THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

Nivolumab plus Cisplatin/Pemetrexed or Cisplatin/Gemcitabine as Induction in Resectable Non-Small Cell Lung Cancer

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APPENDIX D: UNANTICIPATED PROBLEM FORM

Sidney Kimmel Cancer Center at Thomas Jefferson University

UNANTICIPATED PROBLEM REPORT FORM
For Sub-Site Reporting

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

Subject ID: _____ Approx. Date of Problem: _____ Date Aware: ____

Description of Problem: _____

_____

Is this Unanticipated Problem a Protocol Deviation? Yes ☐ No ☐

Did the Unanticipated Problem pose risk to subjects or others? Yes ☐ No ☐

If no, have PI or Co-I sign the form. If YES, describe the risk below:

Describe the Corrective Action Plan: _____

_____

Has the problem been resolved? Yes ☐ No ☐

Does the consent or protocol require modification? Yes ☐ No ☐

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number

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Staging NSCLC

T (Primary Tumor)		Label
T0	No primary tumor	
Tis	Carcinoma in situ (Squamous or Adenocarcinoma)	Tis
T1	Tumor ≤3 cm,	
T1a(mi)	Minimally Invasive Adenocarcinoma	T1a*(mi)*
T1a	Superficial spreading tumor in central airways[a]	T1a *SS*
T1a	Tumor ≤1 cm	T1a *≤1*
T1b	Tumor >1 but ≤2 cm	T1b *>1-2*
T1c	Tumor >2 but ≤3 cm	T1c *>2-3*
T2	Tumor >3 but ≤5 cm or tumor involving:	
	visceral pleura[b],	T2 *Visc Pl*
	main bronchus (not carina), atelectasis to hilum[b]	T2 *Centr*
T2a	Tumor >3 but ≤4 cm	T2a *>3-4*
T2b	Tumor >4 but ≤5 cm	T2b *>4-5*
T3	Tumor >5 but ≤7 cm	T3 *>5--7*
	or invading chest wall, pericardium, phrenic nerve	T3 *Inv*
	or separate tumor nodule(s) in the same lobe	T3 *Satell*
T4	Tumor >7 cm	T4 *>7*
	or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine;	T4 *Inv*
	or tumor nodule(s) in a different ipsilateral lobe	T4 *Ipsi Nod*
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	
N3	Metastasis in contralateral mediastinal/hilar, or supraclavicular nodes	
M (Distant Metastasis)		
M0	No distant metastasis	
M1a	Malignant pleural/pericardial effusion[c]	M1a *Pl Dissem*
	or pleural /pericardial nodules	
	or separate tumor nodule(s) in a contralateral lobe;	M1a *Contr Nod*
M1b	Single extrathoracic metastasis	M1b *Single*
M1c	Multiple extrathoracic metastases (1 or >1 organ)	M1c *Multi*

TX, NX: T or N status not able to be assessed

[a] Superficial spreading tumor of any size but confined to the tracheal or bronchial wall
[b] such tumors are classified as T2a if >3≤4 cm, T2b if >4≤5 cm.
[c] Pleural effusions are excluded that are cytologically negative, non-bloody, transudative, and clinically judged not to be due to cancer.

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name:

Title:

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

AE	Adverse Event/Adverse Experience
BOR	Best Overall Response
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
CTOC	Clinical Trials Oversight Committee
DSF	Disease Free Survival
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federal wide Assurance
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRC	Imaging Response Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
OAR	Organ At Risk

OHRP	Office for Human Research Protections
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PR	Partial Response
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SDS	Safety Data Sheet (formerly MSDS; Material Safety Data Sheet)
SKCC	Sidney Kimmel Cancer Center
SOP	Standard Operating Procedure
TJU	Thomas Jefferson University
UAP	Unanticipated Problem
ULN	Upper Limit of Normal

Study Summary

Title: Nivolumab plus Cisplatin/Pemetrexed or Cisplatin/Gemcitabine as Induction in Resectable Non-Small Cell Lung Cancer

Précis: Patients with NSCLC who are candidates for curative intent surgery will be treated with a combination of induction cisplatin/pemetrexed or cisplatin/gemcitabine plus nivolumab, to assess the rate of major pCR over historical control with induction chemotherapy alone.

Lead Site: Thomas Jefferson University

Phase: Phase II

Number of Sites:
- 3: Thomas Jefferson University (lead site), Abington Memorial Hospital, Main Line Health

Objectives:

Primary:

- The primary objective of the study is to estimate major pathologic response (mpCR) at the in patients with newly diagnosed and untreated NSCLC Stage I-IIIA treated with three courses of induction Nivolumab added to either cisplatin/pemetrexed or cisplatin/gemcitabine prior to surgery.

Secondary:

- Safety
- Complete Pathologic Response
- Overall Clinical Response Rate
- Clinical Complete Response Rate
- 1 year PFS
- Overall survival

Exploratory:

- To explore whether PDL1 expression is associated with treatment response
- To explore whether there is a net change in the Th1/Th2 ratio (IFN-gamma, IL-4, IL10, etc.) or cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells, etc.) within a patient's peripheral

blood either at baseline or in response to treatment is associated with treatment response
- To explore whether exosomes or other immune related serum biomarkers change after combination therapy.
- To explore the predictive value of serial cell free DNA levels and response
- PD-L1 assessment in tumor. Blood correlatives for immune markers before and after treatment.

Blood correlatives of immune function before, during, and after treatment.
- Flow Cytometry
  - White blood cell subset: CD3, CD4, CD8, CD11c, CD14, CD15, CD19, CD56, CD123
  - White blood cell activation: CD25, CD163, CD204, CD206, PD1, PDL1
- Luminex, multiplex ELISA – Millipore human cytokine panel I (HCYTOMAG-60K-PX41)

Population: Men and women, 18 and above, resectable non-squamous and squamous NSCLC who will have planned surgery.

Statistics: A Simon two-stage design will be used. The null hypothesis is that the true major pathologic response rate at the primary tumor site is ≤ 0.19 and will be tested against the alternative that it is >0.19. After testing the regimen on 21 patients in the first stage, the trial will be terminated if 3 or fewer respond. If the trial goes on to the second stage, a total of 34 patients will be studied. If the total number responding is less than or equal to 9, the regimen is rejected. This design yields a type I error rate of 9.5% and power of 80% when the true response rate is 0.35. The mpCR rate and its associated score 95% confidence interval will be estimated using the methods of Tsai et al (2008).[20]

Description of Intervention: This is a phase II trial looking at the combination of cisplatin/pemetrexed or cisplatin/gemcitabine to which nivolumab is added as induction therapy prior to planned surgery for the definitive management of non-squamous and squamous NSCLC respectively.

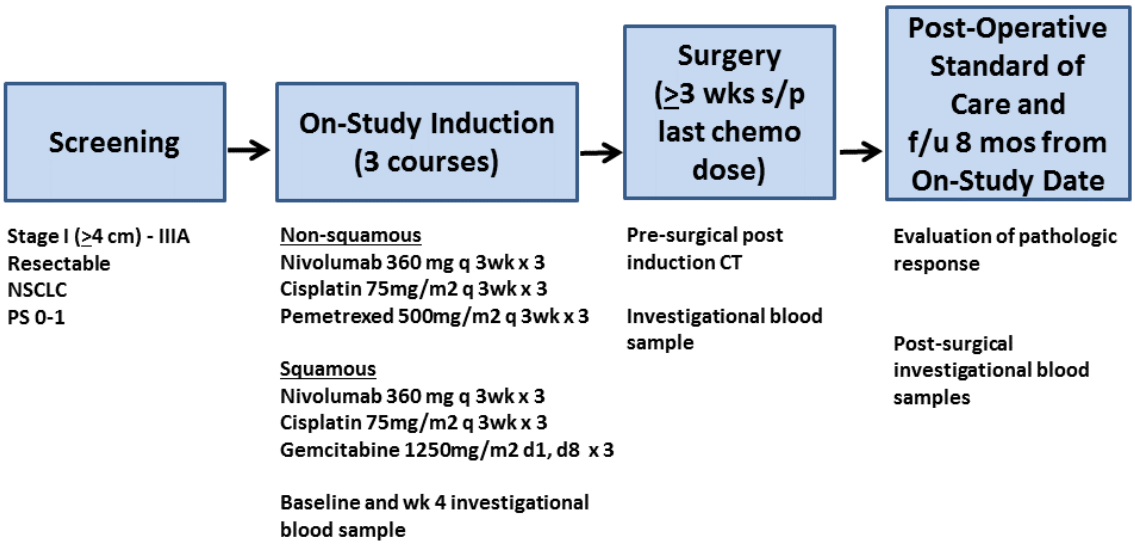
TREATMENT PLAN

Non-squamous NSCLC
Nivolumab 360mg q 3w x 3
Cisplatin 75mg/m^2 q 3w x 3
Pemetrexed 500 mg/m^2 q 3w x 3

Squamous NSCLC
Nivolumab 360mg q 3w x 3
Cisplatin 75mg/m^2 q 3w x 3
Gemcitabine 1250mg/m^2 d1, d8 x 3

Study Treatment Duration:	9 weeks
Patient Participation Duration:	8 months from study entry
Estimated Time to Complete Enrollment:	24 months
Estimated Time to Study Completion	32 months

Schematic of Study Design:



1 Introduction

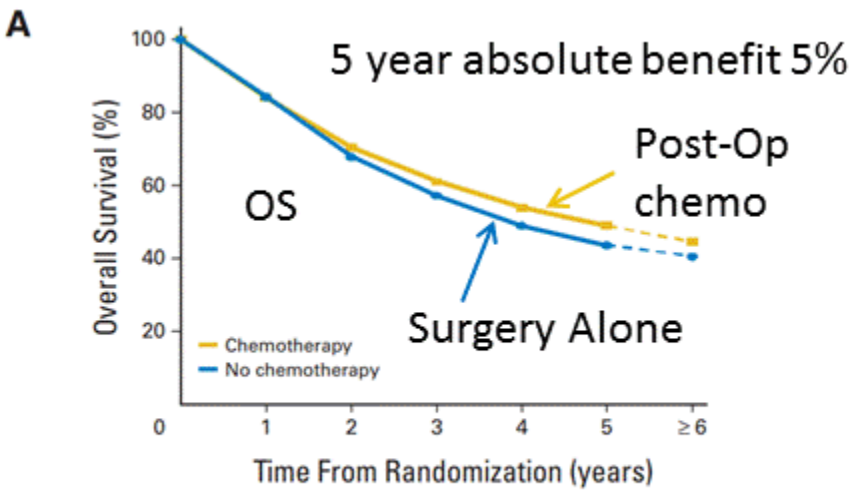
1.1 Background Information

Lung cancer is the second most common cancer in both men and women in North America *[Siegel 2017]*. Worldwide, 1.8 million cases of lung cancer are diagnosed annually *[Ferlay 2013]*. Non-small cell lung cancer (NSCLC) accounts for 80-85% of all pulmonary neoplasms *[Travis 2000]*. Although incidence and death rates have stabilized and are falling slowly, lung cancer is still the leading cause of cancer related-deaths in the US, with an overall all-stage 5-year survival of 18% *[Siegel 2017]*. The primary treatment of early stage (I-IIIA) NSCLC is curative surgery. Currently only ~30% of patients present with stages I-IIIA lung cancer *[Datta 2003]*, however, with the advent of lung cancer screening this percentage is expected to increase *[The National Lung Screening Trial Research Trial 2011]*. Although patients treated with curative surgery have a better prognosis, the 5-year survival for patients treated with surgery alone remains low, ranging from 67% (stage IA) to 23% (stage IIIA) *[Mountain 1997]*.

The poor survival rates following surgical resection for patients with stage II and III disease have led several groups to investigate the utility of adjuvant chemotherapy in improving lung survival outcomes. Five large randomized trials have been done to determine if adjuvant platinum-based chemotherapy after curative surgery for NSCLC confers a survival advantage: ALPI *[Scaggliotti 2003]*; IALT *[Arriagada 2004]*; JBR10 *[Winton 2005]*; CALGB 9633 *[Strauss 2008]*; and ANITA *[Douillard 2006]*. Three of

these five trials showed statistically significant improvements in overall survival, ranging from 4% *[IALT]* to 15% *[JBR10]* at 5 years, corresponding to an absolute improvement in relapse-free survival from 49% to 61%. Of the two trials that did not demonstrate improved survival, one *[ALPI]* suffered from poor compliance to the treatment regimen (69%), and the second, CALGB 9633, was a smaller trial (n=344) limited to patients with stage IB disease *[Strauss 2008]*, which was likely underpowered to detect a 20% reduction in hazard ratio (HR=0.8) statistically significant improvement in overall survival. Interestingly, despite being limited to patients with stage IB disease, CALGB 9633 did demonstrate an overall survival hazard ratio comparable to the other adjuvant trials (HR=0.8) that included patients with more advanced disease, despite not achieving statistical significance *[Strauss 2008]*.

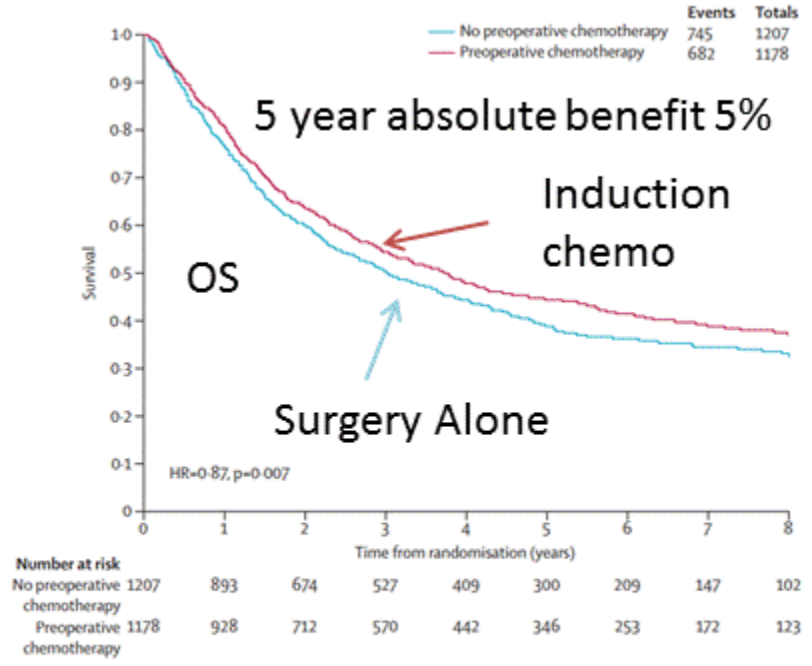
Since the publication of original adjuvant chemotherapy trials, a number of meta-analyses have confirmed the benefit of adjuvant platinum-based chemotherapy after surgical resection for NSCLC *[Pignon 2008; NSCLC Meta-analysis Collaborative Group 2010]* (figure 1). In these meta-analyses, all-stage (IB-IIIa) hazard ratios were in the range of HR=0.86, corresponding to an absolute benefit of chemotherapy on overall survival of 4-5% at 5 years *[Pignon 2008; NSCLC Meta-analysis Collaborative Group 2010]*. The benefit of adjuvant chemotherapy, however, was demonstrated to be stage dependent (although using older staging criteria versions), with the benefit only reaching statistical significance for stages II and III *[Pignon 2008]*. While the role of adjuvant chemotherapy in stage I disease has historically been controversial *[Wakelee 2007]*, subgroup analyses in a number of trials in high-risk patients with stage IB disease (tumors > 4cm) suggests that there may be an overall survival advantage with adjuvant chemotherapy in this subgroup of patients, comparable to those observed in stage II and III disease *[Strauss 2008]*. Neoadjuvant chemotherapy has also become accepted in some countries *[NSCLC Meta-analysis Collaborative Group 2014].*



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Pignon JCO, 2008

Figure 1



NSCLC Meta-analysis Collaborative group, Lancet 2014

Figure 2

Preoperative induction chemotherapy is also an established option *[NCCN 2016].* A meta-analysis of 15 randomized controlled trials (2385 individual patients analyzed) of preoperative chemotherapy vs. surgery alone in patients with stage IB-IIIA showed significant OS HR 0.87 comparable to postoperative adjuvant chemotherapy *[NSCLC Meta-analysis Collaborative Group 2014].* However, the addition of both pre- or post-operative adjuvant platinum doublet chemotherapy increases overall survival (OS) by only 5% *[Pignon 2008; NSCLC Meta-analysis Collaborative group 2014; Strauss 2008]* (figure 2). .

Despite the established benefit of adjuvant and induction chemotherapy with curative surgery for NSCLC, 30-60% of patients, depending on stage, will eventually relapse and die of their disease *[Hotta 2004]*. Furthermore, not all patients with early stage disease are eligible or willing to undergo chemotherapy following complete surgical resection. As such, the long-term prognosis of patients with NSCLC, even among those with early stage disease, remains poor. Novel therapies are, therefore, required to improve the clinical outcomes of completely resected NSCLC. Among these, are the checkpoint inhibitors.

Immune Therapy

Immunotherapy with checkpoint inhibitors has demonstrated clinical efficacy in several solid tumors types, including melanoma, renal cell carcinoma, Head and Neck Cancer, bladder cancer among others. Early success was achieved with the CTLA4 antagonist ipilimumab in the treatment of advanced melanoma.[7] Nivolumab, a PD-1 checkpoint inhibitor, is approved as second line therapy in both squamous and non-squamous NSCLC regardless of PD-L1 status. Pembrolizumab, also a PD-1 checkpoint inhibitor, is approved in as second line therapy in squamous and non-squamous NSCLC in patients whose tumors show PD-L1 of 1% or more. It is also approved as first line therapy in advanced NSCLC in patients whose tumors show >50% PD-L1. Atezolizumab, a PD-L1 inhibitor, is approved as second line therapy in squamous and non-squamous NSCLC irrespective of PD-L1 status.

The impressive results of T cell-directed immunotherapies are contrasted by the fact that only a subset of patients enjoys long-lasting remissions after single modality immune checkpoint therapy. This circumstance has reinvigorated interest in understanding how systemic and local factors may interfere with the function of T cells and other effector immune cells critical to tumor control. It is now widely accepted that immunosuppressive cells and factors in the tumor microenvironment (TME) contribute to suboptimal responses to immune checkpoint therapeutics. Thus, there is interest in testing combination approaches to “boost” the responses seen with nivolumab monotherapy.

Nivolumab

Nivolumab (Opdivo) is in clinical development for the treatment of subjects with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck carcinoma and other tumors (e.g., gastric cancer, glioblastoma multiforme, hodgkins lymphoma, small cell lung cancer). Nivolumab as monotherapy has been approved in the US in multiple indications, including, unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor, if BRAF V600 mutation positive; previously untreated patients with BRAF wild-type unresectable or metastatic melanoma, as second line therapy in advanced recurrent squamous Head and Neck cancer, and advanced renal cell carcinoma who have received prior anti-angiogenic therapy. Nivolumab is established as second line therapy in both squamous and nonsquamous NSCLC based on results from Checkmate 017 and 057 respectively. To further improve outcomes in the advanced disease setting, multiple combination studies in first and latter line therapy are in various stages of investigation. In addition, nivolumab is being evaluated in earlier stage disease in various combinations and sequences with surgery and radiation.

Mechanism of action

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD 1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes33. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (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 technologies. The clinical study product is a sterile solution for parenteral administration.

