Official title: SPOC-2015-01: Phase 1 trial of dose escalated BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC)

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PROTOCOL NUMBERS: **SPOC-2015-01**

TITLE: Phase 1 trial of dose escalated Bemcentinib BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC)

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SITE: Non-small cell lung cancer (NSCLC)
HISTOLOGY:
STAGE: Advanced (Stage IV—AJCC 7th edition)
MODALITY: Intravenous
TYPE: Chemotherapy
ARMS: Single

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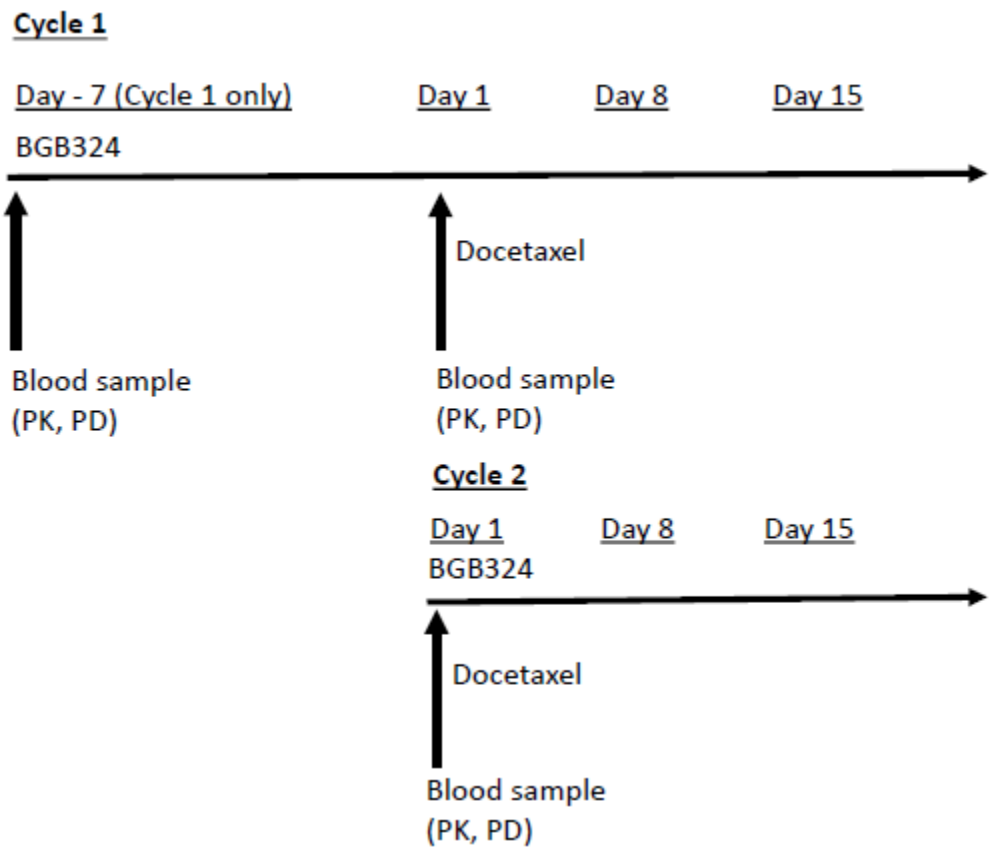
TREATMENT SCHEMA

NOTE: PK samples will be drawn only for the first 15 enrolled subjects.



Bemcentinib and Docetaxel Dose Cohorts

	Bemcentinib dose (mg)			Docetaxel dose (mg/m^2 IV on Day 1 of each cycle)
	Cycle 1 Days -7, -6, and -5	Cycle 1 Days -4 to 21	Cycles ≥ 2 All days	
Cohort -1[a, b]	200* daily	100 daily	100 daily	60
Cohort 1	200* daily	100 daily	100 daily	75
Cohort 2	400* daily	200 daily	200 daily	75
Cohort 2A[a]	400* daily	200 daily	200 daily	60

NOTE: Cohort -1 will be enrolled only if Cohort 1 or Cohort 2 dosing exceeds the maximum tolerated dose.

a. If Cohort -1 is enrolled without exceeding the MTD, bemcentinib may be dose escalated to 400 mg daily on Days -7, -6, and -5, then 200 mg daily on subsequent days (Cohort 2A).

b. If Cohort -1 or Cohort 2A is enrolled without exceeding the MTD, a subsequent cohort with docetaxel dose re-escalated to 75 mg/m^2 every 21 days with concurrent myeloid growth factor support every cycle will be enrolled.

If dose-limiting toxicity (DLT) is experienced during or attributed to (ie, occurs shortly after) the 3-day loading period, dose de-escalation will occur as follows without adjustment of daily maintenance dose:

Loading Cohort 1: loading dose x 3 days
Loading Cohort -1: loading dose x 2 days
Loading Cohort -2: loading dose x 1 day
Loading Cohort -3: no loading dose; initiate treatment with standard daily dose

This is a single-arm phase 1 clinical trial. Dose escalation will be according to a standard 3+3 schema with a planned expansion cohort at the recommended phase 2 dose (RP2D). At least 3 weeks must elapse between initiation of study therapy for the first patient on a new dose level after the treatment of the last patient on the previous dose level.

To permit assessment of pharmacodynamic and pharmacokinetic effects of bemcentinib alone and in combination, the trial will employ a staggered initiation during Cycle 1. Specifically, bemcentinib will be administered alone on Days -7 to -1 prior to docetaxel administration.

Docetaxel will be administered on Day 1 of each 21-day cycle. Bemcentinib will be self-administered daily every day of each 21-day cycle. On Docetaxel administration days, bemcentinib will be administered first.

A loading dose of bemcentinib will be given during the first three days of the run-in period prior to Cycle 1 (Day -7 , Day -6 and Day -5), followed by a lower daily maintenance dose during the remainder of the run-in period and throughout continuous 21-day treatment cycles. Bemcentinib dosing can be interrupted, per protocol, for a maximum of 14 days to manage adverse events. If dosing is interrupted for >7 days dosing will re-commence at the loading dose for the first three days. Treatment will continue with both agents until disease progression or unacceptable toxicity.

Correlative and pharmacodynamic studies, including tissue and blood analyses, will be performed on all patients.

1.0 OBJECTIVES

1.1 Primary Objective

- To determine the safety and tolerability and recommended Phase 2 dose (RP2D) of bemcentinib administered with the standard dose of docetaxel in patients with NSCLC.

1.2 Secondary Objectives

- To determine the response rate, progression-free survival and overall survival of bemcentinib therapy in combination with docetaxel in patients with NSCLC.
- To determine pharmacokinetics and pharmacodynamics of bemcentinib alone and in combination with docetaxel.
- To assess the PK of docetaxel in combination with bemcentinib.

2.0 BACKGROUND AND HYPOTHESES

2.1 Lung Cancer

Lung cancer remains the leading cause of cancer-related deaths worldwide with an estimated incidence of 1.6 million cases resulting in 1.4 million deaths in annually.[1] Non-small-cell lung cancer (NSCLC) represents 80-85% of cases, and adenocarcinoma is the most common histology.[2] The majority of NSCLC patients present with advanced or metastatic disease that is not amenable to surgical resection. Platinum-based combination chemotherapy has reached a therapeutic plateau with a median overall survival (OS) of 7.4 to 9.9 months.

2.2 Second-Line Chemotherapy for Advanced NSCLC

There exists a critical need to improve second-line therapy for advanced non-small cell lung cancer (NSCLC). Currently, three drugs are FDA approved for this indication: docetaxel, pemetrexed, and erlotinib. In unselected lung cancer populations, these agents have radiographic response rates less than 10%, median progression-free survival ranging 2.2-2.9 months, and median overall survival ranging 6.7-8.3 months.[1-3] In 2014, clinical practice has evolved to the point that use of pemetrexed is restricted to nonsquamous histology (based on differential efficacy according to histology that has been attributed to differential levels and activity of thymidylate synthase) and is commonly used as a first-line and/or maintenance agent rather than a second-line agent. Regarding erlotinib, its current clinical use is largely

restricted to patients with activating epidermal growth factor receptor (EGFR) gene mutations, where it is commonly employed as first-line therapy. As a result, both on protocol and in standard practice, docetaxel has emerged as the predominant second-line therapy for this challenging disease. Recently, the addition of the vascular endothelial growth factor receptor (VEGFR) monoclonal antibody ramucirumab to docetaxel chemotherapy has been shown to improve clinical outcomes slightly.[3]

2.3 Axl

Axl is a member of the TAM (Tyro3, Axl, Mer) family of receptor tyrosine kinases (RTKs) that regulate multiple cellular processes. These include cell survival, proliferation, and migration. Mer and Axl share the natural ligand Gas6, which binds Axl with 3-10 fold greater intensity than Mer.[4] The role of these RTKs in normal physiology appears related to clearance of apoptotic cells, cytokine secretion, platelet aggregation, erythropoiesis, and natural killer cell differentiation and maturation.[5-8]

The oncogenic potential of Axl has been attributed to autocrine and paracrine functions. In addition to signaling through canonical PI3K/Akt and MAPK/Erk pathways, Axl may also mediate tumor-stromal cell interactions, resulting in modification of the inflammatory response and angiogenesis.[9,10] Recently, Axl has also been implicated in epithelial-to-mesenchymal transition (EMT), which promotes metastasis and giving cells the ability to migrate through extracellular matrix and intravasate into blood vessels.[11]

In non-small cell lung cancer (NSCLC), Axl expression is associated with poor clinical outcomes, lymph node involvement, and higher disease stage.[12] Axl and Gas6 ligand have been detected at high levels in more than 50% of NSCLC cell lines.[13] Further suggesting a major role in NSCLC biology, Axl is also among the most highly phosphorylated (ie, activated) RTKs in NSCLC cell lines and tumors.[14,15]

It has been reported that Axl mediates chemoresistance in a variety of cancer types, including NSCLC,[16] breast cancer,[17] and esophageal adenocarcinoma.[18] Epithelial to mesenchymal transition (EMT) is a common mechanism of resistance to chemotherapy, including resistance to docetaxel. Axl activation causes EMT[19], while inhibition of Axl can reverse mesenchymal phenotype, thereby restoring drug sensitivity.

2.4 Bemcentinib (BGB324)

Bemcentinib (BGB324) is a potent selective small molecule inhibitor of Axl, a surface membrane protein kinase receptor that is over-expressed in many metastatic solid tumors and has been identified as a marker of a poor prognosis in patients with non-small cell lung cancer (NSCLC).

Please refer to the current version of the bemcentinib Investigator's Brochure for more information of the non-clinical and clinical data available on bemcentinib.

2.4.1 Nonclinical Studies with bemcentinib

2.4.1.1 Specificity of Inhibition of Axl Kinase Activity

Bemcentinib demonstrates potent inhibition of Axl in biochemical and cell-based kinase inhibition assays. The selectivity of bemcentinib for Axl is illustrated in Table 1.

Table 1: Bemcentinib Kinase Selectivity Profile

Kinase	Kinome Scan binding assay (K_d)		KinaseProfiler kinase activity assay (IC_{50})		BaF3 cell-based kinase activity assay (IC_{50})	
	nM	Fold	nM	fold	nM	fold
Axl	0.4	1	4.6	1	63	1
Tie2	270	680	30	6.4	355	5.5
Ret	73	180	38	8.1	>316	>5
Flt1	400	>1000	40	8.7	>1000	>15
Flt4	460	>1000	41	8.8	>1000	>15
Yes	810	>1000	43	9.2	n/a	n/a

n/a = not applicable

2.4.1.2 Inhibition of Proliferation of Non-Small Cell Lung Cancer Cells

The anti-proliferative activity of bemcentinib was demonstrated in a panel of human NSCLC cell lines by either resazurin cell viability assay or colony formation assay. As summarized in Table 2, bemcentinib inhibited proliferation of several human lung cancer cell lines with IC50 values of 0.4 - 0.8 μM; the anti-proliferative effect was dose-responsive (not shown).

Table 2. Effect of Bemcentinib on Proliferation of Human NSCLC Cell Lines

Tumor Type	Cell Line	IC_{50} (μM)
NSCLC	A549	0.56
	NCI-H1299	0.67
	HCC827	0.76
	H358	0.43

The ability of bemcentinib to inhibit cell proliferation was investigated in a panel of 654 human tumor cell lines. When administered at a concentration of 1μM, bemcentinib inhibited proliferation by >50% in 48 of the cell lines tested, including 10/101 NSCLC.

2.4.1.3 Bemcentinib and corticosteroids

In an academic model of osteoporosis, bemcentinib was administered in combination with high dose corticosteroids (12.5 mg/kg per day of prednisolone). In this research study, 6 out of 7 mice experienced severe toxicity after five continuous days of combination therapy. Four out of 7 animals died and the other 2 were euthanized for humane reasons. The exact mechanism of this effect is currently under investigation. The mice received very high levels of corticosteroids to induce rapid onset of osteoporosis – on a mg/kg basis, the corticosteroid dose was 20-fold higher than a typical high dose commonly used in clinical practice. Additionally, the dose of bemcentinib used in this model was 50mg/kg, which is 6-fold higher than the maximum exposure observed in human clinical studies.

However, following the investigational toxicology studies conducted during the last year, it has been established that effects of steroids are not exacerbated by co-administration of bemcentinib.

However investigators are encouraged to follow their local guidelines for monitoring if a patient requires treatment with high dose steroids. If required, additional advice on the concomitant use of steroids with bemcentinib should be obtained from the appointed study Medical Monitor. (See Sections 6.5.1 and 4.3.3.1 of IB, version 12.)

2.4.2 Clinical Studies with Bemcentinib

There has been one previous clinical study conducted with bemcentinib (Protocol BGBC001). This study explored the effect of a single administration of bemcentinib in healthy male volunteers. Eight dose levels (50 mg, 100 mg, 150 mg, 200 mg, 400 mg, 600 mg, 1000 mg and 1500 mg) were evaluated under fasted conditions in cohorts of four subjects (32 subjects in total). Seven of these subjects went on to receive a single administration of the same dose of bemcentinib under fed conditions.

In general, exposure to bemcentinib was well tolerated with all toxicities being spontaneously reversible and predominantly gastrointestinal in nature. No serious adverse events were reported. Adverse events judged as related to bemcentinib are summarized in Table 3.

