Combination Immunotherapy with Ipilimumab and Nivolumab plus a Dendritic Cell based p53 Vaccine (Ad.p53-DC) in patients with relapsed Small Cell Lung Cancer (SCLC)

NCT03406715

Version 8

September 19, 2018

SPONSOR: Moffitt Cancer Center

Protocol Title: Combination Immunotherapy with Ipilimumab and Nivolumab plus a Dendritic Cell based p53 Vaccine (Ad.p53-DC) in patients with relapsed Small Cell Lung Cancer (SCLC)

BMS Protocol Number: CA209-9KN

Moffitt Protocol Number: MCC 19163

MultiVir Protocol Number: MVIR-Adp53DC-001

Principal Investigator: Alberto Chiappori, MD
Senior Member
Thoracic Oncology Department
Moffitt Cancer Center
12902 Magnolia Drive
Tampa, FL 33612
Phone: 813-745-3050
Fax: 813-745-3027
Email: alberto.chiappori@moffitt.org

Version/Date: 8/September 19, 2018

Amendment/date: 7/September 19, 2018

TABLE OF CONTENTS – INDEX

.

1.0 TRIAL SUMMARY

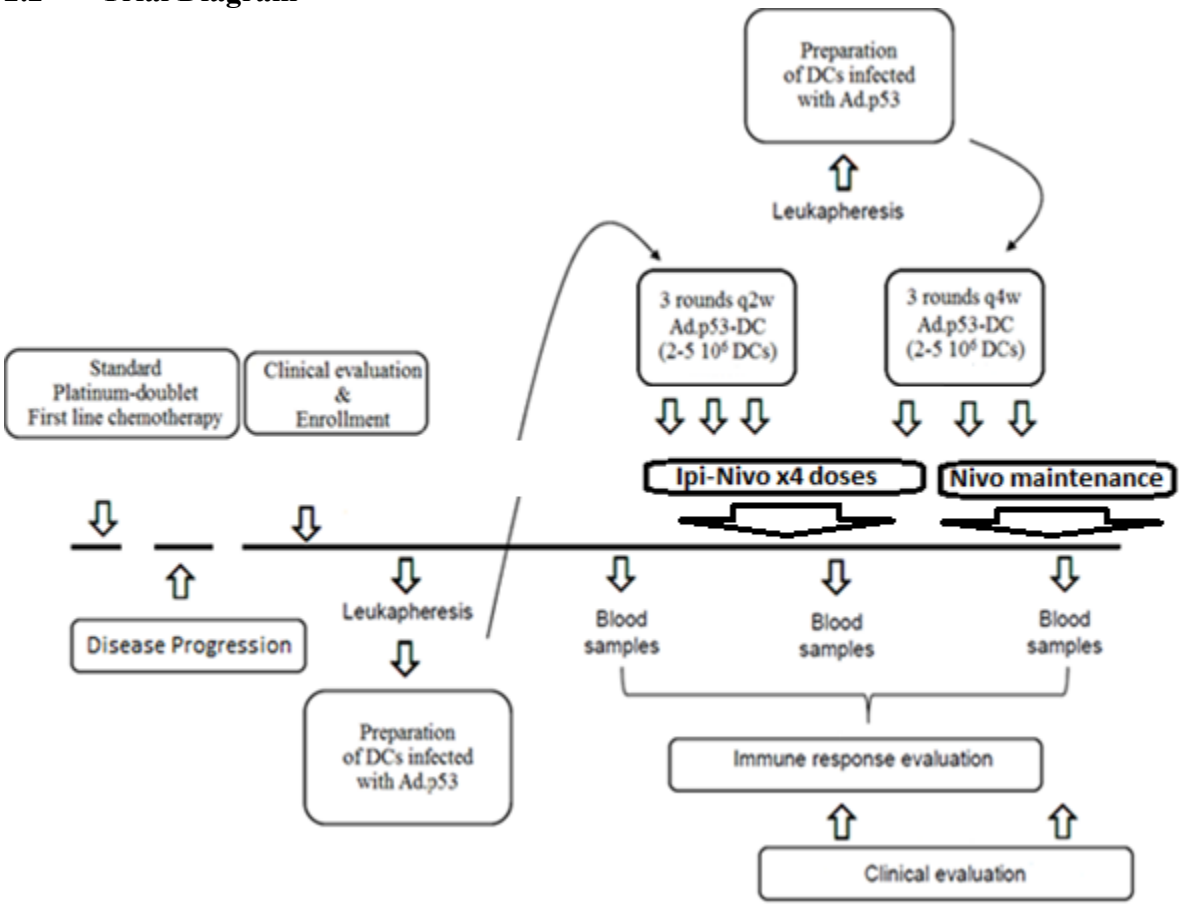
Abbreviated Title	**Combination Immunotherapy in Relapsed SCLC**
Trial Phase	Phase II
Clinical Indication	SCLC, progressive after first-line (platinum-based) chemotherapy
Trial Type	Single arm
Type of control	Historical
Route of administration	Ipilimumab – Intravenous Nivolumab – Intravenous Ad.p3-DC – Intradermal/Subcutaneous
Trial Blinding	Open label
Treatment Groups	Ipilimumab-Nivolumab + Ad.p53-DC vaccine
Number of trial subjects	41 (39 + 10% screen failures)
Estimated enrollment period	2.5 years
Estimated duration of trial	3 years
Duration of Participation	3 years

2.0 TRIAL DESIGN

2.1 Trial Design

Here we propose a phase II trial where relapsed (progressive), SCLC patients after treatment with first line (platinum-based) chemotherapy (after disease progression) will receive Ad.p53-DC in combination with ipilimumab and nivolumab to assess the impact of this combination immunotherapy regimen on clinical outcomes. We hypothesize that this combination immunotherapy strategy will improve overall disease response or control and/or survival in this population.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS

General Scientific Hypothesis:

Inhibition of the PD-1 receptor pathway with an anti PD-1 inhibitor (nivolumab) and the CTLA-4 receptor pathway with an anti CTLA-4 inhibitor (ipilimumab) will enhance the p53-specific cytotoxic immune response (IR) elicited by a p53-based DC vaccine (Ad.p53-DC) and this improvement will translate into improved outcomes (disease control rate [DCR], progression free survival [PFS], overall survival [OS], overall response rate [ORR]) in patients with relapsed (progressive) SCLC, after standard, platinum-doublet, first line chemotherapy.

3.1 Co-Primary Objective(s) & Hypothesis(es)

- To determine the DCR of patients with relapsed (progressive) SCLC (after standard, first line platinum-doublet chemotherapy) treated with combination immunotherapy (Ad.p53-DC plus ipilimumab-nivolumab)
- To determine the safety of combination immunotherapy with Ad.p53-DC plus ipilimumab-nivolumab in patients with relapsed (progressive) SCLC

3.2 Secondary Objective(s) & Hypothesis(es)

- To determine the PFS, OS and ORR of combination immunotherapy with Ad.p53-DC plus ipilimumab-nivolumab in patients with relapsed (progressive) SCLC
- To determine the immune response (IR) of combination immunotherapy with Ad.p53-DC plus ipilimumab-nivolumab in patients with relapsed (progressive) SCLC

4.0 BACKGROUND & RATIONALE

4.1 Background/Introduction

4.1.1 Overview of Small Cell Lung Cancer

In the United States, 224,390 new cases of lung cancer were diagnosed and 158,080 patients with lung cancer died in 2016[1], with small cell lung cancer (SCLC) accounting for 13-15% of them. SCLC typically disseminates early, with 70-80% of patients diagnosed with metastatic disease or extensive stage, (ES)-SCLC), and is initially also chemo-responsive, so that considerable survival improvements are achieved with (first-line) chemotherapy[2-4].

Etoposide-platinum remains the preferred first-line treatment and the standard against which new therapies are measured. By this standard, patients with ES-SCLC achieve overall response rates (ORR) of ≥ 70% and complete response rates of 20-30%, but rarely survive beyond 2 years (10-20%), with median survival times (MST) ranging from 7-10 months [2-4]. The ORR to second-line therapy is also very disappointing and dependent on the previous chemotherapy response. Patients with "platinum-sensitive" disease (ORR = 20-25%) progress ≥ 90 days after initial chemotherapy, whereas those with "platinum-resistant" (ORR ≤ 10%) disease progress sooner than 90 days after initial chemotherapy[5-7].

Clearly, new therapies are urgently needed, and evidence suggests that immunotherapy may have a potential role in SCLC, including if used in conjunction with chemotherapy[8-12].

4.1.2 p53 as a Target for Cancer Immunotherapy

The p53 tumor suppressor gene plays a central role in the control of cell growth and differentiation. Normally, p53 is a short-lived protein localized in the nuclei of cells. Approximately 50% of all human cancers and >90% of patients with SCLC have altered p53 function, mostly as a result of single-point mutations or abnormalities in degradation of wild-type (wt) p53. This leads to accumulation of mutant (mu) or wt-p53 protein (whereas normal tissues have low to undetectable levels) and expression of p53-derived epitopes on the surface of tumor cells in the context of MHC class I[13].

Furthermore, since mutant forms of p53 can result in oncogenic gain of function[14,15] it is unlikely that they can escape anti-p53 cytotoxic T lymphocytes (CTLs) by restoring wt-p53 status (no antigen-loss variants). Thus, p53 has many characteristics of an "ideal" tumor-associated antigen (TAA), which makes it a very attractive candidate target for immune recognition and anti-p53-based cancer immunotherapy.

4.1.3 Anti-p53 Dendritic Cell-Based Immunotherapy

Different approaches to p53-based cancer immunotherapy have been explored. The role of wt-p53 peptide sequences in the induction of antitumor CTL responses has been investigated in both human and animal *in vitro* studies, with encouraging results[13,16-20]. However, peptide-based approaches assume knowledge of precise HLA types and the peptides present on particular tumors, leading to several limitations[21,22], such as technical difficulties with generating custom mutant-specific peptides.

These difficulties can be circumvented with the use of TAA proteins and dendritic cells (DCs). DCs are the most potent antigen presenting cells (APCs) and the most effective in inducing a primary CTL response. There are numerous methods of loading DCs with a variety of different TAAs, and animal models show that the approach of using viral vectors to introduce these TAAs into DCs is practical, safe, and effective[23-25]. Because cells with mu-p53 usually overexpress the protein and because there is a large human experience in melanoma with targeting overexpressed but not mutant proteins such as MAGE and MART, a much more practical approach would be to develop a strategy that targets the non-mutant portions of the p53 overexpressed in tumors.

Therefore, we have focused on utilizing DCs transfected with the full-length p53 gene. The rationale for this approach is based on *1*) the assumption that multiple MHC class I and II matching p53-derived epitopes are present on the surface of DCs, eliminating the need for selecting matching patients as well as providing conditions for activation of $CD4^+$ T cells, and *2*) the fact that previous studies have demonstrated that each of the different minimal epitopes combined in a single fusion protein can be recognized by specific CTLs[26].

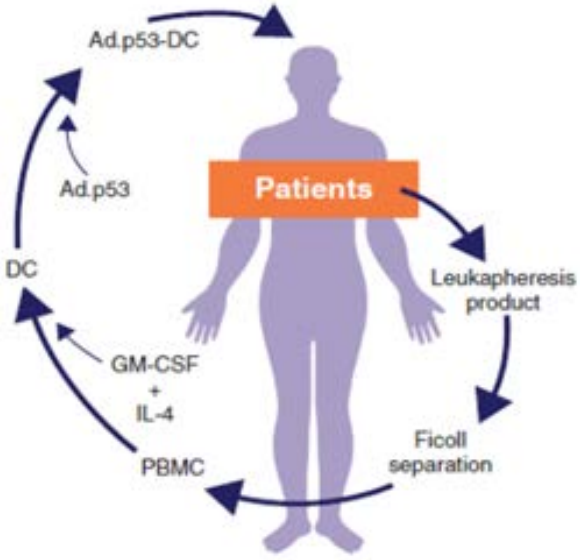
4.2 Vaccine (Ad.p53-DC) Immunotherapy

Adenovirus (Ad) provides a high-level transduction efficacy for many cell types, regardless of their mitotic status[27], and replication-defective Ad (deletions in the E1 region) has been safely injected into patients[28]. Successful transduction of DCs with model antigens has been reported, and transduced DCs have effectively presented the recombinant protein antigens[29-31]. In this case, DCs were infected with an adenoviral construct containing wt-p53 to generate Ad.p53-DC.

4.2.1 Manufacturing of Ad.p53-DC

DCs were prepared from peripheral blood mononuclear cells (PBMC) collected by leukapheresis, separated over a Ficoll density gradient, washed, and cryostoraged in liquid nitrogen in the Cell Therapy Core at the H. Lee Moffitt Cancer Center.

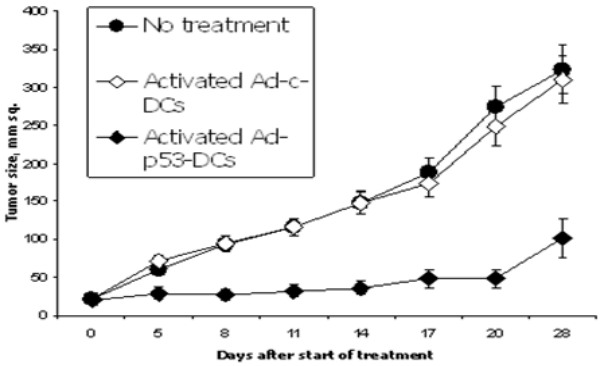
Preparation of the DC and their characterization was described previously[32,33]. Briefly, after thawing, PBMCs were placed in X-VIVO-15 medium (Biowhittaker, Walkersville, MD) in tissue culture flasks at a concentration of 1.3-1.7 × 10^6 cells per cm^2. After 2-hr culture non-adherent cells were removed and the flasks were recharged with X-VIVO-15 medium supplemented with 5ng/ml GM-CSF (Immunex), and 5ng/ml IL-4 (R&D Systems, Minneapolis, MN). The flasks were incubated for 48 hours, at which time additional cytokine supplemented medium was added to the flasks. The flasks were then incubated for an additional 72 hours. The non-adherent and loosely adherent cells were collected and infected with Ad.p53 and incubated for 2 hours after which X-VIVO-15 medium was added for a 10^6 cells/ml concentration and cells incubated for an additional 46 hours.



The optimal viral particle to cell ratio used was 15,000:1 as determined for our previous study[32]. The vaccine release criteria included: (a) negative Gram's staining; (b) negative *Mycoplasma* test by PCR analysis; (c) maximum endotoxin concentration of 5 EU/mL; and (d) a mature DC-p53 expressing phenotype. DC phenotype was defined as lineage (CD3, CD14, CD19, CD20, CD56) negative, HLA-DR positive, CD86 positive, and p53 positive cells. Intracellular staining for p53 was performed using the kit from Caltag, Burlingame, CA. DC vaccines in 1 ml were injected intradermally into 4 separate sites (0.25 ml at each site) in bilateral proximal upper and lower extremities (in the regions of the axillary and inguinal nodal basins) three times after the baseline blood samples were drawn and at 2 week intervals.

4.2.2 Preclinical Animal Studies with Ad.p53-DC

To determine the optimal dose of Ad.p53 vector that produces the highest level of human p53 expression with the least amount of toxicity to the DCs, mice were given a human p53-transduced DC vaccine[34,35]. We found that infecting murine DCs with the Ad.p53 vector at a multiplicity of infection (MOI) of 50-200 viral particles per cell (vp/cell) did not adversely affect DC viability. MOI in excess of 500 significantly reduced DC viability. However, transduction of DCs at an MOI of 100 produced very good transduction efficiency, with 40-45% of the DCs becoming positive for p53. Similarly, infecting human DCs with the Ad.p53



MethA sarcoma-bearing BALB/c mice were treated with $6x10^5$ activated Ad.c- or Ad.p53-DCs 4 times on days 0, 5, 11, and 17. Four mice treated with Ad.p53-DCs rejected their tumor. Tumor growth in 2 remaining mice is shown.

vector at a MOI of 10,000-20,000 vp/cell did not adversely affect DC viability and showed better transduction efficiency with the higher dose. At a MOI of 40,000 vp/cell, DC viability was adversely affected despite transduction rates similar to the lower doses. Thus, 20,000 vp/cell was the MOI chosen to manufacture Ad.p53-DC.

