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CTEP P10002

TITLE: A Phase I Study of Indenoisoquinoline LMP744 in Adults With Relapsed Solid Tumors and Lymphomas

Short Title: Phase I LMP744

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PRÉCIS

Background:

- Indenoisoquinolines are non-camptothecin inhibitors of topoisomerase 1 (top1) with improved characteristics over their predecessors. Indenoisoquinolines have better chemical stability, producing stable DNA-top1 cleavage complexes, and exhibit a preference for unique DNA cleavage sites, compared with their camptothecin counterparts.
- They have demonstrated activity against camptothecin-resistant cell lines and produce DNA-protein crosslinks, which are resistant to reversal. They also show less or no resistance to cells overexpressing the ATP-binding cassette (ABC) transporters, ABCG2, and multidrug resistance (MDR-1).

Primary Objectives:

- To establish the safety, tolerability and the maximum tolerated dose (MTD) of LMP744 (NSC 706744) administered intravenously (IV) daily for 5 days (QD x 5) schedule in patients with refractory solid tumors and lymphomas.

Secondary Objectives:

- Characterize the pharmacokinetic (PK) profile of LMP744.

Exploratory Objectives:

- Evaluate the effect of LMP744 on markers of DNA damage (γH2AX, pNbs1, pATR, ERCC1, RAD51, Topo1cc, Top1, SLFN11) and epithelial-mesenchymal transition (EMT) in circulating tumor cells (CTCs) and pre- and post- treatment tumor biopsies in patients at the expansion cohort.
- Assess preliminary antitumor activity of LMP744.
- Examine genomic alterations in circulating tumor DNA (ctDNA) that may be associated with response or resistance to treatment.

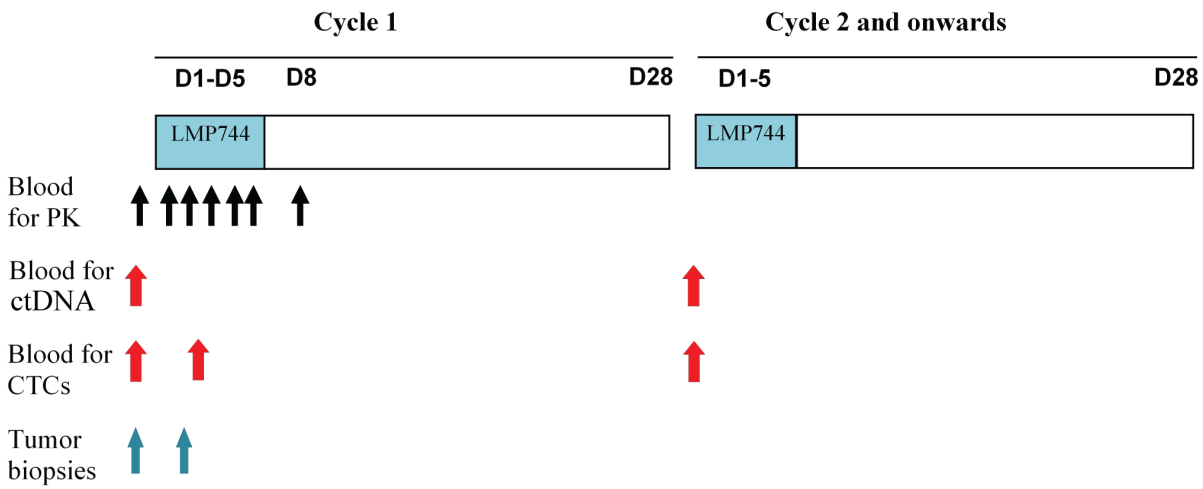
Eligibility:

- Adult patients must have histologically documented, relapsed solid tumors which have progressed after one line of therapy, or lymphoma which has progressed after initial therapy and without potentially curative options, or patient refuses potentially curative therapy.

Study Design:

- Cycle 1 and subsequent cycles: Patients will receive LMP744 administered IV QD over 1 hour on days 1–5 followed by 23 days without drug (28-day cycle).
- PK and PD samples will be collected. Tumor biopsies will be mandatory during the expansion phase.

SCHEMA



LMP744 will be administered IV over 1 hour on days 1-5 of each 28-day cycle

Blood samples for PK analyses will be collected at the following timepoints in cycle 1 only:

- Day 1, prior to drug administration, 2 minutes (+/- 2 minutes) before end of infusion, and at appropriate time points post infusion (15 minutes, 30 minutes, and 1, 2, 4, and 6 hours post infusion)
- Day 2, 24 hr post day 1 start of infusion (prior to day 2 infusion), and 2 minutes (+/- 2 minutes) before the end of infusion
- Day 3, 24 hr post day 2 start of infusion (prior to day 3 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 4, 24 hr post day 3 start of infusion (prior to day 4 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 5, 24 hr post day 4 start of infusion (prior to day 5 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 8, 72 hr post day 5 start of infusion

Blood for circulating tumor cells (CTCs) (optional) will be collected at baseline, on day 3 of cycle 1 (within 2 to 4 hours after the start of LMP744 infusion), on day 1 of every subsequent cycle (prior to drug infusion), and at disease progression.

Tumor biopsies (mandatory in expansion phase) will be obtained at baseline and then on day 2 (1-4 hours after the LMP744 infusion) in cycle 1 only.

Dose Escalation

Dose Levels	
Dose Level	LMP744 mg/m^2/day x 5 days every 28-days (IV)
Level-1	3
Level 1	6
Level 2	12
Level 3	24
Level 4	48
Level 5	96
Level 6	190
Level 7	260
Level 8	360
Level 9	500
* *Doses are stated as exact dose in units (mg/m^2)*	

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- To establish the safety, tolerability and the maximum tolerated dose (MTD) of LMP744 (NSC 706744) administered intravenously (IV) daily for 5 days (QD x 5) schedule in patients with refractory solid tumors and lymphomas.

1.2 Secondary Objectives

- Characterize the pharmacokinetic (PK) profile of LMP744

1.3 Exploratory Objectives

- Evaluate the effect of LMP744 on markers of DNA damage (γH2AX, pNbs1, pATR, ERCC1, RAD51, Topo1cc, Top1, SLFN11) and epithelial-mesenchymal transition (EMT) in circulating tumor cells (CTCs) and pre- and post- treatment tumor biopsies in patients at the expansion cohort
- To assess preliminary anti-tumor activity of LMP744

2. BACKGROUND

Indenoisoquinolines are non-camptothecin inhibitors of topoisomerase I (Top1), an enzyme necessary for transcription, replication, recombination, and the repair of double-strand DNA breaks(1). Top1 relaxes the supercoiled DNA by introducing a single-strand break, generating a free strand that rotates around the Top1-bound DNA complex. Once DNA is relaxed, Top1 re-ligates the break. In the absence of external triggers, these Top1-DNA cleavage complexes are generally short lived and re-ligation is favored over cleavage(2). Top1 inhibitors are potent anticancer agents because they stabilize the formation of the cleavage complex, which induces replication transcription-mediated DNA damage, delays DNA repair, and results in cell cycle arrest and apoptosis.

Despite the potency and specificity of the Top1-inhibitor class, the therapeutic profile of camptothecin and its derivatives (such as topotecan and SN-38), has been offset by a number of shortcomings; including chemical instability induced by the fast conversion of the α-hydroxylactone in the E-ring to a carboxylate exhibiting high affinity for human serum albumin, fast reversibility of the trapped DNA-Top1 cleavage complex following drug removal, drug resistance mediated by ATP-binding cassette (ABC) transporters, such as ABCG2 (MXR or BCRP) and multidrug resistance (MDR-1 or ABCB1), and dose limiting toxicities (DLTs).

Indenoisoquinolines were identified as potential Top1 inhibitors following a COMPARE analysis of the NCI's in vitro anticancer drug discovery screen (3). They have improved characteristics over their camptothecin predecessors, with better chemical stability (lack of the labile hydroxylactone E-ring) producing stable DNA breaks that are resistant to reversal of the

trapped DNA-Top1 cleavage complex (2, 4). Additionally, they trap the cleavage complex at different DNA sequences than camptothecins, which may result in differential activity within the cell (2). Finally, indenoisoquinolines have been shown to have activity against camptothecin-resistant cell lines and mouse models (4).

Two of the indenoisoquinolines developed through the DCTD Developmental Therapeutics Program, LMP400 and LMP776, have already undergone clinical evaluation at the NCI in patients with refractory solid tumors: the first-in-human phase I study of LMP400 and LMP776 (10-C-0056, NCT01051635) evaluated an intravenous (iv) daily for 5 days (QDx5) schedule, and the phase I study of LMP400 (13-C-0080, NCT01794104) evaluated a weekly iv (days 1, 8, 15 q28-day cycle) schedule. For LMP400, an MTD of 60 mg/m^2/day was established for the daily regimen and an MTD of 90 mg/m^2 for the weekly regimen. Although no objective responses were observed on either schedule, 4 patients had best response of stable disease. The TopI response to drug showed target engagement in a subset of tumor biopsies, and the pharmacokinetics profiles demonstrated a prolonged terminal half-life and tissue accumulation compared to topotecan. Dose-dependent decreases in total CTCs were measured in 7 patients, and formation of γH2AX-positive foci in CTCs and hair follicles were measured following treatment. The principal toxicity of both schedules was myelosuppression; no significant gastrointestinal problems were observed.

Patients continue to be accrued to the LMP776 arm of 10-C-0056; 6 of the 32 LMP776 patients have had stable disease SD with an average of 109.3 days duration (range 56 to 249 days).

The structurally related indenoisoquinoline LMP744 (NSC 706744), developed in parallel with LMP776 and LMP400, has also undergone extensive preclinical evaluation. LMP744 exhibited antitumor activity in rats without the dose-limiting neutropenia that occurred with similar doses of LMP400 (unpublished data) and has shown marked clinical activity in dogs with lymphoma; LMP744 induced greater and more sustained reduction in tumor burden in these animals compared to either LMP400 or LMP776 (unpublished data).

2.1 Preclinical Activity

In in vitro hollow fiber activity studies at the NCI, the mean graph midpoint (MGM) for LMP744 growth inhibition of all human cancer cell lines in the NCI 60 cell line screen was 15.5 μM (5). In in vitro studies, LMP744 inhibited TopI to a similar extent as 1 μM camptothecin, and although camptothecin and LMP744 trap Top1 at similar sites on DNA, LMP744 was more potent(6). LMP744 also inhibited Top1 in CEM human leukemia cells, and time course studies demonstrated that Top1-DNA cleavage complexes reversed more slowly after drug removal than those produced by camptothecin. Notably, human CEM/C2 leukemia cells resistant to CPT were sensitive to LMP744 at 0.1 μM (4).

LMP744 also had modest activity in human tumor xenograft models. In the HCT-116/H1 colon tumor model, the highest non-lethal dose of LMP744, 33.5 mg/kg/dose (100 mg/m^2/dose) IV on a qdx 5 schedule, caused a mean tumor growth delay of 53% (%T/C=38). In the A375 melanoma model, an LMP744 dose of 22.4 mg/kg/dose (67.2 mg/m^2/dose) IV on a qdx 5 schedule resulted in a mean growth delay of 34% (%T/C=38). Topotecan (NSC 609099) was

more active than NSC706744 at a dose of 4 mg/kg IP using the same schedule.