1.2 Rationale for the Proposed Study

For patients with localized NSCLC, 5 year post-surgical survivals for stage pIIA-IIIA have been modest at 46% - 24% *[Goldstraw 2007].* Though, post-operative adjuvant chemotherapy is more the default standard, preoperative induction chemotherapy is also an established option *[NCCN 2016].* A meta-analysis of 15 randomized controlled trials (2385 individual patients analyzed) of preoperative chemotherapy vs. surgery alone in patients with stage IB-IIIA showed significant OS HR 0.87 comparable to postoperative adjuvant chemotherapy *[NSCLC Meta-analysis Collaborative Group*

2014]. However, the addition of both pre- or post-operative adjuvant platinum doublet chemotherapy increases overall survival (OS) by only 5% *[Pignon 2008; NSCLC Meta-analysis Collaborative group 2014; Strauss 2008].* Thus, there remains a large unmet need to improve outcomes.

Potential advantages of induction include the higher rate of chemotherapy delivery compared to when chemotherapy is postoperatively administered. It does so without decreasing the rate of surgery compared to postoperative adjuvant chemotherapy *[Westeel2013;Felip 2010].* Moreover, given the protracted length of time required to assess OS in the surgical population, induction strategy is an important opportunity to speed discovery of promising regimens by using response as a surrogate endpoint for OS. Use of major pathological response defined as < 10% viable tumor is a promising endpoint. In a retrospective analysis of 192 patients stages I-IV (4% had stage IV) who had received induction (89% with a platinum doublet) with a median of three cycles, 36 patients (19%) of samples showed major pathologic response defined as having $\leq$ 10% viable cells averaged across 10 slides *[Pataer 2012].* Patients whose tumors showed a major pathologic response had a 5 year OS of 85% versus 40% ($p<0.0001$) and 5 year DFS, 78% vs. 35% ($p<0.001$). Of interest, from the same retrospective study, in a set of 166 patients who had not had induction therapy, none of the patients' tumor specimens showed $\leq$ 10% viable cells. Thus major pathologic response is both predictive and common enough to serve as a strong surrogate for OS *[Hellmann 2014].*

PD-1/PD-L1 axis checkpoint inhibitors (nivolumab and pembrolizumab (PD-1) and atezolizumab (PD-L1)) are established as second line therapy for squamous and nonsquamous NSCLC *[Brahmer 2015; Borghei 2015; Herbst 2016; Barlesi 2016].* Pembrolizumab is FDA approved as first line therapy in patients who have tumor proportion score for PD-L1 >50% *[Reck 2016].* They all have the property of equal or superior median survivals depending on PD-L1 status, very sustained responses, and tolerability superior to standard chemotherapy.

There are also preliminary single agent nivolumab data in early stage disease in a window trial. In a small study, patients with stage I-IIIa NSCLC were treated 4 and 2 weeks before surgery with 3mg/kg nivolumab *[Forde 2016].* There were reportedly no significant safety concerns or delays to surgery in the 16 analyzed for safety, and 12 of 15pt (80%) showed some regression. Forty percent had major pathological response manifested by tumor specimens with either complete pathologic response or isolated remaining tumor cells with the specimens dense with an infiltration of immune cells

including T cells which were not detected in the pre-treatment biopsy. These data suggest the potential efficacy and safety of inclusion of nivolumab as induction therapy.

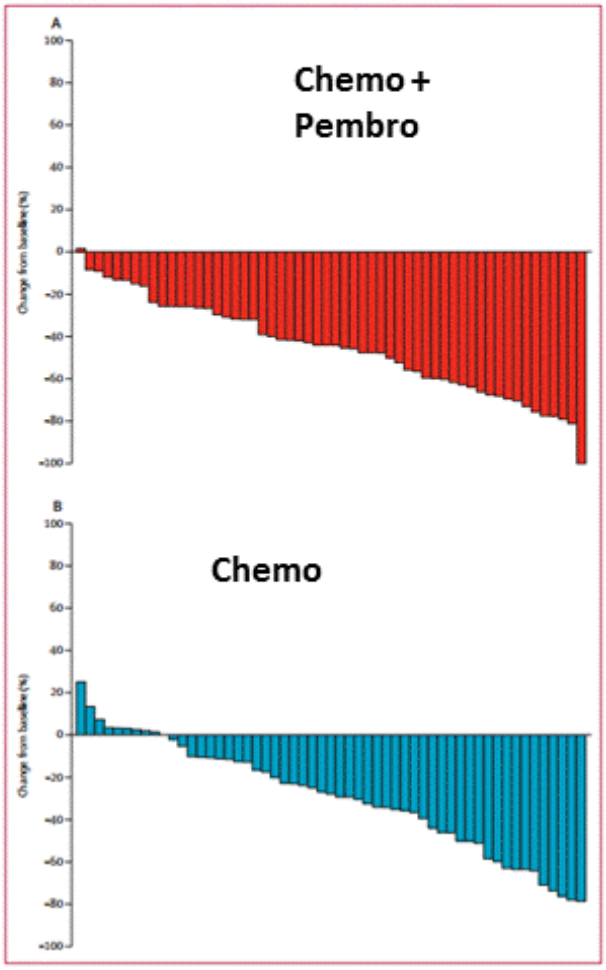
There is preclinical evidence supporting the addition of PD-1/PD-L1 axis checkpoint inhibitors to standard cytotoxic agents *[Hato 2014; Nowak 2002].* Clinical data include a randomized carboplatin and pemetrexed plus/minus pembrolizumab phase II in first-line advanced non-squamous NSCLC. Response rates were 55% vs. 29% (p=0.0016) in the triplet vs. doublets arms and median PFS was 13.0 vs. 8.1 (HR 0.53; p=0.01) *[Langer 2016]* (figure 3). Numerically improved response and PFS were seen in all PD-L1 subsets though numbers of patients were small. Severe adverse events were similar with 39% and 26% grade 3 in the triplet vs. doublet with 1 and 2 treated related deaths in the respective arms. In a multi-arm study of four nivolumab containing triplets including 10mg/kg nivolumab with cisplatin/ gemcitabine, cisplatin-pemetrexed or carboplatin-paclitaxel or nivolumab 5mg/kg with carboplatin-paclitaxel in first line advanced NSLCC, response rates were 33%, 47%, 47%, and 43% with efficacy seen irrespective of PD-L1 expression *[Rizvi 2016].* Forty-five percent had > grade 3 toxicity with only 2/56 (4%) discontinuing therapy due to toxicity during the triplet treatment (and another 10/56 during maintenance nivolumab). These NSCLC data support the safety and efficacy of standard chemotherapy combined with PD-1 inhibitors.

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE

RR:

Chemo/Pembro	**55%**
Chemo	**29%**
(p=0.0016)	



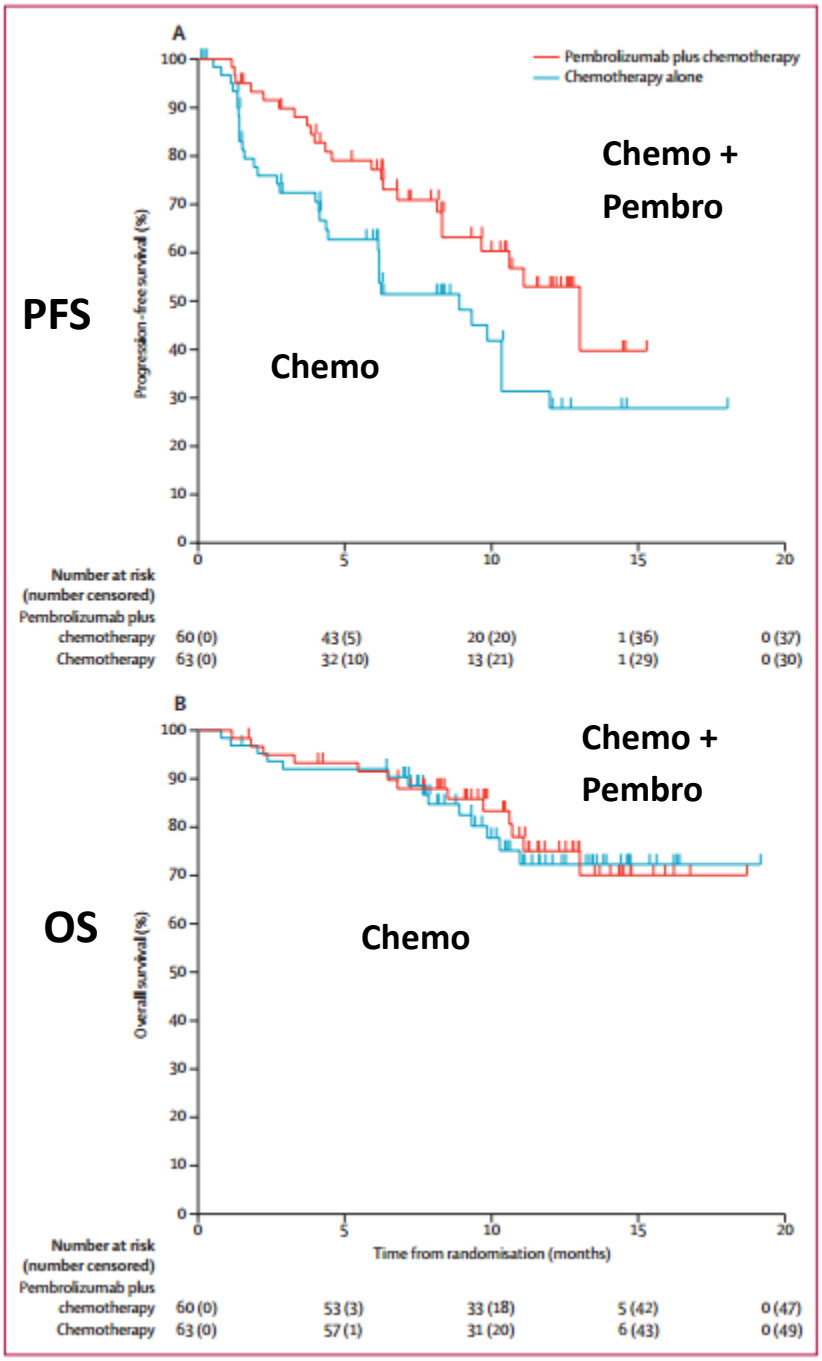

A
Pembrolizumab plus chemotherapy
Chemotherapy alone
Chemo +
Pembro
PFS
Chemo
Progression-free survival (%)
Number at risk
(number censored)
Pembrolizumab plus
chemotherapy 60 (0) 43 (5) 20 (20) 1 (36) 0 (37)
Chemotherapy 63 (0) 32 (10) 13 (21) 1 (29) 0 (30)
B
Chemo +
Pembro
OS
Chemo
Overall survival (%)
Time from randomisation (months)
Number at risk
(number censored)
Pembrolizumab plus
chemotherapy 60 (0) 53 (3) 33 (18) 5 (42) 0 (47)
Chemotherapy 63 (0) 57 (1) 31 (20) 6 (43) 0 (49)

Figure 3

Given the single agent efficacy and relative safety of nivolumab in both squamous and nonsquamous NSCLC in advanced disease and preliminary evidence in pre-surgical disease, and the promising data with platinum-based doublets and immune checkpoint inhibitors in advanced NSCLC, we propose to study cisplatin and gemcitabine plus nivolumab in squamous and cisplatin pemetrexed plus nivolumab in non-squamous NSCLC as an induction regimen in resectable stage Ib (>4cm) – IIIa NSCLC. It is tenable that the addition of nivolumab to these doublets will be both well tolerated and improve efficacy including major pathologic response, and long term disease control. The induction setting is especially appealing to study nivolumab added to platinum doublets in resectable NSCLC given the ability to rapidly reach an endpoint, major pathological response, which is predictive of OS. Moreover, it affords the opportunity to obtain repeat tissue sampling for pharmacodynamics endpoint evaluation.

Hypothesis:

The addition of nivolumab to induction cisplatin pemetrexed or cisplatin gemcitabine will increase the rate of major pathologic response over historical control with induction chemotherapy alone.

Immunotherapy in NSCLC

Indications in squamous and non-squamous NSCLC as second line therapy irrespective of PD-L1 status was supported by two large studies. In Checkmate 017, a phase III study in 272 patients with advanced squamous NSCLC who had recurrence after a platinum doublet were randomized to docetaxel (75mg/m2 q 3 wks) or nivolumab (3mg/kg q 2wks). The median overall survivals (OS) were 9.2 and 6.0 months for nivolumab and docetaxel respectively (HR 0.59; p<0.001) *[Brahmer 2015].* Responses were 19% vs. 12% (p=0.02) in nivolumab and docetaxel treated patients respectively with the median duration of response for nivolumab not reached (range 2.9-20.5+) and in the docetaxel group the median was 8.4 months (1.4+-15.2+). Treated related adverse events grade 3 or 4 were 7% in nivolumab vs. 55% of patients treated with docetaxel with a lower rate of both grade 3 and 4 hematologic and non-hematologic toxicities.

In a very similar phase III study, Checkmate 057, 582 patients with advanced squamous NSCLC who had recurrence after a platinum doublet were randomized to docetaxel (75mg/m2 q 3 wks) or nivolumab (3mg/kg q 2wks). The median OS were 12.2 and 9.4 months for nivolumab and docetaxel respectively (HR 0.73; p<0.002) *[Borghaei 2015].* Responses were 20% vs. 9% (p=0.008) in nivolumab and docetaxel treated patients respectively with the median duration of response for nivolumab 17.2 months (range 1.8-22.6+) and in the docetaxel group the median was 5.6 months (1.2+-15.2+). Notably, patients with EGFR mutated cancer did not have improved OS and had a numerically

worse PFS than docetaxel. Unlike 017, patients randomized to nivolumab whose tumors had <10, 5 or 1% PD-L1 expression at baseline did not have superior OS, but rather equal OS. Treated related adverse events grade 3 or 4 were 10% in nivolumab vs. 54% of patients treated with docetaxel with a lower rate of both grade 3 and 4 hematologic and non-hematologic toxicities. In conclusion, nivolumab was at least as effective as docetaxel in patients irrespective of baseline PD-L1 expression and better tolerated and thus approved by the FDA for advanced second line NSCLC without requiring PD-L1 assessment.

Combination of Nivolumab and chemotherapy

The interaction of a tumor with the immune system is complex. Tumors and the tumor microenvironment are known to express a variety of factors that impede a robust immune response from eliminating the tumor. Soluble and membrane-bound factors have been shown to inhibit the cytolytic activity of tumor infiltrating T-cells (e.g., PD-L1 expression; TGF-beta). In addition, some tumor-derived factors are able to enhance immune system counter-regulatory systems (e.g., increased T-regulatory cells). Finally, suboptimal tumor antigen delivery and presentation has been postulated as another mechanism by which tumors can successfully evade immune system recognition.

Cancer therapeutics such as chemotherapy may modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.

Clinical insights into the toxicity and efficacy of combination nivolumab chemotherapy can be gleaned from a trial in NSCLC. Nivolumab added to chemotherapy has been evaluated in several cohorts of chemotherapy-naive subjects with advanced NSCLC in study CA209012 [Rizvi 2016]. Nivolumab 10 mg/kg was combined with gemcitabine + cisplatin (12 patients), pemetrexed + cisplatin (15 patients) and Nivolumab 10 mg/kg, and 5 mg/kg, was combined with paclitaxel and carboplatin (15 and 14 patients respectively).

The safety profile of nivolumab plus platinum-doublet chemotherapy reflects additive toxicities of the individual agents, which were manageable using established safety guidelines (Table 1.1.5-1). The frequency of most immune-related select AEs was higher than what has been observed for nivolumab monotherapy. However, these treatment-related AEs, including pneumonitis, were effectively managed and did not lead to any deaths.

Table 1.1.5-1: Treatment-related AEs Reported in ≥ 10% of all NSCLC Subjects Treated with Nivolumab plus Platinum-based Chemotherapy

	Total (n=56)	
Treatment-related AE, n (%)	All Grades	Grade 3/4
Patients with any AE	53 (95)	25 (45)
Fatigue	40 (71)	3 (5)
Nausea	26 (46)	1 (2)
Decreased appetite	20 (36)	1 (2)
Alopecia	17 (30)	0
Anemia	15 (27)	2 (4)
Rash	14 (25)	2 (4)
Diarrhea	12 (21)	1 (2)
Arthralgia	12 (21)	0
Constipation	11 (20)	0
Peripheral neuropathy	11 (20)	0
Dysgeusia	8 (14)	0
Hypersensitivity	8 (14)	1 (2)
Vomiting	8 (14)	0
Mucosal inflammation	7 (12)	0
Myalgia	7 (12)	0
Pneumonitis	7 (12)	4 (7)
Infusion-related reaction	6 (11)	0
Leukopenia	6 (11)	0
Lymphopenia	6 (11)	0

Activity was also evaluated by PD-L1 expression and was observed in subjects with both PD-L1 expressing and non-expressing tumors (Table 1.1.4-3). Overall, 79% (44/56) of subjects had evaluable tumor samples. At the 1% expression level, the response rate was 48% and 43% for expressers and non-expressers, respectively. The 1-year overall survival was 70% and 76% for expressers and non-expressers, respectively.

Table 1.1.4-3: Efficacy in Nivolumab + Chemotherapy by PD-L1 Expression Level

	≥ 1% expression (n=23)	< 1% expression (n=21)
ORR, n (%)	11 (48)	9 (43)
Median duration of response (95% CI)	27.3 (12.3, 85.4)	25.4 (13.1, 56.7)
PFS rate at 24 wks (95% CI)	59 (34,77)	44 (22, 64)
Median PFS, wks	25.9	22.6
1-year OS rate, % (95% CI)	70 (47, 84)	76 (52, 89)

Table 1.1.4-3: Efficacy in Nivolumab + Chemotherapy by PD-L1 Expression Level

	≥ 1% expression (n=23)	< 1% expression (n=21)
18-mo OS rate, % (95% CI)	57 (34, 74)	51 (28, 70)
Median OS, wks	88 (47, 118)	83 (53, 103)

Given the small number of patients in the study, conclusions are tentative. However, the data are consistent with the conclusion that the predictive value for PD-L1 expression may be attenuated in the nivolumab + chemotherapy setting, compared to what has been observed in the nivolumab monotherapy and nivolumab + ipilimumab settings in NSCLC. In NSCLC, there was no detectable diminution in activity for patients with PD-L1 non-expressing tumors, and response rates appear to be greater than in patients with PD-L1 non-expressing tumors treated with nivolumab, or nivolumab + ipilimumab. In patients with PD-L1 expressing tumors, nivolumab + chemotherapy showed a similar response rate compared to the N3 nivolumab + ipilimumab cohorts, but with higher toxicity. In patients with PD-L1 non-expressing tumors, nivolumab + chemotherapy showed a higher response rate compared to any of the nivolumab + ipilimumab cohorts.

Correlative Studies

PDL1 expression

Immune inhibitory receptors are expressed by tumor cells, tumor-infiltrating macrophages, and peripheral blood monocytes. Nivolumab has the capacity to alter expression of PDL1 in these cells. Therefore, we plan to monitor changes in PDL1

expression in these different cell subsets by immunohistochemistry and flow cytometry at various stages of treatment and look for association with clinical outcome.