Additionally, T cells recovered from immunized mice contained significant numbers of CTLs that could specifically kill tumor cells previously modified to express the human p53 gene, and Ad.p53-DC-immunized mice developed a significant CTL response to murine p53, probably due to the significant homology between murine and human p53. Ad.p53-DC-induced anti-p53 CTL response resulted in protection of mice from challenges with tumor cells that overexpressed human or murine p53. Furthermore, tumors that were established in mice prior to immunization exhibited significantly slowed growth as a result of the immunization with Ad.p53-DC[34,35].

4.2.3 Preclinical Experiments Using Human T Cells

To determine whether this response was sufficient to recognize and eliminate tumor cells in cancer patients, peripheral blood-derived T cells and autologous DCs were obtained from 3 healthy volunteers and 9 cancer patients, all of whom were HLA-A2 positive[36]. T cells were *in vitro* primed with Ad.p53-DC and then tested for their ability to kill (HLA-A2-positive) target cells with normal to low or overexpressed levels of p53 protein.

Selective CTL killing of p53-overexpressing cells but not of cells with normal p53 expression levels was generated in blood from all 3 healthy donors and 8 cancer patients. Furthermore, when cells that expressed normal to low levels of p53 were forced to overexpress p53 by gene transfection, they became sensitive to Ad.p53-DC-primed CTLs. Additionally, when an excess of NK cell-sensitive target cells or an anti-CD4 antibody was added to the cytotoxicity assays, very little effect or a small decrease in cytotoxicity activity was seen. Conversely, when anti-CD8 was added, we observed a very significant decrease in cytotoxicity, demonstrating that neither NK nor CD4 cells but CD8-positive CTLs are the relevant effector cells primed with Ad.p53-DC.

4.3 Phase I/II Clinical Trial of Ad.p53-DC in SCLC

p53 gene mutations and p53 protein overexpression are present in ≥ 90% of SCLC cases[37,38]. With many characteristics of an "ideal" TAA present, p53 is an attractive candidate for cancer immunotherapy. Therefore, an approach where an adenoviral vector carrying the intact human wt-p53 gene is used to overexpress the p53 protein in autologous DCs and that allows endogenous processing mechanisms to select and present the appropriate p53 peptides for each individual's HLA type encourages the use of these transduced cells (Ad.p53-DC) as a vaccine.

4.3.1 Study Design and Patient Characteristics

The trial was designed to assess the clinical and immune response of SCLC to Ad.p53-DC[32,33]. Fifty-four patients (24 male, 30 female) with extensive stage disease (initial or recurrent) were enrolled. All had previously been treated with chemotherapy. Patients with stable disease or better underwent leukopheresis 8 weeks after the last dose of chemotherapy to manufacture Ad.p53-DC. Patients received 3 doses of Ad.p53-DC intra-dermally every 2

weeks. If after reassessment, stable disease or better persisted, 3 more monthly doses of Ad.p53-DC were given.

4.3.2 Ad.p53-DC Dose and Safety

The number of $p53^+$ DCs (Ad.p53-DC dose) was evaluated using flow cytometry. The initial goal was to escalate the dose from 5×10^6 to 5×10^7 $p53^+$ DC. However, generation of $>5 \times 10^6$ $p53^+$ DC per dose was difficult to achieve (on average, 7.7×10^7 DCs and 8.6×10^6 $p53^+$ DCs were generated per dose and $\geq 10^7$ $p53^+$ DCs were generated in < 10% of cases). Thus, to maintain consistency throughout the trial, the single doses of $p53^+$ DC were not escalated beyond 5×10^6 cells. On average, each patient received 3.8×10^6 $p53^+$ DCs per dose. However, 5 patients received $<10^6$ $p53^+$ DCs because of production difficulties.

Ad.p53-DC toxicities were infrequent and mostly mild. Only 2 patients experienced grade 2 toxicities (1 fatigue, 1 arthralgia), and Ad.p53-DC was never withheld. The most frequent toxicities were grade 1 arthralgia/myalgia (9 patients), fatigue and injection site erythema (5 patients each), and injection site pain (4 patients). Occurrence of toxicities was independent of the number of Ad.p53-DC doses received.

4.3.3 Immune Response to Ad.p53-DC

The p53-specific immune response was evaluated by ELISPOT using autologous PBMCs infected with a canary pox virus (ALVAC) containing wt-p53 or empty vector as control. The number of γ-interferon producing cells was evaluated using an automated ELISPOT reader[39]. In 12 HLA-A2-positive patients, immune responses were tested with p53-derived or control HLA-A2 matched peptides pulsed onto autologous PBMCs and tetramers.

Response was considered significant if ≥ 2 SD higher than the response to ALVAC or peptide controls. Increase over baseline (pre-Ad.p53-DC) was considered significant if p53-specific responses (post-Ad.p53-DC) were ≥ 2 SD higher than p53-specific responses pre-Ad.p53-DC and at least 2 SD higher than responses to ALVAC or peptides. Because the generation of a p53-specific T-cell response not only depends on the quality of antigen stimulation but also on the functional activity of T cells and DCs in the host, they were also tested.

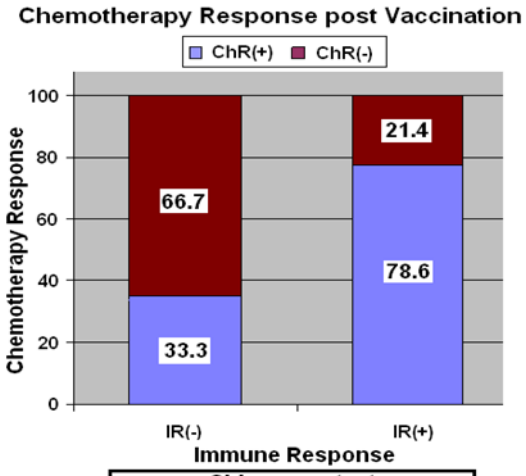
Full immune response evaluation was possible in 43 patients. Overall, 18 patients (41.8%) had a statistically significant p53-specific response using ALVAC and 7 of 12 patients (58.3%) using p53-derived peptide. Three patients with a significant response to Ad.p53-DC using the p53-derived peptide were not tested with ALVAC (technical reasons). The baseline p53-specific immunity level was similar in Ad.p53-DC responsive and non-responsive patients. The level of the p53-specific immune response decreased 2 months after completing Ad.p53-DC, coinciding with the start of additional chemotherapy.

Presence and functional activity of DCs were both decreased, and the p53-specific immune response to Ad.p53-DC did not correlate with T cell functional activity, presence of Tregs, or pre-existing levels of DC activity. Because myeloid-derived suppressive cells (MDSC) are implicated in the host's immunosuppressive state[40,41], we examined patients for the presence of these cells. Pre-Ad.p53-DC MDSC ($Lin^-HLA\text{-}DR^-CD3^+$) levels were elevated compared

to control donors (p=0.01). Post-Ad.p53-DC levels increased even further (p=0.002). All patients with normal levels of MDSCs prior to Ad.p53-DC developed a p53-specific immune response compared to only 33% of patients who had elevated levels of MDSC (p=0.012).

4.3.4 Clinical Efficacy of Ad.p53-DC and Enhanced Effect on Salvage Chemotherapy

Two patients (3.7%) achieved a partial response (PR), and 13 had stable disease with Ad.p53- DC. All but 5 patients developed progressive disease (PD), and response data were available for 33 patients who received additional chemotherapy post-Ad.p53-DC progression. The ORR for all 33 patients treated with "second"-line chemotherapy was 51.5% and 45.5% for the 22 platinum-resistant patients. The MST (from the date of the first Ad.p53-DC dose) for platinum-resistant patients was 10.5 months (95% CI = 5.3-14.4) and 8.8 months (95% CI = 5.2-11.8) for all 54 patients.



Chi-square test

	ChR(+)	ChR(-)	Total
IR(+)	11	3	14
IR(-)	5	10	15
Total	16	13	29

X2= 5.993, p= 0.01437 (1 df)

We also evaluated the relation between immune response to Ad.p53-DC and clinical response to second-line chemotherapy. Eleven of 14 patients (78.6%) with a positive immune response experienced a clinical response to second-line chemotherapy compared to 5 of 15 patients (33.3%) with a negative immune response (p=0.014). Patients with a positive immune response had a trend toward improved survival; however, the difference did not reach statistical significance (MST = 12.6 vs. 8.2 months, p = 0.131)[33].

4.4 Improved Ad.p53-DC Immunotherapy Strategy

4.4.1 Role of MDSCs in the Immune Response

It is now fully appreciated that tumor-specific immune responses in cancer are inhibited. Large numbers of different factors have been implicated in this process, including regulatory T cells (Treg), myeloid cells, various soluble factors and cytokines, inhibitory molecules expressed by immune and tumor cells, etc.[42-44]. Among these factors MDSC play a prominent role.

MDSC are a heterogeneous group of pathologically activated immature myeloid cells and myeloid precursors with potent immune suppressive activity[45-48]. Two major groups of MDSC have been identified: polymorphonuclear (PMN) and mononuclear (M) MDSC. These cells share common features (immature myeloid cells with immune suppressive activity) but differ in morphology, phenotype, and mechanisms of suppressive activity[46]. In cancer patients, these MDSC have partially overlapping phenotype that can be identified using several markers, which largely depends on the type of tumor. In most tumors, immune suppressive MDSC are defined as $Lin^{-}HLA\text{-}DR^{-}CD33^{+}$ or $CD33^{+}CD14^{-}CD11b^{+}$ cells that can be further sub-divided into $CD15^{+}$ PMN-MDSC and $CD15^{-}$ M-MDSC. In some tumors,

most notably melanoma, M-MDSC are defined as $CD14^{+}HLA\text{-}DR^{-}/^{lo}$[49,50]. MDSC are characterized by potent immune suppressive activities in both antigen-specific and non-specific experimental systems.

The association between tumor progression and the presence of MSDC in cancer patients was demonstrated in a number of studies. In patients with solid tumors, a significant correlation between circulating MDSC and clinical cancer stage was observed. Among stage IV patients, those with extensive metastatic tumor burden had the highest percent and absolute number of MDSC[51]. Patients with lower levels of circulating MDSC at baseline and on the last cycle of chemotherapy had significantly higher probability of a pathologic complete response[52].

Increased circulating MDSC correlated with clinical stage and pathological grade in patients with bladder cancer[53,54] and pancreatic cancer[55]. Recently, first report linked clinical response to vaccination to accumulation of MDSC in patients with renal cell cancer[56]. Experiments in mice demonstrated that elimination of MDSC with antibodies or different compounds could substantially improve antitumor immune responses, which resulted in antitumor effect[46]. However, no data are available testing the hypothesis that depletion of MDSC can improve the effect of cancer vaccines or another immune therapeutic modality in cancer patients.

4.4.2 Rationale for the Use of ATRA in Combination with Ad.p53-DC

Because all-trans-retinoic acid (ATRA) causes differentiation of acute promyelocytic leukemia (APL) cells and lineage features between MDSCs and APL cells are comparable, the effect of ATRA on DC differentiation and function was tested in patients with metastatic renal cell carcinoma[57]. As expected, patients had a substantially increased proportion of MDSCs, decreased presence of DCs, and decreased MDSC/DC ratio. Treatment with ATRA significantly decreased the presence of MDSC and improved MDSC/DC ratio to control levels. Patients had profound defects in the ability to respond to tetanus toxoid and to stimulate allogeneic T cells and treatment with ATRA improved those defects as well, although not significantly.

$Gr\text{-}1^{+}$ cells (analogous to human MDSC) inhibit antigen-specific T cell response and are present in excess in tumor-bearing mice. ATRA differentiates these cells *in vitro* and removes their immunosuppressive effect[58,59]. Furthermore, *in vivo* administration of ATRA to tumor-bearing mice dramatically reduces the presence of $Gr\text{-}1^{+}$ cells and improves the effect of tumor vaccines[60]. Similarly, *in vitro* treatment of human MDSCs with ATRA results in their differentiation (2/3 become DC-like and 1/3 myeloid)[61]. These data confirm the effect of ATRA on DCs and MDSCs and strongly suggest a valuable role in cancer immunotherapy.

4.4.3 Randomized Phase II Clinical Trial in SCLC

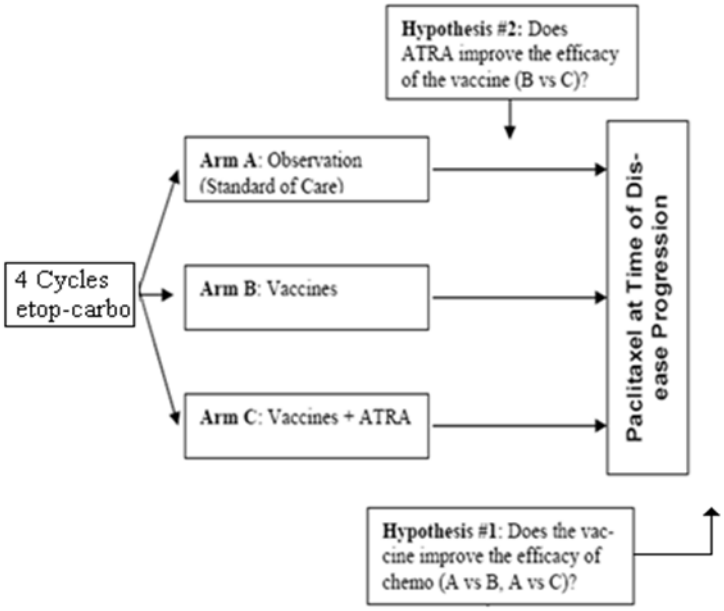
Previously we demonstrated that: (1) Ad.p53-DC was safe and induced immune responses (IR ~ 40-50%), (2) lack of IR was related to immunosuppressive myeloid derived suppressive cells (MDSCs), (3) a high rate of objective tumor regressions was seen in patients treated with chemotherapy after vaccination, particularly if a positive IR was

obtained and (4) ATRA reduces the number of MDSCs and enhances IR. However, confirmation of this evidence required a prospective, comparative (randomized) trial[62].

Thus, we designed and recently completed a randomized phase II study to address the question of whether combination of Ad.p53-DC with ATRA improved the clinical outcome of patients. Our hypotheses were *1*) salvage chemotherapy in combination with Ad.p53-DC results in a substantial improvement in clinical outcomes, and *2*) ATRA, by reversing the immunosuppressive influence of MDSCs, substantially improves the p53-specific immune response to Ad.p53-DC and hence clinical outcomes.

Patients with ES-SCLC were enrolled to this randomized phase II study. The trial was registered at ClinicalTrials.gov (NCT00617409). All patients provided a written informed consent and treatment protocol was approved by University of South Florida Institutional Review Board. After receiving initial chemotherapy, (4-6 cycles of a standard platinum/etoposide regimen as first-line chemotherapy), patients were enrolled and randomized.

Additional eligibility included; stable disease (SD) or better with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and adequate organ function were screened for initial registration approximately 4-6 weeks after the completion of first-line chemotherapy. Prophylactic cranial irradiation (PCI) was permitted.



Eligible patients were randomized in a 1:1:1 ratio to one of three treatment arms: Arm A (control patients or observation), Arm B: (patients treated with Ad.p53-DC vaccine only), or Arm C (patients treated with Ad.p53-DC vaccine in combination with ATRA). Each vaccine consisted of 2-5 × 10^6 Ad-p53 DCs. Cells were injected intradermally, at two-week intervals for three times (three vaccine doses).