Table 3. Bemcentinib-Related Adverse Events Reported Following a Single Oral Administration of Bemcentinib to Healthy Male Subjects

Bemcentinib Dose (mg)	Number of Subjects Treated	Adverse Event	Maximum Grade
50	4 fasted; 1 fed	Non-cardiac chest pain	1
100	4 fasted; 2 fed	Orthostatic hypotension	1
150	4 fasted; 1 fed	Abdominal distension (2 pts)	1
400	4 fasted; 2 fed	Diarrhea	1
600	4 fasted	Diarrhea Flatulence Nausea (2 pts)	1 1 1
1000	4 fasted	Nausea	1
1500	4 fasted	Diarrhea Nausea Vomiting Headache Dizziness	1 2 2 1 1

2.4.2.1 ECG Findings

In light of the recoverable, non-adverse decreases in heart rate and corresponding increases in the RR interval durations observed in the cardiovascular study in monkeys, each subject in Study BGBC001 underwent serial ECG assessment after administration of bemcentinib. The overall pattern indicated that

bemcentinib administration was accompanied by a variable increase in QTcF, the magnitude of which was related to systemic exposure. The maximum QTcF recorded was Grade 1 in severity.

2.4.2.2 Bemcentinib Pharmacokinetics

In Clinical Study BGBC004 (A Multi-Center Open-Label Phase I/2 Study of bemcentinib in Combination with Erlotinib in Patients with Stage IIIb or Stage IV Non-Small Cell Lung Cancer), plasma concentration profiles of bemcentinib have been modelled (first-order absorption, one-compartment disposition) from seven patients administered 600 mg/200 mg bemcentinib as monotherapy. In general, the PK model adequately fitted the individual plasma profile, with generally good precision of estimated parameters.

PK parameters, at steady state, for seven patients administered 200 mg bemcentinib daily are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of Bemcentinib, at Steady State, Following a Loading Dose of 600 mg and Daily Oral Administration of 200 mg Bemcentinib (BGBC004)

Patient #	$AUC_{0\text{-}24h}$		C_{av}		C_{max}		$t_{½}$	
	(ng.h/mL)	CV (%)*	(ng/mL)	CV (%)*	(ng/mL)	CV (%)*	(h)	CV (%)~
312-101	5011	222	209	222	228	769	51.4	44.1
312-102	10208	2364	425	2364	443	18723	117	23.4
311-103	12249	12.7	510	12.7	525	49.7	76.2	19.8
310-105	4334	9.82	181	9.82	191	35.7	93.3	27.9
311-106	6313	11.6	263	11.6	267	18.0	28.7	3338
310-107	14127	5.22	589	5.22	595	20.2	293	11.6
310-108†	935	966	40.0	966	42.0	879	87.5	26.3
Geometric mean	7895		329		342		84.3	
CV (%) ~	52.4		52.4		50.2		92.4	

Abbreviations: $AUC_{0\text{-}\infty}$=area under plasma concentration versus time curve extrapolated to infinity; C_{av}=average concentration at steady state; C_{max}=maximum plasma concentration; CV=coefficient of variation; $t_{1/2}$= half-life

CV* represents precision of PK parameter; CV~ represents between-patient variability; † Anomalously low exposure, excluded from summary statistics

2.5 Rationale for this study

2.5.1 Axl inhibition sensitizes chemoresistant mesenchymal NSCLC cells to docetaxel

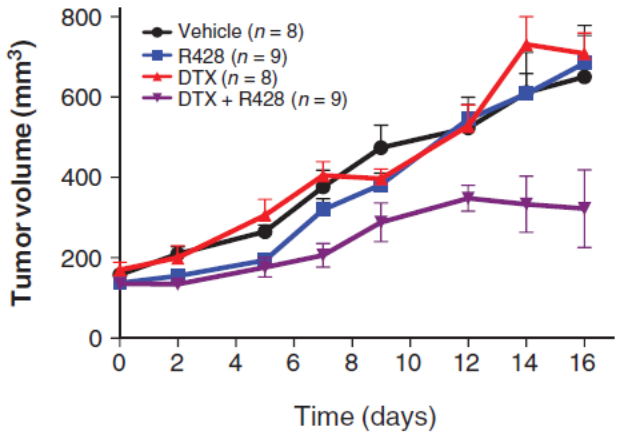
In vitro studies indicate that signaling through Axl stimulates a number of pro-survival pathways, some of which are mediated by AKT phosphorylation and up-regulation of the epithelial receptor kinase pathway. Recent non-clinical data indicate that Axl inhibition selectively sensitizes cancer cell to antimitotic agents. This study is designed primarily to evaluate the safety of the Axl inhibitor bemcentinib when administered in combination with docetaxel, and to establish the maximum tolerated dose and recommended Phase II dose of the combination of bemcentinib and docetaxel in patients with Stage IIIb or Stage IV NSCLC.

Wilson et al screened 643 NSCLC and breast cancer cell lines and found a strong correlation between Axl expression and mesenchymal phenotype.[20] Mesenchymal phenotype was associated with increased drug resistance, especially increased resistance to docetaxel. They also confirmed that induction of EMT with

exposure of epithelial cells to TGF-b increases Axl expression and docetaxel resistance. Furthermore, inhibition of Axl with R428, Axl tyrosine kinase inhibitor, increased docetaxel sensitivity 1000-fold and caused synergistic increase in cell death. This synergy was confirmed in multiple cell lines and is not specific to R428. In fact, Axl inhibition with siRNA or by sequestering Axl ligand, GAS6, with Axl-Fc chimera causes synergistic cell death in cell lines exposed to docetaxel. Similarly, Axl inhibition with R428 increases cell susceptibility to other antimitotic agents, such as inhibitors of Aurora kinase and polo kinase.

The anti-tumor activity of R428 in combination with docetaxel was evaluated in the human MDA-MB231 xenograft model. Treatment was initiated when tumors reached 100-200 mm^3. Mice were treated with vehicle control, R428 alone at 125 mg/kg orally 5 times a week, docetaxel at 10 mg/kg once a week intravenously or combination of the two. While neither treatment alone had significant effect on tumor growth in this docetaxel-resistant tumors, combination of R428 and docetaxel resulted in significant ($p<0.005$) anti-tumor activity.[20]

Figure 1. Anti-Tumor Effect of R428 and docetaxel in the MDA-MB231 Xenograft Model



Potentiation of docetaxel effect with Axl inhibition is believed to be in part mediated by inhibition of PI3K signaling. PI3K inhibitors, PWT-458 and GDC-0941, enhance efficacy of taxane-based therapy in NSCLC and breast cancer, respectively.[21,22] Axl is known to cause activation of PI3K/Akt pathway. This process is inhibited by R428.

Given excellent synergistic effect of docetaxel and Axl inhibition in NSCLC and a good tolerance of Axl inhibitor, bemcentinib, the current phase I trial of the combination of docetaxel and bemcentinib was designed.

2.5.2 Rationale for Bemcentinib Starting Dose

In BGBC004 eight patients with previously treated NSCLC were treated with a loading dose of 600 mg on days one and two followed by 200 mg daily. Treatment was well tolerated and no patients withdrew from the study as a result of toxicity. Two patients remain on treatment for more than six months with a best response of stable disease. The most common treatment affected System Organ Class was gastrointestinal disorders. A further four patients received an identical dose regimen of bemcentinib in combination with erlotinib at a dose of 150 mg BD. In patients receiving the combination gastrointestinal disorders were more

marked during the period of the loading dose but returned to baseline once patients became established on the 200 mg daily dose of bemcentinib.

In healthy subjects who received a single oral dose of bemcentinib, the elimination of bemcentinib was slow, with $t_{1/2} > 24$ hours. The administration schedule and starting dose of bemcentinib proposed for this study is based on fitting a one-compartment model, incorporating a lag time and no weighting, to the available clinical PK data. It is anticipated that administration of a loading dose of bemcentinib on the first 3 days (Day -7, Day -6 and Day -5) prior to Cycle 1 followed by daily dosing at a lower level will deliver the optimum exposure of bemcentinib. The application of a loading dose will facilitate achievement of therapeutic levels, while daily dosing will prevent wide changes in systemic concentration during therapy. The simulated mean plasma concentration-time profile of bemcentinib, based on the PK model, following dosing of bemcentinib at 600 mg on Day 1 and 600 mg on Day 2 and 200 mg daily thereafter is presented in Figure 2A.

Figure 2A. Predicted (fasted in healthy subjects) and observed (fasted) plasma profile of Bemcentinib in patients after daily oral administration of 200 mg Bemcentinib **(Study BGBC004)**

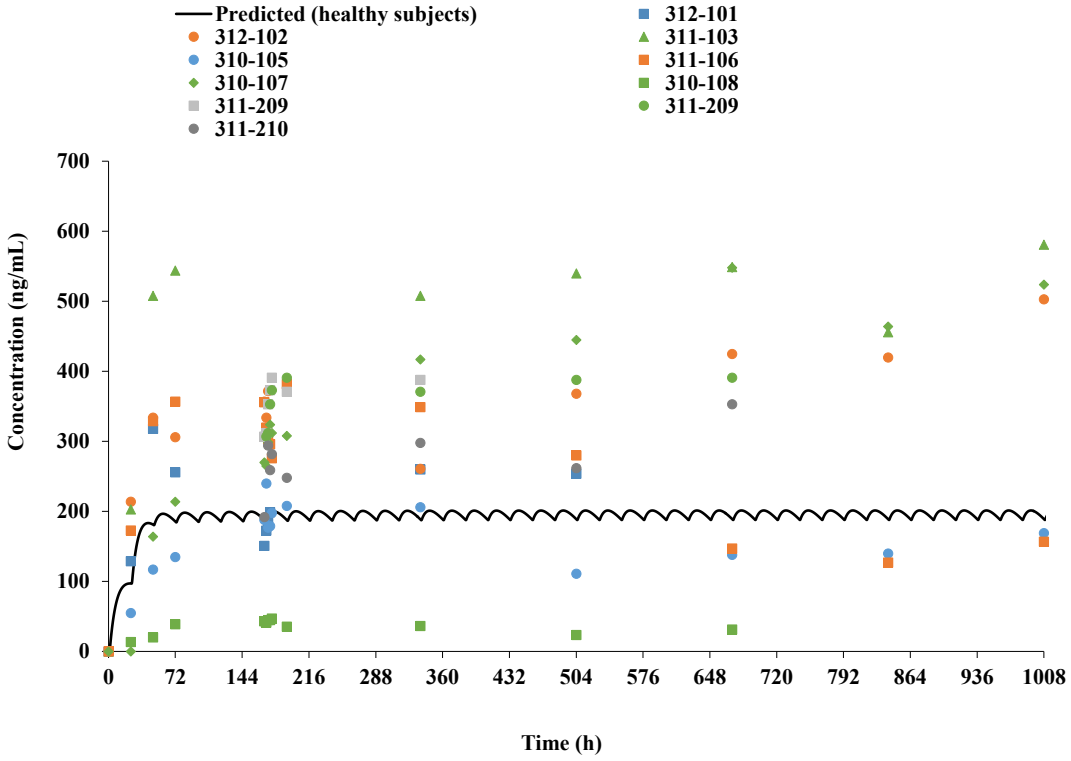
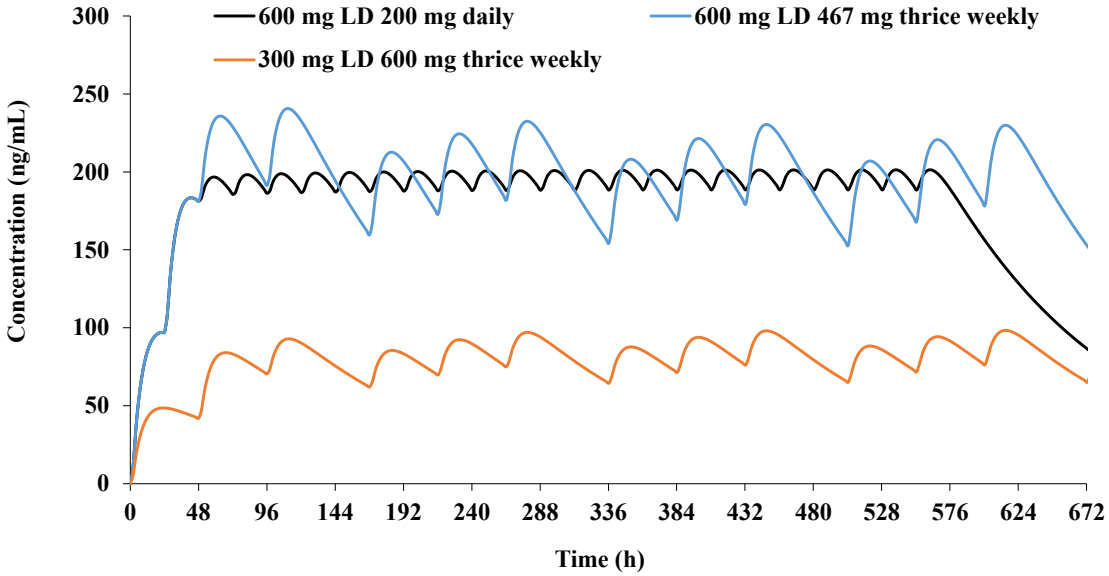


Figure 2B. Predicted plasma profile of bemcentinib after oral administration of 200 mg daily, 467 mg thrice weekly or 600 mg thrice weekly



Administration of bemcentinib three times per week is expected to achieve a similar weekly steady state as a 7 days per week daily dosing. As shown in Figure 2B, administration of 467 mg bemcentinib three times per week (a total of 1400 mg a week) should achieve a similar steady as 200 mg bemcentinib daily administration (a total of 1400 mg a week). Therefore, administration of 100 mg bemcentinib thrice weekly (300 mg a week) is expected to achieve a similar steady state as administration of 43 mg bemcentinib daily (300 mg a week).

2.5.3 Study Design

This is a multi-center, open-label Phase I study on bemcentinib in combination with docetaxel in advanced NSCLC. The study will be conducted at up to 2 clinical sites in the US.

The study is designed to determine the maximum dose of bemcentinib that can be safely administered in combination with docetaxel. It is anticipated that a minimum of two bemcentinib dose levels will be evaluated, with up to approximately 12 patients enrolled (6 per cohort if expansion required) in the dose-escalation phase. Including an expansion cohort, a maximum of 30 patients will be enrolled on this trial. In the absence of unacceptable toxicity, patients will be allowed to continue receiving bemcentinib in combination with docetaxel until disease progression.

The starting dose of docetaxel will be 75 mg/m^2 given IV every 21 days, with dose de-escalation to 60 mg/m^2 IV q21 days if the starting dose exceeds the MTD. The dose of bemcentinib will be escalated in a standard 3+3 fashion until an MTD or the RP2D is reached. At the recommended phase 2 dose (RP2D), an additional 18-24 patients will be enrolled in an expansion cohort, for a total accrual of 30 patients.