Analysis of peripheral blood mononuclear cells and cytokines

We have documented extensive immune bias in peripheral blood of astrocytoma patients. We have performed preliminary studies on blood samples from patients with HNSCC and observed similar results. In this HNSCC patient cohort, we have found that immune bias begins in tumor draining lymph nodes and extends to the peripheral blood. We have developed a novel in vitro assay where we co-culture normal human monocytes with various patient samples to investigate polarization capacity. Using this assay, we have shown that astrocytoma-derived exosomes and soluble factors can bias normal monocytes towards M2. HNSCC patient sera can also bias monocytes towards M2 in this assay.

Evidence collected in other tumor models suggests that PDL1 is preferentially expressed on M2 monocytes and tumor-infiltrating macrophages with an M2 phenotype, thereby making them targets in nivolumab. To date, there have been no studies looking at the capacity of nivolumab to alter immune bias or macrophage polarization. Therefore, we plan to analyze peripheral blood mononuclear cells (PBMC) subsets before treatment to establish a baseline and at every blood draw thereafter to monitor changes in these compartments due to nivolumab therapy. We will stain PBMC with monoclonal antibodies specific for human CD3, CD4, CD8, CD11b, CD11c, CD14, CD33, CD163, CD204, and HLA-DR. Samples will be analyzed by flow cytometry. These phenotypic markers will enable us to monitor the effect of nivolumab therapy sizes of cell populations and activation status.

We routinely perform multiplex cytokine analyses on serum samples in our astrocytoma clinical trial. We plan to utilize magnetic Milliplex assays (HCYTOMAG-60K) to track changes in serum cytokines over the course of treatment.

Exosomes and nivolumab therapy

Exosomes are small membranous vesicles released by tumor cells which modulate the local microenvironment and communicate with distant cells. In order to accomplish these tasks, exosomes contain a variety of RNA species including miRNA, protein and specialized lipids. These attributes make exosomes attractive therapeutic targets, excellent biomarkers, and indicators of therapeutic responses. We have developed novel flow cytometric analyses where we utilize fluorescent dyes to track and quantify exosomes directly from patient sera. We plan to monitor

exosomes levels in patient sera and look for changes in frequency or content following nivolumab therapy.

Patient Reported Outcomes (PRO):

There has been increasing recognition that Patient-Reported Outcome (PRO) measures—including, in particular, measures of health-related quality of life (HRQOL)—can convey essential supplementary information for assessing the overall burden of cancer and the effectiveness of interventions [32]. Hence, we will collect Functional Assessment of Cancer Therapy - General (FACT-G) and cancer specific FACT scales. The FACT questionnaires have been used by researchers previously and have shown to be optimal for use in oncology trials[33] .It has also been shown that depression is the most frequently found psychological symptom among individuals with cancer, up to 38% of cancer patients meeting criteria for a diagnosis of major depression [34]. Prevalence rates of depression in cancer patients differ extensively across studies [35, 36]. Previous studies have also shown that depression might affect behavior and adherence to medical treatment [37].Hence, we will collect Patient Health Questionnaire (PHQ2&9). The PHQ-2 comprises the first two items of the PHQ-9. It is a screen for depression; patients who screen positive are further evaluated with the PHQ-9 which is used for making a criteria-based diagnosis of depression (based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for depression). The PHQ-2 has been validated in several studies [38]. The diagnostic validity of the PHQ was established in two large studies in primary care and obstetrics [39].

Additional Lab tests and waist to hip ratio:

C - reactive protein (CRP) is an acute phase reactant [40], which reflects tissue injury .It is also a well-established marker for inflammation[10]. However, in recent literature it has also been shown to be a predictive biomarker for immunotherapy[41], elevated CRP also predicted prognosis and treatment response[42]. The frequency of significant Immune Related adverse Events (irAE) in Immune Checkpoint Inhibitors (ICI) treated patients are about 10–20% and early recognition is critical to prevent serious morbidity and even mortality[43]. New onset autoimmune Diabetes Mellitus (DM) associated with immune checkpoint inhibitor treatment is extremely rare [44, 45]. Even though it is very rare possibility having Glycated Hemoglobin (HbA1c) levels will be beneficial to capture these rare events. Lipid metabolism is altered in proliferating cells and impact tumor progression[46, 47]. Therefore, tumor dependence towards lipids might hold potential for the treatment of the most intractable cancers.

Waist to hip ratio (WHR) has been associated with metabolic syndrome and higher mortality[48, 49]. Hence, WHR should be assessed in combination with BMI as part of risk assessment for obesity related premature mortality and risk of metabolic related conditions.

1.3 Potential Risks and Benefits

Potential Risks

The safety profile of nivolumab is well characterized from a large safety database at different dose and schedules as monotherapy or in combination. Consistent with the mechanism of action of nivolumab, the most frequently reported drug-related adverse events observed in clinical trials are those associated with activation of the immune system. The most common types of immune-mediated adverse events include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis and rash. In the combination regimen, the frequency and intensity of these events may vary and depend on the specific dose and schedule used.

- The safety of this drug combination with chemotherapy in Non-small cell lung cancer has shown the following. [18]

Table 3. Treatment-Related Select AEs Reported in Patients With Advanced NSCLC Treated With Nivolumab Plus PT-DC

	No. of Patients (%)									
	Nivolumab 10 mg/kg						Nivolumab 5 mg/kg			
	Gem-Cis (n = 12)		Pem-Cis (n = 15)		Pac-Carb (n = 15)		Pac-Carb (n = 14)		All Patients (N = 56)	
Select AE Category	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Skin	2 (17)	0	6 (40)	0	6 (40)	2 (13)	6 (43)	1 (7)	20 (36)	3 (5)
Rash	1 (8)	0	5 (33)	0	4 (27)	0	5 (36)	1 (7)	15 (27)	1 (2)
Pruritus	0	0	2 (13)	0	4 (27)	0	0	0	6 (11)	0
Rash maculopapular	1 (8)	0	0	0	2 (13)	2 (13)	0	0	3 (5)	2 (4)
Erythema	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Rash pruritic	0	0	0	0	0	0	1 (7)	0	1 (2)	0
GI	2 (17)	0	3 (20)	1 (7)	5 (33)	1 (7)	3 (21)	0	13 (23)	2 (4)
Diarrhea	2 (17)	0	2 (13)	0	5 (33)	1 (7)	3 (21)	0	12 (21)	1 (2)
Colitis	0	0	1 (7)	1 (7)	1 (7)	0	0	0	2 (4)	1 (2)
Hypersensitivity/infusion reaction	1 (8)	0	6 (40)	1 (7)	6 (40)	0	0	0	13 (23)	1 (2)
Hypersensitivity	1 (8)	0	3 (20)	1 (7)	4 (27)	0	0	0	8 (14)	1 (2)
Infusion-related reaction	0	0	4 (27	0	2 (13)	0	0	0	6 (11)	0
Renal	1 (8)	0	3 (20)	1 (7)	1 (7)	0	3 (21)	2 (14)	8 (14)	3 (5)
Blood creatinine increased	1 (8)	0	1 (7)	0	1 (7)	0	1 (7)	0	4 (7)	0
Acute renal failure	0	0	1 (7)	1 (7)	0	0	2 (14)	2 (14)	3 (5)	3 (5)
Allergic nephritis	0	0	1 (7)	1 (7)	0	0	1 (7)	1 (7)	2 (4)	2 (4)
Blood urea increased	0	0	0	0	0	0	1 (7)	0	1 (2)	0
Creatinine renal clearance decreased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Renal failure	0	0	0	0	0	0	1 (7)	0	1 (2)	0
Tubulointerstitial nephritis	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Pulmonary	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Pneumonitis	2 (17)	1 (8)	3 (20)	2 (13)	0	0	2 (14)	1 (7)	7 (13)	4 (7)
Endocrine	2 (17)	0	1 (7)	0	0	0	1 (7)	0	4 (7)	0
Hypothyroidism	1 (8)	0	0	0	0	0	1 (7)	0	2 (4)	0
Blood corticotropin decreased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
Blood TSH increased	1 (8)	0	0	0	0	0	0	0	1 (2)	0
Hyperthyroidism	1 (8)	0	0	0	0	0	0	0	1 (2)	0
Hepatic	0	0	1 (7)	0	0	0	0	0	1 (2)	0
ALT increased	0	0	1 (7)	0	0	0	0	0	1 (2)	0
AST increased	0	0	1 (7)	0	0	0	0	0	1 (2)	0

NOTE. Data are based on a September 2014 database lock. Table includes events reported between first dose date and 100 days after the last dose of study drug. No grade 5 events were reported. The causal relationship (related or not related) between study drug and AEs was determined by the investigator. Some patients had more than one AE.

Abbreviations; AE, adverse event; Carb, carboplatin; Cis, cisplatin; Gem, gemcitabine; NSCLC, non–small-cell lung cancer; Pac, paclitaxel; Pem, pemetrexed; PT-DC, platinum-based doublet chemotherapy; TSH, thyroid-stimulating hormone.

The safety of chemotherapy vs. chemotherapy plus pembrolizumab in NSCLC assists in making a judgement about the combination of nivolumab plus chemotherapy, and thus, the randomized chemotherapy plus/minus pembrolizumab data are instructive.[19] The incidence of grade 3 or worse toxicities were 39% and 26% with chemotherapy plus pembrolizumab vs. chemotherapy alone. There was 1 and 2 treatment related deaths in the pembrolizumab containing vs. control arm respectively. The authors concluded the triplet pembrolizumab containing regimen was tolerable.

	Pembrolizumab plus chemotherapy (N=59)				Chemotherapy (N=62)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Related to treatment*								
Any	32 (54%)	18 (31%)	4 (7%)	1 (2%)	40 (65%)	12 (19%)	2 (3%)	2 (3%)
Serious	2 (3%)	10 (17%)	3 (5%)	1 (2%)	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Led to discontinuation	1 (2%)	4 (7%)	0	1 (2%)	5 (8%)	1 (2%)	0	2 (3%)
Led to death	0	0	0	1 (2%)	0	0	0	2 (3%)
Occurring in ≥10% of patients in either group or of grade 3, 4, or 5 severity†								
Fatigue	36 (61%)	2 (3%)	0	0	25 (40%)	0	0	0
Nausea	33 (56%)	1 (2%)	0	0	27 (44%)	0	0	0
Anaemia	12 (20%)	7 (12%)	0	0	24 (39%)	9 (15%)	0	0
Vomiting	15 (25%)	1 (2%)	0	0	11 (18%)	0	0	0
Rash	15 (25%)	1 (2%)	0	0	9 (15%)	0	0	0
Decreased appetite	11 (19%)	0	0	0	11 (18%)	0	0	0
Diarrhoea	12 (20%)	0	0	0	6 (10%)	1 (2%)	0	0
Increased aspartate aminotransferase	10 (17%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Decreased neutrophil count	7 (12%)	2 (3%)	1 (2%)	0	6 (10%)	2 (3%)	0	0
Increased alanine aminotransferase	9 (15%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Constipation	11 (19%)	0	0	0	6 (10%)	0	0	0
Dysgeusia	10 (17%)	0	0	0	6 (10%)	0	0	0
Increased lacrimation	7 (12%)	0	0	0	6 (10%)	0	0	0
Alopecia	8 (14%)	0	0	0	2 (3%)	0	0	0
Increased blood creatinine	6 (10%)	0	0	0	4 (6%)	0	0	0
Dizziness	6 (10%)	0	0	0	4 (6%)	0	0	0
Neutropenia	3 (5%)	2 (3%)	0	0	4 (6%)	1 (2%)	0	0
Decreased white blood cell count	4 (7%)	1 (2%)	0	0	4 (6%)	1 (2%)	0	0
Peripheral oedema	7 (12%)	0	0	0	2 (3%)	0	0	0
Decreased platelet count	1 (2%)	0	1 (2%)	0	6 (10%)	0	1 (2%)	0
Pruritus	7 (12%)	0	0	0	2 (3%)	0	0	0
Hypokalaemia	5 (8%)	1 (2%)	0	0	2 (3%)	0	0	0
Decreased lymphocyte count	3 (5%)	2 (3%)	0	0	2 (3%)	1 (2%)	0	0
Thrombocytopenia	1 (2%)	1 (2%)	1 (2%)	0	2 (3%)	0	2 (3%)	0
Stomatitis	3 (5%)	0	0	0	2 (3%)	1 (2%)	0	0
Dehydration	1 (2%)	1 (2%)	0	0	2 (3%)	1 (2%)	0	0
Acute kidney injury	0	2 (3%)	0	0	1 (2%)	0	0	0
Hypocalcaemia	2 (3%)	1 (2%)	0	0	0	0	0	0
Leukopenia	0	1 (2%)	0	0	2 (3%)	0	0	0
Sepsis	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Pancytopenia	0	0	0	0	0	1 (2%)	0	1 (2%)
Cellulitis	1 (2%)	1 (2%)	0	0	0	0	0	0
Anaphylactic reaction	0	0	1 (2%)	0	0	0	0	0
Febrile neutropenia	0	1 (2%)	0	0	0	0	0	0
Myocardial infarction	0	1 (2%)	0	0	0	0	0	0
Pneumonia	0	1 (2%)	0	0	0	0	0	0
Rash macular	0	0	0	0	0	1 (2%)	0	0
Increased transaminases	0	1 (2%)	0	0	0	0	0	0

(Table 3 continues on next page)

Benefits

In this population, the safety profile of nivolumab was shown to be favorable as compared to standard of care chemotherapy. In the case of pembrolizumab, the addition of this agent to platinum doublets in NSCLC improved response and progression free survival compared to chemotherapy alone and in the case of nivolumab plus platinum doublets, also appeared more active compared to historical controls. Given the activity of both cisplatin pemetrexed and cisplatin gemcitabine, the known sustained responses of single agent nivolumab and the promising combination platinum doublet PD-1 inhibitor data in advanced disease in NSCLC, the proposed regimens offer is substantial promise of improved major pathologic response which in turn historically implies improved long term survival outcomes when given as induction prior to surgery in stage I-IIIa.

Study Objectives

1.4 Objectives

Primary

The primary objective of the study is to estimate major pathologic response (mpCR) in patients with newly diagnosed and untreated NSCLC Stage I-IIIA treated with three courses of induction Nivolumab added to either cisplatin/pemetrexed or cisplatin/gemcitabine prior to surgery.

Secondary

- Safety
- Complete Pathologic Response at all sites of disease
- Major pathologic response rate at primary site
- Clinical Complete Response Rate
- 1 year PFS
- Overall survival.

Exploratory

- To explore whether PDL1 expression is associated with treatment response
- To explore whether there is a net change in the Th1/Th2 ratio (IFN-gamma, IL-4, IL10, etc.) or cell subset frequencies (M2 monocytes, myeloid-derived

suppressor cells, etc.) within a patient's peripheral blood either at baseline or in response to treatment is associated with treatment response
- To explore whether exosomes or other immune related serum biomarkers change after combination therapy.
- To explore the predictive value of serial cell free DNA levels and response
- PD-L1 assessment in tumor. Blood correlatives for immune markers before and after treatment.

Blood correlatives of immune function before, during, and after treatment.
- Flow Cytometry
- White blood cell subset: CD3, CD4, CD8, CD11c, CD14, CD15, CD19, CD56, CD123
- White blood cell activation: CD25, CD163, CD204, CD206, PD1, PDL1
- Luminex, multiplex ELISA – Millipore human cytokine panel I (HCYTOMAG-60K-PX41)

- The aims for collecting PROs are to identify risks for poor physical and mental health outcomes; examine bio-behavioral factors associated with cancer treatment outcomes; to describe the longitudinal pattern of quality of life and depression from baseline to end of treatment; and evaluate the physical and psychosocial needs of cancer survivors.
  Patient Reported Outcomes Measures-: Depression: PHQ2 and PHQ9, Quality of Life: FACT-G and FACT-L

Tumor specimen:

PD-L1 will also be assessed using IHC on the baseline tumor tissue and the surgical specimen. For this, the SP263 rabbit monoclonal antibody of Ventana will be used. Note for the baseline, an archived formalin fixed paraffin embedded sample can be used. Also, we anticipate that some patients will have a pCR. However, peri-cancerous tissue can also be PD-L1 assessed.

Baseline p16 status will also be obtained for all oropharyngeal cancer patients.

1.5 Endpoints/Outcome Measures

Primary

The primary objective of the study is to estimate major pathologic response (mpCR defined as < 10% viable tumor) in patients with newly diagnosed and untreated NSCLC Stage I-IIIA treated with three courses of induction Nivolumab added to either cisplatin/pemetrexed or cisplatin/gemcitabine prior to surgery.

Secondary

Safety will be continually assessed using the CTCAE version 5.0.

Progression Free Survival (PFS) is defined as the time between the date of study entry and the date of either documented progression (by RECIST v1.1- Appendix F) or death whichever comes first. PFS at one year will be the percent of patients who have PFS by 1 year. For patients without documentation of death or evaluation of tumor status, PFS will be censored on the last date the subject was known to be alive or had documented tumor status assessment, whichever comes first.

Overall Survival (OS) is defined as the time between the date of study entry and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

The proportion of subjects with each category of overall clinical response will be summarized by presence of baseline measurable disease (i.e., CR, PR, SD, PD, UE, ND). Beta(2,5) will be used as priors for combination regimens in calculating the posterior distribution of the pCR for each respective treatment group. Among subjects with measurable disease, a 95% credible region will be calculated for the odds ratio for each treatment combination relative to each other.

Exploratory

- PDL1 expression
  We plan to monitor changes in PDL1 expression on tumor cells, tumor-infiltrating macrophages, and circulating monocytes by immunohistochemistry and flow cytometry. We will look for correlations between PDL1 expression on these cell subsets and treatment-induced clinical responses.
- Immune bias
  We will monitor changes in immune bias during treatment using three assays.
  1) Changes in PBMC cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells, etc.)
  2) Changes in patient serum cytokines (IL2, IL4, IL10, IL13, IFNg, etc.)
  3) Changes in the capacity to polarization normal human monocytes in vitro.

- Exosomes
  We will look for changes in exosome quantity and content following nivolumab and chemotherapy therapy.

Blood correlatives of immune function before, during, and after treatment.
- Flow Cytometry
  - White blood cell subset: CD3, CD4, CD8, CD11c, CD14, CD15, CD19, CD56, CD123
  - White blood cell activation: CD25, CD163, CD204, CD206, PD1, PDL1
- Luminex, multiplex ELISA – Millipore human cytokine panel I (HCYTOMAG-60K-PX41)

2 Study Design

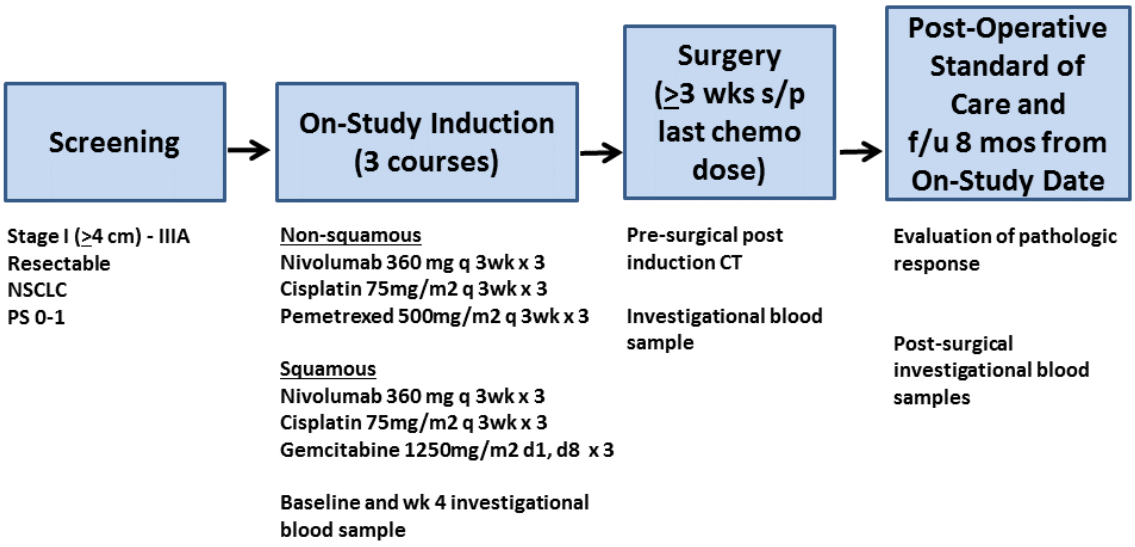
2.1 Characteristics

This is a phase II trial looking at the either cisplatin/pemetrexed or cisplatin/gemcitabine to which nivolumab is added as induction therapy prior to planned surgery for the definitive management of NSCLC.