Patients were restaged approximately 2 weeks after the 3rd vaccine dose. Patients without signs of disease progression (PD) underwent a second leukapheresis and then vaccinated 3 more times at 4-week intervals. Patients on Arm C also received 150 mg/m^2 ATRA for 3 days prior to each vaccine administration (followed by vaccine administration on the next day). This scheduling was based on our previous data[57] that demonstrate persistence of the ATRA effect on MDSC for minimum 2 weeks.

All patients were followed until PD at which time they received salvage or second line chemotherapy with single agent paclitaxel (200 mg/m2 IV every 3 weeks, 4-6 cycles).

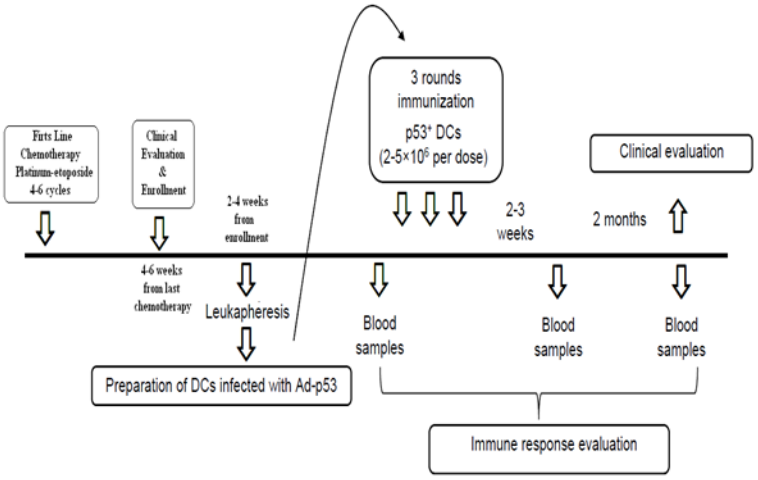


Figure 1

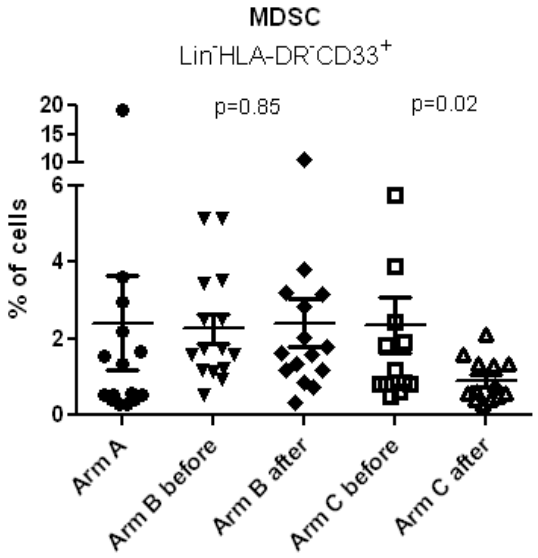
The primary objective was to evaluate the efficacy of second line paclitaxel in the two experimental regimens (Arms B and C). Objective response (OR) to paclitaxel in each arm was the endpoint of the study. An optimal two-stage design was used in planning of this study[63] because it has been successfully applied in randomized phase II trials to rank experimental agents[64]. The control arm was used to examine consistency with historical control data and to assure that patients entering the phase II trial are comparable to historical controls.. Using the optimal two-stage design, if 3 responses were observed in the first 9 patients, the second stage would accrue 14 additional patients.

To assess immune response, PBMCs were collected from patients at different time points during the treatment (**Fig. 1**) and kept frozen in liquid nitrogen. All samples from one patient were analyzed simultaneously to reduce inter-experimental variability. PBMCs were thawed, incubated overnight in complete medium (RPMI-1640 supplemented with antibiotics and 10% FBS) and then used in experiments. Cell viability was greater than 80%. T-cell responses were assessed using IFN-γ ELISPOT after infection with a recombinant canarypox virus (ALVAC) containing wild-type p53 or empty vector (obtained from Aventis Pasteur, Toronto, Canada), and incubation for 48 hours. Empty ALVAC virus served as a control.

		Arm A	Arm B	Arm C	Total
Subtotal		18	19	17	54
Gender	M	11	7	13	31
	F	7	12	4	23
Age	Median	63	63	63	62
	Range	43-73	51-74	48-73	43-74
Race	White	16	19	17	52
	AA/Other	1/1	0/0	0	1/1
PS	0	4	6	4	14
	1	14	13	13	40
Chemotherapy	≤ 4 cycles	4	5	2	11
	> 4 cycles	14	14	15	43
Radiotherapy	PCI	2	3	2	7
	WBRT (S)	3	0	5	8
	Thoracic	5	3	1	9
	Distant	2	1	1	4
Leukopheresis	Total		24	19	43
	0/1		1/12	0/15	1/27
	2		6	2	8
Vaccinations	Median		3	3	3
	Range		0-6	1-6	0-6
	<3/3/>3		4/11/4	5/10/2	9/21/6
	Total		56	58	114

The initial infection step was performed in serum free media (supplemented with cytokines) for 90 minutes after which, complete media was added. In IFN-γ ELISPOT assay 2×10^5 PBMCs were seeded in triplicates or quadruplicates in 96-well plates pre-coated with an anti-IFN-γ antibody. To ascertain that T cells are functionally competent for each sample we prepared additional controls (unstimulated or PHA (5μg/ml) stimulated cells), and the plate was further incubated for 36 hours. The number of IFN-γ producing cells was evaluated as described previously[32] using an automated ELISPOT reader (Cellular Technology, Ltd, OH).

54 patients were enrolled during the first stage, 18, 19 and 17 in arms A, B and C respectively. Median age (range) = 62 (43-74). Male/female = 31/23, ECOG PS 0/1 = 14/40. Median # of vaccines was 3 (range 0-6) and total # vaccines administered was 114. AEs associated with vaccine were mild and no grade 3-4 AE was vaccine related. OR to vaccine was observed in 3/36 patients. OR to paclitaxel (or other second line treatment) was seen in 1/11, 2/12 and 3/14 patients for arms A, B and C respectively. Only arm C moved to stage two. An additional 15 patients have been accrued to the Arm C second stage of the trial and their study data and results is currently being collected for the proposed protocol analysis[62].



Pre-treatment levels of MDSC populations in patients from all three arms was similar (p>0.07). Treatment of patients from arm B with vaccine alone did not affect the proportion of MDSC **(Fig. 2)**, whereas in patients treated with ATRA the presence of $Lin^-HLA\text{-}DR^-CD33^+$ MDSC decreased more than two-fold (p=0.02). The proportion of $CD11b^+CD14^-CD33^+$ MDSC decreased less dramatically but also significantly (p=0.03). No significant differences were observed in the proportion of conventional DC and Treg[65].

Next, we evaluated the p53-specific immune response using IFN-γ ELISPOT assay. Prior to start of the treatment no patients had detectable p53 specific response. Consecutive measurements did not show positive p53 responses in any of the arm A patients. After three immunizations, 3 out of 15 tested patients (20%) from arm B met the criteria for p53-specific immune response, which was not significantly different from arm A (p=0.22). In contrast, in arm C 5 out of 12 patients (41.7%) had detectable p53 response, which was significantly higher than in control group (p=0.012) **(Fig. 3)**[65].

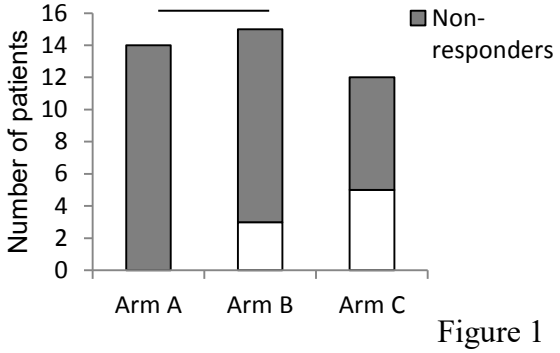


Figure 1

The proportion of p53-specific IFN-γ

positive cells $CD4^+$ and $CD8^+$ T cells was evaluated using intracellular cytokine staining. Prior to the treatment no statistically significant differences between the arms were seen ($p>0.07$). The immunization significantly increased the proportion IFN- γ positive $CD8^+$ and $CD4^+$ T cells. The proportion of granzyme B (GrzB) positive $CD8^+$ T cells was increased only in patients from arm C but not from arm B[65].

To evaluate the possible link between the immune response to vaccination and the clinical outcome, patients in arms B and C were split based on the presence of p53 specific responses after vaccination. Patients who did not develop immune response had median survival of 11.7 months, as compared with 16.4 months in patients who developed p53 immune responses (hazard ratio 0.52, 95% CI 0.22-1.22) (p=0.1). Patients with brief immune response had the same median survival as non-responders (11.1 months vs. 11.7 months). In contrast, patients who had p53 immune response at least two months after completion of the vaccination had median survival of 41 months (hazard ratio 0.26 (0.09-0.74), p=0.03) suggesting that improving upon the immune response obtained through this strategy could manifest in clinical outcome improvement for patients (internal data not yet published).

4.5 Checkpoint Inhibitors Immunotherapy

4.5.1 Nivolumab

Nivolumab is a fully humanized, IgG4 (kappa) isotype monoclonal antibody (mAb) that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. PD-1, (CD279), a 55-kDa type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM).

Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T cell activation on binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD 1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.

The emergence of these autoimmune phenotypes is dependent on the genetic background of the mouse strain, and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent on

various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by mAbs can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1. This suggests that host mechanisms (i.e., expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells *in vitro*. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells. Additional details are available in the Nivolumab Investigator Brochure.

4.5.2 Ipilimumab

Ipilimumab is a fully humanized, IgG1 (kappa) isotype mAb that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of TILs. Inhibition of CTLA-4 signaling can also reduce Treg cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

4.6 Study Rationale

4.6.1 Rationale for Immuno-Oncology Therapeutic Approaches in SCLC

SCLC has classically been associated with immune-mediated paraneoplastic processes, such as cerebellar degeneration, limbic encephalitis and Lambert-Eaton myasthenic syndrome [66]. For example, antibodies generated against human neuronal RNA-binding proteins (e.g. Hu), which are expressed on neurons and SCLC tumors, leads to an encephalomyelitis[67]. Interestingly, SCLC patients that present with these 'early' paraneoplastic syndromes have a more favorable prognosis[68,69], suggesting that an underlying immune response is being generated against these onconeural antigens.

Proof of an active immune environment in SCLC has been described in a few analyses of patient samples. First, analysis of sixty-four SCLC tumors demonstrated that a wide range of CD45+ cells infiltrated the tumor, an average of 40 immune cells/field, and that high CD45+ counts were associated with a better prognosis[70]. Secondly, a separate study found that various tumor-infiltrating lymphocyte (TIL) subsets were present in SCLC brain metastases and that programmed death ligand 1 (PD-L1) was heterogeneously expressed[71]. Finally, evaluation of peripheral blood cells in 35 SCLC patients demonstrated a high CD4+ effector T cell to T regulatory (Treg) cell ratio in patients with LD-SCLC vs. ED-SCLC[72]. This implies that in some respect, SCLC pathology integrates with the immune response.

Furthermore, SCLC is known to have one of the highest mutational loads[73], which is thought to be a reflection of myriad insults inflicted by carcinogens from smoking. Additionally, comprehensive genomic profiling of SCLC tumors has identified that the vast majority lack functional p53 (90%) and Rb1 (65%) [74]. This universal genetic aberration facilitates poor genomic stability [75], thus perpetuating the generation of tumor-associated antigens (TAAs).

Interestingly, recent studies have highlighted that the clinical efficacy of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) blockade in melanoma and non-small cell lung cancer (NSCLC), respectively, are partially driven by the mutational burden of the tumor and the presence of neoantigens [76,77]. Thus, the high mutational burden in SCLC may facilitate enhanced immune recognition. Though SCLC pathology appears to be intertwined with the immune response and is predisposed by a substantial mutational load, prior evidence indicates that major histocompatibility complex (MHC) surface expression is reduced in SCLC [78,79], which may preclude robust immune recognition.

4.6.2 Rationale for Nivolumab/Ipilimumab Combination in SCLC

In a phase I/II study of nivolumab and nivolumab/ipilimumab for treatment of recurrent SCLC (CA209032), participants who were platinum sensitive or refractory and had progressive disease were enrolled regardless of tumor PD-L1 status or number of prior chemotherapy regimens [80]. This open-label study randomized participants to nivolumab 3 mg/kg IV every 2 weeks or nivolumab + ipilimumab (1 + 1 mg/kg, 1 + 3 mg/kg or 3 + 1 mg/kg) IV every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks. The primary objective was objective response rate. Other objectives were safety, PFS, OS and biomarker analysis.

All participants had prior platinum-based first-line treatment and progression after the most recent treatment regimen. Baseline characteristics were typical for a SCLC population with respect to age, smoking history, and gender.

Safety. While the incidence of drug-related adverse events (AEs) in the nivolumab 1 mg kg/ipilimumab 3 mg/kg cohort (79% any grade, 30% grade 3-4) was higher than in the nivolumab monotherapy group (53% any grade, 13% grade 3-4), the treatment discontinuation rate for treatment-related AEs was only 11% (nivolumab 1 mg/kg / ipilimumab 3 mg/kg): 5 patients with diarrhea, myasthenia gravis [subsequently developing complications with fatal outcome], pneumonitis, cardiomyopathy, and 1 patient with hypothyroidism, hyperglycemia, and increased ALT levels).

The most frequent (≥10%, any grade) drug-related AEs were diarrhea, fatigue, rash, pruritus, hypothyroidism, rash maculo-papular, nausea, hyperthyroidism, and increased lipase levels. One treatment-related death in the nivolumab 1 mg/kg / ipilimumab 3 mg/kg cohort occurred. This participant developed myasthenia gravis (reported as grade 4) after treatment start and suffered from complications resulting in death. Limbic encephalitis was reported in 3 participants, which resolved with immunosuppressive treatment in 2 cases. Another participant had a minor response to immunosuppressive treatment and eventually died due to the underlying tumor disease.

Efficacy. Patients treated at the recommended phase III dose of ipilimumab 3mg/kg and nivolumab 1mg/kg (n=61) were noted to have an overall response rate (ORR) of 23%, and the disease control rate (CR + PR + SD) was 44%. Objective responses were long lasting, with a median duration of response of 7.7 months in the nivolumab 1mg/ipilimumab 3 mg combination group. The median PFS was 2.6 months (95% CI: 1.4, 4.1) The median OS was 7.7 months (95% CI: 3.6, 18) in the nivolumab 1 mg /ipilimumab 3 mg combination group, which compares favorably with historical controls [81]. There is an ongoing phase III randomized, placebo-controlled study (CA209-451) evaluating PFS and OS among patients with ED-SCLC with at least stable disease after 4 cycles of EP chemotherapy. More than 800 patients are to be randomized to placebo, nivolumab 240 mg delivered every 2 weeks, or ipilimumab 3 mg + nivolumab 1 mg combination therapy for 4 cycles followed by nivolumab 240 mg every 2 weeks until progression. Patients will be carefully monitored on this protocol, and we expect results from our study with comparable inclusion criteria to be available in the coming years.

4.6.3 Rationale for the Use of Ipi-Nivo in Combination with Ad.p53-DC

The efforts in cancer immune therapy are focused on increasing the frequency of CTL-mediated tumor destruction by applying cancer vaccines, adoptively transferred antigen-specific T cells, inhibitors of check-point blockade (CTLA4, PD-1) or other immune therapeutics[82]. However, even in tumor-bearing mice, once tumors are established these interventions have relatively limited efficacy, and the rate of clinical responses in cancer patients, although encouraging, remains relatively low[83,84].

Ad.p53-DC has demonstrated to be safe and to produce specific cytotoxic immune responses in patients with SCLC. However, the impact on clinical outcomes is still insufficient and strategies that further improve the vaccine driven immunotherapy results are necessary. Depletion of MDSC with ATRA, substantially improved the immune response to Ad.p53-DC vaccination supporting an approach of immunotherapy combinations to enhance the effect of immune mediated anti-cancer interventions.