3.0 Due to the occurrence of high-grade neutropenia during early cycles of combination docetaxel + bemcentinib, this protocol was modified to require myeloid growth factor

administration starting with Cycle 1. Specifically, treatment-emergent neutropenia during Cycle 1 led to myeloid growth factor use starting in Cycle 2 for nine of 19 patients. Although the degree of observed neutropenia did not necessarily constitue a dose limiting toxicity, it became apparent that serial administration of this regimen would not be practical. In modifying the protocol, it was also recognized that some patients may not tolerate or require ongoing myeloid growth factors over time, either because they are less susceptible to cytopenias or undergo treatment dose reductions for non-hematologic reasons. Accordingly, allowance has been made for discontinuation of growth factors with subsequent treatment cycles. DRUG INFORMATION

After registration, all eligible patients will receive the combination regimen of bemcentinib and docetaxel as described in the study design.

3.1 Bemcentinib

3.1.1 Shipping, Storage, and Handling of Pharmaceutical Form

Accountability for study treatment bemcentinib is the responsibility of the Investigator. The Investigator/designee must ensure that bemcentinib will be dispensed to patients in accordance with the protocol and that any unused bemcentinib will be disposed of or returned in accordance with written instructions from the IMP supplier.

Study staff should refer to the Directions for Handling and Administration document for specific instructions regarding the handling, storage, dispensing and destruction, if applicable, of bemcentinib.

Bemcentinib has been manufactured in accordance with appropriate Good Manufacturing Practice (GMP) standards. Bemcentinib will be labeled in compliance with GMP Annex 13 requirements, FDA requirements and local regulatory guidelines.

Bemcentinib will be supplied in size zero Swedish orange hydroxypropyl methylcellulose (HPMC) capsules at a dose strength of 100 mg for oral dosing. Please refer to Section 4 of the current version of the Investigator's Brochure for additional information on the physical, chemical and pharmaceutical properties of bemcentinib.

Bemcentinib will be shipped to the site and must be stored at the site in a secure location under ambient temperature conditions.

3.1.2 Bemcentinib administration

Bemcentinib will be administered on an empty stomach first thing in the morning with water and at least 1 hour before or 2 hours after food at approximately the same time on each dosing day, other than on the morning of study visit days when bemcentinib should be administered during the visit. Patients should record dosing in the dosing diary provided. Bemcentinib should be administered before docetaxel administration (where applicable). In dose de-escalation cohort -2 or certain dose reductions, bemcentinib will be administered three times weekly.

3.1.3 Bemcentinib Accountability

The investigator/designee must maintain complete and accurate accountability records for bemcentinib, showing the date of receipt and quantity of all supplies of investigational product. These records must include accurate patient-specific dispensing information, including quantity of capsules and/or bottles dispensed, date dispensed and quantity and date returned (or disposed of).

At the end of the study, reconciliation must be made between the amount of bemcentinib supplied, dispensed and subsequently returned to the sponsor or destroyed at site, with reconciliation of any discrepancies.

Destruction of bemcentinib at site may be performed only by authorized personnel following written receipt of approval from the sponsor. The procedure should be fully documented as outlined in the Directions for Handling and Administration document.

3.2 Docetaxel

Commercially available docetaxel will be used for this study. It will be supplied in accordance with applicable local laws and regulations.

Docetaxel 75 mg/m^2 will be administered as a 1-hour IV infusion. In dose de-escalation cohorts, docetaxel 60 mg/m^2 will be administered as a 1-hour IV infusion. The amount of docetaxel administered will be determined on Day 1 of each cycle, or per institutional guidelines, by calculating the patient's BSA. When calculating the dose of docetaxel, rounding the BSA according to institutional practice is permitted. The dose of docetaxel may be capped at the dose corresponding to a BSA of 2 m^2 if necessary to comply with institutional practices. Premedication for docetaxel will follow the local institutional standard of care guidelines.

3.2.1 Storage and Handling of Docetaxel

See product information for complete information including storage and handling precautions.

3.2.2 Docetaxel Administration Information

See product information for complete information including preparation and administration instructions.3.4 Concomitant Medications

All prescription, non-prescription, or over-the-counter medications, including herbal remedies, taken by the patient at entry and during the study must be clearly documented in the CRF.

The patients must be instructed that no additional medication will be allowed without the prior consent of the Investigator.

Concurrent treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index is an exclusion criterion for the study.

Concurrent treatment with any agent known to cause Torsade de Points is an exclusion criterion for the study and is prohibited while receiving study therapy. A comprehensive list of these prohibited medications is provided in Appendix J.

In general, concomitant medications to control side effects of therapy may be given during treatment, with specific guidelines described in the sections below.

3.2.3 Prior Treatment

All prior treatments received within 14 days prior to enrollment will be recorded on the eCRF, including the name of the drug, route, indication, start date, and stop date (if applicable). Prior therapy for the treatment of NSCLC will also be recorded on the eCRF.

3.2.4 Birth Control

The effects of bemcentinib on conception, and the unborn fetus, are not known. Female patients having any chance of becoming pregnant must either abstain from sexual intercourse or use 2 methods of birth control. This must include at least 1 highly active method such as the intrauterine device (IUD), hormonal birth control pills/injections/implants, tubal ligation or partner's vasectomy, and one additional effective method such as latex condoms, diaphragm, or cervical cap, prior to, during, and for 3 months after, completion of study drug treatment. Men must use a latex condom every time they have sexual intercourse during therapy and for 4 weeks after discontinuing bemcentinib, even if they had a successful vasectomy.

3.2.5 Supportive Care

Supportive care can be prescribed as medically appropriate, including but not limited to:

- Erythropoietin or other specific RBC growth factors; RBC transfusions.
- Bone marrow colony stimulating factors. NOTE: due to the occurrence of neutropenia considered dose-limiting or complicating the feasibility of long-term treatment administration in earlier cohorts, starting with subjects enrolled on protocol Version 5.0 or later, patients receiving docetaxel 75 mg/m^2 and/or bemcentinib maintenance dose of 200 mg daily must receive myeloid growth factors (eg, G-CSF, preferably pegylated G-CSF) starting with cycle 1. In certain cases, myeloid growth factors may be omitted from subsequent treatment cycles. Examples include intolerance of myeloid growth factors, dose-reduction of docetaxel, or suspicion [based on available laboratory and clinical data] that patient would tolerate treatment and not develop severe neutropenia if myeloid growth factors were omitted.
- Platelet transfusions
- Steroids (inhaled, topical, or for physiologic replacement, or for short term treatment of conditions such as allergic reactions and asthma flares, or for appetite stimulation). A standard 3-5 day course of dexamethasone following the institutions standard of care for the prevention of chemotherapy-induced nausea and vomiting is allowed.
- Bone-modifying agents, eg, bisphosphonates or denosumab, to reduce the number and frequency of skeletal-related complications of bone metastases,.
- Other concomitant medications may be given as clinically indicated. Please consult with the medical monitor.
- Appropriate analgesics, antibiotics, blood products, anti-emetics (see ondansetron contraindication in Appendix J), fluids, electrolytes and general supportive care are to be used as necessary
- Palliative radiation therapy is permitted on study. bemcentinib should be withheld the day before, during, and day after radiation. Docetaxel should not be administered during palliative radiation therapy.

3.2.6 Treatment Beyond Progression

In some instances, a patient may be deemed to be receiving benefit from study therapy despite RECIST progressive disease. In these cases, study treatment may be continued if the following criteria are met:

- No ongoing intolerable treatment-related AEs
- Patient informed of available treatment options

- Case discussed with and decision to treat beyond progression approved by Study Chair

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion criteria

A patient is eligible for the study if the following criteria are met:

1. Provision of written informed consent to participate in this investigational study
2. Histologically or cytologically confirmed advanced (stage 4, according to the American Joint Committee on Cancer [AJCC] Staging manual) NSCLC
3. Up to three previous lines of therapy for advanced NSCLC, of which one must have been a platinum-based doublet therapy and no more than two were cytotoxic chemotherapy.
4. Radiographic disease recurrence or progression during or after the last line of chemotherapy
5. Patients with known activating *EGFR* mutations or *ALK* rearrangements should have progressed after appropriate targeted treatment in addition to progressing during or after platinum-based doublet chemotherapy
6. European Cooperative Oncology Group (ECOG) performance status 0 or 1
7. Age 18 years or older
8. Measurable or evaluable disease according to RECIST v1.1
9. Previously treated brain metastases (surgery and/or radiation therapy) are eligible, provided that patients are asymptomatic and not requiring corticosteroids
10. The following minimum intervals are required between prior treatment and initiation of study therapy:
    Cytotoxic chemotherapy: 3 weeks
    Molecularly targeted therapy or immunotherapy: 2 weeks
    Conventional fractionated radiation therapy: 2 weeks
    Stereotactic radiation therapy: 1 week
    Major surgery: 3 weeks
11. Adequate hematologic function (absolute neutrophil count [ANC] ≥ 1500 cells/μL; hemoglobin ≥ 9 g/dL; platelets ≥ 100,000/μL
12. Adequate renal function (serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault equation)
13. Adequate hepatic function: total bilirubin ≤ upper limit of normal [ULN], alanine aminotransferase [ALT] ≤ 1.5 x ULN, aspartate aminotransferase [AST] ≤ 1.5 x ULN). ALT and AST ≤ 5x ULN if documented liver metastases
14. Previous treatment-associated toxicities resolved to CTCAE grade ≤2 (except alopecia) or to their baseline. NOTE: Prior immunotherapy-related endocrinopathy controlled with ongoing medical management (eg, hypothyroidism, adrenal insufficiency, diabetes) is permitted.

15. Adequate archival tissue (10-15 slides, or 5 slides with 3 sections per slide) for biomarker analysis. If an otherwise eligible candidate does not have adequate archival tissue, enrollment will be considered on a case-by-case after discussion with Study Chair.
16. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to taking their first dose of bemcentinib. Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception (such as hormonal implants, combined oral contraceptives, injectable contraceptives, intrauterine device with hormone spirals, total sexual abstinence, vasectomy) throughout the study and for ≥3 months after the last dose of bemcentinib. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility, including tubal ligation, or evidence of post-menopausal status defined as any of the following:
    - Natural menopause with last menses >1 year ago
    - Radiation induced oophorectomy with last menses >1 year ago
    - Chemotherapy induced menopause with last menses >1 year ago

4.2 Exclusion Criteria

A patient is excluded from the study if any of the following criteria are met:

1. Pregnant or lactating
2. Abnormal left ventricular ejection fraction on echocardiography (less than the lower limit of normal for a patient of that age at the treating institution or <45%)
3. History of an ischemic cardiac event including myocardial infarction within 3 months of study entry
4. Peripheral neuropathy NCI CTCAE ≥Grade 2 at baseline
5. Pulmonary hemorrhage or hemoptysis > 2.5 mL blood within 6 weeks (or within 2 weeks if source definitively treated [eg, radiation therapy or bronchoscopic procedure])
6. Congestive cardiac failure of >Grade 2 severity according to the NYHA defined as symptomatic at less than ordinary levels of activity
7. Unstable cardiac disease, including unstable angina or unstable hypertension, as defined by the need for change in medication for lack of disease control within the last three months
8. History or presence of sustained bradycardia (less than or equal to 60 BPM) or history of symptomatic bradycardia, left bundle branch block, cardiac pacemaker or significant atrial tachyarrythmias, as defined by the need for treatment
9. Previous treatment with docetaxel or an Axl inhibitor
10. Current treatment with agents that may prolong QT interval and may cause Torsade de Points which cannot be discontinued at least five half-lives prior to treatment. Please see Appendix J for list of relevant medications
11. Known family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy
12. Previous history of Grade 3 or worse drug-induced QTc prolongation requiring treatment withdrawal
13. Screening 12-lead ECG with a measurable QTc interval according to Fridericia's correction >450 ms

14. Ongoing infection requiring systemic treatment
15. Inability to tolerate oral medication
16. Impaired coagulation as evidenced by:
    - INR >1.5 times ULN, or
    - aPTT > 1.5 times ULN

    NOTE: a therapeutic PT and/or INR is acceptable if the patient is on a relevant anticoagulant such as warfarin
17. Clinically active existing gastrointestinal disease affecting drug absorption, such as celiac disease or Crohn's disease
18. Previous bowel resection anticipated to affect drug absorption
19. Any evidence of severe or uncontrolled systemic conditions (e.g., severe hepatic impairment) or current unstable or uncompensated respiratory or cardiac conditions which makes it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol
20. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index
21. Active, uncontrolled central nervous system (CNS) disease
22. Known active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses (screening not required)
23. Major surgery within 28 days prior to the start of bemcentinib, excluding skin biopsies and procedures for insertion of central venous access devices

5.0 PATIENT REGISTRATION

This is a study of the South Plains Oncology Consortium (SPOC). Registration and assignment to the dose level will be done centrally at data coordinating center (DCC) at Texas Tech University Health Sciences Center, Lubbock (see Appendix A).

5.1 Informed Consent

Informed Consent must be obtained before the patient is registered. The FDA requires that both the signature and the date be in the handwriting of the subject or the subject's legally authorized representative, that the date be the actual date on which the form is signed, and that the informed consent process be documented in the physician's progress notes or the nurse's notes.

5.2 Patient Registration

Registration will be done centrally at the South Plains Oncology Consortium (SPOC). To register a patient, the research nurse or data manager (at the treating institution) must complete the eligibility form and the registration form and give (or FAX) copies to the SPOC Consortium Manager at 806-743-2691. The research nurse or data manager will call the SPOC Consortium Manager at 806-743-2690 and after verifying the eligibility, the SPOC Consortium Manager will assign a study number, assign a dose, and register the patient onto the study (see Appendix A: Registration Procedures for Phase I Trials).

5.3 Protocol Waivers and Treatment Deviations

Protocol waivers and/or treatment deviations are generally not allowed. However, should the need arise to amend the protocol in order for the protocol document to more accurately reflect the initial intent of the investigator(s), then the treating physician must contact the PI who originated the protocol for the Consortium to obtain approval. If approved, the Consortium protocol PI must immediately submit an

amendment to the protocol. A backup for the originating PI has been designated and is specified in the registration worksheet.

6.0 STUDY DESIGN AND RULES FOR DOSE ESCALATION/DE-ESCALATION

Rules for dose escalation, de-escalation, dose expansion, and termination of escalation are given below.

Patient enrollment, adverse events relevant to dose escalation, and toxicity follow-up will be recorded in a Phase 1 tracking log in addition to case report forms. This log will be consulted prior to enrolling each cohort of new patients, to verify that the criteria for dose escalation have been met. The Phase 1 Tracking log is maintained at the Data Coordinating Center (DCC), and is kept current on a weekly basis.

Toxicity will be assessed and reported on all patients who begin to receive treatment. Patients who do not complete the first cycle (for any reason other than toxicity or tolerability of the regimen) and who do not experience toxicity will not be counted as having successfully completed one cycle and will be considered unevaluable for toxicity. All patients who are not evaluable for toxicity will be replaced.