Efficacy in a Comparative Oncology Trial with Canine Lymphoma (Protocol COTC007b)
Antitumor activity was also observed with LMP744 in a canine clinical trial of 21 dogs with lymphoma. LMP744 was administered via 1 h IV infusion qdx5 in 28-day cycles. The MTD was determined to be 5 mg/kg (100 mg/m^2). The waterfall plot below (Figure 1) shows the best overall response per RECIST criteria for each dog; the majority (16/21) had partial responses (tumor shrinkage > 30%) and 5/21 had stable disease. Responses were observed at all dose levels, with a single complete response occurring in Dose Level 2 (2.5 mg/kg or 50 mg/m^2). There was no correlation between dose and extent of response. Another 12 dogs were treated at the study MTD in a planned expansion cohort. The overall response rate (PR or better) for all animals treated at this dose (6 escalation + 12 expansion) was 78%. The overall response rate across all dose levels was 80%. However, the responses were not durable, and most dogs had progressive disease in cycle 1 (manuscript in preparation).

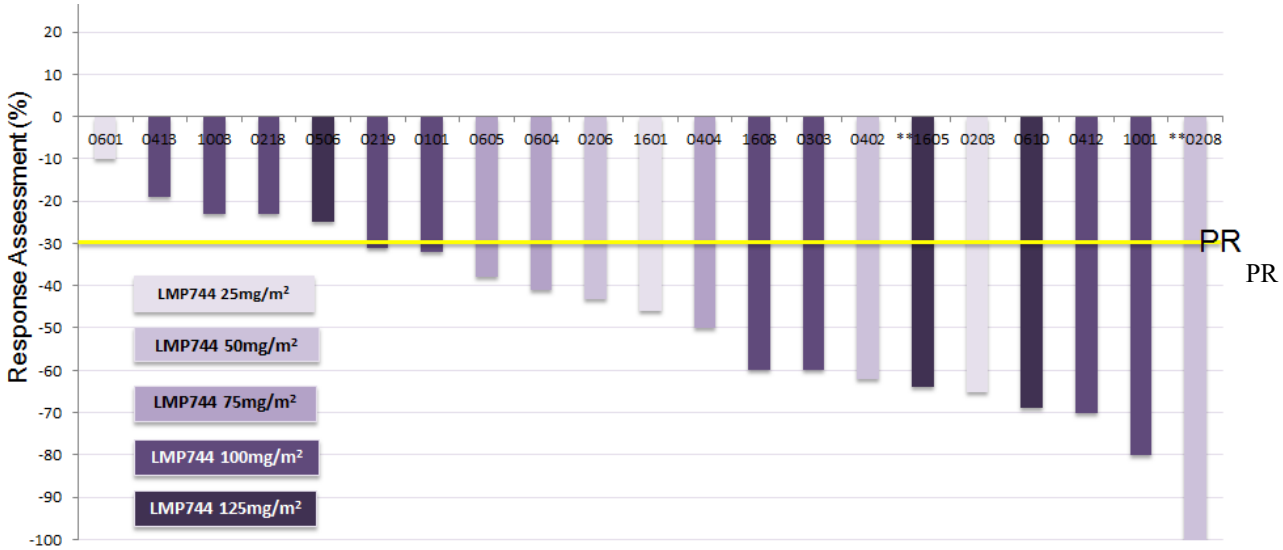


Figure 1: Canine COTC007b Trial best overall response (RECIST criteria) to increasing doses of LMP744.

2.2 Preclinical Pharmacokinetics

The pharmacokinetics of LMP744 following IV administration were evaluated in IND-directed studies in rats and beagle dogs and in a canine comparative oncology trial. Plasma drug concentrations were determined using a validated LC-MS/MS method. Non-compartmental PK parameters were calculated for each animal (Phoenix WinNonlin, Version 6.3).

Pharmacokinetics in Rats
Rats (3 rats/sex/dose group) were given LMP744 at doses in the table below as a one-hour IV infusion on days 1-5. Blood samples were drawn on Day 1 for plasma drug level determination immediately prior to the end of the infusion, 5, 15, 30, 60, 120 min and 4, 8, and 24 hrs post-infusion; then pre-dose and just prior to the end of infusion on Day 5. On Day 1, mean Cmax (M + F) was 39.0, 234, and 259 ng/mL at 1, 5, and 10 mg/kg/day, respectively. The mean AUClast was 110 hr*ng/mL, 399 hr*ng/mL, and 530 hr*ng/mL for the above doses, respectively. The

resulting plasma clearance was similar across dose levels (7.0-13.7 L/hr/kg in males and females combined. On day 1, systemic exposure, as represented by Cmax and AUC generally increased in a dose-proportional manner between 1 and 5 mg/kg, but was not dose-proportional between 5 and 10 mg/kg. Mean Cmax did not change significantly between Days 1 and 5, suggesting that LMP744 did not accumulate over the 5-day dosing period. There was no difference in systemic exposure between males and females.

LMP744 PK Parameters in rats (IITRI Study 2330-013-001)							
Dose (mg/kg/day)	Male or female*	C_{max} (ng/mL)	AUC_{last} (hr•ng/mL)	AUC_{inf} (hr•ng/mL)	$T_{1/2}$ (hr)	CL (L/hr/kg)	Vz (L/kg)
1	M Day 1	47.4 ± 28.4	109 ± 53.6	146 ± 92.4	10.8 ± 10.8	9.7 ± 7.18	86.8 ± 46.9
	M Day 5	41**					
	F Day 1	30.6 ± 9.87	111 ± 11.7	137 ± 17.5	11.6 ± 1.16	7.39 ± 0.90	123 ± 12.1
	F Day 5	41.1 ±15					
5	M Day 1	221 ± 130	431 ± 115	713***	24.6***	7.01***	24.8***
	M Day 5	132 ± 57.9					
	F Day 1	246 ± 100	367 ± 73.3	549 ± 91.0	23.9 ± 6.52	9.27 ± 1.55	315 ± 78.8
	F Day 5	113 ± 87.8					
10	M Day 1	252 ± 22.4	518 ± 55.1	730 ± 47.2	19.0 ± 2.02	13.7 ± 0.88	378 ± 63.3
	M Day 5	196 ± 8.83					
	F Day 1	265 ± 20.9	541 ± 51.4	821 ± 90.2	22.3 ± 1.31	12.3 ± 1.36	394 ± 29.0
	F Day 5	160 ± 66.2					
LMP744 PK parameters in dogs (IITRA Study No. 2330-013-002)							
Dose (mg/kg/day)	Male or female	C_{max}* (ng/mL)	AUC_{last} (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	$T_{1/2}$ (hr)	CL (L/hr/kg)	Vz (L/kg)
0.5	M Day 1	44.5 ± 14.4	122 ± 23.2	139 ± 28.9	6.39 ± 4.22	3.73 ± 0.76	31.0 ± 16.3
	M Day 5	41.3 ± 8.00					
	F Day 1	40.3 ± 4.48	88.3 ±18.7	101 ± 20.0	4.96 ± 3.41	5.10 ± 0.87	33.5 ± 15.4
	F Day 5	41.4 ± 3.71					
2.5	M Day 1	284 ± 198	579 ± 56.6	712 ± 79.3	14.5 ± 2.65	3.55 ± 15.4	73.9 ± 12.7
	M Day 5	270 ± 21.7					
	F Day 1	177 ± 20.3	446 ± 52.3	575 ± 91.5	15.0 ± 3.32	4.44 ± 0.78	94.5 ± 13.9
	F Day 5	156 ± 33.6					
5	M Day 1	412 ± 62.9	868 ± 79.2	1157± 144	18.0 ± 3.84	4.37 ± 0.56	112 ± 16.3
	M Day 5	363 ± 56.4					
	F Day 1	177 ± 45.2	798 ± 62.2	996 ± 112	14.4 ± 3.70	5.07 ± 0.60	104 ± 18.8
	F Day 5	308 ± 96.4					
*Tmax was 1 hr (the end of infusion) for all dose groups. Only 1 time point (end of infusion) was sampled on Day 5. ** N=2; ***Lambda z and dependent parameters determinable for only 1 of 3 rats							

Pharmacokinetics in Dogs

LMP744 was given to dogs (8 dogs/sex/dose group) as a one-hour infusion qdx5 at the doses in the table above. Blood samples were drawn from each dog for plasma drug level determinations just prior to the end of the infusion, and at 30, 120, 360, 480 min and 24 hr post-infusion on Day 1; then pre-dose and just prior to the end of infusion on Day 5.

On Day 1, mean Cmax (M + F) was 42.4, 230, and 294 ng/mL at 0.5, 2.5, and 5 mg/kg/day, respectively. The T1/2 ranged from 4.96 to 18 hr and was shorter at the lowest dose. This is likely a result of analytical sensitivity limiting plasma quantification to 8 hr post-infusion in the

low dose group vs. 24 hr in the other groups. The mean (M+F) AUCinf was 120 hr*ng/mL, 643 hr*ng/mL, and 1076 hr*ng/mL for the 0.5, 2.5, and 5 mg/kg/day groups, respectively. Plasma clearance was relatively constant across dose levels (range 3.7 to 5.1 L/hr/kg) and the values were similar to those obtained in the pilot studies. Systemic exposure on Day 1, as represented by Cmax and AUC, increased in an approximately proportional manner over the dose range studied. Mean Cmax (at end of infusion) did not change appreciably between Days 1 and 5, suggesting that LMP744 did not accumulate over the 5-day dosing period. Systemic exposure tended to be slightly higher for male dogs compared with females (1.1 to1.6-fold for Cmax and 1.1-1.4-fold for AUCinf).

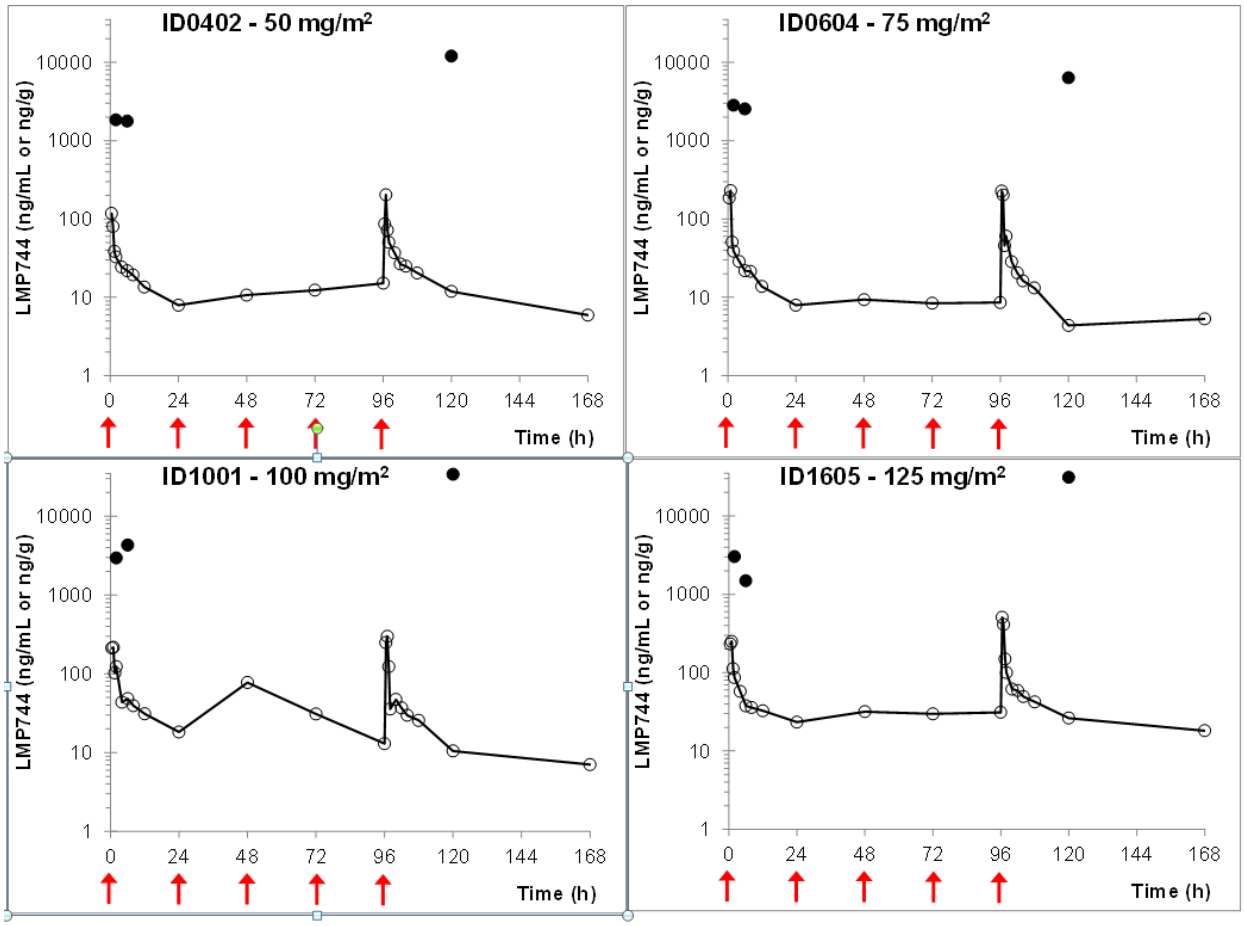


Figure 2: Plasma and tumor concentration-time plots from representative animals receiving LMP744 at the doses indicated (Study COTC007b).

