Protocol Title

Randomized Phase II Trial of single agent chemotherapy plus Nivolumab or single agent chemotherapy alone in patients with advanced squamous, non-squamous or not otherwise specified NSCLC with primary resistance to prior PD-1 or PD-L1 inhibitor
HCRN LUN15-233

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 16OCT2018

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

_____

Site Investigator Title

_____

Name of Facility

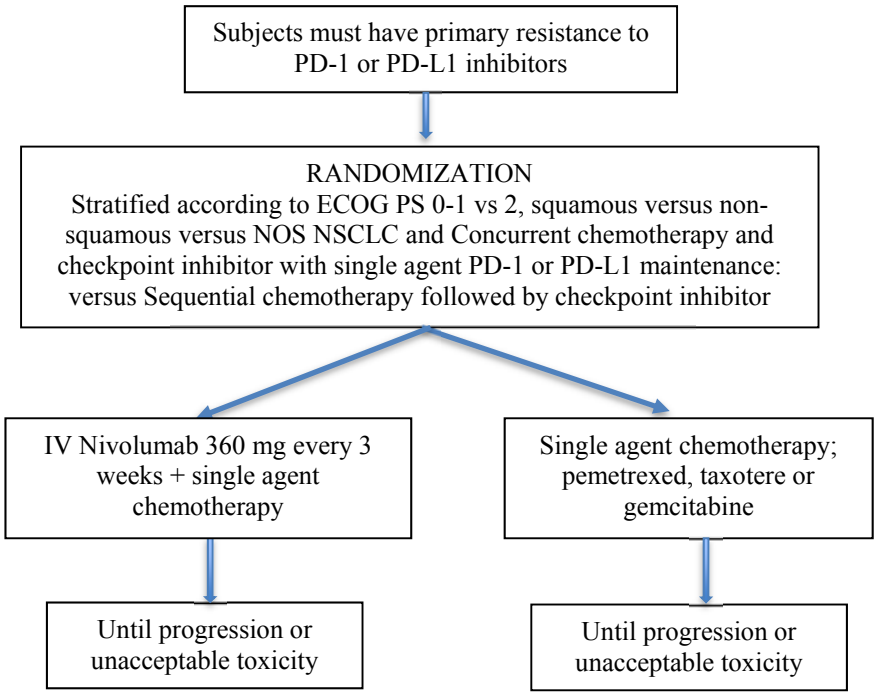
_____

Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	Randomized Phase II Trial of single agent chemotherapy plus Nivolumab or single agent chemotherapy alone in patients with advanced squamous, non-squamous or not otherwise specified NSCLC with primary resistance to prior PD-1 or PD-L1 inhibitor; HCRN LUN15-233
SHORT TITLE	Single agent chemotherapy plus Nivolumab or single agent chemotherapy alone in patients with advanced NSCLC with primary resistance to prior PD-1 or PD-L1 inhibitor
PHASE	Phase 2, randomized
OBJECTIVES	Primary Objective: Determine Progression Free Survival (PFS) according to RECIST 1.1 criteria for subjects with primary resistance to prior PD-1 or PD-L1 inhibitor when administered Nivolumab with single agent chemotherapy compared to single agent chemotherapy alone. Secondary Objectives: • Assess toxicity of Nivolumab plus single agent chemotherapy compared with single agent chemotherapy alone • Estimate the response rate and clinical benefit of treatment (defined by stable, partial response, or complete response disease for at least 3 months) in each arm by both RECIST 1.1 and immune-related response criteria (irRECIST) • Determine PFS by irRECIST criteria Exploratory Objectives: • Assess the PD-L1 status of the tumor at the following time points: o OPTIONAL: Baseline from archival tissue o OPTIONAL: At time of progression on PD-1 or PD-L1 inhibitor from new biopsy or fine needle aspirate (FNA) (prior to randomization to Nivolumab plus single agent chemotherapy vs. single agent chemotherapy alone) • Compare genetic analysis (Sequencing of select exons of AKT1, BRAF, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, KIT, KRAS, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SMO, SRC, TP53, as well as ALK FISH, HER2 FISH, MET FISH, PTEN FISH, RET FISH, ROS1 FISH and PD-L1 IHC) at the following timepoints: o OPTIONAL: Baseline from archival tissue o OPTIONAL: At time of progression on PD-1 or PD-L1 inhibitor from new biopsy/FNA (prior to randomization to Nivolumab plus single agent chemotherapy vs. single agent chemotherapy alone) • Explore the association of proteomic tests at baseline with measures of response including OS and PFS.

	• Explore changes over time and associations with toxicity and response including OS and PFS.
STUDY DESIGN	
ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	**Inclusion Criteria** 1. ECOG Performance Status of 0-2 within 28 days prior to randomization. 2. Histological or cytological confirmed squamous or non-squamous or not otherwise specified (NOS) non-small cell lung cancer. 3. Measurable disease according to RECIST 1.1 within 28 days prior to randomization. 4. Subjects must meet one of the following treatment groups: • **Concurrent chemotherapy and checkpoint inhibitor with single agent PD-1 or PD-L1 maintenance:** If subjects receive platinum-based doublet therapy concurrently with checkpoint inhibitor followed by single agent PD-1 or PD-L1 maintenance, then primary resistance to PD-1 or PD-L1 is defined as progressive disease after ≤ 3 treatments on single agent PD-1 or PD-L1 maintenance treatment • **Sequential chemotherapy followed by checkpoint inhibitor:** If subjects receive platinum-based doublet therapy without concurrent checkpoint inhibitor, then primary resistance to PD-1 or PD-L1 is defined as progressive disease after ≤ 3 treatments on single agent PD-1 or PD-L1 monotherapy 5. Most recent therapy does not have to have been a checkpoint inhibitor. Intercurrent treatment is acceptable as long as subjects meet all other inclusion criteria.

	6. Subjects must have recovered from all reversible acute toxic effects (other than alopecia) to ≤ Grade 1 or baseline. 7. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to randomization. **Exclusion Criteria** 1. Previous autoimmune complication from PD-1 or PD-L1 inhibitor requiring discontinuation of therapy. 2. Prior treatment with the single agent chemotherapy the site investigator chooses to use for this protocol (pemetrexed, taxotere or gemcitabine). 3. Subjects whose tumors express EGFR mutations on exons 19 and 21, ALK rearrangement, or ROS1 rearrangement who still have FDA approved targeted therapy options.
STATISTICAL CONSIDERATIONS	• Null hypothesis - both arms will have a median PFS of 3 months (constant hazard ratio = 1). • Alternative hypothesis - Nivolumab plus single agent chemotherapy arm will have a median PFS of 6 months (constant hazard ratio = 2) The primary analysis will be to compare PFS in the two groups using a log-rank test. Kaplan-Meier plots will also be generated. Groups will be compared for response rate and clinical benefit using chi-square tests. PD-L1 status of the tumors at baseline, at time of progression on PD-1 or PD-L1 inhibitor, and at time of progression on combination of Nivolumab and single agent chemotherapy in subjects who had clinical benefit will be compared using paired t-tests. Toxicities will be tabulated.
TOTAL NUMBER OF SUBJECTS	N = 62 subjects The trial will enroll patients for 24 months and have a minimum follow-up of 24 months. The total study duration is 4 years. Uniform patient entry is assumed for both groups. The number of events needed to achieve an 80% power with 1-sided test at 0.05 level of significance is 51. Assuming a drop-out rate of approximately 3% uniformly during the study duration, we anticipate to recruit 62 patients (31 in chemotherapy plus nivolumab and 31 in chemotherapy alone). The accrual rate is estimated to be about 31 per year.
ESTIMATED ENROLLMENT PERIOD	Estimated 12 months
ESTIMATED STUDY DURATION	Estimated 36 months