TREATMENT PLAN

Non-squamous NSCLC
Nivolumab 360mg q 3w x 3
Cisplatin 75mg/m^2 q 3w x 3
Pemetrexed 500 mg/m2 q 3w x 3

Squamous NSCLC
Nivolumab 360mg q 3w x 3
Cisplatin 75mg/m^2 q 3w x 3
Gemcitabine 1250mg/m^2 d1, d8 x 3



If in the opinion of the treating physician, the cisplatin is not tolerated Well, the patient may be switched to standard carboplatin (AUC 5) for both squamous and nonsquamous for the remaining courses.

Nonsquamous for the remaining courses:
Carboplatin AUC 5
Pemetrexed 500mg/m^2
Nivolumab 360mg

Squamous for the remaining courses:
Carboplatin AUC 5
Gemcitabine 1250mg/m^2
Nivolumab 360mg

Evaluation of Response to Chemotherapy

Clinical response to chemotherapy will be measured by repeat CT of thorax. PET/CT and MRI brain will be obtained during the initial staging work-up for all patients (if not PET/CT then baseline CT chest abdomen and pelvis with bone scan). If the treating medical oncologist determines that there is evidence the patient is progressing while on treatment, the appropriate repeat imaging will be obtained. For patients who are determined to have progression during treatment by their medical oncologist, study treatment will be discontinued and the patient will be considered for immediate surgery, as determined at the discretion of their treating oncologist and surgeon. Finally, the level of pathologic response will be assessed in the final tumor specimen, and attainment of

major pathologic response will be determined by pathologic review. Assessment of pathologic response of the entire tumor will also include all sampled lymph nodes.

Surgery

All patients will undergo surgery after completing the induction regimen. Surgery will be scheduled at least 3 weeks after the last dose of platinum doublet (last dose of gemcitabine can be 2 weeks before surgery).

Number of Participants

34 total subjects. 24 subjects will be enrolled at Thomas Jefferson University, 5 subjects will be enrolled at Abington Memorial Hospital, and 5 subjects will be enrolled at Main Line Health.

2.2 Duration of Therapy

9 weeks

2.3 Duration of Follow Up

6 months after surgery or about 8 months after enrollment on trial.

2.4 Study Timeline

Primary Completion

We anticipate accrual of 34 patients to the study over 24 month time period. Patients will remain on study for 8 months total, 2 months of induction and then 6 months of follow-up after surgery whether or not patients receive post-operative radiation.

Study Completion

We anticipate completion of the study in 32 months.

3 Study Enrollment and Withdrawal

3.1 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. The written informed consent must be obtained from the patient prior to screening procedures being performed. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.1..1 *Inclusion Criteria*

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Patients must be 18 years of age and older.
2. Pathologically confirmed NSCLC, not previously treated, with a plan to undergo surgery
3. Stage I-IIIA (stage I tumors must be ≥4cm) per AJCC 8th edition
4. Tumor sample must be available for PD-L1 testing. Archival tissue within 3 months of study enrollment will be used. If archival tissue is unavailable, a fresh biopsy will be taken.
5. ECOG Performance status 0-1.
6. Adequate organ function:
    - While blood cells 2000/ul or more
    - Absolute neutrophil count 1500/ul or more;
    - Platelets 100,000/ul or more,
    - Hemoglobin 9 g/dl or more; (transfusion permitted)
    - Bilirubin less than or equal to 1.5 x the upper limit of normal (except subjects with Gilbert syndrome, who can have total bilirubin <3 mg/dl);
    - AST and ALT less than or equal to 3 x the upper limit of normal,
    - GFR greater than or equal to 40 ml/min using the Cockcroft-Gault formula or Serum creatinine less than or equal to 1.5 x ULN
7. Women of reproductive potential should have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 21 days of the study enrollment.
8. Women of reproductive potential must use highly effective contraception methods to avoid pregnancy for 23 weeks after the last dose of study drugs. “Women of reproductive potential” is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. 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 55 must have a documented serum follicle stimulating hormone (FSH) level more than 40 mIU/mL.
9. Men of reproductive potential who are sexually active with women of reproductive potential must use any contraceptive method with a failure rate of less than 1% per year. Men who are receiving the study medications will be instructed to adhere to contraception for 31 weeks after the last dose of study drugs. Men who are azoospermic do not require contraception.
10. Informed Consent: All subjects must be able to comprehend and sign a written informed consent document.

3.1..2 ***Exclusion Criteria***

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have participated in a study with an investigational agent or device within 2 weeks of enrollment
2. Any prior radiotherapy to the lung.
3. Any prior treatment for NSCLC.
4. EGFR or ALK activating alteration
5. Any prior therapy with anti-PD-1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
6. Any history of a sever hypersensitivity reaction to any monoclonal antibody.
7. Any history of allergy to the study drug components.
8. Any concurrent malignancies- exceptions include- basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer that has undergone potentially curative therapy. Patients with a history of other prior malignancy must have been treated with curative intent and must have remained disease-free for 3years post-diagnosis.
9. Participants with an active autoimmune disease or any other condition requiring systemic treatment with either corticosteroids within 14 days (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
10. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
11. Patients with evidence of interstitial lung disease or active, non-infectious pneumonitis. Patients with a history of interstitial lung disease or non-infectious pneumonitis requiring treatment with steroids are also excluded.
12. Patients with a known Human Immunodeficiency Virus infection (HIV 1/2 antibodies) or Acquired Immunodeficiency Syndrome (HIV/AIDS), active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
13. Patients who have received a live vaccine within 30 days prior initiation of the systemic regimen.
14. Patients must not be receiving any other investigational agents.
15. Patients with uncontrolled intercurrent illnesses including, but not limited to an active infection requiring systemic therapy or a known psychiatric or substance

abuse disorder(s) that would interfere with cooperation with the requirements of the trial.

16. Women must not be pregnant (as above) or breastfeeding.

3.2 Gender/Minority/Pediatric Inclusion for Research

We will not exclude potential subjects from participating in this study based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients in this protocol and therefore address the study objectives in a patient population representative of the entire squamous cell and nonsquamous cell lung cancer population treated at Thomas Jefferson University Hospital. There is nearly a 3:1 predominance of males to females in this diagnosis. We will review accruals to this trial quarterly in the Lung MDG and review the number of males and females accrued. If this deviates from the expected ratio we will review our actual patient ratio for that time and determine a remediation plan within the MDG to ensure accrual of women.

3.3 Strategies for Recruitment and Retention

Thirty-four subjects will be recruited. No advertisement will be conducted. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Surgical offices. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study. Patients will be screened based on pathology, image studies etc. 34 patients will be enrolled (see Statistical Analysis Plan) with replacement of patients who do not begin therapy.

3.4 Affiliate Site Enrollment Procedures

When a potential patient is identified at the Affiliate Site, the Thomas Jefferson University (TJU) Study Site Contact should be contacted within 1 business day via email or phone. Please see the Site Contact List for email and phone number for the TJU Study Site Contact. The Affiliate Site will send the following to the TJU Study Site Contact

1. Notify them of the pending patient registration
2. Confirm the method of sending registration documents (i.e. fax, email, etc.). Registration documents should include at least a completed eligibility checklist and supporting documentation to confirm eligibility.

3. Communicate the desired timeline of the registration.

Once eligibility has been confirmed, TJU will email the Research Coordinator at the Affiliate Site to confirm . The participant will then be assigned a registration number. This number is unique to the participant on this trial and must be used moving forward. The Affiliate Site Research Nurse/Coordinator will enter patients enrolled at the Affiliate Site into the protocol management system, JeffTrial, within 5 business days of enrollment.

A master study enrollment log will be maintained by the study team at Thomas Jefferson University. The Affiliate Site will also be asked to maintain an enrollment/screening log on-site, and email this information to the TJU Study Site Contact at least once a month.

Patients cannot be registered to this study on the weekends. If a patient is to be registered on a Friday, the Affiliate Site will need to contact the TJU Study Site Contact by Friday at noon at the latest.

If a patient is enrolled at the Affiliate Site without approval from the lead site, TJU will:

1) Temporarily suspend the Affiliate Site

2) Complete mandatory re-training of staff at the Affiliate Site on the enrollment process. This training will be fully documented.

If enrollment without approval occurs a second time, the Affiliate Site will not be able to continue to participate in this study.

3.5 Participant Withdrawal

3.5..1 *Reasons for Withdrawal*

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant’s participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

3.5..2 *Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention*

Patients who are discontinued from the study prior to initiation of radiation will not be considered as evaluable for this study and will be replaced.

3.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

4 Study Intervention

4.1 Study Products:

- Nonsquamous cohort
  - Nivolumab
  - Cisplatin
  - Pemetrexed
- Squamous cohort
  - Nivolumab
  - Cisplatin
  - Gemcitabine

4.2 If in the opinion of the treating physician, the cisplatin is not tolerated well, the patient may be switched to standard carboplatin (AUC 5) for both squamous and nonsquamous for the remaining courses. Study Product Description

Nivolumab:

- Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (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 technologies. The clinical study product is a sterile solution for parenteral administration. OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

4.2..1 *Acquisition*

Nivolumab will be supplied by Bristol-Myers Squibb directly to each site involved in the research (Thomas Jefferson University and Affiliate Sites).

Chemotherapy (cisplatin, pemetrexed, gemcitabine, and carboplatin) at each site will be supplied commercially.

4.2..2 *Formulation, Packaging, and Labeling*

Nivolumab:

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are:

BMS Number	*BMS-936558-01*
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons (143,619.17 daltons, protein portion)
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in

sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

4.2..3 ***Product Storage and Stability***

Nivolumab:

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

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°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

4.3 Dosage, Preparation, and Administration

Nivolumab:

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) 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. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Dosage & Administration Time of Nivolumab

The dose of nivolumab is a flat dose 360mg administered intravenously over at least 30 minutes. Do not co-administer other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

Frequency of Treatment:

For the duration of the study, nivolumab is to be administered on a Q3 weeks and cisplatin/pemetrexed or cisplatin/gemcitabine Q 3 weeks, all agents on the same day. Nivolumab administration will precede chemotherapy administration.

4.4 Study Product Accountability

Table 1 Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume) / Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	10 mL vial	5-vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing

Drug Destruction:

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. **The procedures must be filed** with the Sponsor SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for BMS to review throughout the clinical trial period as per the study agreement.
- If conditions for destruction cannot be met, please contact BMS.

- It is the Sponsor Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.5 Cisplatin

Please see package insert for detailed information regarding side effects related to this drug.

Other Names
Cisdiaminedichloroplatinum, Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875.

Classification
Alkylating agent

Mode of Action
Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

Storage and Stability
Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

Preparation
The desired dose of cisplatin is diluted with 250-1000 mL of saline and/or dextrose solution. Varying concentrations of 0.225-5% sodium chloride and 5% dextrose may be used. To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

Administration
Cisplatin solution must be administered over a 60 to 120 minute period.

Dosage
75mg/m^2 on day 1 of each 3 week cycle for three cycles.
Incompatibilities
Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, and thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

Availability
Commercially available as a mg/mL solution in 50 and 100 mg vials.

Side Effects
Please see package insert for detailed information regarding side effects related to this drug.
A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus, occurs in about 30% of subjects. Mild leukopenia and thrombocytopenia occur in 25-30% of subjects, but are rarely dose-limiting. Nausea and vomiting occur in almost 100% of subjects unless adequate antiemetic prophylaxis is given. Allergic reactions are reported in up to 20% of subjects. Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia.

4.6 Pemetrexed

Availability
Pemetrexed is commercially available and is approved for this indication.

Chemical Name
Pemetrexed disodium heptahydrate has the chemical name L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate.

Classification
An antifolate antineoplastic agent

Molecular Formula
C20H19N5Na2O6•7H2O **Molecular Weight**: 597.49

Mode of Action
Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication.

How Supplied
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.
NDC 0002-7623-01 (VL7623): single-use vial with flip-off cap individually packaged in a carton (500 mg vial). NDC 0002-7640-01 (vl7640); single use vial with flip-off cap individuality packaged in a carton (100 mg vial).

Storage and Stability
Pemetrexed for injection, should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. 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) [see USP Controlled Room Temperature]. When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Discard unused portion.
Pemetrexed is not light sensitive.

Dose Specifics and Administration
All patients on Arm B or Arm C of Maintenance Phase of protocol treatment will receive pemetrexed at 500 mg/m^2 IV over 10 minutes every 21-day cycle.

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. Coadministration of pemetrexed with other drugs and diluents has not been studied, and therefore is not recommended.

Route of Administration
Intravenous Infusion.

Incompatibilities and Potential Drug Interactions
Chemotherapeutic Agents — Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum is unaltered by pemetrexed.

Vitamins — Coadministration of oral folic acid or intramuscular vitamin B12 does not affect the pharmacokinetics of pemetrexed.

Drugs Metabolized by Cytochrome P450 Enzymes — Results from in vitro studies with human liver microsomes predict that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to determine the cytochrome P450 isozyme induction potential of pemetrexed, because Pemetrexed used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction.

Aspirin — Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

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 pharmacokinetics 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 and gastrointestinal toxicity.

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

Pregnancy
Category D

Nursing/Patient Implications
1. Monitor CBC's and chemistries.
2. Administer Adequate Antiemetics.
3. Monitor renal toxicity: Calculate Creatinine Clearance prior to administering pemetrexed.
a. Patient use of Ibuprofen: Refer to precautionary guidelines
4. Administer 1000 micrograms Vitamin B12 intramuscularly within 1 week of first dose of pemetrexed and repeat every 3 cycles until the end of treatment.
5. 400-1000 micrograms of folate (folic acid) beginning at least 5-7 days prior to initial dose of pemetrexed and continuing for at least 3 weeks after last dose.
6. Monitor for adequate hydration.
7. Patients may receive dexamethasone 4mg orally twice daily (or equivalent corticosteroid) on the day before, day of, and day after each dose of pemetrexed to prevent the occurrence of rash.

4.7 Gemcitabine

Please see package insert for detailed information regarding this medication

Other Names
2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

Classification
Antimetabolite (nucleoside pyrimidine analogue)

Mode of Action
Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).

Storage and Stability
Unreconstituted drug vials are stored at controlled room temperature (15ºC to 30ºC, 59ºF to 86ºF). Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; as crystallization may occur. The unused portion should be discarded.

Preparation
Gemcitabine may be further diluted with normal saline as per institutional standards.

Route of Administration
IV infusion.

Dosage
Gemcitabine 1250mg/m^2 on Day 1 and Day 8 of each 3 week cycle.

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

Side Effects
Please see package insert for detailed information regarding side effects related to this drug.

Below are some common side effects related to Gemcitabine
Neutropenia, anemia, thrombocytopenia, and leukopenia are reported. Rash with pruritus and injection-site reactions are can occur. Nausea and vomiting, diarrhea, constipation and mucositis have been reported. Abnormalities of hepatic transaminase enzymes occur in two-thirds of subjects, but they are usually mild, non-progressive, and rarely necessitate stopping treatment. Bronchospasm and/or dyspnea within a few hours of infusion of the drug, cough, rhinitis, pneumonitis may occur. Somnolence, insomnia, paresthesia, pain. Peripheral edema is reported in about 30% of subjects. Flu-like symptoms are reported for about 20% of subjects. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia.

4.8 Carboplatin

PARAPLATINÆ (carboplatin aqueous solution) INJECTION is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine [1,1- cyclobutane-dicarboxylato(2-)-0,0í]-,(SP-4-2). Carboplatin is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

Unopened vials of PARAPLATIN (carboplatin aqueous solution) INJECTION are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F) [see USP Controlled Room Temperature]. Protect from light. PARAPLATIN (carboplatin aqueous solution) INJECTION multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

Preparation and administration must be performed per standard of care.

4.9 Treatment Schedules Nivolumab/Cisplatin/Pemetrexed and Nivolumab/Cisplatin/Gemcitabine

Nivolumab/Cisplatin/Pemetrexed

On days 1, 22 and 42, the medicine administration sequence will be nivolumab, pemetrexed, cisplatin. Pegfilgrastim or filgrastim will be administered per standard of care schedule.

	Day 1	Day 22	Day 42
Nivolumab	**360 mg IV**	**360 mg IV**	**360 mg IV**
Pemetrexed	**500 mg/m2 IV**	**500 mg/m2 IV**	**500 mg/m2 IV**
Cisplatin	**75 mg/m2 IV**	**75 mg/m2 IV**	**75 mg/m2 IV**

4.9..1 ***Nivolumab Administration***

Nivolumab will be administered as a flat dose of 360mg IV over approximately 30 minutes in NS 100 mL. on day 1 of each 3 week cycle. Premedication not required.

4.9..2 ***Pemetrexed Administration:***

Pemetrexed 500/m^2, will be administered on Days 1 of each 3 wk cycle in NS, 100 mL, IV over 10 minutes.

4.9..3 ***Cisplatin Administration:***

Cisplatin 75mg/m^2, will be administered Q 3 weeks in D5/NS, 250 -1000mL, IV over 1 – 2 hours on day 1 of each 3 week cycle

<u>Nivolumab/Cisplatin/Gemcitabine</u>

On days 1, 22 and 42, the medicine administration sequence will be nivolumab, gemcitabine, cisplatin. Pegfilgrastim or filgrastim will be administered per standard of care schedule.

	Day 1	Day 8	Day 22	Day 29	Day 42	Day 49
Nivolumab	**360 mf IV**		**360 mg IV**		**360 mg IV**	
Gemcitabine	**1250 mg/m2 IV**	**1250 mg/m2 IV**	**1250 mg/m2 IV**	**1250 mg/m2 IV**	**1250 mg/m2 IV**	**1250 mg/m2 IV**
Cisplatin	**75 mg/m2 IV**		**75 mg/m2 IV**		**75 mg/m2 IV**	

4.9..4 ***Nivolumab Administration***

Nivolumab will be administered as a flat dose of 360mg IV over approximately 30 minutes in NS 100 mL. on day 1 of each 3 week cycle Premedication not required.

4.9..5 ***Gemcitabine Administration:***

Gemcitabine, 1250mg/m^2, will be administered on Days 1 and 8 of each 3 wk cycle in NS, 250 mL, IV over 30 minutes.