LMP744 was also evaluated in a multicenter comparative oncology clinical trial in dogs with lymphoma. Drug (1.25, 2.5, 3.75, 5.0, and 6.25 mg/kg) was administered over 1 h IV daily x 5, in 28-day cycles. Plasma samples were obtained for drug level determination during the infusion and for 24 hr after the infusion on days 1 and 5; levels of LMP744 were also determined in tumor biopsies obtained prior to treatment, at 2 and 6 hr after the start of the infusion on day 1, and at 24 hr after the last infusion. The mean elimination half-life was 17 hr and the plasma clearance was 3.95 L/hr/kg, values similar to those observed in the IND-directed PK-toxicology study at comparable doses. Non-compartmental analysis also suggested linear relationships

between plasma Cmax and dose and between AUC and dose. LMP744 distributed extensively to tumor tissue and mean tumor concentrations were at least an order of magnitude higher than plasma concentrations in most animals at equivalent time points of 2, 6, and 120 hr (Figure 2).

Levels of LMP744 also appeared to increase in tumor tissue over the 5-days of dosing, with levels at 120 hr (24 hours after the last dose) approximately 10-fold higher than levels measured at 2 and 6 hr on day 1.

2.3 Preclinical toxicology

LMP744 was administered to Fischer rats and beagle dogs orally or as an intravenous infusion in pilot/range-finding studies using a single dose or multiple dose (daily x 5) schedule. The data from these studies were used to select doses for IND-directed studies in which LMP744 was administered as a 1-hr infusion once daily for five days (the intended clinical route and schedule).

An initial range-finding study in rats explored the toxicity of LMP744 administered as a single oral gavage or intravenous bolus dose. Bone marrow toxicity was observed with both routes of administration. Renal and injection site toxicity occurred only with the iv route. The maximum tolerated dose (MTD) using the iv route was >100 mg/kg or >600 mg/m^2; for the oral route, the MTD was between 500 and 750 mg/kg (3000 and 4500 mg/m^2) due to lethality.

A definitive study was conducted in rats. Doses of 1, 5, or 10 mg/kg/day (6, 30, or 60 mg/m^2/day) LMP744 were given as a 1-hr infusion once daily for 5 consecutive days. Bone marrow, thymic, and renal toxicity and pulmonary thrombi were observed. Decreases in total WBC, neutrophils, and reticulocytes occurred in all LMP744 dose groups. Thymic atrophy was noted in the high dose group. Adverse effects in the kidney consisted of elevated BUN in the mid- and high-dose groups and minimal and/or mild microscopic renal tubular degeneration in all dose groups including vehicle control. Minimal and/or mild tubular single cell necrosis was also noted in mid- and high-dose group males. On the last day of the study (Day 19), BUN values were normal in all dose groups. Tubular single cell necrosis was absent on Day 19, and tubular degeneration was present at a lower incidence and/or severity at the same time point. Tubular degeneration was not present in the vehicle control group on Day 19. Pulmonary thrombosis occurred in all LMP744 dose groups on Days 6 and/or 19 and in one vehicle control animal on Day 19—incidence and severity were highest in the high dose group on Day 6. The finding in the vehicle control animal suggests that the indwelling catheter contributed to the formation of pulmonary thrombi. The MTD for the study was >10 mg/kg/day (>60 mg/m^2/day). LMP744 peak plasma levels and AUCs on this study were 39 ng/mL to 259 ng/mL and 110 hr·ng/mL to 530 hr·ng/mL, respectively, over the dose range studied.

A single dose non-GLP toxicology study was conducted using LMP744 as a 1-hr iv infusion in dogs. Lethality occurred at both doses on the study (35 and 50 mg/kg) (700 and 1000 mg/m^2). Liver, gastrointestinal, bone marrow, renal, lung, injection site, and skin toxicity were observed. A subsequent study in dogs was conducted using doses of 5, 25, or 50 mg/kg given as a 15-min iv infusion. A dose of 50 mg/kg was lethal. The MTD on this study was between 5 and 25 mg/kg (100 and 500 mg/m^2) due to liver, renal, and bone marrow toxicity. A third study was

conducted in dogs given LMP744 via a 1-hr infusion once daily for 5 days. Bone marrow and GI toxicity occurred, but renal and hepatic toxicities were not observed. The MTD for this study was 5 mg/kg/day (100 mg/m^2/day). Allergic reactions (erythema of the eyes, face, and legs) were observed in dogs on all of the above studies. This schedule (daily x 5) and rate of administration (1-hr infusion) were used for the definitive toxicology study in dogs.

A definitive toxicology study was conducted in which dogs were given a 1-hr infusion of LMP744 once daily for 5 consecutive days. The no-observable adverse effect level (NOAEL) was 0.5 mg/kg/day (10 mg/m^2/day). The MTD was between 2.5 and 5 mg/kg/day (50 and 100 mg/m^2/day) based on irreversible bone marrow, bladder, and liver toxicity. Dogs that received 5 mg/kg/day had facial swelling, a potential allergic reaction. LMP744 also caused hematological toxicity at doses of 2.5 or 5 mg/kg/day (50 or 100 mg/m^2/day). Hematologic toxicity consisted of decreased total WBC, neutrophils, lymphocytes, eosinophils, and reticulocytes. Decreased bone marrow hematopoiesis was noted microscopically in the 5 mg/kg/day dose group. Hepatic toxicity was observed in the 5 mg/kg/day dose group and was characterized by increased levels of ALP, fibrinogen, AST, ALT, GGT, and total bile acids. Bile duct hyperplasia and inflammation of the portal tracts of the liver were noted microscopically in the same dose group. Mononuclear cell inflammation suggestive of hemorrhagic cystitis was noted in the bladder of one female given 5 mg/kg/day.

Based on the results of these nonclinical studies, the first-in-human dose (FHD) will be 6 mg/m^2/day administered as a 1-hr intravenous infusion once daily for 5 days. This dose is approximately one-fifth the highest non-severe toxic dose (HNSTD; 5 mg/kg/day = 30 mg/m^2/day) in rats, the more sensitive of the two preclinical species tested. Target organs of toxicity identified considering both species were bone marrow, kidney, liver, bladder, and lung. Allergic reactions (e.g., facial swelling and erythema) may also occur.

2.4 Correlative Studies Background

2.4.1 γ-H2AX

One of the earliest markers of DNA double-strand breaks is phosphorylation of histone H2AX, (γH2AX) (7-9). γH2AX is phosphorylated at its C-terminus (serine 139 in humans) within minutes following DNA double-strand breaks and forms macromolecular foci, marking the chromatin domain around the broken chromosomal DNA ends, thus allowing the recruitment of repair factors(7, 8, 10-12). Levels of γH2AX directly correlate with the amount of double-strand breaks per cell. Hence γH2AX can be used as a dosimeter and biomarker for DNA double-strand breaks (13).

In this study, drug-induced changes in γH2AX in circulating tumor cells and tumor biopsies will be measured by %NAP (representing the percent of nuclear area that is γH2AX-positive based on nuclear DAPI and γH2AX staining). γH2AX analysis will be complemented by the measurement of cleaved caspase-3 levels. Caspase-3 cleavage and activation is a marker of apoptosis, and increased levels suggest that delayed repair of DNA double-strand breaks is resulting in tumor cell death. In addition to apoptotic markers, tumor biopsies will be analyzed for autophagic activity based on expression of the autophagosomal marker LC-3.

2.4.2 Circulating tumor cells (CTCs)

Recent progress in monitoring treatment responses of patients with breast cancer has provided evidence that a significant number of circulating tumor cells (CTCs) are present in peripheral blood, and these CTCs can be detected in a significant portion of patients with advanced disease. Decreases in CTC levels were shown to predict disease-free and overall survival, independent of treatment, at the end of a treatment regimen (14-18). CTCs in the peripheral blood of cancer patients may potentially represent a compartment of solid tumor cells that allows more frequent PD assessment of molecular drug action than it is currently possible using tumor biopsy procedures. CTCs will be isolated from whole blood samples collected at baseline and then throughout the study for assessment of DNA damage response markers such as γH2AX. We will also evaluate whether we can measure changes in the number and phenotype (epithelial-mesenchymal transition) of CTCs in patients over time to explore any correlation with response to treatment or disease progression. This analysis will be performed in Dr. Kinders' lab with the ApoStream instrument, which uses antibody independent CTC isolation technology that can isolate viable CTCs from epithelial and nonepithelial cancers.

2.4.3 Topoisomerase 1

Recent preclinical and clinical data suggest that levels of top1 in pre-dose biopsies may serve as a potential predictor of response to top1 inhibitors (18, 19). Results from the FOCUS (Fluorouracil, Oxaliplatin, CPT-11) clinical trial in patients with advanced colorectal cancer suggested a correlation between top1 levels and the efficacy of irinotecan-based chemotherapy; the overall survival benefit for patients with high levels of top1 (median benefit 5.3 months, hazard ratio 0.60) was substantially greater than for patients with moderate or low levels (median benefit 1.09, hazard ratio 0.92)(19). Further clinical studies and analyses are ongoing to confirm these results. A validated immunoassay has been developed that could potentially provide a means of screening patients prior to treatment as well as monitoring patient response during treatment with top1 inhibitors.

2.5 Rationale

Indenoisoquinolines possess structural improvements over camptothecin and its derivatives (6, 20). They have better chemical stability, produce stable DNA breaks that are resistant to the reversal of the trapped DNA-top1 cleavage complex (2, 4, 21), trap the cleavage complex at unique DNA sequences, possibly leading to differential activity within the cell (2), and have shown activity against camptothecin-resistant cell lines (4). Based on promising preclinical data, specifically in dogs with lymphoma, and data from studies of two related indenoisoquinolines, we are conducting this trial of LMP744 to evaluate its safety, pharmacokinetic, and pharmacodynamic profile in patients with refractory solid tumors.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically documented metastatic solid tumors which have progressed after one line of therapy, or lymphoma which has progressed after initial therapy and without potentially curative options, or patient refuses potentially curative therapy.

3.1.2 Patients must have measurable or evaluable disease.

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status ≤2 (see Appendix A).