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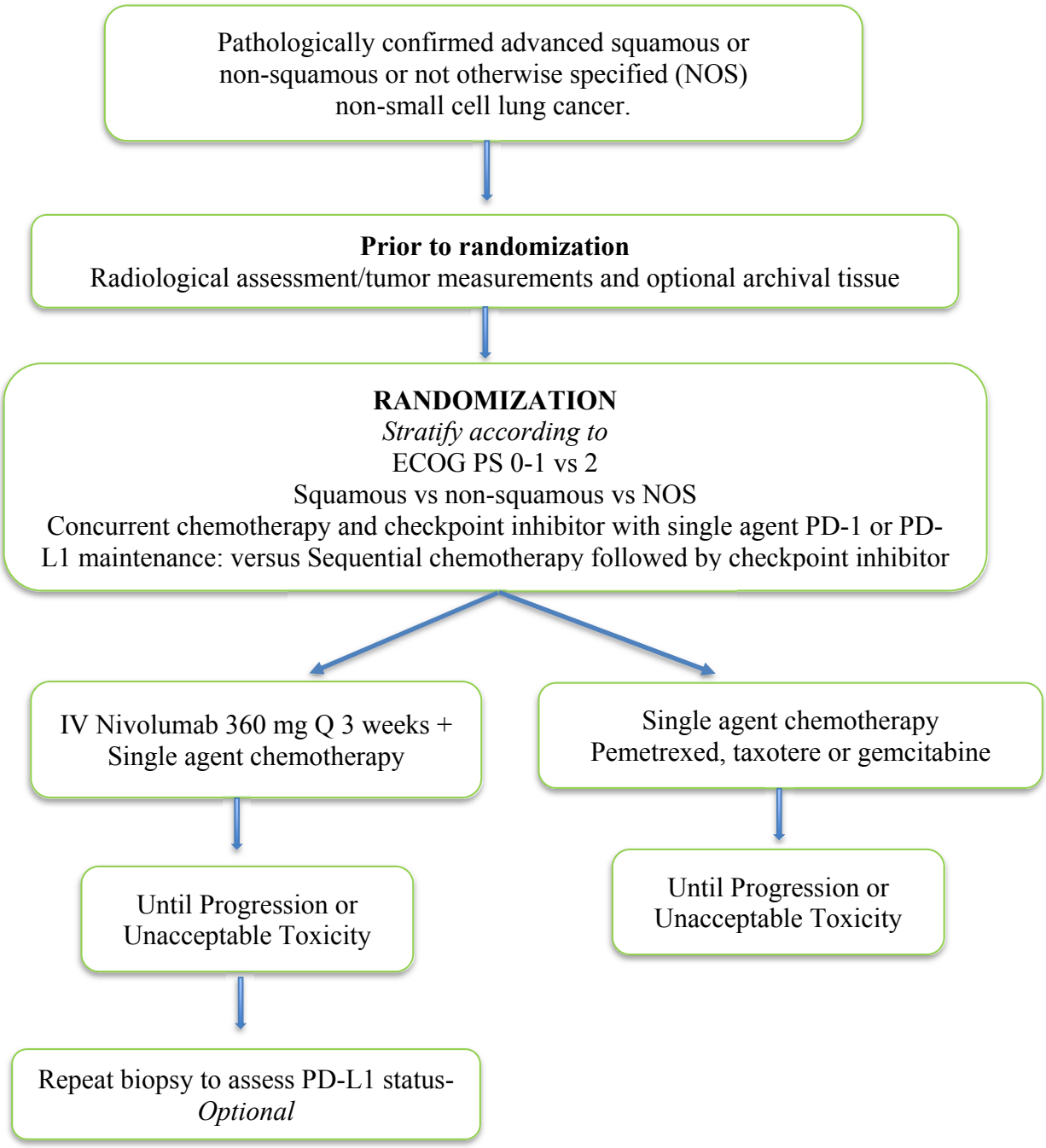
SCHEMA


Pathologically confirmed advanced squamous or non-squamous or not otherwise specified (NOS) non-small cell lung cancer.
Prior to randomization
Radiological assessment/tumor measurements and optional archival tissue
RANDOMIZATION
Stratify according to
ECOG PS 0-1 vs 2
Squamous vs non-squamous vs NOS
Concurrent chemotherapy and checkpoint inhibitor with single agent PD-1 or PD-L1 maintenance: versus Sequential chemotherapy followed by checkpoint inhibitor
IV Nivolumab 360 mg Q 3 weeks + Single agent chemotherapy
Single agent chemotherapy Pemetrexed, taxotere or gemcitabine
Until Progression or Unacceptable Toxicity
Until Progression or Unacceptable Toxicity
Repeat biopsy to assess PD-L1 status- Optional

1. BACKGROUND AND RATIONALE

1.1 Background of non-small cell lung cancer

Lung cancer is the second most common malignancy in both men and women after prostate and breast cancer, respectively. [1] Over 80% of lung cancer cases are non-small cell lung cancer (NSCLC), and it is broadly divided into squamous cell carcinoma and non-squamous cell carcinoma that comprises adenocarcinoma, large-cell, and other histological subtypes. [2] Lung cancer remains the leading cause of cancer related mortality in the U.S. and around the world. In 2015, it was estimated that 221,200 cases would be diagnosed, and 158,040 patients would die from lung cancer in the U.S.A. [1] The 5-year survival rate for lung cancer is only 17.4%, mainly because most patients have advanced disease at time of diagnosis.

1.2 Current Standard of Care in the treatment of advanced, metastatic non-squamous, NSCLC

The current standard of care for treatment of patients with metastatic non-squamous, NSCLC depends on whether the tumors are suitable for targetable therapies. Patients whose tumors carry sensitizing EGFR mutations (Exon19del/ LREA deletion and L858R), ALK gene rearrangements, ROS1, or some MET tyrosine kinases (high-level MET amplification or MET exon 14 skipping mutation) – these patients are treated with targeted therapies. Patients with EGFR mutations receive EGFR inhibitors such as erlotinib, gefitinib, or afatinib as the first line. Patients with ALK gene rearrangements, ROS1 or sensitizing MET tyrosine kinases are treated with crizotinib as first line therapy.

For the majority of patients who are not candidates for targeted therapy and have good performance status (usually defined as an Eastern Cooperative Group, ECOG performance status of 0-2), platinum-based doublet chemotherapy has been shown to prolong survival and improve quality of life and is now established as a standard of care. With first line chemotherapy, the 1 year survival rates are between 30-40%. Bevacizumab may also be combined with paclitaxel/ carboplatin in the first line setting for non-squamous NSCLC. [2]

In the second line setting, the immune checkpoint inhibitors programmed death receptor-1 (PD-1) Nivolumab and Pembrolizumab have received FDA approval for use in the second line setting for all patients with NSCLC; Pembrolizumab is approved only for patients with PD-L1 positive tumors, and both agents have been proven to be superior to single-agent Docetaxel with a better toxicity profile and are now the preferred second line agents in patients who have progressed on chemotherapy. [3-6]

For patients who progress on PD-1 inhibitors and continue to have good performance status, or who are ineligible to receive PD-1 inhibitors, docetaxel alone or may be combined with ramucirumab, an anti-angiogenic agent to improve both response rates and overall survival. [7] EGFR inhibitors are also approved for use in the second line setting in patients who have progressed on platinum-doublet based chemotherapy regardless of EGFR mutation status. [2]

1.3 Background of Nivolumab

Immunotherapy, in particular immune checkpoint inhibitors for programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) have been found to be clinically active in NSCLC, both squamous and non-squamous subtypes. PD-1 is a T-cell co-receptor that, when activated, suppresses antitumor immunity by its interaction with its ligands, PD-L1 and PD-L2. It has been proposed that this is one of the mechanisms by which NSCLC proliferates and escapes the immune system. PD-L1 expression on lung cancer cells have been shown to be associated with a worse prognosis. In addition, blockade of the PD-1 antibody was associated with improved survival and enhancement of effector T cell function.

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody that targets the PD-1 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification. [8]

Checkmate 017, a randomized phase III study comparing Nivolumab and Docetaxel in the second line setting in patients with unresectable or metastatic NSCLC Squamous cell subtype demonstrated significant improvement in overall survival (OS) in patients treated with Nivolumab monotherapy from 6.0 months to 9.2 months which was clinically meaningful and statistically significant with a HR=0.59 [96.85% CI: 0.43, 0.81]); stratified log-rank test p-value = 0.0002). Nivolumab treatment also resulted in a clinically meaningful and statistically significant improvement in PFS with a 38% reduction in the risk of progression as compared with docetaxel. This trial led to the FDA approval of Nivolumab in this subset of patients. [3]

Checkmate 057 was another randomized phase III study looking at Nivolumab versus Docetaxel, this time in the adenocarcinoma subtype in unresectable or metastatic NSCLC, in patients who progressed on a platinum-based doublet chemotherapy. Nivolumab monotherapy demonstrated superior OS compared with docetaxel (median OS 12.2 months versus 9.4 months in the Docetaxel arm), with a clinically meaningful and statistically significant improvement observed (HR=0.73 [95.92% CI: 0.59, 0.89]; stratified log-rank test p-value = 0.0015). The PFS was not statistically different between treatment groups; however, while the median PFS favored docetaxel, the overall HR and 1-year PFS rate favored Nivolumab, indicating the potential for long-term PFS benefit from Nivolumab in a subset of subjects.