4.9..6 ***Cisplatin Administration:***

Cisplatin 75mg/m^2, will be administered Q 3 weeks in D5/NS, 250 -1000mL, IV over 1 – 2 hours on day 1 of each 3 week cycle

4.10 Dose Modifications and Dosing Delays

The following sections detail the allowable dose modifications and dose delays for the study treatment.

If a patient discontinues one of the drugs in the three drug regimen (Nivolumab/Cisplatin/Pemtrexed or Nivolumab/Cisplatin/Gemcitabine), the patient will discontinue all drugs in the regimen.

If in the opinion of the treating physician, the cisplatin is not tolerated well, the patient may be switched to standard carboplatin (AUC 5) for both squamous and nonsquamous for the remaing courses.

Thus:

<u>Nonsquamous:</u>

Carboplatin auc 5, pemetrexed 500mg/m^2 and nivolumab (current dose)

<u>Squamous</u>
Carboplatin auc5, gemcitabine (current dose) and nivolumab (current dose).

4.10..1 ***Nivolumab:***

There will not be dose modifications

<u>Dose Delays:</u>
Dose delay criteria apply for all drug-related AEs. Treatment delay is up to 2 weeks for nivolumab and up to 2 weeks for either cisplatin/pemetrexed of cisplatin/gemcitabine;

the maximum prior to the last planned dose before surgery (any dose delays greater than these will require review and approval from the TJU PI).

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade ≥ 3 skin *drug-related* AE
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase
    - Grade 3 lymphopenia does not require a 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 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 TJU PI should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

<u>Rescheduling:</u>

- Nivolumab may be delayed until the next planned cisplatin/pemetrexed of cisplatin/gemcitabine dose.

<u>Criteria to Resume Nivolumab Dosing:</u>

- Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, 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* (non-radiation dermatitis) skin AE may resume treatment in the presence of Grade 2 skin toxicity.
    - 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 may be eligible for retreatment if discussed with and approved by the TJU PI.

- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The TJU PI should be consulted prior to resuming nivolumab in such subjects.
- Dose delay of nivolumab which results in treatment interruption of > 2 weeks requires treatment discontinuation.

<u>Criteria to Discontinue Nivolumab</u>

Treatment with nivolumab should be permanently discontinued for any of the following:

- Any 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
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Any Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Any Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Any Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
  - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):
    - AST or ALT > 8x 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:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - 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. The TJU PI should be consulted for Grade 4 amylase or lipase abnormalities
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy adverse events such as 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, may not require discontinuation after discussion with and approval from the TJU PI.
- Dosing delays lasting > 2 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the TJU PI. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the TJU PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Please see the Appendix for **Strategies to Treat Adverse Events.**

For subjects expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE 5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or

paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

The assessment of a dose delay or discontinuation is to be made independently of the consideration of radiation treatments, please see below.

4.10..2 ***Cisplatin pemetrexed***

(for cisplatin alterations please see below in the section describing cisplatin gemcitabine

Pemetrexed

In the event of toxicity, patient should be enquired about compliance with intake of folic acid. Administration of vitamin B12 every 3 cycles of therapy should be ensured.

Hematological toxicity

Before initiation of a new cycle of therapy, the following hematological indices must be met:

- ANC ≥ 1500/mm3
- Platelets ≥ 100,000/mm3

If the indices have not improved to this level, pemetrexed should be delayed until recovery. Upon recovery, patients should be treated using the guidelines below. The complete blood count should be checked at least once a week when the pemetrexed is held. Pemetrexed should be discontinued if a patient experiences any hematologic Grade 3 or 4 toxicity after 2 dose reductions.

Dose Reduction for Pemetrexed and Cisplatin- Hematologic Toxicities	
ANC <500/mm3 and platelets ≥50,000/m3	75% of full dose
Platelets <50,000/mm3 without bleeding, regardless of ANC	75% of full dose
Platelets <50,000/mm3 with bleeding, regardless of ANC	50% of full dose

For febrile neutropenia:

Grade 3 or 4 Febrile neutropenia		Pemetrexed
	1st occurrence	**375mg/m²**
	2nd occurrence	**250mg/m²**
	3rd occurrence	**Off study**

Leucovorin can be considered for grade 4 leukopenia lasting > 3 days, grade 4 neutropenia lasting > 3 days, and immediately for grade 4 thrombocytopenia, or bleeding associated with grade 3 thrombocytopenia. The following intravenous doses and schedules of leucovorin are recommended if it is used: 100mg/m², intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8 days.

Non-hematological toxicity
For non-hematologic toxicities (considered related to pemetrexed) ≥ grade 3, pemetrexed should be delayed until resolution to less than or equal to the patient's baseline value by the start of the cycle, before proceeding. If treatment is delayed for > 3 weeks for any pemetrexed related toxicity, the patient should be treated as follows: Discontinue all protocol treatment.

Dose Reduction for Pemetrexed and Cisplatin- NonHematologic Toxicities		
	Dose of Pemetrexed (mg/m2)	**Dose of cisplatin (mg/m2)**
Any Grade 3 or 4 toxicities except mucositis	75% of dose	75% of dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of dose	75% of dose
Grade 3 or 4 mucositis	50% of dose	1000% of dose

Pemetrexed should be discontinued if a patient experiences any non-hematologic Grade 3 or 4 toxicity after 2 dose reductions.

Neurotoxicity
In the event of neurotoxicity, the recommended dose adjustments for pemetrexed and cisplatin are described below. Patients should discontinue therapy immediately if Grade 3 or 4 neurotoxicity is experienced.

Dose Reduction for Pemetrexed and Cisplatin- Neurotoxiticy		
Grade	**Dose of Pemetrexed (mg/m2)**	**Dose of cisplatin (mg/m2)**
0-1	100% of dose	100% of dose
2	100% of dose	50% of dose

Renal Toxicity
Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (CrCl < 45mL/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. All patients taking NSAIDs with longer elimination half-lives 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 renal toxicity.

Stomatitis
Leucovorin may be considered for grade 3 or 4 stomatitis and can be given on the following schedule: 100mg/m², intravenously once, followed by leucovorin, 50 mg/m², intravenously every 6 hours for 8 days.

Clinically Significant Effusions

For patients who develop or have baseline clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) before or during initiation of pemetrexed therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator's opinion, the effusion represents progression of disease, the patient should be discontinued from study therapy after confirmation of progression of disease.

Upon resolution, pemetrexed treatment will resume as follows:

- In the event of grade 3 nausea or vomiting, and/or grade 4 vomiting, pemetrexed may resume without dose reduction. Grade 3 nausea or vomiting and/or Grade 4 vomiting should be managed with appropriate changes in antiemetic regimen.

- In the event of grade 3 or 4 mucositis, pemetrexed should be resumed at 50% of the previous level.

- In the event of grade 4 transaminase elevation, grade 3 or 4 diarrhea, or any grade diarrhea requiring hospitalization, a 25% dose reduction of pemetrexed is mandatory. Thus, pemetrexed should resume at 75% of the previous dose level.

- For other grade 3 or 4 non-hematologic toxicities, treatment should resume at 75% of the previous dose level, if deemed appropriate by the treating physician.

4.10..3 ***Cisplatin/Gemcitabine and Cisplatin Pemetrexed Dose Modifications:***

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 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 the Schedule of Events.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit during the treatment portion of the study.

Subjects discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days (± 7) after the last dose of study drug.

Dose Level	Gemcitabine
0	1250mg/m^2
-1	1000mg/m^2
-2	750mg/m^2

Subjects who require more than two permanent dose reductions will be removed from gemcitabine treatment

Dose Level	Cisplatin
0	75mg/m2
-1	60mg/m2
-2	45mg/m2

Subjects who require more than two permanent dose reductions will be removed from cisplatin treatment

Hematologic Toxicity: gemcitabine-cisplatin
Gemcitabine and cisplatin doses may be modified separately based on individual toxicity according to the rules outlined below. There is no dose reduction below level -2 for gemcitabine or cisplatin. If dose reduction below level -2 is required, gemcitabine and/or cisplatin should be discontinued.

Recommended Dose Reductions for Gemcitabine in Non-Small Cell Lung Cancer			
Absolute granulocyte count (x10^9/L)		**Platelet Count (x10^6/L)**	**% of full dose**
≥1000	And	≥100,000	100%
500-999	OR	50,000-99,999	75%
<500	OR	<50,000	Hold

Recommended Dose Modifications for Cisplatin in Non-Small Cell Lung Cancer	
Grade 4 neutropenia lasting >5 days w/Grade 1-2 thrombocytopenia	15% of dose
Grade 3 neutropenia and thrombocytopenia	15% of dose
Grade 4 neutropenia w/Grade 3 thrombocytopenia	25% of dose
Grade 4 thrombocytopenia	50% of dose

If a patient requires more than two dose reductions for hematologic toxicity, treatment should be discontinued.

Non-Hematologic Toxicity
Please see section 4.9.2 for cisplatin dose modifications for non-hematologic toxicity.

Neurotoxicity
Please see section 4.9.2 for cisplatin dose modifications for neurotoxicity.

Criteria for initiation of a new cycle with gemcitabine-cisplatin:

For Day 1 of each cycle, subjects must have an ANC ≥ 1,500 AND platelets ≥ 100,000 before receiving treatment with gemcitabine-cisplatin or nivolumab. Subjects that do not meet these values on Day 1 will have their cycle start delayed and any nivolumab doses during that cycle will be similarly delayed. Resume the gemcitabine-cisplatin new cycle and nivolumab dosing once the ANC improves to ≥1,500 AND platelets ≥100,000 (see 5.10.2.3 for nivolumab guidelines).
If treatment is/was delayed:

- For up to 1 week, resume treatment at the previous doses of gemcitabine-cisplatin. After the delay, nivolumab dosing and interval should resume to stay “in-sequence” with gemcitabine-cisplatin cycle.
- For more than 1 week and less than 4 weeks, reduce gemcitabine and cisplatin by one dose level for this and all subsequent cycles. Once the cycle is resumed, nivolumab dosing and its’ interval should resume to stay “in-sequence” with gemcitabine-cisplatin cycle. No nivolumab dosing interval change.
- If a second treatment delay of more than one week and less than 4 weeks occurs, reduce gemcitabine and cisplatin an additional dose level. Nivolumab dosing should restart on the planned cycle day (for Cohort I, this is generally Day8), however the nivolumab dosing interval should be permanently increased by 1 week for subsequent doses.
- Greater than 4 weeks due to hematologic toxicity, discontinue all therapy and initiate workup to optimize the subject for surgical consideration.

Workup of cytopenia etiology beyond bone marrow suppression is encouraged at any time, and per treating physician judgment.

Febrile Neutropenia
For febrile neutropenia (defined here as temperature ≥ 38.5° C [101° F] sustained for more than one hour concomitant with ANC ≤ 500/mm^3) reduce gemcitabine and cisplatin by one dose level for this and subsequent cycles. Consider filgrastim or peg-filgrastim in subsequent cycles.

Hepatic Dysfunction (See Table 6 below)
Hepatic dysfunction should prompt consideration of workup for etiology such as medication and supplement review, infection, imaging, pancreatico-biliary evaluation, and amylase, lipase. Consideration should be given to evaluation of concomitant pancreatitis in the appropriate setting. This evaluation and workup is at the treating physician discretion.

For bilirubin > 1.5 x ULN (or > 3 x ULN for subjects with Gilbert's syndrome), delay nivolumab treatment until bilirubin ≤ 1.5 x ULN (< 3 x ULN for subjects with Gilbert's syndrome), then resume with one dose level reduction of gemcitabine and at the previous dose of cisplatin.

If bilirubin is > 1.5 x ULN despite two gemcitabine dose reductions, gemcitabine should be discontinued but cisplatin. For subjects with Gilbert's syndrome, if bilirubin is > 3 x ULN despite two gemcitabine dose reductions, gemcitabine and cisplatin should be permanently discontinued.

Guidelines for Dose Modifications due to LFT abnormalities. LFT	**Gemcitabine**	**Cisplatin**
AST/ALT >ULN to 2xULN and Total bilirubin >1.5 xULN OR >3 xULN for subjects with Gilbert's syndrome1	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume with one dose level	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume at

	reduction of gemcitabine. After 2 dose level reductions, gemcitabine should be discontinued.	previous dose of cisplatin. For subjects with Gilbert's, discontinue both gemcitabine and cisplatin after 2 occurrences of total bili >1.5.
AST/ALT >2 xULN to ≤8 xULN and Total bilirubin ≤1.5 xULN OR ≤3 for subjects with Gilbert's syndrome1	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume with one dose level reduction of gemcitabine. Consider hepatologist consult.	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume at previous dose of cisplatin. Consider hepatologist consult.
AST/ALT>2 xULN to ≤8 xULN and Total bilirubin >1.5 xULN OR >3 for subjects with Gilbert's syndrome1	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume with one dose level reduction of gemcitabine. After 2 dose level reductions, gemcitabine should be discontinued. Consider hepatologist consult.	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume at previous dose of cisplatin. For subjects with Gilbert's, discontinue both gemcitabine and cisplatin after 2 occurrences of total bili >1.5. Consider hepatologist consult.

AST/ALT >8 x ULN and Total Bilirubin any level	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume with one dose level reduction of gemcitabine. Consider hepatologist consult.	delay treatment until AST/ALT ≤2 xULN and total bilirubin ≤ 1.5 xULN (≤3 xULN for subjects with Gilbert's syndrome1), then resume at previous dose of cisplatin. For subjects with Gilbert's, discontinue both gemcitabine and cisplatin after 2 occurrences of total bili >1.5. Consider hepatologist consult.

For grade 3 sensory or motor neuropathy, skip cisplatin until the toxicity resolves to ≤grade 2 and then resume therapy with one dose level reduction of cisplatin on Day 1 of the next scheduled cycle. If cisplatin is skipped for two consecutive cycles, permanently discontinue cisplatin. Treatment with gemcitabine and nivolumab may continue.

For grade 4 sensory or motor neuropathy, skip gemcitabine and cisplatin therapy until resolution to ≤ grade 2. If sensory neuropathy improves to grade 3, but not grade 2 or better, within 4 weeks, resume gemcitabine at the previous dose without cisplatin. If the sensory neuropathy remains at grade 4 within 4 weeks, discontinue gemcitabine and cisplatin, then prepare the subject for surgery within 2-7 weeks.

Gastrointestinal Toxicity
For grade 3 or 4 nausea or vomiting despite maximal antiemetic therapy (including 5HT-3 antagonist, corticosteroids up to 5 days, and aprepitant), discontinue cisplatin. Continue gemcitabine at the previous dose when symptoms resolve to ≤ grade 1.

Kidney Dysfunction –
A Ccr from properly collected timed (24 hours; 18-24 hours acceptable) urine supersedes a calculated value for determination of cisplatin eligibility and dosing. Accuracy of timed urine collection, however, is dependent on patient compliance; proper collection adherence should be confirmed with the patient. Improper collection methods

disqualify use of the timed collection results and a calculated serum value should be used.

For creatinine clearance < 50 mL/min (measured or calculated) on Day 1 of a cycle, delay all treatment until creatinine clearance improves to ≥ 50 mL/min as follows:

- If creatinine clearance improves to ≥ 60 mL/min within 1 week, resume with one dose level reduction for cisplatin and gemcitabine for all subsequent dose.
- If creatinine clearance improves to ≥ 50 and < 60 mL/min within 1 week, resume with one dose level reduction of cisplatin for this and all subsequent cycles. Administer cisplatin as a split dose on Days 1 and 2 (preferred) or Days 1 and 8 of this cycle. Resume gemcitabine at the same dose.

If creatinine clearance does not improve to ≥ 50 mL/min within 1 week, skip cisplatin for this cycle only. Treat with cisplatin at one lower dose level for this and all subsequent cycles with split dosing over Days 1&2 (or Days 1 and 8, per treating physician discretion as previously described) ule. For a subsequent cycle, if creatinine clearance is again < 50 mL/min, discontinue cisplatin

Gemcitabine Non-Hematologic Toxicity Grade	**Dose Modification**
0-2	Full dose
3-4	Hold until resolution to ≤ Grade 2, then decrease by 1 dose level from current dose. This dose reduction is not permanent. If toxicity does not resolve within 4 weeks, discontinue gemcitabine treatment.

4.11 Assessing Participant Compliance with Study Product Administration

Patient records will be reviewed for compliance with chemotherapy and nivolumab treatments with all deviations and delays noted.

4.12 Concomitant Medications/Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication and therapies will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

All concomitant medications received within 28 days before informed consent is signed and 30 days after the last dose of trial treatment must be recorded. Concomitant medications administered to treat SAEs and ECIs should be recorded as defined.

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids, with the following exceptions:
    - Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
    - Adrenal replacement steroid doses > 10 mg daily prednisone are permitted.
    - A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer.
- The use of amifostine is not permitted.
- The use of hematopoietic growth factors (erythropoietin) can be considered at the discretion of the treating physician

All other medications are permitted except those that are contraindicated in the exclusion criteria (section 4.1.2).

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. The

indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction. Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

All supportive measures consistent with optimal patient care will be given throughout the study. This includes the use of antiemetic therapy at the discretion of the treating physician, as well as pilocarpine and cevimeline. Use of these agents will be recorded on the data forms.

Aggressive oral and skin can is recommended, as are analgesics.

The prophylactic placement of a gastrostomy tube before treatment begins is at the discretion of the treating physician but it not encouraged. It is strongly recommended for patients with significant dysphagia and weight loss.

Salvage surgery may be performed after chemo-radiotherapy is there is local and / or regional progression of disease.

4.13 Dietary Restrictions

There are no dietary restrictions.

