SUMMARY OF CHANGES

Date: March 7, 2019

Document: NCI Protocol #9837, PhI-76: "Phase I Study of TRC102 in Combination with Cisplatin and Pemetrexed in Patients with Advanced Solid Tumors / Phase II Study of TRC102 with Pemetrexed in Patients Refractory to Pemetrexed and Cisplatin or Carboplatin."

Note: The following is a Summary of Changes between the 11.13.18 and 3.7.19 versions of the protocol

Section	**Description of Change (v. 11.13.18 and v. 3.7.19)**
Face page	Updated protocol version in header and added new version date March 7, 2019 to protocol history.
TOC	Updated page numbers.
5.5	Clarified that patients who have clinical benefit may continue on treatment (even if meeting the protocol definition of progression) at the discretion of the treating MD.
8.1.2.1	Replace section with the following: 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), Biosketch, Agent Shipment Form, 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. 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, a "current" password, and active person registration status. 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. **PI Response:** Done.

Section	Description of Change (v. 11.13.18 and v. 3.7.19)
8.1.2.2	Replace section with the following: 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. **PI Response:** Done.
8.1.2.3	Insert as a new subsection 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://ctepcore.nci.nih.gov/OAOP • CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/ • CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov • IB Coordinator: IBCoordinator@mail.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) **PI Response:** Done
8.1.2.4	Insert this as a new subsection Investigator Brochure Availability The current versions of the IBs for the agents 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. **PI Response:** Done.
12.2	Please revise the following paragraph as indicated. 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

Section	Description of Change (v. 11.13.18 and v. 3.7.19)
	access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) ~~(Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator)~~ on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) ~~Rave CRA role or CRA Lab Admin~~ role, the user must hold a minimum of an AP registration type. To hold the Rave ~~Site~~ Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL. (*Note: A DTL is NOT required for this study*.). **PI Response:** Done.

NCI Protocol #: 9837

Local Protocol #: PhI-76

ClinicalTrials.gov Identifier: NCT02535312

TITLE: Phase I Study of TRC102 in Combination with Cisplatin and Pemetrexed in Patients with Advanced Solid Tumors / Phase II Study of TRC102 with Pemetrexed in Patients Refractory to Pemetrexed and Cisplatin or Carboplatin

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NOTE:
As of March 13, 2018, Arm A (3-drug combination) is open to all ETCTN sites.

Arm B (2-drug combination) is open to all ETCTN sites.

Participating Organizations

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LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
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NCI-Supplied Agent: TRC102 (Methoxyamine hydrochloride, NSC 3801)
Other Agent(s): Cisplatin (Platinol) – commercial supply
Pemetrexed (Alimta) – commercial supply

IND #:
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

December 17, 2014	Initial Protocol
February 17, 2015	Response to Consensus Review
February 26, 2015	Response to Follow Up Review
May 11, 2015	Amendment (cIRB stipulations)
June 18, 2015	Amendment (cIRB stipulations)
August 4, 2015	Amendment
November 10, 2015	Amendment
January 4, 2016	Amendment
February 25, 2016	Amendment
October 24, 2016	Amendment
January 13, 2017	Amendment
July 26, 2017	Amendment
September 28, 2017	Amendment
March 13, 2018	Amendment
November 13, 2018	Amendment
March 7, 2019	Amendment

SCHEMA

NOTE:
As of March 13, 2018, Arm A (3-drug combination) is open to all ETCTN sites.

Arm B (2-drug combination) is open to all ETCTN sites.

Arm A:
This arm is a Phase I trial to select a Recommended Phase 2 Dose (RP2D) of TRC102 in combination with Cisplatin and Pemetrexed in patients with advanced solid tumors. During the initial dose escalation, patients will be accrued in cohorts of 3, with dose escalation based on toxicities experienced during the first cycle (see sections 5.3 and 13.1). Escalation is planned to proceed through 4 dose levels (Table 1), unless the escalation rules require stopping at a lower maximum tolerated dose level (tentative MTD). In that case, Dose Level 4 will be re-defined to combine the TRC102 dose from the tentative MTD with Cisplatin at 75 mg/m^2 (per Table1) and escalation will proceed to the re-defined Dose Level 4. Six patients will be treated at the final RP2D before expanding that dose level

Cohorts of patients will receive escalating doses of TRC102, orally, daily (days 1-4) in combination with cisplatin and pemetrexed on day 1, as shown in Table 1.

Table 1

Dose Level	TRC102 (days 1-4, q 21 days)	Pemetrexed (day 1, q 21 days)	Cisplatin (day 1, q 21 days)
– 1	25 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
1	50 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
2	75 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
3	100 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
4 {chemotherapy-naïve patients}	100 mg/day, **or** MTD w/ 60 mg/m^2 cisplatin, whichever is lower, PO	500 mg/m^2, IV	75 mg/m^2, IV

Arm B:
This arm is designed as the first stage of a two stage (Gehan) design trial of patients with mesothelioma who had progressed while being treated with or had recurred within 6 months of being treated with pemetrexed + cisplatin frontline. Patients will be treated at dose level 1 **without cisplatin** (Table 1). Given the low probability of responses in this population being retreated with pemetrexed, one response out of 14 would be of interest.

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1. OBJECTIVES

We hypothesize: (1) TRC102 combined with pemetrexed and cisplatin can be administered safely in patients with advanced solid tumors;(2) the combination may be effective in patients with advanced unresectable malignant mesothelioma; (3) TRC102 combined with pemetrexed will produce responses in patients with advanced malignant mesothelioma who progressed on or had a recurrence with 3 months of treatment with pemetrexed and cisplatin.

1.1 Primary Objectives

Arm A:

1. To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for the combination of TRC102 with pemetrexed and cisplatin in patients with advanced solid tumors
2. To describe the toxicities of TRC102 combined with pemetrexed and cisplatin at each dose studied
3. To describe responses to the drug combination at each dose level

Arm B:

1. To detect activity of the combination of TRC 102 and pemetrexed, as evidenced by tumor response in patients with advanced malignant mesothelioma previously treated with pemetrexed and cisplatin

1.2 Secondary Objectives:

1. To describe pharmacokinetic parameters of TRC102 given concurrent with pemetrexed and cisplatin
2. To evaluate the pharmacodynamic parameters of TRC102 given concurrently with pemetrexed and cisplatin
3. To explore the feasibility of establishing pleural and peritoneal effluent-derived cell lines and to evaluate the response of cultured pleural and peritoneal mesothelioma cells to cisplatin, pemetrexed, and TRC102
4. To document all objective clinical responses to TRC102 in combination with pemetrexed and cisplatin

2.0 BACKGROUND

2.1 Malignant Mesothelioma

Malignant pleural mesothelioma (MPM) is a life-threatening malignancy with an incidence that is increasing worldwide. Projections from Europe indicate a doubling of the number of new cases, from 5,000 in 1998 to an estimated 9,000 in 2018. Mesothelioma is estimated to occur in approximately 2,500 people in the United States every year (1, 2). Malignant peritoneal mesothelioma (MPeM) accounts for approximately 10% of all mesotheliomas, with the vast majority of the remaining cases arising from the pleura (3, 4).The disease is difficult to treat,

because most patients have advanced disease at presentation. Median overall survival is approximately 1 year and the cure with even triple modality (cytoreductive surgery, chemotherapy and radiation) is rare. MPM occurs mainly in older men (median age of 72 years) who have been exposed to asbestos, although it occurs decades after exposure years later) (5). Treatment options for patients with malignant pleural and peritoneal mesothelioma are limited, with only one approved chemotherapy regimen, pemetrexed and cisplatin, which results in modest survival improvement (6, 7). Therefore, the limited responses to treat MPM suggest that new therapeutic avenues should be explored.

In a phase I clinical and pharmacokinetic study, the combination of pemetrexed and cisplatin showed antitumor activity in different tumor types, including patients with MPM, and the recommended dose was 500 mg/m^2 plus cisplatin 75 mg/m^2. In a large, phase III, randomized trial using the same dose, pemetrexed yielded a response rate of 41.3% in combination with cisplatin and a prolonged survival time when compared with single-agent cisplatin (12.1 versus 9.3 months)(37). The combination of pemetrexed and cisplatin, which has emerged as the most effective chemotherapeutic regimen in MPM, is associated with higher response rates and improved survival and quality of life. This combination has been approved by the United States Food and Drug Administration and the European regulatory agency [The European Medicines Agency/Committee for Medicinal Products for Human Use] as a first-line chemotherapy regimen in MPM.

The resistance of MPM to conventional treatment and poor clinical outcome has prompted basic research to identify possible new molecular targets. However multiple randomized phase II trials, with and without new drugs in combination with platinum doublet failed to give a better signal activity than single arm phase II trials (38-40). Given the modest improvement in survival with the standard of care combination of pemetrexed and cisplatin, new treatment options are needed to improve patients' outcomes. The addition of a drug like TRC102 with the potential to enhance efficacy of this combination may provide a new therapeutic option for patients with malignant mesothelioma.

Despite the initial responses to systemic chemotherapy, recurrence or progression of disease occurs in almost all patients. There are currently no effective treatment options for either patients who relapse following first-line chemotherapy or do not respond to cisplatin-pemetrexed combination. Second-line options include pemetrexed (if not administered first line), vinorelbine, or gemcitabine. Data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed. Limited data is available to guide second-line therapy. There is unmet need to develop novel agents for second-line treatment of patients with advanced mesothelioma.

2.2 TRC102

2.3 BER Inhibition by TRC102

TRC102 (methoxyamine hydrochloride, TRACON Pharmaceuticals Inc.) is a novel inhibitor of base excision repair (BER) with a unique mechanism of action. The active molecule is a small organic amine that is highly water soluble and nearly completely bioavailable after oral

administration. TRC102 acts through a novel mechanism to inhibit BER and has demonstrated the ability to potentiate the activity of the alkylating agents temozolomide and carmustine, and the antimetabolite agents fludarabine and pemetrexed, in murine models of human cancer.

Among the various mechanisms by which resistance to chemotherapy can develop, the base excision repair (BER) pathway has been shown to promote resistance to both alkylating and antimetabolite chemotherapy. TRC102 is a biochemical inhibitor of the BER pathway. Pharmacology studies have demonstrated its ability to inhibit BER induced by treatment with alkylating agents, including temozolomide, and anti-metabolite chemotherapy, including pemetrexed. TRC102 binds to apurinic or apyrimidinic DNA that is produced in cells actively engaged in the process of BER. Available data support the hypothesis that TRC102 bound DNA is a substrate for topo II, which cleaves TRC102-bound DNA sites to produce strand breaks in cancer cells that cause cellular apoptosis. As a result, TRC102 is able to potentiate the activity of temozolomide and pemetrexed (and other chemotherapeutics that activate the BER pathway) in cancer cells that express high levels of topo II (both *in vitro* and *in vivo*), without increasing toxicity in non-cancerous cells (i.e., bone marrow cells) that express low levels of topo II.

2.4 Nonclinical Studies

In vitro and xenograft studies indicate that low doses of TRC102 are able to potentiate the activity of temozolomide and pemetrexed on human cancer cell lines. TRC102 interrupts BER by binding AP sites induced by chemotherapy treatment and thereby increases DNA strand breaks. Notably, doses of 2 to 4 mg/kg given by intraperitoneal injection reversed resistance of human cancer cell lines grown in mice to concurrently administered temozolomide or pemetrexed.