Results of secondary endpoints of ORR, DOR, and TTR further support the antitumor activity of Nivolumab in both squamous and non-squamous NSCLC subjects. Both studies found that the safety profile of Nivolumab was more favorable than chemotherapy with only 11% of patients with grade 3-4 events (mainly consisting of fatigue, anorexia, and pneumonitis), compared to Docetaxel where 55% patients had grade 3-4 adverse events (neutropenia, fatigue, alopecia, and nausea). Based on this study, Nivolumab has received FDA approval for use in the second line setting in patients with adenocarcinoma of the lung. [4, 8]

Note: With monotherapy, there is no pattern in the incidence, severity, or causality of adverse effects (AEs) to nivolumab dose level. In Phase 3 controlled studies, the clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. [8]

1.4 Background of combination chemotherapy and Nivolumab in patients with advanced NSCLC

Checkmate 012 is an ongoing phase 1 dose de-escalation, four-cohort study looked at chemotherapy-naive patients with advanced NSCLC (both squamous and non-squamous) treated with Nivolumab 10mg/kg (N10) 3-weekly versus 5mg/kg (N5) 3-weekly in combination with a platinum doublet (gemcitabine/cisplatin plus N10 for squamous histology, pemetrexed/cisplatin plus N10 for non-squamous subtypes, paclitaxel/carboplatin plus N10 vs. N5 in both subtypes) in the first line setting, with the platinum doublet given for 4 cycles, followed by maintenance Nivolumab until progression of disease or unacceptable toxicity. 56 patients were enrolled and no dose-limiting toxicities were observed in the first 6 weeks of trial with a maximum dose of Nivolumab 10mg/kg, hence there was no maximum tolerated dose defined in combination with chemotherapy.

At median follow-up of 75 weeks, Grade 3-4 adverse effects were reported in 45% of patients across all arms, comprising of pneumonitis, fatigue, and acute renal failure (ARF). The most common reported adverse event was fatigue (71.4%). 20% (11 patients) discontinued study medication due to treatment-related adverse effects; pneumonitis, ARF, colitis, hypersensitivity, and allergic nephritis.

ORR was 33% (N10 + gemcitabine/cisplatin), 47% (N10 + pemetrexed/cisplatin), 47% (N10 + paclitaxel/carboplatin) and 43% (N5 + paclitaxel/carboplatin), with the median duration of response being 45 weeks, 25.4 weeks, 23.9 weeks, and not reached, respectively. PFS at week 24 was 51%, 71%, 38%, and 51%, respectively. One-year OS rates were 50%, 87%, 60%, and 85%, respectively; median OS was 50.5 weeks, 83.4 weeks, 64.9 weeks, and NR, respectively. All deaths in this cohort of patients were related to disease progression. These results were considered acceptable at the expense of additive toxicity of the Nivolumab with chemotherapy, but have not surpassed the current standard of care and is not current practice. [9]

Current ongoing studies (Checkmate 370, NCT02574078) are looking at the combination of Nivolumab either as monotherapy or in combination with standard chemotherapy and Bevacizumab in the first line setting as well as Nivolumab maintenance following chemotherapy in all patients with advanced NSCLC regardless of histological subtype. The aim of the study is to look for clinical benefit and the toxicity profile in the combination arms.

PembroPlus (NCT02331251) is another study looking at the combination of PD-1 inhibitor Pembrolizumab in combination with chemotherapy in advanced solid tumors, but this does not include patients with NSCLC. Another study (not yet recruiting patients, NCT02574598) will evaluate the combination of Pembrolizumab and Docetaxel vs. Docetaxel monotherapy in the second line setting to assess the efficacy of the combination arm along with the safety profile.

1.5 Activity of chemotherapy after administration of PD-1/PD-L1 inhibitors in NSCLC

Recent studies have evaluated the antitumor effects of salvage chemotherapy administered after immunotherapy in patients with NSCLC. Park et al reported on 73 patients, 10 who received PD-1/PD-L1 inhibitors as first line therapy and 63 who received PD-1/PD-L1 inhibitors after prior chemotherapy (19). They reported an overall response rate for chemotherapy of 39.5-66.7% in these populations. This activity far exceeds historical controls of chemotherapy in similar settings (10-30%). The mechanism by which chemotherapy may be more active after exposure to immunotherapy is not fully understood. One preclinical study supports the superiority of the sequence of immunotherapy followed by chemotherapy (20). Mice bearing lung cancer tumors shrunk markedly when exposed to immunotherapy followed by chemotherapy, whereas immunotherapy alone did not shrink the tumors and chemotherapy followed by immunotherapy resulted in only slight tumor shrinkage.

1.6 Rationale of combination chemotherapy and Nivolumab after progression on Nivolumab monotherapy in the second line setting

The concept of maintenance therapy with a targeted agent and adding onto it at the time of disease progression is a proven effective strategy in several disease settings. For example, in patients with metastatic colon cancer the continued use of Bevacizumab (combined with a new chemotherapy agent) beyond progression has resulted in improved survival when compared with abandoning Bevacizumab and changing to a new chemotherapy agent alone. [10] Similarly, the continued use of Herceptin in combination with chemotherapy after progression on Herceptin in HER2neu positive metastatic breast cancer improves outcomes in patients with breast cancer compared with abandoning HER-2 therapy and switching to chemotherapy alone. [11]

The mechanism of resistance to PD-1 inhibitors after prior response is poorly understood. As seen in prior trials looking at PD-1 inhibitors in NSCLC and PD-L1 status, there are patients whose tumors express PD-L1 that do not respond, and patients without PD-L1 expression who have sustained response to PD-1 inhibitors. Although data are lacking in this area, there are many theories about both the intrinsic and acquired resistance to immune checkpoint inhibitors.

It has been shown in many tumor types that the presence of lymphocytic infiltrates with CD4 and CD8 T-cells within the tumor correlates with better outcomes. The principle of immune checkpoint inhibitors is to reactivate the endogenous tumor-specific T-cell immune response leading to tumoricidal activity. However there is a subset of patients whose tumors lack lymphocytic infiltrates or who fail to produce a T-cell response with immune therapy thereby having intrinsic resistance. Tumors with low mutational burden have also been shown to have intrinsic resistance to the immune checkpoint inhibitors, likely by expressing fewer antigens that are recognized as foreign by the immune system, hence more likely to evade immune detection compared to tumors with a higher mutational load such as smoking-related NSCLC. The last theory is that the tumor microenvironment may prevent T-cells from exerting their effector function leading to intrinsic resistance. TGF-b, IL-10 and IDO are inhibitory molecules that have a direct negative effect on T-cell function in the microenvironment. The immature dendritic cells, myeloid derived suppressor cells or (inducible) regulatory CD4 T-cells within the microenvironment may also have an indirect effect on immune therapy. Additionally, the loss of MHC class 1 expression in certain tumor cell population/subclones or other defects in antigen processing cascade may cloak the tumor cells from the immune system.

Therapy-induced resistance, occurs when patients initially respond to immunotherapy then relapse or progress. This may be a result of immune-editing. This occurs when a heterogeneous tumor selects out clones that lack antigens that stimulate the immune response resulting in immune evasion. To overcome resistance, it is possible that pre-conditioning of the tumor in the form of chemotherapy, or radiation therapy may promote an immune supportive tumor microenvironment that may re-sensitize the tumors to the effects of immune therapy. [12]

Based on these data, we hypothesize that in patients who have primary resistance to prior PD-1 or PD-L1 inhibitor will experience clinical benefit from use of Nivolumab in combination with single agent chemotherapy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Determine progression free survival (PFS) for subjects with primary resistance to prior PD-1 or PD-L1 inhibitor when administered Nivolumab with single agent chemotherapy compared to single agent chemotherapy alone.

2.1.2 Secondary Objectives

- Assess toxicity of Nivolumab plus single agent chemotherapy compared with single agent chemotherapy alone.
- Estimate the response rate (RR) and clinical benefit rate of treatment (CBR)
- Determine PFS by irRECIST criteria.

2.1.3 Correlative/Exploratory Objectives

- Assess the PD-L1 status of the tumor at the following time points:
  - OPTIONAL: Baseline from archival tissue
  - OPTIONAL: At time of progression on a PD-1 or PD-L1 inhibitor from new biopsy/FNA (prior to randomization to Nivolumab plus single agent chemotherapy vs. single agent chemotherapy alone)
- Compare genetic analysis (Sequencing of select exons of AKT1, BRAF, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, KIT, KRAS, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SMO, SRC, TP53, as well as ALK FISH, HER2 FISH, MET FISH, PTEN FISH, RET FISH, ROS1 FISH and PD-L1 IHC) at the following timepoints:
  - OPTIONAL: Baseline from archival tissue
  - OPTIONAL: At time of progression on a PD-1 or PD-L1 inhibitor from new biopsy/FNA (prior to randomization to Nivolumab plus single agent chemotherapy vs. single agent chemotherapy alone)
- Explore the association of proteomic tests at baseline with measures of response including OS and PFS.
- Explore changes over time and associations with toxicity and response including OS and PFS.

2.2 Endpoints

2.2.1 Definition of Primary Endpoint

The primary endpoint is PFS; defined as the time from date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause. If a patient does not have any event (disease progression or death), PFS will be censored at the date of last follow-up.

2.2.2 Definition of Secondary Endpoints

- Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4
- Overall response rate (ORR) refers to the proportion of subjects with reduction in tumor burden according to RECIST 1.1 and immune-related response criteria (irRECIST) criteria.
- Clinical Benefit Rate (CBR) is defined by (defined by stable, partial response, or complete response disease for at least 3 months) in each arm by both RECIST 1.1 and irRECIST criteria.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0-2 within 28 days prior to randomization.

4. Histological or cytological confirmed squamous or non-squamous or not otherwise specified (NOS) non-small cell lung cancer.

5. Measurable disease according to RECIST 1.1 within 28 days prior to randomization.

6. Subjects must meet one of the following treatment groups:
   - **Concurrent chemotherapy and checkpoint inhibitor with single agent PD-1 or PD-L1 maintenance:** If subjects receive platinum-based doublet therapy concurrently with checkpoint inhibitor followed by single agent PD-1 or PD-L1 maintenance, then primary resistance to PD-1 or PD-L1 is defined as progressive disease after ≤ 3 treatments on single agent PD-1 or PD-L1 maintenance treatment
   - **Sequential chemotherapy followed by checkpoint inhibitor:** If subjects receive platinum-based doublet therapy without concurrent checkpoint inhibitor, then primary resistance to PD-1 or PD-L1 is defined as progressive disease after ≤ 3 treatments on single agent PD-1 or PD-L1 monotherapy

7. Most recent therapy does not have to have been a checkpoint inhibitor. Intercurrent treatment is acceptable as long as subjects meet all other inclusion criteria.

8. Subjects must have recovered from all reversible acute toxic effects (other than alopecia) to ≤ Grade 1 or baseline.

9. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to randomization.

System	Laboratory Value
Hematological	
White blood cell (WBC)	≥ 2 k/mm^3
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Platelet	>100k
Renal	
Estimated creatinine clearance[1] OR	≥ 40 cc/min
Serum creatinine	≤ 1.5 x upper limit of normal (ULN)
Hepatic	
Bilirubin	1.5 ≤ (ULN)[2]
Aspartate aminotransferase (AST)	≤ 1.5 × ULN
Alanine aminotransferase (ALT)	≤ 1.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 2 × ULN (Note: use of vitamin K antagonist is not allowed)

1 Cockcroft-Gault formula will be used to calculate creatinine clearance (See SPM)
2 Except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL

10. A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to randomization, have been off of corticosteroids for ≥ 2 weeks, and are asymptomatic.

11. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test **within 14 days** prior to registration. WOCBP randomized to Arm A must also have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) **within 24 hours** prior to the start of Nivolumab then **every 6 weeks** thereafter. WOCBP on randomized to Arm B do not require a pregnancy testing during treatment. **NOTE:** Women are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are post-menopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

12. Women of childbearing potential randomized to Arm A must be willing to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until 5 months after treatment discontinuation. Women cannot breast feed from the

time of informed consent to 5 months after last dose of study treatment. See below for adequate methods of contraception. Women randomized to Arm B should be instructed to abstain from heterosexual activity or use an effective method of contraception from the time of informed consent until a timeframe as suggested by the package insert for the single agent chemotherapy.

13. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men randomized to Arm A who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab. Men randomized to Arm B who are sexually active with WOCBP will be instructed to adhere to contraception for a timeframe as suggested by the package insert for the single agent chemotherapy. See below for methods of contraception.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

* A male and female condom must not be used together

14. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Prior treatment with the single agent chemotherapy the site investigator chooses to use for this protocol (pemetrexed, taxotere or gemcitabine).

2. Previous autoimmune complication from PD-1 or PD-L1 requiring discontinuation of therapy or treatment with steroids (ongoing treatment with more than 10 mg of prednisone or steroid equivalent daily, excluding inhaled or topical steroids).
3. Previous discontinuation from PD-1 or PD-L1 due to an adverse event.

4. Any serious or uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy.

5. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

6. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least five years.

7. Active central nervous system (CNS) metastases. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for [lowest minimum is ≥ 4 weeks] after treatment is complete and within 28 days prior to study randomization. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

8. Treatment with any investigational drug within 30 days prior to randomization.

9. Subjects whose tumors express EGFR mutations on exons 19 and 21, ALK rearrangement, or ROS1 rearrangement who still have other FDA approved targeted agents available for treatment.

10. Subjects with an active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger. (Subjects with vitiligo, autoimmune thyroiditis, or type I diabetes mellitus are permitted to enroll.)

11. As there is potential for hepatic toxicity with Nivolumab, drugs with a predisposition to hepatoxicity should be used with caution in subjects treated with Nivolumab-containing regimen.

12. Any positive test result for hepatitis B virus or hepatitis C virus indicating current presence of virus, (Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

13. Subjects with known acquired immunodeficiency syndrome (AIDS).Subjects with a positive test result for human immunodeficiency virus (HIV) (positive HIV 1/2 antibodies) may be eligible if their CD4+ T-cell counts ≥ 350 cells/μL, they are stable and have been on treatment for ≥ 4 weeks before initiation of nivolumab.

14. History of allergy to study drug components.

15. Prior solid organ or stem cell transplant.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered and randomized prior to starting protocol therapy. Subjects must begin therapy **within 14 days** of randomization.

4.1 Randomization and Stratification

Upon registration, subjects will be randomized in a 1:1 ratio to either treatment with single agent chemotherapy alone or single agent chemotherapy in combination with nivolumab. Randomization is un-blinded and open-label; therefore there will be no placebo treatment for subjects randomized to single agent chemotherapy.

Stratification factors for randomization are to include:

- ECOG PS 0 or 1 versus 2
- Squamous versus non-squamous versus NOS non-small cell lung cancer
- Concurrent chemotherapy and checkpoint inhibitor with single agent PD-1 or PD-L1 maintenance: versus Sequential chemotherapy followed by checkpoint inhibitor

5. TREATMENT PLAN

This is a randomized phase II study assessing the activity of single agent chemotherapy combined with nivolumab (Arm A) compared to single agent chemotherapy alone (Arm B) in squamous or non-squamous or NOS NSCLC subjects with primary resistance to prior PD-1 or PD-L1 inhibitor as defined above. The single agent chemotherapy chosen is at the discretion of the site investigator and may include pemetrexed, gemcitabine or taxotere. Institutional standards should be used for administration of the single agent chemotherapy. For both treatment arms, 21 days equals 1 cycle of therapy and subjects will be eligible to continue treatment until progressive disease by RECIST v1.1 or unacceptable toxicity.

Arm A: Single agent chemotherapy of choice (pemetrexed, gemcitabine or taxotere) plus nivolumab 360 mg IV every 21 days

Arm B: Single agent chemotherapy of choice (pemetrexed, gemcitabine or taxotere)

5.1 Pre-medications and Hydration

There are no required pre-medications or intravenous hydration for treatment with either the chemotherapy as listed below or nivolumab. Please follow institutional standards for pre-medications and/or intravenous hydration for treatment with either the chemotherapy or nivolumab

5.2 Nivolumab and Chemotherapy Administration

Arm	Drug	Administration Sequence	Dose[1]	Route	Schedule[2]	Cycle Length
Arm A	Nivolumab	1st	360 mg	IV over 30 minutes	Day 1	21 days
Arm A and Arm B	Gemcitabine	2nd	1000mg/m^2	IV	Days 1, 8	21 days
	Taxotere		60-75mg/m^2	IV	Day 1	
	Pemetrexed[3]		500mg/m^2	IV	Day 1	
[1] Body surface area (BSA) should be recalculated per institutional standards for weight changes .						
[2] A window of ±3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).						
[3] Cyanocobalamin (vitamin B_{12}) should be given at a dose of 1000mcg intramuscularly every 3 cycles (9 weeks), and folic acid should be given at a dose of 1mg PO daily while on pemetrexed.						