5 Study Schedule

Nonsquamous NSCLC

Study Period	Baseline	Treatment	Observation (d)

Week			1	4	7	10	12	Monthly
Treatment			Pemetrexed + Cisplatin Nivolumab			Surgery (q)	Standard of care (d)	
Nivolumab			X	X	X			
Pemetrexed			X	X	X			
Cisplatin(t)			X	X	X			
Consent form signed by patient	X							
History and physical exam (including vital signs, weight, BMI, height)	X(o)		X(n)	X	X	X(o)		X
ECOG Performance Status	X		X (n)	X	X	X		X
Assessment of concurrent medications	X		X(n)	X	X	X	X	X
PET/CT or CT chest, abdomen, pelvis and bone scan. (l)	X	Within 4 weeks				X(j)		X (e)
MRI brain (l)	X							
CBC, differential, platelet count	X	Within 21 days	X(n)	X	X	X (r)		X
CMP (m)	X		X(n)	X	X	X (r)		X
Serum chemistries (m)	X		X(n)	X	X			
C-reactive protein (CRP), HbA1c, lipid panel (s)	X						X	
PT/PTT	X		X(n)			X (p)		

Endocrine (TSH, T4, T3, cortisol)	X		X(n)	X	X	X (p)		X(u)
Pregnancy test (women of childbearing potential)	X	Within 21 days	X (k)	X (k)	X (k)			
Viral studies (HepB, HepC)	X	Within 28 days						
Assessment of cardiac function EKG	X	Within 2 weeks				X (h)		
Blood Draw for CTCs (correlative studies)	X			X		X (b)	X(c)	X(c)
Patient Reported Outcomes (s)	X						X	
Adverse Event Assessment + PRO-CTCAE	X		X	X	X	X (p)		X
Tumor Biopsy	X (a)					X (f, g)		

(a) Five cores or excisional biopsy (to be processed as in appendix). If available, archival tissue within 3 months of study enrollment will be used. If archival tissue is unavailable, a fresh biopsy will be taken. Tissue sample will be assessed for PD-L1 expression.
(b) Must be drawn on the morning of surgery
(c) At least a week after surgery and less than 4 weeks after surgery. If post-operative therapy to be done, draw prior to this therapy. A fifth blood draw 2 months later. If radiation is given after surgery, then this last blood draw 2 months after
(d) Observation or further therapy (for example post-operative radiation) as per standard of care. Follow for adverse events at least until 6 months s/p surgery. Patient's medical records will be reviewed every 3 months for 6 months to obtain survival and disease recurrence information.
(e) Timing of post-operative repeat as per standard of care, chest CT only
(f) Specimen to be processed as in appendix.
(g) Formal assessment and documentation of degree of pathologic response (as in appendix)
(h) EKG alone
(i)
(j) Standard CT thorax within a week prior to planned surgery date
(k) Must be done within 24 hours of receiving each dose of Nivolumab

(l) Scans must be done with contrast, unless otherwise contraindicated for a patient. MRI brain must be performed with and without contrast.
(m) Serum chemistries and CMP includes: Albumin, LDH, AST, ALK Phos, T. Bili, BUN, Creatinine, Calcium, Mag, Phos, Na, Cl, Glucose, Amylase, Lipase. Drawn within 7 days of first administration and within 3 days of subsequent administration
(n) Performed within 7 days of first dose of nivolumab/cisplatin/pemetrexed
(o) Physical examination at baseline and end of treatment must include BMI and waist hip ratio (WHR) only for patients enrolled at the lead site.
(p) Procedures including PRO-CTCAE must be completed within 1 week prior to planned surgery date.
(q) Patients must meet with the surgeon within 1 week of planned surgery date. Surgery can occur no later than 90 days from enrollment.
(r) Must be performed the morning of surgery
(s) Performed only for patients enrolled at the lead site (only one PRO is needed, either before or on the day of treatment)
(t) If in the opinion of the treating physician, the cisplatin is not tolerated well, the patient may be switched to standard carboplatin (AUC 5) for the remaining courses.
(u) TSH, T4, T3, cortisol will be collected every 3 months during follow up visits

Squamous NSCLC

Study Period	**Baseline**		**Treatment**					**Observation (d)**	
Week			**1**	**4**	**7**	**10**		**12**	**Monthly**
Treatment			**Gemcitabine + Cisplatin Nivolumab**			**Surgery (q)**		**Standard of care (d)**	
Nivolumab			X	X	X				
Gemcitabine (j)			X(j)	X(j)	X(j)				
Cisplatin(u)			X	X	X				

Consent form signed by patient	X									
History and physical exam (including vital signs, weight, BMI, height)	X (s)			X(o)	X	X	X (s)			X
Performance Status	X			X (o)	X	X	X			X
Assessment of concurrent therapies	X			X(o)	X	X	X		X	X
PET/CT or CT chest, abdomen, pelvis and bone scan.(m)	X	Within 4 weeks					X(k)			X (e)
MRI brain(m)	X									
C-reactive protein (CRP), HbA1c, lipid panel (t)	X								X	
CBC, differential, platelet count	X	Within 21 days		X(j, o)	X(j, o)	X(j, o)	X (r)			X
CMP (n)	X			X(j, o)	X(j)	X(j)	X (r)			X
Serum chemistries (n)	X			X	X	X				
PT/PTT	X			X(n)			X (p)			

Endocrine (TSH, T4, T3, cortisol)	X			X(n)	X	X	X (p)			X(v)
Pregnancy test (women of childbearing potential)	X	Within 21 days		X(l)	X(l)	X(l)				
Assessment of cardiac function EKG	X	Within 4 weeks					X (h)			
Viral studies (HepB, HepC)	X	Within 28 days								
Blood Draw for CTCs (correlative studies)	X				X		X (b)		X(c)	X(c)
Patient Reported Outcomes (t)	X								X	
Adverse Event Assessment + PRO-CTCAE	X			X	X	X	X (p)			X
Tumor Biopsy	X (a)						X		X (f,g)	

(a) Five cores or excisional bx (to be processed as in appendix) . If available, archival tissue within 3 months of study enrollment will be used. If archival tissue is unavailable, a fresh biopsy will be taken. Tissue sample will be assessed for PD-L1 expression.
(b) Must be drawn on the morning of surgery
(c) At least a week after surgery and less than 4 weeks after surgery. If post-operative therapy to be done, draw prior to this therapy. A fifth blood draw 2 months later. If radiation is given after surgery, then this last blood draw 2 months after
(d) Observation or further therapy (for example post-operative radiation) as per standard of care. Follow for adverse events at least until 6 months s/p surgery
(e) Timing of post-operative repeat as per standard of care, chest CT only
(f) Specimen to be processed as in appendix.

(g) Formal assessment and documentation of degree of pathologic response (as in appendix)
(h) EKG
(i)
(j) Weeks 2, 5, 8 patients to get single agent gemcitabine and accompanying CBC, CMP
(k) Standard CT thorax within a week prior to planned surgery date
(l) Must be done within 24 hours of receiving each dose of Nivolumab
(m) Scans must be done with contrast, unless otherwise contraindicated for a patient. MRI brain must be performed with and without contrast.
(n) Serum chemistries and CMP includes: Albumin, LDH, AST, ALK Phos, T. Bili, BUN, Creatinine, Calcium, Mag, Phos, Na, Cl, Glucose, Amylase, Lipase. Drawn within 7 days of first administration and within 3 days of subsequent administration
(o) Performed within 7 days of first dose of nivolumab/cisplatin/gemcitabine. Subsequent labs are performed within 3 days of administration of nivolumab/cisplatin/gemcitabine.
(p) Procedures including PRO-CTCAE must be completed within 1 week prior to planned surgery date.
(q) Patients must meet with the surgeon within 1 week of planned surgery date. Surgery can occur no later than 90 days from enrollment.
(r) Must be performed the morning of surgery
(s) Physical examination at baseline and end of treatment must include BMI and waist hip ratio (WHR) for patients enrolled at the lead site only
(t) Performed only for patients enrolled at the lead site (only one PRO is needed, either before or on the day of treatment)
(u) If in the opinion of the treating physician, the cisplatin is not tolerated well, the patient may be switched to standard carboplatin (AUC 5) for the remaining courses.
(v) TSH, T4, T3, cortisol will be collected every 3 months during follow up visits

5.1 Baseline/Screening (for both nonsquamous and squamous NSCLC cohorts)

Screening window for laboratory tests and scans (unless otherwise indicated) is days -28 to -1.

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain and document consent from potential participant on study consent form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.

- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Verify collection of baseline tumor tissue specimen.
    - Tumor sample prior to therapy is mandatory to confirm the presence of squamous or non-squamous non-small cell lung cancer, and for PD-L1 testing for all patients. If a recent (obtained within 3 months of enrollment without interim therapy as dictated in the eligibility criteria) tumor sample is not available at screening, a fresh biopsy will be taken prior to enrollment. Archival tissue can be FFPE or frozen.

  *Note: If a fresh tissue sample is taken, need adequate tumor to assess PD-L1 testing for all patients ideally 5 cores or excisional. If tumor sample is not available at screening, a fresh biopsy will be taken prior to enrollment.
- PET/CT or CT chest, abdomen, pelvis and bone scan. must be completed within 28 days of initiation of therapy. Scan must be performed with contrast, unless otherwise contraindicated for the patient.
- MRI brain with and without contrast must be completed within 28 days of initiation of therapy.
- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical, medication history, alcohol, and tobacco use history.
- Record results of physical and ECOG Performance Status, Vital Signs, Complete Physical Exam
- Collect blood for baseline correlative studies (Luminex panel and exosomes)
- Pre-treatment serum chemistries (Albumin, LDH, AST, ALT, ALK Phos, T.Bili, BUN, creatinine, Calcium, Mag, Phos, Na, Cl, Glucose, Amylase, Lipase, TSH, Free T4, Free T3, cortisol), blood counts with differential, viral studies (HepB surface antigen and hepatitis C antibody or hepatitis C RNA) serum or urine pregnancy test for women of childbearing potential within 21 days of study enrollment.
- Schedule study visits for individuals who are eligible and available for the initial treatments of the trial- either cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab, based on histology

The following procedures are only to be performed for patients enrolled at the lead site:

- Body Mass Index with Waist Hip Ratio (WHR)
- C-reactive protein (CRP), glycated hemoglobin (HbA1c), and lipid panel

- Patient Reported Outcomes (PROs):
  - PHQ2
  - PHQ9
  - FACT-G
  - FACT-L

5.2 Treatment Period (for both nonsquamous and squamous NSCLC cohorts)

Study Procedures: Administration of cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab and Surgery

Cycle 1-3 (Medical Oncologist): Each cycle is 3 weeks long. Full medical history, general physical exam, comprehensive metabolic panel (CMP), CBC, height, weight. Intravenous administration of cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab. On week 10, surgery.

Non-squamous NSCLC
Nivolumab 360mg q 3w x 3
Cisplatin 75mg/m2 q 3w x 3
Pemetrexed 500 mg/m2 q 3w x 3

Squamous NSCLC
Nivolumab 360mg q 3w x 3
Cisplatin 75mg/m2 q 3w x 3
Gemcitabine 1250mg/m2 d1 & d8 x 3

If in the opinion of the treating physician, the cisplatin is not tolerated well, the patient may be switched to standard carboplatin (AUC 5) for both squamous and nonsquamous for the remaining courses. The doses of Nivolumab, pemetrexed and gemcitabine will be given as describe aboved.

Visit 2, Week 1, Day 1

- Targeted physical examination within 7 days
- Review entry labs, performed within 7 days of first administration of either cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab.

- Review concomitant medications within 7 days
- Ensure that surgery dates and treatment planning are scheduled
- Women of childbearing potential must have a pregnancy test done within 24 hours of receiving study drug
- Administer the either cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab.

Visit 3 , Week 4, Days ±4 days-

- Record adverse events as reported by participant or observed by investigator.
- Targeted physical examination.
- CBC, CMP, Mag, Phos prior to administration of the study drug; to be drawn within 3 days of administration.
- Women of childbearing potential must have a pregnancy test done within 24 hours of receiving study drug
- Draw CTCs (correlative blood draws)
- Review concomitant medications.
- Administer the either cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab.

Visit 4, Week 7± 4 days

- Record adverse events as reported by participant or observed by investigator.
- Targeted physical examination.
- CBC, CMP, Mag, Phos prior to administration of the study drug; to be drawn within 3 days of administration.
- Women of childbearing potential must have a pregnancy test done within 24 hours of receiving study drug
- Review concomitant medications.

- Administer the either cisplatin/pemetrexed/nivolumab or cisplatin/gemcitabine/nivolumab.

Visit 5, Week 10 - 4 days or + 20 days(Surgery scheduled)

- CT scan Preop (within a week prior to planned surgery date)
- Record adverse events as reported by participant or observed by investigator.
- Targeted physical examination.
- Correlative labs
- Safety Assessment:
    - CBC and Complete Metabolic Panel (CMP) on the morning of surgery
    - Endocrine (TSH, T4, T3, cortisol), PT/PTT completed within a week prior to planned surgery date
- Intraoperative specimens sent fresh on ice for correlative studies.

Surgery will be performed by surgeons Board Certified in Thoracic Surgery. Surgeons will have expertise in lung cancer and significant experience in minimally invasive lung resection as well as resection after induction therapy as determined by the Surgical PI.

Surgery will be performed approximately 3 weeks (Week 10) after the last dose of study treatment. Surgery is to be performed no later than 90 days after enrollment.

5.3 Post-surgical/Follow-Up

Visit 6, Week 12 ± 4 days

- Postop evaluation and exam
- Correlative labs
- Wound assessment
- Safety assessment

- The following procedures are for patients enrolled at the lead site only:
    - Body Mass Index with Waist and Hip Ratio (WHR)

- C-reactive protein (CRP), glycated hemoglobin (HbA1c), and lipid panel
- Patient Reported Outcomes (PROs):
  - PHQ2
  - PHQ9
  - FACT-G
  - FACT-L

Visit 7, 3 months ± 2 weeks post- operative completion

- Evaluation and exam
- Correlative labs
- Wound assessment
- Safety assessment includes PRO-CTCAE, CBC, and CMP, TSH, T4, T3, cortisol
- CT thorax

5.4 End of Treatment Study Procedures

Final Study Visit (Visit 8, 6 months ± 3 weeks post-surgical completion)

- Record adverse events as reported by participant or observed by investigator.
- Complete Physical Exam
- Review concomitant medications.
- Wound assessment
- CT thorax

5.5 Post-treatment/Follow-Up

Patient's medical records will be reviewed every 3 months for the next 6 months to obtain information on survival and disease recurrence.

Follow Up Imaging is to be completed per the institutional standards.

5.6 Withdrawal Visit/Discontinuation of Therapy

At the time of withdrawal from the study, patients will be offered the opportunity to provide serum samples for correlative studies.

Adverse events will be collected and recorded as will the reason for discontinuation.

5.7 Surgery

The resection plans will be considering the tumor extension at the initial clinical evaluation, but the final surgical choice will be left to the judgment of the responsible surgeon, also on the basis of the actual extent at the time of surgery.

5.8 Study Procedures/Evaluations

- Medical History including intercurrent illnesses and specific attention to autoimmune disorders, may be obtained from the medical record
- Concomitant meds: prescription medications taken for the 28 days prior to enrollment
- Physical exam: height, weight, obtained from the medical record
- ECOG performance status from the medical record
- Obtain histologic confirmation of disease
- Standard presurgical assessments including lung function and staging
- Vital Signs

The following procedures are only for patients enrolled at the lead site:

- PROs are self-administered

PRO assessment completed at baseline will be conducted before any treatment or procedures.

Waist Hip Ratio: measurement to be taken per the NHLBI, NIH guideline to measure waist circumference. https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf

- To measure waist circumference, locate the upper hip bone and the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is made at the end of a normal expiration.
- Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor.

Body Mass Index (BMI) to calculated as kg/m2

5.9 Laboratory Procedures/Evaluations

5.9..1 *Clinical Laboratory Evaluations*

- Pregnancy Test: WOCBP must have serum or urine pregnancy test performed within 24 hours prior to dosing chemotherapy with nivolumab.
- A serum or urine pregnancy testing is required for WOCBP within 21 days. of study enrollment..
- Laboratory testing prior to each dose of nivolumab: Within 72 hours prior to re-dosing- CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Phos, Na, K, Cl, LDH, Glucose, amylase, lipase. Within 72 hours prior to re-dosing- TSH (with reflexive Free T4 and Free T3, cortisol)

Special Assays or Procedures

Specimen Preparation, Handling, and Storage

Two 10 ml purple top tubes will be collected for correlative studies. Samples can be held at room temperature and will be brought directly to the Harshyne Laboratory: 233 South 10th Street, Room 606.

Correlative samples collected at sub-site(s) should be shipped to Thomas Jefferson University:

Attn: Larry Harshyne, PhD
233 South 10th Street, Room 606
Philadelphia, PA 19147

See Laboratory Manual for additional information.

5.10 Patient Assessments

Patients must be offered the opportunity to participate in patient-reported outcomes (PROs) assessments as a component of the study. One instrument. will be used to measure patient reported outcomes PRO-CTCAE.

This assessment will be completed prior to start of treatment (baseline), at completion of nivolumab and chemotherapy, before surgery (during follow-up) and post-treatment follow-up.

PRO-CTCAE

To integrate the patient perspective into adverse event reporting, the National Cancer Institute developed a patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE. It is designed for patient reporting of symptomatic adverse events with an item bank of questions derived from the CTCAE adverse event items and is meant to be complimentary to the CTCAE.

6 Evaluation of Safety

6.1 Specification of Safety Parameters

6.1..1 *Unanticipated Problems*

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1..2 *Adverse Events*

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

6.1..3 *Serious Adverse Events*

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death

- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition. Potential drug induced liver injury (DILI) is also considered an important medical event
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is an SAE
- Although pregnancy, overdose, cancer and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs

Following the subject's start of treatment, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected, that occur within 100 days of discontinuation of dosing.

- A ***nonserious adverse event*** is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

- The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

6.2 Safety Assessment and Follow-Up

Adverse event reporting will begin after study treatment, unless the AE/SAE is caused by a study specific screening procedure, and continue until 100 days (for non-serious AEs) or 100 days (for SAEs) after the last day of study participation. At each study visit,

the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

6.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 6.2.

6.3..1 *Relationship to Study Intervention*

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

6.3..2 *Expectedness*

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator’s brochure, published medical literature, the protocol, or the informed consent document.

6.3..3 *Severity of Event*

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

6.3..4 *Intervention*

Any intervention implemented to treat the adverse event must be documented for all adverse events.

6.4 Safety Reporting

Reporting to IRB

6.4..1 *Unanticipated Problems*

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 6.1..1Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

6.4..1.1 Affiliate Site Unanticipated Problems Reporting

Unanticipated problems (UAPs) occurring at the Affiliate Site are to be reported to the TJU Study Site Contact using the Unanticipated Problems Form (see Appendix D). The TJU study site contact will submit the UAPs occurring at the sub-site to the TJU IRB. .

6.4..2 *Adverse Events*

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

6.4..3 *Serious Adverse Events*

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

SAEs occurring at the sub-site are to be reported to the TJU IRB per above guidelines.

6.4.3.1 Sub-Site SAE Reporting Procedures

All SAEs occurring at the Affiliate Site must be reported to the TJU Study Site Contact within 24 hours of notification. This initial notification can take place via email, followed by the submission of a formal report.

SAEs occurring at the Affiliate Site that are reportable to BMS should be reported to TJU Study Site Contact using the BMS SAE Reporting Form or Pregnancy Surveillance Form, and should comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

SAEs occurring at the Affiliate Site that are reportable to both the FDA and BMS should be reported to TJU Study Site Contact using the FDA Medwatch 3500A, and should comprise a full written summary, detailing relevant aspects of the adverse events in questions, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

SAE Reports should be signed by the sub-site PI, and then emailed to the Thomas Jefferson University Study Site Contact within 24 hours.

The TJU coordinator will notify the TJU PI and obtain the TJU PI signature, and report these events to the TJU Medical Monitor/IRB appropriately (within 5 working days if it deems an amendment, or in a spreadsheet at the time of annual review if no amendment is necessary).

Additional follow-up SAE reports should be submitted when available.

All reportable Adverse Events (AEs) should be reported to the TJU Research Coordinator within 48 hours using the SAE reporting form in Appendix E.

A reportable AE is any adverse event NOT identified in the IB or consent form as a risk.

Any non-reportable AE must be kept by the Affiliate Site on an ongoing tracking log to be reviewed by TJU quarterly.

6.5 Reporting to SKCC DSMC

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the DSMP. The report to DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

See the table below for the DSMC AE/SAE Reporting Requirements:

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

The Affiliate Site is required to provide copies of any Unanticipated Problems, protocol deviations, and AE logs to the TJU Study Site Contact for submission to the DSMC.

6.6 Reporting to Funding Supporter

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Site specific forms will be requested for review.