In vitro and *in vivo* TRC102 safety pharmacology studies were conducted in compliance with Good Laboratory Practice regulations. These included an *in vitro* hERG assay and *in vivo* studies to assess respiratory and central nervous system function in rats and cardiovascular safety in dogs. TRC102 had no effect on hERG channel current at the highest concentration tested of 3000 ng/mL and also had no effect on QT intervals in dogs at the highest dose tested of 25 mg/kg (approximately 489 mg/m^2), which was associated with high plasma concentrations of TRC102 (Cmax of > 470 ng/mL). The dose of 25 mg/kg produced non-cardiac adverse events, including emesis, tremors or convulsions, and a modest increase in heart rate that may have been secondary to stress at this dose level, but other parameters, such a blood pressure and body temperature, were unaffected. Respiratory and CNS safety pharmacology studies in Sprague-Dawley rats indicated no effect at the highest dose tested of 100 mg/kg (approximately 600 mg/m^2), which resulted in high plasma concentrations of TRC102 (Cmax of > 7000 ng/mL)). Taken together, the safety pharmacology studies indicate that single doses well in excess of those shown to potentiate the efficacy of chemotherapy in pre-clinical models (2 to 4 mg/kg resulting in a Cmax of approximately 50 to 100 ng/mL) had little or no effect on cardiovascular parameters in dogs and no effect on respiratory or neurologic function in rats.

The collective PK/TK studies of TRC102 indicated high oral availability and systemic exposure proportional to dose. TRC102 was rapidly absorbed in rats and dogs following oral gavage and cleared with a half-life of approximately 3 hours in the rat and 7 hours in the dog. Twice daily administration for 5 days of a 14-day cycle resulted in expected increases in trough concentrations within a dosing cycle, but did not lead to accumulation across cycles of dosing. Importantly, TRC102 pharmacokinetics were not affected by concurrent administration of pemetrexed, and, similarly, pemetrexed pharmacokinetics were not affected by concurrent administration of TRC102. Protein binding studies indicate minimal binding of TRC102 to plasma proteins.

TRC102 was not mutagenic at concentrations up to 1250 μg/mL in the bacterial mutagenicity assay and 2200 μg/mL in the mouse lymphoma assay. Thus, there is no indication based on the available data that TRC102 would pose a potential genotoxic risk to humans.
A primary manifestation of toxicity was anemia in both rats and dogs. This effect was consistent between the single-cycle and three-cycle studies, and resulted in secondary alterations in related hematology parameters and changes in the histomorphology of bone marrow, spleen and liver consistent with a red blood cell regenerative response. However, there was no evidence of a cumulative effect over multiple (3) repeated dose cycles in either species and the effect was reversible. In addition to this effect, mortality occurred in dogs that received TRC102 doses more than four times higher than those that caused anemia. The cause of death was not elucidated.

In the rat, extravascular removal of red blood cells by the spleen appeared to be the primary cause of the peripheral anemia, which was evident from the microscopic observation of hemosiderin deposition in the spleen (within macrophages) and from the increase in spleen weight, as well as from the sporadic detection of increased serum levels of bilirubin, a breakdown product of hemoglobin. There may also have been some RBC removal by the liver, as reflected by the microscopic finding of green pigment in the liver, but there was no increase in liver weight. There was clearly not an underproduction of erythrocytes in the bone marrow, as the marrow was hypercellular and there were several alterations in hematology parameters that were hallmarks of an ongoing regenerative response (i.e., increased reticulocyte counts and MCV and MCH, with a decrease in MCHC). The absence of hemoglobinuria and other hallmarks of intravascular hemolysis, coupled with the findings noted above, indicated extravascular red cell lysis in the spleen was the most likely explanation for anemia.

Similarly, in the dog, RBC counts, hemoglobin, hematocrit and MCHC were decreased, while MCV, MCH and reticulocyte counts were increased, with the microscopic finding of bone marrow hypercellularity. However, microscopic changes in the spleen were not observed. There were slight, isolated increases in serum bilirubin. The hypercellularity of the bone marrow and reticulocytosis were indicative of an erythrocytic regenerative response to the peripheral anemia. In addition, bone marrow cytology on the dose range-finding study was also consistent with a compensatory response to anemia. Given the absence of clinical signs of significant blood loss and the slight elevation of bilirubin (a hemoglobin catabolism product) in some dogs, red cell lysis was felt to be the most likely explanation for anemia. The absence of hemoglobinuria and other hallmarks of intravascular hemolysis, coupled with the findings noted above, indicated anemia was due to extravascular red cell lysis. Therefore, as in the rat,

microscopic changes in the bone marrow coupled with alterations in hematology and serum chemistry parameters represented accelerated erythropoiesis in response to red cell loss.

Other TRC102-related effects in the repeat dose studies in dogs consisted of abnormal excreta and emesis. While these findings are consistent with the known effects of pemetrexed, and in fact were present in all groups that received pemetrexed, their incidence was similar in dogs that received only TRC102 at the high dose of 12 mg/kg/day, and thus a relationship to TRC102 could not be discounted. Body weight and food consumption were unaffected in this group, and the abnormal excreta and emesis subsided upon cessation of treatment.

One additional study was conducted to support clinical administration of TRC102 as part of a standard pemetrexed regimen. Leucovorin is an approved rescue agent for pemetrexed overdosage or toxicity. A rescue study was conducted in eight dogs that were given an exaggerated dose of pemetrexed alone (50 mg/kg twice within four days) and concurrently with five days of oral TRC102 at the HNSTD of 12 mg/kg/day, as determined in the three-cycle GLP toxicology study in dogs. The dogs were divided into two groups, one of which received leucovorin treatment and one that did not. The effectiveness of the leucovorin treatment was evident. The survival rate of dogs that received leucovorin was 100% versus 25% in those that did not. Leucovorin treated dogs also had improved clinical condition, the reversal of pemetrexed-induced inappetence and corresponding body weight loss, and reduction of pemetrexed-induced leukopenia within one to four days after starting the leucovorin treatment. Therefore, leucovorin's effectiveness as a rescue treatment in dogs was not compromised by the presence of TRC102 (12 mg/kg/day for five consecutive days) at an exaggerated pemetrexed dose.

Given the high degree of similarity in the major toxicologic effect in both species and in all studies, the NOAELs and HNSTDs served as the basis for determining the more sensitive toxicology species, and therefore the more appropriate species upon which to base the clinical starting dose. In the single-cycle toxicity studies, the rat NOEL and HNSTD were both approximately 1.6-fold higher than the dog NOAEL and HNSTD. A similar trend held true for the three-cycle studies, where the rat NOAEL and HNSTD were approximately 2.7- and 2.2-fold higher than the dog NOAEL and HNSTD. Thus, across the range of doses tested and in both single and multiple cycle studies, the dog was more sensitive to the effects of TRC102 and was judged to be the more conservative toxicology model upon which to base the clinical starting dose.

2.5 Clinical Studies

TRC102 was studied in 28 patients in a completed multicenter, open label, phase 1 clinical study (102ST101) that evaluated the maximum tolerated dose (MTD), safety profile, pharmacokinetics, and pharmacodynamics of TRC102 alone and in combination with standard-dose pemetrexed in patients with advanced cancer. The TRC102 dose was escalated in serial cohorts of patients using a standard 3 + 3 design. TRC102 doses studied were 15, 30, 60, and 100 mg/m^2/d given p.o. for four days of repeating two or three week cycles.

The MTD of TRC102 was exceeded at 100 mg/m^2/d due to the dose limiting toxicity (DLT)

of grade 3 anemia in three of six patients. Anemia was the only DLT reported and was consistent with preclinical toxicology studies in dogs and rats showing that anemia from extravascular hemolysis (in the spleen) was dose limiting. The frequency and severity of anemia did not increase as the number of treatment cycles accumulated. Hematologic toxicity other than anemia was not observed after treatment with TRC102 alone, and treatment with TRC102 and pemetrexed resulted in myelosuppression similar to that reported for pemetrexed alone. Treatment-related nonhematologic adverse events were generally mild to moderate. The only exceptions were one patient with grade 3 fatigue and another with grade 3 diarrhea. Both grade 3 nonhematologic adverse events occurred at 100 mg/m^2/d.
TRC102 given by intravenous administration is being studied in two ongoing trials sponsored by Case Comprehensive Cancer Center. Case 1Y05 is evaluating TRC102 in combination with temozolomide and Case 2Y10 is evaluating TRC102 in combination with fludarabine. Fifty-nine patients have been treated at doses ranging from 15 mg/m^2/day to 150 mg/m^2/day in Case 1Y05 and nineteen patients have been treated at doses ranging from 15 mg/m^2/day to 30 mg/m^2/day in Case 2Y10 to date. Dose limiting toxicities occurring in Case-sponsored trials included psychosis and allergic reaction; which were observed in study Case 1Y05 in combination with temozolomide. Of note, the single episodes of psychosis and allergic reaction were seen at the 15 mg/m^2/day dose level and were not observed following escalation to the 150 mg/m^2/day dose level in study Case 1Y05. Currently patients are being dosed at the 150 mg/m^2/day dose level in study Case 1Y05 and at 30 mg/m^2/day in study Case 2Y10. Correlative studies demonstrate that TRC102 interrupts base excision repair in treated patients, even at the lowest level. Several patients have demonstrated stable disease [14].

TRC102 is also being studied in an ongoing clinical trial sponsored by NCI CTEP. Study 9483 is evaluating TRC102 in combination with temozolomide in patients with relapsed solid tumors and lymphomas. As of this update, fifteen patients have been treated in study 9483. One unexpected serious suspected adverse reaction was reported, of grade 4 platelet count decrease and grade 4 neutrophil count decrease in a patient with colorectal cancer treated with TRC102 (75 mg p.o. qD) in combination with temozolomide (150 mg/m^2 p.o. qD) for the initial five days of recurring 28 day cycles.

2.6 Potential Risks

TRC102 has been studied in three clinical studies evaluating doses from 15 mg/m^2/day to 100 mg/m^2/day in combination with pemetrexed, temozolomide or fludarabine. The most common adverse event (and dose limiting toxicity) observed in patients treated to date has been anemia. Anemia is characterized by a reactive reticulocytosis, increased bilirubin and decreased haptoglobin in the absence of hemoglobinuria. These clinical findings are consistent with extravascular hemolysis, which was observed in preclinical studies in dog and rat. The anemia is reversible and treatable with transfusion, growth factors and dose reduction.

Toxicology studies have been conducted using TRC102 in two relevant animal models, rats and dogs. Studies in both species involved the administration of 15 doses over 32 days and studies in dogs assessed the toxicity of TRC102 when administered with the approved dose of pemetrexed. These studies indicated that TRC102 caused anemia in both species that was consistent with splenic sequestration and lysis of erythrocytes that resulted in physiologically

responsive hematologic changes (e.g., reticulocytosis), slight isolated increases in serum bilirubin and bone marrow hypercellularity. Importantly, these adverse effects were reversible and not influenced by the concurrent administration of the approved dose of pemetrexed.

Convulsions or tremors, impaired muscle coordination and hyperactivity were noted in dogs treated with repeated doses of TRC102 more than 4-fold higher than those that resulted in anemia. This potential toxicity has not been observed in clinical trials of TRC102 [14] Patients with a history of seizures or central nervous system tumors, who may be at increased risk for convulsions were excluded from initial clinical study.

Myelosuppression was not worse in preclinical models administered pemetrexed with TRC102. Patients treated with TRC102 at the maximum tolerated dose in combination with standard dose pemetrexed also did not appear to exhibit an increased frequency of myelosuppression compared with historical controls. However, an increased frequency of temozolomide-induced neutropenia was observed following dosing of intravenous TRC102 in rats and a serious adverse event of grade 4 neutropenia and thrombocytopenia was observed in one patient who received TRC102 with temozolomide. An increased frequency of myelosuppression is possible in patients receiving myelosuppressive chemotherapeutics with TRC102.