Nivolumab monotherapy and nivolumab plus ipilimumab showed antitumour activity with durable responses and manageable safety profiles in previously treated patients with SCLC. In the phase I/II trial (CA209-032), in participants with heavily pretreated SCLC, nivolumab monotherapy showed an ORR of 10%, whereas the combination of nivolumab-1 and ipilimumab-3 demonstrated an ORR of 30% [80].

Thus, combining these 3, individually safe, partially effective and potentially synergistic strategies into one single strategy is a reasonable approach that deserves clinical testing. Here we propose a phase II trial where ES-SCLC patients with recurrent disease (previously treated with first line chemotherapy) will receive Ad.p53-DC in combination with ipilimumab and nivolumab to assess the impact of this combination immunotherapy regimen on clinical outcomes. We hypothesize that this combination immunotherapy strategy will improve overall disease response or control and/or survival in this population.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

1) Histologic or cytologic diagnosis of SCLC
2) Recurrence to at least one prior treatment with a platinum containing regimen (cisplatin or carboplatin) including limited stage (LS) and ES initial presentations.
   NOTE: *In patients with SCLC the most frequent platinum containing doublet used is etoposide-carboplatin. However, etoposide-cisplatin and irinotecan or topotecan combined with either carboplatin or cisplatin are platinum doublet regimens that can sometimes be used and thus would be allowed for the purposes of trial enrollment and eligibility.*
3) Excluded are patients who upon relapse may be still considered for a salvage concurrent chemo-radiation approach

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Have a performance status of 0 - 1 on the ECOG Performance Scale.
5. Demonstrate adequate organ function as defined in
6. Table 1, all screening labs should be performed within 30 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥8 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[a] CrCl (GFR can also be used in place of creatinine or CrCl)	≤2.0 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels ≤ 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥3.0 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance (CrCl) should be calculated per institutional standard.	

7. Life expectancy of > 4 months

8. Favorable tumor p53 biomarker profile defined by ≥ 50% p53 positive tumor cells by immunohistochemistry. Tumor p53 biomarker evaluations may be performed with either original or recurrent tumor although samples from recurrent disease are preferred.
9. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Therapy.
   NOTE: *Systemic steroid doses of ≤ 10 mg of prednisone daily or its equivalent are allowed in patients receiving physiologic replacement steroid doses for both, 5.1.3.2 and 5.1.3.8.*
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to Ipilimumab and/or nivolumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) excluding any anti-PD-1 and/or anti-PD-L1checkpoint inhibitor within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
   - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
   - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. Other malignancies that remain without evidence of disease or recurrence, 2 years or more after curative therapy are also considered part of this exception.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 2 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
9. Any diagnosis of autoimmune disease (confirmed by medical records or appropriate laboratory testing)
10. Has known history of, or any evidence of active, non-infectious pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
17. Has received a live vaccine within 30 days of planned start of study therapy.
    NOTE: *Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

5.1.4 Women and Minorities

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

5.1.5 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

☐☐ 1 week minimum for vaginal hormonal products (rings, creams, gels)

☐☐ 4 week minimum for transdermal products
☐☐ 8 week minimum for oral products

Postmenopausal women may continue HRT after FSH testing is completed and postmenopausal status is confirmed. Other parenteral products may require washout periods as long as 6 months.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose Potency	Dose Frequency	Route of Administration	Regimen Treatment Period	Use
Induction Immunotherapy					
Ipilimumab	3 mg/kg	Q3W	IV infusion	Day 1 x4 cycles	Investigational
Nivolumab	1 mg/kg	Q3W	IV infusion	Day 1 x 4 cycles	Investigational
Ad.p53-DC	1-5x10^6 viable p53+ DC	Q2W	ID injection	x3 per study calendar	Investigational
Maintenance Immunotherapy					
Nivolumab	480 mg	Q4W	IV infusion	Day 1 x until disease progression (PD)	Investigational
Ad.p53-DC	1-5x10^6 viable p53+ DC	Q4W	ID injection	x3 per study calendar	

Trial treatment should begin within 2-3 weeks of the leukopheresis.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of ipilimumab and nivolumab are provided in the Investigator Brochure. Details on preparation and administration of Ad.p53-DC are provided in Appendix 11.4.

5.2.1.2 Dose Modification

Ad.p53-DC

There will no pre-planned dose modifications for the vaccine Ad.p53-DC. Holding one individual vaccine (Ad.p53-DC) dose or complete discontinuation of vaccine doses will be at the discretion of the treating physician and in coordination with the study principal investigator and sponsor.

Temporal of permanent discontinuation of Ipi-Nivo or Nivo due to adverse events, will not preclude continuation and/or completion of vaccine administration as planned per protocol.

Ipilimumab-Nivolumab (Ipi-Nivo) or Nivolumab (Nivo)
Adverse events (both non-serious and serious) associated with Ipi-Nivo or Nivo exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Ipi-Nivo or Nivo must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below.

See Section 11.6 Management Algorithms for supportive care guidelines, including use of corticosteroids.

NOTE: In cases of an unexpected or unforeseen discrepancy between the guidelines or instructions in Table 3 (below) and Section 11.6 Management Algorithms, the latter guidelines/instructions should prevail for the purposes of patient management on protocol.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or	Hold IPI-NIVO OR NIVO for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume IPI-NIVO OR NIVO when patients are clinically and metabolically stable.
	3-4	Permanently discontinue	Permanently discontinue
Hypophysitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2	Therapy with IPI-NIVO OR NIVO can be continued while treatment for the thyroid disorder is instituted	Therapy with IPI-NIVO OR NIVO can be continued while treatment for the thyroid disorder is instituted.
	3-4	Permanently discontinue	Permanently discontinue
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	Any Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

Trial antibody (checkpoint inhibitor treatment should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 7 days before or after the scheduled day due to any medical or administrative/logistical reasons.

All trial treatments will be administered on an outpatient basis.

Induction Immunotherapy:

- Ipilimumab, 3 mg/kg IV q3w x4 cycles
- Nivolumab, 1 mg/kg IV q3w x4 cycles.

Maintenance Immunotherapy:

- Nivolumab, 480 mg (flat dose) IV q4weeks until PD.

Sites should make every effort to target infusion timing to be as close as possible (60 min for nivolumab and 90 min for ipilimumab). However, given the variability of infusion pumps from site to site, a window of -10 minutes and +15 minutes is permitted (i.e., infusion time is 60 or 90 minutes: -10 min/+15 min, respectively).

The Pharmacy Manual contains specific instructions for the preparation of the Ipi-Nivo or Nivo infusion fluid and administration of infusion solution.

Ad.p53-DC (2-5x10^6 DC depending on manufacture cell number yield) will be administered as an intradermal injection as per the trial schema, every 2 weeks x 3 after the first leukopheresis (induction immunotherapy) and in cases of persistant SD upon restaging, again every 4 weeks x 3 after the second leukopheresis (maintenance immunotherapy).

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Not applicable

5.4 Stratification

Not applicable

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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 BMS Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

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 medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Ipi-Nivo
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in Section 11.6. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Ipi-Nivo.
It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of Ipi-Nivo.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of IPI-NIVO OR NIVO with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 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	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Contraception

IPI-NIVO OR NIVO may have adverse effects on a fetus in utero. Furthermore, it is not known if IPI-NIVO OR NIVO has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to BMS. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with Ipi-Nivo the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to BMS without delay and within 24 hours to the Sponsor and within 2 working days to BMS if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to BMS and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether Ipi-Nivo is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1

- Unacceptable adverse experiences as described in Section 5.2.1.2

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with maintenance Nivo and had at least two treatments with Nivo beyond the date when the initial CR was declared.

Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with Ipi-Nivo (similar schedule) via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of Ipi-Nivo or Nivo, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open.

Concomitant administration of the Ad.p53-DC vaccine together with Ipi-Nivo or Nivo is desired and included as part of the Second Course Phase described above if feasible from a medical and logistical point of view.

5.9 Subject Replacement Strategy

Subjects deemed not eligible will be replace and will not count towards achieving the trial sample size calculation

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of BMS decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.11 Assessment of Outcomes

5.11.1 Safety Assessments.

NCI CTCAE version 4 will be used to assess toxicities in all patients in this study.

Careful toxicity assessments will be performed with standard laboratory studies (CBC, BUN, creatinine, electrolytes, and LFTs) before each treatment. In addition, a medical history and physical examination will be performed monthly.

Three unusual toxicities can occur with anti-PD-1 therapy. These include induction of autoimmunity (nephritis, colitis, pneumonitis, and endocrinopathies). Careful, frequent clinical evaluation for the development of autoimmunity symptoms will be performed. Detailed plans for management of these toxicities will be present in the clinical protocol. Patients who develop uncontrolled grade 3/4 pneumonitis will permanently discontinue IPI-NIVO OR NIVO. Patients will be treated in the Moffitt Clinical Research Unit, which is staffed by nurses experienced in the management of infusion reactions and cytokine release syndrome.

We are also very experienced in managing the toxicities associated with immune checkpoint inhibitors as we have treated over 200 lung cancer patients with either anti-PD-1 or anti-PD-L1 therapy since June 2011. All SAEs with a determination of SAE-relatedness to the investigational therapy will be reported as described in the data and safety-monitoring plan detailed in the protocol.

5.11.2 Clinical Efficacy.

Radiographic assessments will be performed at the end of vaccines 1-3 (“first 3 vaccines”) and twice in patients receiving vaccines 4-6 (“second three vaccines”). First, after vaccine 4 and then, after all 6 vaccines. Subsequently, assessments will be done every 12 weeks.

Response will be assessed primarily using the response evaluation criteria in solid tumors (RECIST v1.1). Response rate, overall survival, and progression-free survival will be determined. Subjects with progressive disease by RECIST but without rapid clinical deterioration may continue to be treated at the discretion of the investigator.

The immune related (ir)RECIST will also be used secondarily for research purposes only. This is a modification of RECIST and allows measurement of response patterns unique to immune therapy, such as tumor progression of index lesions and appearance of new lesions prior to tumor regression[85]. Patients who are found to have stable disease (SD), partial response (PR), or complete response (CR) will continue on study until evidence of disease progression, intolerance, or withdrawal from study.

5.11.3 Immunological Efficacy

Criteria used to determine the presence of immune responses: Individual patient will be considered responders if at any time point the response in IFN-γ ELIPOT assay is higher than 30 spots per 2×10^5 AND the response in IFN-γ ELISPOT to ALVAC p53 is more than 2 SD

higher than the response to corresponding ALVAC control at the same time point AND 2 SD higher than the corresponding response at the base line (before start of the treatment).s

5.11.4 Biomarker Testing

A pre-treatment tumor biospy will be performed (mandatory) and utilized to evaluate tumor p53 biomarker status. To be eligible for the study, patients must have a favorable tumor p53 biomarker profile defined by ≥ 50% p53 positive tumor cells by immunohistochemistry. Tumor p53 biomarker evaluations may be performed with either original or recurrent tumor although samples from recurrent disease are preferred.

The mandatory pre-treatment tumor biopsy specimen will be used to evaluate p53 protein expression using a CLIA-certified p53 assay. If sufficient tumor sample remains available, additional immunohistochemistry evaluations will be performed for PD-1, PDL-1, PDL-2 protein expression as well as tumor infiltration by immune cells expressing CD3, CD8, CD4, CD25, FoxP3, CD11b, and CD56.

Tumor mutational burden will also be evaluated using Foundation One CDx, if possible depending on tissue availability.

Simultaneously, all efforts will be made to collect archival tumor tissue from previous biopsies, either in the form of a FFPE block or unstained slides (ideally 5-10, but any number will be acceptable depending on availability).

6.0 TRIAL FLOW CHART

All laboratory studies, visits and procedures included in these Flow chart have a +/- 7 day window. This rule applies in addition to any existing window included for specific laboratory studies, visits or procedures at the discretion of the investigators.

	Screening	Leukopheresis #1[A,E]	Visit #1[C,E]	Visit #2	Visit #3	Visit #4	Visit #5	Leukopheresis #2[B,E]	Visit #6[D,E]	Visit #7	Visit #8	Visit #9	Visit #10	Visit #11	Visit #12	Visit #13,[F] +	End of Study Visit[G]
			Induction Immunotherapy							Maintenance Immunotherapy							
	Wk -4 to 0	Wk -3 to 0	Wk 1 C1 D1	Wk 3 C1D15	Wk 4 C2D1	Wk 5 C2D8	Wk 7 C3D1	Wk 8 to 12	Wk 10 C4D1	Wk 13 C5D1	Wk 15 C5D15	Wk 17 C6D1	Wk 19 C6D15	Wk 21 C7D1	Wk 23 C7D15	Wk 25, + C8,+ D1	
ICF[1]	X																
H+P[2]	X		X		X		X			X			X			X	X
MD[3] visit	X		X		X		X			X			X			X	
Mid-Level visit				X		X		X	X		X	X		X	X	X	X
CTC[7] visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent Medications	X	X X															X
Adverse event (AE) evaluation[CC]	X	X X															X
CBC, diff	X		X	X	X	X	X	X	X	X		X	X	X		X	X
CMP	X		X	X	X	X	X	X	X	X		X	X	X		X	X
Mg	X	X[4]					X										
LDH	X						X									X	X
PT/INR, PTT	X	X[4]						X									
Thyroid studies[13]	X						X				X				X		
EKG, U/A	X	X[4]															
Pregnancy test	X	X[4]						X[4]									
CT chest/abd.[6]	X						X			X			X			X[6]	X
Brain MRI[5,8]	X[5]						X[5]									X[5]	X[5]
Nivolumab[AA]			X		X		X		X	X[AA]		X		X		X	
Ipilimumab			X		X		X		X								
Ad.p53-DC[BB]			X	X		X				X[BB]		X		X			
Immune response evaluation[9]	X	X[10]					X				X				X		
Image guided core biopsy[11]	X																
Tumor Biomarkers (p53 IHC)[12]	X																
Life-expectancy >4 months	X																

1 Informed consent form (ICF) must be signed within 3 weeks of first leukopheresis (start of study)

2 Brief history and physical (H+P) to include vital signs (VS), weight (W), height (H) and performance status (PS) and AE evaluation on Mid-Level visits and Full H+P on MD visits.
3 Can also be performed by protocol assigned Mid-Level: Nurse Practitioner (NP) or Physician Assistant (PA)
4 Only need repeated if leukopheresis being performed more than 4 weeks since a prior test performed
5 Only required for patients with CNS symptoms suspicious of brain metastasis or for patients known to have untreated brain metastasis. Otherwise it is only required if clinically indicated per treating physician discretion
6 Starting with visit #13 and beyond, while only receiving maintenance nivolumab, patients will have restaging CT scans every 3 months
7 When the patient is seen by the MD, then only a clinical trials coordinator (CTC) visit will be required. For all other appointments, a Mid Level (Mid L) visit will be required
8 The type and site of any other imaging scan will only be performed when clinically indicated, at the discretion of the treating physician
9 Including MDSC determination
10 Not necessary if blood drawn at screening
11 Tumor biopsy is mandatory. Ideally, 4-6 core samples should be obtained. A lesser number of cores (1-3) will be acceptable in cases where patient safety so requires or if in the judgement of the physician performing the biopsy less number of cores should be performed.. Simultaneously, all efforts will be made to collect archival tumor tissue from previous biopsies, either in the form of a FFPE block or unstained slides (ideally 5-10, but any number will be acceptable depending on availability).
12 Tumor Biomarker Testing for p53 expression at enrollment is required. Tumor p53 biomarker evaluations can be performed with either original or recurrent tumor although samples from recurrent disease are preferred. Additional biomarkers will also be performed depending on tissue availability as per section 5.11.4.
13 See Table 5, (T3, T4 and TSH)

A First leukopheresis should occur within 2-3weeks of completing screening evaluation (date of the last screening test performed)
B Second leukopheresis should occur within 2-3weeks of completing restaging evaluation
C Visit #1 should be scheduled within 2week of leukopheresis #1
D Visit #5 should be scheduled within 2 week of leukopheresis #2
E For clarity and consistency purposes, if visits #1 and/or #5 occur more than 2 weeks from leukopheresis, they will still be considered to occur on weeks 1 and/or 10 respectively
F patients will be seen on a monthly schedule after visit #13
G The mandatory Safety Follow-Up Visit (End of trial, EOT) should be conducted approximately 30-45 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first (End of trial, EOT).

AA Nivolumab is administered at a fixed dose of 480 mg every 4 weeks during the maintenance period until PD
BB First booster vaccine (vaccine #4) should be administered with the first cycle of maintenance immunotherapy (C5D1), in combination with single agent (maintenance) nivolumab. The subsequent second and third booster vaccines will be administered 4 weeks later, on C7D1 and C9D1, respectively with the corresponding dose of nivolumab.
CC The study stopping criteria incorporated to the protocol are applicable (as described in …..) ONLY PRIORr to D1C3.

NOTE: IN CASE THAT, DURING THE CONDUCTION OF THE TRIAL, A DISCREPANCY WAS NOTED BETWEEN THE PROTOCOL CONTENT AND THIS CALENDAR, THE INFORMATION OR REQUIREMENTS INCLUDED IN THE CALENDAR WILL BE FOLLOWED

6.1 TRIAL FLOW CHART: Second Course Phase (Retreatment Period)

All laboratory studies, visits and procedures included in these Flow chart have a +/- 7 day window. This rule applies in addition to any existing window included for specific laboratory studies, visits or procedures at the discretion of the investigators.

	Screening	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6	Visit #7	Visit #8,[A] +	End of Study Visit[B]
		Induction Immunotherapy				Maintenance Immunotherapy				
	Wk -4 to 0	Wk 1 C1 D1	Wk 4 C2D1	Wk 7 C3D1	Wk 10 C4D1	Wk 13 C5D1	Wk 17 C6D1	Wk 21 C7D1	Wk 25, + C8 +D1	
H+P[14]	X	X[20]	X	X	X	X	X	X	X	X
MD[15]/Mid-Level visit	X	X[20]	X	X	X	X	X	X	X	X
CTC[18] visit	X	X	X	X	X	X	X	X	X	X
Concurrent Medications	X	X ……..… X								X
AE evaluation	X	X ……..…… X								X
CBC, diff	X	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X									
CT chest/abd.[17]	X			X		X			X[17]	X
Brain MRI[16,19]	X[16]			X[16]					X[16]	X[16]
Nivolumab[AA]		X	X	X	X	X[AA]	X	X	X	
Ipilimumab		X	X	X	X					

14 Brief history and physical (H+P) to include vital signs (VS), weight (W), height (H) and performance status (PS) and AE evaluation on Mid-Level visits or MD visits.

15 Can also be performed by protocol assigned Mid-Level: Nurse Practitioner (NP) or Physician Assistant (PA)
16 Only required for patients with CNS symptoms suspicious of brain metastasis or for patients known to have untreated brain metastasis. Otherwise it is only required if clinically indicated per treating physician discretion
17 At the time of visits #8 and beyond, while only receiving maintenance nivolumab, patients will have restaging CT scans every 3 months
18 When the patient is seen by the MD, then only a clinical trials coordinator (CTC) visit will be required. For all other appointments, a Mid Level (Mid L) visit will be required
19 The type and site of any other imaging scan will only be performed when clinically indicated, at the discretion of the treating physician
20 This visit is not necessary if screening visit performed within 4 weeks of D1C1

A patients will be seen on a monthly schedule after visit #8
B The mandatory Safety Follow-Up Visit (End of trial, EOT) should be conducted approximately 30-45 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first (End of trial, EOT).

AA Nivolumab is administered at a fixed dose of 480 mg every 4 weeks until PD

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or BMS for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

Once a patient is enrolled in the study, he/she will be assigned a simple 3 digit number, with the first patient assigned to 001 and so on. A separate spreadsheet with password protection will be maintained that contains the patient study number along with personally identifiable information. Password protection will be maintained in order to keep patient information strictly confidential. Upon signing the informed consent form, the patient will be assigned a subject number by the investigator or his/her designee. Once assigned to a patient, a subject number will not be reused. If the patient fails to be started on treatment for any reason, the reason will be entered on the Eligibility Tab in OnCore, and his/her demographic information

will be entered on the Demography Tab in OnCore. All laboratory, radiologic, and pathologic data collected on trial participants will be assigned the unique treatment number and stored in the OnCore system database.

7.1.1.7 Assignment of Randomization Number

Not applicable

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. Oncore is the password protected, web-based electronic secure, database of record for all CRF entries and will be verified with source documentation. The review of medical records within the EMR will be done in a manner to assure that patient confidentiality is maintained.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

AEs will be collected from time of C1D1. The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with Ipi-Nivo or Nivo alone exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Patients will undergo a CT Thorax and Abdomen at baseline, then every 2 cycles or the frequency indicated by the Trial Flow Chart (see section 6.0). Radiographic assessments will be based on Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1, Appendix 11.3). Subjects with progressive disease by RECIST v1.1 but without rapid clinical deterioration may continue to be treated at the discretion of the investigator under the assumption that clinical benefit continues.

7.1.2.7 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)
Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

- Should be performed every 8 weeks or as indicated on study calendars (section 6.0 and 6.1)

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.2.8 Pharmacokinetic/Pharmacodynamic Evaluations

This study does not include Pharmacokinetic analysis. For Pharmacodynamic analysis see section 7.1.5

7.1.3 Other Procedures-Leukopheresis

Mononuclear cell collection will be conducted by the Moffitt Cancer Center apheresis team.

Patients presenting for apheresis must have been screened for soundness of health consistent with undergoing apheresis. Females of child-bearing potential must also have been tested for pregnancy within the same time frame, per requirements of the FDA and American Association of Blood Banks. Patients must also have been tested within the preceding 30 days for infectious disease markers including HIV, Hepatitis, HTLV I/II (Human T Lymphotropic Virus), Hepatitis B, Hepatitis C and RPR (Rapid Plasma Reagin). At presentation for leukopheresis, patients will have their vital signs taken. Based on criteria that are outlined in standard operating procedures, patients are cleared to begin apheresis, or if failing the criteria, will be examined by qualified medical personnel.

Patients will be connected to the apheresis instrument and associated disposables by bilateral venipuncture, generally in the median cephalic vein, using 18 gauge needles. Patients who do not have suitable veins to support apheresis will have to be assessed for placement of an indwelling catheter.

Following initiation of apheresis, approximately 1 – 2 blood volumes will be processed using the mononuclear cell collection protocol. At the conclusion of apheresis, it is anticipated that approximately 50 - 200 mL of apheresis product will be retained, which should ideally contain at least 10^{10} nucleated cells and less than 15 - 25 mL of RBC volume.

7.1.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 (Assessing and Recording AEs).

Subjects who a) attain a CR or b) complete 12 months of treatment with Ipi-Nivo and Nivo may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5.
After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.5 Tumor Tissue Collection and Correlative Studies Blood Sampling

We will evaluate p53-specific IR and MDSC levels as well as other immune cells in patients during treatment. These parameters will be correlated with clinical outcomes. Peripheral blood will be collected prior to the treatment and at different time points (see calendar section 6.0) during and after the treatment. Mononuclear cells will be isolated and kept frozen in aliquots in liquid nitrogen. All samples from one patient will be tested simultaneously to avoid the impact of inter-experimental variation.

7.1.5.1 Evaluation of p53-specific immune response against TAAs.

7.1.5.1.1 Analysis of IFN-γ production by PBMC.

The number of IFN-γ producing cells will be evaluated using ELISPOT assays as described earlier39. Briefly, 2x105 mononuclear cells obtained from the peripheral blood of patients will be plated in quadruplicates in 96-well multiscreen HA filtration plates (Millipore, Bedford, MA) pre-coated with mouse anti-human IFN monoclonal antibody (MAB285, R&D System, Minneapolis, MN) and incubated for 36 hr at 37oC with ALVAC-p53, or ALVAC-c and 2ng/ml IL-2. Total volume is 200 l. After incubation, the wells will be washed and then incubated overnight at 4oC with a biotinylated goat anti-human IFN-γ antibody (BAF285, R&D System), followed by incubation with avidin-alkaline phosphatase (Sigma). The wells will then be washed and spots will be visualized with BCIP/NBT substrate (Sigma). The plates will be air-dried and the colored spots counted using C.T.L. ELISPOT reader. The number of spots will be calculated per 106 cells. Untreated PBMC will represent a negative control and PBMC stimulated with 10 g/ml ConA – positive control.

7.1.5.1.2 Analysis of cell proliferation and IL-2 production.

PBMC (4x105 per well in round-bottom 96-well plates) will be cultured in triplicate in X-VIVO 15 medium supplemented with antibiotics and 50 M 2-mercaptoethanol. ALVAC-p53 or ALVAC-c will be used as described above. Non-stimulated cells will be used as a negative control. For evaluation of cell proliferation, 1 Ci/well of [3H]thymidine will be added on day 4 and cells will be harvested on day 5. Thymidine incorporation will be measured using a scintillation counter.

7.1.5.2 Determination of the relationship between MDSC numbers and anti-p53 T cell responses.

Blood (7 sodium heparin vacutainer tubes, 10 ml each and 1 red top tube) will be obtained from each patient on several different occasions. The PBMC will be analyzed by flow cytometry for the presence of MDSCs, and the absolute numbers as well as ratios will be determined. PBMC from each sample will be stained immediately to evaluate the presence of MDSC.

The following criteria will be used to evaluate MDSC by flow cytometry:

1.Lin (CD3, CD14, CD19, CD56) negative, HLA-DR-, CD33+;
2.MDSC: CD11b+CD14-CD33+;
3.PMN-MDSC: CD11b+CD14-CD33+CD15+;
4. M-MDSC: CD11b+CD14-CD33+CD15-;
5. M-MDSC: CD14+HLA-DR-/lo;

7.1.5.3 Analysis of other Immune Cells

Correlative analysis will be performed on the peripheral blood mononuclear cells (PBMC) of all the patients enrolled in the study. This will include flow cytometry based assessment of presence of suppressive cell types such as myeloid-derived suppressor cells (MDSC) and Tregs. In addition, we will determine expression of activation and resistance markers in lymphocytic lineages, including T cells, by flow cytometry and gene expression studies.

7.1.5.4 Immunohistochemical Stains

Archival or fresh paraffin-embedded tissue blocks containing formalin-fixed tumor or needle aspirate slides will be obtained for evaluation of the expression of p53 and PD-L1 using IHC methods with commercial antibodies. Paraffin blocks may be processed according to standard institutional protocols. If blocks are unavailable, 15 unstained slides are acceptable alternatives. This IHC scores will be correlated with the clinical efficacy endpoints and the blood surrogate biomarkers. Approximately half of the patients are expected to contribute with an archival tumor biopsy.

Sections of formalin-fixed, paraffin-embedded tissue from the SCLC will be cut and stained with the respective antibodies against PD-L1 (TBD) and p53 (DO7, DAKOcytomation, 1:50). In brief, the slides will be immersed in citrate buffer solution for antigen retrieval and boiled in microwave for 10 min and washed in buffer solution (TBS). They will be incubated with primary antibody for 1 hr at room temperature and then washed in TBS. After 1 hr of incubation in the secondary antibody, the sections will be incubated with streptavidin-biotin-complex (DAKOcytomation). Appropriate positive and negative controls will be used.

Results of IHC staining will be evaluated in the following 2 ways: (1) For estimation of positive reaction, only the strongly stained nuclei are counted as a percentage of all tumor nuclei. Less than 5% are estimated as negative. Samples with greater than 5% of cells exhibiting strong nuclear staining would be considered positive. (2) protein staining is scored, taking into account percentage of positive cells (from 1 to 100%) and intensity of staining (from 1 to 3), as compared with the protein intensity level 3 of the background lymphocytes. Total score is established by multiplying the percentage by intensity, giving scores of 0 to 300. Final scores of 1, 2, and 3 are given for total scores of 10-50, 50-100, and 100-300, respectively.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening

Screening evaluation requirements are outlined in Section 6.0 - Trial Flow Chart.

7.1.6.1.1 Screening Period

Defined in Section 6.0 - Trial Flow Chart

7.1.6.2 Treatment Period

Defined in Section 6.0 - Trial Flow Chart

7.1.6.3 Post-Treatment Visits

Defined in Section 6.0 - Trial Flow Chart

7.1.6.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30-45 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first (End of trial, EOT). All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with Ipi-Nivo or Nivo (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.6.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with Ipi-Nivo or Nivo as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with Ipi-Nivo or Nivo according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.6.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.6.5 Second Course Phase (Retreatment Period)

Subjects who stop Ipi-Nivo or Nivo with SD or better may be eligible for up to one year of additional Ipi-Nivo or Nivo therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with Ipi-Nivo or Nivo after attaining an investigator-determined confirmed CR according to RECIST 1.1

    OR
  - Had SD, PR or CR and stopped Ipi-Nivo or Nivo treatment after 6-12 months of study therapy for reasons other than disease progression or intolerability

AND

- Did not receive any anti-cancer treatment since the last dose of Ipi-Nivo or Nivo
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and interval as per the original treatment schedule in section 5.2.2. Treatment will be administered for up to one additional year. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the investigational product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

BMS product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by BMS for human use.

Adverse events may occur during the course of the use of BMS product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1 and section 11.7 BMS guidelines for Adverse Event Reporting.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to BMS

For purposes of this trial, an overdose of Ipi-Nivo or Nivo will be defined as any dose of 2400 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of IPI-NIVO OR NIVO. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a BMS product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of BMS's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to BMS

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to BMS

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death,

miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to BMS (see section 11.7)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to BMS

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of BMS's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to BMS product, must be reported within 24 hours to the Sponsor and within 2 working days to BMS.

Non-serious Events of Clinical Interest will be forwarded to BMS and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to BMS product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to BMS.

SAE reports and any other relevant safety information are to be forwarded to the BMS

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the BMS Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to BMS at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to BMS (see section 11.7)
Events of clinical interest for this trial include:

1. an overdose of BMS product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 Safety Stopping Criteria

The purpose of safety stopping criteria is to control the number of subjects put at risk, in the event that early experience uncovers important safety problems.

The event I have chosen to utilize as our safety target or endpoint is: "*grade 4 adverse events that are at least possibly related to the investigational treatment*".

Based on our SCLC historical control population treated with the ipilimumab-nivolumab combination[86], grade 3-4 treatment related adverse events occurred in 30% of patients. Given that an additional investigational agent/treatment (vaccine) is being added, we are willing to accept similar to slightly higher frequency of adverse events.

Thus, the protocol we will abide by the following study stopping criteria:

7.3.1 We will first accrue 10 patients to the study.

a. If at the end of the first 3 vaccine administrations, the event occurs in 4 or less patients, we will accept the safety profile of our combination to be comparable to that of our SCLC historical control[86] and the regimen will be consider safe for further treatment and the study will open to accrual unrestricted, until study completion
b. If at the end of the first 3 vaccines administrations, the event occurs in 5 or 6 patients, we will accrue an additional 10 patients before the study opens to accrual unrestricted, until study completion.
c. If at the end of the first 3 vaccine administrations, the event occurs in 7 or more patients, we will consider our treatment combination unsafe and the study will be closed.

7.3.2 In case that an additional 10 patients need to be accrued (see above item 1b)

d. If at the end of the first 3 vaccine administrations, the event occurs in 4 or less patients, we will accept the safety profile of our combination to be comparable to that of our SCLC historical control[86] and the regimen will be consider safe for further treatment and the study will open to accrual unrestricted, until study completion
e. If at the end of the first 3 vaccine administrations, the event occurs in more than 4 patients, we will consider our treatment combination unsafe and the study will be closed.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of BMS product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the BMS product to be discontinued?	
Relationship to test drug	Did the BMS product cause the adverse event? The determination of the likelihood that the BMS product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the BMS product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the BMS product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the BMS product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the BMS product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to BMS product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the BMS product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the BMS product; or (3) the trial is a single-dose drug trial); or (4) BMS product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the BMS product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) BMS product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE BMS PRODUCT, OR IF REEXPOSURE TO THE BMS PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the BMS product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a BMS product relationship).**
Yes, there is a reasonable possibility of BMS product relationship.		There is evidence of exposure to the BMS product. The temporal sequence of the AE onset relative to the administration of the BMS product is reasonable. The AE is more likely explained by the BMS product than by another cause.
No, there is not a reasonable possibility BMS product relationship		Subject did not receive the BMS product OR temporal sequence of the AE onset relative to administration of the BMS product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

8.1.1 Study Design

This is a single institution, phase II study. The primary endpoint is disease control rate (DCR). Secondary endpoints include response rate, progression-free survival (PFS), overall survival (OS). Biomarkers correlative studies are also included.

8.2 Statistical Analysis Plan

8.2.1 Sample size

A sample size of 39 achieves 91% power to detect a difference of 0.20 using a one-sided binomial test. The target significance level is 0.100. The actual significance level achieved by this test is also 0.100. These results assume that the population proportion under the null hypothesis is 0.50.

8.2.2 Analysis of Primary and Secondary Endpoints

The disease control (DCR=CR+PR+SD) rates, overall response rate (ORR=CR+PR) will be summarized using both point estimates and exact confidence intervals based on the binomial distribution by group. The PFS, defined as time from enrollment (eligible date) to date of progression/death, whichever happens first, or censor at last clinical follow-up date. The OS, defined as the time from study enrollment (eligible date) to death from any cause. Both PFS and OS will be summarized utilizing the K-M method.

8.2.3 Safety Analysis - Toxicity

Toxicity from this trial will be collected on all study drug treated patients. Simple descriptive statistics will be utilized to display the data on toxicity seen from both groups. Toxicities will be assessed using NCI CTCAE v.4.1.

8.2.4 Laboratory Correlative Studies

Results from the different correlative variables will be reported descriptively. Cox proportional hazards regression models will be employed to explore the association of various such variables with DCR, PFS and OS. The Fisher exact/Chi-square test and logistic regression will be considered to study the association between various disease or patient characteristics and FFPE archival tissue studies (protein expressions by IHC).

In some cases, due to the small sample size, these analyses may have low sensitivity for the predictive impact of the biomarkers, and will be exploratory by necessity.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Products

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

9.1.1 Clinical Supplies provided by BMS as summarized in Table 7.

Table 7 Product Descriptions

Product Description/Class and Dosage Form	IP/Non-IMP	Potency	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	IP	100 mg (10 mg/mL)	10 mL/vial (5 or 10 vials/carton)	Store at 2-8°C; protect from light and freezing
Ipilimumab Solution for Injection	IP	200 mg (5 mg/mL)	40 mL/vial (4 vials/carton)	Store at 2-8°C; protect from light and freezing

9.1.2 Clinical Supplies provided by Moffitt Cell Therapy Facility

Adp53-DC (see Appendix 11.4)

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as outlined in the investigator's brochure. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact the principal investigator and BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert (in this case in accordance with Moffitt Cell Therapy Laboratory). Please refer to Section 10.2.2 for guidance on IP records and documentation. Infusion-related supplies (eg, IV bags, in-line

filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab. The infusion duration of nivolumab is 30 minutes and for ipilimumab is 90 minutes.

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt/dispensing of trial medication must be recorded by authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the 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.

10.0 DATA SA DATA SAFETY MONITORING PLAN

10.1 Risk to Subjects

10.1.1 Human subject involvement and characteristics

Human subjects who have the diagnosis of advanced NSCLC are eligible to participate in the clinical trial described in this proposal. The risk to subjects will be outlined clearly and in detail in the informed consent. Women who are pregnant are not eligible.

10.2 Recruitment and Informed Consent

Patients who present to the Thoracic Oncology Program at the Moffitt Cancer Center or the OSU Thoracic Clinics who have advanced NSCLC are offered participation in the clinical trial described in this proposal. The trial is explained in detail to the patients by one of the investigators on the trial. The patients are given the opportunity to read the informed consent document and are given a chance to ask questions. If they wish to participate the patient will then sign the informed consent document in the presence of a witness. The study team member who participates in the informed consent process also documents, in a clinic note, the nature of the consent process that occurred.

10.3 Protection Against Risk

To protect participants from excess risk, the above-mentioned study procedures and dose-escalation scheme were instituted. Additional protection is provided through the data safety and monitoring plan described below. The complete care of each patient, including the clinical management of all toxicities, is provided to the patient by physicians at the Moffitt Cancer Center. The clinical data are kept in the patient's individual electronic hospital record. Research study documentation charts are kept in a locked secure room with limited access and through Oncore (a Web-based, password-protected database), with privacy protected to the full extent of the law. Authorized research investigators, the Department of Health and Human Services, and the Institutional Review Board may inspect the records. Final protocol and ICF approvals will be obtained from the IRB.

Additional protection is provided in the data safety and monitoring plan described below.

10.4 Importance of the Knowledge to be Gained

The development of a well-tolerated and effective regimen in a disease could potentially at worst add to the armamentarium of available regimens and at best change standard of care. Specific strategies to improve the care of patients relapsing following chemotherapy for lung cancer are direly needed.

10.5 Data Safety and Monitoring Plan

The Data Safety & Monitoring Plan (DSMP) will ensure that this trial is well designed, responsibly managed, appropriately reported, and that it protects the rights and welfare of patients. The following internal and external review and monitoring processes provide oversight and active monitoring of this trial:

- The Principal Investigators (PI)
- The Clinical Trials Office (CTO)
- The Scientific Review Committee (SRC)
- The Protocol Monitoring Committee (PMC);
- The Research Compliance Division (RCD) of the Cancer Center's Compliance Office;
- Institutional Review Board (IRB).

The protocol includes a section that specifies the following with respect to Adverse Event reporting: what constitutes an adverse event (versus what is a serious adverse event), the entities to which adverse events should be reported, the timing of this reporting, and the person or persons responsible for reporting. This includes prompt (within one day of knowledge of the event) reporting to the IRB for unanticipated risks to subjects and reporting in writing within five working days to the IRB and sponsor.

10.6 Scientific Review Committee (SRC)

The two Therapeutic boards of the SRC meet every other week one on the first Wednesday and the second one meets on the third Thursday of every month.

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific

merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at each Cancer Center. The SRC is responsible for evaluating the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process.

10.7 PI Responsibility

The PI of each study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol. All protocols include a DSMP and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events. The plan must include data and safety-monitoring procedures for subjects enrolled who may be receiving a part of their protocol-required treatment at community sites.

In all cases, the PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMB and/or to the PMC and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

10.8 The Protocol Monitoring Committee (PMC)

The PMC meets once a month. The PMC reviews and evaluates safety and/or efficacy data for all physician authored clinical intervention trials. The PMC ensures the safety of patients and the validity and integrity of data. PMC reviews SAEs, deviations, Interim analysis, interim and final reports from the external Data Monitoring Committee (DMC) as well as audits both internally and externally. The PMC can make the following determinations, Accepted, Acceptable with Corrective Action and Tabled.

Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide an interim analysis report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

10.9 Suspension/Termination

The PMC and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies,

including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

10.10 Monitoring of the Study and Regulatory Compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. Oncore is the database of record for all CRF entries and will be verified with source documentation. The review of medical records within PowerChart will be done in a manner to assure that patient confidentiality is maintained.

10.11 Internal Monitoring Plan

Data will be captured in Oncore, Moffitt's Clinical Trials Database.
Regulatory documents and case report forms will be reviewed routinely by the MCC Clinical Research Monitoring Core for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to MCC Monitoring Policies.

10.12 Protocol Modifications

No modifications will be made to the protocol without the agreement of the investigators. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Scientific Review Committee and Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the case report form and the source documentation.

10.13 The Institutional Review Board (IRB)

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the Food and Drug Administration. A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

10.14 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers. The US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection.

10.15 Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs,

consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

10.16 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

11.4 Pharmaceutical Information for Ad.p53-DC Vaccine

A. Generation of Ad.p53 DC vaccine

Mononuclear cells for the production of dendritic cells (DC) will be obtained through a single apheresis procedure and stored in liquid nitrogen at the Moffitt Cancer Center . After collection through apheresis, the product will be enriched for mononuclear cells via density centrifugation using Ficoll. The enriched product will be cryopreserved in 3 – 4 fractions and stored in cryoprotectant in validated LN2 freezers. Approximately one week prior to each scheduled vaccination, one fraction of cells will be thawed by the Moffitt Cell Therapy Facility staff and placed in CellGenix DC Medium in tissue culture flasks at a concentration of 1.3 – 1.7x10^6 cells/cm^2. After culturing for 1.5 – 2 hours in a 37 C, 5%CO2 incubator, non-adherent cells will be removed. Fresh DC Medium supplemented with 100 ng/ml GM-CSF and 50 ng/ml IL-4 will be added. Cells will be cultured for approximately 5 days in a 37 C, 5%CO2 incubator. At the completion of incubation, non-adherent and loosely adherent cells will be collected and transduced with Ad.p53 for 2 – 3 hours at a concentration of approximately 10x10^6 cells/ml. At the completion of the transduction, cells will be diluted 10 fold with medium supplemented with 5 ng/ml GM-CSF and 5 ng/ml IL-4. Transduced cells will be cultured for approximately 40 hours in a 37 C, 5%CO2 incubator, then harvested, washed and analyzed prior to administration. Vaccines will not be released for patient use until release criteria are met.

Release criteria for vaccine administration include:

Test	Criteria
Mycoplasma	Negative
Gram Stain	No Organisms Seen
Endotoxin	< 5 EU/kg
Phenotype	> 10% DC expressing p53
Dose	1 – 5x10^6 viable p53+ DC

The vaccine cell suspension will be injected intra-dermally (or subcutaneously) into 4 separate sites to include proximal upper and lower extremities (in the regions of the axillary and inguinal nodal basins. The patients will be monitored in the Clinical Research Unit at the H. Lee Moffitt Cancer Center for acute toxicity for 1 hour after their injections.

11.5 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.

NOTE: In cases of an-expected or unforeseen discrepancy between the guidelines or instructions in Table 3 (below) and Section 11.6 Management Algorithms, the latter guidelines/instructions should prevail for the purposes of patient management on protocol.

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.

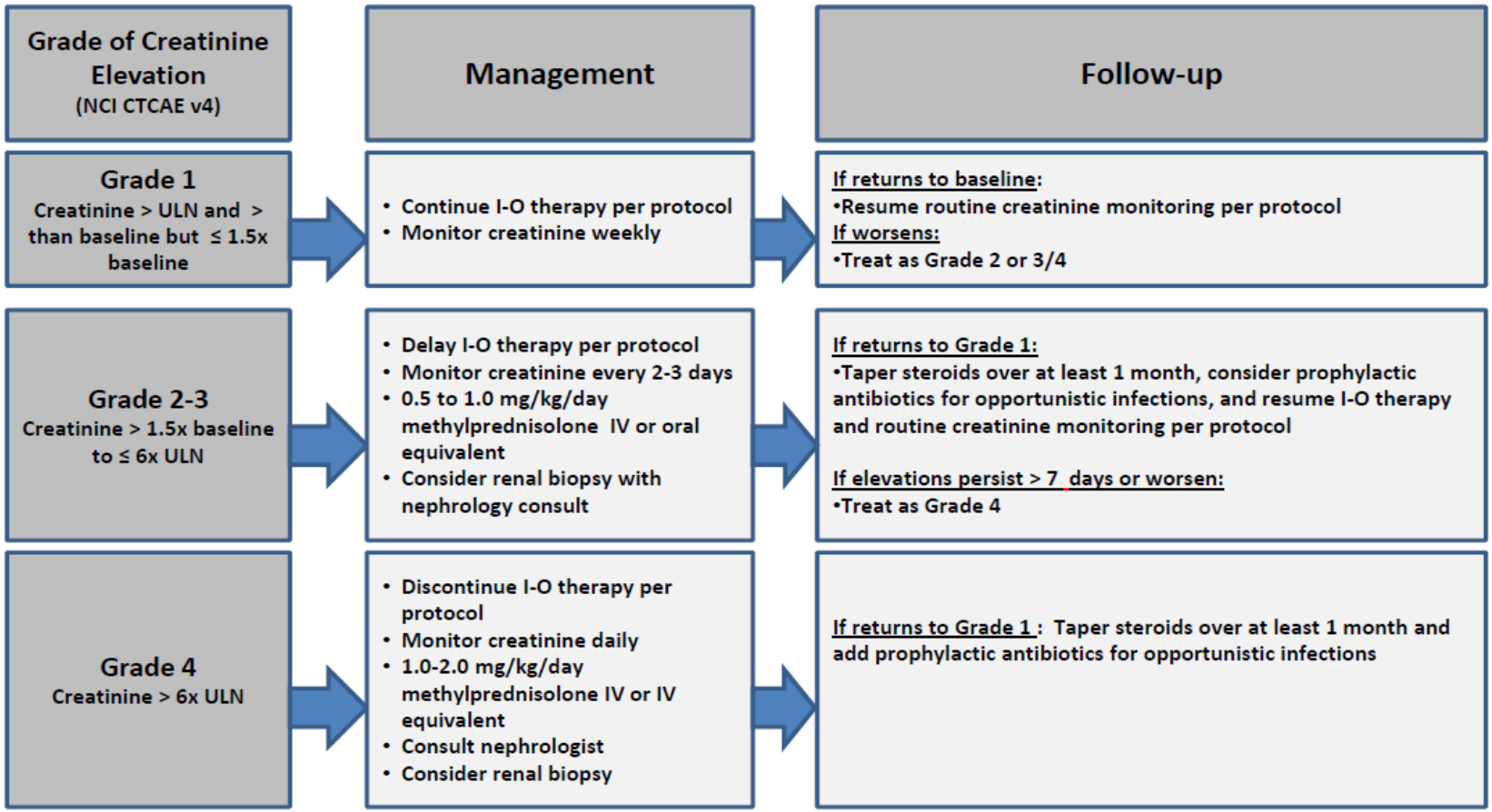
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Renal Adverse Event Management Algorithm

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

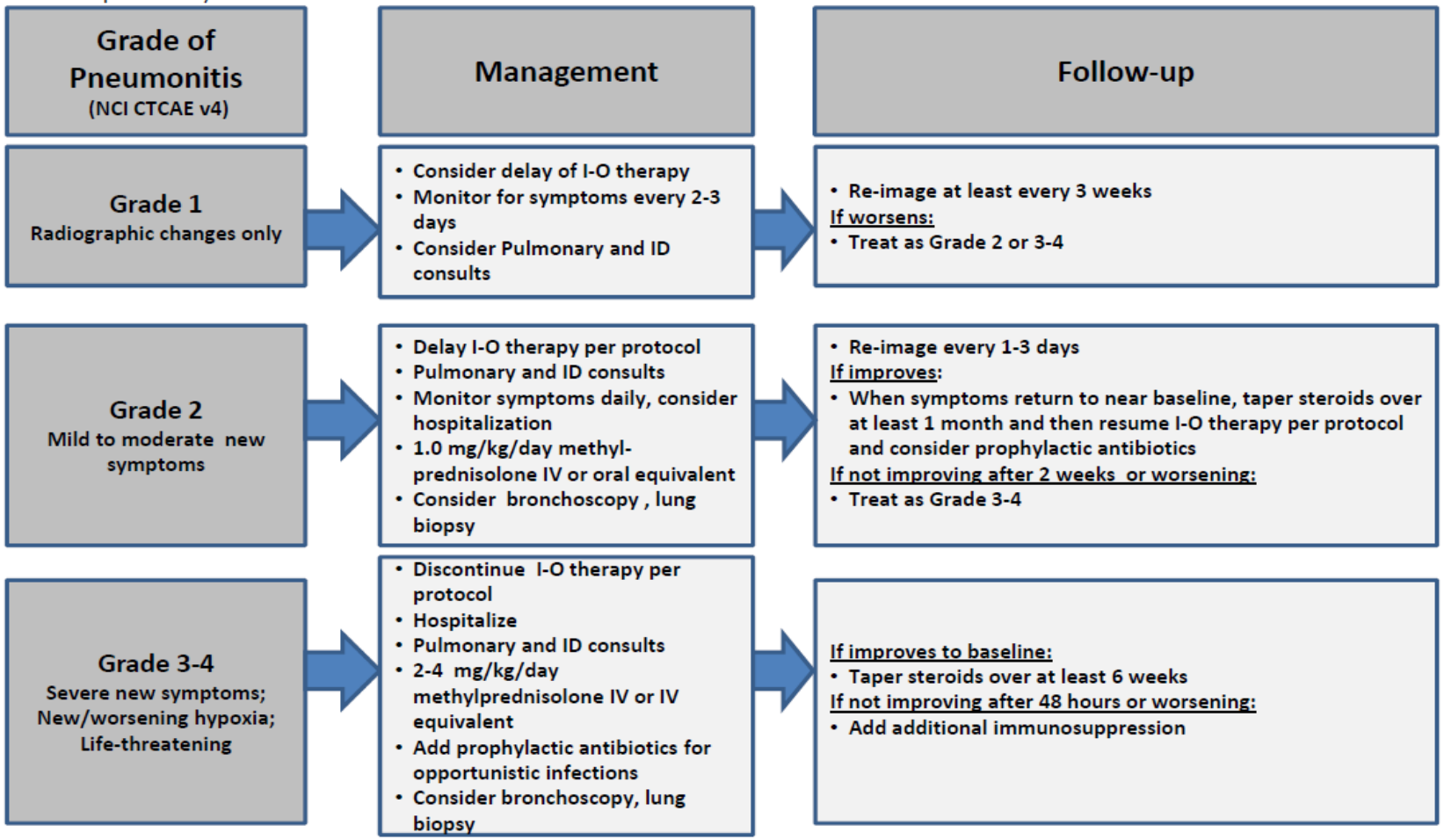


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

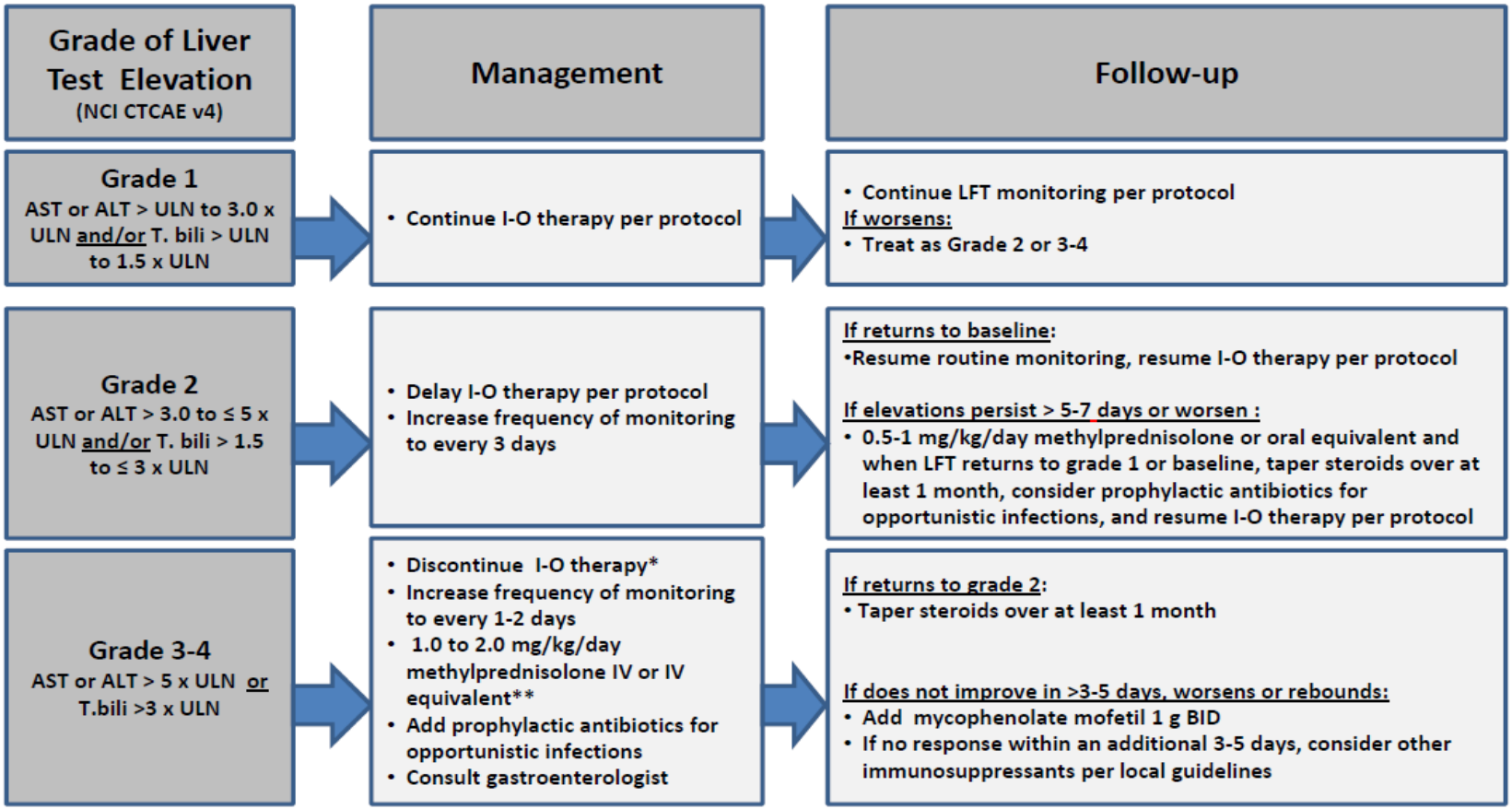


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

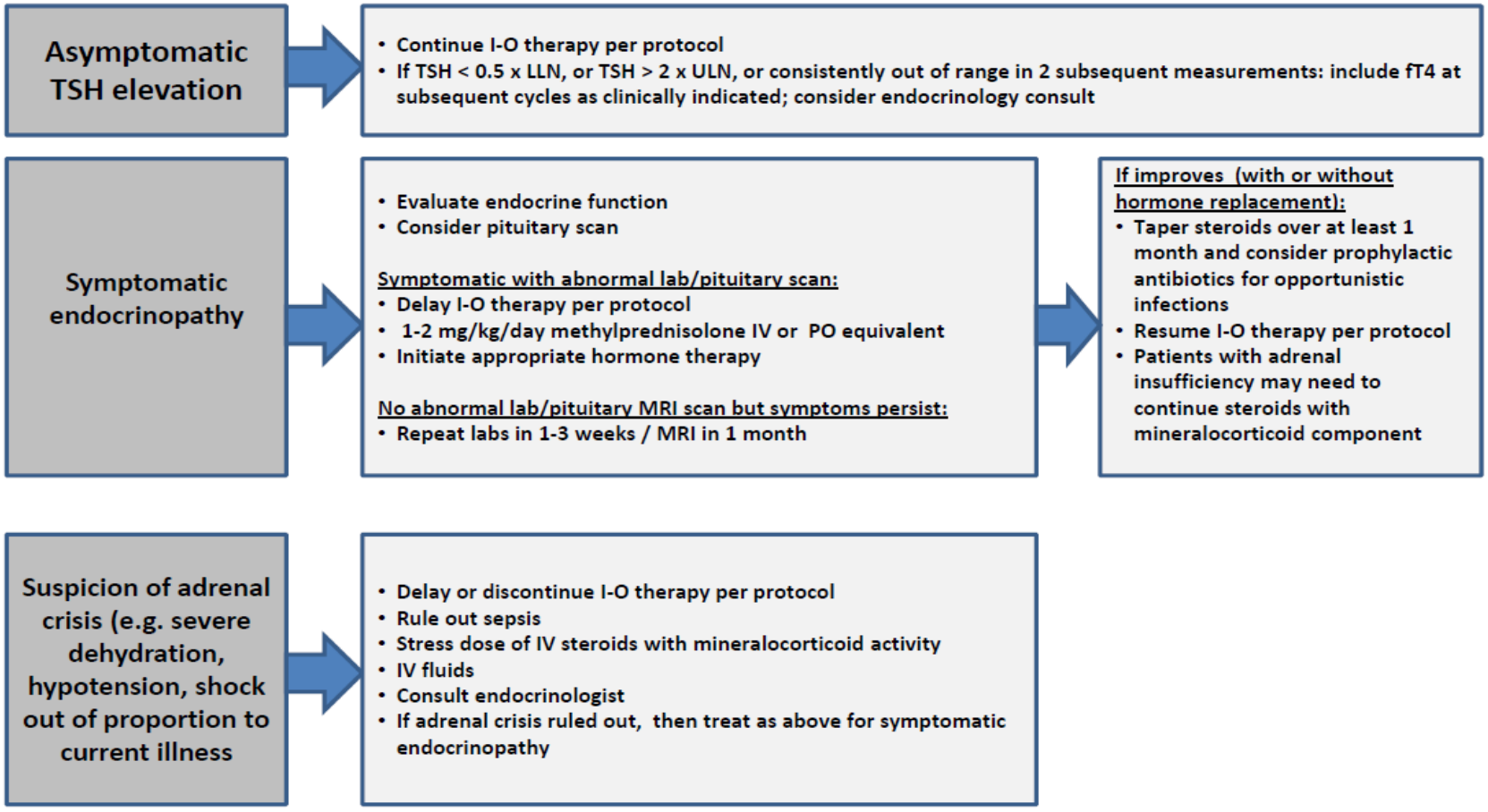
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Updated 05-Jul-2016

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.

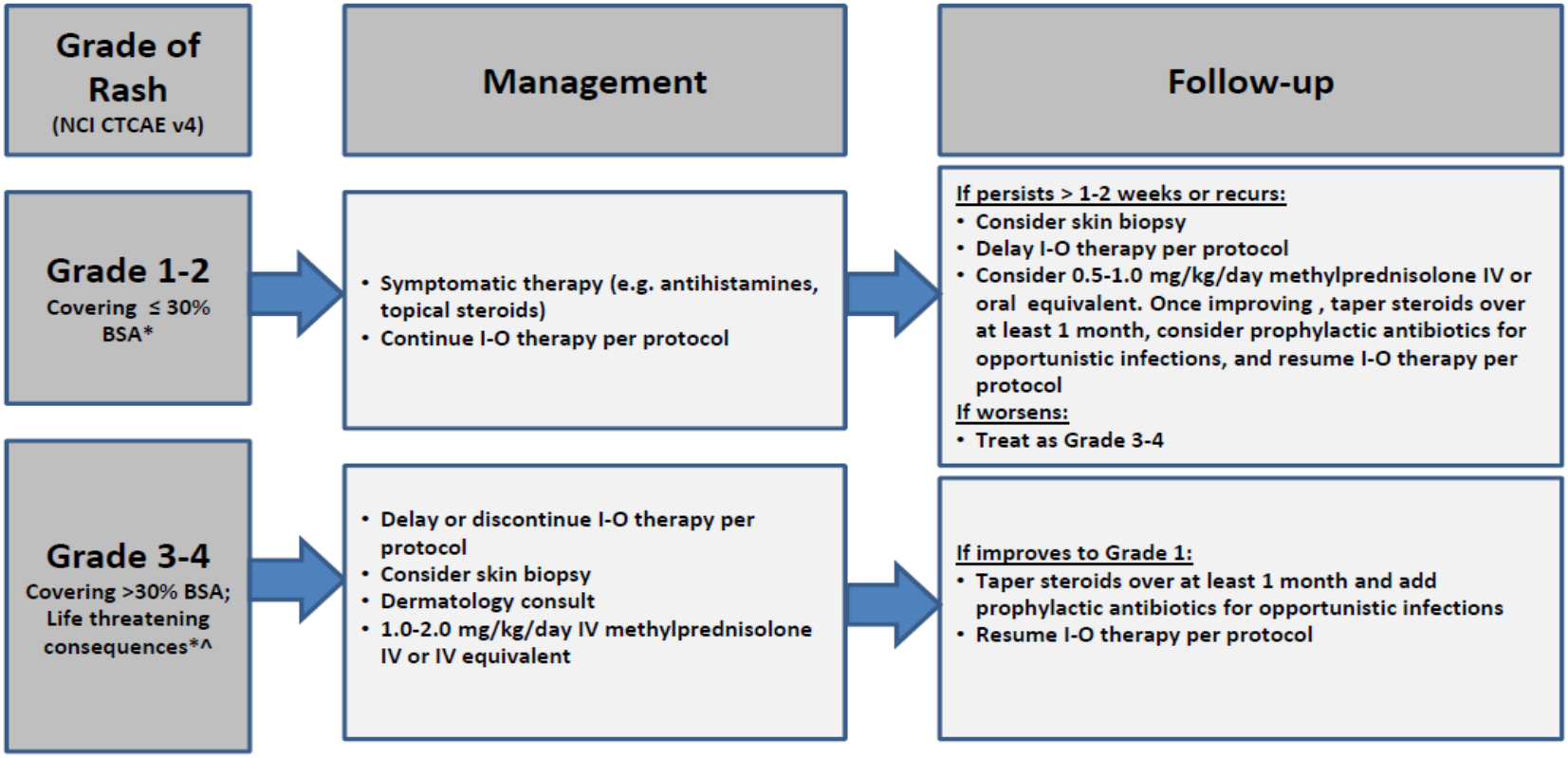


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

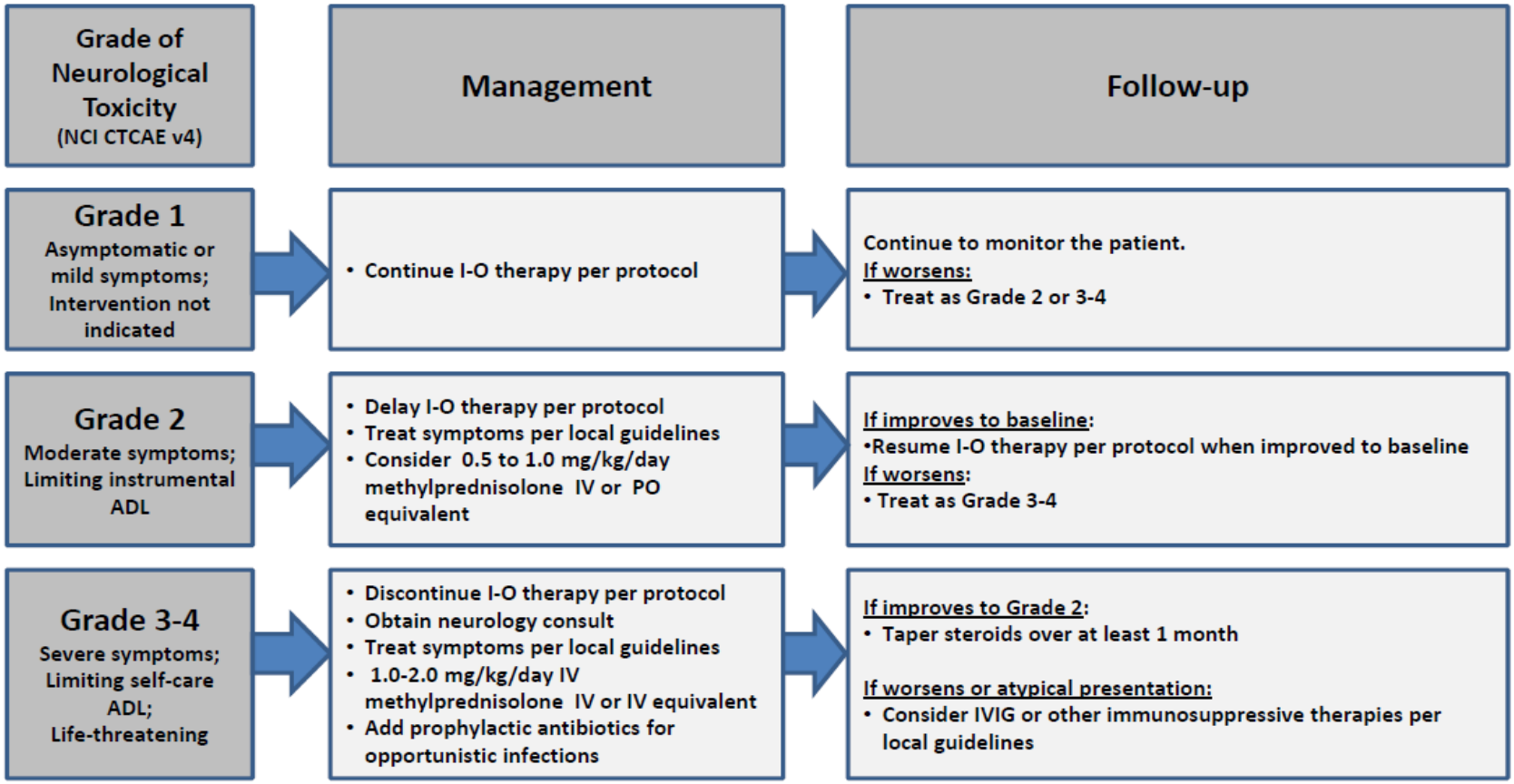


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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



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

11.6 BMS Guidelines for Adverse Event Reporting

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 90 days of discontinuation of dosing must be reported to BMS Worldwide Safety.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
-
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
    - Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the

informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, 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 90 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

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 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 the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study including periodic reconciliation.