The sponsor/investigator will be required to reconcile SAEs reported in the clinical database with SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E); worldwide.safety@bms. BMS requests this to be done quarterly and prior to the database lock or final data summary.

A summary of the process for the sponsor/investigator:

- Sponsor/Investigator sends a request to BMS GPV&E for a "*GPV&E reconciliation report"*. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The request should provide the BMS protocol ID, study title and PI, and sponsor/investigator protocol ID.
- BMS will send a report back to the sponsor/investigator. The data elements listed on the GPV&E reconciliation report will contain information the investigator can use for individual case identification. Cases on the list from BMS GPV&E should be compared to the SAE cases in the clinical database.
- If the sponsor/investigator determines a SAE case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS

The TJU Study Site Contact is responsible for submitting all SAE reports occurring at TJU and the Affiliate Site to the study funder.

6.7 Reporting to FDA

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA)

as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

The TJU Study Site Contact is responsible for submitting all SAE reports occurring at TJU and the Affiliate Site to the FDA.

6.8 Reporting of Pregnancy

- Women of childbearing potential" is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. 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 55 must have a documented serum follicle stimulating hormone (FSH) level more than 40 mIU/ml.
- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. *WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug*
- Women of childbearing potential must 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
- Women must not be breastfeeding
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year *Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception*
- Should a woman be found to be pregnant during the study further treatment will be immediately discontinued. Permission from the patient will be sought to continue to assess her for adverse events and for fetal outcomes.

6.9 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities must be captured as appropriate

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted

- any laboratory test result that required the subject to receive specific corrective therapy
- It is expected that wherever possible the clinical rather than laboratory term would be used by the reporting investigator

6.10 **Overdose**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

Any such events will be recorded on an SAE form and reported to BMS within 24 hours/1 business day.

6.11 **Potential Drug Induced Liver Injury (DILI)**

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should
occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.12 **Halting Rules**

Please see Section 11.3 for stopping rules.

7 **Study Oversight**

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC).The DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the Clinical Trials Oversight Committee (CTOC).

8 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC).The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the DSMP.

9 Statistical Considerations

9.1 Study Hypotheses

The addition of nivolumab to induction cisplatin pemetrexed or cisplatin gemcitabine will increase the rate of major pathologic response over historical control with induction chemotherapy alone.

The primary objective of the study is to estimate major pathologic response (mpCR) in patients with newly diagnosed and untreated NSCLC Stage I-IIIA treated with three courses of induction Nivolumab added to either cisplatin/pemetrexed or cisplatin/gemcitabine prior to surgery. The null hypothesis is that the mpCR rate is ≤ 0.19 vs. the alternative that it is >0.19. We have powered under the specific alternative that the true rate is 0.35 or greater (section 9.4).

9.2 Analysis Plans

Primary Endpoint Evaluation: A minimax Simon two-stage design will be used. After testing the regimen on 21 patients in the first stage, the trial will be terminated if 3 or fewer have a mpCR of the primary tumor. If the trial goes on to the second stage, a total of 34 patients will be studied. If the total number having a mpCR of the primary tumor is less than or equal to 9, the regimen is rejected. The mpCR rate and its associated score 95% confidence interval will be estimated using the methods of Tsai et al (2008) which appropriately account for the two-stage design in the estimation process.

Secondary Endpoint Analyses:

Safety data will be summarized descriptively.

Response rates for secondary outcomes (i.e.,clinical: CR, PR, SD, PD, UE, ND and pathologic including CR at all sites of disease and, mpCR at primary site) will be estimated along with appropriate 95% confidence intervals.

The distribution of progression-free survival and overall survival will be estimated using the Kaplan-Meier method. Estimates of 1-year PFS and OS will be obtained from the Kaplan-Meier analysis.

Exploratory Endpoint Analyses (CORRELATIVE STUDIES):

Changes in markers will be summarized descriptively. Primary and secondary endpoints will be summarized by PD-L1 status. Baseline marker values and changes in markers will be summarized by response status. Association of continuous baseline marker levels with response will be evaluated using logistic regression. Differences between response groups with respect to change in markers will be evaluated using two-sample tests (e.g., t-tests or Wilcoxon rank sum tests). When longitudinal marker measurements are available, responders will be compared to non-responders using mixed effects linear regression.

We plan to conduct descriptive statistics on all study variable, including PROs, lab data, demographics, and anthropometrics using standard statistics such as frequency tables, means, and standard deviations.

For the correlative studies on PROs and metabolic measures (e.g., CRP, HbA1c, and lipid panel), we plan to estimate Spearman's ranks-based correlations and explore multivariable relationships with ordinary least squares regression modeling. These variables will also be considered for their potential role in the planned Cox survival and logistic regression response modeling.

9.3 Interim Analyses and Stopping Rules

Stopping Rules:
The study will stop for futility if pathologic complete response at the primary tumor is not observed in more than 3 of the first 21 patients.

Rates of grade 3-5 toxicities will be monitored continually. The selected doses of nivolumab were safe in previous studies. There is no dose escalation or de-escalation planned in this study. Individual patients can have dose modification during the study.

The study will stop if 2 of the first 10 patients or 3 of the first 21 patients experience excessive toxicity due to study treatment, leading to delays in definitive surgery greater than 90 days from enrollment.

Toxicity leading to delays in definitive surgery will be assessed after the first 10 patients have undergone treatment, and will be re-assessed after the first 21 enrolled patients.

9.4 Sample Size Considerations

A minimax Simon two-stage design will be used. The null hypothesis is that the true mpCR response rate at the primary site is ≤ 0.19 and will be tested against the alternative that it is >0.19. After testing the regimen on 21 patients in the first stage, the trial will be terminated if 3 or fewer respond. If the trial goes on to the second stage, a total of 34 patients will be studied. If the total number responding is less than or equal to 9 the regimen is rejected. This design yields a type I error rate of 9.5% and power of 80% when the true response rate is 0.35.

Replacement Policy

Patients who do not have surgery will be replaced on the study.

10 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

11 Quality Control and Quality Assurance

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all of the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

12 Ethics/Protection of Human Participants

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

12.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical

care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

12.4 Exclusion of Women, Minorities, and Children (Special Populations)

Pregnant and breastfeeding women are excluded from this trial due to the nature of the agents being used. Otherwise, we will attempt to accrue women and men equally on this study, representative of the epidemiologic distribution of the disease.

12.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

12.6 Future Use of Stored Specimens and Other Identifiable Data

No identifiable data will be retained.

13 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

13.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are

accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

13.2 Data Capture Methods

Data will be captured on paper case report forms and transferred to an electronic database which will be kept behind a password protected firewall- RedCap. Each site will enter data as described into the electronic database. The lead site (Thomas Jefferson University) will query the database at regular intervals.

13.3 Types of Data

Data that will be collected include patient history and physical examination data, safety, laboratory studies, pathology staging studies, and immunohistochemistry as determined in the laboratory.

13.4 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

14 Study Finances

14.1 Funding Source

Bristol-Myers Squibb, who is providing the investigational products, Nivolumab, for this study.

14.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

14.3 Participant Stipends or Payments

Subjects will receive a payment of $50 at each study visit for participation in the study. Subjects will be paid via Clincard.

15 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or

designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

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Appendices

The following documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

APPENDIX A: ECOG Performance Status:

APPENDIX B: AJCC 8th Edition Staging System

APPENDIX C: Management Algorithms

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

APPENDIX A: ECOG Performance Status:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX B: AJCC 8th Edition Staging System

Staging NSCLC

T (Primary Tumor)		Label
T0	No primary tumor	
Tis	Carcinoma in situ (Squamous or Adenocarcinoma)	Tis
T1	Tumor ≤3 cm,	
T1a(mi)	Minimally Invasive Adenocarcinoma	T1a*(mi)*
T1a	Superficial spreading tumor in central airways[a]	T1a *SS*
T1a	Tumor ≤1 cm	T1a *≤1*
T1b	Tumor >1 but ≤2 cm	T1b *>1-2*
T1c	Tumor >2 but ≤3 cm	T1c *>2-3*
T2	Tumor >3 but ≤5 cm or tumor involving:	
	visceral pleura[b],	T2 *Visc Pl*
	main bronchus (not carina), atelectasis to hilum[b]	T2 *Centr*
T2a	Tumor >3 but ≤4 cm	T2a *>3-4*
T2b	Tumor >4 but ≤5 cm	T2b *>4-5*
T3	Tumor >5 but ≤7 cm	T3 *>5--7*
	or invading chest wall, pericardium, phrenic nerve	T3 *Inv*
	or separate tumor nodule(s) in the same lobe	T3 *Satell*
T4	Tumor >7 cm	T4 *>7*
	or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine;	T4 *Inv*
	or tumor nodule(s) in a different ipsilateral lobe	T4 *Ipsi Nod*
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	
N3	Metastasis in contralateral mediastinal/hilar, or supraclavicular nodes	
M (Distant Metastasis)		
M0	No distant metastasis	
M1a	Malignant pleural/pericardial effusion[c] or pleural /pericardial nodules	M1a *Pl Dissem*
	or separate tumor nodule(s) in a contralateral lobe;	M1a *Contr Nod*
M1b	Single extrathoracic metastasis	M1b *Single*
M1c	Multiple extrathoracic metastases (1 or >1 organ)	M1c *Multi*

TX, NX: T or N status not able to be assessed

[a] Superficial spreading tumor of any size but confined to the tracheal or bronchial wall
[b] such tumors are classified as T2a if >3≤4 cm, T2b if >4≤5 cm.
[c] Pleural effusions are excluded that are cytologically negative, non-bloody, transudative, and clinically judged not to be due to cancer.

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Updated 05-Jul-2016

Appendix C: Management Algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

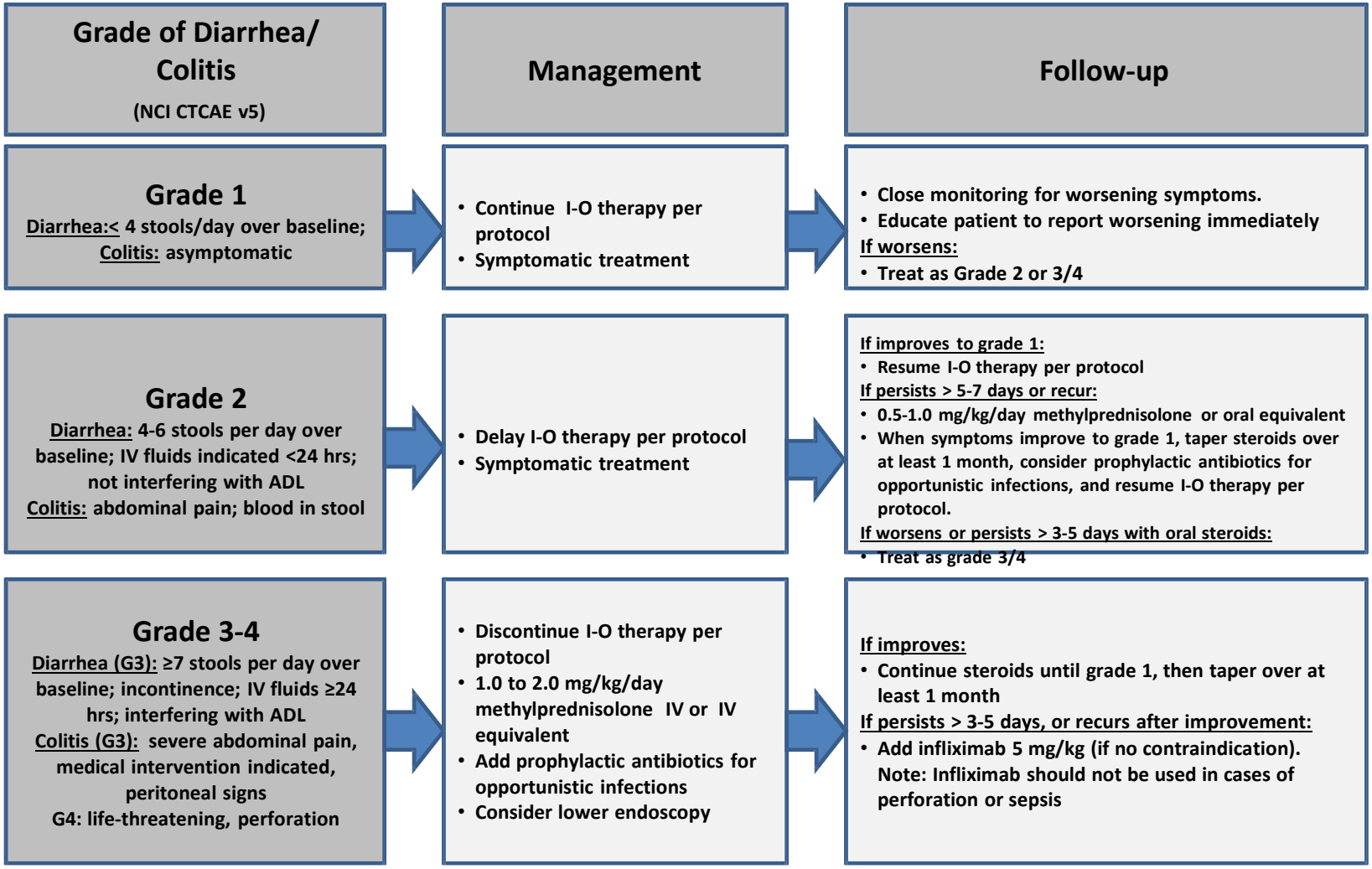
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

