SPONSOR: The University of Chicago

PROTOCOL TITLE: A phase II prospective, open-label trial of perioperative combination nivolumab and ipilimumab in patients with resectable malignant peritoneal mesothelioma.

Principal Investigator:
Hedy Kindler, MD,
Professor of Medicine
Section of Hematology/Oncology, University of Chicago Medical Center
Tel: 773-702-0360
hkindler@medicine.bsd.uchicago.edu

Co-Investigators:
Divya Sood, MD
Kiran Turaga, MD, MPH
Aliya Husain, MD
Oliver Eng, MD
Samuel Armato, PhD
Michael Drazer, MD
Ankit Dhiman, MBBS
Emily Fenton, PA
Aytekin Oto, MD, MBA
Carla Harmath, MD
Aditya Juloori, MD

Statistician: Mihai Giurcanu, PhD

Amendment: 4
Protocol Version Date: September 21, 2022

Table of Contents

TRIAL SUMMARY

Abbreviated Title	Nivolumab and Ipilimumab in resectable peritoneal mesothelioma

Trial Phase	Phase II
Clinical Indication	Malignant peritoneal mesothelioma
Trial Type	Treatment
Type of control	None
Route of administration	Intravenous
Trial Blinding	None
Treatment Groups	1
Number of trial subjects	37 subjects
Estimated enrollment period	24 months
Estimated duration of trial	42 months
Duration of Participation	18 months