For studies conducted under an Investigator IND in the US include the following timelines or text:

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.

DEFINITIONS

The protocol must include a definition for Serious Adverse Events (SAE)

SERIOUS ADVERSE EVENTS

A **S*erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

NOTE: (PI- determines if this information should be included. This is provided as supplemental information that is included in BMS-sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing,

economic inadequacy, caregiver respite, family circumstances, administrative reason).

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) 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 AST/ALT 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.

ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

NONSERIOUS ADVERSE EVENT

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

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

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

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.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

NOTE: In cases of an anexpected or unforeseen discrepancy regarding procedures for the reporting of adverse events between the content of the protocol (section 7.2) and the BMS guidelines outlined in section 11.7, it is the latter guidelines/instructions that should prevail for the purposes of patient management on protocol.

12.0 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians 2016;66:7-30.
2. Johnson DH. Management of small cell lung cancer: current state of the art. Chest 1999;116:525S-30S.
3. Johnson BE. Management of small cell lung cancer. Clin Chest Med 2002;23:225-39.
4. Simon GR, Wagner H. Small cell lung cancer. Chest 2003;123:259S-71S.
5. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-67.
6. Ardizzoni A. Topotecan in the treatment of recurrent small cell lung cancer: an update. Oncologist 2004;9 Suppl 6:4-13.
7. Davies AM, Evans WK, Mackay JA, Shepherd FA. Treatment of recurrent small cell lung cancer. Hematol Oncol Clin North Am 2004;18:387-416.
8. Mattson K, Niiranen A, Ruotsalainen T, et al. Interferon maintenance therapy for small cell lung cancer: improvement in long-term survival. J Interferon Cytokine Res 1997;17:103-5.
9. Prior C, Oroszy S, Oberaigner W, et al. Adjunctive interferon-alpha-2c in stage IIIB/IV small-cell lung cancer: a phase III trial. Eur Respir J 1997;10:392-6.
10. Zarogoulidis K, Ziogas E, Papagiannis A, et al. Interferon alpha-2a and combined chemotherapy as first line treatment in SCLC patients: a randomized trial. Lung Cancer 1996;15:197-205.
11. Clamon G, Herndon J, Perry MC, et al. Interleukin-2 activity in patients with extensive small-cell lung cancer: a phase II trial of Cancer and Leukemia Group B. J Natl Cancer Inst 1993;85:316-20.
12. Kelley MJ, Linnoila RI, Avis IL, et al. Antitumor activity of a monoclonal antibody directed against gastrin-releasing peptide in patients with small cell lung cancer. Chest 1997;112:256-61.
13. Chikamatsu K, Nakano K, Storkus WJ, et al. Generation of anti-p53 cytotoxic T lymphocytes from human peripheral blood using autologous dendritic cells. Clin Cancer Res 1999;5:1281-8.
14. Liu DP, Song H, Xu Y. A common gain of function of p53 cancer mutants in inducing genetic instability. Oncogene 2009.
15. van Oijen MG, Slootweg PJ. Gain-of-function mutations in the tumor suppressor gene p53. Clin Cancer Res 2000;6:2138-45.
16. Vierboom MP, Nijman HW, Offringa R, et al. Tumor eradication by wild-type p53-specific cytotoxic T lymphocytes. The Journal of experimental medicine 1997;186:695-704.
17. Mayordomo JI, Loftus DJ, Sakamoto H, et al. Therapy of murine tumors with p53 wild-type and mutant sequence peptide-based vaccines. J Exp Med 1996;183:1357-65.
18. Zwaveling S, Vierboom MP, Ferreira Mota SC, et al. Antitumor efficacy of wild-type p53-specific CD4(+) T-helper cells. Cancer research 2002;62:6187-93.
19. Parajuli P, Pisarev V, Sublet J, et al. Immunization with wild-type p53 gene sequences coadministered with Flt3 ligand induces an antigen-specific type 1 T-cell response. Cancer research 2001;61:8227-34.

20. Eura M, Chikamatsu K, Katsura F, et al. A wild-type sequence p53 peptide presented by HLA-A24 induces cytotoxic T lymphocytes that recognize squamous cell carcinomas of the head and neck. Clin Cancer Res 2000;6:979-86.
21. Theobald M, Ruppert T, Kuckelkorn U, et al. The sequence alteration associated with a mutational hotspot in p53 protects cells from lysis by cytotoxic T lymphocytes specific for a flanking peptide epitope. J Exp Med 1998;188:1017-28.
22. Vierboom MP, Gabrilovich DI, Offringa R, Kast WM, Melief CJ. p53: a target for T cell mediated immunotherapy. In: Kast WM, ed. Peptide-based Cancer Vaccines. Landes Bioscience 2000:40-55.
23. Brossart P, Goldrath AW, Butz EA, Martin S, Bevan MJ. Virus-mediated delivery of antigenic epitopes into dendritic cells as a means to induce CTL. J Immunol 1997;158:3270-6.
24. Wan Y, Bramson J, Carter R, Graham F, Gauldie J. Dendritic cells transduced with an adenoviral vector encoding a model tumor-associated antigen for tumor vaccination. Hum Gene Ther 1997;8:1355-63.
25. Specht JM, Wang G, Do MT, et al. Dendritic cells retrovirally transduced with a model antigen gene are therapeutically effective against established pulmonary metastases. J Exp Med 1997;186:1213-21.
26. Thomson SA, Khanna R, Gardner J, et al. Minimal epitopes expressed in a recombinant polyepitope protein are processed and presented to CD8+ cytotoxic T cells: implications for vaccine design. Proc Natl Acad Sci USA 1995;92:5845-9.
27. Becker TC, Noel RJ, Coats WS, et al. Use of Recombinant Adenovirus for Metabolic Engineering of Mammalian Cells. Meth Cell Biol 1994;43:161-76.
28. Roth JA, Cristiano RJ. Gene therapy for cancer: what have we done and where are we going? J Natl Cancer Inst 1997;89:21-39.
29. Brossart P, Goldrath AW, Butz EA, Martin S, Bevan MJ. Virus-mediated delivery of antigenic epitopes into dendritic cells as a means to induce CTL. J Immunol 1997;158:3270-6.
30. Dietz A, B., , Vuk-Pavlovic S. High efficiency adenovirus-mediated gene transfer to human dendritic cells. Blood 1998;91:392-8.
31. Wan Y, Bramson J, Carter R, Graham F, Gauldie J. Dendritic cells transduced with an adenoviral vector encoding a model tumor-associated antigen for tumor vaccination. Human Gene Therapy 1997;8:1355-63.
32. Antonia SJ, Mirza N, Fricke I, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 2006;12:878-87.
33. Chiappori AA, Soliman H, Janssen WE, Antonia SJ, Gabrilovich DI. INGN-225: a dendritic cell-based p53 vaccine (Ad.p53-DC) in small cell lung cancer: observed association between immune response and enhanced chemotherapy effect. Expert opinion on biological therapy 2010;10:983-91.
34. Nikitina EY, Chada S, Muro-Cacho C, et al. An effective immunization and cancer treatment with activated dendritic cells transduced with full-length wild-type p53. Gene therapy 2002;9:345-52.

35. Ishida T, Chada S, Stipanov M, et al. Dendritic cells transduced with wild-type p53 gene elicit potent anti-tumour immune responses. Clinical and experimental immunology 1999;117:244-51.
36. Nikitina EY, Clark JI, Van Beynen J, et al. Dendritic cells transduced with full-length wild-type p53 generate antitumor cytotoxic T lymphocytes from peripheral blood of cancer patients. Clinical cancer research : an official journal of the American Association for Cancer Research 2001;7:127-35.
37. D'Amico D, Carbone D, Mitsudomi T, et al. High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumors. Oncogene 1992;7:339-46.
38. Bodner SM, Minna JD, Jensen SM, et al. Expression of mutant p53 proteins in lung cancer correlates with the class of p53 gene mutation. Oncogene 1992;7:743-9.
39. Pisarev V, Yu B, Salup R, Sherman S, Altieri DC, Gabrilovich DI. Full-Length Dominant-Negative Survivin for Cancer Immunotherapy. Clin Cancer Res 2003;15:6523-33.
40. Kusmartsev S, Gabrilovich DI. Immature myeloid cells and cancer-associated immune suppression. Cancer Immunol Immunoth 2002;51:293-8.
41. Gabrilovich D. The mechanisms and functional significance of tumour-induced dendritic-cell defects. Nat Rev Immunol 2004;4:941-52.
42. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. Annu Rev Immunol 2007;25:267-96.
43. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8:467-77.
44. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. J Clin Invest 2007;117:1147-54.
45. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009;9:162-74.
46. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 2012;12:253-68.
47. Peranzoni E, Zilio S, Marigo I, et al. Myeloid-derived suppressor cell heterogeneity and subset definition. Curr Opin Immunol 2010.
48. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol 2009;182:4499-506.
49. Filipazzi P, Valenti R, Huber V, et al. Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. J Clin Oncol 2007;25:2546-53.
50. Poschke I, Mougiakakos D, Hansson J, Masucci GV, Kiessling R. Immature immunosuppressive CD14+HLA-DR-/low cells in melanoma patients are Stat3hi and overexpress CD80, CD83, and DC-sign. Cancer Res 2010;70:4335-45.
51. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother 2009;58:49-59.
52. Montero AJ, Diaz-Montero CM, Deutsch YE, et al. Phase 2 study of neoadjuvant treatment with NOV-002 in combination with doxorubicin and cyclophosphamide followed

by docetaxel in patients with HER-2 negative clinical stage II-IIIc breast cancer. Breast Cancer Res Treat 2012;132:215-23.
53. Yuan XK, Zhao XK, Xia YC, Zhu X, Xiao P. Increased circulating immunosuppressive CD14(+)HLA-DR(-/low) cells correlate with clinical cancer stage and pathological grade in patients with bladder carcinoma. The Journal of international medical research 2011;39:1381-91.
54. Eruslanov E, Neuberger M, Daurkin I, et al. Circulating and tumor-infiltrating myeloid cell subsets in patients with bladder cancer. Int J Cancer 2011.
55. Goedegebuure P, Mitchem JB, Porembka MR, et al. Myeloid-derived suppressor cells: general characteristics and relevance to clinical management of pancreatic cancer. Curr Cancer Drug Targets 2011;11:734-51.
56. Walter S, Weinschenk T, Stenzl A, et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med 2012.
57. Mirza N, Fishman M, Fricke I, et al. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer research 2006;66:9299-307.
58. Bronte V, Apolloni E, Cabrelle A, et al. Identification of a CD11b(+)/Gr-1(+)/CD31(+) myeloid progenitor capable of activating or suppressing CD8(+) T cells. Blood 2000;96:3838-46.
59. Gabrilovich DI, Velders MP, Sotomayor EM, Kast WM. Mechanism of immune dysfunction in cancer mediated by immature Gr-1+ myeloid cells. J Immunol 2001;166:5398-406.
60. Kusmartsev S, Cheng F, Yu B, et al. All-trans-retinoic acid eliminates immature myeloid cells from tumor-bearing mice and improves the effect of vaccination. Cancer research 2003;63:4441-9.
61. Almand B, Clark JI, Nikitina E, et al. Increased production of immature myeloid cells in cancer patients: A mechanism of immunosuppression in cancer. J Immunol 2001;166:678-89.
62. Alberto A. Chiappori SA, Charles Williams, Mary Pinder-Schenck, Tawee Tanvetyanon, Jhanelle Gray, Eric Haura, Ben Creelan, Soner Altiok, Germaine Gonzalez-Vazquez, Dung-Tsa Chen, Dmitry Gabrilovich Randomized Controlled Phase II Study of a p53 Dendritic Cell based vaccine (Ad.p53-DC) with or without all-trans Retinoic Acid (ATRA) for the Treatment of Patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC). J Thoracic Oncol (LALCA Supplement) 2014.
63. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials 1989;10:1-10.
64. Wieand HS. Randomized phase II trials: what does randomization gain? J Clin Oncol 2005;23:1794-5.
65. Iclozan C, Antonia S, Chiappori A, Chen DT, Gabrilovich D. Therapeutic regulation of myeloid-derived suppressor cells and immune response to cancer vaccine in patients with extensive stage small cell lung cancer. Cancer immunology, immunotherapy : CII 2013;62:909-18.
66. van Oosterhout AG, van de Pol M, ten Velde GP, Twijnstra A. Neurologic disorders in 203 consecutive patients with small cell lung cancer. Results of a longitudinal study. Cancer 1996;77:1434-41.

67. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001;124:1138-48.
68. Maddison P, Newsom-Davis J, Mills KR, Souhami RL. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. Lancet 1999;353:117-8.
69. Graus F, Dalmou J, Rene R, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. J Clin Oncol 1997;15:2866-72.
70. Wang W, Hodkinson P, McLaren F, et al. Histologic assessment of tumor-associated CD45(+) cell numbers is an independent predictor of prognosis in small cell lung cancer. Chest 2013;143:146-51.
71. Berghoff AS, Ricken G, Wilhelm D, et al. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). J Neurooncol 2016.
72. Koyama K, Kagamu H, Miura S, et al. Reciprocal CD4+ T-cell balance of effector CD62Llow CD4+ and CD62LhighCD25+ CD4+ regulatory T cells in small cell lung cancer reflects disease stage. Clin Cancer Res 2008;14:6770-9.
73. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
74. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53.
75. Hanel W, Moll UM. Links between mutant p53 and genomic instability. J Cell Biochem 2012;113:433-9.
76. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
77. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.
78. Tanio Y, Watanabe M, Osaki T, et al. High sensitivity to peripheral blood lymphocytes and low HLA-class I antigen expression of small cell lung cancer cell lines with diverse chemo-radiosensitivity. Jpn J Cancer Res 1992;83:736-45.
79. Yazawa T, Kamma H, Fujiwara M, et al. Lack of class II transactivator causes severe deficiency of HLA-DR expression in small cell lung cancer. J Pathol 1999;187:191-9.
80. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. The Lancet Oncology;17:883-95.
81. Schiller JH, Adak S, Cella D, DeVore RF, 3rd, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:2114-22.
82. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480-9.
83. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol 2012;12:269-81.
84. Pardoll D, Drake C. Immunotherapy earns its spot in the ranks of cancer therapy. J Exp Med 2012;209:201-9.

85. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:7412-20.
86. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. The Lancet Oncology 2016;17:883-95.