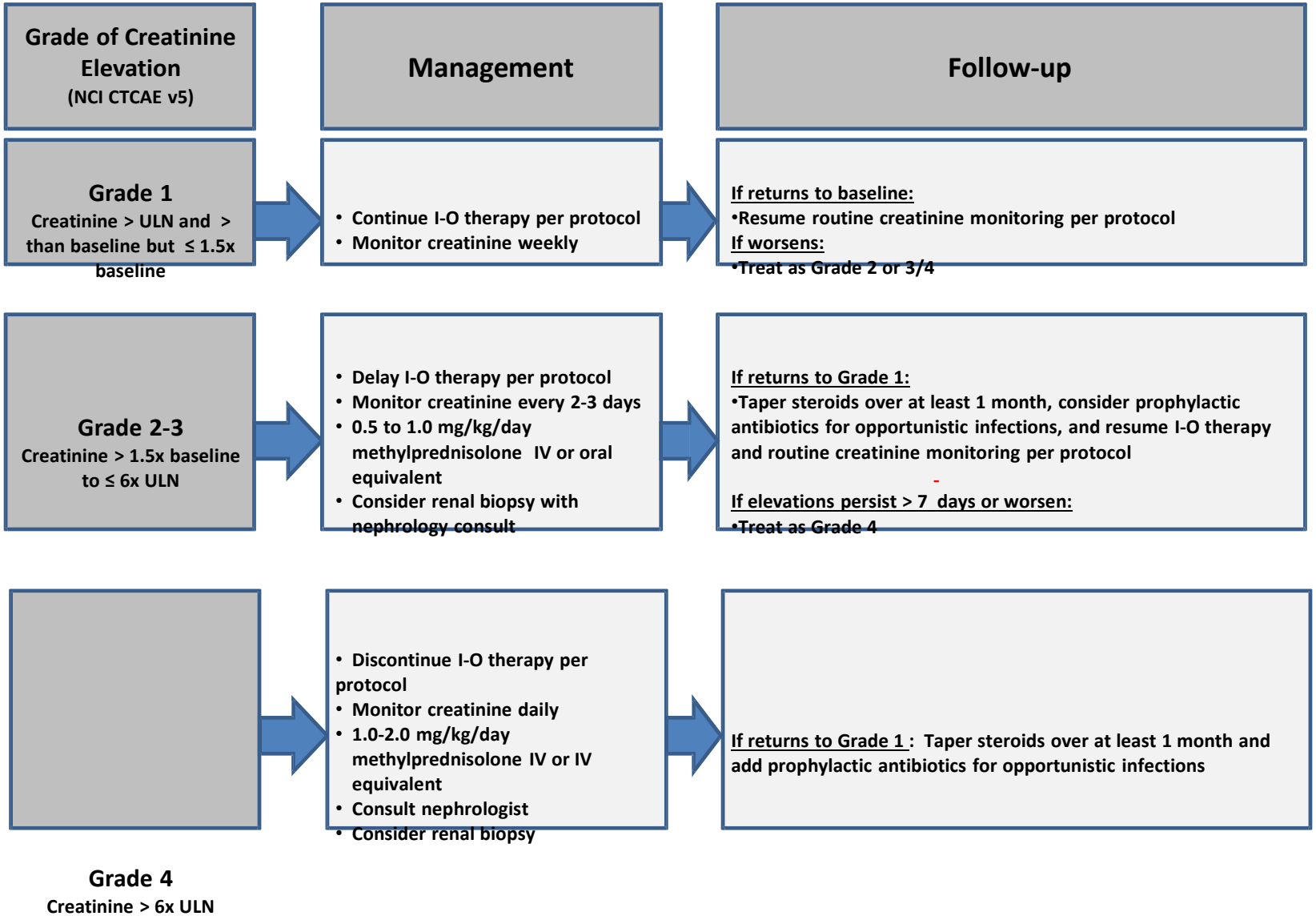


Updated 05-Jul-2016

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

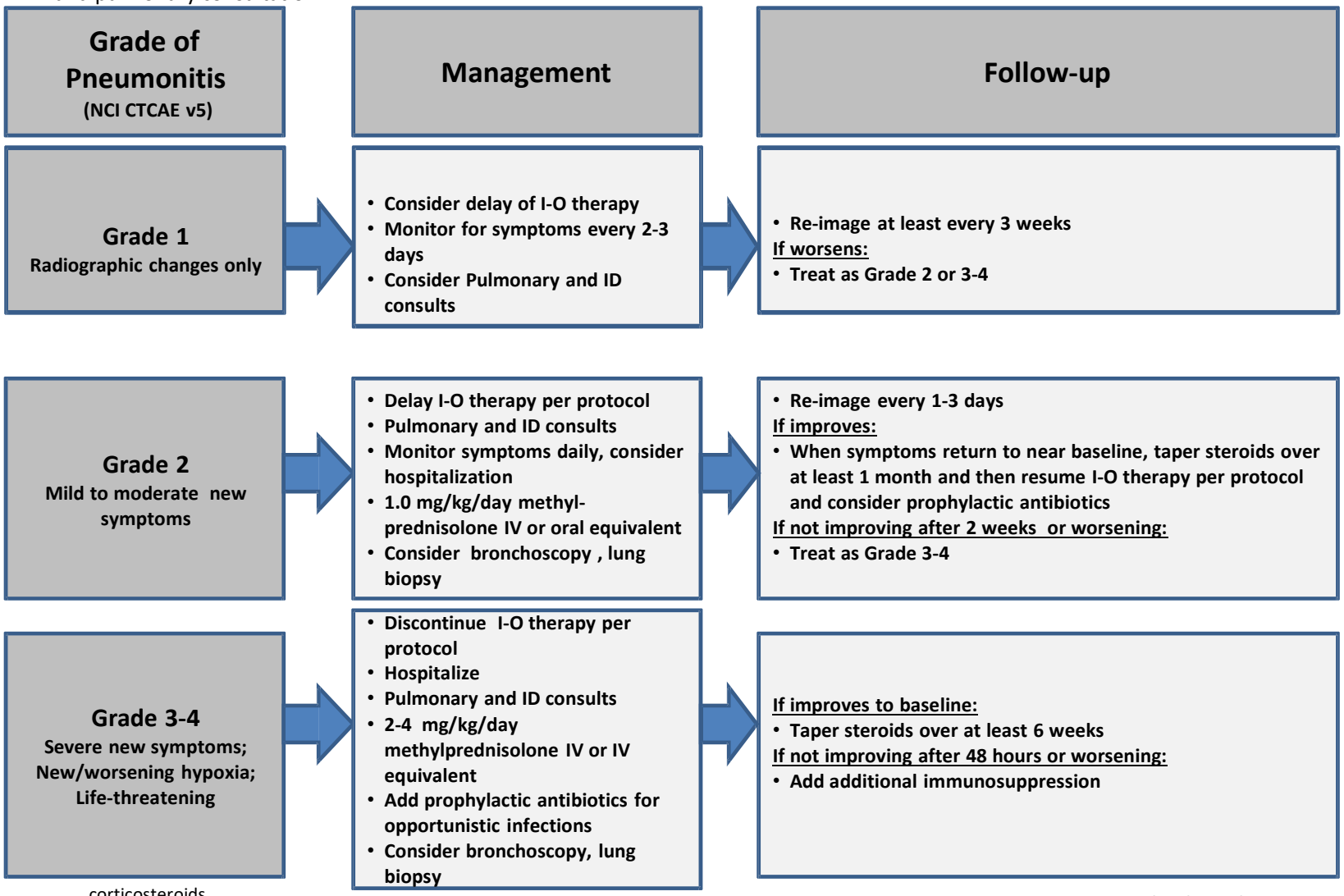


Updated 05-Jul-2016

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



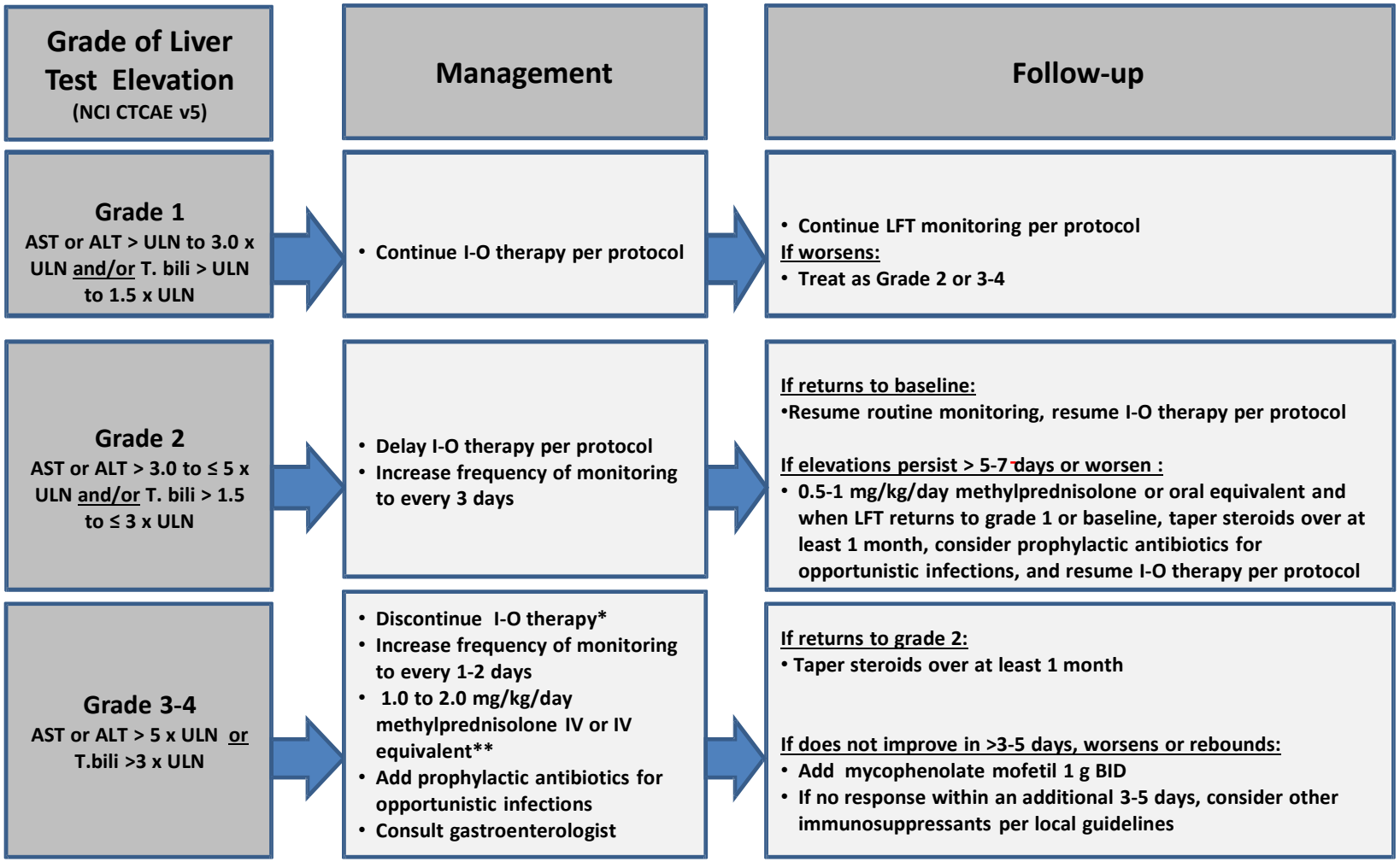
corticosteroids.

Updated 05-Jul-2016

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



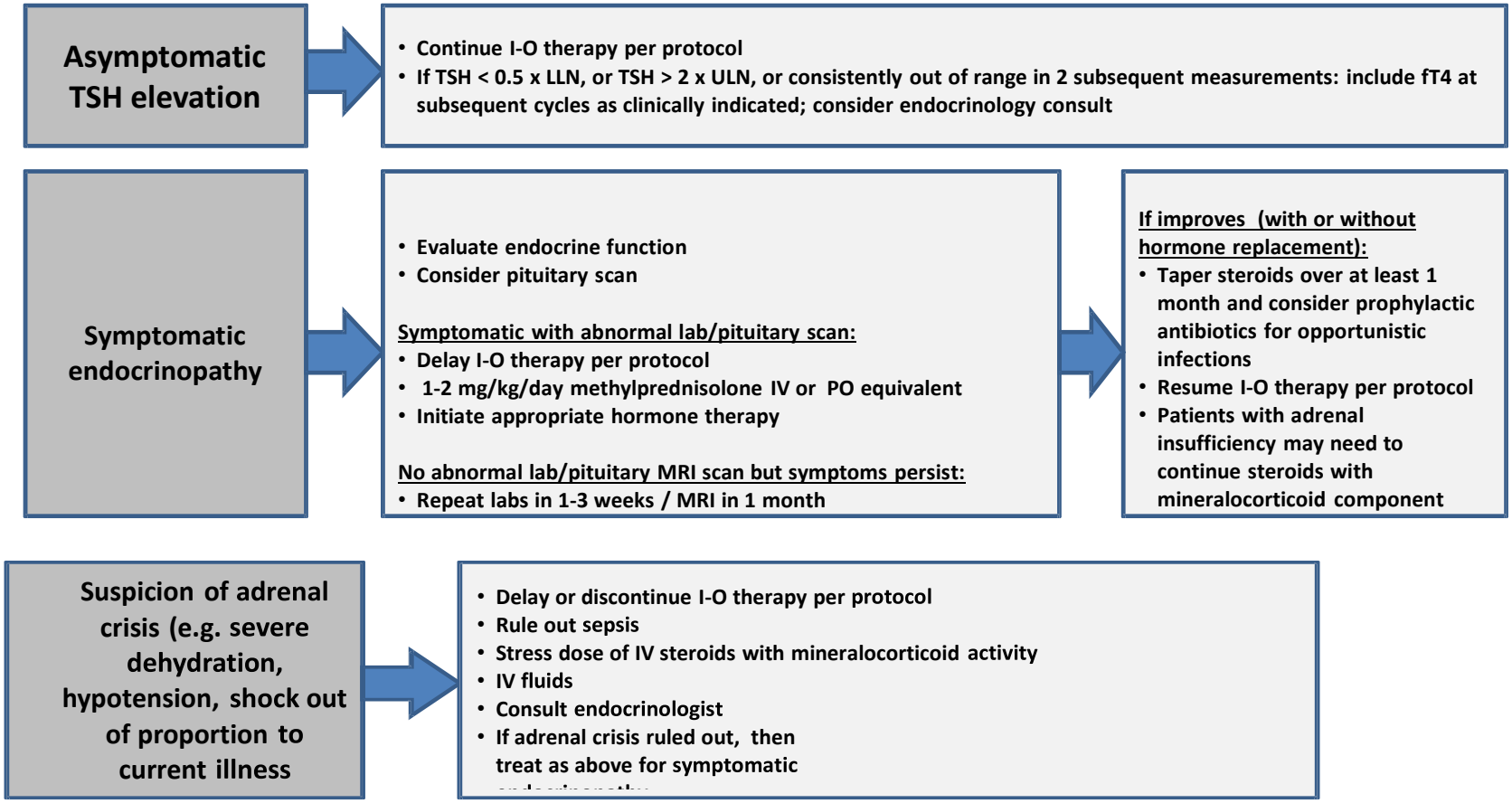
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

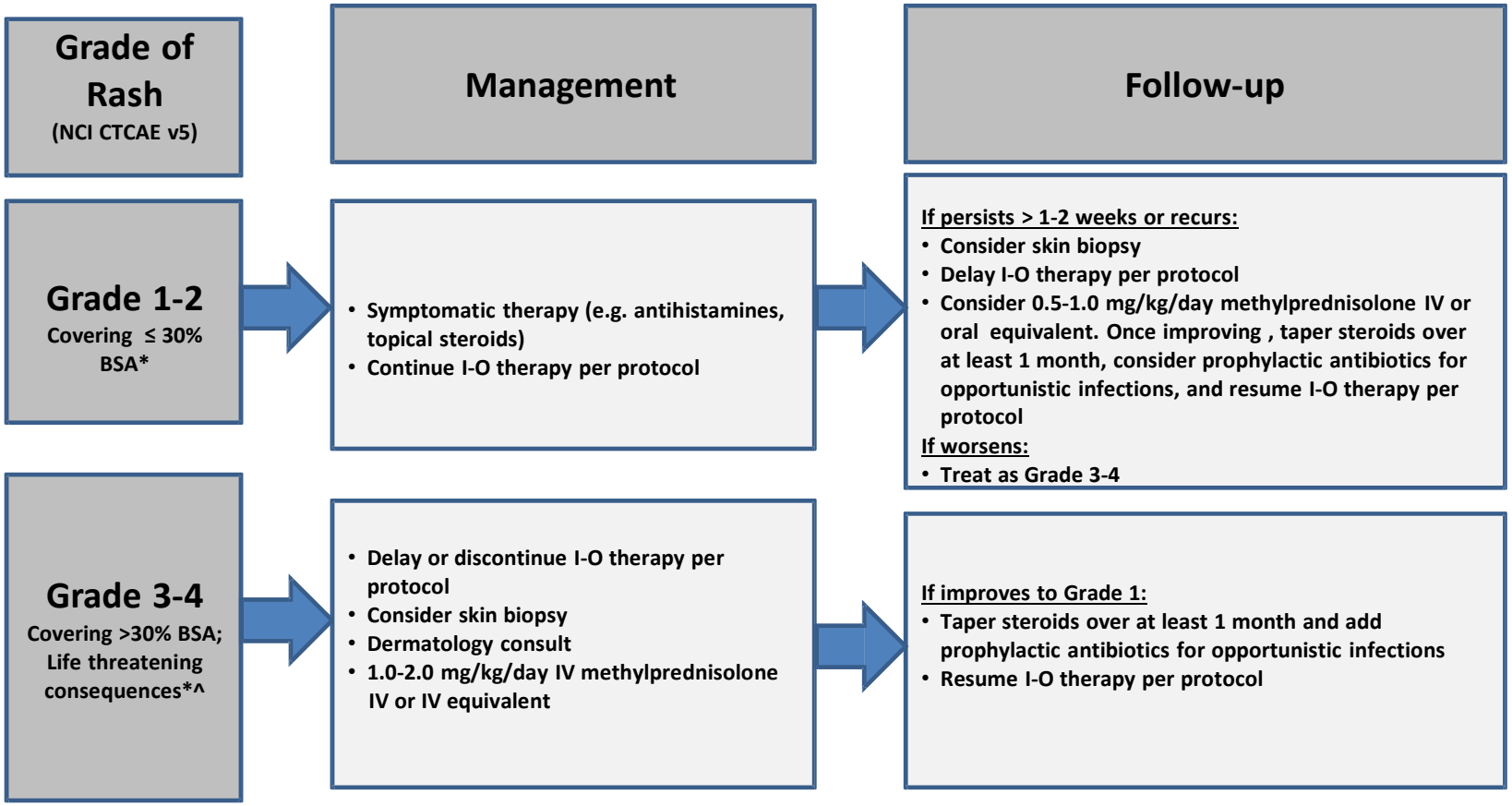


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

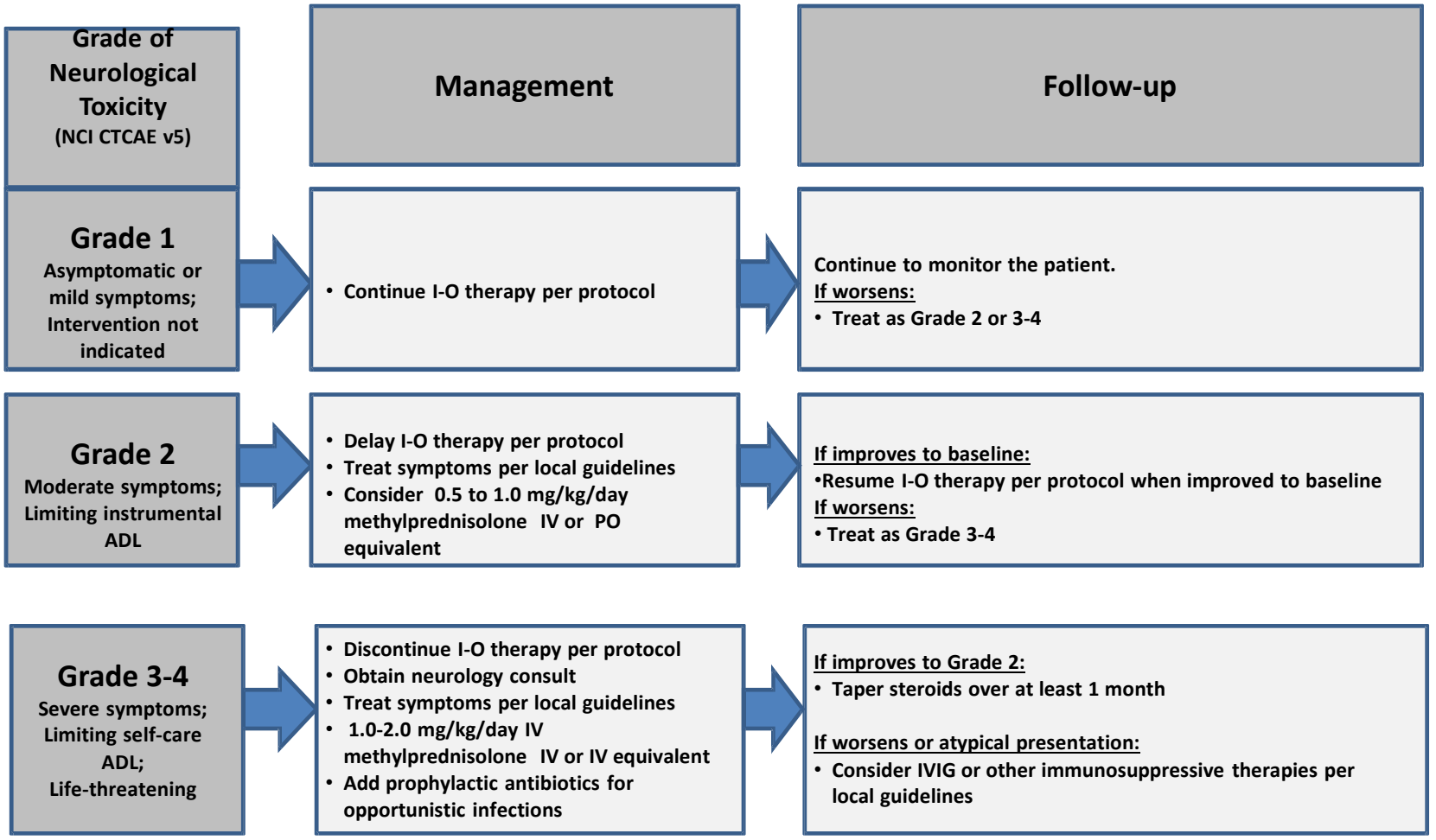
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Updated 05-Jul-2016

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX D: UNANTICIPATED PROBLEM FORM

UNANTICIPATED PROBLEM REPORT FORM
For Sub-Site Reporting

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

Subject ID: _____ Approx. Date of Problem: _____ Date Aware: ____

Description of Problem: _____

_____

Is this Unanticipated Problem a Protocol Deviation? Yes ☐ No ☐

Did the Unanticipated Problem pose risk to subjects or others? Yes ☐ No ☐

If no, have PI or Co-I sign the form. If YES, describe the risk below:

Describe the Corrective Action Plan: _____

_____

Has the problem been resolved? Yes ☐ No ☐

Does the consent or protocol require modification? Yes ☐ No ☐

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number

APPENDIX E: SERIOUS ADVERSE EVENT PROBLEM FORM

SAE REPORT FORM FOR SUBSITE REPORTING

Thomas Jefferson University Principal Investigator: _____

Sub-Site Principal Investigator: _____

TJU IRB Control Number/Sub-Site Identifier: _____

Protocol Title: _____

_____

Subject Initials and ID: _____

Event Date- Onset: _____ Terminated: ____ Ongoing?: ____ Date PI/TJU Aware: ____

Study Drug(s)/Device: _____

Description of adverse event: _____

Severity of adverse reaction: _____

Action Taken: _____

☐ Resulted in or prolonged inpatient hospitalization ☐ Resulted in permanent disability ☐ Subject died Autopsy

Cause of adverse reaction (if not related to research): ☐ Underlying disease ☐ concomitant medication ☐ Other

If other explain:

If List concomitant medications:

Is this: A new report? Yes ☐ No ☐ A Follow Up Report? Yes ☐ No ☐ Date of First Report

In your opinion, was the SAE caused by the therapy/procedures associated with this protocol?

Is the risk of this adverse reaction described in the consent form? Yes ☐ No ☐

If **Not Currently in consent form**, should this risk be described in the consent form: Yes ☐ No ☐

If No, please provide justification for not including this reaction as a risk in the consent form:

Has this adverse reaction been reported to the sponsor? Yes ☐ No ☐ To FDA? Yes ☐ No ☐

Should presently enrolled subjects be informed of event? Yes ☐ No ☐

_____
Signature of person preparing report Date Email/Phone number

_____
Sub-site PI signature Date Email/Phone number

APPENDIX F: Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Criteria for

Evaluating Response in Solid Tumors

http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf