SYNOPSIS OF PROTOCOL

TITLE	A Randomized, Single Blinded, Phase 3 Study of Second- or Third-Line Chemotherapy with Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients with Advanced Non-Small Cell Lung Cancer with at Least One Measurable Lung Lesion (DUBLIN-3)
SPONSOR	BeyondSpring Pharmaceuticals, Inc.
CLINICAL PHASE	3
INDICATION	Patients with advanced or metastatic NSCLC with at least one measurable lung lesion, and with the patient having progressed after treatment with one or two prior non-docetaxel-containing systemic therapy regimen(s). The patient must have received a platinum-based regimen in first line or second line prior to entering this study. The first or second line can be immunotherapy with a PD-1/PD-L1 checkpoint inhibitor.
STUDY DURATION	Approximately 36 months recruitment and approximately12 months follow-up
NUMBER OF SITES	Approximately 30 sites in China and 57 sites in the Rest of the World (RoW)
DRUG PRODUCT	Plinabulin (BPI-2358) (Formerly NPI-2358)
OBJECTIVES	<u>Primary efficacy objectives:</u> To compare the overall survival (OS) of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm) for advanced or metastatic disease. <u>Secondary efficacy objectives:</u> • To compare overall response rate (ORR) of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm) for advanced or metastatic disease. • To compare progression free survival (PFS) of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm) for advanced or metastatic disease. • To compare incidence of Grade 4 neutropenia (absolute neutrophil count [ANC] < 0.5×10^9/L) on Day 8 (+/- 1 day)

	of Cycle 1 of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm) for advanced or metastatic disease. • To compare 24-month and 36-month OS rate of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm) for advanced or metastatic disease. • To compare duration of response (DoR) of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm) for advanced or metastatic disease. • To compare the mean difference in quality-adjusted time without symptoms of disease and toxicity (Q-TWiST) between patients in the DP Arm and the D Arm. • To compare the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30) global health status/QoL and the combined symptom scales/items (excluding financial difficulties) between the 2 treatment arms. • To compare QoL in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Lung Cancer 13 (QLQ-LC13) in patients in the DP Arm to the D Arm. • To compare proportion of patients who received docetaxel > 8 cycles, 10 cycles, and >12 cycles. • To compare 18-month OS rate of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm). • To compare relative dose intensity (RDI) [where the dose intensity is defined as dose in mg/m^2/week]) of docetaxel (percent dose administered compared to the planned dose) over the first 4, 6, 8, 10, and 12 cycles between the 2 treatment arms. • To compare 1-year OS rate of NSCLC patients receiving 2nd- or 3rd-line systemic therapy with docetaxel + plinabulin (DP Arm) to patients treated with docetaxel + placebo (D5W) (D Arm).

	Exploratory efficacy objectives: • To compare the rate of new brain metastases of the DP Arm to the D arm. • To compare differences in ORR and OS based on tumor KRAS mutation status. • To compare differences in ORR, OS, and DoR based on prior PD-1/PD-L1 therapy received. • To compare the health utility obtained with the mapping of the EORTC QLQ-C30 score into European quality of life, 5-dimension, 5-level scale (EQ-5D-5L) health utility. • To compare the RDI of docetaxel, between the two treatment arms, from Cycle 1 until the first observed time point among disease progression, death, loss to follow-up, or end-of study. Safety objectives: • To compare the safety and adverse events profile of the DP Arm to D Arm. • To evaluate population pharmacokinetics in patients enrolled in China and in the Rest of the World (RoW). • To compare incidence of docetaxel dose reduction and/or docetaxel dose withheld in Cycle 2 due to Neutropenia in Cycle 1 between the 2 treatment arms. • To compare the number of docetaxel doses over all cycles. • To compare the treatment exposure-adjusted AE rates for AE of Grades 3 and 4 between the 2 treatment arms. • To compare the treatment exposure-adjusted AE rates for AE of Grade 4 between the 2 treatment arms.
NUMBER OF PATIENTS	Approximately 554 NSCLC patients will be enrolled in the study of which approximately 444 patients will be from China and approximately 110 will be from the RoW. At the second interim analysis, the study may be stopped due to superiority.
TARGET POPULATION	Patients with non-squamous or squamous NSCLC who have progressed after treatment with one or two, non-docetaxel-containing systemic treatment regimen(s) for advanced or metastatic disease and with at least one measurable lung lesion; patients might also have had failed prior immunotherapy with a PD-1/PD-L1 inhibitor.