Other adverse events observed in the Phase 1 study considered possible related to TRC102 included fatigue, anorexia, nausea, vomiting, diarrhea, pyrexia, mucosal inflammation and rash. Two unexpected serious events (one event of psychosis and one of idiosyncratic allergic reaction) were observed at a dose of intravenous TRC102 (15 $mg/m^2/d$) below the maximum tolerated dose and were considered possible related to the drug. These events have not recurred at higher doses as of August 21, 2014.

2.7 Drug Interactions

Drug interaction studies of oral TRC102 and intravenous pemetrexed in dogs and rats indicate that TRC102 pharmacokinetics are not influenced by concurrent administration of intravenous pemetrexed and pemetrexed pharmacokinetics are not influenced by concurrent administration of TRC102. Studies also indicated no pharmacokinetic interaction between intravenous TRC102 and temozolomide. Studies with other anti-cancer agents have not been conducted. There is no information available on the potential of drug interaction via the P450 enzyme system.

2.8 Pemetrexed, Cisplatin and TRC102

At present MPM and MPeM protocols use both cisplatin and pemetrexed. Platinum-based compounds are among the most commonly prescribed drugs used to treat solid tumors(8, 9). Cisplatin binds to DNA hindering both DNA replication and RNA translation, eventually triggering apoptosis. Pemetrexed inhibits enzymes used in purine and pyrimidine biosynthesis that can lead to incorporation of uracil into DNA that can lead to strand breaks(10-14). Both drugs lead to cell death if the damage generated is not repaired. To counteract those effects, cells have evolved DNA repair mechanisms that preserve genomic integrity and eliminate

damage. Cisplatin damage to DNA is removed by nucleotide excision repair (NER) and other mechanisms repairing DNA cross links(11, 15-19). Uracil in DNA is eliminated by uracil-DNA glycosylase (UNG) in base excision repair (BER). In normal cells, DNA repair functions to limit mutations and prevent cell death. However, in tumor cells, DNA repair pathways can counteract therapeutic effects of drug treatments and can assist in the development of resistance. Thus, both NER and BER can present obstacles to effective treatment (20, 21) using the presently accepted therapeutic protocol.

One method to enhance the cytotoxic effects of chemotherapeutic drug attack on tumor cells is by limiting a tumor's capacity to repair DNA damage. Excision repair, including NER and BER, is a major repair pathway and both parts of excision repair have multiple proteins contributing to re-establishing genetic information and protecting against cell death. NER generally removes bulky DNA adducts in a 29nt-long oligonucleotide leaving a gap that must be filled in by a DNA polymerase. The other excision repair pathway, BER, acts on individual DNA bases that have been damaged directly through alkylation, abnormal bases incorporated into DNA by the action of antimetabolite agents, as well as some mispaired bases. The initial step in BER leaves an abasic (AP or apurinic/apyrimidinic) site. If there is a failure to complete repair and the repair intermediates remain, cell death can occur. Thus, if constrained to tumor cells, the residual repair intermediates have the potential to improve the therapeutic index of alkylating agents and antimetabolites (11, 15, 16).

Most drugs inhibiting cellular pathways are directed toward blocking the activity of specific enzymes. In contrast, targeting abasic sites in DNA using TRC102 (methoxyamine hydrochloride, TRACON Pharmaceuticals Inc.) impairs growth and potentiates the antitumor effect of cisplatin and methotrexate in osteosarcoma cells, and could work in concert with other alkylating agents and antimetabolites(10, 11, 22-28). TRC102 modifies a central DNA substrate in BER, the AP site aldehyde (29). Although known to modify AP sites for over 30 years, TRC102 has only been pursued as a therapeutic agent since ~1999(30-33). TRC102 rapidly and covalently binds to AP sites generated during BER, and TRC102-bound DNA causes topoisomerase II-dependent irreversible strand breaks and apoptosis(27) The induction of apoptosis by TRC102 is more selective for cancer cells, due to the overexpression of topoisomerase II in many tumors. In nonmalignant cells with low topoisomerase II expression, TRC102-bound DNA is excised and replaced by the long patch DNA repair system(34). The TRC102 activity is independent of O6-methylguanine-DNA methyltransferase (MGMT) expression in tumors, DNA mismatch repair status, or p53 status. TRC102 potentiates the activity of other DNA repair inhibitors, including PARP inhibitors(11, 24, 27, 29). Pemetrexed induces BER in response to uracil incorporation into DNA, which is removed by uracil-DNA glycosylase (13, 26). TRC102 modifies the resulting AP sites and acts as a topoisomerase II poison, causing DNA strand breaks, and ultimately apoptosis. In vivo, using a mouse model with a human non-small cell lung cancer xenograft, TRC102 extended median tumor growth delay from 2 days with pemetrexed alone to 9 days with the combination without added toxicity(35). In repeat-dose toxicity studies, TRC102 caused anemia by extravascular red cell lysis (i.e., through splenic sequestration of erythrocytes) at a dose 10-fold higher than that required for activity positive response to treatment. The anemia was reversible, not cumulative or severe and was unaffected by coadministration of pemetrexed. (TRACON Pharmaceuticals, unpublished data).

Clinical investigations have evaluated criteria for pemetrexed use. The standard approved single dose for pemetrexed in humans is 500 mg/m^2. The first study to assess the pharmacological effects of TRC102 in combination with the pemetrexed in humans established a maximum tolerated (MTD) daily oral dose(36). The MTD was 60 mg/m^2/d for 4 days in combination with standard dose pemetrexed every 3 weeks. Consistent with preclinical testing data, at 100 mg/m^2/d, the MTD TRC102 dose was exceeded due to extravascular hemolytic anemia requiring transfusion and dose-reduction. Anemia was the only dose-limiting toxicity (DLT) and was predicted by animal studies where extravascular hemolysis occurred at doses 20-fold higher than required for efficacy. TRC102 accumulated with daily dosing in a manner consistent with its half-life >24 hours, but did not accumulate between cycles. Pharmacodynamic data confirmed the capacity of TRC102 to modify AP sites generated following pemetrexed treatment (36).

2.9 Rationale

Chemotherapy represents the largest class of treatment used for patients with metastatic or advanced solid tumors. However, for majority of patients, disease progression occurs despite treatment with various combinations of chemotherapeutics, and most eventually succumb to their cancer. Resistance to chemotherapy is a primary reason that patients fail treatment. Among the various mechanisms by which resistance to chemotherapy can develop, the base excision repair (BER) pathway has been shown to promote resistance to both alkylating and antimetabolite chemotherapy. TRC102 acts through a novel mechanism to inhibit BER and can potentially enhance the activity of cisplatin and pemetrexed and reverse resistance to pemetrexed. We hypothesize:

1. TRC102 combined with pemetrexed and cisplatin can be administered safely in patients with advanced solid tumors;
2. The combination may be effective in patients with advanced unresectable malignant mesothelioma;
3. TRC102 combined with pemetrexed will produce responses in patients with advanced malignant mesothelioma who progressed on or had a recurrence with 3 months of treatment with pemetrexed and cisplatin.

2.10 Correlative Studies Background

2.10.1 Pharmacokinetics of TRC102 and cisplatin

Previous Phase I clinical investigation demonstrated no significant effect of pemetrexed on the PK of TRC102 and vice versa (36). Similarly, no PK interaction has been identified when pemetrexed and cisplatin are given together (41). Therefore, we will focus on the PK of TRC102 and cisplatin in this 3 drug combination regimen.

2.10.2 Establishment of pleural and peritoneal effluent-derived cell lines

The pleural and peritoneal effluent are often collected from mesothelioma patients. These

cells potentially have tumor associated cells that can be evaluated for response to therapies. Moreover, the mesotheliomas are classified as epithelial, fibrous, or mixed. Depending on the type, there may also be differential response to treatments and these cells will provide a valuable resource for evaluation of different therapies and to also provide a molecular basis for the classification of the histopathological assignments.

2.10.3 Response of cultured pleural and peritoneal cells to cisplatin, pemetrexed, and TRC102

The cell lines developed above could present a possible advance in treatment of mesothelioma. We will test the response of the cells to TRC102 in conjunction with cisplatin and pemetrexed. The results that we obtain will be compared to the patient responses in the study. We will vary the amounts of cisplatin, pemetrexed, and TRC102 to evaluate the cell death for each drug individually, as pairs, and finally all together. We have used these techniques in the past (50) and will apply them to this work.

2.10.4 Determination of abasic site modification in patient samples

TRC102 reacts with the C1' aldehyde of the deoxyribose at the AP site and leads to a modification of DNA that is not easily repaired. The TRC102 modification of the AP site blocks the reaction with a reagent that is designated as an aldehyde reactive probe (ARP)(52). We will use the ARP to determine the effect of the TRC102 on AP sites.

2.10.5 Determination of cisplatin modification levels using ELISA methods

Use of a cisplatin specific antibody will permit at least the examination of the relative levels of cisplatin adducts formed in DNA to provide an evaluation of the level found in cells. We will use an ELISA method that detects low levels of cisplatin (53-55).

2.10.6 Circulating tumor cells isolated from patient blood samples

Prior to treatment, patient blood samples will be processed to obtain CD146-positive circulating tumor cells (CTC) and those cells will be used for culture because it is anticipated that the CTCs have a high potential to be involved in metastasis. The cultured CTCs could yield provide a resource for the study of therapeutic response.

3 PATIENT SELECTION

NOTE:
As of March, 13, 2018, Arm A (3-drug combination) is open to all ETCTN sites.

Arm B (2-drug combination) is open to all ETCTN sites.

3.1 Eligibility Criteria

3.1.1 **Arm A Dose Escalation:** Patients with histologically or cytologically proven advanced solid tumors for which standard treatments are not available, or for whom the current dose level of cisplatin in combination with pemetrexed is appropriate; ≤ 2 prior cytotoxic chemotherapy regimen.

3.1.2 **Arm A Dose Level 4 (75 mg/m^2 Cisplatin):** Patients with histologically proven chemotherapy-naïve advanced unresectable solid tumors for which pemetrexed combined with cisplatin is an indicated regimen

3.1.3 **Arm B (First stage of Phase II of TRC102 and pemetrexed):** Patients with malignant pleural or peritoneal mesothelioma who had progressed while being treated with or had recurred within 6 months of being treated with pemetrexed and cisplatin or carboplatin frontline. Intervening treatment is allowed.

3.1.4 Prior pemetrexed is allowed except Arm A Dose Level 4 (Cisplatin 75 mg/m^2).

3.1.5 Male or female Age ≥18 years.
Because no dosing or adverse event data are currently available on the use of TRC102 in combination with Pemetrexed and Cisplatin in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.6 ECOG performance status 0 -1 (Karnofsky ≥70%, see Appendix A).

3.1.7 Life expectancy of greater than 3 months.

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

– absolute neutrophil count	≥1,500/μL
– platelets	≥100,000/μL
– hemoglobin	≥ 10.0 g/dl
– prothrombin time or INR	≤ 1.5 x ULN
– total bilirubin	< 1.5 x ULN
- AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN or ≤ 5 x ULN if metastatic disease involves liver
- Serum creatinine	≤ 1.5 x ULN or a calculated creatinine clearance ≥60 ml/min/1.73 m^2 (Cockcroft-Gault method) for patients receiving combination of cisplatin and pemetrexed and ≥45 ml/min/1.73 m^2 for patients receiving pemetrexed; 24 hour urine for creatinine clearance is acceptable if the calculated creatinine clearance is insufficient;

3.1.9 **For patients enrolled in Arm B (First stage of Phase II of TRC102 and pemetrexed)** measurable disease is required according to the RECIST criteria for patients with solid tumors and modified RECIST criteria as described by Byrne and Novak for patients with malignant pleural mesothelioma. Pleural effusion and ascites are not considered measurable disease.