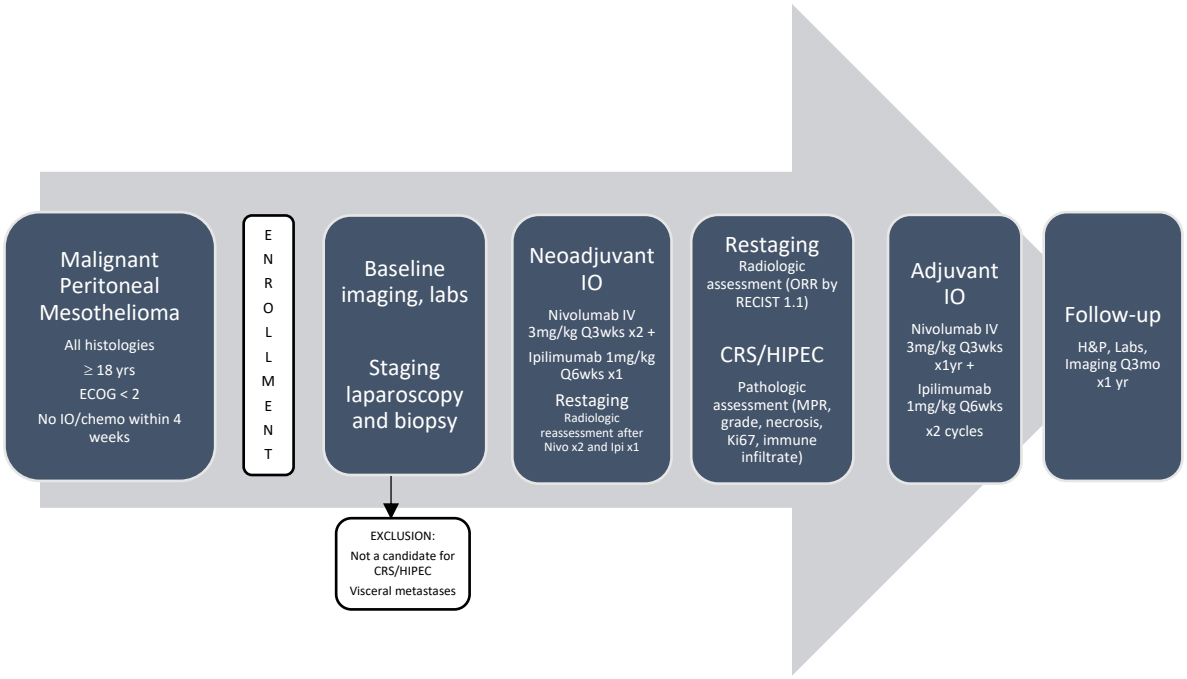
1.0 TRIAL DESIGN

1.1 Trial Design

This is a single institution, single-arm, phase II trial of perioperative combination immunotherapy (nivolumab + ipilimumab) in patients with resectable malignant peritoneal mesothelioma. All patients will undergo pretreatment cross-sectional imaging (CT or MRI) for clinical staging, as well as a laparoscopy to stage the peritoneum, assess resectability, and acquire pretreatment tissue, all of which is part of standard of care. Enrolled patients will then receive neoadjuvant combination immunotherapy, which will include 2 doses of nivolumab (3 mg/kg IV every 21 days) and 1 cycle of ipilimumab (1 mg/kg IV). Repeat cross-sectional imaging (CT or MRI) will be performed to assess response to neoadjuvant immunotherapy. Surgical intervention via cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC) with mitomycin-C will occur 2-6 weeks following the last dose of the neoadjuvant therapy, at which point additional pathologic assessments will be made. About 6-8 weeks following surgery and after new baseline cross-sectional imaging is completed, patients will receive adjuvant ipilimumab (2 cycles; 1mg/kg IV every 6 weeks) + nivolumab (1 year). Restaging cross sectional scans will be obtained to assess response every 6 weeks while on adjuvant therapy and every 3 months for an additional year after completing therapy.

The primary objective of the study is to assess the rate of major pathologic response (MPR), defined as ≤10% residual viable tumor (RVT) in the resected surgical specimen following neoadjuvant nivolumab + ipilimumab. Secondary objectives include assessment of the safety profile and feasibility of the neoadjuvant regimen, radiologic response rate, and overall and progression-free survival. Samples will be obtained pretreatment via laparoscopy and after nivolumab + ipilimumab treatment at surgical resection. Additional correlatives will be assessed including immune status/infiltration of the tumor, CA-125 serum levels, serum SRMP (soluble mesothelin-related peptide), circulating tumor cells, as well as radiologic correlatives.

1.2 Trial Schema



2.0 OBJECTIVES

2.1 Primary Objectives

1. To determine pathologic response of the tumor to neoadjuvant treatment with nivolumab + ipilimumab via Major Pathologic Response (MPR), defined as ≤10% residual viable tumor (RVT) cells, as well as grade, necrosis, and Ki67.

2.2 Secondary Objectives

1. To determine the safety profile of neoadjuvant nivolumab + ipilimumab, as defined by rate of grade III/IV adverse events according to CTCAE v5.0, occurring up to 30 days post-operatively.
2. To determine feasibility of neoadjuvant nivolumab + ipilimumab, as measured by the number of participants who complete neoadjuvant treatment with nivolumab + ipilimumab and proceed to surgery without extended treatment-related delay (> 6-week delay) or progression precluding surgery.
3. To determine the Overall Survival (OS) effect from neoadjuvant nivolumab + ipilimumab, defined as time from enrollment on study to death from any cause.
4. To determine the Progression-free Survival (PFS) effect from neoadjuvant nivolumab + ipilimumab, defined as time from enrollment on study to disease progression or death.

5. To determine the safety profile of adjuvant nivolumab + ipilimumab after cytoreductive surgery and HIPEC.

6. To determine the radiologic response to neoadjuvant nivolumab + ipilimumab utilizing RECIST 1.1 pre- and post-treatment.

7. To determine the effect of neoadjuvant nivolumab + ipilimumab on peritoneal carcinomatosis index (PCI).

2.3 Exploratory Objectives

1. To determine immune status/infiltration of the tumor in response to neoadjuvant nivolumab + ipilimumab, including the change in presence of TILs/macrophages (CD3, CD4, CD8, CD11b, CD68, CD20) and PDL1 status.

2. To determine blood-based changes with nivolumab + ipilimumab treatment, including PBMC inflammation expression profile, serum mesothelin (SMRP), osteopontin, CA-125, and circulating tumor cells.