INCLUSION CRITERIA	1. Males and females ≥ 18 years of age. 2. ECOG performance status ≤ 2. 3. Histopathologically or cytologically confirmed non-squamous or squamous non-small cell lung cancer (NSCLC). 4. Disease progression during or after treatment with one or two treatment regimen(s). Treatment regimens can be chemotherapy, targeted therapy, biological therapy, or immunotherapy for advanced (Stage IIIB) or metastatic disease (Stage IV). Modification of a regimen to manage toxicity with a different drug does not constitute a new regimen. Maintenance therapy following platinum-based chemotherapy is not considered a separate regimen. Adjuvant or neoadjuvant chemotherapy and/or chemo-radiation for early stage disease do not count as prior systemic therapy. Prior radiation therapy is not exclusionary. Prior immunotherapy with a PD-1/PD-L1 inhibitor is not exclusionary. Prior treatment for advanced or metastatic disease must have included a platinum-based regimen. (Treatment of early stage disease [Stage IIIA or earlier] with a platinum-containing therapy does not count). 5. Patients with active brain metastasis or leptomeningeal involvement with brain metastases who are asymptomatic and whose lesions by imaging are at least stable and without interim development of new lesions for at least 4 weeks may be enrolled. Patients who require continued therapy with steroid medication for management for their brain metastases are eligible; dosing must be stable for at least 4 weeks prior to randomization. 6. Patients must have at least one measurable lung lesion of ≥10 mm by CT or MRI per RECIST 1.1 criteria. Radiographic tumor assessment is to be performed within 28 days prior to randomization. 7. All patients with non-squamous NSCLC must have been tested for 19 deletion and exon 21 L858R substitution mutation. Only patients without EGFR sensitizing mutations are eligible, and they must have progressed on platinum-based chemotherapy. Patients with known ALK-rearrangements should be treated with an appropriate tyrosine kinase inhibitor (TKI) before entering the study. The TKI regimen would count as a line of treatment. 8. All adverse events of any prior systemic therapy, surgery, or radiotherapy, must have resolved to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade ≤2, except for neurological adverse events that must have resolved to Grade ≤1. 9. The following laboratory results from the central laboratory within 14 days prior to Cycle 1 Day 1 study drug administration.

	• Hemoglobin ≥9 g/dL independent of transfusion or growth factor support • Absolute neutrophil count ≥1.5 x 10^9/L independent of growth factor support • Platelet count ≥100 x 10^9/L independent of transfusion or growth factor support • Serum total bilirubin ≤ the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert's disease in which case serum bilirubin ≤3.0 times ULN • AST and ALT ≤2.5 x ULN (≤1.5 x ULN if alkaline phosphatase is >2.5 x ULN) • Serum creatinine ≤1.5 x ULN 10. Life expectancy of more than 12 weeks. 11. Female patients of childbearing potential have a negative pregnancy test at baseline. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression. a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug. b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner; c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 11b above during the treatment period and for at least 3 months after the last dose of study drug.