3.1.5 Life expectancy of greater than 3 months.

3.1.6 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal (ULN)
– serum creatinine	≤1.5 × institutional ULN OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with serum creatinine levels >1.5 × higher than institutional normal

3.1.7 Anticoagulation with low-molecular-weight heparin (LMWH) or any direct oral anticoagulant (DOAC, *e.g.,* rivaroxaban, apixaban, dabigatran, or edoxaban) will be permitted. Patients receiving treatment with warfarin will be given the option to switch to LMWH or a DOAC.

3.1.8 Patients must have recovered to grade 1 or baseline from adverse events (22) and/or toxicity of prior chemotherapy or biologic therapy. They must not have had chemotherapy, biologic therapy, or definitive radiotherapy within 4 weeks (6 weeks for nitrosoureas and mitomycin C) or 5 half-lives, whichever is shorter, prior to entering the study. Palliative-intent radiotherapy (30 Gy or less) must be completed at least 2 weeks prior to start of treatment, and may not be to a lesion that is included as measurable disease. Patients must be ≥2 weeks since any investigational agent administered as part of a Phase 0 study (where a sub-therapeutic dose of drug is administered) at the PI's discretion, and should have recovered to grade 1 or baseline from any toxicities.

3.1.9 Patients receiving denosumab or bisphosphonates for any cancer, or undergoing androgen deprivation therapy for prostate cancer, are eligible for this therapy.

3.1.10 Prior therapy with topoisomerase I inhibitors is allowed.

3.1.11 Patients with known HIV-positive status are eligible provided the following criteria are met: CD4 count >350/mm^3, an undetectable viral load, and not receiving prophylaxis antibiotics. Diagnostic HIV testing will not be performed during screening or throughout this study.

3.1.12 The effects of LMP744 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Women and men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of LMP744 administration.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.1.14 Willingness to provide blood and new tumor biopsy samples for research purposes if on the expansion phase of the study.

3.2 Exclusion Criteria

3.2.1 Patients who are receiving any other investigational agents.

3.2.2 Patients with clinically significant illnesses which would compromise participation in the study, including, but not limited to active or uncontrolled infection, immune deficiencies, Hepatitis B, Hepatitis C, uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.3 Patients with known brain metastases or carcinomatous meningitis are excluded from this clinical trial, with the exception of patients whose brain metastatic disease status has remained stable for ≥ 1 month after treatment of the brain metastases. Patients on anti-seizure medications or steroid therapy may be enrolled at the discretion of the Principal Investigator.

3.2.4 Pregnant women are excluded from this study because LMP744 is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with LMP744, breastfeeding should be discontinued if the mother is treated.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Eligibility Screening Evaluation

3.4.1 History and physical examination: Complete history and physical examination (including height, weight, vital signs, and ECOG performance score) will be conducted within 8 days prior to enrollment.

3.4.2 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to enrollment. MRI or CT scan with contrast of the brain, MRI liver, MRI for other disease sites, or bone scan may be done as clinically indicated. When indicated, gadolinium contrast will be used for MRI scans and iodine-based contrast will be used for CT scans. A PET scan will be done additionally to CT or MRI for lymphoma patients at baseline.

3.4.3 Laboratory Evaluation: Laboratory data are to be obtained within 8 days prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, alkaline phosphatase, total bilirubin, BUN, bicarbonate, calcium, chloride, creatinine, glucose, phosphorus, total protein, SGOT (23), SGPT (10), TSH, sodium, GGT. Uric acid and LDH levels will also be measured in patients with lymphoma only.
- Urinalysis

- Coagulation Profile: PT, PTT, INR (on the expansion cohort)
- Serum or urine pregnancy test for female participants of childbearing potential.

3.4.4 Cardiac Evaluation:

- EKG: to be conducted within 8 days prior to enrollment
- ECHO: to be conducted within 28 days prior to enrollment

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (24) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster

- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

4.2 Patient Registration

Authorized staff must register an eligible candidate with NCI Central Registration Office (25) and through the Theradex Interactive Web Response System (IWRS) within 24 hours after signing consent. Access IWRS through https://iwrs.theradex.com under the "Patient" tab utilizing your CTEP-IAM Username and Password. A registration Eligibility Checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to the NCI Central Registration Office (HOIS; ncicentralregistration-l@mail.nih.gov). After confirmation of eligibility at the Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Patient enrollment data entered in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

Please note that it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information.

Off Protocol Therapy and Off-Study Procedure: Authorized staff must notify the Central Registration Office (25) when a patient is taken off protocol therapy and when a patient is taken off-study. The Participant Status Updates Form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to the NCI Central Registration Office (HOIS; ncicentralregistration-l@mail.nih.gov).

4.2.1 Interactive Web Response System (IWRS)

Patient Enrollment will be facilitated using the Interactive Web Response System (IWRS). IWRS is a web-based registration system available to users on a 24/7 basis. On a successful registration, IWRS will assign a patient number and assign the treatment. Patient enrollment data entered by Registrars in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave. IWRS will provide a printable confirmation of registration and treatment information. Please print this confirmation for your records.

- Users must have a valid CTEP-IAM account (i.e., CTEP username and password) to access the IWRS system.
- Users defined with the Registrar role will have the ability to register patients in the study.
- Users defined with the Client Administrator role will have the ability to manage accrual limits, open and close treatment assignments as well as approve slot reservations, if applicable to the study.
- For trials with slot reservation requirements, Registrars will have the ability to request to reserve a slot, which may require approval from users at the lead institution defined as a 'Client Administrator' for the study.

5. TREATMENT PLAN

This is a multicenter phase I trial evaluating the intravenous administration (IV) of LMP744 over 1 hour on days 1-5 followed by 23 days without drug (28-day cycle, see Schema). After cycle 1, the infusion may be administered over 1 hour +/- 10 minutes. After cycle 2, the start of a new cycle may begin up to 3 days earlier than it would otherwise be scheduled or be delayed up to 1 week to accommodate scheduling conflicts and other unexpected events. LMP744 will be administered via central line. If the patient has a central line (such as a port-a-cath or a tunneled Hickman catheter) at the time of enrollment, treatment will be administered via this route. If the patient does not have one, a temporary central line (such as a PICC) will be placed and removed after the last treatment infusion of LMP744.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, pre-treatment tumor biopsy, laboratory evaluations, urinalysis, and EKG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the screening evaluations (see Section 3.4), the screening evaluations may be used as baseline measurements. If >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, urinalysis, and EKG must be repeated prior to starting protocol therapy. Tumor imaging and baseline ECHO must be performed within 28 days prior to start of protocol therapy.

History and physical examination will be done at baseline (within 8 days prior to start of protocol therapy), during week 2 of cycle 1, and at the start of every cycle thereafter (within 3 days prior to treatment).

Labs (CBC with differential; serum chemistries) and urinalysis will be performed at baseline (within 8 days prior to start of protocol therapy), on D8 and D15 of cycle 1, on D1 and D15 of cycles 2 and 3, and then at the start of each cycle (up to 3 days before start of a new cycle).

Blood and urine samples for correlative research studies will be collected as described in Section 9. Tumor biopsies will be mandatory in the expansion phase.

CT scans will be performed at baseline (within 28 days prior to start of protocol therapy), and repeat imaging scans will be performed every 2 cycles (every 3 cycles for patients on study for more than 1 year; every 4 cycles for patients on study more than 3 years). For patients with

lymphoma, a PET scan will be done at baseline if clinically indicated, and repeated at restaging if clinically indicated or required for restaging purposes.

CT-guided biopsies (mandatory for patients in the expansion phase) will be collected at baseline and on D2 of cycle 1 for research purposes.

Baseline EKG (within 8 days prior to start of protocol therapy) and baseline ECHO (within 28 days prior to start of protocol therapy) will be performed. EKG and ECHO will be repeated before cycles 3 and 5 (up to 1 week prior to start of cycle), and as clinically indicated thereafter.

5.1 Indenoisoquinoline Administration

Treatment may be administered in the outpatient service. Patients must be monitored in clinic for allergic/hypersensitivity reactions for a minimum of 1 hour after receiving drug during cycle 1 and as clinically indicated thereafter.

5.1.1 Dose Levels

Dose escalation in this study initially followed design 3 of the Simon accelerated titration designs (26, 27). This trial design minimizes the number of patients exposed to lower dose levels by using single-patient cohorts, reverting to a standard 3+3 design once a "stop decision" is taken. Intra-patient dose escalation is permissible in the Simon design 3, and is separately described in Section 6.2.

As of Amendment G (10/18/18), a "stop decision" was taken and the study reverted to a standard 3+3 design.

Dose escalation proceeded initially with single patient cohorts per dose level, with 100% increments in dose level for the next single-patient cohort. As of Amendment G (10/18/18), a "stop decision" was taken at Dose Level 6 to revert to the 3+3 dose-escalation cohorts. The subsequent dose levels are 40% increments in the dose until a maximum dose is reached.

Dose Levels	
Dose Level	LMP744 mg/m^2/day QD x 5 days every 28-days (IV)
Level-1	3
Level 1	6
Level 2	12
Level 3	24
Level 4	48
Level 5	96
Level 6	190
Level 7	260
Level 8	360
Level 9	500
* *Doses are stated as exact dose in units (mg/m^2)*	

5.1.2 Dose Escalation Cohorts

During the accelerated phase, there will be one patient per dose level. The patient will be assessed for dose-limiting toxicity (DLT) and grade 2 toxicity (both parameters defined in Section 5.2) during cycle 1 of treatment.

The accelerated phase of dose-escalation will end, and change to a standard 3+3 design, when:

- one patient experiences DLT during cycle 1, OR
- at the first instance of grade 2 drug-associated toxicity, when two additional patients will be enrolled. If two different patients experience Grade 2 toxicity during cycle 1, the escalation plan will end.

As of Amendment G (10/18/18), a patient on Dose Level 6 experienced DLT during cycle 1, and the study reverted to a standard 3+3 design.

5.1.2.1 Standard 3+3 Dose Escalation Phase

In the standard phase of the dose escalation, 3 patients will be treated at the final accelerated dose level and initially at each new dose level. Dose escalation will be based on DLTs observed during the first cycle of treatment. If none of the 3 patients develop DLT at the dose administered, escalation will continue in cohorts of 3 patients each. If a DLT during the first cycle is observed in any of the 3 patients, then the cohort will expand to 6 patients. If a second DLT is observed during cycle 1, then up to a total of 6 patients will be enrolled to the next lower cohort. If no more than 1 in 6 patients in a dose level have DLT during the first cycle, dose escalation is permitted.

At the PI's discretion, up to an additional 3 patients may be accrued at a dose level with 1 DLT observed among the 6 patients or no DLTs observed among the first 3 patients, to further assess safety. Dose escalation will proceed if no additional DLTs are observed. If 1 additional DLT is observed, the prior dose will be declared the MTD, once 6 patients have been treated with no more than 1 DLT observed.

DLTs seen after the first cycle will not affect the dose escalation decisions.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped,

	and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

The MTD is the dose level at which no more than 1 in 6 patients experience DLT, and the dose below that at which ≥ 2 (of ≤ 6) patients have DLT as a result of the drug. If ≥2 patients experience DLT on dose level -1 for LMP744, the study will be placed on hold and all data reviewed to make a decision about further evaluation of the study drug.

5.1.2.2 Expansion Cohort

Once the MTD is identified, another 15 patients will be treated at the MTD on an expansion cohort. With 15 patients and a biopsy QA failure rate of 50% with respect to paired biopsies, there is an 85% likelihood of having at least 6 usable samples and a 95% likelihood of having at least 5 usable samples.

With Amendment L (date 6/7/2021), the MTD is identified as dose level 6 (190 mg/m^2/day) and the expansion cohort will begin accrual.

