenograft models (2). In the present study, the extended-duration cPRs in two patients with AOGCT who did

not respond to prior paclitaxel therapy suggest potential greater-than-single-agent clinical activity for this combination.

It seems unlikely that nilotinib is the primary driver of combination activity given the general paucity of single-agent nilotinib activity in preclinical solid tumor models (2) and little evidence of nilotinib activity in patients with solid tumors (other than melanoma or gastrointestinal stromal tumors harboring specific activating mutations in c-Kit, a nilotinib target; refs. 32, 33). In addition, nilotinib inhibits the proliferation of AOGCT KGN cells *in vitro* (34) but only at concentrations five-fold greater than the clinical C_{max} (EC_{50}, 13.1 μmol/L; clinical C_{max}, ~2 μmol/L for 300 mg twice-daily dosing; ref. 35). Imatinib yielded disease stabilization in case reports of two patients with AOGCT; these patients experienced stable disease for over 16 months (36) or 12 months (37). However, no RECIST objective responses to nilotinib or imatinib in patients with AOGCT have been reported. Although we cannot exclude the possibility that these responses were driven by nilotinib alone, these data suggest that nilotinib is unlikely to fully account for the activity of the combination in these two patients.

Though both patients with ERs to nilotinib–paclitaxel also exhibited ERs to their immediately preceding therapy with the combination of temozolomide and TRC102, the full treatment history for these patients indicates that such protracted responses to nilotinib–paclitaxel are indeed exceptional relative to their responses to other therapies. First, although the responses to temozolomide-TRC102 and corresponding treatment durations of 22 and 13 months for patients 10 and 12, respectively (8), were deemed exceptional for this tumor type, these were far surpassed by the durations of nilotinib–paclitaxel treatment for these responding patients (≥80+ and 64 months, respectively), suggesting that nilotinib–paclitaxel may be particularly effective in this setting. Furthermore, it is important to note that despite these ERs to both temozolomide-TRC102 and nilotinib–paclitaxel, the molecular characteristics of these tumors that underlie the ER do not seem to confer broad sensitivity to myriad therapies, as both patients progressed rapidly on numerous other therapies.

The nilotinib–paclitaxel combination did not induce biologically significant changes in tumor EMT phenotype at the time point examined (C1D28), nor were such changes observed after paclitaxel alone on C1D2. The C1D2 biopsies demonstrated the expected paclitaxel effect (i.e., mitotic arrest indicated by increased percentages of $pHH3^+$ cells) that was not predictive of EMT or clinical outcome; this effect was observed in patients who had prior taxane treatment. It is possible that any combination-induced changes in EMT phenotype were not captured at the single post-combination time point examined in patients (C1D28) or that such changes occur predominantly in tumors that are responding to nilotinib–paclitaxel. Combination-induced EMT phenotype changes were observed in a xenograft model (MDA-MB-468) that responded to the combination (13). The lack of responding patients in the biopsy expansion cohort precluded any analysis of tumor pharmacodynamic effects of the combination that may be associated with response.

The CTC EMT analysis provided some insights into tumor evolution in responding patients, with potential implications for the management of treatment holidays. For patient 10, who remains on treatment after ≥80 cycles of therapy, the onset of a partial response to the combination at cycle 4 coincided with a transition to a more epithelial-like tumor phenotype; a subsequent drug holiday yielded a transition back to a more mesenchymal-like CTC phenotype, and CTC numbers decreased again following treatment resumption. For patient 12, the onset of a partial response at cycle 19 occurred at a time of relatively low CTC numbers and was followed by an increase in mesenchymal-like CTCs during the remainder of the PR; the treatment holiday initially resulted in the resumption of low CTC counts, but another spike in CTC counts (with epithelial-like, mesenchymal-like, and mixed E/M phenotype cells) occurred in the cycles following the treatment holiday and preceding disease progression. Likewise, disease progression in patient 8 was preceded by an increase in mesenchymal-like and mixed E/M phenotype CTCs. Although the small sample size precludes analysis of associations between response and CTC EMT phenotype, these data suggest that longitudinal CTC pharmacodynamic monitoring may be useful in managing treatment holidays and anticipating disease progression in patients receiving nilotinib–paclitaxel; such monitoring has been incorporated into the ongoing study of this combination in patients with rare tumors (NCT04449549).

Though the dose escalation schema for this IND-exempt study adhered to the paclitaxel and nilotinib administration schedules utilized in approved, standard-of-care settings for the respective monotherapies, it is possible that the combination dosage regimen could be further optimized for improved activity and/or tolerability. For example, high-dose, intermittent administration of other tyrosine kinase inhibitors has been demonstrated to yield higher plasma C_{max} values relative to lower-dose, continuous administration, suggesting the potential for improved activity with the former (38). Such optimization of the nilotinib dosage regimen in the nilotinib–paclitaxel combination could yield additional clinical benefit and, upon identification of the combination mechanism of action, can be aided by the collection of pharmacokinetic and pharmacodynamic data to establish a PK/PD relationship for the relevant nilotinib target kinase(s).

The promising antitumor activity and therapeutic index for the nilotinib–paclitaxel combination reported here led to the opening of several additional studies of this combination. In addition to the phase 2 study in patients with rare cancers, phase 2 trials assessing this combination in patients with peritoneal carcinomatosis (NCT05185947) and a ComboMATCH trial in patients with prior taxane treatment who do not have molecular aberrations qualifying them for other ComboMATCH treatment arms (NCT05554341) are currently active. No data from these studies have been reported to date. Notably, a phase 1b study is actively assessing the efficacy of intermittent nilotinib dosing in attenuating PIPN in patients with breast cancer (NCT04205903), although no results have been reported (6). Further analyses from these trials and ongoing preclinical studies will be needed to understand the mechanism(s) of action of the nilotinib–paclitaxel combination and inform further clinical studies on the efficacy and possible improved tolerability of the combination versus either single agent.

Authors' Disclosures

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Note

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