Clinical Cancer Research

Weekly *nab*-Rapamycin in Patients with Advanced Nonhematologic Malignancies: Final Results of a Phase I Trial

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Abstract

Purpose: This dose-finding phase I study investigated the maximum-tolerated dose (MTD) and safety of weekly nanoparticle albumin-bound rapamycin (*nab*-rapamycin) in patients with untreatable advanced nonhematologic malignancies.

Experimental Design: *nab*-Rapamycin was administered weekly for 3 weeks followed by 1 week of rest, with a starting dose of 45 mg/m^2. Additional doses were 56.25, 100, 150, and 125 mg/m^2.

Results: Of 27 enrolled patients, 26 were treated. Two dose-limiting toxicities (DLT) occurred at 150 mg/m^2 [grade 3 aspartate aminotransferase (AST) elevation and grade 4 thrombocytopenia], and two DLTs occurred at 125 mg/m^2 (grade 3 suicidal ideation and grade 3 hypophosphatemia). Thus, the MTD was declared at 100 mg/m^2. Most treatment-related adverse events (TRAE) were grade 1/2, including thrombocytopenia (58%), hypokalemia (23%), mucositis (38%), fatigue (27%), rash (23%), diarrhea (23%), nausea (19%), anemia (19%), hypophosphatemia (19%), neutropenia (15%), and hypertriglyceridemia (15%). Only one grade 3 nonhematologic TRAE (dyspnea) and one grade 3 hematologic event (anemia) occurred at the MTD. One patient with kidney cancer had a partial response and 2 patients remained on study for 365 days (patient with mesothelioma) and 238 days (patient with neuroendocrine tumor). The peak concentration (C_{max}) and area under the concentration–time curve (AUC) of rapamycin increased with dose between 45 and 150 mg/m^2, except for a relatively low AUC at 125 mg/m^2. *nab*-Rapamycin significantly inhibited mTOR targets S6K and 4EBP1.

Conclusions: The clinical dose of single-agent *nab*-rapamycin was established at 100 mg/m^2 weekly (3 of 4 weeks) given intravenously, which was well tolerated with preliminary evidence of response and stable disease, and produced a fairly dose-proportional pharmacokinetic profile in patients with unresectable advanced nonhematologic malignancies. *Clin Cancer Res; 19(19); 5474–84. ©2013 AACR.*

Introduction

The prognosis for patients with advanced solid tumors is poor, as most malignancies are not responsive to standard treatments at the advanced stage. mTOR, a serine/threonine-specific protein kinase, is downstream of the phosphoinositide 3-kinase (PI3K)/Akt pathway, and a key regulator of cell survival, proliferation, stress, and metabolism (1). mTOR inhibition with rapamycin and rapalogs (everolimus and temsirolimus) has proven to be effective in various solid tumors including renal cell carcinoma, neuroendocrine tumors, and breast cancer (2–12).

Although rapamycin is an efficacious allosteric inhibitor of mTOR complex 1 (mTORC1), it has low oral bioavailability, poor solubility, and dose-limiting intestinal toxicity (13, 14). Other rapalogs, including everolimus and ridaforolimus, are also oral preparations and are often associated with significant stomatitis (15). Temsirolimus, a prodrug of rapamycin, requires conversion by the CYP3A enzyme and also carries a significant risk for developing skin rash and stomatitis (16). Because none of the rapalogs are highly water soluble, they require surfactants and solvents in an intravenous formulation, such as polysorbate 80 for temsirolimus (17). The use of surfactants can potentially cause irritation, local inflammation, and potential reduction of drug efficacy due to micellar sequestration, and the need for premedication to avoid potential hypersensitivity reactions (17). The nanoparticle albumin-bound rapamycin (*nab*-rapamycin; Celgene Inc.),