	12. Signed informed consent form.
EXCLUSION CRITERIA	Patients with any of the following are excluded from the study: 1. Administration of chemotherapy, immunotherapy, biological, targeted, or radiation therapy or investigational agent (therapeutic or diagnostic) within 3 weeks prior to receipt of study medication. Major surgery, other than diagnostic surgery, within 4 weeks before first study drug administration. 2. Significant cardiac history: • History of myocardial infarction or ischemic heart disease within 1 year (within a window of 18 days) before first study drug administration • Uncontrolled arrhythmia • History of congenital QT prolongation • ECG findings consistent with active ischemic heart disease • New York Heart Association Class III or IV cardiac disease • Uncontrolled hypertension: blood pressure consistently greater than 150 mm Hg systolic and 100 mm Hg diastolic in spite of antihypertensive medication 3. Patients who have received prior treatment with docetaxel. 4. Prior transient ischemic attack or cerebrovascular accident with in the past year (within an 18-day window). Any neurologic toxicities ≥ Grade 2 within 3 weeks of randomization. 5. History of hemorrhagic diarrhea, inflammatory bowel disease or active uncontrolled peptic ulcer disease. (Concomitant therapy with ranitidine or its equivalent and/or omeprazole or its equivalent is acceptable). History of ileus or other significant gastrointestinal disorder known to predispose to ileus or chronic bowel hypomotility. 6. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy. 7. Known infection with human immunodeficiency virus (HIV) or active hepatitis A, B, or C. 8. Known prior hypersensitivity reaction to any product containing polysorbate 80, polyoxyethylene 15-hydroxystearate/Macrogol 15 hydroxystearate (Solutol HS 15/ Kolliphor HS 15). 9. Female subject who is pregnant or lactating. 10. Second malignancy unless in remission for >5 years (non-melanoma skin cancer or carcinoma *in situ* of the cervix treated with curative intent is not exclusionary.) 11. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient. Examples of such conditions

	include uncontrolled diabetes, infection requiring parenteral anti-infective treatment, liver failure, any altered mental status or any psychiatric condition that would interfere with the understanding of the informed consent form. 12. Unwilling or unable to comply with procedures required in this protocol.
STUDY DESIGN	Multicenter, Phase 3, randomized, single-blinded, active-controlled trial. Only 2 treatment arms will be studied: the experimental arm (docetaxel + plinabulin [DP]) and the control arm (docetaxel + placebo [D]). Patients from the DP Arm who stop treatment with docetaxel due to toxicity or another medically acceptable reason, may continue treatment with plinabulin alone providing they meet the relevant criteria below and with agreement from the Global Medical Monitor: • The patient must have been randomized to the DP Arm of the current study • The patient must have met the criteria for discontinuing docetaxel for toxicity (• Table 5) after an appropriate dose delay and modifications to the protocol specified dose reduction of 55 mg/m^2 or if the investigator has a justifiable medical reason to discontinue docetaxel and it was discussed and agreed with the Global Medical Monitor. • The patient does not meet criteria for discontinuing plinabulin • There is no evidence of progressive disease and restaging has been obtained as described in End of Treatment • The patient must have received a minimum of 6 cycles, unless docetaxel toxicity (see Table 5) occurs regardless of the number of cycles • The Principal Investigator believes the risk: benefit to the patient is favorable compared to another treatment option • The Principal Investigator and patient agree to follow the same schedule of assessments to include safety and efficacy requirements and data entry, as outlined for the randomized portion of the study, to include re-treatment criteria. **Randomization** Eligible patients will be randomized in a 1:1 ratio between the experimental arm (DP) and control arm (D), using randomized blocks. Patients will be stratified by (1) region (China and RoW), (2) ECOG performance status (0-1 or 2), and (3) prior lines of therapy.