3.1.10 Patients must be able to swallow whole capsules; nasogastric or G-tube administration is not allowed.

3.1.11 The effects of TRC102 on the developing human fetus are unknown. For this reason and because TRC102 as well as other therapeutic agents used in this trial are known to be teratogenic, 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, for the duration of study participation, and 4 months after completion of the study drugs. 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. 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 TRC102, pemetrexed and cisplatin administration.

Non-childbearing potential is defined as (by other then medical reasons): ≥ 45 years of age and has not had menses for ≥ 2 years, amenorrheic for < 2 years without hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pretrial (screening) evaluation, or post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit though 4 months after the last dose of study drugs.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Patients who have had targeted therapy will be required to wait 2 weeks due to short half-life of the drugs. Treatment with bisphosphonates is permitted.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with active brain metastases or carcinomatous meningitis are excluded from this clinical trial. Patients with treated brain metastases, whose brain metastatic disease has remained stable for greater than or equal to 4 weeks without requiring steroid and anti-seizure medications are eligible to participate.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to TRC102 or pemetrexed and cisplatin

3.2.5 http://medicine.iupui.edu/clinpharm/ddis/No studies have been performed to assess potential metabolic and transport interactions of TRC102. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of

interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. The case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. [See Section 5.4.]

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because TRC102 is 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 TRC102, breastfeeding should be discontinued if the mother is treated with TRC102. These potential risks may also apply to other agents used in this study.

3.2.8 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with TRC102. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.9 Patients with known disorders associated with hemolysis.

3.2.10 Patients with thromboembolic disease and on anticoagulation.

3.2.11 Patients with a prior cumulative cisplatin dose > 300 mg/m^2 (pertains to Arm A only).

Inclusion of Women and Minorities

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

4 REGISTRATION PROCEDURES (ROSTERED PROTOCOL MODEL)

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) 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).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval

- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI protocol # 9837 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO – CA043, and protocol #9837
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above

4.2.2 Submitting Regulatory Documents

Requirements For 9837 Site Registration:

• IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.3 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration subtab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: If possible, please allow three working days for site registration approval before attempting to enroll your first patient. The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

• Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).

• City of Hope Cancer Center will receive notification via the IWRS when a slot has been reserved. An email will be sent from the City of Hope Cancer Center to the site requesting further information such as: the patient initials, tumor type and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION FORM/ELIGIBILITY CHECKLIST accompanied with the signed consent, baseline labs, pathology report, CT/x-ray reports to the City of Hope Cancer Center at ccc@coh.org for review and confirmation of eligibility.

• Once the Registration has been reviewed, the City of Hope Cancer Center will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the City of Hope Cancer Centre will update the spot to 'reserved' in IWRS.

• The site can now enroll the patient into the study in OPEN

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL. (*Note: A DTL is NOT required for this study.)*
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website:

http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *5* days.* Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator (ccc@coh.org) should be notified of cancellations as soon as possible.

5 TREATMENT PLAN

5.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.
Screening tests and evaluations will be performed within 7 days prior to study treatment initiation, unless otherwise specified. Screening tumor assessments must be obtained within 28 days of study treatment and Informed Consent must be obtained within 28 days. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria.
Eligible patients will be treated either on Arm B or Arm A as specified in the Eligibility Criteria.

Arm A – TRC102 in combination with Cisplatin and Pemetrexed.

Arm B – TRC 102 in combination with Pemetrexed

5.2 Agent Administration

5.2.1 Arm A: TRC102 in combination with Cisplatin and Pemetrexed

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2.1.1 Premedication
Folic acid 350-1000µg, PO, daily beginning approximately 7 days prior to the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed; Vitamin B12 1000µg IM or subcutaneous every 9 weeks beginning approximately 1-2 weeks before the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed; Dexamethasone 4 mg twice daily the day prior to, the day of and the day after each infusion of

pemetrexed (may be discontinued if toxicities of steroids develop and cutaneous side effects do not occur). Anti-emetics will be given per standard institutional practice guidelines. An aprepitant in combination with a 5-HT3 antagonist is recommended.

5.2.1.2 TRC102

Patients will receive escalating doses of TRC102, orally, daily (days 1-4) in combination with cisplatin and pemetrexed on day 1, as shown in **Table 1**. The study drug TRC102 will be self-administered (by the patients themselves). Capsules are taken in the morning after patients have fasted for at least two hours. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush. Patients should refrain from eating or drinking for one hour following TRC102 dosing. The investigator will instruct the patient to take the study drug exactly as specified in the protocol. For TRC102 the patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course (Appendix D). For TRC102 the patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

Patients will receive 4 doses of oral TRC102 day 1-4 of each cycle. On day 1 of each cycle, TRC102 will be administered prior to pemetrexed and cisplatin; pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes; and cisplatin 60 mg/m^2 (75 mg/m^2 for dose level 4) will be administered as an IV infusion over 30-60 minutes after the end of the pemetrexed. Pemetrexed will be administered prior to cisplatin.

The Pemetrexed and Cisplatin will be administered as an IV infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, withdrawal from study or for maximum of 6 cycles as outlined in section 5.5.

Table 1

Dose Level	TRC102 (days 1-4, q 21 days)	Pemetrexed (day 1, q 21 days)	Cisplatin (day 1, q 21 days)
– 1	25 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
1	50 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
2	75 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
3	100 mg/day, PO	500 mg/m^2, IV	60 mg/m^2, IV
4 {chemotherapy-naïve patients}	100 mg/day, **or** MTD w/ 60 mg/m^2 cisplatin, whichever is lower, PO	500 mg/m^2, IV	75 mg/m^2, IV

At the RP2D, the cohort will be expanded to treat a total of 14 mesothelioma patients to obtain additional safety data, PK data, and a preliminary indication if the combination might be effective.

5.2.1.3 Pemetrexed

Pemetrexed for injection will is commercially available and will not be supplied. Pemetrexed is administered by intravenous infusion over 10 minutes per local practice guidelines. Refer to package insert for more information.

5.2.1.4 Cisplatin

On day 1 of each cycle, cisplatin 60 mg/m^2 (75 mg/m^2 for dose level 4) will be administered as 30 -60 minutes infusion after the end of the pemetrexed. Cisplatin will be administered to patients in Arm A on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity, withdrawal from study or for maximum of 6 cycles as outlined in section 5.5.

Cisplatin for infusion is commercially available and will not be supplied. Cisplatin is administered by intravenous infusion over 30 - 60 minutes per local practice guidelines. Refer to package insert for more information. The starting dose (60 mg/m^2) and all appropriate subsequent doses must be diluted in a chloride-containing vehicle (preferably NS or D5NS) to achieve a final concentration < 1 mg/ml less than 8 hours prior to administration and administered intravenously over 30 – 60 minutes. **Cisplatin** is a renally excreted and potentially nephrotoxic agent and requires careful attention to patient hydration for safe administration to avoid nephrotoxicity. Cisplatin must be given with at least 1 liter of NS intravenous hydration (total pre-and post-hydration), of which at least 500 ml must be administered as pre-hydration immediately prior to administering the cisplatin. Patient should be also encouraged to drink fluids generously on the day of cisplatin treatment. It is left to the discretion of the treating investigator whether furosemide or mannitol-forced diuresis should be given immediately following cisplatin infusion or whether potassium or magnesium should be included in the NS hydration solution. **Anti-emetics** will be given per standard institutional practice guidelines. An aprepitant in combination with a 5-HT3 antagonist is recommended. To prevent delayed emesis, on Days 2, 3, and 4 after each cisplatin administration, dexamethasone 4 – 8 mg PO BID and a dopamine receptor antagonist (prochlorperazine/compazine) 10 – 15 mg PO, BID, or metoclopramide (Reglan) 10 mg PO every 6 hours is recommended. Ondansetron 8 mg PO TID may be substituted for the dopamine antagonist. Other supportive treatment such as antidiarrheals, (eg, loperamide, rehydration), analgesics, blood products, etc, are permitted at any time and should be administered according to the institutional standard practice of care.

5.2.2 Arm B: TRC102 in combination with Pemetrexed

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2.2.1 Premedication

Folic acid 350-1000µg, PO, daily beginning approximately 7days prior to the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed; Vitamin B12 1000µg IM or subcutaneous every 9 weeks beginning approximately 1-2 weeks before the first infusion of pemetrexed and continuing until 3 weeks after discontinuation of pemetrexed.

Dexamethasone 4 mg twice daily the day prior to, the day of, and the day after each infusion of pemetrexed (may be discontinued if toxicities of steroids develop and cutaneous side effects do not occur).

5.2.2.2 TRC102

Patients will receive TRC102 dose level 1, 50 mg/day (Table 1, Section 4.2), orally, daily (days 1-4) in combination with pemetrexed 500 mg/m^2 on day 1. The study drug TRC102 will be self-administered (by the patients themselves). Capsules are taken in the morning after patients have fasted for at least two hours. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush. Patients should refrain from eating or drinking for one hour following TRC102 dosing. The investigator will instruct the patient to take the study drug exactly as specified in the protocol. For TRC102 the patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. On day 1 of each cycle, TRC102 will be administered prior to pemetrexed.

5.2.2.3 Pemetrexed

Pemetrexed for injection will is commercially available and will not be supplied. Pemetrexed is administered by intravenous infusion over 10 minutes per local practice guidelines. Refer to package insert for more information. The Pemetrexed will be administered as an IV infusion on Day 1 of each 21-day cycle until disease progression, unacceptable toxicity or withdrawal from study as outlined in section 5.5.

5.3 Definition of Dose-Limiting Toxicity

DLT Dose Limiting Toxicity is defined as an adverse event that occurs in during cycle 1 that is related (possibly, probably, or definitely) to administration of study drug and fulfills one of the following criteria:

♦Grade ≥ 3 non-hematological toxicity will be considered dose limiting with the following clarifications:

- Grade 3 diarrhea will only be considered dose limiting if it is refractory to maximal supportive care measures. Bloody or grade 4 diarrhea will be dose limiting.
- ≥ Grade 3 nausea and vomiting will only be considered dose limiting if it is refractory to maximal anti-emetic therapy.
- ≥ Grade 3 rise in creatinine, not able to be corrected to grade 1 or less with IV fluids will be considered dose limiting. All grade 4 rises in creatinine will be dose limiting.
- ≥ Grade 3 electrolyte toxicities unable to be corrected to grade 1 or baseline with maximal electrolyte repletion will be considered dose limiting.
- Tumor pain will not be considered dose limiting.

♦Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding
♦ Grade 3 anemia
♦Grade 4 neutropenia lasting ≥ 7 days or febrile neutropenia.
♦Treatment delay > 2 weeks as a result of unresolved toxicity.
♦Inability to administer 3 of the 4 doses of TRC102 in the 1st week (7 days) of a cycle as a result of unresolved toxicity.

The trial will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE), as

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

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

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 non-tolerated 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 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 non-tolerated 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 any non-tolerated dose	This is generally the recommended phase 2 dose (RP2D). At least 6 patients must be entered at the RP2D. In this study, if dose level 3 is non-tolerated, and a lower dose level is the RP2D by these rules, dose level 4 will be re-defined per Table 1, and tried as the next dose level.

5.4 General Concomitant Medication and Supportive Care Guidelines

No studies have been performed to assess potential metabolic and transport interactions of TRC102. Because there is a potential for interaction of TRC102 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if a drug-drug interaction is a suspected component of an adverse event.

Colony Stimulating Factors (CSFs) should not be used during the first course of treatment. The prophylactic use of CSFs is not recommended as long as the subject remains on study. In the event of neutropenia without fever following subsequent courses of treatment, current ASCO guidelines recommend that CSFs should not be routinely used.
In the event of febrile neutropenia following subsequent courses of treatment, CSFs may be administered according to current ASCO guidelines.

For subsequent courses, it is recommended that CSF be initiated no earlier than 24 hours after the administration of chemotherapy.

If administered, CSFs must be discontinued at least 24 hours before receiving the next course of treatment with study drug.

The use of recombinant erythropoietin for the treatment of chemotherapy-induced anemia is permitted in Arm B and following cycle 2 in Arm A at the discretion of the treating physicians. Blood transfusion is allowed.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 6 cycles* or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

*For patients on Arm A, patients must discontinue cisplatin, but may continue treatment with TRC102 and pemetrexed beyond cycle 6 if the patient continues to benefit (even if meeting the protocol definition of progression) from treatment at the discretion of the treating physician. For patients on Arm B, patients may continue treatment with TRC102 and pemetrexed beyond cycle 6 if the patient continues to benefit (even if meeting the protocol definition of progression) from treatment at the discretion of the treating physician.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed.

The primary reason for a patient’s withdrawal from the study is to be recorded in the source documents.

5.6 Duration of Follow Up

Patients will be followed for 8 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6 DOSING DELAYS/DOSE MODIFICATIONS

The trial will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and Adverse Event Reporting until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. A copy of the CTCAE version 5.0 can be downloaded from the CTEP home page http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. .

6.1 Arm A: TRC102 in combination with Cisplatin and Pemetrexed

On day 1 Cycle 1, administration of TRC102, pemetrexed and cisplatin requires an absolute neutrophil count (ANC) of > 1500 and platelets count of > 100,000, and calculated creatinine clearance > 60 ml/min/1.73 m^2 (Cockcroft-Gault method); 24 hour urine for creatinine clearance is acceptable if the calculated creatinine clearance is insufficient. In the subsequent cycles that include cisplatin, patients can receive a reduced dose of cisplatin (See table in 6.1.3.2.) if creatinine clearance > 50 ml/min/1.73 m^2 and < 60 ml/min/1.73 m^2 (Cockcroft- Gault method) on day 1. In the subsequent cycles that do NOT include cisplatin, administration of TRC102 and pemetrexed requires an absolute neutrophil count (ANC) of $\geq$ 1500 and platelets count of $\geq$ 100,000, and calculated creatinine clearance $\geq$ 45 ml/min/1.73 m^2 (Cockcroft-Gault method) on day 1; 24 hour urine for creatinine clearance is acceptable if the calculated creatinine clearance is insufficient.

The start of the next cycle may be delayed a maximum of 14 days.

6.1.1 **TRC102**

TRC102 can be held for up to two weeks for resolution toxicity per the guidelines below. If TRC102 is held on day 1 of a cycle, pemetrexate and cisplatin will be held as well, i.e. the entire cycle will be held for up to two weeks. If TRC102 is held on days 2-4, the remaining TRC102 doses for the cycle will be administered when the re-treatment criteria are met provided that they can be administered in the 1st week (7 days) of the cycle. No TRC102 doses will be administered on day 8 or following of a cycle. The next cycle will begin as scheduled provided that re-treatment criteria are met.

6.1.1.1 Hematologic Toxicity

Subjects with grade $\geq$ 2 anemia and requiring blood transfusion will have work up with laboratory tests: CBC with red cell indices, platelet count, and examination of the peripheral smear; reticulocyte count; routine hepatic function, including direct and indirect bilirubin; LDH; autoimmune studies (eg, Coombs testing) as appropriate; serum/urine free hemoglobin and urinary hemosiderin if intravascular hemolysis is suspected; Hematology consultation may be requested.

Anemia	**Management/Next Dose for TRC102**
≤ 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**.
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.	
Patients can receive blood transfusion.	

6.1.1.2 Non-hematologic Toxicity

If a patient experiences ≥ grade 3 drug related toxicity at any time in a cycle, treatment will be held. If TRC102 is held for transient, correctable, non-DLT toxicity (See Section 5.3), the remaining TRC102 doses for the cycle will be administered at the same dose level when the re-treatment criteria are met, provided that they can be administered in the 1st week (7 days) of the cycle. No TRC102 doses will be administered on day 8 or following of a cycle and TRC102 will be administered at the same dose level in the next cycle. If TRC102 is held for toxicity qualifying as DLT, no more TRC102 doses will be administered for the remaining of the cycle and TRC102 will be reduced by one dose level for the next cycle. Patient should not be retreated until all toxicities resolve to ≤ grade 1. Start of a new cycle of therapy may be held up to two weeks for toxicities to resolve. If the patient experiences another ≥ 3 toxicity, treatment will be held for up to two weeks. Patient can be retreated if all toxicities resolve to ≤ grade 1. TRC102 will be reduced by one dose level. Maximum two dose reductions are permitted. If the toxicities don't resolve, patient should be removed from study.

6.1.2 **Pemetrexed**

There is no dose reduction for hematologic or nonhematologic toxicity. If pemetrexed is held, TRC102 and cisplatin will be held as well, i.e. the entire course will be held for up to two weeks.

6.1.3 **Cisplatin**

Day 1 Cycle 1 cisplatin administration, of each cycle, requires an absolute neutrophil count (ANC) of ≥ 1500 and platelets count of ≥ 100,000, and calculated creatinine clearance ≥ 60 m/min (Cockcroft-Gault method); 24 hour urine for creatinine clearance is acceptable if the calculated creatinine clearance is insufficient. In the subsequent cycles patients can receive a reduced dose of cisplatin (See table in 6.1.3.2.) if creatinine clearance ≥ 50 ml/min/1.73 m^2 and ≤ 60 ml/min/1.73 m^2 (Cockcroft- Gault method). If cisplatin is held, TRC102 and pemetrexed will be held as well, i.e. the entire course will be held for up to two weeks.

6.1.3.1 Hematologic Toxicity

There is no cisplatin dose reduction for hematologic toxicity in this regimen.

6.1.3.2 Renal Toxicity- Cisplatin Modification for Renal Function

Calculated Creatinine Clearance	Treatment

$\geq$ 60 ml/min/1.73 m^2	Full dose of cisplatin
< 60 ml/min/1.73 m^2 but $\geq$ 50 ml/min/1.73 m^2	Reduce dose (See table below.)
< 50 ml/min/1.73 m^2	Hold cisplatin until recovery;* monitor weekly retreat with cisplatin dose decreased by 1 dose level.

*****If treatment is held for > 2 weeks, the patient should be removed from the protocol treatment (per Section 5.5). Recovery is defined as $\geq$ 50 ml/min/1.73 m^2.

Cisplatin starting dose	1st dose reduction	2nd dose reduction
60 mg/m^2	45 mg/m^2	Off study
75 mg/m^2	60 mg/m^2	45 mg/m^2

6.2 Arm B: TRC102 in combination with Pemetrexed

On day 1, administration of TRC102 and pemetrexed requires an absolute neutrophil count (ANC) of > 1500 and platelets count of > 100,000, and calculated creatinine clearance > 45 ml/min/1.73 m^2 (Cockcroft-Gault method); 24 hour urine for creatinine clearance is acceptable if the calculated creatinine clearance is insufficient.

The start of the next cycle may be delayed a maximum of 14 days.

6.2.1 **TRC102**

TRC102 can be held for up to two weeks for resolution toxicity per the guidelines below. If TRC102 is held on day 1 of a cycle, pemetrexate will be held as well, i.e. the entire cycle will be held for up to two weeks. If TRC102 is held on days 2-4, the remaining TRC102 doses for the cycle will be administered when the re-treatment criteria are met provided that they can be administered in the 1st week (7 days) of the cycle. No TRC102 doses will be administered on day 8 or following of a cycle. The next cycle will begin as scheduled provided that re-treatment criteria are met.

6.2.1.1 Hematologic Toxicity

Subjects with grade $\geq$ 2 anemia and requiring blood transfusion will have work up with laboratory tests: CBC along with red cell indices, platelets count, and examination of the peripheral smear; reticulocyte count; routine hepatic function, including direct and indirect bilirubin; LDH; autoimmune studies (eg, Coombs testing) as appropriate; serum/urine free hemoglobin and urinary hemosiderin if intravascular hemolysis is suspected; Hematology consultation may be requested.

Anemia	**Management/Next Dose for TRC102**
≤ 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**.
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.	
Patients can receive blood transfusion.	

6.2.1.2 Non-hematologic Toxicity

If a patient experiences ≥ grade 3 drug related toxicity at any time in a cycle, treatment will be held. If TRC102 is held for transient, correctable, non-DLT toxicity (See Section 5.3), the remaining TRC102 doses for the cycle will be administered at the same dose level when the re-treatment criteria are met, provided that they can be administered in the 1st week (7 days) of the cycle. No TRC102 doses will be administered on day 8 or following of a cycle and TRC102 will be administered at the same dose level in the next cycle. If TRC102 is held for toxicity qualifying as DLT, no more TRC102 doses will be administered for the remaining of the cycle and TRC102 will be reduced by one dose level for the next cycle. Patient should not be retreated until all toxicities resolve to ≤ grade 1. Start of a new cycle of therapy may be held up to two weeks for toxicities to resolve. If the patient experiences another ≥ 3 toxicity, treatment will be held for up to two weeks. Patient can be retreated if all toxicities resolve to ≤ grade 1. TRC102 will be reduced by one dose level. Maximum two dose reductions are permitted. If the toxicities don't resolve, patient should be removed from study.

6.2.2 **Pemetrexed**

There is no dose reduction for hematologic or nonhematologic toxicity. If pemetrexed is held, TRC102 will be held as well, i.e. the entire course will be held for up to two weeks.

6.3 Management of Specific Adverse Events – Chemotherapy

Please refer to each drug's package insert for further detail Pemetrexed [package insert] 2012; Cisplatin [package insert] 2012

6.4 Maximum Treatment Delay

If the treatment delay is >2 weeks the patient will be taken off study.

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)

The Comprehensive Adverse Event 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 of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The 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/adverse_effects.htm for further clarification.

The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. 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.

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for **Methoxyamine hydrochloride (TRC102, NSC 3801)**

Version 1.0, February 8, 2013[1]

Adverse Events with Possible Relationship to Methoxyamine hydrochloride (TRC102) (CTCAE 4.0 Term)		**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS		
	Diarrhea	***Diarrhea (Gr 1)***
	Mucositis oral	***Mucositis oral (Gr 1)***
	Nausea	***Nausea (Gr 2)***
	Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	***Fatigue (Gr 2)***
	Fever	***Fever (Gr 1)***
INVESTIGATIONS		
	Blood bilirubin increased	***Blood bilirubin increased Gr 1)***
	Haptoglobin decreased	***Haptoglobin decreased (Gr 1)***
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	***Anorexia (Gr 1)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	***Pruritus (Gr 1)***

	Rash maculo-papular	***Rash maculo-papular (Gr 1)***

[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.

Also reported on methoxyamine hydrochloride (TRC102) trials but with the relationship to methoxyamine hydrochloride (TRC102) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis
GASTROINTESTINAL DISORDERS - Constipation
IMMUNE SYSTEM DISORDERS – Allergic reaction
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Creatinine increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypocalcemia
NERVOUS SYSTEM DISORDERS - Dysgeusia
PSYCHIATRIC DISORDERS – Psychosis
RESPIRATORY, THORACIC, & MEDIASTINAL DISORDERS - Dyspnea
VASCULAR DISORDERS - Thromboembolic event

Animal Data: The following toxicities have been observed in animal studies with methoxyamine hydrochloride (TRC102):

Dogs:
BLOOD AND LYMPHATIC SYSTEM DISORDERS - bone marrow hypercellularity; epididymal cellular debris; small thymus
GASTROINTESTINAL DISORDERS - abnormal excreta
INVESTIGATIONS – increased reticulocytes, lymphocytes increased
NERVOUS SYSTEM DISORDERS - convulsions; tremors
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - seminiferous tubule degeneration

Rats:
BLOOD AND LYMPHATIC SYSTEM DISORDERS - enlarged or swollen spleens; increased spleen weight
INVESTIGATIONS - increased monocytes; increased reticulocytes; lymphocytes increased

Note: Methoxyamine hydrochloride (TRC102) 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.

7.1.2 **Adverse Event List(s) for Cisplatin**

Cisplatin injection produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen (BUN), creatinine clearance, and

magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, cisplatin injection should not be given more frequently than once every 3 to 4 weeks. Elderly patients may be more susceptible to nephrotoxicity.

There are reports of severe neuropathies in patients in whom regimens are employed using higher doses of cisplatin injection or greater dose frequencies than those recommended. These neuropathies may be irreversible and are seen as paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. Elderly patients may be more susceptible to peripheral neuropathy.

Loss of motor function has also been reported. Anaphylactic-like reactions to cisplatin injection have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to cisplatin injection, and have been alleviated by administration of epinephrine, corticosteroids, and antihistamines.

Cisplatin injection can commonly cause ototoxicity which is cumulative and may be severe.
Audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug.

Cisplatin injection can cause fetal harm when administered to a pregnant woman. Cisplatin injection is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice cisplatin injection is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant.

The carcinogenic effect of cisplatin injection was studied in BD IX rats. Cisplatin injection was administered intraperitoneally to 50 BD IX rats for 3 weeks, 3 X 1 mg/kg body weight per week. Four hundred and fifty-five days after the first application, 33 animals died, 13 of them related to malignancies: 12 leukemias and 1 renal fibrosarcoma.

The development of acute leukemia coincident with the use of cisplatin injection has been reported. In these reports, cisplatin injection was generally given in combination with other leukemogenic agents.

Injection site reactions may occur during the administration of cisplatin injection. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.
Please refer to the package insert for the comprehensive list of adverse events.

7.1.3 **Adverse Event List(s) for Pemetrexed**

Patients treated with Pemetrexed must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related hematologic and GI toxicity. In clinical studies, less overall toxicity and reductions in Grade 3/4 hematologic and nonhematologic toxicities such

as neutropenia, febrile neutropenia, and infection with Grade 3/4 neutropenia were reported when pretreatment with folic acid and vitamin B12 was administered.

Skin rash has been reported more frequently in patients not pretreated with a corticosteroid in clinical trials. Pretreatment with dexamethasone (or equivalent) reduces the incidence and severity of cutaneous reaction.

Pemetrexed can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia); myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on nadir ANC, platelet count, and maximum nonhematologic toxicity seen in the previous cycle.

Pemetrexed is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance < 45 ml/min/1.73 m^2. Insufficient numbers of patients have been studied with creatinine clearance < 45 ml/min/1.73 m^2 to give a dose recommendation. Therefore, pemetrexed should not be administered to patients whose creatinine clearance is < 45 ml/min/1.73 m^2. One patient with severe renal impairment (creatinine clearance 19 ml/min/1.73 m^2) who did not receive folic acid and vitamin B12 died of drug-related toxicity following administration of pemetrexed alone.

Caution should be used when administering NSAIDs concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min/1.73 m^2).

Patients should not begin a new cycle of treatment unless the ANC is > 1500 cells/mm3, the platelet count is > 100,000 cells/mm3, and creatinine clearance is > 45 ml/min/1.73 m^2.

Based on its mechanism of action, pemetrexed can cause fetal harm when administered to a pregnant woman. Pemetrexed administered intraperitoneally to mice during organogenesis was embryotoxic, fetotoxic, and teratogenic in mice at greater than 1/833rd the recommended human dose. If pemetrexed is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Women should be advised to use effective contraceptive measures to prevent pregnancy during treatment with pemetrexed.

Please refer to the package insert for the comprehensive list of adverse events.

7.1.4 **Other Agent(s)**

To reduce toxicity, patients treated with pemetrexed must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis (Alimta [package insert] 2012). At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed; and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive one intramuscular or subcutaneous injection of vitamin B12 during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed. In clinical trials, the dose of folic acid studied ranged from 350 to 1000 μg, and the dose of vitamin B12 was 1000 μg. The most commonly used dose of oral folic acid in clinical trials was 400 μg.

Patients should receive appropriate hydration prior to and/or after receiving platinum therapy.

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.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **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 the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

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, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

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, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** under 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 (NCI) **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

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave.

7.5 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/IDE be reported expeditiously 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.

7.6 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 AE reporting unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent

8.1.1 *CTEP IND Agent TRC102 (NSC 3801))*

Chemical Name: Methoxyamine hydrochloride

Other Names: Methoxyamine HCl

Classification: Biochemical inhibitor of the BER pathway

Molecular Formula: **$CH_3ONH_2 \bullet HCl$** **M.W.:** 83.52 Daltons

Approximate Solubility: At ambient temperature, TRC102 is freely soluble in water, sparingly in ethanol (70mg/mL), and slightly in DMSO (140mg/mL).

Mode of Action: TRC102 has the ability to interrupt the process of base excision repair (BER) by binding to apurinic/apyrimidinic sites produced during the initial step of the BER pathway. These sites are substrates for topoisomerase II (topo II); an enzyme that cleaves damaged DNA. TRC102 has demonstrated the ability to potentiate the activity of the alkylating agents temozolomide and carmustine, and antimetabolite agents fludarabine and pemetrexed, in murine models of human cancer. Therefore, TRC102 may be able to potentiate the activity of alkylating and antimetabolite chemotherapy in patients.

Description: TRC102, a white, crystalline solid, is the hydrochloride salt of methoxyamine.

How Supplied: TRC102 is supplied by Tracon Pharmaceuticals and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. The white, opaque, size 2, hard gelatin capsules contain 25 mg of Methoxyamine HCl powder, microcrystalline cellulose, crosspovidone, sodium starch glycolate, colloidal silicon dioxide, and talc. Each HDPE bottle with child-resistant screw cap contains 30 capsules.

Storage: Store bottles of TRC102 at refrigerated temperature (2-8°C).

Stability: Shelf life surveillance of the intact bottles in ongoing.

Route of Administration: Oral

Method of Administration: Capsules are taken in the morning after patients have fasted for at least two hours. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush. Patients should refrain from eating or drinking for one hour following TRC102 dosing.

Availability

TRC102 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

TRC102 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 *Agent Ordering and Agent Accountability*

8.1.2.1 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), Biosketch, Agent Shipment Form, 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.

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, a "current" password, and active person registration status. 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.

8.1.2.2 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.

8.1.2.3 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://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.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)

8.1.2.4 Investigator Brochure Availability

The current versions of the IBs for the agents 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.

8.1.3 *Cisplatin Commercial Agent*

Description: Cis-diamminedichloroplatinum (Platinol or cisplatin) is a heavy metal complex and is water soluble. It is a white lyphilized powder with a molecular weight of 300.1.

Formulation: Cisplatin is available as 50mg/50ml and 100mg/100ml multi-dose vials. Each ml also contains 9mg sodium chloride. Hydrochloric acid and/or sodium hydroxide is added to adjust the pH.

Storage and Stability: The intact vials may be stored at room temperature (15 - 25%), protected from light, for the lot life indicated on the package. Do not refrigerate. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitate occurs in D5W) and stored at room temperature for up to 24 hours.

Administration: Cisplatin should be given immediately after preparation as slow intravenous infusion over 30 - 60 minutes. Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin (Platinol) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes. Please refer to the approved package labeling for complete prescribing and toxicity

information.

Supplier: Cisplatin is commercially available. This drug will not be supplied by the NCI.

8.1.4 *Pemetrexed Commercial Agent*

Description: Pemetrexed (Alimta) is a folate analog metabolic inhibitor; it is a white to either light-yellow or green-yellow lyophilized powder

Formulation: Pemetrexed for injection is commercially supplied as a sterile, lyophilized powder for intravenous infusion packaged in a single-use glass vials containing 100 mg or 500 mg pemetrexed. The freeze-dried drug product is pemetrexed disodium and mannitol in a 1:1 ration. Sodium hydroxide and/or hydrochloric acid solution maybe added during processing to adjust the pH. Each vial contains an excess of pemetrexed to facilitate the withdrawal of the label amount.

Storage and Stability: The drug product is stable when stored at controlled room temperature and normal lightning conditions.

Administration: Each vial must be reconstituted with sodium chloride (0.9%) solution for injection, without preservative, resulting in a solution containing 10mg/mL to 50 mg/mL. Pemetrexed infusion solutions prepared in this manner are compatible with polyvinyl chloride and polyolefin line administration sets and infusion bags. Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's injection.

Supplier: Pemetrexed is commercially available. This drug will not be supplied by the NCI.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacokinetics of TRC102 – Not Applicable

9.2 Correlative Studies

9.2.1 **Establishment of pleural and peritoneal effluent-derived cell lines**

The pleural and peritoneal effluent are often collected from mesothelioma patients. These cells potentially have tumor associated cells that can be evaluated for response to therapies. Moreover, the mesotheliomas are classified as epithelial, fibrous, or mixed. Depending on the type, there may also be differential response to treatments and these cells will provide a valuable resource for evaluation of different therapies and to also provide a molecular basis for the classification of the histopathological assignments.

Only patient samples from City of Hope will be used for the establishment of mesothelial cells from pleural or peritoneal effluents. **For City of Hope patients only, samples will be transported to Dr. O'Connor's laboratory in the Gonda Bldg, Rm 4131A (see Appendix E for specimen collection form). The day prior to the procedure, please**

contact Dr. O'Connor at x68220 and/or Ms. Yesenia Thompson at x63696.

Methods: We will centrifuge the pleural or peritoneal effluent at 300Xg for 10 minutes to pellet cells. Cells remaining after centrifugation will be resuspended in RPMI, 10% fetal calf serum with Glutamax, and supplemented with penicillin, streptomycin. Cells will be plated onto 6 cm culture dishes and cultured at 5% CO_2 and 37^{o}C and allowed to develop into colonies. Different cell types will be isolated based on morphology as clones assigned generally as epithelial or fibrous. Following isolation, next-generation RNA sequencing (RNA-seq) will be performed to identify expression levels of the ensemble of genes in the mesothelioma cell lines. Those will be analyzed using data mining techniques to establish differences in the cell types. Differences in cell types will be assigned and compared to a recent publication that used microarray analysis (44). We will examine topoisomerase II levels in these cell lines, because that has been directly linked to response to TRC102 (27).

Expected Results: We anticipate that a majority of pleural and peritoneal effluents will produce viable cell lines based on the literature. Furthermore, we will possibly identify more diagnostic biomarkers that have prognostic or therapeutic value. We will particularly focus on CDKN21, CDKN2B, BAP1, NF2, and TP53 expression levels, which were recently presented as important in diagnosis (44).

Alternative methods/results: If no cells arise using the initial culturing techniques, we will change the conditions, based on rational evaluation of the culture media from different laboratories and based on the experience in our group to culture from tissue explants. However, based on literature reports, we do not anticipate that culturing the effluents will be overwhelming. If we identify different markers, those are potentially important and could be publishable (44-49).

9.2.2 Response of cultured pleural and peritoneal cells to cisplatin, pemetrexed, and TRC102.

The cell lines developed above could present a possible advance in treatment of mesothelioma. We will test the response of the cells to TRC102 in conjunction with cisplatin and pemetrexed. The results that we obtain will be compared to the patient responses in the study. We will vary the amounts of cisplatin, pemetrexed, and TRC102 to evaluate the cell death for each drug individually, as pairs, and finally all together. We have used these techniques in the past (50) and will apply them to this work.

Methods: The cell culture parameters will be established in the previous aim. The cells will be cultured and the conditions to establish clonality will be empirically determined. Cells will be exposed to cisplatin, pemetrexed, or TRC102 or the different combinations (51). From the clonal survival data, we will determine the LD50 values for each of the drugs and the combinations, along with the level of synergy or antagonism. These data will be compared to the responses obtained in the Phase I patients.

Expected Results: We expect that the results we obtain in vitro will provide information

that can be used to alter drug treatment in subsequent studies. The results are expected to parallel the response of patients to the combination therapy.

Alternative methods/results: It is possible that the pleural and peritoneal effluents will not be clonal. If that is the case another viability assay will be used (e.g., Trypan blue permeability). The drug treatment regime in vitro could be different from what is observed in patients. If that is the case, we will consider a mouse xenograft model using a treatment with drug ratios similar to that found in cell culture. If that revised combination ratio shows more promise, it would be considered for future patient trials.

9.2.3 **Determination of abasic site modification in patient samples**

TRC102 reacts with the C1' aldehyde of the deoxyribose at the AP site and leads to a modification of DNA that is not easily repaired. The TRC102 modification of the AP site blocks the reaction with a reagent that is designated as an aldehyde reactive probe (ARP) (52). We will use the ARP to determine the effect of the TRC102 on AP sites.

Methods: Based on previous work (36), we will collect peripheral blood mononuclear cells (PBMCs) (buffy coat from 12 ml heparinized whole blood) on day 1 cycle 2 before cisplatin/pemetrexed treatment and then following treatment at 4 ± 1 hour and 24 ± 4 hours. The AP sites will be determined using the ARP (Dojindo Molecular Technologies, Gaithersburg, MD) and will be normalized to the pre-treatment levels for each patient.

Expected Results: The level of ARP reacted with the cisplatin/pemetrexed/TRC102 treated patient PBMCs should be lower than for the cisplatin/pemetrexed treated patient samples. This indicates that the TRC102 has limited the number of AP sites because the sites are already modified by TRC102. Therefore, blocking of the ARP modification will indicate functionality of the TRC102.

Alternative methods/results: If the ARP reactivity is low, there is a possibility that the TRC102 is not reacting with the AP sites in the PBMCs. It is still possible that the TRC102 has modified the mesothelioma cells and will have a therapeutic effect. If there is a positive effect on patient responses to mesothelioma in the cisplatin/pemetrexed/TRC102 arm even though not shown to modify the AP sites in this assay, the PBMCs could be a poor indicator of pharmacological response.

9.2.3.1 **Processing of Buffy Coat for PBMCs**

Equipment

- 12 mL of blood collected in Sodium Heparin or Lithium Heparin green-top tubes (3 4-ml vacutainer tubes, BD Cat. # 367884 or equivalent; OR 2 6-ml vacutainer tubes, BD Cat. #367886 or equivalent)
- One 15 ml size plastic conical centrifuge tube with screw cap
- Transfer pipettes
- Two polypropylene 2.0 mL screw-top cryovials (Corning Cat #430659 or equivalent; available 50/pk from Cole-Parmer Item # EW-44351-02)

Reagents

- Phosphate Buffered Saline (PBS) **without Ca^{++} or Mg^{++}** (Sigma Aldrich catalog #D8537 or equivalent)

Procedure

- Samples will be collected into green-top tubes with sodium heparin or lithium heparin on day 1 of cycle 2 just prior to treatment and then at 4 and 24 hours post treatment. Blood samples will be kept at room temperature (18-26ºC) and properly labeled with patient information and study number.
- Once each blood sample is collected, the tube should be inverted approximately 8-10 times to ensure that the whole blood is mixed thoroughly with the anticoagulant.
- The green-top tubes should be transported to the local processing laboratory and centrifuged as soon as possible to preserve the abasic sites (no longer than 30 minutes after blood collection). The tubes will be centrifuged at room temperature for 10 min at 1000 RCF (relative centrifugal force).
- The plasma layer will be removed, taking care not to disturb the off-white buffy coat layer, and discarded.
- The buffy coat will be transferred to a 15 ml conical centrifuge tube using a transfer pipette and add 10 mL of ice-cold PBS to the tube. Cap the tube and invert several times to mix.
- The cells suspension should be centrifuged at 300RCF for 10 min at 4◦C. When the centrifugation is finished, the supernatant will be taken off and discarded.
- Resuspend cells in 2 ml PBS and transfer to 2 x 2.0 mL screw-top cryovial that have been labeled with the study name (PHI-76), patient's study accession number, the sample date, and nominal time (i.e. pre, 4 hour, or 24 hour).
- The freezer vials should be centrifuged at 300RCF for 5 min at 4ºC (if feasible) and the supernatant removed using a transfer pipette so that only the dry pellet remains.
- Cell pellets should be stored at -80°C until batch shipping.
- The complete set of PBMC samples should be shipped overnight on dry ice to the following address with specimen collection form (Appendix E):

  Dr. Timothy Synold
  Shapiro Building Room 1042
  City of Hope National Medical Center
  1500 E. Duarte Rd.
  Duarte, CA 91010
  Phone (626) 256-4673, ext. 62110
  Fax – (626) 471-9376
  Email – tsynold@coh.org

9.2.4 Determination of cisplatin modification levels using ELISA methods

Use of a cisplatin specific antibody will permit at least the examination of the relative levels of cisplatin adducts formed in DNA to provide an evaluation of the level found in cells. We will use an ELISA method that detects low levels of cisplatin (53-55).

Methods: We will perform staining for the cisplatin adducts as described. PBMCs from the samples described above will be used to determine the level of modification by cisplatin using an ELISA assay with a commercial antibody (Anti-Cisplatin modified DNA antibody [CP9/19])(55). Extracts from the PBMCs will be isolated and compared to cisplatin modified standards. The same patient samples used from the previous aim will be used to determine the cisplatin levels.

Expected results: We anticipate that the level of cisplatin modification will not change based on treatment using TRC102.

Alternative methods/results: If there is not enough PBMC sample to obtain a reproducible cisplatin determination, we will only determine the level for AP sites, because that is anticipated to be the major factor.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 7 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. 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. Arm B patients will receive TRC102 and pemetrexed without cisplatin.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk[e] 12	Off Study[f]
TRC102 dosing: Day 1-4, q 21 days		X			X			X			X			
Cisplatin dosing		X			X			X			X			
Pemetrexed dosing		X			X			X			X			
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam[g]	X	X			X			X			X			X
Vital signs[g]	X	X			X			X			X			X
Height	X													
Weight[g]	X	X			X			X			X			X
Performance status[g]	X	X			X			X			X			X
CBC w/diff, plts[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prothrombin time or INR	X													
EKG (as indicated)	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every 2 cycles (6 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
Radiologic tumor assessment/response evaluation (CT scans)[b]	X	Radiologic measurements should be performed every 2 cycles (6 weeks). After 6 cycles of therapy, scans can be performed every 3 cycles (9 weeks).												X
B-HCG[c]	X													
Correlative studies as defined in section 9.2	X				X									

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Radiological assessment should be performed within 28 days before start of treatment and subsequently every 2 cycles (6 weeks), until disease progression, or end of treatment. All assessment should be performed within +/- 7 days of the scheduled day of assessment.
c: Serum pregnancy test (women of childbearing potential).
e: Patients may receive up to 6 cycles of therapy; For patients on Arm A, Dose level 4 (chemotherapy-naïve), patients may discontinue cisplatin and continue treatment with TRC102 and pemetrexed at the discretion of the treating physician.
f. Off-study evaluation. Follow-up per Section 5.6.
g. Laboratory evaluations and clinic visits at specified timepoints +/- 2 days.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 2 cycles (6 weeks). Once a patient completes 6 cycles of therapy, scans can be performed every 3 cycles (9 weeks). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new 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.

In the current study, tumor thickness perpendicular to the chest wall or mediastinum will be assessed according to modified RECIST criteria for Malignant Pleural Mesothelioma [57]. Accordingly, at least 6 measurable lesions (2 measurements per CT section, taken perpendicularly to a bony structure, in 3 different sections) should be identified as **target lesions** and recorded and measured at baseline. A sum of the longest diameter for all target lesions will be calculated and reported at the baseline sum longest diameter. It will be used as the reference by which to characterize the objective tumor response. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax will be chosen to allow reproducible assessment at later time points. At reassessment, pleural thickness will be measured at the same position at the same level. The minimum size of a measurable lesion should be no less than double the slice thickness and also have a minimum size of 10 mm.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with TRC102.
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.

11.1.2 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. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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.

11.1.3 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 Response Criteria

11.2.1 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.

11.2.2 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).

11.2.3 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 beaccepted 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		

11.2.4 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.

12 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

See also Section 14 'CCC POLICIES FOR MONITORING CONSORTIUM TRIALS,' Subsection 14.1 'Oversight.

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and

statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician through IWRS and Medidata Rave.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 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 (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL. (*Note: A DTL is NOT required for this study.)*.

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. Trainings 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.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will 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/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the

recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to

restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

N/A

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary objectives in **Arm A** are to select a Recommended Phase 2 Dose (RP2D) for TRC102 in combination with cisplatin and pemetrexed for use in patients with malignant solid tumors. In **Arm B** the primary objective is look for preliminary evidence of activity of the starting dose level in patients with advanced malignant mesothelioma previously treated with pemetrexed and cisplatin.

Arm A: The RP2D will be established using escalation rules in section 5.3, design to escalate, in cohorts of 3, through four planned dose levels, with an additional de-escalation dose if needed (Table 1). The primary endpoint is dose-limiting toxicity (DLT), which is defined in section 5.3, along with dose escalation rules. Toxicity is graded NCI Common Terminology Criteria for Adverse Events (CTCAE), as specified in section 6.

For the first 3 dose levels, TRC102 dose will be escalated with Cisplatin held constant at 60 mg/m^2. The fourth dose level holds TRC 102 constant, and escalates Cisplatin. An important detail is that dose level 4 has an alternate definition in the event that dose escalation stops short of dose level 3 (where TRC 102 is at its maximum planned dose). Assuming that the escalation rules establish a lower dose as the RP2D, we will regard that as tentative, and use the TRC102 dose from that level (with 75 mg/m^2 Cisplatin and 500 mg/m^2 Pemetrexed) in a re-defined dose level 4. Six patients will be treated at the tentative RP2D before escalating to the re-defined dose level 4 as the final dose level. If, however, the dose escalation does not stop short of dose level 3, then dose escalation may proceed to level 4 directly, as originally defined, in accordance with the escalation rules. This does not necessarily require more than 3 subjects at dose level 3.

Patients will be enrolled in cohorts of three until a final RP2D is established. Definitions of "evaluable for toxicity" and "evaluable for response" are given in section 10.5.1. Dose escalation decisions will be based on patients who are fully treated (patients must receive the prescribed doses of pemetrexed and cisplatin, and ≥ 75% of the prescribed dose of TRC102 in the cycle) without DLT, or who experience DLT after any amount of treatment.

Arm B will enroll 14 patients with advanced malignant mesothelioma previously treated with pemetrexed and cisplatin who are evaluable for response. Patients will be treated with 50 mg/day of TRC102, orally, days 1-4, every 21 days and 500 mg/m^2 of pemetrexed, intravenously, day 1, every 21 days. This is the first stage of a two stage Gehan design looking for RECIST responses. Because the expectation of response to any agent is very low for this group, any responses will be of interest. If no responses are seen among 14 subjects, the upper 95% confidence limit for response rate would be below 20%. If any responses are seen among the 14 subjects, demonstrating that responses are possible, additional study will be needed to

better obtain an estimate of the response rate with an acceptable confidence interval (the second stage of the Gehan design).

13.2 Sample Size/Accrual Rate

Arm A is expected to require between 12 and 19 subjects, who are treated until DLT or completion of their first course. **Arm B** will require 14 subjects evaluable for response. Mesothelioma occurs predominantly in older men, although adult men and women of all races and ethnic groups are eligible for this trial. The total sample size target is between 26 and 33 subjects, with 30 expected.

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					
Asian	1	4	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	2	0	0	**2**
White	3	14	1	5	**23**
More Than One Race	0	0	0	0	**0**
Total	**4**	**20**	**1**	**5**	**30**

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13.3 Stratification Factors

Not applicable in this study.

13.4 Analysis of Secondary Endpoints

Evaluation and analysis of pharmacokinetic parameters is described in section 8. Briefly, individual PK parameter estimates (e.g., Cmax, Vss, CLsys, t1/2, and area under the curve [AUC]) will be determined for TRC102 and cisplatin for each patient and tabulated using

summary statistics (means and coefficients of variation).

Feasibility of establishing pleural and peritoneal effluent-derived cell lines will be reflected in the number successfully established. Response of cultured pleural and peritoneal mesothelioma cells to cisplatin, pemetrexed, and TRC102 will be studied using standard experimental design approaches and generalized linear model analyses.

RECIST-defined responses will be summarized as a fraction of all subjects, and as a fraction of all subjects in **Arm B**, using exact binomial 9 percent confidence intervals.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

As noted above, all patients will be evaluable for toxicity from the time of their first treatment with TRC102, but subjects must be fully treated or experience DLT to be included in escalation decisions.

13.5.2 Evaluation of Response

All patients included in the Arm B must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient with measurable disease will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

Conclusions about response rates in Arm B will be based on all patients treated in that arm. Supplementary analyses may then be performed including dose-escalation subjects and correlative information. Any subset analyses will only serve to supplement main conclusion about responses in Arm B, which will include all subjects enrolled in those arm, and to describe responses to the drug combination at each dose level in Arm A.

13.6 Study Status Updates and Study Closure

13.6.1 Definitions of Study Status Changes

13.6.1.1 Temporarily Closed to Accrual

The study status is Temporarily Closed to Accrual when no patient slots are currently available, but there is the possibility that the trial will re-open for accrual (patient slots become available). Sites are not permitted to accrue additional patients until CTEP is notified of Re-Activation.

Study status will need to be changed to Temporarily Closed to Accrual when any of the following criteria are met:

- Sites are notified by CTEP (via Request for Rapid Amendment [RRA]) of changes in the risk/benefit ratio that necessitate changes to the patient Informed Consent document. Requested changes will be specified in the RRA and must be reviewed by the study's IRB.
- CTEP and the lead investigator agree that unacceptable toxicities necessitate a discussion to change the dosing/regimen.
- A protocol-defined benchmark has been achieved (such as an interim analysis before proceeding to the next stage).
- Investigators encounter any of the stopping criteria described in Section 13.1.

13.6.1.2 Closed to Accrual

The study status is (permanently) Closed to Accrual when no more patient enrollment slots are available, and at least one patient is still actively receiving the study treatment. Sites are no longer permitted to enroll additional patients.

Patient slots are no longer available when the following criteria are met:

- The pre-specified number of evaluable patients has been successfully enrolled, treated, and evaluated.
- The study treatment has failed to meet the pre-specified efficacy goal at the stage 1 interim analysis.
- CTEP and the investigators agree that unacceptable toxicities preclude further enrollment.
- Investigators encounter any of the stopping criteria described in Section 13.1.

13.6.1.3 Closed to Accrual and Treatment

The study status is Closed to Accrual and Treatment when no more patient enrollment slots are available and no patients are currently receiving the study treatment. Patients may still be enrolled on the protocol only for the purposes of follow-up.

Patient accrual and treatment will be permanently halted when any of the following criteria are met:

- Enrollment was previously closed (study status of "Closed to Accrual"), and no patients are receiving the study treatment.
- CTEP and the investigators agree that unacceptable toxicities preclude further

enrollment. In this case, CTEP and the investigators must collaborate to alter the regimen or to halt the study treatment altogether as soon as it can be safely done for patients currently receiving treatment.

CTEP and Theradex **must be notified** when patients are no longer receiving treatment [*i.e.*, when the last patient(s) to be receiving treatment is/are no longer receiving the study regimen for any reason].

13.6.1.4 Closed to Follow-Up

The study is considered Closed to Follow-Up when all protocol-defined follow-up procedures have been completed for all patients who have not been removed from the study for other reasons. That is, there are no outstanding follow-up procedures to be performed as mandated by the protocol.

CTEP does **not** need to be notified of a status change to "Closed to Follow Up."

13.6.1.5 Complete

Study is considered Complete if it has been at least thirty (30) days since the last patient follow-up evaluation.

A citation to a final study report (manuscript, meeting abstract, etc.) is required with the submission of the Protocol Status Update Form to CTEP PIO.

13.6.2 Responsibility for Filing Protocol Status Update Forms

CTEP must be notified of all study status changes in Section 14.1 (except for Closed to Follow-Up) by the Corresponding Organization via Protocol Status Update Form, available from the CTEP website at http://ctep.cancer.gov/protocolDevelopment/default.htm#amendments.

Theradex must be notified as soon as all patients are off treatment (*i.e.*, when study status changes to Closed to Accrual and Treatment). Theradex will produce a report within 90 days of this notification.

14 CCC POLICIES FOR MONITORING CONSORTIUM TRIALS

This protocol is monitored at several levels, as described in this section. To summarize: The trial PI has access to the data at all times. The CCC Data Coordinating Center reviews accrual and toxicities monthly. An external, independent DSMC reviews the study progress twice yearly. In addition, for the Phase I portion, the study PI will have monthly - and as needed - conference calls with study investigators to review accrual, progress, and any unforeseen issues. Dose escalation/expansion/de-escalation decisions require sign-off by the study PI (or his or her designee) and study statistician (or his or her designee). During the Phase II portion, the study PI will have quarterly - and as needed - conference calls with study investigators to review accrual, progress, and any unforeseen issues. Decisions to proceed to the second stage of the Phase II

trial will require sign-off by the study PI and (the trial statistician).

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase II trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7.0) and case report forms. The Data Coordinating Center for the CCC Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCC that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCC initiated trial on the CCC website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase I trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
(b) for Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCC teleconference meeting for review and approval.

14.1 Oversight

Oversight of the conduct of CCC trials occurs at several levels:

1. The Data Coordinating Center for the CCC flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism or his or her designee, and are communicated to the participating centers by the CCC Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCC institution; this audit is initiated by CTEP.

3. An independent CCC DSMC will review CCC trials every 6 months. This DSMC will consist of 6 voting members (3 medical oncologists or hematologists involved in Phase I/II

cancer clinical trials but not participating in CCC studies, a patient representative and a statistician) and a non-voting CCC statistician.

a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
b. This DSMC will review each CCC trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.
c. The DSMC will report to the CCC leadership.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Not Applicable: No studies have been performed to assess potential metabolic and transport interactions of TRC102. Because there is a potential for interaction of TRC102 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if a drug-drug interaction is a suspected component of an adverse event.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent TRC102 (NSC 3801). This clinical trial is sponsored by the NCI. There is no information on how TRC102 interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial	➢ Your study doctor's name is _____ and can be contacted at_____.

APPENDIX C NOT APPLICABLE

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CTEP-assigned Protocol # 9837
Consortium Protocol PhI-76
Local Protocol # _____

APPENDIX D PATIENT MEDICATION DIARY

Today's date _____ **Cycle Number:** _____ **Agent:** TRC102

Patient Name_____(*initials acceptable)*

Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take **TRC102 capsules by mouth for the first four days of each cycle.** Capsules are taken in the morning after you have fasted for at least two hours. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush. You should refrain from eating or drinking for one hour following TRC102 dosing. Dose: take _____ 25 mg capsules. If you miss a dose (do not take it within 6 hours of scheduled time), skip the dose and resume taking TRC 102 at the next scheduled time.
4. Record the date, the number of capsules that you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of TRC102 capsules when you return for each appointment.
7. Please store TRC 102 capsules in the refrigerator.

Day	**Date**	**Time of dose**	**TRC102 # of capsules taken**	**Comments**
			25 mg	
1				
2				
3				
4				

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose

_____

3. Total number of capsules taken this month **of TRC102**_____

4. Physician/Nurse/Data Manager's Signature

_____

APPENDIX E SPECIMEN COLLECTION FORM FOR PHARMACODYNAMIC STUDIES NCI PROTOCOL #9837, PHI-76

Title: Phase I Study of TRC102 in Combination with Cisplatin and Pemetrexed in Patients with Advanced Solid Tumors / Phase II Study of TRC102 with Pemetrexed in Patients Refractory to Cisplatin and Pemetrexed

Patient's Name_____ _____**Patient Accession #** _____ _____ _____

(first) (last)

Study Site _____

TRC102 Dose _____ mg/dose **Start Date/time** _____

Sample Type (Check one)

Plural Effusion (City of Hope Only – See **Section 9.2.1**) **[ ]**

Peritoneal Effusion (City of Hope Only – See **Section 9.2.1)** **[ ]**

Peripheral Blood for Buffy Coat/PBMCs (All Sites – See **Section 9.2.3.1)** **[ ]**
[12 mL of blood collected in Sodium Heparin or Lithium Heparin green-top tubes (3 4-ml vacutainer tubes, BD Cat. # 367884 or equivalent; OR 2 6-ml vacutainer tubes, BD Cat. #367886 or equivalent)]

Sample Acquisition **Date and Time** _____

Sample Processing Started **Start Date and Time** _____

Shipping Date Date _____

-SHIPPING INFORMATION ON APPENDIX E PAGE 2-

APPENDIX E – Page 2

SPECIMEN COLLECTION FORM FOR PHARMACODYNAMIC STUDIES
NCI Protocol #9837, PHI-76

Shipping information:

Plural Effusion or Peritoneal Effusion (City of Hope Only):

Samples will be transported to Dr. O'Connor's laboratory in the Gonda Bldg, Rm 4131A. The day prior to the procedure, please contact Dr. O'Connor at x68220 and/or Ms. Yesenia Thompson at x63696.

Peripheral Blood for Buffy Coat/PBMCs (All Sites):

Dr. Timothy Synold
Shapiro Building Room 1042
City of Hope National Medical Center
1500 E. Duarte Rd.
Duarte, CA 91010
Phone (626) 256-4673, ext. 62110
Fax – (626) 471-9376
Email – tsynold@coh.org