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Translational Relevance

In this first clinical evaluation of nanoparticle albumin-bound rapamycin (*nab*-rapamycin), an mTOR inhibitor, it was well tolerated given intravenously in patients with unresectable advanced solid tumors. Most rapalogs are oral preparations requiring toxic surfactants for intravenous formulation due to poor water solubility. The *nab*-technology exploits the natural properties of human albumin to achieve a solvent-free drug delivery. Dose-limiting toxicities (DLT) including mucositis/stomatitis that were observed with mTOR inhibitors were not dose-limiting with *nab*-rapamycin. Notably, 27% of patients were 65 years or older, a frail population that are more prone to toxicities and receive lesser benefits than younger patients from everolimus/temsirolimus. Preliminary proof-of-efficacy was observed in this phase I study. *nab*-Rapamycin produced a fairly dose-proportional peak concentration (C_{max}) and area under the concentration–time curve (AUC) increase of rapamycin, and significantly inhibited mTOR targets.

with a mean particle size of about 100 nm, is freely dispersible in saline and is suitable for intravenous administration, and may be an advantageous alternative to oral rapamycin or oral rapalogs. Human albumin has broad binding affinity and accumulates in tumors, making it an ideal candidate for drug delivery (18, 19). In preclinical studies, *nab*-rapamycin was safe and highly effective in multiple tumor types; it reduced cell viability and decreased downstream signaling in various xenograft cancer models, including pancreatic, colorectal, multiple myeloma, and breast cancer (20–23). In addition, in human breast xenograft models, *nab*-rapamycin alone produced 75% tumor growth inhibition without weight loss and antitumor activity was further enhanced with the combination of doxorubicin (a topoisomerase inhibitor), SAHA [an histone deacetylase (HDAC) inhibitor], erlotinib (an EGF tyrosine kinase inhibitor), and perifosine (an Akt inhibitor) with 15% or less weight loss, indicating high tolerability in the combination regimens (24).

On the basis of the promising preclinical results, this dose-finding phase I study investigated the maximum-tolerated dose (MTD) and safety of intravenous single-agent weekly *nab*-rapamycin in patients with untreatable advanced nonhematologic malignancies.

Patients and Methods

This study was conducted at MD Anderson Cancer Center (Houston, TX), and the Sarcoma Oncology Center (Santa Monica, CA). The study was approved by the Institutional Review Board of both participating medical institutions and was conducted in compliance with the World Medical Association Declaration of Helsinki and Good Clinical Practice, Guidelines of the International Conference on Harmonization (25). Written informed consent was obtained from all patients before study initiation.

Patients

Eligible patients were 18 years or older, had histologically or cytologically confirmed diagnosis of stage IV cancer that was not amenable to curative therapy. Advanced disease was defined as metastatic disease or locally advanced disease that was surgically unresectable and considered unmanageable with standard therapies such as radiation or systemic therapies. Patients had a measurable disease by Response Evaluation Criteria in Solid Tumor (RECIST) v1.0, life expectancy 3 or more months, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, adequate renal function (serum creatinine <1.5 mg/dL and/or creatinine clearance ≥60 mL/min), and were off all therapy for at least 4 weeks before study drug administration. Patients were excluded from the study if they had brain metastasis, history of interstitial lung disease and/or pneumonitis, or a history of allergy or hypersensitivity to the study drug or any compounds of similar chemical or biologic composition.

Study design

This dose-finding study evaluated MTD and dose-limiting toxicities (DLT) of *nab*-rapamycin in patients with advanced nonhematologic malignancies. Following baseline evaluations, patients entered into the treatment period. *nab*-Rapamycin was administered by intravenous infusion for 30 minutes weekly for 3 weeks followed by 1 week of rest (28-day cycle), with a starting dose of 45 mg/m^2. The starting dose of *nab*-rapamycin was chosen on the basis of nonclinical toxicology data of *nab*-rapamycin. Additional dose levels were 56.25, 100, 150, and 125 mg/m^2. The original protocol was amended to add the 125 mg/m^2 dose cohort for refinement of MTD.

The first cycle was considered the treatment interval for determination of DLTs and the MTD. The MTD for *nab*-rapamycin was determined using a standard 3+3 design, where 3 patients were enrolled at each dose level. The protocol was amended to ensure that all patients at a given dose level complete one cycle of therapy before patients were enrolled at the next dose level. If no DLT was observed, 3 additional patients were enrolled at the next dose level. If one DLT was observed, the dose level was expanded to 6 patients. If two DLTs were observed at a given dose level, the MTD was considered to be exceeded. Of the 6-patient expanded cohort, if ≤1 of 6 patients experienced a DLT, this was defined as the MTD. All patients at a given dose level completed one cycle of therapy before patients were enrolled at the next dose level.

A DLT was defined [using the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI CTCAE) v3.0] as any grade 3/4 nonhematologic toxicity, grade 3/4 nausea, or vomiting that occurred despite treatment, grade 4 thrombocytopenia of any duration and grade 4 uncomplicated neutropenia (i.e., without fever or infection) lasting more than 7 days, grade 4 febrile

neutropenia that required hospitalization, and any grade 3 hematologic toxicity that required treatment delay beyond 3 weeks.

Throughout the study, patients were routinely assessed for toxicities, response, and possible need for a dose modification. Patients continued on treatment until they experienced progressive disease or unacceptable toxicity, withdrew consent, or their physician felt it was no longer in their best interest to continue on treatment. Discontinued patients completed the end of study evaluation and entered into a 30-day follow-up period.

Assessments and statistical methods

All patients who received at least one dose of study drug (treated population) were evaluated for safety. Safety and tolerability endpoints included the incidence of treatment-related adverse events (TRAE) by NCI CTCAE v3.0 and the percentage of patients experiencing TRAEs that required dose delays/modifications, and/or premature discontinuation of the study drug.

The exploratory efficacy analysis included the summary of percentage of patients who achieved an objective with confirmed complete or partial tumor response (CR or PR, respectively) and the percentage of patients with confirmed stable disease for at least 12 weeks, using RECIST v1.0. The objective tumor responses of target or nontarget lesions were classified individually based on RECIST v1.0. The overall tumor response was determined by taking into account the responses of target lesions and nontarget lesions as well as the presence of new lesions.

Tumor response assessments were carried out every 12 weeks. A waterfall plot was used to illustrate the percentage change of target lesion from baseline for all patients with target tumor evaluation. The corresponding objective target lesion responses, dose level cohorts, and tumor types were also provided in the graph.

Molecular analyses

Evaluation of PTEN loss was carried out with immunohistochemistry (IHC) using monoclonal mouse anti-human PTEN antibody clone 6H2.1 from Dako at 1:100 dilution, as described by Gonzalez-Angulo and colleagues (26). Briefly, both cytoplasmic and nuclear PTEN staining in the tumor and non-neoplastic ductal epithelium and stroma were quantified. PTEN expression level was scored semiquantitatively on the basis of staining intensity (SI) and distribution using the immunoreactive score (IRS) as follows: IRS = SI × percentage of positive cells. Staining intensity was determined as 0, negative; 1, weak; 2, moderate; and 3, strong. Percentage of positive cells was defined as 0, <1%; 1, 1%–10%; 2, 11%–50%; 3, 51%–80%; and 4, >80% positive cells. Tumors with IRS of 0 were considered to have PTEN loss. A mass spectroscopy–based approach evaluating single-nucleotide polymorphisms (SNP) was used to detect known mutations in members of the PI3K pathway. Molecular analysis was conducted in patients who showed clinical benefit using archival tissue.

Pharmacokinetics

Whole-blood samples (4 mL each) were collected in vacutainer tubes containing EDTA as the anticoagulant for determination of rapamycin. Samples were obtained only during cycle 1 and were taken immediately predose (before infusion), during the infusion (15 and 30 minutes before end of the infusion), and postinfusion at 1.0, 1.5, 2, 4, 6, 8, 24, 48, 72, 96, and 168 hours. The samples were stored frozen at a temperature between −20°C and −80°C until shipment for analysis to St. George's Hospital at the University of London (London, United Kingdom).

The whole-blood samples were analyzed for total (free + bound) rapamycin using high-performance liquid chromatography–tandem mass spectrometry (HPLC/MS-MS). Rapamycin concentrations in whole blood were validated from 10 to 2,000 ng/mL with 32-desmethoxyrapamycin used as an internal standard. Analytes were extracted using a solvent mixture and detected and quantified by reverse phase HPLC with detection via turbo ion-spray mass spectrometry.

The concentration-versus-time data for rapamycin in whole blood were analyzed using a noncompartmental analysis technique and WinNonlin software. Pharmacokinetic analysis was based on whole-blood concentrations due to the known instability of rapamycin in plasma. Calculated parameters included peak concentration (C_{max}), half-life ($t_{1/2}$), area under the concentration–time curve (AUC), clearance (CL), and steady-state volume of distribution (V_{ss}). A simple regression model was applied to assess the relationship of the pharmacokinetic parameters with dose.

Peripheral blood mononuclear cells and reverse phase protein arrays

Whole blood for pharmacodynamics evaluation was collected only during cycle 1 at four time points: C1 D1 (pretreatment), C1 D2, C1 D4, and C1 D8 (immediately before next dose) in an 8-mL cell preparation tube with sodium citrate (Becton, Dickinson and Company). Separation of peripheral blood mononuclear cells (PBMC) from whole blood was accomplished through density gradient centrifugation using Ficoll following the manufacturer's recommendations. After centrifugation, plasma component from the upper half of the tube was transferred to cryotubes and snap-frozen. The layer containing the cells was transferred to a fresh tube, washed, and centrifuged. After removal of the supernatant, PBMC pellet was also snap-frozen.

Reverse phase protein array (RPPA) was conducted in the MD Anderson Cancer Center Functional Proteomics RPPA Core Facility as described previously (27). PBMC samples were resuspended in RPPA lysis buffer containing 0.25% sodium deoxycholate. Protein concentrations were determined using BCA method (Pierce) and 4× SDS sample buffer was added. Final protein concentration was adjusted to 3 μg/μL. Samples were probed with antibodies that were validated for RPPA. A total of 135 proteins and 21 replicates were analyzed, including S6 S240/244, S6 S235/236,

S6KT389, 4EBP1 T37/46, and 4EBP1 T70. Proteomics assessment of S6 S240/244 and 4EBP1 T37/46 was carried out using Meso Scale discovery (MSD) phosphoprotein assays (Meso Scale Discovery).

The RPPA spot signal intensity data obtained from MicroVigene automated RPPA module (VigeneTech, Inc.) were analyzed using the R package SuperCurve (version 1.4.3; ref. 28), available at "http://bioinformatics.mdanderson.org/OOMPA". RPPA raw data were treated with median centering across samples, and then a centering by the sample median was undertaken on the treated data and the final normalized data were obtained by applying median absolute deviation (MAD) scaling to the data. Linear mixed models and ANOVA tests were developed and applied to test the pre- versus posttreatment and inhibition effects at each dose level and each pair of time points. Tukey tests were also used for pairwise comparisons. To test the association of proteins expression on patients' response, patients with stable disease and progressive disease were also compared using logistic models adjusted by time points, and their interactions were also taken into account.

Results

Patients

Twenty-seven patients were enrolled in the study and 26 patients were treated of which 19 have evaluable tumor assessment data. Specifically, 7 patients were treated in the 45 mg/m^2 arm, 1 additional patient was added after a patient did not complete a full cycle, 3 in the 56.25 mg/m^2, 7 in the 100 mg/m^2, 2 in the 150 mg/m^2, and 7 in 125 mg/m^2 arm. Seven patients had no tumor assessments beyond the baseline evaluation as a result of loss to follow-up (3 patients), patient request (1 patient), drug shortage (1 patient), and incomplete tumor evaluation (1 patient). All patients had discontinued therapy at the time of this analysis. Eighteen (69%) patients discontinued treatment because of disease progression, 4 (15%) due to adverse events/toxicities, 2 (8%) for patient request, and 2 (8%) for drug shortage. Patient baseline demographics and characteristics were described in Table 1. Briefly, the median age was 60.5 years, and with the majority of patients were male (62%), Caucasian (81%), and had a baseline ECOG score of 1 (73%). The most common sites of primary tumor diagnosis were head and neck, colorectal, and kidney (12% each). Most patients had a carcinoma/adenocarcinoma (54%) and the rest had sarcoma. All patients had visceral metastases. The most common sites of metastases were lung/thoracic (69%), liver (46%), lymph node (42%), and abdomen/peritoneal (42%).