	Randomized patients who withdraw from the study prior to the initiation of study treatment will not be replaced. **Duration of Study** Approximately 24 months are allocated to enroll 554 patients. Patients may be treated in this study as long as he/she has evidence of clinical benefit (stable disease or a response) and in the absence of unacceptable adverse events. The primary analysis of the study data is planned after 439 deaths have been observed.
INVESTIGATIONAL PRODUCT, DOSE, ROUTE AND REGIMEN	A treatment cycle is 21 days. Treatment duration is until disease progression is confirmed by imaging studies, unacceptable toxicities are encountered, the patient withdraws from the study treatment, or in the clinical opinion of the Investigator it is not safe to continue treatment. <u>Docetaxel (DP Arm and D Arm)</u> On Day 1 of each 21-day cycle, all patients will receive docetaxel 75 mg/m^2 by intravenous (IV) infusion over 1 hour (± 10 minutes). Dose reductions for docetaxel, as deemed necessary per the docetaxel label, are to be made after Cycle 1. Premedication with dexamethasone (16 mg, given as 8 mg twice daily, IV or oral administration) will be given on the day prior to the day of dosing with docetaxel; prior to dosing on the day of the docetaxel infusion (Day 1); and the day following the docetaxel infusion (Day 2). Premedication with dexamethasone is only required to be taken when docetaxel is given. Other premedication regimens as per institutional standard clinical practice are acceptable. Anti-emetic prophylaxis will be administered according to institutional guidelines for docetaxel. <u>Plinabulin (DP Arm only)</u> On Days 1 and 8, all patients in the DP arm will receive plinabulin diluted in 5% dextrose in water (D5W) according to the randomization assignment, administered via IV infusion over 60 minutes (± 10 minutes). On Day 1, the plinabulin infusion should begin 2 hours (± 10 minutes) after the start time of docetaxel infusion, i.e., approximately 60 minutes from the end of docetaxel infusion. On Day 8 of each cycle, patients must be given an anti-emetic prophylactically before the plinabulin infusion. On Cycle 1 Day 8 palonosetron (which is not known to prolong QT/QTc intervals) is to be chosen over other serotonin-3 (5-HT$_3$) receptor antagonists. However, if palonosetron is not available, other 5-HT$_3$ receptor antagonists can be used. Tropisetron is the preferred substitute for 5-HT3 receptor antagonists other than

	palonosetron. On Day 8 of each additional cycle any anti-emetic prophylactically can be given. If emesis persists after Day 8, with a grade >1, plinabulin will be reduced to 20 mg/m^2. Patients from the DP Arm who stop treatment with docetaxel due to toxicity or another medically acceptable reason, may continue treatment with plinabulin alone as previously described. Placebo (D5W) (D arm only) On Days 1 and 8, all patients in the D arm will receive D5W as the placebo, according to the randomization assignment, administered via IV infusion in 60 minutes (± 10 minutes). On Day 1, the infusion begins 2 hours (± 10 minutes) from the starting time of docetaxel infusion, i.e., approximately 60 minutes from the end of docetaxel infusion. No 5HT3 receptor antagonist is to be administered on Day 8 with D5W. Other study related medications (DP and D arms) Institutional guidelines should be followed in the event of infusion/hypersensitivity reaction. Diphenhydramine and dexamethasone infusion may be administered in the event of infusion reaction. **STUDY PROCEDURES** **Screening**: (within 28 days prior to randomization) Screening assessments include signing of the informed consent form, obtaining the patient medical history and recording concomitant medications, NSCLC diagnosis, cancer treatment history, radiographic tumor assessments, and EGFR analyses for non-squamous histopathology. The results of assessments done as standard of care prior to the signing of the Informed Consent Document may be used as screening assessments. **Baseline Assessments**: (within 14 days prior to randomization) These assessments include physical examination, vital signs, ECOG performance status, EORTC Quality of Life questionnaire, central safety laboratory tests (hematology, chemistry, coagulation, and urinalysis), urine pregnancy test, a single ECG, and MRI of the brain (assessment can be performed up to 28 days prior to randomization). If there is any history or findings suggestive of significant heart disease, a cardiology consultation should be obtained. **Randomization**: Patients meeting all eligibility criteria will be randomized using randomized blocks, within strata. Stratified randomization will be used to randomize at a 1:1 ratio to receive docetaxel + plinabulin (DP Arm) or docetaxel + placebo (D5W) (D Arm). Stratification