5.2 Definition of Dose-Limiting Toxicity

5.2.1 Grade ≥3 non-hematologic toxicity will be considered dose limiting, with the following exceptions:

5.2.1.1 Grade 3 fatigue lasting ≤ 7 days.

5.2.1.2 Grade 3 diarrhea will only be considered dose limiting if, after 48 hours, it is refractory to treatment as outlined in Section 5.3.2. Grade 4 diarrhea will be dose limiting.

5.2.1.3 Grade 3 nausea and vomiting will be considered dose limiting after 48 hours if it is refractory to maximal anti-emetic therapy and unable to be corrected to Grade 1 or baseline. Grade 2 nausea or vomiting after 72 hours despite three anti-emetogenic agents will also be considered dose limiting.

5.2.1.4 Grade 3 rise in creatinine, not corrected to Grade 1 or baseline after intravenous fluids within 24 hours, will be considered dose limiting. All Grade 4 rises in creatinine will be dose limiting.

5.2.1.5 Grade 3 electrolyte toxicities unable to be corrected to Grade 2 or baseline within 24 hours will be considered dose limiting.

5.2.2 Grade 4 hematological toxicity will be considered dose limiting if it meets the criteria below. Lymphopenia (any grade) will not be considered dose limiting for all

subjects.

5.2.2.1 Neutropenia: Grade 4 neutropenia for >5 days without fever or infection will be considered dose limiting. Grade 4 neutropenia of any duration accompanied by fever or infection will be considered dose limiting. Twice weekly blood draws will be needed (after onset of grade 4 neutropenia) to monitor duration of neutropenia for the first 2 cycles. On subsequent cycles (cycle 3 and beyond), weekly blood draws will be monitored at the onset of grade 4 neutropenia.

5.2.2.2 Thrombocytopenia: Grade 4 thrombocytopenia will be considered dose limiting. Grade 3 thrombocytopenia associated with bleeding will be considered dose limiting.

5.2.2.3 Anemia: Grade 4 anemia will be considered dose limiting.

5.2.3 Any neurotoxicity Grade ≥2 that is not reversible to a Grade ≤1 within 2 weeks will be considered dose limiting.

5.2.4 Any non-hematologic Grade 2 toxicity that does not resolve to Grade ≤1 or baseline within 14 days despite adequate treatment as described in Section 5.3 will be considered dose limiting, except for alopecia.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.3 General Concomitant Medication and Supportive Care Guidelines

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biologic response modifiers, or immunotherapy. Palliative-intent single-fraction radiation therapy after cycle 1 is permissible at the PI's discretion, but may not be administered concurrently with LMP744. A delay of up to one week prior to starting a subsequent cycle of treatment will be permitted to enable marrow recovery. No medications, including over-the-counter products, should be started without first consulting with the investigator.

5.3.1 Vomiting

Anti-emetics will not be administered prophylactically for the first dose, only for subsequent doses if nausea or emesis occurs. However, if a patient develops nausea/vomiting, anti-emetics, such as Ondansetron will be instituted prior to treatment. If nausea or emesis persists, a second agent such as olanzapine or lorazepam should be added.

5.3.2 Diarrhea

Patients will not be given anti-diarrheal prophylactically. If a patient develops diarrhea, if clinically indicated a test for C. difficile will be ordered. If a patient is found to have C. difficile colitis, appropriate antibiotics will be instituted. If noninfectious diarrhea

develops and does not have an identifiable cause other than study drug administration, anti-diarrheal (such as diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg PO after the first unformed stool with 2 mg PO every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). No more than 16 mg of loperamide should be taken in during a 24-hour period. This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 48 hours to Grade 2 with the above suggested regimens.

5.3.3 Neutropenia

Febrile neutropenia is a life-threatening complication and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode.

Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

5.3.4 Anemia

Symptomatic anemia should be treated with red blood cell infusion, which is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines.

5.3.5 Thrombocytopenia

Thrombocytopenia will be treated conservatively. In the absence of bleeding, fever, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10,000/mm3. If invasive procedure(s) is (28) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

5.3.6 Tumor lysis syndrome

At the discretion of the PI, patients at risk of tumor lysis will receive allopurinol 24 hours prior to the initiation of therapy. Additional measures such as hospitalization with aggressive iv hydration, use of rasburicase, and urinary alkalization will be used at the discretion of the investigator.

5.3.7 Allergic Reaction

If a patient develops hives or swelling, the LMP744 infusion will be held and at a minimum diphenhydramine administered at a dose of 50 mg IV. Other medications (such as steroids or epinephrine) can be used at the discretion of the clinician. Once the reaction has subsided, patients may be rechallenged with the original dose of LMP744. In case the reaction does not subside within 2 hours or the patient develops a subsequent reaction on rechallenge, the study drug will be discontinued and the patient taken off study. A grade ≤ 2 allergic reaction will not be considered a DLT; pre-medication will be added to treatment on subsequent dosing if patients experience ≤ grade 2 infusion

reaction.

5.3.8 Inhibitors and Inducers of ABCG2 and P-gp

LMP744 is a substrate for ATP-binding cassette transporter protein ABCG2 and P-gp. Unless medically necessary, avoid the use of strong inhibitors and inducers of these transporters.

5.3.9 Cytochromes P450 Inhibitors and Inducers, and Inhibitors of Drug Transporters

The pathways by which LMP744 is eliminated are not known. Unless medically necessary, avoid the use of strong inhibitors and inducers of all major drug metabolizing enzymes and drug transporters.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- DLT recurs after two dose reductions for DLT or no lower dose level exists (as described in Sections 5.1 and 6.2)
- Patient decides to withdraw from the study
- Noncompliance at the discretion of the PI

5.5 Duration of Follow Up

Patients will be followed for 30 days after the last dose of study drug is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Unacceptable toxicities (i.e., AEs related to the intervention) that have not resolved by Day 30 post-treatment will be followed via biweekly phone calls until stabilization or resolution.

5.6 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow-up period, toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives other type of treatment-intent therapy. The reason for study removal and the date the patient was removed must be documented in the medical record.

6. DELAYS/DOSE MODIFICATIONS

See below for dose delay and management guidance, indicating when the study agent should be held or discontinued due to specific adverse events.

6.1 Drug-related toxicity

6.1.1 If a patient has a DLT during cycle 1, no further treatment will be administered for that cycle and the dose will be reduced by one dose level for the next cycle.

6.1.2 If the patient has a DLT during any subsequent cycle, no further treatment will be administered for that cycle and the dose will be reduced by one dose level for the next cycles and the patient will not be eligible for intra-patient dose escalation.

6.1.3 If Grade 3 diarrhea occurs (increase of >6 stools/day over baseline) but resolved to ≤ grade 2 with anti-diarrheal within 72 hours, the patient will receive the same dose on subsequent cycles with anti-diarrheal treatment as stated in Section 5.3.2. If Grade ≥3 diarrhea continues > 72 hours despite treatment, this constitutes a DLT (see Section 5.2) and LMP744 will be dose reduced by one dose level for subsequent cycles.

Diarrhea grade after 72 hours of anti-diarrheal med	**Management/Next Dose for LMP744**
≤ Grade 1	No change in dose
Grade 2	Resume at same dose level.
Grade 3	Hold* until ≤ Grade 2. Resume at one dose level lower, if refractory.**
Grade 4	
*Patients requiring a delay of >2 weeks will be taken off protocol therapy. **Patients requiring > two dose reductions will be taken off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

6.1.4 If Grade ≥2 nausea and vomiting require anti-emetics, the patient will receive anti-emetics prior to the administration of subsequent doses of LMP744 as described in Section 5.3.1.

Nausea grade after 72 hours of antiemetic support	**Management/Next Dose for LMP744**
≤ Grade 1	No change in dose
Grade 2	Resume at same dose level.
Grade 3	Hold* until ≤ Grade 2. Resume at one dose level lower if refractory.**
Grade 4	Off protocol therapy
* Patients requiring a delay of >2 weeks will be taken off protocol therapy. **Patients requiring > two dose reductions will be taken off protocol therapy.	
Recommended management: antiemetics.	

Vomiting grade after 72 hours of antiemetic support	**Management/Next Dose for LMP744**
≤ Grade 1	No change in dose

Vomiting grade after 72 hours of antiemetic support	Management/Next Dose for LMP744
Grade 2	Resume at same dose level.
Grade 3	Hold* until ≤ Grade 2. Resume at one dose level lower, if refractory.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

6.1.5 Patients will be allowed to continue treatment for decreased leucocytes, ANC and hemoglobin that recover to a Grade ≤ 2 toxicity and platelets to Grade ≤ 1. Dose reduction to one dose level lower may also be considered if ≥4 occurrences of symptomatic anemia requiring blood transfusion, at the discretion of the clinician.

Neutropenia	Management/Next Cycle
≤ Grade 1	No change in dose
Grade 2	Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at same dose level.
Grade 4	Hold* until < Grade 2. Resume at one dose level lower**
*Patients requiring a delay of >2 weeks will be taken off protocol therapy. **Patients requiring > two dose reductions will be taken off protocol therapy.	
Use of growth factors per ASCO guidelines.	

Thrombocytopenia	Management/Next Cycle
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until < Grade 1. Resume at one dose level lower.**
*Patients requiring a delay of >2 weeks will be taken off protocol therapy. **Patients requiring > two dose reductions will be taken off protocol therapy.	

Anemia	Management/Next Cycle
≤ Grade 1	No change in dose
Grade 2	Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Hold* until < Grade 2. Resume at one dose level lower.**
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

6.1.6 If a patient develops hives or swelling, the patient will receive at minimum diphenhydramine as described in Section 5.3.7. Once the reaction has subsided, patients may be rechallenged with the original dose of LMP744. In case the reaction does not subside within 2 hours or the patient develops a subsequent reaction on rechallenge, the study drug will be discontinued and the patient taken off study. A grade ≤ 2 infusion reaction will not be considered a DLT; pre-medication will be added to treatment on subsequent dosing if patients experience ≤ grade 2 infusion reaction.

6.2 Intra-patient Dose Escalation and De-escalation

Intra-patient dose ESCALATION is permitted ONLY if:

1. Patients did not experience toxicity >Grade 1 that is possibly, probably, or definitely related to the study drug after one cycle at the initial dose level (subsequent cycles may be delayed up to 14 days past the end of the previous cycle of 28 days to allow for toxicities to resolve).
2. Higher doses have been evaluated and completed without a DLT.
3. The patient's disease has not progressed.
4. There is no concern of cumulative toxicity.

Doses may be escalated by one dose level for every subsequent cycle, provided conditions 1-4 are met, up to the last evaluated dose level NOT associated with DLT.

If a patient experiences DLT during a cycle, the dose will be REDUCED by one level (if there is a lower dose level, see Section 5.1.2) for the next cycle, provided toxicity has recovered to ≤ Grade 1 within 14 days after completing a 28-day cycle, and the patient's disease is stable or responding. If a patient is dose reduced twice and still experiences a DLT, then the patient would be removed from the study. If no lower dose level exists, then the patient will be removed from the study.

6.3 Dose and Cycle delays

Subsequent cycles may be delayed up to 14 days past the end of the previous cycle of 28 days for resolution of toxicity. Patients will be allowed up to 2 dose reductions. If more than 2 dose reductions are required, the patient will be removed from the study. For patients on dose level 1, only 1 dose reduction will be allowed (see Section 5.1.2).

6.4 Reporting and Exclusions

6.4.1 Evaluation of toxicity: A cycle is defined as being 28 days, with Day 1 starting the first day of the 5-day treatment. . All patients who receive a dose of LMP744 will be evaluable for toxicity regardless of whether they complete a cycle. If therapy is delayed, the next cycle day 1 will be the day therapy is administered.