3. To evaluate health-related quality of life (HRQoL) for patients with peritoneal mesothelioma undergoing perioperative immunotherapy, measured by the EORTC QLQ C30, which was developed specifically to assess quality of life in patients with cancer.

4. To correlate radiologic tumor measurements based on RECIST 1.1 and tumor volume with patient survival.

5. To relate pathologic assessment of immune infiltrate with pre-operative image-based tumor signatures.

6. To assess the response of neoadjuvant immunotherapy in those with BAP1 mutations identified on next-generation sequencing.

3.0 BACKGROUND

3.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors (Facciabene, 2012).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under

healthy conditions, is to down-regulate unwanted or excessive immune responses. PD-1 is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).

PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor.

Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma, consistent with the understanding that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and thereby is an attractive target for therapeutic intervention.

Nivolumab is a potent human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.
The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that 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 tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition has also been shown to result in enhanced T-cell function that is greater than the effects of either antibody alone, suggesting a synergistic effect of the combination, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity (Fiegle, 2019).

3.2 Rationale

3.2.1 Rationale for the Trial and Selected Subject Populations

Around 500-800 new cases of peritoneal mesothelioma occur every year in the United States (Miura, 2014). In contrast to pleural mesothelioma, an antecedent exposure to asbestos cannot always be found in patients with this disease. However, we previously demonstrated that germline mutations (with *BAP1* mutations being most common) are found in as many as 25% of peritoneal mesothelioma patients, compared to only 7% of those with pleural disease (Panou, 2018), implying that inherited susceptibility may play a larger role in peritoneal mesothelioma. Patients generally present with ascites or malignant bowel obstructions, which are significantly life limiting due to the resulting malnutrition and inanition. Cross sectional imaging such as CT scans or MRIs are

utilized in the diagnosis of peritoneal mesothelioma but they generally underestimate the burden of disease. There are 3 major histologic subtypes of mesothelioma: epithelial, sarcomatoid, and mixed or biphasic (Husain, 2009). Pathologic subtype is one of the most important prognostic indicators in this disease, so an accurate determination of pathology is essential (Rusch, 2012).

The prognosis of patients with peritoneal mesothelioma is rather dismal in the absence of treatment, with a median survival of 12 months (Alexander, 2013). The standard of care for patients with peritoneal mesothelioma is the performance of cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC). The surgery consists of extirpation of peritoneal tumor with parietal and visceral peritonectomy procedures and visceral resections as necessary. During the surgery, the burden of disease is assessed by the peritoneal cancer index (PCI score). This score is measured by dividing the abdomen into 13 zones (including 4 zones for the bowel) and ranges from 0-39 (39 being the most disease). At the end of the operation the residual tumor is assessed by the completeness of cytoreduction which is an important prognostic factor for the survival of these patients. Heated chemotherapy is then applied to the peritoneal surfaces for 90 minutes and circulated at 600 ml-1500ml/min at 42 ^{0}C (Turaga K 2016).

Patients undergoing CRS+HIPEC have an overall median survival of 53 months, with a more favorable prognosis for patients that undergo a complete cytoreduction (CC-0/1)(Yan TD 2009). The agent of choice for the intra-operative chemotherapy is either platinum based (cisplatin/carboplatin) or mitomycin C (Helm, 2015). Grade III-IV complication rates after this surgery can be as high as 31-40% (Kepenekian 2016). Major complications include death, anastomotic leak, deep or superficial site infection, anemia, re-operations, organ failure including renal failure, cardiac failure or respiratory failure, neutropenia, thromboembolic events, dehydration and failure to thrive.

Due to the relatively low incidence of peritoneal mesothelioma, there are no large randomized controlled trials for either surgery or chemotherapy to guide management, leaving no clear consensus on optimal treatment approach. Therefore, much of the management is extrapolated from the studies in pleural mesothelioma. Standard chemotherapy for pleural mesothelioma consists of pemetrexed plus cisplatin. This regimen was FDA-approved for MM based on a single-blind, placebo-controlled, phase III trial, which randomized 456 patients to cisplatin with or without pemetrexed. Patients who received the combination achieved a longer median overall survival (12.1 vs. 9.3 months, $p = 0.020$), a superior time to progression (5.7 vs. 3.9 months, $p = 0.001$), and a higher objective response rate (41% vs. 17%, $p < 0.001$) than patients who received cisplatin alone (Vogelzang, 2003).

However, the benefits of cytotoxic chemotherapy for peritoneal mesothelioma are less clear and alternative therapies such as immunotherapy warrant investigation. PD-1/PD-L1 and CTLA4 are immune checkpoints that mediate immune evasion in a wide spectrum of tumors. While the normal function of PD-1 and CTLA4 is to counteract excessive immune responses directed against normal tissues, various types of cancer have manipulated this function by up-regulating the natural ligands of these checkpoints to evade immune recognition. The critical role of this pathway became evident with the promising results of clinical trials of PD-1/PD-L1 and CTLA4 inhibitors, such as pembrolizumab (Hamid, 2013), nivolumab (Wolchok, 2013), and MPDL3280A (Powderly, 2013). While immune checkpoint blockers have not been evaluated in mesothelioma in the neoadjuvant setting, they are being used safely in the preoperative setting in a variety of tumor types.

In an analysis presented at ASCO 2014 (Kindler, 2014), we analyzed gene expression data on 44 malignant mesothelioma tumors (Gordon, 2005), applied a melanoma-derived signature of T-cell inflammation (Harlin, 2009), and analyzed other immune response related genes. We identified that 32% of malignant mesotheliomas showed high CD8 gene expression, and a T-cell inflamed phenotype analogous to melanomas was present in multiple tumors.

We evaluated MM tumor tissues from patients by multi-color immunohistochemistry (IHC), staining for CD68 (macrophages), CD8 (tumor infiltrating lymphocytes), and PD-L1 (immune checkpoint, MTA: Lieping Chen) We observed PD-L1 expression in 75% of MM tumors tested, which was 2-3+ in 37.5%, and 1+ in 37.5%. Patchy higher level PD-L1 expression was observed in stromal or CD68 cells located close to CD8+ cells. CD8 tumor infiltrating lymphocytes (TILs) were present in all epithelial tumors. Prominent CD68 infiltration was seen in all tumors.
Thus, we identified high PDL-1 expression, a CD8 infiltrative pattern with a T-cell inflamed expression, and presence of PD-1/PD-L1 immune checkpoints in a subset of MM (approximately 1/3 of MM tumors) similar to the phenotype found in other tumors such as melanoma that benefit from immune checkpoint blockade. Furthermore, we recently identified a marked heterogeneity in PD-L1 expression specifically in peritoneal mesothelioma associated with either systemic or intraperitoneal chemotherapy administration (White, 2020). This demonstrates the pliability of PD-L1 as a biomarker, indicating that a low PD-L1 status at a single timepoint should not preclude patients from immune checkpoint inhibition therapy.

Based on these and other studies, MM is an ideal target disease for anti-PD-1 therapy, and further investigation of the biology of this agent in this disease is warranted. This hypothesis is further supported by the recently reported data from the CheckMate 743 study. This was a randomized, open-label trial in patients with unresectable malignant pleural mesothelioma, with a primary endpoint of overall survival. Patients were randomized to receive either combination immunotherapy with nivolumab + ipilimumab for up to 2 years or standard chemotherapy with pemetrexed + either cisplatin or carboplatin for 6 cycles. The trial demonstrated a statistically significant improvement in OS for patients randomized to immunotherapy compared to chemotherapy. While it was efficacious in all histologies, there was a greater benefit noted in the sarcomatoid subgroup. The results of this trial have established a new standard of care in the treatment of malignant pleural mesothelioma, with immunotherapy now considered first line therapy. (Baas 2020).

Therefore, we expect to see a similar response to immunotherapy in the peritoneal disease setting, and with this study we aim to evaluate that response. Of note, while resection is typically offered only to patients with non-sarcomatoid histology, in this trial we plan to include sarcomatoid histologies as well. Due to the robust response in the CheckMate 743 trial, which demonstrated that immunotherapy allowed for an equivalent survival in the sarcomatoid cohort to the epithelioid cohort, we anticipate that the sarcomatoid peritoneal patients will have a similar response, making their disease more amenable to cytoreduction.

3.2.2 Rationale for Endpoints

Tumor response is a surrogate marker of benefit from immune therapies that has been used for studies with nivolumab, ipilimumab, and other immune therapies. Response is considered a reliable marker of benefit for malignant mesothelioma and correlates with a survival benefit

(Blayney, 2012). Response in pleural mesothelioma is generally assessed via the modified RECIST 1.1 criteria for assessment of response in mesothelioma (Armato 2018). However, radiologic assessments of tumor response in peritoneal disease are poor and usually underestimate the burden of disease.

Retrospective analyses have revealed that Major Pathologic Response (MPR) after neoadjuvant chemotherapy was related to improved overall survival and disease-free survival. Chaft *et al.* examined neoadjuvant chemotherapy for non-squamous NSCLC (non-small cell lung cancer) and reported that 22% of tumors showed MPR, with these responses being associated with long-term survival. Furthermore, MPR has since been used in several prospective and randomized studies and has now been recommended as a surrogate endpoint specifically in the context of neoadjuvant immunotherapy (Hellmann, 2014). Pathologic responses, such as MPR and pathologic complete response are to date the most commonly used metrics for assessing response to neoadjuvant immunotherapy, and have been used in trials for melanoma, colon cancer, NSCLC, muscle-invasive bladder cancer, and several others (Chalabi, 2020; Yang, 2020). Patients with non-small cell lung cancer who received neoadjuvant nivolumab were found to have a 45% rate of MPR (Bott, 2019), and 30% of those with resectable stage III/IV melanoma who received just a single dose of pembrolizumab had MPR, 100% of which had a durable disease-free survival at 24 months (Huang, 2019). This pathologic response is seen not only in those with known susceptibility to immunotherapy, such as those with mismatch repair deficient (dMMR) tumors. In the NICHE study, though colorectal cancer patients with dMMR tumors had a 95% MPR rate, those with MMR-proficient tumors still had a robust response with 20% MPR rate (Chalabi, 2020).

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Number of Subjects

This is a single-center phase II study and will enroll 37 patients for a total of 42 months. The University of Chicago will attempt to enroll 18-19 patients each year for two consecutive years.

4.2 Gender, Age, Racial and Ethnic Origin of Subjects

Both male and female patients who are at least 18 years of age, of any ethnic or racial background, are included. Children (≤18 years of age) will be excluded from this study to limit variability in the study population and avoid this vulnerable population. There is no restriction on the racial or ethnic origin of subjects. Please see the inclusion and exclusion criteria for full details. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.3 Inclusion Criteria

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

1. Have a diagnosis of histologically or cytologically confirmed peritoneal mesothelioma, of epithelial, biphasic, or sarcomatoid subtypes

2. Have disease burden amenable to cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC), as determined by a surgeon specializing in mesothelioma

3. Have measurable or evaluable disease based on RECIST 1.1 or on laparoscopy

4. Have no definitive evidence of visceral metastases by best staging

5. Be willing to undergo laparoscopy or mini-laparotomy for peritoneal staging

6. Demonstrate adequate organ function as determined by screening labs, with criteria defined in Table 1

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /μL
Platelets	≥ 100,000 / μL
Hemoglobin	≥ 9 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 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
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN. Patients on anticoagulation are expected to hold anticoagulation for at least 5 days prior to surgery.
[a]Creatinine clearance should be calculated per institutional standard.	

7. Have an ECOG performance status of < 2

8. Be ≥ 18 years of age on day of signing informed consent

9. Be willing and able to provide written informed consent for the trial

4.4 Exclusion Criteria

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

1. Is currently participating in a study of an investigational agent and received an investigational agent within 4 weeks of the first dose of treatment on this protocol

2. Has received any immunotherapy agents outside of this protocol within 4 weeks of the first dose of treatment on this protocol

3. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (>10 mg of prednisone daily or equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study drug.

4. Has a known history of active TB infection (Bacillus tuberculosis)

5. Has active COVID-19 infection

6. Has known history of, or any evidence of active, non-infectious pneumonitis that required steroids, or active pneumonitis

7. Has a severe hypersensitivity to nivolumab or any of its excipients

8. Has a severe hypersensitivity to ipilimumab or any of its excipients

9. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs)

10. Has a known additional malignancy that is progressing or required active treatment within the 3 years prior to enrollment - 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 or other tumors that will not affect life expectancy

11. Has an active infection requiring systemic therapy

12. Has a known history of HIV, Hepatitis B, or Hepatitis C

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 screening visit through 120 days after the last dose of trial treatment
    a. Female subjects 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.

    b. 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 5.8.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

c. 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.

15. Is on anticoagulation that cannot be discontinued in the perioperative period

16. Has received a live vaccine within 30 days of planned start of study therapy

4.5 Subject Identification & Recruitment

Patients will be identified during the initial medical oncology or surgical oncology appointment. Patients will be screened for the appropriate inclusion and exclusion criteria and recruited to the trial as appropriate. There will be no use of advertisements, but it will be listed on the Cancer Center website. Patients will not be identified through medical records.

4.6 Location

This trial will be a single institution study. Recruitment of all patients will happen at the University of Chicago main site. Patients will undergo all interventions at the University of Chicago main site, but may receive the immunotherapy at the satellite sites.

4.7 Discontinuation of Study and Participant Withdrawal

Discontinuation of study intervention does not represent withdrawal from the study. As data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. Also, a participant may be discontinued from study intervention by the investigator if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.
A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

1. The participant or participant's legally acceptable representative requests to discontinue study intervention.
2. Any occurrence of another malignancy that requires treatment.
3. Unacceptable AEs or toxicities
4. The participant interrupts study intervention administration for >28 consecutive days
5. The participant has a medical condition or personal circumstance which, in the opinion of the investigator, placed the participant at unnecessary risk from continued administration of study intervention.
6. The participant has a confirmed positive serum or highly-sensitive urine pregnancy test.

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

1. The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
2. The investigator must make every effort to regain contact with the participant at each missed visit (e.g. telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
3. Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

5.0 TRIAL INTERVENTIONS

5.1 Pre-intervention Testing

Once consent is obtained, if not already performed patients will have a CT or MRI of the Abdomen and Pelvis and a CT of the Chest to determine extent of disease. They will also undergo a laparoscopy or mini-laparotomy for peritoneal carcinomatosis index (PCI) staging and pre-treatment tissue biopsy. The laparoscopic surgery is performed under general anesthesia, and involves inserting a 5 or 10 mm camera inside the peritoneal cavity to visually assess the peritoneal disease burden. Tissue biopsy is obtained by inserting a second 5 mm port and biopsying one or multiple areas of diseased peritoneum. Each biopsy site will be clearly marked by location for pathological identification. Patients with extensive prior surgery that precludes a safe laparoscopy could undergo a mini-laparotomy, in which a small incision is made to assess the burden of disease in the peri-incisional area. This laparoscopy or mini-laparotomy is standard of care for patients with peritoneal mesothelioma who are considered for CRS/HIPEC.

5.2 Neoadjuvant Nivolumab and Ipilimumab

5.2.1 Drug Supply

Both nivolumab and ipilimumab will be obtained through commercial drug supply.

5.2.2 Dose Selection

Neoadjuvant nivolumab is delivered at a dose of 3 mg/kg over 30 minutes every 21 days via IV infusion on day 1 and day 22 of each 42-day cycle for 2 doses (1 cycle).

Neoadjuvant ipilimumab is delivered at a dose of 1 mg/kg over 30 minutes every 42 days via IV infusion on day 1 of each 42-day cycle for 1 dose (1 cycle). When given on the same day as nivolumab, ipilimumab is to be given following nivolumab infusion.