5.2.1 Taxotere Administration

Taxotere 75 mg/m^2 will be administered intravenously over 60 minutes (± 15) on Day 1 of each 21 day Cycle. Institutional standards will be used regarding the infusion.

5.2.2 Pemetrexed Administration

Pemetrexed 500mg/m^2 will be administered over 10 minutes (± 5) on Day 1 of each 21 day Cycle. Institutional standards will be used regarding the infusion.

5.2.3 Gemcitabine Administration

Gemcitabine 1000 mg/m2 IV will be administered intravenously over 30 minutes (± 5) on Day 1 and 8 of each 21 day Cycle. Institutional standards will be used regarding the infusion.

5.2.4 Nivolumab Administration

Nivolumab administration only applies to subjects randomized to Arm A. Nivolumab will be delivered over 30 (± 15) minutes intravenously on Day 1 of each 21 day Cycle. Nivolumab should be administered first followed by chemotherapy of choice by the site investigator.

5.3 Concomitant Medications

All concomitant medications should be reported to the site investigator and recorded on the appropriate eCRF.

5.3.1 Allowed Concomitant Medications

All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care.

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (eg, prednisone ≤ 10 mg/day) are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. The potential for overlapping toxicities with radiotherapy and Nivolumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving Nivolumab. If palliative radiotherapy is required, then Nivolumab should be withheld for at least 1 week before, during and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming Nivolumab. Only non-target bone lesions without lung tissue included in the planned radiation field may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

5.3.2 Prohibited Concomitant Medications

The following strong CYP3A4 inhibitors should be avoided during the study. This includes (but is not limited to):

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanvir
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.2).

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC).

* Palliative and supportive care for disease related symptoms (including local radiotherapy, bisphosphonates and RANK-L inhibitors) may be offered to all subjects prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to randomization per Inclusion Criteria 3.1).

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

6.1.1 Dose Delays for Nivolumab

Please refer to the current Investigator's Brochure for additional information regarding Adverse Event Management Algorithms.

Dose reductions or dose escalations of Nivolumab are not permitted. Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab). All study drugs must be delayed until treatment can resume.

Nivolumab administration should be delayed for the following:

Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Grade 3 skin, drug-related AE

Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

- Grade ≤ 3 lymphopenia or leukopenia does not require dose delay.
- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has a baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The

sponsor-investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the site investigator, warrants delaying the dose of study medication.
Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

6.1.2 Criteria to Resume Treatment with Nivolumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month will be eligible to restart treatment at the discretion of the treating physician.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment at the discretion of the treating physician.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

6.1.3 Discontinuation Criteria for Nivolumab

Treatment should be permanently discontinued for the following:

- Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation

  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT > 8 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
  - Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
- Grade 4 drug-related endocrinopathy adverse events require discontinuation with the following exceptions: adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively. The sponsor-investigator must be consulted.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the sponsor-investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
  - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the sponsor-investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the sponsor-investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the sponsor-investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

6.1.4 Dose Modifications for Taxotere

Drug	Dose Level	Dose
Taxotere	Full Dose	60-75 mg/m^2/d
Taxotere	Dose Level –1	20% reduction of full dose
Taxotere	Dose Level –2	40% reduction of full dose

Subjects who permanently discontinue taxotere due to toxicity but who have not progressed may remain on single-agent nivolumab until progression or intolerable toxicity.

6.1.4.1 Hematologic Adjustments

- Grade 3 febrile neutropenia should be retreated after recovery with a one level dose reduction.
- Grade 4 neutropenia lasting > 7 days should be retreated after recovery with a one level dose reduction.
- Grade 4 thrombocytopenia or thrombocytopenic bleeding should be retreated after recovery with a one level dose reduction.

6.1.4.2 Peripheral Neuropathy Adjustments

- Grade 2 = subsequent retreatment after recovery should be with a one level dose reduction.
- Grade 3 or higher peripheral neuropathy toxicity = discontinuation of study treatment.

6.1.4.3 Hypersensitivity Reaction Adjustments

- No dose reductions will be made for any hypersensitivity reactions. If, despite proper pretreatment with dexamethasone as outlined in the protocol, the subject experiences a hypersensitivity reaction, treatment should be as indicated below:
    - Grade 1 symptoms (eg., mild flushing, rash, pruritis) = complete infusion. Supervise at bedside. No treatment required.
    - Grade 2 symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) = Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a slower rate, then increased incrementally to the initial planned rate. Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment and the rate of infusion should be decreased initially and then increased back to the recommended 1 hour infusion.
    - Grade 3 symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria) = Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The subject will go off study
    - Grade 4 symptoms = Anaphylaxis—Discontinue protocol treatment.

6.1.4.4 Hepatic Adjustments

Subjects who develop abnormal liver function tests for any reason while on the study will have the following docetaxel dose reductions:

Abnormal Liver Function Dose Modifications for Docetaxel (Taxotere)

Bilirubin	Alkaline Phosphatase	SGOT (AST)	Action
> ULN	or > 5 X ULN	or > 5 X ULN	Wait ≤2 weeks. If recovered*, reduce docetaxel (Taxotere) dose by –1 dose level. If not, off study.

≤ ULN	and ≤ 5 X ULN	and 1.6-5 X ULN	Reduce docetaxel (Taxotere) dose by –1 dose level.

*Bilirubin < ULN and alkaline phosphatase < 5 X ULN and SGOT (AST) < 5 X ULN.
Note: A maximum of two dose reductions per patient are allowed.

6.1.4.5 Fluid Retention Adjustments

- If symptomatic, subjects developing fluid retention may be treated with diuretics at the investigator's discretion.
- Grade 3 = Docetaxel should be held until resolution to < Grade 1, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.

6.1.4.6 Stomatitis Adjustments

- Grade 3 or 4 stomatitis = retreatment after recovery to ≤ Grade 1 with a one level dose reduction.

6.1.4.7 Other Non-Hematologic Toxicities

- Grade > 3 AE = Docetaxel should be held until resolution to ≤ Grade 1 or less, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.
- Subjects requiring a > 2 week delay in starting Cycle 2 or 3 due to non-hematologic toxicity will be removed from protocol treatment.

6.1.5 Gemcitabine

- Gemcitabine should be given at an initial dose of 1000mg/m^2 IV Day 1 and 8 every 3 weeks.
- Dose delays of >6 weeks will result in permanent discontinuation of gemcitabine.
- Subjects who permanently discontinue gemcitabine due to toxicity but who have not progressed may remain on single-agent nivolumab until progression or intolerable toxicity.

Dose Level	Dose Modification
Full dose gemcitabine	1000 mg/m^2
75% of full dose	750 mg/m^2
50% of full dose	500 mg/m^2

If hematologic toxicity develops, dose reductions should be per drug label guidelines **or** as follows at discretion of site investigator:

Hematologic Toxicity	Gemcitabine dose modification
ANC[a] ≥1000/mm^3 and platelet count ≥100,000/mm^3	Administer 100% full dose
ANC[a] 500-999/mm^3 or platelet count 50,000-99,999/mm^3	Administer 75% of full dose
ANC[a] <500/mm^3 or platelet count <50,000/mm^3	Hold dose
[a]=absolute neutrophil count	

Gemcitabine may resume when ANC is ≥ 1000/mm^3 and platelet count ≥100,000/mm^3.

For non-hematologic toxicity, dose reductions should be per drug label guidelines or as follows at discretion of site investigator:

Non-Hematologic Toxicity	Gemcitabine dose modification
Severe (grade 3 or 4) non-hematologic toxicity (excludes nausea, vomiting, or alopecia- no dose modifications recommended)	Hold until resolved and then resume at 50% dose
Unexplained dyspnea (or other evidence of pulmonary toxicity), severe hepatotoxicity, hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), posterior reversible encephalopathy syndrome (PRES)	Permanently discontinue gemcitabine

6.1.6 Pemetrexed

- Pemetrexed should be given at an initial dose of 500mg/m^2 IV every 3 weeks. Pemetrexed should be discontinued if subjects develop grade 3 or 4 toxicity after two dose reductions or immediately if grade 3 or 4 neurotoxicity develops.
- Dose delays of >6 weeks will result in permanent discontinuation of pemetrexed.
- Subjects who permanently discontinue pemetrexed due to toxicity but who have not progressed may remain on single-agent nivolumab until progression or intolerable toxicity.