Patients who do not complete a cycle of therapy for reasons other than toxicity will be replaced.

6.4.2 Evaluation of response: All patients included in the study who receive any treatment at all will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. All patients who meet the eligibility criteria will be included in the main analysis of the response rate. Secondary analyses may be restricted to patients without major protocol violations.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

7.1.1 CAEPR for LMP744

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
LMP744 (NSC 706744)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for LMP744.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 1.3, October 20, 2021[1]

Adverse Events with Possible Relationship to LMP744 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	
Febrile neutropenia	
GASTROINTESTINAL DISORDERS	
Nausea	
Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Death NOS	
INVESTIGATIONS	
Alanine aminotransferase increased	
Aspartate aminotransferase increased	
GGT increased	
Lymphocyte count increased	***Lymphocyte count increased (Gr 2)***
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hypokalemia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Hypoxia	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Animal Data: The following toxicities have been observed in animal studies with LMP744:

Dogs

Congenital, familial and genetic disorders - Increased levels of total bile acids; Inflammation of the portal tracts of the liver; Lethargy/fatigue; Low albumin; Microscopic biliary hyperplasia; Mononuclear cell inflammation suggestive of hemorrhagic cystitis
General disorders and administration site conditions - Decreases in monocytes, basophils, RBCs, and/or large unstained cells; Fever; Gastrointestinal toxicities including vomiting and diarrhea; Hives in the inner ear; Increased levels of ALP
Injury, poisoning and procedural complications - ALK increased; ALP increased; Anorexia; Arrhythmia; Aspiration/pulmonary infiltrates; Bile duct hyperplasia; Creatinine increased; Decreased bone marrow hematopoiesis; Decreased total eosinophils
Investigations - Increased levels of fibrinogen; Nausea; Neutrophilia with left shift; Pain; Ptyalism; Skin toxicity; Supraventrical and nodal arrhythmia -- Sinus; Swollen leg; Tachycardia; Tarry feces; Weight loss

Other
General disorders and administration site conditions - Injection site toxicity including lesions, ulceration, necrosis, necrosis in the tail, inflammation; Liver toxicity; Lung toxicity; Decreased appetite; Hematological toxicity including lymphopenia and reticulocytopenia
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Allergic reactions/hypersensitivity including facial swelling and erythema of the eyes, face, legs; Bladder toxicity; Bone marrow toxicity; Decreased hematocrit counts

Rats
General disorders and administration site conditions - Alopecia/scabbing; Decreased albumin; Decreased phosphorus; Decreased triglycerides; Elevated BUN; Emaciation; Increased globulin; Pulmonary thrombi; Red inguinal fur; Renal tubular degeneration; Rough coat
Investigations - Thymic atrophy; Thymic toxicity; Tubular single cell necrosis

Note: LMP744 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1) for expedited reporting purposes only. 'Expected' AEs (the SPEER) are **bold and italicized** in the CAEPR (Section 7.1.1).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. These requirements are briefly outlined in the tables below.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (24) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Lymphopenia (any grade), alopecia (any grade), anemia (grade 2), electrolytes (grade 2: sodium, potassium, phosphorous, and magnesium), albumin (grade 2), hyperuricemia (grade 3), INR (grade 2), and PTT (grade 2) will not be reported via CTEP-AERS but will be included in the routine data submissions.

7.3.5 NIH Reporting Requirements/ Data and Safety Monitoring Plan

7.3.5.1 **Definitions**

Please refer to definitions provided in Policy 801: Reporting Research Events https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs).

7.4 OHSRP Office of Compliance and Training / IRB Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events, and Policy 802: Non-Compliance in Human Subjects Research (found in https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs). Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

1.1.1 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here: https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

7.5 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to the Clinical Director/designee at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.5.1 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.5.2 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

LMP744 (NSC 706744)

Chemical Name: 6-[3-(2-hydroxyethyl)aminopropyl]-5,6-dihydro-5,11-diketo-2,3-dimethoxy-8,9-(methylenedioxy)-11H-indeno[1,2-c]isoquinoline hydrochloride

Classification: Indenoisoquinoline

Molecular Formula: $C_{24}H_{25}ClN_2O_7$ **M.W.:** 488.92 (HCl salt)

Mode of Action: Inhibition of topoisomerase 1

How Supplied: LMP744 is supplied by the DCTD, NCI and distributed by the Pharmaceutical Management Branch, NCI as sterile, non-preserved, single-use glass vials sealed with rubber stoppers and aluminum crimp seals and flip-top caps. Each vial contains 15 mg/15 mL or 50 mg/50 mL of LMP744 (1 mg/mL) in Water for Injection as a clear, dark red solution, pH~2.8. pH is adjusted with hydrochloric acid.

Preparation: LMP744 solution for infusion may be diluted with 5% Dextrose Injection, USP (D5W) to concentrations ≥ 0.3 mg/mL or may be transferred to an empty infusion container and administered undiluted. Discard unused vial portion after use.

LMP744 solution for infusion is compatible with non-PVC and non-DEHP containing infusion containers and non-DEHP infusion sets.

Storage: Store intact vials refrigerated (2°C – 8°C).

If a storage temperature excursion is identified, promptly return LMP744 to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life testing of the intact vials is on-going. Prepared solutions for infusion should be administered within 4 hours of preparation if stored at room temperature or within 24 hours if stored refrigerated.

Route of Administration: Intravenous

Method of Administration: Intravenous as a 1-hour infusion. A central line is required for administration.

Potential Drug Interactions: LMP744 is a substrate for ATP-binding cassette transporter protein ABCG2 and P-gp and potentially subject to drug interactions.

8.1 Agent Ordering and Agent Accountability

8.1.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.1.1 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation, and ordering investigator on this protocol.

8.2 Investigator Brochure for LMP744

The current version of the IB will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- PMB IB Coordinator: IBcoordinator@mail.nih.gov
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. CORRELATIVE STUDIES

9.1 Pharmacokinetics

Blood Samples

Blood samples for PK analyses will be collected at the following timepoints in cycle 1 only:

- Day 1, prior to drug administration, 2 minutes (+/- 2 minutes) before end of infusion, and at appropriate time points post infusion (15 minutes, 30 minutes, and 1, 2, 4, and 6 hours post infusion)
- Day 2, 24 hr post day 1 start of infusion (immediately prior to day 2 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 3, 24 hr post day 2 start of infusion (immediately prior to day 3 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 4, 24 hr post day 3 start of infusion (immediately prior to day 4 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 5, 24 hr post day 4 start of infusion (immediately prior to day 5 infusion), and 2 minutes (+/- 2 minutes) before end of infusion
- Day 8, 72 hr post day 5 start of infusion

The total volume of blood collected for PK studies during the initial treatment cycle is expected to be < 50 mL per patient. Based on results from initial measurements, sampling times may be adjusted, but neither the total number of samples nor the total amount of blood drawn per patient will be increased.

Samples will be collected in K2-EDTA tubes with 3 mL of blood per sample. Samples should be kept on ice until centrifugation. All samples will be centrifuged at 2000×g at 4°C for 10 minutes and plasma will be stored at -70℃ for analysis. Samples will be analyzed using a validated LC-MS or LC-MS/MS method for LMP744 in human plasma. The plasma concentration-time data will be analyzed using the WinNonlin (Pharsight, Mountain View, CA) or other appropriate PK software. The maximum plasma concentration, time to maximum concentration, AUC extrapolated to infinity, and apparent terminal half-life will be calculated by non-compartmental analysis.

The parent drug molecule and possibly metabolites in plasma will be analyzed by the Molecular Therapeutics/Drug Discovery Program at the University of Pittsburgh Cancer Institute. This facility has extensive experience in the measurement of drugs and metabolites

in body fluids. The laboratory has multiple HPLC instruments, including ultraviolet absorption detectors and several single- and triple-quadrupole mass spectrometers.

Plasma samples for PK analysis will be sent to:

[redacted]
University of Pittsburgh Cancer Institute
[redacted]
5117 Centre Avenue
Pittsburgh, PA 15213-1863

Please notify [redacted] and [redacted] at least 24 hours prior to shipment. An alternate qualified analytical site (DTP or DTP contractor's site) may be used, if necessary, for timely analysis of all samples.

9.2 Pharmacodynamics

We plan to evaluate the in vivo molecular effects of LMP744 in CTCs and tumor biopsy specimens.

9.2.1 Biopsy procedure and processing

The timing of tumor biopsy samples will be at baseline (pre-treatment) and on day 2 (1-4 hours after the LMP744 infusion). Based on initial results from the trial, tumor biopsy timing may be adjusted, but the number of biopsies will not be increased without an amendment. Tumor biopsies will be mandatory during the expansion phase.

Biopsies will be obtained on selected patients when lesions are safely accessible (including cutaneous, subcutaneous, and easily accessed parenchyma lesions).

Serial tumor biopsies will be obtained by the Interventional Radiology team by a percutaneous approach (if a SQ lesion is identified, biopsies may be obtained by a surgeon or dermatologist). It is preferred that up to 5 core biopsies ≥18 gauge in diameter and ≥1 cm in length will be obtained during each procedure if considered safe and feasible. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology team, an attempt for biopsy will be made. The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and Interventional Radiology.

If the participant chooses not to undergo the day 2 tumor biopsy, he/she will still remain in the study and receive study medication, and all the other correlative studies will be performed.

If an initial attempt at percutaneous biopsy is unsuccessful, the participant will be given an option to proceed with a repeated attempt at percutaneous biopsy. In case biopsy samples cannot be obtained for a given participant, the participant will still remain in the study and receive study medication, and all the other correlative studies will be performed.

Up to 5 core biopsies will be obtained at each time point and processed according to the National Clinical Target Validation Laboratory (NCTVL) SOP 340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). Briefly, cores will be transferred into a 1.5-mL pre-chilled cryovial and then flash frozen in liquid nitrogen. Biopsies should be collected, placed in prechilled cryogenic vials, and frozen within 2 minutes of collection.

The frozen biopsy specimens should be transferred to PADIS on dry ice, where the core biopsy samples are stored at -80°C until processing. Biopsies for PD analysis will be shipped via FedEx to:

Attention: Leroy Smith
NCI-F/FNLCR
Natural Products and Tumor Repositories | Charles River
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21702
Phone: 301-846-5748
NCI_PD_Support@mail.nih.gov

For NCI Clinical Center specimens only: Shipment should be by CSP Courier and may be arranged by contacting Jenn Bangh, FNLCR, Tel.: 301-846-5893

Frozen biopsy samples will be used for molecular analysis, including γH2AX and cleaved caspase-3 measurement (apoptosis; as described in Section 2.4.1), LC-3 (autophagy), epithelial-mesenchymal transition (EMT) analysis, and DNA damage response (DDR) analysis. The EMT panel will analyze the fraction of CTCs that are positive for vimentin and/or cytokeratin in conjunction with a tumor marker (UC1, CEA, or TFE1, depending on tumor histology). The DNA damage response (DDR) panel will analyze levels of ERCC1, RAD51, pATR, pNbs1, Topo1cc, Top1, and SFLN11 proteins involved in the repair of DNA breaks.

If for some reason only one core is able to be obtained, the core will be divided, with half submitted to Surgical Pathology and half used for PD studies. Priority will be given to performing γH2AX and cleaved caspase-3 analysis on paired biopsy samples.