5.2.3 Dose Modification

Adverse events (both non-serious and serious) associated with nivolumab or ipilimumab 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. No dose reduction for nivolumab or ipilimumab is recommended. In general, withhold nivolumab and ipilimumab for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue the agents for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for nivolumab or ipilimumab in combination for adverse reactions that require management different from these general guidelines are summarized in the prescribing information (Appendix).

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 Principal Investigator. The reason for interruption should be documented in the patient's study record.

5.3 Surgical Intervention

After completion of 2 cycles of nivolumab and 1 cycle of ipilimumab, patients will undergo restaging CT or MRI and labs to assess disease response. A surgical re-evaluation will be conducted to determine if patients remain suitable candidates for surgery. Surgical cytoreduction and HIPEC with mitomycin-C will be performed approximately 2-6 weeks after the last dose of nivolumab, to achieve an adequate cytoreduction of all residual gross tumor. CRS+HIPEC, which can be performed via a laparoscopic or an open laparotomy approach, includes but is not limited to peritonectomy procedures whereby the parietal peritoneum is resected, omentectomy and other visceral resections as necessary to reduce the tumor burden to minimal residual disease. Completeness of cytoreduction and PCI scores will be documented. The dose of intraperitoneal chemotherapy will be 40 mg of mitomycin in split dosing of 30mg at time 0 and 60 mg at time 60 minutes, with a complete washout at 90 minutes. Tumor resections from matched sites of the original pre-neoadjuvant therapy biopsy will be marked clearly for pathological identification.

Patients will be closely monitored for potential complications following surgery. Major complications include death, anastomotic leak, deep or superficial site infection, anemia, re-operations, organ failure including renal failure, cardiac failure or respiratory failure, neutropenia, thromboembolic events, dehydration and failure to thrive.

5.4 Adjuvant Nivolumab and Ipilimumab

Following surgery, patients will have 6-8 weeks of recovery prior to the initiation of adjuvant immunotherapy. Cross-sectional imaging will be obtained prior to starting adjuvant therapy and will be repeated every 6 weeks while on therapy. Adjuvant immunotherapy with nivolumab and ipilimumab will be administered according to the same dosing and schedule as it was given in the neoadjuvant phase, but with the first cycle to include nivolumab alone.

The first 2 cycles in the adjuvant phase will include nivolumab delivered at a dose of 3 mg/kg over 30 minutes every 21 days via IV infusion on day 1 and day 22 of each 42-day cycle for 4 doses (2 cycles) and ipilimumab delivered at a dose of 1 mg/kg over 30 minutes every 42 days via IV infusion on day 22 of each 42-day cycle for 2 doses (2 cycles). When given on the same day as nivolumab, ipilimumab is to be given following nivolumab infusion. Following these first 2 adjuvant cycles, nivolumab will be delivered alone at the same dose, route, and rate every 21 days on days 1 and 22 of each 42-day cycle, continuing until 1 year post-operatively.

6.0 ADDITIONAL METHODOLOGY

6.1 Trial Blinding/Masking

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

6.2 Randomization or Treatment Allocation

There will be no randomization. All patients that meet criteria will be enrolled in the single arm.

6.3 Stratification

No stratification will be done.

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

6.4.1 Acceptable Concomitant Medications

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

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 as well.

6.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Treatment Phase of this trial:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy
- 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 while on nivolumab and ipilimumab 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 Principal Investigator.

Subjects who, in the assessment by the treating 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 treating investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.5 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. 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 treating investigator determines the events to be related to the study treatment.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:

    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

    - For **T1DM** or **Grade 3-4** Hyperglycemia

        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):

  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

- **Grade 3-4** hyperthyroidism

  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

  - Treat with IV or oral corticosteroids

- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:

- For **Grade 2** events, treat with corticosteroids.

- For **Grade 3-4** events, treat with systemic corticosteroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions:

Discontinue nivolumab and ipilimumab in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions.

6.6 Diet/Activity/Other Considerations

6.6.1 Diet

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

6.6.2 Contraception

Nivolumab and ipilimumab may have adverse effects on a fetus in utero. Furthermore, it is not known if nivolumab or ipilimumab have 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 progesterone 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. 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.