	variables include geographic region (China versus RoW); ECOG status (0 or 1 versus 2); and prior lines of therapy, as follows: • 1st-line platinum containing therapy (platinum combined with anything except docetaxel); • 1st-line platinum containing therapy and 2nd-line PD-1 or PD-L1 inhibitor; • 1st-line PD-1 or PD-L1 inhibitor and 2nd-line platinum containing therapy; or • any other 1st or 2nd-line therapies (one of these 2 lines must have been a platinum-based regimen). Patients who withdraw after randomization and before study treatment will not be replaced. Every effort should be made to keep patients blinded to their treatment even though there are differences in procedures between the 2 treatment arms on Day 8. **Treatment Phase**: Before Cycle 1 Day 1, archival tumor tissue such as paraffin blocks will be obtained if available. This material will be sent for analysis including KRAS mutation and PD-L1 expression diagnostic testing. For the KRAS mutation analysis, blood panel may be used instead of tumor tissue. Blood samples for biobanking should be collected from patients who consent to the procedure (C1D1 and C2D1). Safety assessments will be performed prior to each study treatment. Patients will undergo local laboratory tests (complete blood count (CBC) with differential/platelets and clinical chemistry or per local hospital standard). Required laboratory tests to assess re-treatment criteria are detailed in Section 12.5.1. Blood draws must be done within 24 hours (or 1 day) prior to each treatment to ensure safety parameters are met. Laboratory test results for CBC and clinical chemistry need to be reviewed prior to each dose of study treatments. In addition, a central lab panel (CBC with differential/platelets and clinical chemistry) must be taken at the visit day. From Cycle 5 forward; central labs will not be required on the Day 8 visit; however, local labs must still be taken at least 1 day prior to infusion on Day 8. Assessment of response to treatment will be scheduled every 6 weeks from Cycle 1 Day 1 (screening scans used for eligibility can be used as the baseline timepoint for tumor reassessments, beginning on Cycle 1 Day 1), or sooner if the patient develops clinical signs and/or symptoms of disease progression. Treatment will continue until radiographic evidence of progressive disease is confirmed, there is unacceptable treatment-related adverse events, if the patient withdraws from the study treatment, or in the

	clinical opinion of the Investigator it is not safe to continue treatment. The patients discontinued from study treatment will be followed for survival unless consent to follow has been withdrawn. However, patient will have the option to consent to follow-up assessment even if consent for study treatment is withdrawn. Patients in the DP Arm may continue with plinabulin treatment alone, as previously described. **End-of-Treatment visit**: All patients receiving at least one dose on either treatment arm and discontinuing treatment for any reason will have an End of Treatment assessment performed on the day of discontinuation (or as soon as possible thereafter). The end of treatment assessment will include a physical examination, vital signs including body weight, and documentation of ECOG performance status, completion of the EORTC Quality of Life questionnaire, laboratory tests (hematology and clinical chemistry), MRI of the brain, single ECG, and assessment of any ongoing adverse events will be obtained. All female patients of childbearing potential will undergo a urine pregnancy test. An additional assessment of adverse events will be performed 30 days (+3 days) after last active dose of study treatment. **Follow-up visits** Follow-up visits will be required to monitor ongoing treatment-related adverse events. Patients with drug related adverse events of Grade ≥2 observed at the End-of-Treatment assessment should be followed-up at least every 4 weeks from the End of Treatment date until the adverse event has resolved to Grade ≤1, the event is determined to be chronic, or the patient receives another anti-cancer therapy. Follow-up for survival should occur monthly from the End of Treatment date. The survival follow-up is conducted by phone call. Patients should continue to be followed for survival regardless of the administration of post-study anticancer therapy.