9.2.2 Circulating tumor cells (optional)

For the current protocol, optional blood for CTCs will be collected from patients at the following timepoints:

- baseline (prior to drug infusion)
- on day 3 of cycle 1 (within 2 to 4 hours after the start of LMP744 infusion)
- on day 1 of every subsequent cycle (prior to drug infusion)
- at time of disease progression

These samples will be used to determine:

1) The number of CTCs in the blood sample
2) Whether the level of γH2AX expression has increased (assessing the fraction of γH2AX expression in CTCs via immunofluorescence)
3) The dose response in the fraction of CTCs that is γH2AX positive
4) EMT panel (as described above)

These values will be compared to baseline values collected from samples from the same patient. At the NCI clinical center, each blood specimen (7.5 mL) will be collected into one 10 mL Streck tube (catalog number 218962). One 10 mL RareCyte tube (catalog number 24-1070-005) is also acceptable. Tubes must be inverted 8 times to ensure adequate mixing of the additive. At other participating sites, each blood specimen will be collected into one 7.5-mL CellSave tube or one 10 mL Streck tube as described in Appendix D (kits will be provided). Refer to NCI DCTD SOP LHTP003.08.19 for additional guidance regarding blood collection in a Streck tube: https://dctd.cancer.gov/ResearchResources/biomarkers/emt/LHTP003.08.19_Streck.pdf

Blood for CTC analysis will be shipped at room temperature to the PADIS laboratory on the day it is collected as described in Appendix D. Samples may not be held at the external site or shipped with frozen biopsy samples. **Prior to CTC collection, each outside participating site should e-mail a request for specimen collection and shipping materials from NCI_PD_Support@mail.nih.gov.**

At NCI only: arrangements will be made for pickup with the CSP courier service. At least 24 hours prior to blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov; Pager (preferred): 102-12798; Phone: 240-858-3963; Fax: 301-480-5871. The NCI Phase I/II PK/PD Support Group will arrange for same day processing or immediate shipment to FNLCR; specimens should be held at controlled room temperature (15˚C to 30˚C) prior to processing.

9.2.3 **At NCI only:** Blood collection for ctDNA analysis in expansion phase patients

9.2.3.1 Timing of ctDNA blood collection

Plasma, derived from whole blood collected from expansion cohort patients (as of Amendment Q, 6/14/22), will undergo ctDNA assessment by the TSO500 panel to quantitatively assess longitudinal changes in ctDNA levels (as a percentage of total circulating, cell-free DNA) and to identify any tumor genomic alterations that may be associated with response or resistance to the LMP744 treatment; the results of these studies will not be returned to patients. Once a patient has come off study, ctDNA from blood samples correlating to clinically informative time points (minimally, before treatment and at restaging scans suggesting tumor growth) will be analyzed.

Three whole blood samples of at least 7.5 mL each will be collected into three respective 10-mL Streck tubes at each of the following time points and shipped to MoCha within 3 days for ctDNA analysis:

- baseline (pre-treatment; up to 8 days prior to the start of treatment and within ± 8 hours of the biopsy at this time point)
- day 1 of every subsequent cycle (at any time)
- at time of disease progression

9.2.3.2 Blood specimen shipping for ctDNA analysis

Labeling:

Blood specimens should be labeled with:

- Sample type (e.g., whole blood)
- Time point (e.g., C1D1 pre-dose)
- Collection date and time
- Sample ID, containing:
  - CTEP protocol number
  - Site LAO code
  - Unique patient ID (**Do NOT include patient name, medical record number, or initials**)
  - Consecutive 800-series sample collection number (i.e., 800, 801, 802)
- The 2 tubes for each time point should be designated using "A" and "B" (e.g., the two pretreatment specimens should be labeled 800A and 800B).

For example, the sample ID for the C1D1 pre-dose ctDNA blood sample collected on Study 10002 for NCI DTC patient #004 should be: 100002_NCIDTC_004_800.

Ship blood specimens at ambient temperature to:
Attn: Gloryvee Rivera
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.

1050 Boyles Street
Building 321 Room 107
Frederick, MD 21702
MoChaSampleReceiving@nih.gov

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893.

Please contact Alyssa Chapman at 301.846.1718 (MoChaSampleReceiving@nih.gov) to ask any questions regarding storage or shipment of these specimens. MoCha should be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s).

Samples should **arrive at MoCha within 2 days of collection when possible; arrival within 3 days of collection is permissible when necessary**. Note that FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays.

10. STUDY CALENDAR

Eligibility screening evaluations (see Section 3.4) are to be performed within 8 days prior to patient enrollment, with the exception of informed consent, ECHO, and tumor imaging scans, which must be performed within 28 days prior to patient enrollment. Baseline history, physical examination, laboratory evaluations, urinalysis, and EKG are to be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the screening evaluations, values from the screening evaluations may be used as baseline measurements. If >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, urinalysis, and EKG must be repeated prior to starting protocol therapy. Baseline imaging scans and ECHO must be done within 28 days prior to the start of protocol therapy.

After cycle 2, the start of a new cycle may begin up to 3 days earlier than it would otherwise be scheduled or be delayed up to 1 week to accommodate scheduling conflicts and other unexpected events. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study Screening	C1 D1	C1 D2	C1 D3	C1 D8	C1 D15	C2 D1	C2 D15	C3 D1	C3 D15	Time of progression
LMP744*		X					X		X		
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									
Physical exam[c]	X	X[i]			X		X		X		X
Vital signs	X	X[i]			X		X		X		X
Height	X										
Weight	X	X[i]			X		X		X		X
Performance status	X	X[i]					X		X		X
CBC w/diff, plts[a]	X	X[i]			X	X	X	X	X	X	X
Serum chemistry[a]	X	X[i]			X	X	X	X	X	X	X
Urinalysis[a]	X	X[i]			X	X	X	X	X	X	X
Adverse event evaluation		X----------X									X
Tumor measurements	X	Tumor measurements are repeated per Section 11.1. Documentation (radiologic) must be provided for patients removed from study for progressive disease.									X
B-HCG[b]	X						X		X		
PK sampling-blood[d]		X			X						
Blood for CTCs[e]		X		X			X		X		X
Blood for ctDNA[f]		X					X		X		X
Tumor biopsies[g]		X	X								
ECHO/EKG[h]	X	X[i]							X		

*: LMP744 will be administered via central line. Doses as assigned; days 1-5 intravenously over 1 hour; dose escalation as defined in Section 5. After cycle 1, the infusion may be administered over 1 hour +/- 10 minutes. After cycle 2, a new cycle may begin up to 3 days earlier than it would otherwise be scheduled or be delayed up to 1 week. Monitor patients in clinic for allergic/hypersensitivity reactions for a minimum of 1 hour after receiving drug during cycle 1 and as clinically indicated thereafter.

a: Labs (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT (23), SGPT (10), TSH, sodium, GGT) and urinalysis will be performed at baseline/D1 of cycle 1, D8 and D15 of cycle 1, D1 and D15 of cycles 2 and 3, and then only at the start of each cycle (up to 3 days before start of a new cycle). For patients with lymphoma only, uric acid and LDH will be performed on a similar schedule. Patients on the expansion cohort will also have coagulation profile performed per Section 3.4.

b: Urine or serum pregnancy test (women of childbearing potential) prior to every cycle.

c: History and physical, including vital signs and weight, during weeks 1 and 2 of cycle 1, and at the start of each cycle thereafter (within 3 days prior to treatment).

d: Blood samples for PK analyses will be collected per Section 9.1.

e: Blood for circulating tumor cells (optional) will be collected at baseline, on cycle 1 day 3, at the start of every subsequent cycle, and at disease progression per Section 9.2.2.

f: Blood samples for analysis of circulating tumor DNA (ctDNA) will be collected at baseline (pre-treatment, up to 8 days prior to the start of treatment and within ±8 hours of the biopsy at this time point), on cycle 1 day 2, on day 1 of every subsequent cycle (at any time), and at time of disease progression.

g: Tumor biopsies will be collected at baseline (pre-treatment) and on cycle 1 day 2 post therapy per Section 9.2 (mandatory during the expansion phase).

h: EKG and ECHO at baseline, up to 1 week prior to cycles 3 and 5, and as clinically indicated thereafter.

i: Values from eligibility screening evaluations may be used as baseline (C1D1) values if test was performed within 8 days of start of protocol therapy (within 28 days of start of protocol therapy for ECHO). See Sections 3.4 and 5.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

11.2 Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Patients should be re-evaluated for response every 2 cycles (every 3 cycles for patients on study for more than 1 year; every 4 cycles for patients on study more than 3 years). In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

11.2.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with LMP744.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.2.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately

measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be

used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal

FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.2.4 Response Criteria

11.2.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.2.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.3 Lymphomas

11.3.1 Complete response (CR): Disappearance of all signs and symptoms of lymphoma for a period of at least one month. All lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse after treatment or by more than 75% in the sum of the products of the greatest diameters. The spleen, if consider to be enlarged before therapy on the basis of a CT scan must have regressed in size and must not be palpable on physical examination. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present.

11.3.2 Complete response unconfirmed (CRu): A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by > 75% in sum of the products of the greatest diameters, does not change over the last two treatments, has a negative PET scan, and any biopsies obtained are negative will be considered to be in CR. In organs involved by disease, any residual lesions that have decreased by > 75% in sum of the products of the greatest diameters or are < 1 cm, are consistent with scar, and stable over the last two treatments will be considered to fulfill criteria for CR.

11.3.3 Partial response (PR): 50% or greater decrease in the sum of the products of the longest perpendicular diameters of all measured lesions lasting for a period of at least one month. No individual lesions may increase in size and no new lesions may appear.

•Patients in PR with an estimated >80% reduction in initial tumor bulk whose measurable disease does not change between cycles 4 and 6, and have a negative PET scan after cycles 4 or 6 will be considered to be in clinical CR.

11.3.4 Stable disease (SD): Tumor measurements not meeting the criteria of CR, PR, or PD.

11.3.5 Progression (PD): Increase of 25% or more in the sum of the products of the longest perpendicular diameters of all measured lesions compared to the smallest previous measurements, or the appearance of any new lesion(s).

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

12.1 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Training will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/CTMS. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2 NIH Required Data Safety and Monitoring Plan

The investigators at each participating center will be responsible for the collection, maintenance, and quality control of the study data. Adverse events observed in patients enrolled on the trial will be monitored in real time by the Principal and Associate Investigators, and attribution of these events to the research will be determined at the end of each treatment cycle in each subject. The clinical research team (PI, associate investigators, research nurses, data managers) will meet weekly when patients are being actively treated on the trial to discuss each patient in detail and ensure that all events are graded appropriately, and that the attribution to study drug is correct.

The Coordinating Center is responsible for establishing conference calls between participating sites at least on a monthly basis to discuss the observed toxicities and protocol issues.

All SAEs will be reported through CTEP-AERS to CTEP, to the Coordinating Center PI at NCI, and forwarded to the IRB per Section 7. In all cases where the dose of the study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to the study treatment, the investigator must contact and inform the Coordinating Center PI. All sites will be monitored by the CTEP drug monitor, who will receive data from all participating sites.

Data will be monitored regularly by the PI in order to identify significant toxicity trends. Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients.

Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient's name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the FDA or other authorized user, only under guidelines established by the Federal Privacy Act.

Safety Monitoring Committee:
Because this is a multi-institutional protocol for which the NCI CCR is the Coordinating Center, it will be monitored by the DTC Safety Monitoring Committee, NCI.

12.3 Multicenter Guidelines

This protocol will open initially at the NCI. The NIH IRB will be notified once the participating centers' IRBs have approved the studies to open. This protocol will follow the CCR's Clinical Research Operations' SOPs for multicenter trials.

12.3.1 IRB Approvals

As the Coordinating Center for a trial, it is the PI's responsibility to ascertain that no patients are entered on the trial at a participating institution without full IRB approval. Thus, the NIH IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution before NIH IRB approval will be granted.

The PI will provide the NIH IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH IRB.

12.3.2 Amendments and Consents

The NCI PI will provide the NIH IRB with copies of all amendments, consents, and approvals from each participating institution.

12.3.3 Data Collection

The investigators will be responsible for the collection, maintenance, and quality control of the study data. Each site investigator is also responsible for maintaining all source documentation related to the study, including any films, tracings, computer discs or tapes. NCI will be responsible for data management, data analysis, and reporting. Data collection forms will be provided to the participating institutions. Required data include, not exclusively: prior disease-related therapies with dates, disease type, stage, disease sites, with measurements, and concurrent medications.

12.3.4 Human Data Sharing Plan

What data will be shared?

We will share human data generated in this research for future research as follows:

x De-identified data in an NIH-funded or approved public repository
x Identified data in BTRIS (automatic for activities in the NIH Clinical Center)
x De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?

Data will be shared through:

x An NIH-funded or approved public repository: clinicaltrials.gov
x BTRIS (automatic for activities in the NIH Clinical Center)
x Approved outside collaborators under appropriate individual agreements
x Publication and/or public presentations

When will the data be shared?

x At the time of publication or shortly thereafter

12.3.5 Data and Center Audits

Audits will be conducted yearly to ensure data integrity and provide quality control. These audits will be conducted by the NCI research team. Selected patient charts should be audited as well as the participating institution's Standard Operating Procedures (SOP) at the time of the visit. Data from participating institutions should be available when the protocol is audited at the NCI.

12.4 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only

after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) (except for Group studies).

12.5 Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary objective of this trial is to establish the safety, tolerability, and MTD of LMP744 administered intravenously daily for 5 days in 28-day cycles, to patients with refractory solid tumors. This study will follow design 3 of the Simon accelerated titration designs (26), with dose escalation proceeding in 1-patient cohorts and switching to standard 3+3 dose escalation of dose levels when specific criteria are met (Section 5.1.1). (*Note: As of Amendment G [10/18/18], the study switched to standard 3+3 dose escalation. As of Amendment I [9/25/19], there is flexibility to accrue up to an additional 3 patients on any dose level that has 1 DLT observed among 6 patients [see Section 5.1.2.1]. As of Amendment L [date 6/7/2021], the MTD has been identified and the expansion cohort will begin accrual [see Section 5.1.2.2].*)

Following this, another 15 patients will be treated at the MTD on an expansion cohort, which will include mandatory biopsies. With 15 patients and a tumor biopsy QA criteria failure rate of 50% with respect to paired (pre- and post-dose) biopsies, we have an 85% likelihood of having at least 6 usable PD samples, and 95% likelihood of having at least 5 usable samples from the expansion cohort. Biopsy tissue quality will be monitored and accrual to the expansion phase will stop once we have obtained 6 usable paired samples. With 6 PD sample pairs, there is 90% power to detect a treatment effect equivalent to 1.85 SD's (associated with the intra-patient baseline variability of the PD marker) with the paired 2-sample T-test, at the 1-sided .05 significance level, for a given PD variable of interest. PD variables may be log-transformed to achieve more nearly normal distributions.

DLTs will be summarized descriptively according to dose level. In addition, the relation of dose level with presence or absence of DLT will be analyzed using logistic regression, as described by Simon (20).

All AEs will be tabulated by type and grade according to dose level. In addition, the presence or absence of grade 2 or higher toxicity for each patient in each treatment cycle will be modeled using random effects logistic regression as described by Simon (20), incorporating dose during the cycle and total dose for previous cycles, with intra-patient random effects.

13.2 Sample Size/Accrual Rate

As of Amendment G (10/18/18), if all dose levels are evaluated, we anticipate enrolling a minimum of 35 patients and a maximum of 47 patients. In order to allow for a small number of patients who may not be evaluable, the accrual ceiling for this trial is set at 53 patients.

It is anticipated that 1 patient may be enrolled per month onto this study during the accelerated titration stage (already completed) and 1-2 patients/month thereafter. It is expected that 25-35 months will be required to accrue the number of patients necessary to complete the trial.

13.3 Analysis of Secondary and Exploratory Endpoints

Exploratory evaluations will be performed, with results reported with appropriate caveats about the exploratory nature of the analysis, and without formal adjustment for multiple comparisons.

14. HUMAN SUBJECTS PROTECTION

14.1 Rationale for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, pregnant women and children are excluded from this study. The NCI is the coordinating center for this multi-institutional study. This study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer.) Participants should realize that there is no guarantee of benefit to them from participation in this trial. The results of this trial may benefit future cancer patients. To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Inclusion of Women and Minorities:

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met.

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	0	0	**1**
Asian	2	3	0	0	**5**
Native Hawaiian or Other Pacific Islander	1	1	0	0	**2**
Black or African American	7	7	1	0	**15**
White	12	13	2	2	**29**
More Than One Race	0	1	0	0	**1**
Total	**23**	**25**	**3**	**2**	**53**

14.2 Justification for Exclusions

Due to lack of knowledge on the effects of LMP744 on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Participants with unstable or serious medical conditions are due to the possibility that the underlying condition may obscure the attribution of adverse events to study drug.

14.3 Participation of Children

Participants under the age of 18 will be excluded from study because no dosing or adverse event data are currently available for the use of LMP744 in participants <18 years of age.

14.4 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 10. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.4.1 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication and from undergoing biopsy and blood sampling procedures.

14.4.2 Radiation Risks

As biopsies will be performed with CT guidance, this research study involves exposure to radiation from up to 2 CT scans solely for research purposes with a combined effective dose of 1.6 rem. This is below the guideline of 5.0 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

14.5 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided a study chart and an IRB-approved consent for review and signature, and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary, and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason, and because there is a prospect of direct benefit from

research participation, all subjects ≥ age 18 **at the NCI only** will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.5.1 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients enrolled at other sites will be given information regarding their local patient advocate. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP Form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
- The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
- The Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
- Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP (See Section 8). Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C: PD/PK COLLECTION WORKSHEETS AT THE NCI

RESEARCH URINE SAMPLE COLLECTION SHEET: CYCLE 1 DAY 1

CTEP Protocol 10002 **Site:**
Dose level: **LMP744 Dose:**
Patient ID:

Page ----------
for sample pick-up
Lab phone: 301-451-1169
[redacted]

PLEASE ENTER DATE, TIME, and VOLUME OF EACH VOID FOR 24 HOURS POST DRUG ADMINISTRATION
KEEP SAMPLES REFRIGERATED UNTIL PICKED UP

Date	Time	Volume of Void	Aliquot Obtained (Please check box)	Record comments (i.e., if collection missed), and sign each time you collect a sample
Pre-Drug Administration (SAMPLE #100)				
Administer LMP744 IV, Start Time:				
DAY 1 urine for the first 8 hours after start of infusion (0-8 hours), refrigerate. Send entire urine collection for PK analysis (SAMPLE #101)				
DAY 1 urine for the next 8 hours after start of infusion (8-16 hours), refrigerate. Send entire urine collection for PK analysis (SAMPLE #102)				
Date	**Time**	**Volume of Void**	**Aliquot Obtained**	**Record comments (i.e., if collection missed), and sign each time**

			(Please check box)	you collect a sample
DAY 1 urine for the last 8 hours after start of infusion (16-24 hours), refrigerate. Send entire urine collection for PK analysis (SAMPLE #103)				
End 24-hour Urine Collection Time:				

Please Send a Copy of this sheet with the last specimen.

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: Cycle 1 Days 1-5**

CTEP Protocol 10002 **Ht:**

Dose level: **Dose LMP744:** **Wt:**

Patient ID: **BSA:**

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for Sample Pick-up
Lab phone: 301-451-1169

[redacted]

*******PK SAMPLES GO ON ICE********

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to LMP744 administration**	**PK 200** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**Prior to LMP744 administration**	**PD 400** Streck tube, 1 x 7.5 mL Label tubes: drug, draw date and time **Room temperature**			
Administer LMP744 IV, Start Time:					
Day 1	**2 min before end of infusion**	**PK 201** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**15 min after infusion**	**PK 202** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**30 min after infusion**	**PK 203** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**1 hour after end of infusion**	**PK 204** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**2 hours after end of infusion**	**PK 205** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**4 hours after end of infusion**	**PK 206** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 1	**6 hours after end of infusion**	**PK 207** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			

Continued next page

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 2	**Prior to infusion**	**PK 208** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**	*24 hr after start of D1 Infusion*		
Day 2	**2 min before end of infusion**	**PK 209** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 3	**Prior to infusion**	**PK 210** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**	*24 hr after start of D2 Infusion*		
Day 3	**2 min before end of infusion**	**PK 211** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 3	**Within 2-4 hours after the start of LMP744 infusion**	**PD 401** Streck tube, 1 x 7.5 mL Label tubes: drug, draw date and time **Room temperature**			
Day 4	**Prior to infusion**	**PK 212** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**	*24 hr after start of D3 Infusion*		
Day 4	**2 min before end of infusion**	**PK 213** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			
Day 5	**Prior to infusion**	**PK 214** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**	*24 hr after start of D4 Infusion*		
Day 5	**2 min before end of infusion**	**PK 215** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**			

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: Cycle 1 Day 8**

CTEP Protocol 10002 **Ht:**

Dose level: **Dose LMP744:** **Wt:**

Patient ID: **BSA:**

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for Sample Pick-up
Lab phone: 301-451-1169

[redacted]

*******PK SAMPLES GO ON ICE********

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 8	**Prior to LMP744 infusion**	**PK 216** K2-EDTA 3 mL Label tube: drug, draw date and time **PLACE ON ICE**	*72 hr after start of D5 Infusion*		

Date: **PK/PD BLOOD SAMPLE COLLECTION SHEET: Day 1 of each cycle/at progression per PI**

CTEP Protocol 10002 **Ht:**

Dose level: **Dose LMP744:** **Wt:**

Patient ID: **BSA:**

Page ----------
for Sample Pick-up
Lab phone: 301-451-1169

[redacted]

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to LMP744 administration**	**PD 40X** Streck tube, 1 x 7.5 mL Label tubes: drug, draw date and time **Room temperature**			

APPENDIX D: PROCEDURE FOR SAMPLES FOR PHARMACODYNAMIC STUDIES COLLECTED AT PARTICIPATING SITES

Isolation of CTCs

Prior to CTC collection, each participating outside site should e-mail a request for specimen collection and shipping materials from NCI_PD_Support@mail.nih.gov. Allow at least six business days for receipt of the blood shipment containers; a confirmation e-mail with the expected shipping date will be sent.

Blood will be collected aseptically by venipuncture or from a venous port into one 7.5 mL CellSave preservative tube (catalog number 413988) or one 10 mL Streck Cell-Free DNA BCT blood collection tube (catalog number 218962); the collected blood samples are stable for up to 48 hours at room temperature (15˚C to 30˚C) prior to processing.

Samples from participating sites will be sent to:

Attention: Dan Danner
NCI-F/FNLCR
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21701
Phone: 301-846-5748

E-mail NCI_PD_Support@mail.nih.gov prior to shipping with expected arrival date/time and a description of contents. All shipments should include a description of contents on the outside label/shipping slip, and a detailed packing slip should be included with the samples. Because of the 48-hour window of CTC sample stability, CTC samples should be shipped to arrive when specified below:

Collection Day	Day/time samples **must** arrive at PADIS
Monday	Wednesday (early morning)
Tuesday	Thursday (early morning)
Wednesday	Friday (early morning)
Thursday	Friday (early morning)
Saturday	Monday (early morning)
Sunday	Tuesday (early morning)

CTC samples may not be collected on Fridays.