A standard 3 + 3 design will be used; the usual rules for dose escalation, expansion, and de-escalation will apply based on patients who are "evaluable for toxicity." Dose escalation decisions will be based on toxicities observed during cycle 1 (7-day lead-in plus 21-day combination period) of treatment.

For all patients receiving more than one cycle of therapy, toxicities will continue to be monitored and recorded; for all patients who are classified as not "evaluable for toxicity," all toxicities will be monitored and recorded.

6.1 Dose Limiting Toxicity (DLT)

DLT will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03 (See Appendix B) during the first cycle of treatment (7-day lead-in plus 21 days of combination therapy) for the purposes of establishing the MTD and RP2D of bemcentinib in combination with the standard dose of docetaxel. DLTs will include:

- Grade 3 or 4 nausea, vomiting, or diarrhea that persists despite maximum prophylactic and supportive care
- Any other Grade 3 or 4 non-hematological toxicity that is considered to be clinically significant and causally related to bemcentinib or the combination of docetaxel + bemcentinib
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia persisting for seven days or more (despite myeloid growth factors)
- Treatment discontinuation or dose reduction for more than 72 hours during the first cycle as a result of treatment-related toxicity

To be evaluable for dose limiting toxicity, a patient must have received at least one dose of bemcentinib. To be considered not to have experienced DLT, a patient must complete one 21-day cycle of treatment before a dose-escalation evaluation is made. To be considered as informative to support dose escalation of the loading dose (Days -7, -6, and -5), a patient must receive three loading doses. To be considered as informative to support dose escalation of the daily dose, a patient must miss no more than 3 daily doses (including the lead-in period). Patients who are not evaluable for toxicity will be replaced.

Although all toxicities at each course will be recorded, only DLTs thought possibly, probably, or definitely attributable to bemcentinib and docetaxel during the first treatment cycle will be used in the decision to dose escalate, expand, or de-escalate.

Treatment will be discontinued if a patient experiences a DLT which does not resolve to ≤ Grade 1 or baseline (if higher) prior to the next cycle, or which, in the opinion of the physician, is likely to recur on subsequent treatment.

6.2 Maximum Tolerated Dose (MTD)

The maximum tolerated dose (MTD) is defined as the highest dose tested in which none or only one patient experienced DLT attributable to the study protocol, when at least six patients were treated at that dose level and are evaluable for toxicity. The MTD is one dose level below the lowest dose tested in which 2 or more patients experienced DLT attributable to the study protocol. At least 6 patients will be treated at the MTD.

Once the MTD has been established (and presumably this will be the dose selected for further phase 2 testing—ie, recommended phase 2 dose [RP2D]), up to an additional 12 patients will be treated at that dose level. The experience of patients treated in this expansion cohort will be used to (a) better estimate the true proportion of patients who cannot complete the first cycle of therapy at the MTD, (b) obtain additional preliminary activity data (c) obtain additional pharmacokinetic data, and (d) obtain additional pharmacodynamic data.

6.3 Dose Escalation/De-Escalation Schedule

The docetaxel dose will be fixed at the standard intravenous dose of 75 mg/m^2 every 21 days, or 60 mg/m^2 every 21 days if de-escalation or dose reduction occurs.

The dose levels of bemcentinib are presented in Table 5; in each dose level, a loading dose of bemcentinib will be administered during the first three days of the run-in period prior to Cycle 1 (Days -7, -6, and -5), followed by a lower daily maintenance dose during the remainder of the run-in period and throughout continuous 21-day treatment cycles. At least three evaluable patients will be entered per cohort in a standard 3+3 study design as described below. A minimum of 6 patients will be treated at the MTD or RP2D.

Table 5.
Bemcentinib-Docetaxel Dose Cohorts

	Bemcentinib dose (mg)			Docetaxel dose (mg/m^2 IV on Day 1 of each cycle)
	Cycle 1 Days -7, -6, and -5	Cycle 1 Days -4 to 21	Cycles ≥ 2 All days	
Cohort -1[a, b]	200* daily	100 daily	100 daily	60
Cohort 1	200* daily	100 daily	100 daily	75
Cohort 2	400* daily	200 daily	200 daily	75

Cohort 2A[a]	400* daily	200 daily	200 daily	60

NOTE: Cohort -1 (and potentially Cohort -2) will be enrolled only if Cohort 1 dosing exceeds the maximum tolerated dose.

a. If Cohort -1 is enrolled without exceeding the MTD, bemcentinib may be dose escalated to 400 mg daily on Days -7, -6, and -5, then 200 mg daily on subsequent days (Cohort 2A).

b. If Cohort -1 or Cohort 2A is enrolled without exceeding the MTD, a subsequent cohort with docetaxel dose re-escalated to 75 mg/m^2 every 21 days with concurrent myeloid growth factor support every cycle will be enrolled.

*If dose-limiting toxicity (DLT) is experienced during or attributed to (ie, occurs shortly after) the 3-day loading period, dose de-escalation will occur as follows without adjustment of daily maintenance dose:

Level 1: loading dose x 3 days
Level -1: loading dose x 2 days
Level -2: loading dose x 1 day
Level -3: no loading dose; initiate treatment with standard daily dose

This is a single-arm phase 1 clinical trial. Dose escalation will be according to a standard 3+3 schema with a planned expansion cohort of up to 12 additional patients at the recommended phase 2 dose (RP2D). At least 1 week must elapse between initiation of study therapy for patients within a dose cohort. At least 3 weeks must elapse after the treatment of the last patient on the previous dose level before initiation of study therapy for the first patient on a new dose level.

Initially three patients will be recruited into Cohort 1 and must complete one 21-day cycle of treatment before a dose-escalation evaluation is made. A patient must receive all three days of the loading dose and miss no more than 3 daily doses in Cycle 1 in order to be considered as informative to support dose escalation.

The decision to dose escalate (or not) will be made by the SPOC Safety Monitoring Committee (SMC). Minutes of the SMC meeting will be recorded and circulated for final approval before being placed in the Trial Master File (TMF). The decision to dose escalate will be based on the safety and tolerability of bemcentinib observed in the first cycle of treatment.

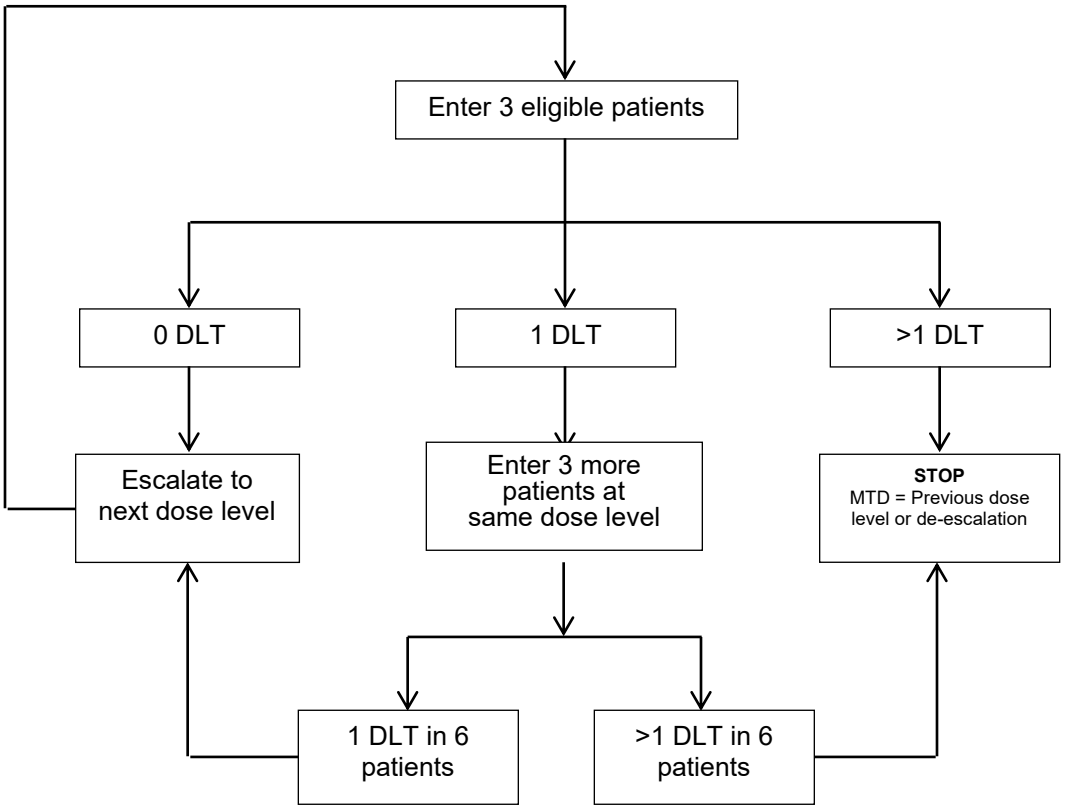
Three patients will be treated at each dose level unless DLT criteria are exceeded. If 0/3 patients experience DLT attributable to the study protocol, 3 patients will be treated at the next higher dose cohort.

If one patient in a cohort experiences a DLT during Cycle 1, the cohort will be expanded to six patients. If two of three or two of six patients in a cohort experience DLT, no further dose-escalation will take place and the next lower dose cohort will be explored, according to the Table 6. The maximum dose at which no more than one out of three or one out of six patient experienced DLT, will be nominated as the MTD. A recommended dose for Phase II (RP2D) will be established; the RP2D may be lower than the MTD but will not be higher than the MTD. A minimum of 6 patients will be treated at the RP2D.

NOTE: DLTs experienced during or attributed to (ie, occurs shortly after) the 3-day loading period will be interpreted and responded to independently of DLTs occurring during daily maintenance dosing. Separate dose de-escalation levels will be applied (see Table 8A).

If a patient withdraws or is withdrawn for reasons other than DLT prior to completing Cycle 1, the patient will be replaced for the purposes of evaluation of MTD. The operating characteristics of the 3+3 dose escalation process are summarized in Figure 3.

Figure 3. Operating Characteristics of the 3+3 Dose Escalation Process



7.0 STUDY PROCEDURES

Eligible patients will visit the study site to receive study treatment and protocol-specified procedures according to the relevant Schedule of Events table in Table 6. The treatment period will consist of continuous 21-day treatment cycles.

Patients will attend the clinic once per week during Cycle 1 and then once per cycle thereafter. All patients will continue to receive docetaxel and bemcentinib for as long as, in the opinion of the Investigator, they continue to derive clinical benefit or until unacceptable toxicity, clinically significant disease progression, death or withdrawal of consent. NOTE: treatment beyond formal progression may be considered for patients if (1) the treating investigator feels they are deriving clinical benefit; (2) the patient is not experiencing substantial treatment-related toxicity; (3) the case is reviewed with and approved by the Study Chair.

Table 6. Schedule of Events

Cycle		**1**										**≥2**			**End-of-Study[r]**
		Week -1				**Week 1**		**Week 2**		**Week 3**		**≥ 4 Weeks**			**28 days after last dose**
Cycle Day	**-28 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2-7**	**8**	**9-14**	**15**	**16 - 21**	**1**	**2 - 20**	**21**	
Visit window days		0	0	0	0	+2		± 2	0	±2	0	+2	0	-5/+2	+7
Informed consent	X														
Demographics	X														
Medical history	X														
Inclusion/Exclusion	X														
Performance status	X											X			X
Physical examination[a]	X[a]	X				X		X		X		X			X[a]
Vital signs[b]	X	X	X	X		X		X		X		X			X
12-Lead ECG[c]	X		X	X	X	X		X		X		X			X
Serum pregnancy test[d]	X	X[e]													
Clinical chemistry[f]	X	X[e]	X			X		X		X		X			X

Cycle		**1**										**≥2**			**End-of-Study[r]**
		Week -1				**Week 1**		**Week 2**		**Week 3**		**≥ 4 Weeks**			**28 days after last dose**
Cycle Day	**-28 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2-7**	**8**	**9-14**	**15**	**16 - 21**	**1**	**2 - 20**	**21**	
Hematology[g]	X	X[e]	X			X		X		X		X			X
Coagulation[h]	X	X[e]						X		X		X			X
Urinalysis[i]	X	X[e]						X		X		X			X
Echocardiogram or MUGA scan	X											X[j]			
PK blood sampling[k]			X	X		X	X					X			
Tissue collection for PD[l]	X					X				X[l]				X[q]	X[q]
Blood collection for mRNA isolation, PBMC isolation and PD[m]		X				X								X[q]	X[q]
Disease assessment[n]	X													X	X[o]
Bemcentinib administration[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Docetaxel administration						X						X			
Drug accountability						X		X		X		X			X

Cycle		**1**										**≥2**			**End-of-Study[r]**
		Week -1				**Week 1**		**Week 2**		**Week 3**		**≥ 4 Weeks**			**28 days after last dose**
Cycle Day	**-28 to -8**	**-7**	**-6**	**-5**	**-4**	**1**	**2-7**	**8**	**9-14**	**15**	**16 - 21**	**1**	**2 - 20**	**21**	
Adverse events	X	X ---------- X													
Concomitant medications		X---------- X													

a. Physical examination conducted at the Screening and End-of-Study visits. A symptom-directed examination will be conducted at other visits

b. Blood pressure, pulse, respiratory rate, temperature

c. Triplicate 12-lead ECG, 5 minutes apart, after resting for ≥10 minutes in supine position during screening and during each visit (pre-dose). On Cycle 1 an additional triplicate ECG will be conducted pre-dose on Day-5 and Day -4. Patients who re-start bemcentinib following interruption for QTc prolongation should also have ECGs performed according to this schedule , QT interval correction will be performed using the Friderica formula

d. For women of child-bearing potential only

e. Unless conducted as part of the screening procedures within 3 days prior to Day -7

f. Clinical chemistry laboratory parameters uric acid, electrolytes, blood urea nitrogen (BUN), total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, creatinine phosphokinase, alkaline phosphatase, albumin, calcium, phosphorus, glucose, magnesium and amylase and lipase (during Screening ONLY)

Efforts should be made to maintain the patient's serum potassium levels at >4 mmol/L during treatment with bemcentinib and for 2 weeks following completion of therapy. Serum calcium and magnesium should be measured and reasonable efforts made to maintain at normal levels throughout treatment.

g. Hematology laboratory parameters (full blood count including differential white cell count, haemoglobin, hematocrit and platelets)

h. Coagulation parameters: prothrombin time (PT) and/or INR, activated partial thromboplastin time (aPPT)

i. Dipstick measurement of blood, nitrite, glucose, ketones, leukocytes, protein, and pH. (Microscopic analysis is not required unless clinically indicated)

j. Cycle 4 Day 1 ONLY

k. PK samples will be collected only on the first 15 enrolled subjects. Blood sampling for the determination of bemcentinib and/or docetaxel in plasma will be conducted at the following time-points. Detailed procedures for the collection, processing, storage and shipment of samples will be provided in the Study Laboratory Manual.