If a dose reduction for pemetrexed is required for hematologic toxicity, reductions should be per product labeling **or** as follows at the discretion of the investigator:

Hematologic Toxicity	Pemetrexed dose modification
Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	Reduce dose to 75% of previous dose
Nadir platelets <50,000/mm^3 without bleeding (regardless of nadir ANC)	Reduce dose to 75% of previous dose
Nadir platelets <50,000/mm^3 with bleeding (regardless of ANC)	Reduce dose to 50% of previous dose

If ≥ grade 3 non-hematologic (excluding neurotoxicity) toxicity develops, pemetrexed should be withheld until recovery to baseline. Upon recovery, dose reductions should be per product label or as follows at the discretion of the investigator:

Non-Hematologic Toxicity	Pemetrexed dose modification
Grade 3 or 4 toxicity (excluding mucositis)	Reduce dose to 75% of previous dose
Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization	Reduce dose to 75% of previous dose
Grade 3 or 4 mucositis	Reduce dose to 50% of previous dose
For neurotoxicity: • Grade 0-2 • Grade 3 or 4	 Continue at 100% of previous dose Discontinue treatment

6.2 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances:

- Documented disease progression per RECIST 1.1
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥ 6 weeks.

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF). The subject will continue to be followed per Section 7.

6.3 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 21 days	Screening	On Treatment				Safety follow up visit[11]	Safety follow up evaluation[11]	Long-term Follow up[12]
		Cycle 1		Cycle 2				
	-28 days	Day 1	Day 8	Day 1 ± 3 days	Day 8	30 days ± 7 days	100 days ± 7 days	± 14 days
REQUIRED ASSESSMENTS								
Informed Consent	X							
Medical History including smoking history	X							
Diagnosis and Staging[1]	X							
Physical Exam	X	X		X		X		
Vital signs and ECOG Performance Status[2]	X	X		X		X		
AEs & concomitant medications	X	X		X		X	X	
LABORATORY ASSESSMENTS								
Complete Blood Cell Count with diff (CBC)[3]	X	X[3]	X[3]	X	X[3]	X		
Comprehensive Metabolic Profile (CMP)[3]	X	X[3]		X		X		
Thyroid Function (TSH, T4, free T3)	X					X		
PT/INR/aPTT	X							
Pregnancy test (serum or urine) (WOCBP)[4]	X	X		X[4]				
DISEASE ASSESSMENT								
CT of chest[5]	X			X[5]				X[12]
CT or MRI of abdomen and pelvis[5]	X			X[5]				X[12]
CT or MRI Brain[5]	X							
TREATMENT EXPOSURE								
Arm A: Single Agent Chemotherapy/Nivolumab		X	Gem	X	Gem			
Arm B: Single Agent Chemotherapy		X	Gem	X	Gem			
SPECIMEN COLLECTION								
OPTIONAL: Archival Tumor Tissue[6]	X							
OPTIONAL: Pre-Treatment Biopsy[7]	X							
MANDATORY: Serum and Plasma[8]		X						
MANDATORY: Whole Blood for somatic baseline[9]		X						
SPECIMEN BANKING								
OPTIONAL: Whole Blood, serum, plasma[10]						ARM A		
FOLLOW-UP								
Survival Status, Subsequent Therapy								X

Key to Footnotes

1: Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging.

2: Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

3: If screening CBC and CMP were performed within 7 days of Cycle 1 Day 1 of treatment, these do not need to be repeated. For subjects receiving gemcitabine as their single agent chemotherapy, a CBC will be done on Day 8 of every Cycle. CBC with differential to include Hgb, Hct, WBC, ANC platelet count and differential. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase.

4: For women of childbearing potential (WOCBP): urine or serum βhCG will be done -14 days from registration. For WOCBP randomized to Arm A, a pregnancy test must be done within 24 hrs of 1st dose of study drug, and every 6 weeks during study treatment. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5: Radiology Imaging: Screening radiology imaging should be done -28 days from registration. Tumor response assessment will be performed every odd numbered cycle starting with Cycle 3. Tumor response assessment will consist of evaluation by CT scans of chest and MRI or CT of abdomen (pelvis if known disease site). CT or MRI of brain should be performed at screening only if subject has symptoms concerning for brain metastasis. The imaging selected for each subject should remain the same throughout the study until progression or initiation of new anti-cancer therapy. Radiology imaging may take place within 7 days prior to a study visit. Tumor imaging to be done at treatment discontinuation at discretion of site investigator.

6: OPTIONAL archival tumor tissue (prior to treatment with a PD-1 or PD-L1 inhibitor) if subject consents will be identified prior to registration and obtained by C2D1. Sample requirement is FFPE block + 2 H&E stained slides or 17 unstained slides + 2 H&E stained slides. Sample will be used for PD-L1 status and genetic analyses. Subjects will be consented to optional storage of any remaining tumor samples after protocol-specified studies are complete. Stored samples will be reserved for future cancer-related research. See Correlative Laboratory Manual (CLM) for additional details.

7: OPTIONAL biopsy after registration and prior to C1D1 treatment: Primary tumor or a metastatic lesion amenable to biopsy after registration and prior to C1D1 treatment for PD-L1 status and other correlative studies such as genetic analyses will be collected for subjects that consent. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is allowed as long as there is sufficient cellularity. Sample requirement is block + 2 H&E stained slides or 17 unstained slides and 2 H&E stained slides. See Correlative Laboratory Manual (CLM) for details.

8: MANDATORY serum and plasma for proteomic classifier analysis and somatic comparison. Obtain prior to treatment C1D1. See Correlative Laboratory Manual (CLM) for additional details.

9: MANDATORY whole blood for somatic comparison. Obtain prior to treatment C1D1. See Correlative Laboratory Manual (CLM) for additional details.

10: OPTIONAL Arm A ONLY: whole blood, serum and plasma at progression for subjects randomized to chemotherapy and Nivolumab (Arm A) for banking. See Correlative Laboratory Manual (CLM) for additional details.

11: Safety follow-up visits should occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) and 100 days (±7 days) after the last dose of study treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. The D100 evaluation may be completed via phone call.

12: After the D100 safety visit, subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months up to 12 months after the last patient is enrolled. Once disease progression is documented, subjects will enter a survival follow up period every 6 months until the stated end of study. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

For tumor specimens or blood collected in the protocol, please see the CLM for additional information regarding collection, labeling and shipping.

8.1 OPTIONAL Archived Tumor Sample

Formalin-fixed, paraffin-embedded archival tumor tissue block for biomarker evaluation will be requested for subjects that consent to obtaining this sample. Sample requirement is FFPE block + 2 H&E stained slides or 17 unstained slides + 2 H&E stained slides. Fine needle aspiration is allowed.

Specimens will be submitted for central PD-L1 immunohistochemistry (IHC) assessment. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed. The PD-L1 28-8 FDA (OPDIVO) test will be performed by Neogenomics.

NeoTYPE Lung Tumor Profile Genetic Analysis will also be performed: Sequencing of select exons of AKT1, BRAF, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, KIT, KRAS, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SMO, SRC, TP53, as well as ALK FISH, HER2 FISH, MET FISH, PTEN FISH, RET FISH, ROS1 FISH.

8.2 OPTIONAL Biopsy Prior to C1D1 treatment

A fresh or formalin-fixed, paraffin-embedded tumor tissue block or unstained slides of tumor sample (recent, after progression on a PD-1 or PD-L1 inhibitor therapy) for biomarker evaluation will be performed for subjects that consent to collection. Fine needle aspiration is allowed as long as there is sufficient cellularity. Must be a minimum of 100 tumor cells per section after slides are cut. FNAs must be put directly into an FFP, using a non-alcoholic fixative. In addition, larger gauge needles are preferred in order to retain as much of the tissue architecture and to preserve the integrity of the sample. Sample requirement is FFPE block + 2 H&E stained slides or 17 unstained slides + 2 H&E stained slides.

Specimens will be submitted for central PD-L1 immunohistochemistry (IHC) assessment. These biopsy samples should be excisional, incisional, punch or core needle. Fine needle aspiration is allowed as long as there is sufficient cellularity. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed. The PD-L1 28-8 FDA (OPDIVO) test will be performed by Neogenomics.

NeoTYPE Lung Tumor Profile Genetic Analysis will also be performed: Sequencing of select exons of AKT1, BRAF, EGFR, ERBB2, ERBB4, FGFR1, FGFR2, FGFR3, KIT, KRAS, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PTEN, SMAD4, SMO, SRC, TP53, as well as ALK FISH, HER2 FISH, MET FISH, PTEN FISH, RET FISH, ROS1 FISH.

8.3 MANDATORY Blood Draw Prior to C1D1 Treatment

Peripheral blood will be drawn for somatic baseline by Neogenomics in accordance with the NeoTYPE Lung Tumor Profile (tissue test).