Table 1. Baseline patient demographics and characteristics

	MTD *n* = 7	All treated patients *n* = 26
Age, median years (range)	57 (36, 76)	60.5 (18, 78)
<65 years, *n* (%)	4 (57)	19 (73)
≥65 years, *n* (%)	3 (43)	7 (27)
Gender, *n* (%)		
Male	5 (71)	16 (62)
Female	2 (29)	10 (38)
Race		
Asian, *n* (%)	0	1 (4)
African heritage, *n* (%)	0	2 (8)
Caucasian, *n* (%)	6 (86)	21 (81)
Hispanic, Latino, *n* (%)	1 (14)	2 (8)
ECOG, *n* (%)		
0	2 (29)	5 (19)
1	5 (71)	19 (73)
2	0	2 (8)
Stage at current diagnosis, *n* (%)		
IV	7 (100)	26 (100)
Site of primary diagnosis, *n* (%)		
Bladder	1 (14)	1 (4)
Breast	0	1 (4)
Colorectal	2 (29)	3 (12)
Esophagus	1 (14)	2 (8)
Head and neck	1 (14)	3 (12)
Kidney	0	3 (12)
Lung/thoracic	1 (14)	2 (8)
Prostate	0	1 (4)
Stomach	0	1 (4)
Uterus	1 (14)	1 (4)
Other	0	8 (31)
Histology of primary diagnosis, *n* (%)		
Carcinoma/adenocarcinoma	5 (71)	14 (54)
Sarcoma/sarcomatoid	2 (29)	12 (46)
Site of metastasis, *n* (%)		
Visceral	7 (100)	26 (100)
Nonvisceral	0	0

Treatment exposure

For all patients, the median number of cycles administered was three (1–11, 15, 29), with 27% of patients having more than three cycles of therapy. The median cumulative rapamycin dose was 405 mg/m^2 (100–2,200), with the median dose intensity of 68.9 mg/m^2/wk (11.4–150.0). At the MTD, the median number of cycles was also three (1–3, 15, 29), with the median cumulative dose of 800 mg/m^2 (100–900) and median dose intensity of 78.9 mg/m^2/wk (51.1–100.0).

Safety results

MTD. Following dose escalation to 100 mg/m^2, *nab*-rapamycin dose was initially escalated to 150 mg/m^2. Two DLTs occurred in the 150 mg/m^2 cohort: a grade 3 elevation of aspartate aminotransferase (AST) and a grade 4 thrombocytopenia. After observing DLTs at the 150 mg/m^2 cohort, a new dose level of 125 mg/m^2 was added for refinement of MTD. At the 125 mg/m^2 dose level, two DLTs occurred (grade 3 suicidal ideation and grade 3 hypophosphatemia); therefore, the MTD was reached and declared at 100 mg/m^2.

TRAEs. For all cohorts and all grades, 25 of 26 (96%) patients experienced at least one TRAE. The most common nonhematologic TRAEs reported were mucosal inflammation (10 patients; 38%), fatigue (7 patients; 27%), rash (6 patients; 23%), diarrhea (6 patients; 23%), and nausea (5 patients; 19%; see Table 2). Most of these adverse events were grade 1/2 events, with only three grade 3 nonhematologic adverse events (two elevated AST and one dyspnea). Specifically, at the MTD (100 mg/m^2), all 7 patients experienced at least one TRAE of any grades, and the most common adverse events were mucositis and fatigue (5 patients; 71% each). Four (15%) patients experienced at least one treatment-related serious adverse event, including arrhythmia (grade 2) and mood alteration (grade 3) both in the 125 mg/m^2 cohort, vomiting (grade 3) in the 45 mg/m^2 cohort, and dyspnea (grade 3) in the 100 mg/m^2 cohort.