Bemcentinib = All time points are pre-dose (C1D-6, C1D-5, C1D1, C1D2, C2D1, C4D1)

Docetaxel = C1D1 (0.5, 1, 2, 4, 6, 8 hrs, +/- 20 minutes.), C1D2 (pre-dose), C1D3 (Pre-dose). See Appendix E

l. After consenting patients, optional tissue specimens may be collected for analysis of pharmacodynamic endpoints of bemcentinib. The baseline tissue specimen should be collected after enrollment within 28 days prior to first dose of study drug. The on-treatment tissue collection should be performed during Cycle 1 or Cycle 2 (any time after 14 days of continuous exposure to bemcentinib and initiation of docetaxel). The tissue collection and blood collection should be performed on the same day. Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the Study Laboratory Manual

m. Blood samples will be collected for isolation of PBMC, isolation of mRNA from whole blood sample and for the investigation of other pharmacodynamic effects of bemcentinib. The baseline sample should be collected on Cycle 1, Day -7 prior to administration of the first dose of bemcentinib, then again on Day 1 of Cycles 1 and 2 prior to infusion of docetaxel and finally at the time of disease progression or End of Study visit, whichever comes first. Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the Study Laboratory Manual

n. Disease assessment via RECIST v1.1 will be performed at the end of even-numbered cycles beginning with Cycle 2 (Day 21); the assessment may be performed up to 5 days before Day 21 (Day 17 - Day 21) but attempts should be made to conduct the assessment as close to Day 21 as possible. Disease assessment may be performed prior to initiation of the next cycle, but results must be available prior to initiation of treatment and must confirm continued eligibility for next cycle)

o. If not performed within previous 28 days

p. Bemcentinib will be administered on an empty stomach first thing in the morning with water and at least 1 hour before or 2 hours after food at approximately the same time on each dosing day, other than on the morning of study visit days when bemcentinib should be administered during the visit. Patients should record dosing in the dosing diary provided. Bemcentinib should be administered before docetaxel administration (where applicable). In dose de-escalation cohort -2 or certain dose reductions, bemcentinib will be administered three times weekly.

q. The Time of progression tissue collection for PD (in consenting patients only), blood collection for PD should be performed any time after documentation of clinical/radiographic disease progression and no later than the End-of-Study visit (the tissue specimen should be derived from a lesion exhibiting clinical/radiographic progression).

r. Survival information will be collected by phone, follow-up visit, or medical records approximately every 4 months from date of final tumor assessment until patient's death, until patient is lost to follow up, or until study closure.

7.1 Assessment Schedule During Screening Visit

All patients must sign and date an IRB-approved informed consent document prior to completing any screening assessments. However, evaluations performed before the consent as standard of care for NSCLC can be used for screening assessments as long as they meet the protocol timelines.

Eligibility criteria are evaluated within 28 days prior to enrollment, with confirmation that the patient continues to meet eligibility criteria pre-dose on Cycle 1 Day -7.

All screening evaluations must be completed prior to initiating treatment with the study medication. A maximum of 4 weeks will be allowed to complete screening assessments.

7.2 Screening Assessments to be Completed Within 28 days Prior to Enrollment:

During screening, the following procedures will be performed:

- Written informed consent
- Demographics
- Medical history
- Review of inclusion/exclusion criteria
- Performance status assessment
- Physical examination
- Vital signs
- Serial 12-lead ECGs, in triplicate (≤5 minutes apart), performed after the patient has been supine for ≥10 minutes)
- Serum pregnancy test, if applicable
- Clinical chemistry (including amylase and lipase), hematology, urinalysis, coagulation
- Echocardiogram or MUGA scan
- Tissue collection for PD (consenting patients only)
- Disease assessment, including radiologic assessment as below

Male patients and female patients of reproductive potential must agree to practice highly effective methods of contraception throughout the study and for ≥3 months after the last dose of bemcentinib. Highly effective methods of contraception are defined as:

- Hormonal implants, combined oral contraceptives, injectable contraceptives
- An intrauterine device with hormone spirals
- Tubal ligation
- True total sexual abstinence
- Vasectomy

If it is not possible to use one of these highly effective methods of contraception, two barrier methods used simultaneously are acceptable.

7.2.1 Radiologic Assessments at screening

The following radiologic assessment will be performed within 4 weeks prior to randomization:

- CT/MRI scans of the chest and upper abdomen.
- Brain imaging will be performed only if clinically indicated (headache, focal neurological findings) or if known history of treated brain metastases.
- For patients with baseline abnormalities on brain MRI, these studies will be repeated every 4 cycles (ie, every 12 weeks)

7.3 Study Assessments

7.3.1 Assessments Before Initiation of Treatment on Cycle 1 Day -7

The following laboratory assessments will be performed:

- Hematology and clinical chemistry. If any laboratory values no longer meet eligibility criteria, initiation of Cycle 1 Day -7 treatment should be delayed for 2 to 3 days and laboratory tests should be repeated.
- Serum pregnancy test prior to treatment on Cycle 1 Day -7 for patients of childbearing potential. A negative test is required before the patient may receive study drug.
- Serial 12-lead ECGs, in triplicate per screening procedures

  NOTE: Screening lab tests and procedures may substitute for those on Cycle 1 Day -7 if performed within 3 days of Cycle 1 Day -7.

7.3.2 Safety Assessments During the Treatment Period

NOTE: In dose de-escalation cohort -2 (and after dose reduction in other cohorts), bemcentinib will be administered three times weekly, so administration may not fall precisely on the days indicated below.

NOTE: PK samples will be collected only from the first 15 enrolled subjects.

<u>Cycle 1 (bemcentinib lead-in)</u>

Day -7

- Symptom-directed physical examination
- Vital signs
- Serum pregnancy test (unless conducted as part of Screening procedures within 3 days prior to Day -7) (Day -7 only)
- Clinical chemistry (does not have to be repeated if conducted as part of Screening procedures within 3 days prior to Day -7)
- Hematology, coagulation, urinalysis (unless conducted as part of Screening procedures within 3 days prior to Day -7)
- Blood collection for PD
- Blood collection for mRNA isolation from whole blood
- Blood collection for PBMC isolation from whole blood
- Bemcentinib administration

- Adverse events assessment
- Concomitant medications assessment

Day -6

- Vital signs
- Clinical chemistry
- Hematology

- Blood sampling for PK for bemcentinib (pre-dose)
- Bemcentinib administration

Day -5

- Vital signs
- Pre-dose serial 12-lead ECGs, in triplicate per screening procedures
- Blood sampling for PK for bemcentinib (pre-dose)
- Bemcentinib administration

Day -4

- Pre-dose serial 12-lead ECGs, in triplicate per screening procedures
- Bemcentinib administration

Cycle 1

Day 1

- Symptom-directed physical examination
- Vital signs
- Serial 12-lead ECGs, in triplicate per screening procedures
- Clinical chemistry
- Hematology,

Blood sampling for PK for bemcentinib (pre-dose); for docetaxel 0.5, 1, 2, 4, 6, 8 hrs (± 20 minutes)

- Blood collection for PD before docetaxel administration
- Blood collection for mRNA isolation from whole blood
- Blood collection for PBMC isolation from whole blood

- Docetaxel administration

- Bemcentinib administration

- Drug accountability
- Adverse events assessment
- Concomitant medications assessment

Day 2 (only if PK sampling planned)

- Blood sampling for PK for bemcentinib and docetaxel pre-dose
- Bemcentinib administration

Day 3 (only if PK sampling planned)

- Blood sampling for PK for docetaxel pre-dose (optional)
- Bemcentinib administration

Days 8 and 15

- Symptom-directed physical examination
- Vital signs
- Serial 12-lead ECGs, in triplicate per screening procedures
- Clinical chemistry
- Hematology, coagulation, urinalysis
- Bemcentinib administration
- Drug accountability
- Adverse events assessment
- Tissue collection for PD (in consenting patients, may be any time after 14 consecutive days of bemcentinib administration in Cycle 1 or 2)
- Concomitant medications assessment

<u>Cycle ≥2</u>

Day 1

- Performance status assessment
- Symptom-directed physical examination
- Vital signs
- Serial 12-lead ECGs, in triplicate per screening procedures
- Clinical chemistry, hematology, urinalysis, coagulation
- Blood sampling for PK for bemcentinib (pre-dose)
- Tissue collection for PD (in consenting patients if not performed in Cycle 1)
- Blood collection for PD before docetaxel administration
- Blood collection for mRNA isolation from whole blood
- Blood collection for PBMC isolation from whole blood
- Docetaxel administration

- Bemcentinib administration
- Drug accountability
- Adverse events assessment
- Concomitant medications assessment
- Disease assessment (by RECIST 1.1; may be performed at any point Days 16-21; even-numbered cycles only
- Echocardiogram or MUGA scan (Cycle 4 only)

Disease progression

- Tissue collection for PD from a lesion demonstrating progression (in consenting patients, any time after the documentation of disease progression and no later than the End-of-Study visit)
- Blood collection for PD (any time after the documentation of disease progression and no later than the End-of-Study visit, and at the same time as PD tissue collection in consenting patients)

End-of-Study Visit

The following assessments will be carried out for every patient enrolled into the study 28 days after the last dose of study medication or at study withdrawal.

- Performance status assessment
- Physical examination
- Vital signs
- Serial 12-lead ECGs, in triplicate per screening procedures
- Clinical chemistry, hematology, coagulation, urinalysis
- Tissue collection for PD from a lesion demonstrating progression (in consenting patients, if not already collected)
- Blood collection for PD (if not already collected at the time of disease progression)
- Blood collection for mRNA isolation from whole blood
- Blood collection for PBMC isolation from whole blood
- Drug accountability
- Adverse events assessment
- Concomitant medications assessment

7.3.3 Off-Therapy Evaluations

Survival information will be collected by phone, follow-up visit, or medical records approximately every 4 months from date of final tumor assessment until patient's death, until patient is lost to follow up, or until study closure.

7.3.4 Efficacy Assessments

7.3.4.1 Radiologic Assessments

- CT/MRI scans of the chest and upper abdomen will be performed every 2 cycles. The same imaging technique must be utilized throughout the study. Patients who stop study treatment for reasons other than disease progression should undergo imaging every 9 weeks until disease progression, death, or initiation of subsequent cancer therapy.
- Brain imaging will be repeated only when clinically indicated. If, during baseline brain MRI, it was determined that there were clinically significant abnormalities, brain MRI will be repeated every 4 cycles (ie, every 12 weeks)

7.3.4.2 Pharmacokinetic and Biomarker Assessments: Pharmacokinetic assessments will be performed in the first 15 enrolled patients*

- Bemcentinib PK time points (see Appendix E):
  - Cycle 1 Day -6: pre-dose
  - Cycle 1 Day-5: pre-dose
  - Cycle 1 Day 1: pre-dose
  - Cycle 1 Day 2: pre-dose
  - Cycle 2 Day 1: pre-dose
  - Cycle 4 Day 1: pre-dose
- Docetaxel PK time points:
  - Cycle 1 Day 1: post-dose 0.5, 1, 2, 4, 6, 8 hours (+/-20 minutes). Suggested draw time:
    - 0.5 (24-36 minutes post dose)
    - 1hr (48 - 1h 12 minutes post dose)
    - 2 hrs (1h 36 - 2h 24minutes post dose)
    - 4 hrs (3h 12 - 4h 48 minutes post dose)
    - 6 hrs (4hrs 48 - 7h 12 minutes post dose)
    - 8 hrs (6hrs 24 - 9h 36 post dose)
  - Cycle 1 Day 2: bemcentinib pre-dose
  - Cycle 1 Day 3: bemcentinib pre-dose (optional)

Plasma samples (one 3 ml ACD tube) will be taken at baseline (Cycle 1 Day -7), pre-infusion on Cycle 1 Day 1 and Cycle 2 Day 1, and at disease progression or End-of-Treatment visit, whichever is first.

2.5 ml of whole blood samples will be collected in PAXgene tubes for mRNA isolation and subsequent analysis of cytokines and cell surface markers by qPCR analysis, consistent with a change in immune

activation before and after drug treatment. Two tubes of 8.5 ml whole blood will be collected in ACD tubes for PBMC isolation to monitor immune cells.

Plasma samples will be used for biomarker analysis of potentially relevant biomarkers utilizing proteomic, transcriptomic, somatic mutation profiling, and assays for angiogenic and immunological markers.

7.4 Patient Withdrawal Criteria

7.4.1 Withdrawal from treatment

A patient may be withdrawn ***from <u>treatment</u>*** for any of the following reasons:

- Objective disease progression following radiological assessment as determined by the Investigator (per modified RECIST 1.1 criteria). <u>NOTE</u>: treatment beyond formal progression may be considered for patients if (1) the treating investigator feels they are deriving clinical benefit; (2) the patient is not experiencing substantial treatment-related toxicity; (3) the case is reviewed with and approved by the Study Chair.
- Clinical progression
- Adverse event (including intercurrent illness or unacceptable toxicity)
- Death
- Patient's request/to withdrawal consent from treatment

  NOTE: Because secondary endpoints of this study include overall and progression-free survival, patients should be encouraged to permit follow up for disease and survival status.
- Lost to follow up
- Other Investigator decision (with documentation of reason)
- Study termination or termination of treatment by Sponsor

7.4.2 Withdrawal from study

A patient may be withdrawn ***from the <u>study</u>*** for the following reasons:

- Patient's request/withdrawal of consent

  NOTE: Because secondary endpoints of this study include overall and progression-free survival, patients should be encouraged to permit follow up for disease and survival status.
- Lost to follow up
- Death
- Study termination by Sponsor

8.0 DOSING DELAYS/DOSE MODIFICATIONS

All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

In general, dose reductions and interruptions should be performed for the suspected causative agent. In instances where treatment-related toxicity cannot reasonably be assigned to a single agent, both BEMCENTINIB and docetaxel doses should be reduced. If one of the therapeutic agents is withheld or discontinued for toxicity, the other agent may be continued.

8.1 Bemcentinib

If a patient experiences drug-related toxicity which requires treatment with bemcentinib to be interrupted, a delay of up to 14 days is permitted to allow for resolution of toxicity. Toxicities must have resolved to ≤ Grade 1 or to baseline for treatment to recommence. For Grade 1 or Grade 2 (tolerable) toxicity, the patient may resume dosing at the same dose level. For ≥ Grade 2 (intolerable) toxicity, the patient may resume dosing at a dose level defined by the grade of the toxicity and the number of occurrence(s) of prior toxicity as outlined in Tables 7 and 8.