8.4 MANDATORY Serum and Plasma Collection Prior to C1D1 Treatment

Serum and plasma will be collected for possible proteomic analyses.

8.5 OPTIONAL Blood Collection for Future Unspecified Cancer Related Research

Whole blood, plasma, and serum will also be collected and banked at HCRN for future study. Samples to be collected from only those subjects who have progressed on Docetaxel plus Nivolumab combination therapy. Arm A ONLY at D30 EOT.

8.6 Storage of Biospecimens

Any remaining specimens will be stored for future unspecified cancer related research once protocol described biospecimen-based studies are completed. Consent for storage of leftover samples will be obtained.

8.7 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 RECIST 1.1 Criteria

Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (see Eisenhauer EA et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Can, 2009.45:p.228-247). Refer to the RECIST 1.1 publication for complete details on these criteria.

9.1.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.2 Malignant Lymph Nodes

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

9.1.3 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. **NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions'

thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.1.4 Target Lesions

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

9.1.5 Non-target Lesions

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

9.1.6 Evaluation of Target Lesions

NOTE: In addition to the information below, also see in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.1.7 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.1.8 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects 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) to confirm the complete response status.

9.2 Definitions for Response Evaluation – RECIST 1.1

9.2.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.2.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.2.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.2.4 Duration of Overall Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.2.5 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.2.6 Disease Control Rate

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.2.7 Time to Progression

A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

9.2.8 Progression Free Survival

A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last follow-up.

9.2.9 Overall Survival

Overall survival is defined by the date of randomization to date of death from any cause.

9.3 Immune- Related RECIST (irRECIST) Criteria

Immune-related RECIST criteria (see Bohnsack O. et al. Adaptation of the immune-related response criteria: irRECIST. ESMO 2014 Abstract 4958. http://www.irrecist.com/
Refer to the publication for complete details on these criteria).

9.3.1 Measurable lesion definitions and target lesion selection

Follow the definitions from RECIST 1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of:

- 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions
- 10 mm caliper measurement by clinical exam
- 20 mm by chest X-ray
- At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.
- Baseline: Target and Non-Target Lymph Node Lesion Definitions - Follow the definitions from RECIST 1.1
- Baseline: Bone Lesions- Follow the definitions from RECIST 1.1. Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.
- Baseline: Cystic and necrotic lesions as target lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.
- Baseline: Lesions with prior local treatment during target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

9.3.2 Follow-up

- Only index and measurable new lesions are taken into account. The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.
- Definition of Measurable New Lesions: In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

- Non-Target Lesion Assessment- The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.
- New Non-Measurable Lesions Definition and Assessment: All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.

9.3.3 Best overall response using the irRC

The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- Complete response (irCR) is defined by the complete disappearance of all lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
- Partial response (irPR) is defined by the decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. Stable disease (irSD) is when the measurements do not meet criteria for irCR or irPR, in absence of progressive disease (irPD).
- irPD is defined by a minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.

10. DRUG INFORMATION

10.1 Nivolumab (Opdivo®)

Please see the current IB for details regarding this medication. Each site may follow institutional standards that are consistent with the package insert for preparation and administration of nivolumab in this protocol.

Nivolumab was selected for dosage form development and is also referred to as BMS-936558-01 or BMS-936558. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Appearance is clear to opalescent, colorless to pale yellow liquid, few particulates may be present. Solution pH 5.5 to 6.5

10.1.1 Supplier/How Supplied

BMS will supply nivolumab at no charge to subjects participating in this clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL)
Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micro pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL so as not to exceed a total infusion volume of 120 mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed.

10.1.3 Storage and Stability

Nivolumab Injection, 100 mg/10 mL (10 mg/mL)
Vials of nivolumab injection must be stored at 2° to 8°C (36° to 46°F) and protected from light and freezing.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container.
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°to 8°C, 36°to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20° to 25°C, 68° to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

10.1.5 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis. After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.1.6 Dispensing

Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Nivolumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.7 Adverse Events

For a detailed list of adverse events please see the current investigator's brochure. The most common side effects of nivolumab are:

- Fatigue
- Skin reactions: including rash, itching, hives, redness, and dry skin. Toxic epidermal necrolysis, a potentially life threatening disease characterized by blistering and peeling of the top layer of skin resembling that of a severe burn
- Diarrhea
- Nausea

- Abdominal pain
- Decreased appetite
- Low red blood cells
- Fever
- Joint pain or stiffness

10.2 Docetaxel (Taxotere®)

Please refer to the current package insert for complete prescribing and toxicity information. Institutional guidelines may be used for preparation and administration of this medication.

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

10.2.1 Supplier/How Supplied

One-vial TAXOTERE (Injection Concentrate)
TAXOTERE Injection Concentrate is supplied in a single use vial as a sterile, pyrogen-free, non-aqueous solution.

TAXOTERE (docetaxel) Injection Concentrate 20 mg/1 mL: 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol. The vial is in a blister pack in one carton.

TAXOTERE (docetaxel) Injection Concentrate 80 mg/4 mL: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol. The vial is in a blister pack in one carton.

TAXOTERE (docetaxel) Injection Concentrate 160 mg/8 mL: 160 mg docetaxel in 8 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol. The vial is in a blister pack in one carton.
Docetaxel (Taxotere) is commercially available and will not be supplied for this study.

10.2.2 Preparation

TAXOTERE Injection Concentrate (20 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw TAXOTERE from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate vials to stand at room temperature for approximately 5 minutes before use.

2. Using only a 21 gauge needle, aseptically withdraw the required amount of TAXOTERE injection concentrate (20 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.
   If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.
3. Thoroughly mix the infusion by gentle manual rotation.
4. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.
5. TAXOTERE infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

The TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

10.2.3 Storage and Stability

TAXOTERE final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. TAXOTERE final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration). In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36 and 46°F). Retain in the original package to protect from light. Freezing does not adversely affect the product.

10.2.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

10.2.5 Adverse Events

The most common side effects of TAXOTERE include:

- Changes in your sense of taste
- Feeling short of breath
- Constipation
- Decreased appetite
- Changes in your fingernails or toenails
- Swelling of your hands, face or feet
- Feeling weak or tired
- Joint and muscle pain
- Nausea and vomiting
- Diarrhea
- Mouth or lips sores
- Hair loss
- Rash

- Redness of the eye, excess tearing
- Skin reactions at the site of TAXOTERE administration such as increased skin pigmentation, redness, tenderness, swelling, warmth or dryness of the skin.
- Tissue damage if TAXOTERE leaks out of the vein into the tissues

10.3 Pemetrexed Disodium Heptahydrate (Alimta)

Please refer to the current package insert for complete prescribing and toxicity information. Institutional guidelines may be used for preparation and administration of this medication.

10.3.1 Supplier/How Supplied

Pemetrexed is commercially available.
Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Pemetrexed is supplied in 100mg and 500 mg vials. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Each 100-mg vial of pemetrexed disodium contains equivalent to 100mg pemetrexed and 106mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

10.3.2 Preparation

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of pemetrexed vials needed. Each vial contains 500 mg or 100mg of Pemetrexed. The vial contains an excess of Pemetrexed to facilitate delivery of label amount.
3. Reconstitute 500-mg vials with 20 mL of 0.9% Sodium Chloride Injection (preservative free) to give a solution containing 25 mg/mL Pemetrexed. Gently swirl each vial until the powder is completely dissolved, reconstitute 100mg vials with 4.2 ml of 0.9% Sodium Chloride injection (preservative free) to give a Solution containing 4.3 mg/ml pemetrexed. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted pemetrexed solution is between 6.6 and 7.8. FURTHER DILUTION IS REQUIRED.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.
5. The appropriate volume of reconstituted Pemetrexed solution should be further diluted to 100 mL with 0.9% Sodium Chloride Injection (preservative free) and administered as an intravenous infusion over 10 minutes.
6. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored at refrigerated or ambient room temperature [see USP Controlled Room Temperature] and lighting. When prepared as directed, reconstitution and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard any unused portion. Reconstitution and further dilution prior to intravenous infusion is only recommended with 0.9% Sodium Chloride Injection (preservative free). Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's Injection, USP and Ringer's Injection, USP and therefore these should not be used. Co-administration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

10.3.3 Storage and Stability

Pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C (36-46°F), or at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

10.3.4 Incompatibilities and Potential Drug Interactions

Ibuprofen — Daily ibuprofen doses of 400 mg QID reduce pemetrexed's clearance by about 20% (and increase AUC by 20%) in patients with normal renal function. The effect of greater doses of ibuprofen on pemetrexed PK is unknown. Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. Concomitant administration of nephrotoxic drugs could result in delayed clearance of pemetrexed. Concomitant administration of substances that are also tubularly secreted (e.g., probenecid) could potentially result in delayed clearance of pemetrexed. Although ibuprofen (400 mg QID) can be administered with pemetrexed in patients with normal renal function (creatinine clearance (80 mL/min), caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

10.3.5 Side Effects

1. Renal: creatinine elevation (10%)
2. Neurologic: neuropathy-sensory (9%), taste disturbance (8%)
3. Hematologic: anemia (33%), neutropenia (29%), leucopenia (18%), thrombocytopenia (10%)
4. Gastrointestinal: nausea (56%), vomiting (40%), anorexia (27%), constipation (21%), stomatitis/pharyngitis (14%), diarrhea (12%), dyspepsia/heartburn (5%)
5. Dermatology/skin: alopecia (12%), rash/desquamation (7%)
6. Other: fatigue, febrile neutropenia, infection, pyrexia, dehydration, increased AST, increased ALT, creatinine clearance decrease, renal failure, conjunctivitis, arrhythmia, chest pain, increased GGT, motor neuropathy

10.4 Gemcitabine

Please refer to the current package insert for complete prescribing and toxicity information. Institutional guidelines may be used for preparation and administration of this medication.