EFFICACY, SAFETY, AND PK ASSESSMENTS	**Efficacy** Comparisons will be made between DP Arm and D Arm. The primary efficacy endpoint is overall survival (OS). The secondary efficacy endpoints include ORR, PFS, 1-year OS rate, DoR, and quality of life. **Safety** Adverse events reported by the patients or observed during physical examination, vital signs, ECGs, and laboratory tests will be recorded by severity according to NCI CTCAE v 4.03 and association with study treatment will be assessed. ECOG performance status will be monitored. Dose intensity of docetaxel will also be compared between the two treatment arms. Neutropenia (incidence of Grade 4 neutropenia on Day 8 of Cycle 1), neutrophil count on Day 8 of Cycle 1, incidence of docetaxel dose reduction and/or docetaxel dose withheld in Cycle 2 due to Neutropenia in Cycle 1. **Pharmacokinetics** All patients randomized to the DP arm will participate in the population PK study for plinabulin. Samples from a subset of 24 patients will also be analyzed for docetaxel plasma level in both treatment arms (12 in each arm). In conjunction with population PK study, ECG in triplicate will be obtained to investigate effect of plinabulin, if any, on QTc intervals.
STATISTICAL ANALYSES	**Sample Size:** A total sample size of 498 evaluable patients (split equally between the two groups), or 439 deaths, achieves 85% power to detect a hazard ratio of 0.75 when the proportions surviving at 24 months in each group are 0.080 (docetaxel) and 0.151 (docetaxel and plinabulin) at a significance level of 0.050 using a two-sided log rank test. These results assume that 3 sequential looks are made using the O'Brien-Fleming spending function to determine the test boundaries and that the survival times are exponential. These looks are planned to occur at approximately 33% (146 deaths, nominal alpha is 0.000210, sample size adjustment only), 67% (293 deaths, nominal alpha is 0.01202, hypothesis testing) and 100% (439 deaths, nominal alpha is 0.04626, final analysis) of the statistical information from the study, relating to OS (Chow et al. 2003, Lan and DeMets 1983, O'Brien and Fleming 1979). With a potential drop-out of 10% in each arm it is expected that approximately 554 patients need to be accrued into the study. A potential sample size adjustment is planned to occur at approximately 33% (146 deaths) of the statistical information, with respect to OS (Look 1). The sample size adjustment will result in

	either staying at the initially planned level or will be increased. Enrollment in China will close at approximately 444 patients. Up to approximately 110 additional patients will be enrolled in participating countries from the RoW. **Study Endpoints** **Primary Efficacy Endpoint** Overall survival (OS) **Secondary Efficacy Endpoints** • ORR • PFS • Percent of patients without severe neutropenia on Day 8 of Cycle 1 • Month 24 OS rate (vertical testing of proportions from KM estimates) • Month 36 OS rate • DoR • DoR including SD patients • Q-TWiST • QoL: EORTC QLQ-C30 global health status/QoL and the combined symptom scales/items (excluding financial difficulties) • QoL: EORTC QLQ-LC13 (Symptom combined score) • Proportion of patients who received docetaxel > 8 cycles, >10 cycles, and >12 cycles • Month 18 OS rate • RDI for Cycle 4, 6, 8, 10, and 12 • Month 12 OS rate **Exploratory Endpoint** • Rate of new brain metastases of the DP Arm to the D Arm. • KRAS mutation status correlated with other outcomes (ORR and OS) • Prior PD-l/PD-L1 therapy received correlated with other outcomes (ORR, OS, and DoR) • The health utility obtained with the mapping of the EORTC QLQ-C30 score into EQ-5D-5L health utility

	• RDI of docetaxel, between the two treatment arms, from Cycle 1 until the first observed time point among disease progression, death, loss to follow-up or end-of study The analyses of secondary endpoints will employ a hierarchical closed testing procedure, where the endpoints are ranked by clinical relevance, and tested in sequence of ORR, PFS, 1-year OS rate, DoR, and QoL as described above. No adjustment of the nominal type 1 error will be necessary, with each test at the same nominal significance level. But no confirmatory claims can be based on an endpoint with a rank lower than an endpoint whose null hypothesis could not be rejected. **Safety Endpoints** • Incidence and severity of treatment-emergent adverse event, including deaths, other serious adverse events, and other adverse events resulting in discontinuation of study treatment; • Incidence of laboratory abnormalities; • Incidence of docetaxel dose reduction and/or docetaxel dose withheld in Cycle 2 due to Neutropenia in Cycle 1 • Number of docetaxel doses over all cycles The Statistical Analysis Plan (SAP) will describe in detail how the entire EORTC QLQ-C30 and QLQ LC13 scales and items will be analyzed. **Analysis Populations** • **Intention-to-treat (ITT) population**: all randomized patients classified according to the treatment arms into which they were randomized, regardless of the actual treatment received; • **Safety Population (SP)**: all treated patients, including those receiving part or all of one dose, classified according to the actual treatment received, regardless of random assignment. In the eventuality that a patient that has been randomized to the DP Arm, at a later timepoint is taken off docetaxel due to toxicity and continues on plinabulin alone, the following analysis approach will be applied: • ITT approach: All data will be analyzed together with data from patients in the DP arm that have and have not been taken off docetaxel. • Per Protocol approach: The data that have been collected from the patient up to the timepoint that the patient continues on plinabulin alone will be used for the analysis comparing