Table 7. Dose Modification of Maintenance Bemcentinib for Toxicity

Grade (CTCAE)	Recommended Dose Modification
Grade 1 and Grade 2 (tolerable)	
Any occurrence	Maintain dose if toxicity is tolerated by the patient and at the discretion of the investigator
Grade 2 (intolerable)	
1st or 2nd occurrence of same adverse event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2. Resume dosing at same dose
3rd occurrence of same adverse event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Dose reduce by 100 mg
4th occurrence of same adverse event	Discontinue permanently
Grade 3	
1st occurrence	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Dose reduce by 100 mg or Discontinue permanently if dose has already been reduced
2nd occurrence of same adverse event at G3	Discontinue permanently
Grade 4	
1st occurrence	Discontinue permanently

NOTES:

- If treatment-related toxicity has not resolved to Grade ≤1 or to baseline (with the exception of alopecia) within 14 days, discussion with and approval by Study Chair is required prior to restarting therapy.
- Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg bemcentinib).
- If bemcentinib dose has been decreased to 100 mg daily, it may be reescalated to starting dose of 200 mg daily following adequate recovery from toxicity per investigator discretion.

If one week or more elapses without administration of bemcentinib, the loading doses for the cohort to which the patient is assigned should be repeated when treatment is re-initiated.

In clinical study BGBC001, evidence of bemcentinib exposure-related QTcF prolongation was observed. In order to reduce the risk of QTcF prolongation, **efforts should be made to maintain the patient's serum potassium levels at >4 mmol/L during treatment with bemcentinib and for 2 weeks following completion of therapy. Serum calcium and magnesium should be measured and reasonable efforts made to maintain at normal levels throughout treatment.** Patients with a QTcF of ≥480 ms should be closely monitored until the QTcF falls below 480 ms; electrolytes should be measured and corrected as necessary.

Triplicate 12-lead ECG, 5 minutes apart, after resting for ≥10 minutes in supine position during screening and during each visit (pre-dose). On Cycle 1 an additional triplicate ECG will be conducted pre-dose on Day-5 and Day -4. Patients who re-start bemcentinib following interruption for QTc prolongation should also have ECGs performed according to this schedule.

If a patient experiences QTcF prolongation despite normal serum potassium and magnesium levels, bemcentinib dosing should be modified as outlined in Table 8.

QT interval will be corrected using Friderica's calculation

Table 8. Dose Modification of Bemcentinib for QTcF Prolongation

QTcF	Recommended Bemcentinib Dose Modification
Grade 1 (451-480 ms)	
Any occurrence	No dose modification required
Grade 2 (481-500 ms)	
1st occurrence	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, interrupt treatment for ≤14 days - if QTcF reduces to ≤Grade 1, no dose modification is required, and dosing can recommence at the allocated dose - if QTcF does not reduce to ≤Grade 1, dose reduce by 100 mg
≥2nd occurrence (without dose modification)	Repeat procedure for "1st occurrence" - if treatment interruption is required on more than 2 occasions, dose reduction by 100 mg is recommended
≥2nd occurrence (at reduced dose)	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no further dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, interrupt treatment for ≤14 days - if QTcF reduces to ≤Grade 1, no dose modification is required and dosing can recommence; if treatment interruption is required on more than 2 occasions at reduced dose, dose reduce by another 100 mg or discontinue treatment if dose reduction is not possible - if QTcF does not reduce to ≤Grade 1, dose reduce by another 100 mg or discontinue treatment if dose reduction is not possible
≥Grade 3 (≥501 ms)	
1st occurrence	Interrupt treatment for ≤14 days; - if QTcF reduces to ≤Grade 1, dose reduce by 100 mg or discontinue treatment if dose reduction is not possible - if QTcF does not reduce to ≤Grade 1, discontinue treatment
2nd occurrence	Discontinue permanently
Ventricular arrhythmia	
1st occurrence	Discontinue permanently
Notes: • Electrolytes should be measured at the time of reporting QTc prolongation, and regularly until the QTc has returned to baseline. Any clinically significant electrolytes should be corrected.The mean QTcF value from triplicate ECG readings should be used when considering dose modification • Treatment interruption for bemcentinib-related toxicity should be limited to 14 days • Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg bemcentinib) • Patients being considered for dose reduction or permanent discontinuation of bemcentinib may be discussed with the Medical Monitor	

8.2 Docetaxel

Each cycle of chemotherapy may be delayed until the ANC is ≥ 1500 cells/μL and the platelet count is ≥ 100,000 cells/μL and hepatic function is acceptable. Institutional standard practices may be used to adjust doses for toxicity. However, in the absence of such standard practices, suggested dose adjustments for docetaxel-related hematologic and non-hematologic toxicities are provided in Table 9 and Table 10, respectively.

Table 9. Dose Adjustments for Docetaxel-related Hematologic Toxicities*

Situation	Recommended Docetaxel Dose
First episode of febrile neutropenia	reduce 1 dose level
Second episode of febrile neutropenia	reduce additional dose level
ANC <500/mm^3	reduce one dose level
Grade 4 thrombocytopenia or bleeding associated with thrombocytopenia	reduce one dose level.

ANC= absolute neutrophil count

NOTE: due to the occurrence of neutropenia considered dose-limiting or neutropenia complicating the feasibility of long-term treatment administration in earlier cohorts, starting with patients enrolled on protocol Version 5.0 or later, patients receiving docetaxel 75 mg/m^2 and/or bemcentinib maintenance dose of 200 mg daily must receive myeloid growth factors (eg, G-CSF, preferably pegylated G-CSF). In certain cases, myeloid growth factors may be omitted from subsequent treatment cycles. Examples include intolerance of myeloid growth factors, dose-reduction of docetaxel, or suspicion [based on available laboratory and clinical data] that patient would tolerate treatment and not develop severe neutropenia if myeloid growth factors were omitted.

Table 10. Dose Adjustments for Docetaxel-related Non-hematologic Non-neuropathic Toxicities*

NCI CTCAE Grade	Recommended Docetaxel Dose
0 to 2	Continue current dose
3 (except alopecia)	Reduce one dose level
4	Reduce two dose levels

NCI-CTCAE= National Cancer Institute (United States Common Terminology Criteria for Adverse events (Version 4.03). *treatment may be withheld until the toxicity has been reduced to grade ≤ 2.

In addition to the dose adjustments, patients may receive supportive care as necessary.[23,24] Patients experiencing febrile neutropenia secondary to docetaxel chemotherapy may receive granulocyte colony stimulating factor therapy in association with subsequent chemotherapy doses. Erythropoietin may also be used as clinically indicated, along with other supportive care.

If Cohort -1 or Cohort -2 is enrolled without exceeding the MTD, a subsequent cohort with docetaxel dose re-escalated to 75 mg/m^2 every 21 days with concurrent myeloid growth factor support every cycle will be enrolled.

Dose re-escalation may be considered on a case-by-case basis.

*NOTE: For starting docetaxel dose of 60 mg/m^2, dose reduction is displayed in the table below and compared to the 75 mg/m^2 starting dose

Dose Level	Docetaxel dose	
Starting dose	**60 mg/m^2**	**75 mg/m^2**
-1	**35 mg/m^2**	**60 mg/m^2**
-2	**N/A**	**35 mg/m^2**

In cases where docetaxel or bemcentinib is permanently discontinued for toxicity reasons, the other agent(s) may be continued provided that (a) the patient is tolerating their ongoing administration, and (b) there is evidence of ongoing clinical benefit.

9.0 TOXICITY REPORTING AND ASSESSMENT

It is the responsibility of each treating institution to report all adverse events to the clinical monitor of this IND and the IND sponsor. Copies of adverse events reports will be sent by the IND Sponsor to the FDA (see Section 9.3).

In accordance with good clinical practices, all adverse events and all dose escalations will be reviewed by the South Plains Oncology Consortium (SPOC) Data Safety and Monitoring Committee (DSMC). The SPOC DSMC will record these discussions and decisions in the SPOC Phase I tracking log. This information will be made available as needed.

9.1 Reporting Toxicities

Using the Notification of Toxicity form in Appendix C, report to the SPOC Consortium Manager (office phone: 806-743-2690, cell phone: 806-773-4836 FAX: 806-743-2691, e-mail: amanda.knight@ttuhsc.edu) within 24 hours of knowledge of the event:

- All serious adverse events (SAEs)
- All dose-limiting toxicities (DLTs)
- All unexpected adverse events deemed possibly, probably, or definitely related to study drugs or procedures

The SPOC DSMC will review all serious adverse events and unexpected adverse events in real time with other members of the DSMC by phone conference. This Phase I trial will be monitored by the SPOC DSMC after the first patient, before any dose escalation, with each new event, or at least annually. Meeting minutes will document these reviews and will be made available as needed. A description of the SPOC DSMC is contained in the SPOC "Standard Operating Procedure for the SPOC DSMC.

All toxicities should be reported, whether or not they are attributable to the study drugs**. All life-threatening toxicities mandate a telephone contact within 24 hours of the event between the reporting institution's principal investigator (PI) and the PI's or their designates of the other participating institutions.**

Any supporting documentation (i.e., laboratory, pathology, progress notes, discharge summary, autopsy, etc.) explaining the AE should accompany the submitted report.

9.2 Additional Adverse Event Experience Reporting

Adverse Experience (AE) reports of a serious nature are to be reported by phone to the SPOC Consortium Manager at 806-743-2690, and to the Study Protocol Chair and IND Sponsor (David E. Gerber, MD) at office 214-648-4180, within 24 hours of knowledge of the event:

- All life-threatening events (Grade 4) which might be due to study drugs or procedures
- All fatal events
- Serious events requiring or extending hospitalization which may be due to study drugs or procedures

A written report should be sent within the time specified to all relevant IRB's following the event.

Written reports will be sent to the SPOC Consortium Manager (phone: 806-743-2690, FAX: 806-743-2691, e-mail: amanda.knight@ttuhsc.edu). The Consortium Manager will submit the report to BerGenBio AS, who will be the point-of-contact for IND-related matters. The IND sponsor will review the report and if required submit to the Food and Drug Administration submitted within 10 working days to:

Food and Drug Administration
P.O. Box 3001
Bethesda, MD 20824

A copy of any written reports submitted to the FDA will be provided to:

David Gerber, M.D.
Division of Hematology-Oncology
Harold C. Simmons Cancer Center
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd., Mail Code 8852
Dallas, TX 75390-8852
Ph: 214-648-4180
E-mail: david.gerber@utsouthwestern.edu

All adverse experiences are to be recorded in the patient's medical record, and will be transcribed to the patient's case report form (CRF).

The SPOC Consortium Manager will distribute the report to participating institutions to be filed with each collaborating site's IRB as follows:

TTUHSC: within 5 days
UT Southwestern: within 10 working days
Covenant Health Systems: within 10 working days

9.2.1. Reporting of Serious Adverse Events

Any SAE experienced by a patient between the time of the first administration of BEMCENTINIB and 28 days after the last administration is to be recorded on an SAE Report Form within 24 hours of knowledge by the investigator of its occurrence, regardless of the severity and causality of the event. Related SAEs

should continue to be reported indefinitely. The SAE Report Form should be faxed or e-mailed to the Chiltern International (US fax numbers: 1 888 726 8416; GlobalSAEInbox@chiltern.com)

. A telephone report may only be made in exceptional circumstances and must be followed by completion of the SAE Report Form within 1 working day. Where applicable, information from relevant hospital case records and post-mortem reports should be obtained.

All SAEs that have not resolved by the end of the study, or that have not resolved upon the patient's discontinuation from the study, must be followed until any of the following occur:

- The event resolves
- The event stabilizes
- The event returns to baseline status
- The event can be attributed to agents other than study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained

9.2.2 Immediate Reporting of Serious Adverse Events

Expedited safety reporting within this clinical study complies with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A), investigational new drug (IND) application safety reporting (under 21CFR312.32), and with applicable local regulatory requirements.

The sponsor of the IND assumes responsibility for appropriate reporting of AEs to the Regulatory Authorities and Institutional Review Boards (IRB). Although this responsibility can be delegated, the sponsor of the IND retains ultimate responsibility for safety reporting.

All SAEs that are unexpected and associated with the use of the investigational product are classified as suspected unexpected serious adverse reactions (SUSARs) and must be reported to the IRBs and Regulatory Authorities within 7 calendar days if fatal or life threatening, or within 15 calendar days if non-life threatening and non-fatal. The Sponsor/designee must also report SUSARs to all investigational sites.

Any safety information from other observations that could change the risk-benefit evaluation of bemcentinib should be promptly communicated to the Regulatory Authorities and IRBs. Any other SUSARs associated with bemcentinib should be reported as soon as the Sponsor becomes aware of them, including SUSARs which occur in another clinical study conducted by the same Sponsor or which are identified by spontaneous reports, a publication, or which are transmitted to the sponsor by another Regulatory Authority.

Other safety issues that also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of the bemcentinib (sufficient to consider changes in the administration or in the overall conduct of the trial), include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- Post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the Investigator to the Sponsor
- New events relating to the conduct of the trial or the development of bemcentinib likely to affect the safety of the patients, such as:
    - An SAE which could be associated with study procedures and which could modify the conduct of the study
    - A major safety finding which differs from the underlying disease

Expedited reporting is not usually required for reactions which are serious but expected, and it is inappropriate to report events that are considered unrelated to the investigational product.

The cause of death of a patient in a clinical study, unless it is associated with disease progression, is considered a SAE whether the event is expected or associated with the investigational agent.

9.2.3 Pregnancy

In the event of a pregnancy occurring in female patients, or in the partners of male patients during the study, the pregnancy must be reported to the Chiltern International (US fax numbers: 1 888 726 8416; GlobalSAEInbox@chiltern.com) by the investigational staff within one working day of their knowledge of the event using a Pregnancy Notification Form.

The reporting period for pregnancies will start with the first study-related procedure and end 28 days after the final administration of bemcentinib.

Any female patients who become pregnant while taking part in the study will be withdrawn; a male patient whose partner becomes pregnant can remain in the study. A patient who completes or withdraws from the trial before the full term of the pregnancy will be asked to consent to provision of follow-up information about the pregnancy and its outcome.

9.3 Adverse Events

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with its treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

NOTE: Abnormal vital signs that are considered clinically relevant by the Investigator must be reported as AEs.

9.3.1 Serious Adverse Events

A **serious adverse event (SAE)** is any AE occurring at any dose that meets 1 or more of the following criteria as assessed by either the Sponsor or Investigator:

- Results in death**.**
- Is life-threatening event- an AE is considered to be life-threatening if either the Investigator or the Sponsor determines the occurrence of the event places the patient at immediate risk of death. It does not refer to an AE that, if it occurred in a more severe form, may have resulted in death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization - Hospitalization is defined as an admission to hospital ≥24 hours. Any pre-planned hospitalization for an elective procedure that is unrelated to participation in the study will not be considered an SAE.
- Results in a significant incapacity or disruption of the ability to conduct normal life activities.
- Results in a congenital anomaly or birth defect.
- Important medical event **-** any event that does not meet the above criteria, but that when based upon medical judgment jeopardizes the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definition of "SAE."