10.4.1 Supplier/How Supplied

Gemcitabine is commercially available in 200 mg and 1 gm vials.

10.4.2 Preparation

Reconstitute the 200 mg vial with 5ml and the 1 gm vial with 25 ml preservative free normal saline to make a solution containing 38 mg/ml. Shake to dissolve.

10.4.3 Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

10.4.4 Side Effects

1. Hematologic: Neutropenia, anemia, thrombocytopenia, and leukopenia are reported.
2. Dermatologic: A rash is seen in about 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is usually minimal. Injection-site reactions.
3. Gastrointestinal: Nausea and vomiting are reported in about two-thirds of patients and requires therapy in about 20% of patients. It is rarely dose-limiting, and is easily manageable with standard antiemetics. Diarrhea, constipation, mucositis.
4. Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of patients, but they are usually mild, nonprogressive, and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired hepatic function.
5. Pulmonary: In clinical trials, dsypnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. [Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS) has been reported rarely following one or more doses of Gemzar administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.] The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.
6. Neurologic: Somnolence, insomnia, paresthesia, pain.
7. Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmias have been reported. Peripheral edema is reported in about 30% of patients. Some cases of facial edema have also been reported. Edema is usually mild to moderate, rarely dose-limiting, sometimes painful, and reversible after stopping gemcitabine treatment.
8. Other: Flu-like symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia. Malaise and sweating are reported.

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Pregnancy
- Overdose

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 100 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event. The Pregnancy Surveillance Form is to be used to report pregnancy.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event. The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to Bristol-Myers Squibb (BMS)

HCRN will report all SAEs to BMS **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to BMS as it is received from site.

HCRN will submit all SAEs to BMS Global Pharmacovigilance (GPV&E) via email @ worldwide.safety@bms.com or fax @ 609-818-3804.

11.2.2.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.2.4 HCRN Responsibilities to FDA

For protocols exempt from the requirements of an IND, the above stated requirements are not applicable. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.2.2.5 IND Safety Reports Unrelated to this Trial

BMS will provide IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

General Considerations: Statistical analysis of this study will be the responsibility of Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Cancer Center (IUSCC). Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Missing data will not be imputed.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature of the protocol.

12.1 Study Design

This is a randomized open-label phase II trial comparing the efficacy of a single agent chemotherapy (docetaxel or gemcitabine or pemetrexed) plus nivolumab versus a single agent chemotherapy (docetaxel or gemcitabine or pemetrexed) alone, for treating patients with advanced squamous or non-squamous or not otherwise specified NOS NSCLC who had primary resistance to prior PD-1 or PD-L1 inhibitor. Randomization is unblinded, in a ratio of 1:1, and stratified according to EGOG PS 0-1 vs 2 and squamous vs non-squamous vs NOS NSCLC and concurrent chemotherapy and checkpoint inhibitor with single agent PD-1 or PD-L1 maintenance: versus Sequential chemotherapy followed by checkpoint inhibitor.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint is PFS assessed by RECIST 1.1 and is defined as the time from date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause. PFS will be censored at the date of last follow-up.

12.2.2 Definition of Secondary Endpoints

- Toxicity assessed by CTCAE Version 4.
- Overall response rate (CR+PR) assessed via RECISIT 1.1 and irRECIST
- Clinical Benefit Rate (SD, PR, or CR for at least 3 months) assessed via RECISIT 1.1 and irRECIST
- PFS assessed by irRECIST defined as the time from date of randomization until the criteria for disease progression is met as defined by irRECIST criteria or death as a result of any cause.

12.3 Sample Size and Accrual

The median PFS for 2nd line chemotherapy is historically 3 months. The primary hypothesis we want to test is that a single agent chemotherapy plus nivolumab would double the median PFS to 6 months, corresponding to a hazard ratio of 0.5 compared to a single agent chemotherapy alone.

The trial will enroll patients for 24 months and have a minimum follow-up of 24 months. The total study duration is 4 years. Uniform patient entry is assumed for both groups. The number of events needed to achieve an 80% power with 1-sided test at 0.05 level of significance is 51.

Assuming a drop-out rate of approximately 3% uniformly during the study duration, we anticipate to recruit 62 patients (31 in chemotherapy plus nivolumab and 31 in chemotherapy alone). The accrual rate is estimated to be about 31 per year.

We plan a single interim analysis after observing approximately 1/2 of the required number of events (i.e. 26).

12.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Efficacy	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation. Evaluable subjects will be analyzed via the Intention-to-treat (ITT) principle*
Safety	This will comprise all subjects that contribute data to the safety analysis. This will comprise all subjects who receive at least one dose of trial drug

*ITT Principle - The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

12.5 Assessment of Safety

Safety will be assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4). Please refer to the Study Calendar for the schedule of toxicity assessment. This will comprise all subjects who receive at least one dose of trial drug

12.6 Assessment of Efficacy

All subjects with measurable disease who have received at least one dose of study treatment and have their disease re-evaluated will be evaluable for assessment of PFS and other efficacy outcomes.

12.7 Data Analysis Plans

12.7.1 Analysis Plans for Primary Objective

In the Efficacy population, the primary analysis will be to compare PFS in the two groups using a stratified log-rank test. Kaplan-Meier plots will also be generated with 90% confidence intervals. In the Safety population, toxicities will be tabulated by treatment group.

12.7.2 Analysis Plans for Secondary Objectives

In the Efficacy population, response rate and clinical benefit will be estimated using two-sided 90% exact binomial confidence intervals. Groups will be compared for response rate and clinical benefit using chi-square tests.

12.7.3 Analysis Plans for Exploratory Objectives

In the Efficacy population, PD-L1 status of the tumors at baseline, at time of progression on Nivolumab, and at time of progression on combination of Nivolumab and chemotherapy (when available) in those who show clinical benefit will be compared using paired t-tests. For genetic markers and PD-L1 status (positive or negative), frequencies at each time point will be reported, and changes over time will be assessed with McNemar's tests. In addition, genetic markers and PD-L1 status will be correlated with toxicity using logistic regression and time-to-event variables with Cox proportional hazards regression.

12.7.4 Other Planned Analyses

For the registered population, descriptive statistics will be used the characterize subject demographic and clinical characteristics, disposition, and significant protocol violations. In the Safety population, concomitant medications and exposure will be described.

12.8 Interim Analysis/Criteria for Stopping Study

We plan a single interim analysis after observing approximately 1/2 of the required number of events (i.e. 26). This can be designed as a 1-look group sequential plan (total 2 analyses) that uses sequential log rank test with a cumulative type I error of α=0.05 (1-sided) and a cumulative power of 1-β=80%. According the α-spending function by the method of Lan and DeMets with O'Brien-Fleming type stopping boundary, the trial will stop for outstanding efficacy with a nominal p-value of less than or equal 0.006 at the only interim analysis. The final analysis will be performed when approximately 51 events are observed. A single agent chemotherapy plus nivolumab will be considered to be superior than chemotherapy alone when the nominal p-value is less than or equal 0.048.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the IU Simon Cancer Center's (IUSCC) DSMP.

HCRN oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee according to IUSCC DSMP.

13.2 IUSCC Data Safety Monitoring Committee

The DSMC will review the following:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The IUSCC DSMC will review AE data annually. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

There will be at least one routine visit per site per year for sites that have accrued. Additional for cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by BMS or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Office for this trial. Data will be collected through a web based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, BMS, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.
Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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