	the 2 treatment arms. The data that have been collected after the timepoint that the patient continues on plinabulin alone will be reported separately. **Interim Data Analysis** Two interim looks and a final look are planned for this study: One interim analysis is planned to occur at approximately 33% (146 deaths) of the statistical information, with respect to OS (Look 1). At this occasion, the conditional power (the probability of rejecting a false null hypothesis at the end of the study given the data that have emerged so far) will be calculated, from which an increase in sample size might be made (Pocock 1977, Reboussin et al. 1992, Jennison and Turnbull 2000, Proschan et al. 2006). In addition, a preliminary evaluation of efficacy will be made based on the evaluation of 1-year OS rate or ORR to determine if an early NDA filing with the NMPA is justifiable (see below) but will not have an impact on the study design or future conduct of the study. These calculations will be made by the independent statistician. The only information that will be conveyed is: 1. What the increase in sample size will be or if the sample size will remain the same 2. If an early NDA with the NMPA can be justified based on 1-year OS rate or ORR results. There will be no attempt of making any additional hypotheses testing of any kind at this occasion. The data from the first interim analysis (Look 1) will serve as the dataset to be submitted to the independent statistician, for the purpose of evaluating conditional power and potential sample size adjustment based on OS. At this occasion, efficacy and safety evaluations will be made for the assessment of initial benefit/risk. Based on changes in the regulatory environment in China, contingent approvals can be granted based on promising interim analysis results in areas of unmet medical need. A separate team, independent from the study 103-team, will have as its mission to evaluate and determine if the results at the time of Look 1 can justify an early NDA submission in China; this will be outlined in a specific Charter. If this is the conclusion of this team, then the team will prepare the early submission documents; this will also be outlined in the specific Charter. None of the outcomes from the evaluation for the early NDA submission will be used to make any other decisions regarding the future conduct of the study. The study is expected to be fully enrolled at the time of the early NDA review by the China FDA. For an early NDA submission, data accumulated up to the first interim look will be used. The specific Charter will be developed that

	will outline the focus and content of the submission, as well as who the individuals are (limited number of people), their roles and responsibilities, logistics, a detailed timeline, and an analysis plan. The second interim look (Look 2) is planned to occur at approximately 67% (293 deaths) of the statistical information, with respect to OS. If the test of OS meets the nominal significance level at this second interim look, the study will be deemed to be positive and further patient accrual and follow-up for OS will stop. At this second interim look, the following 2 analyses will also be conducted: • The proportion of patients with Grade 4 neutropenia in Cycle 1 Day 8 will be compared between the 2 treatments arms, DP and D, with the 2-sided Barnard's test; • DoR: percentages and confidence intervals will be calculated using Kaplan-Meier and Nelson-Aalen methods, and p-value for treatment comparison will be calculated using the log-rank test. The third look (Look 3) will be the final look. **Pharmacokinetics** Population pharmacokinetic analyses will be conducted to evaluate the effect of intrinsic and extrinsic factors on the PK of plinabulin and its active metabolite(s), if identified. Drug-drug interaction between plinabulin and docetaxel will be investigated. The pharmacokinetics of docetaxel in a subpopulation of patients from China and the RoW will be compared.