NOTE: If standard of care or institutional practice requires hospitalization of patients for the sole purpose of delivering chemotherapy including study therapy then such hospital admissions will not be considered or reported as SAEs. However, should an SAE develop during such hospitalization, it will be considered and reported as such.

NOTE: All **pregnancies** occurring during this study are reported in the same timeframe as SAEs. If a pregnancy is confirmed during the study, the continued use of the study drug must be immediately evaluated. When possible, all reports of pregnancy must be followed for information regarding the course of the pregnancy and delivery, as well as the condition of the newborn or other outcome. Follow-up information concerning the outcome of the pregnancy will be provided by the Investigator to the study medical monitor in a timely manner and regardless of whether the patient has discontinued participation in the study. If the newborn is healthy, additional follow up is not needed.

9.3.2 Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Unlikely, Possibly, Probably or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related." Definitions of the relationship of an AE to the use of the study medication are as follows:

- **Unrelated-** The AE <u>is clearly not related</u> to study treatment. An AE for which sufficient information exists to indicate that the etiology is unrelated to the study drug. The etiology must be specified.

- **Unlikely -** The AE is doubtfully related to study treatment. The event is most likely produced by other factors such as the patient's clinical condition, therapeutic interventions or concomitant drugs administered to the patient and it does not follow a known response pattern to the study drug.
- **Possibly -** The AE may be related to study treatment. The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's clinical condition, therapeutic interventions, or concomitant drugs administered to the patient.
- **Probably -** The AE is likely related to study treatment. The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the patient's clinical condition, therapeutic interventions, or concomitant drugs administered to the patient.
- **Definitely** - The AE is clearly related to study treatment. An AE that follows a reasonable temporal sequence from administration of the study drug; follows a known response pattern to the drug; and, when appropriate to the protocol, is confirmed by improvement on stopping the drug (de-challenge) and reappearance of the reaction after repeat exposure (re-challenge); and cannot be reasonably explained by the known characteristics of the patient's clinical state or by other therapies.

10.0 DEFINITION OF RESPONSE

This is a Phase I study for which the primary endpoints are determination of treatment tolerability, toxicities, and pharmacokinetics of combined docetaxel plus bemcentinib. In addition, we will record all antitumor responses. To be evaluable for response, patient must have evaluable disease at study entry and must have completed at least one course of therapy, or have discontinued therapy for reasons of toxicity or progression of disease.

Dose-escalation rules and toxicity summaries will include those patients who complete any therapy and who are followed a minimum of 4 weeks after the start of the first cycle, or who experience dose limiting toxicity. Patients who complete one cycle of treatment will be included in the analysis of tumor response. The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients will be reported. Patients who begin treatment will be accounted for in the summaries of toxicity. All patients who complete the first course of treatment will be included in the analysis of survival and time-to-failure.

10.1 Key Definitions

10.1.1 Measurable Disease

- Measurable non-nodal lesions: those that can be accurately measured in at least 1 dimension (LD) to be recorded as ≥10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must measure ≥15 mm in the short axis (SA) when assessed by CT scan (CT slice thickness recommended to be no greater than 5 mm).
- It is recommended that slice gaps not be utilized for the image acquisition procedures.
- ***Superficial lesions (eg, skin lesions) on physical exam will not be considered radiographically measurable unless they are measurable on CT or MRI.***

- All radiographic measurements should be taken and recorded in millimeters utilizing an electronic measurement method based on lesion boundary definition.
- ***Lesions on chest X-ray will not be considered measurable.***

10.1.2 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (LD<10 mm or pathological lymph nodes ≥10 mm to <15 mm in the SA) as well as truly non-measurable lesions are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

10.1.3 Target Lesions

- Target lesions must be measurable lesions.
- ***All lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, will be identified as target lesions, recorded and measured at baseline, and followed consistently throughout the study.***
- Target lesions should be selected on the basis of their size (based on LD for non-nodal lesions or SA for lymph nodes), their suitability for accurate repeated measurements, and on their being most representative of the patient's tumor burden.
- A sum of the diameters for all target lesions will be calculated and reported for each time point. The baseline sum of diameters will be used as a reference by which the objective tumor response will be characterized.
- ***Brain lesions that were previously irradiated cannot be recorded as target lesions. Stable brain lesions post radiotherapy should be documented as non-target lesions. At post-baseline evaluations, the brain lesions should be marked as "Not done" if a brain scan was not done, as follow-up brain scans are only required when clinically indicated.***
- ***Bone lesions should be recorded as non-target lesions regardless of irradiation treatment status.***

10.1.4 Non-Target Lesions

- All other lesions (or sites of disease, including any measurable lesions that were not selected as target lesions) will be identified as non-target lesions and indicated as present at baseline.
- It is possible to record multiple non-target lesions involving the same organ as a single item (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).
- Measurements of these non-target lesions will not be performed, but the presence, absence, or unequivocal progression of these lesions should be noted throughout follow-up assessments.

10.1.5 New Lesions

- The finding of a new lesion should be unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality, etc.).
- If a new lesion is equivocal (ie, because of its small size), and follow-up imaging confirms that it is definitely a new lesion, the progression of that new lesion is from the time it was seen on the initial scan.

- A lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.
- A lesion that reappears at follow up after a PR or SD is not considered new. The lesion's LD (or SA for lymph nodes) is added back into the sum of diameters.
- A lesion that reappears at follow up after a complete response (CR) is automatically considered PD.

10.1.6 Lymph Nodes

- At baseline, lymph nodes with tumor burden will be considered as target lesions if the SA is ≥ 15 mm.
- At baseline, lymph nodes will be considered as non-target lesions if the SA is ≥10 mm and < 15 mm.
- At baseline, lymph nodes will be considered as normal if the SA is <10 mm.
- At follow up, a lymph node must measure ≥10 mm in the SA to be considered a new lesion.
    - ***A lymph node that was identified as target disease at baseline that falls below the measurable threshold at follow up, and then gets larger is not considered new if it follows a PR or SD. The lymph node SA measurement is added back into the sum of diameters.***
    - ***A lymph node that was identified as target disease at baseline that falls below the measurable threshold at follow up, and then gets larger following a CR is automatically PD.***

10.2 Other Considerations

10.2.1 Irradiated Lesions

Previously irradiated lesions cannot be selected as target unless there is a documented disease progression, defined as increase of at least 1 cm in LD compared to nadir scan.

10.2.2 Handling of Lesions that Split

When non-nodal and nodal lesions split or fragment, the individual lesion diameters of the fragmented portions should be added together to calculate the target lesion sum.

10.2.3 Handling of Lesions that Merge

As lesions merge, a boundary between the lesions should be drawn so the LD or SA of each individual lesion can continued to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the LD or SA of the merged lesion should be measured.

10.2.4 Measurement of Small Lesions on Follow-up Scans

<u>Non-Nodal</u>

A non-nodal target lesion that is present but too small to measure (TSTM) accurately at evaluations after baseline (< 5 mm but greater than 0 mm in unilateral dimension) will be classified as TSTM and will be assigned a value of 5 mm for the purposes of determining the sum of diameters. All other lesions will have actual size recorded (ie, ≥ 5 mm).

<u>Lymph Nodes</u>

A target lymph node should always have the actual SA measurement recorded, even if the lymph node regresses to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum

of diameters may not be zero even if CR criteria are met, since a normal lymph node is defined as having an SA of <10 mm.

10.3 Response Criteria

10.3.1 Target Lesion Response Criteria

- Complete Response (CR): Disappearance (or normalization) of all target lesions.
  - Any pathological lymph nodes (whether target or non-target) must have reduction in SA to <10 mm.
- Partial Response (PR): At least 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters 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.
- Non-evaluable (NE): Patient time points that have inadequate or missing images, ***including the inability to visualize >25% of target disease.***

10.3.2 Non-Target Lesion Response Criteria

- CR: Disappearance (or normalization) of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm SA).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s).
- PD: Unequivocal progression of existing non-target lesions.
- NE: Patient time points that have inadequate or missing images, ***including the inability to visualize > 50% of non-target disease.***
- ***No Disease (ND): No non-target disease noted. The absence of non-target lesions at follow-up time points is designated as ND and not SD when there is no non-target disease noted at baseline.***

10.3.3 New Lesion Response Criteria

If at least 1 new lesion is present, the patient is considered to have PD overall.

10.3.4 Response Assessment in Case of Missing or Technically Inadequate Scans

If no lesions were identified at baseline in a specific body region (eg, chest, abdomen) and the scan of that body region is unavailable or technically inadequate at follow up, then the response assessment will be based on the scans of the other regions.

10.4 Response Definitions

10.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions

Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.4.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and 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

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

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

10.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 10.4.4).

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR		No	PR

	Incomplete response/SD		
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

10.4.4 Confirmatory Measurement/Duration of Response

Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 4 weeks.

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 recurrent 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.

11.0 PHARMACOKINETIC AND CORRELATIVE STUDIES

Pharmacokinetic studies will be performed on all patients. Blood and serum biomarker studies will be performed on all patients. Imaging biomarker studies will be performed on a subset of patients treated at UT Southwestern Medical Center

11.1 Pharmacokinetic Analyses

Full details of analysis of the possible effects of bemcentinib on docetaxel will be provided in a Pharmacokinetics Analysis Plan. In brief, the Pharmacokinetics Analysis Population will include those patients who receive ≥1 cycle of bemcentinib and ≥1 dose of docetaxel and have PK data available. PK parameters of docetaxel that will be measured are summarized in Table 11.

Table 11. Docetaxel PK Parameters to be Evaluated

C_{max}	The observed maximum plasma concentration after single dose administration
t_{max}	The time to reach C_{max}
$AUC_{0\text{-}tau}$	The area under the curve within a dosing interval, calculated by the linear up-log down trapezoidal method.
λ_z	The apparent terminal rate constant estimated from individual linear regression of the terminal part of the log concentration vs. time curve
$t_{½}$	The apparent terminal half-life, calculated by $0.693/\lambda_z$

Where possible, individual, mean and median docetaxel plasma concentration-time data will be presented in tabular and/or graphical form.

11.2 Correlative studies

11.2.1 Blood biomarkers

Blood will be collected at the following time-points for biomarker analysis. (Multiplex cytokine and angiogenic factor assay, qPCR for cytokine and immune markers):

- Cycle 1 Day -7,prior to administration of bemcentinib
- Cycle 1 Day 1, pre-infusion
- Cycle 2 Day 1, pre-infusion
- At disease progression/end of treatment

11.2.2 Tissue biomarkers

11.2.2.1 Archival tumor tissue is required and can be collected at:

- Pre-study baseline (optional) or
- Archival material from diagnostic or subsequent biopsies

12.0 STATISTICAL CONSIDERATIONS

12.1 General considerations

This is a Phase I and pharmacologic study. The South Plains Oncology Consortium (SPOC) will be the coordinating center for this study; SPOC will be responsible for registering patients (Section 5.2 and Appendix A) and for maintaining a complete database of the study information (Section 14.0).

12.2 Analysis of Clinical Endpoints

The design of this Phase I trial is described in Section 6.0; the definition of MTD is given in Section 6.2 and the rules for dose escalation are given in Sections 6.3.

The toxicities observed at each dose level will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v4.0 and nadir or maximum values for the laboratory measures), time of onset (i.e., cycle number), duration, and reversibility or outcome.

Tables will be created to summarize these toxicities and side effects by dose and by cycle. Toxicities will be reported for all patients receiving study drug. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented to describe the patients treated in this Phase I study. All responses will be reported. Response rate with its 95% confidence interval will be estimated using the exact Binomial method. The response rate in this study population will be compared with that of the historical control using the one-sample Binomial test. Progression-free survival and the overall survival will be summarized with Kaplan-Meier plots to describe the outcome of patients treated on this protocol.

12.3 Analysis of Pharmacokinetic and Laboratory Studies

Pharmacokinetic data (i.e. plasma concentrations of bemcentinib) will be analyzed using compartmental and non-compartmental models using PCNONLIN™ version 4.2 or equivalent software. The pharmacokinetic parameters will be estimated for each patient and will be summarized by dose level with standard descriptive statistics (means and standard deviations – possibly after transformation, if necessary - or medians and ranges). If appropriate, summary statistics will also be provided for the entire group of patients. The relative plasma levels of bemcentinib will also be tabulated and summarized. These levels will be compared with observed toxicities and clinical response in an exploratory manner. However, the heterogeneity of the patient population and the small number of patients treated at each dose make formal statistical inference of these molecular studies unlikely.

12.4 Estimated accrual time

Review of patient accrual onto recent phase 1 studies suggests that the study should be completed in less than 30 months.

12.5 Results

All patients who receive at least one cycle of bemcentinib will be accounted for in the analysis; the reasons for going off study will be documented for each patient. Baseline and demographic information will be documented for each patient. Observed toxicities will be summarized in terms of type, severity, time of onset, duration, reversibility, and outcome.

Intention to treat analysis will be used to allow for drop-outs and withdrawals, so that data from all study participants will be analyzed. This method will estimate without bias the effect of the treatment policy on

end-points to be analyzed, but may underestimate the magnitude of the treatment effect in patients who complete therapy.

Depending on cohort expansion requirements, a total of 6-12 patients will be accrued to the dose-escalation phase 1 pilot trial, with another 18-24 patients accrued at the MTD for a total of 30 patients. Since the trial population will be drawn from a multi-institution base, it is anticipated that accrual will be completed over 18 to 30 months.

12.6 Sample Size justification

Enrolling 30 patients in the total study population will provide more than 80% power to detect an increase in response rate from 10% (historical control with docetaxel monotherapy) to 25%, using the one-sample Binomial test with a one-sided alpha of 0.1. If only those patients treated at the MTD are included (projected N=18-24), we will have approximately 67% power to detect a similar increase in response rate, with a one-sided alpha of 0.1. The projected 15% absolute increase in response rate is based on marked potentiation of taxane effects in in vitro models and a 50% improvement in tumor growth inhibition in preclinical xenograft studies.[20]

Biomarker Analyses

Exploratory biomarker analyses will examine potential predictive biomarkers for correlation with bemcentinib activity and safety. A separate SAP will be prepared for the biomarker analyses.

13.0 REGISTRATION GUIDELINES

To register a patient, the research nurse or data manager must complete the eligibility form and the registration form and give (or FAX) copies to the SPOC Consortium Coordinator (at 806-743-2691). The research nurse or data manager will call the SPOC Consortium Coordinator (at 806-743-2690), and after verifying the eligibility, the SPOC Consortium Coordinator will assign a study number, assign a dose, and register the patient onto the study. See Appendix A ("Registration Procedures for Phase I Trials").

Informed Consent must be obtained before the patient is registered. The FDA requires that both the signature and the date be in the handwriting of the subject or the subject's legally authorized representative, that the date be the actual date on which the form is signed, and that the informed consent process be documented in the physician's progress notes or the nurse's notes.