The most common hematologic TRAE, for all cohorts and grades, were thrombocytopenia (58%), followed by hypokalemia (23%), anemia and hypophosphatemia (19% each), and neutropenia and hypertriglyceridemia (15% each; see Table 2). Most of these events were grade 1/2, and only one grade 4 hematologic event occurred (thrombocytopenia in the 150 mg/m^2 arm). At the MTD, the only hematologic adverse event was a grade 3 anemia.

Treatment-related study drug reductions, delays, and discontinuations. Five (19%) patients experienced TRAEs that required study drug dose reductions and 50% of dose reductions occurred at cycle 2. Only 1 patient at the MTD had an adverse event that required a dose reduction, which occurred at cycle 4. The specific events requiring dose reductions were one grade 2 thrombocytopenia and one grade 2 dyslipidemia in the 100 mg/m^2 cohort, and two grade 3 thrombocytopenia and one grade 3 suicidal ideation in the 125 mg/m^2 cohort. The patient who experienced suicidal ideation had been on antidepressants before the trial. After the onset of grade 3 suicidal ideation (end of cycle 1), this patient received two cycles of *nab*-rapamycin at a reduced dose (100 mg/m^2), during which no suicidal ideation was reported. In addition, there was a dose reduction for a grade 2 elevated AST in the 45 mg/m^2 cohort. The dose was reduced to 30 mg/m^2, which was not specified in the protocol. This patient responded to treatment and the physician felt that continuing the treatment at a lower dose was in the best interest for this patient.

Sixteen (62%) patients had TRAEs requiring a dose delay: 4 (57%) patients in the 45 mg/m^2, 1 (33%) in the 56.25 mg/m^2, 4 (57%) in the 100 mg/m^2, 2 (100%) in the 150 mg/m^2, and 5 (71%) in the 125 mg/m^2 cohort. Specifically in the 100 mg/m^2 cohort, the treatment-related dose delays were due to three grade 2 thrombocytopenia, a grade 2 elevated triglycerides, a grade 2 mucosal inflammation, and a grade 3 dyspnea. Only 1 patient had a TRAE that resulted in study drug discontinuation (150 mg/m^2 cohort; 1 patient with a grade 4 thrombocytopenia and a grade 2 diarrhea).

Pharmacokinetics

Whole-blood samples obtained during cycle 1 of treatment at the specified time points were analyzed for

Table 2. Treatment-related grade 1–4 hematologic and nonhematologic adverse events reported in 10% or more of all treated patients

	MTD (100 mg/m^2) $n = 7$				All treated patients $n = 26$			
NCI CTCAE v 3.0	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Hematologic AEs, *n* (%)								
Anemia	0	0	1 (14)	0	0	3 (12)	2 (8)	0
Hypokalemia	1 (14)	0	0	0	5 (19)	0	1 (4)	0
Hypophosphatemia	0	1 (14)	0	0	1 (4)	2 (8)	2 (8)	0
Hypertriglyceridemia	1 (14)	1 (14)	0	0	2 (8)	1 (4)	1 (4)	0
Neutropenia	1 (14)	0	0	0	2 (8)	1 (4)	1 (4)	0
Thrombocytopenia	1 (14)	4 (57)	0	0	5 (19)	6 (23)	3 (12)	1 (4)
Nonhematologic AEs, *n* (%)								
AST	0	0	0	0	1 (4)	0	2 (8)	0
Constipation	0	1 (14)	0	0	1 (4)	2 (8)	0	0
Diarrhea	1 (14)	0	0	0	3 (12)	3 (12)	0	0
Dyspnea	0	1 (14)	1 (14)	0	1 (4)	2 (8)	1 (4)	0
Fatigue	1 (14)	4 (57)	0	0	1 (4)	6 (23)	0	0
Infection, oral cavity	1 (14)	1 (14)	0	0	3 (12)	2 (8)	0	0
Mucositis/stomatitis	3 (43)	2 (29)	0	0	7 (27)	3 (12)	0	0
Nausea	1 (14)	1 (14)	0	0	3 (12)	2 (8)	0	0
Rash	1 (14)	0	0	0	4 (15)	2 (8)	0	0
Weight loss	0	0	0	0	1 (4)	2 (8)	0	0

Abbreviations: AE, adverse event; G, grade.

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