13.1 Procedures for On-Study and Treatment Deviations.

Any on-study or treatment deviations need to be discussed with and reported to SPOC and the Study Chair.

14.0 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

14.1 Confidentiality of Records

The original data collection forms will be stored at the originating institution. A copy of all data forms will be maintained in secure files or electronically at the SPOC Operations Center.

14.2 Patient Consent Form

At the time of registration, will fax a copy of the signed and dated informed consent and HIPAA documents to SPOC (see registration procedures in Appendix A).

14.3 Registration Eligibility Worksheet

At the time of registration, the information requested on the On-Study/Eligibility Form will be submitted to the Consortium Coordinator at SPOC as described in the Appendix A ("Registration Procedures for Phase I Trials").

This study will be monitored by SPOC. All centers will submit data collected at their institution to the South Plains Oncology Consortium Operations Center (SPOC). A complete database will reside at SPOC.

All data will be collected using SPOC data collection forms via the electronic database. The original source data collection forms will reside at the originating institution in secure location.

The data manager will complete the Registration Worksheet /Eligibility Form (a SPOC form which includes the eligibility checklist).

Within two weeks of completion of the first cycle, the data manager must complete the Phase I, Cycle I Toxicity form online.

Within two weeks of registration, the data manager will complete and submit the On-Study Form in the database.

Within two weeks of registration, the data manager will have electronically submitted to SPOC the following information:

Treatment

Supplemental Data (if applicable)

Adverse Events

Response/Off-Study/Follow-Up

Within two weeks of going off study, data manager will complete and submit to SPOC, the "Off-Study Summary" information.

SPOC may conduct on-site audits to verify submitted data against primary medical records and will provide periodic data summaries to the Protocol Chairman.

15.0 MINORITIES AND WOMEN STATEMENT

Patients of both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in Section 5.0. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to accrue a representative sample. However, since this is a Phase I trial, considerations for patient safety and a reluctance to expose patients either to a potentially toxic and/or ineffective treatment, will limit the total number of patients entered. If differences in outcome appear to be associated with gender or ethnic identity, then a follow-up study will be designed to investigate those differences more fully.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All Institutional, NCI, Federal, and State of Texas regulations concerning the Informed Consent form will be fulfilled. Bemcentinib will be administered under an IND for each drug, which is approved by and subject to the regulations of the FDA.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to current

legal requirements. However, they will be made available for review, as required by the FDA or other authorized investigators such as the NCI or the IND sponsors (or their delegates), under the guidelines established by the Federal Privacy Act.

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18.0 APPENDICES

APPENDIX A - REGISTRATION PROCEDURES FOR PHASE I TRIALS

I. REGISTRATION POLICIES

A. Registrations for Phase I protocols within this co-operative agreement must be made through the Operations Office of the South Plains Oncology Consortium (SPOC) between the hours of 8:30 a.m. and 4:30 p.m. Central Time Zone, Monday through Friday (except holidays). Documentation of current IRB approval of this protocol must be on file prior to registration of patients at these institutions.

B. Patients must begin protocol therapy within 72 hours of registration.

C. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist in the On-Study/Eligibility Form must be completed. Patients must sign an informed consent prior to registration.

D. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the SPOC Consortium Coordinator at 806-743-2690.

II. "HOLDING A SLOT" FOR A POTENTIAL PATIENT

A. If a potential patient has been identified for a Phase I trial, the data manager or research) must contact the Consortium Coordinator (806-743-2690) to verify that a dose-level is open.

1. If the current dose-level is open, then the Consortium Coordinator will reserve the "slot" for that patient for 14 days to allow sufficient time to complete the required tests and obtain the informed consent. *Only one reserved slot will be allowed per consortium institution at a new dose level (given all sites have simultaneous IRB approval). If an institution has several potential patients, the Phase I Consortium Coordinator must contact each of the other institutions to see if there are pending patient(s). The other Consortium institutions have 7 days to fill an available slot and then 14 days to evaluate a patient. If no patient is available in that time, the institution which has additional patients for the study will then be given another slot at that dose level.*

    a. The research nurse or data manager must call back within 14 days to complete the registration or cancel the patient.

2. If no dose-level is open (based on the criteria for dose expansion or escalation - as described in the protocol), then the Consortium Coordinator can indicate the anticipated date of reopening and the slot may be reserved for that patient.

a. The research nurse or data manager must stay in touch with the Consortium Coordinator and must cancel the slot reservation immediately if the patient for whom a slot has been reserved is no longer available or eligible for enrollment.

3. No more than 3 patients may be held on the waiting list for a single protocol.

a. If a patient on the waiting list becomes ineligible, then the research nurse or data manager must call to remove the patient from the list.

4. No slot reservation at a given dose level will be made prior to escalation or expansion until such time as the 3rd patient at that level has been evaluated for toxicity.

III. REGISTRATION PROCEDURES

A. Once a patient is eligible, all the pre-study requirements have been fulfilled, and informed consent obtained, then the data manager or research nurse will inform the Consortium Coordinator (806-743-2690) and FAX him/her a copy of the signed Informed Consent, HIPAA documents and the completed On-Study/Eligibility Form (FAX Number: 806-743-2691).

1. SPOC will provide copies of the On-Study/Eligibility Form for each Phase I trial under this co-operative agreement.

B. The Consortium Coordinator will verify that the patient is eligible, that pre-study tests have been completed, and that the forms are complete. He/She will then register the patient, confirm the dose-level and provide a Consortium patient ID number. The Consortium Coordinator will call the research nurse or data manager and verbally confirm the registration.

The Consortium Coordinator will send paper confirmation within 24 hours to the site's research nurse or data manager and the Study Chair (Dr. David Gerber).

APPENDIX B - Common Terminology Criteria for Adverse Events v3.0

NCI Common Toxicity Criteria ver4.0 can be found at the CTEP website:

http://ctep.cancer.gov/forms/CTCAEv4.pdf

APPENDIX C - Adverse Events Reporting Material

SOUTH PLAINS ONCOLOGY CONSORTIUM

NOTIFICATION OF TOXICITY

THIS FORM OR A COPY OF A SUBMITTED AdEERS REPORT MUST BE FAX'D (806-743-2691)
TO THE CONSORTIUM COORDINATOR WITHIN 24 HOURS OF ONSET OF ADVERSE EVENT.

PROTOCOL INFORMATION

Consortium Protocol Number: **SPOC- 2015-01** NCI # (if applicable): _____

Protocol Title: Phase 1 trial of dose escalated BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC)

Treating Institution: _____

Reporter Name: _____ Phone #:_____

Email: _____

PATIENT INFORMATION

Patient Name_____ Pt Study ID: _____

ADVERSE EVENT INFORMATION

Adverse Event: _____ Start Date of AE: ____/____/____

If Phase I trial, is the adverse event considered dose-limiting? __ No __ Yes
Is toxicity reportable as defined by NCI Guidelines? __ No __ Yes

Has the event been reported to the following:

Institutional IRB __ No __ Yes Date: __ __ / __ __ / __ __

FDA __ No __ Yes Date: __ __ / __ __ / __ __

AdEERS/MedWatch __ No __ Yes Date: __ __ / __ __ / __ __

Report sent to SPOC? __ No __ Yes Date: __ __ / __ __ / __ __

APPENDIX D: PERFORMANCE SCALE 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 E

Specimen Collection Form for <u>Pharmacokinetics Analysis</u>

SPOC-2015-1 Phase 1 trial of dose escalated BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC).

Patient's Name_____ _____ Patient Accession # _____
(first) (last)

Study Site _____ Height _____cm Weight: _____kg BSA ____. ___m^2

Bemcentinib Dose = _____ mg Docetaxel Dose= _____ mg/m^2

Start Date/time _____ End Date/time _____

Bemcentinib PK collection time-points

Sample Name	Matrix	Description	Sample Date (mm:dd:yy)	Expected Time (hh:mm)	Actual Time (hh:mm)	Drawn By (initials)	Comments
Cycle 1 Day -6, 0hr	Plasm	Pre-dose					
Cycle 1 Day -5, 0hr	Plasm	Pre-dose					
Cycle 1 Day 1, 0hr	Plasm	Pre-dose					
Cycle 1 Day 2, 0hr	Plasm	Pre-dose					
Cycle 2 Day 1, 0hr	Plasm	Pre-dose					
Cycle 4 Day 1, 0 hr	Plasm	Pre-dose					

Docetaxel PK collection time-points

Sample Name	Matrix	Description	Sample Date (mm:dd:yy)	Expected Time (hh:mm)	Actual Time (hh:mm)	Drawn By (initials)	Comments
Cycle 1 Day 1, 0.5hr	Plasma	post-dose					
Cycle 1 Day 1, 1 hr	Plasma	1 hrs					
Cycle 1 Day 1, 2hr	Plasma	2 hrs					
Cycle 1 Day 1, 4hr	Plasma	4 hrs					
Cycle 1 Day 1, 6hr	Plasma	6 hrs					
Cycle 1 Day 1, 8hr	Plasma	8 hrs					
Cycle 1 Day 2, 0 hr	Plasma	Pre-dose (BGB324 predose)					
Cycle 1 Day 3, 0 hr	Plasma	Pre-dose (BGB324 predose)					

Draw Blood (4.5ml) into a sodium or lithium heparin (green top) tube for bemcentinib and K2-EDTA tube (purple top) for docetaxel**. CLAMP INFUSION LINES AND FLUSH LINES OR PORT BEFORE DRAWING DISCARD AND SAMPLE** to prevent entrainment of drug into the sample. IMMEDIATELY WRAP TUBE IN FOIL to protect from light AND CHILL ON ICE. PLASMA to be stored in FOIL WRAPPED TUBES and FROZEN at -80 C. **RECORDING THE EXACT TIME OF DRAW IS MORE IMPORTANT THAN DRAWING EXACTLY ON SCHEDULE.**

. **See lab manual for detailed procedure.**

APPENDIX F

Specimen Collection Form for <u>Multiplex Cytokine and Angiogenic Factor Assay</u> Performance

SPOC-2015-01 Phase 1 trial of dose escalated BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC).

Patient's Name_____ _____ Patient Accession # _____
(first) (last)

Study Site _____ Height _____cm Weight: _____kg BSA ____. ___m^2

Bemcentinib Dose = _____ mg Docetaxel Dose= _____ mg/m^2

Start Date/time _____ End Date/time _____

PD Collection Time-points

Sample Name	Matrix	Description	Sample Date (mm:dd:yy)	Expected Time (hh:mm)	Actual Time (hh:mm)	Drawn By (initials)	Comments
Cycle 1 Day -7	Plasma	Pre-BGB324					
Cycle 1 Day 1	Plasma	Pre-docetaxel					
Cycle 2 Day 1	Plasma	Pre-docetaxel					
EOT/ Disease Progr	Plasma						

Blood will be drawn into a 3ml ACD (yellow top) tube and immediately chilled in an ice-water bath.

ALL SAMPLES MUST BE PROTECTED FROM LIGHT AT ALL TIMES BY WRAPPING IN FOIL IMMEDIATELY.

BLOOD AND PLASMA MUST BE PROTECTED FROM LIGHT AS MUCH AS POSSIBLE DURING HANDLING, AND PLASMA TO BE STORED IN FOIL WRAPPED TUBES.

See lab manual for detailed procedure.

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. **APPENDIX G**

Specimen Collection Form Tissue collection for PD

SPOC-2015-01 - Phase 1 trial of dose escalated BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC).

Patient's Name_____ _____ Patient Accession # _____
(first) (last)

Study Site _____ Height _____cm Weight: _____kg BSA ____. ___m^2

Bemcentinib Dose = _____ mg Docetaxel Dose= _____ mg/m^2

Start Date/time _____ End Date/time _____

Tissue Collection for PD

Sample Name	**Matrix**	**Sample Date (mm:dd:yy)**	**Expected Time (hh:mm)**	**Actual Time (hh:mm)**	**Collected By (initials)**	**Comments**
Baseline	biopsy					
Pre first line treatment	biopsy					
EOT	biopsy					

See lab manual for detailed procedure.

APPENDIX H

Specimen Collection Form for <u>Whole blood collection for mRNA and PBMC isolation</u>

SPOC-2015-01 - Phase 1 trial of dose escalated BGB324 in combination with docetaxel for previously treated advanced non-small cell lung cancer (NSCLC).

Patient's Name_____ _____ Patient Accession # _____
(first) (last)

Study Site _____ Height _____cm Weight: _____kg BSA ____. ___m^2

Bemcentinib Dose = _____ mg Docetaxel Dose= _____ mg/m^2

Start Date/time _____ End Date/time _____

Whole blood Collection for mRNA and PBMC isolation

Sample Name	**Matrix**	**Description**	**Sample Date (mm:dd:yy)**	**Expected Time (hh:mm)**	**Actual Time (hh:mm)**	**Collected by (initials)**	**Comments**
Cycle 1 Day -7	Whole blood	Pre-BGB324					
Cycle 1 Day 1	Whole blood	Pre-docetaxel					
Cycle 2 Day 1	Whole blood	Pre-docetaxel					
EOT Disease Progression	Whole blood						

Collect 2.5ml whole blood in PAXgene tubes and 8.5 ml blood in two ACD tubes.

See lab manual for detailed procedure.

APPENDIX I

Drugs that are Generally Accepted to Have a Risk of Causing Torsades de Pointes

Generic Name	Brand Name
Amiodarone	Coradone/Pacerone
Anagrelide	Agrylin®, Xagrid®
Aresenic trioxide	Trisenox
Astemizole	Hismanal
Azithromycin	Zithromax®, Zmax®
Bepridil	Vascor
Chlorquine	Arelan
Chlorpromazine	Thorazine
Cisapride	Propulsid
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin
Cocaine	Cocaine
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium
Dronedarone	Multaq®
Droperidol	Inapsine
Erythromycin	Erythrocin/E.E.S.
Escitalopram	Cipralex®, Lexapro®
Flecainide	Tambocor®, Almarytm®
Halofantrine	Halfan
Haloperidol	Haldol
Ibutilide	Covert
Levomethadyl	Orlaam
Mesoridazine	Serentil
Methadone	Methadose/Dolophine
Moxifloxacin	Avelox
Ondansetron	Zofran®, Anset®
Petamidine	NebuPent/Pentam
Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl/Procan
Quinidine	Cardioquin/Quinaglute
Sevoflurane	Ulane®, Sojourn®
Sotalol	Betapace
Sparfloxacin	Zagam
Sulpiride	Dogmatil®, Dolmatil®
Terfenadine	Seldane
Thioridazine	Mellaril

Vandetanib	Zactima

Adapted from "The University of Arizona Center for Education and Research on Therapeutics." See the following website for an updated list of drugs that cause Torsades de Pointes: www.AZCERT.org