6.6.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on study, the subject will immediately be removed from the study. The treating investigator and/or their designee 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 Principal Investigator.

If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Principal Investigator and followed as described above.

6.6.4 Use in Nursing Women

There are no data on the presence of nivolumab or ipilimumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children and since many drugs are excreted in human milk, subjects who are breast-feeding are not eligible for enrollment.

6.7 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 principal and/or treating investigator should any untoward effect occur. In addition, a subject may be withdrawn by the principal and/or treating investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Further details are described in Section 4.7.

6.8 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

5. If 2 patient deaths attributed to the investigational drug are seen in the 30 days following surgery. The relationship of the investigational drug to the mortality will be determined by the treating medical oncologist and surgeon.

6. Assuming a major complication rate of 10% from the combination immunotherapy (Taioli, 2015), the trial will be halted if any major complication which is attributed to the investigational drug occurs in the first two patients, or in 3 cases among the first 11 patients, or in any 4 patients during the course of the trial. In order for the trial to be halted, these complications must be determined to result from the investigational drug as will be determined by the treating oncologist and surgeon. A composite adverse event of major complications defined as the occurrence of any ventricular arrhythmia requiring treatment, hemorrhage requiring re-operation, acute respiratory distress syndrome (ARDS), pneumonia, reintubation, placement of a tracheostomy, pulmonary embolus, empyema, sepsis, intra-abdominal sepsis, myocardial infarction and unexpected return to the operating room will be monitored sequentially.

7.0 TRIAL PROCEDURES

7.1 Flow Chart – Schedule of Events

7.1.1 Flow Chart for Screening, Neoadjuvant, and Surgery Phases

Table 2. Trial Flow Chart of Screening, Neoadjuvant, and Surgery Phases

Trial Phase:	Screening Phase	Neoadjuvant Treatment Phase		Pre-Surgery Phase	Surgery Phase	Post-Surgery Recovery Phase
	Screening (Visit 1)	C1 D1	C1 D22C	4 Weeks	3 Weeks	3-4 Weeks
Scheduling Window (Days):	-28 to -1		± 3			
Administrative Procedures						
Informed Consent	X					
Inclusion/Exclusion Criteria	X			X	X	
Demographics and Medical History	X			X	X	
Prior and Concomitant Medication Review	X	X	X	X	X	
Interventions						
Nivolumab Administration		X	X			
Ipilimumab Administration		X				
Surgery					X	
Clinical Procedures/Assessments						
Review Adverse Events	X	X	X	X		
Full Physical Examination	X	X	X	X	X	
Height	X					
Vital Signs and Weight	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	
EORTC QOL C30	X			X		X
Surgeon Assessment	X			X		
Medical Oncology Assessment	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory [a]						
Pregnancy Test – Urine or Serum β-HCG	X					
CBC with Differential	X	X	X	X		
Comprehensive Serum Chemistry Panel	X	X	X	X		
INR, PTT	X			X		
Urinalysis	X					
TSH (reflex T3, T4 if abnormal)	X	X		X		
Efficacy Measurements [b]						
Tumor Imaging with CT/MRI	X			X		
CA-125	X			X		
Circulating tumor cells	X			X		
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood						
Laparoscopy for tissue and PCI score assessment	X					
Correlative Studies Blood Collection [c]	X	X		X	X	

a. Screening lab tests to be performed within 14 days before first dose. After Cycle 1, pre-dose lab procedures can be conducted <72 hours before dosing.
b. For CT scans, scheduling window is +/- 7 days.
c. Serum mesothelin and osteopontin will be obtained at the times of tumor imaging and upon tumor progression.

7.1.2 Flow Chart for Adjuvant and Post-Treatment Phases

Table 3. Trial Flow Chart of Adjuvant and Post-Treatment Phases

Trial Period:	**Adjuvant Therapy Phase**								**End of Treat-ment**	**Post-Treatment Phase**		
					Repeat x 1 year from surgery				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Treatment Week/Title:	C1 D1	C1 D22	C2 D1	C2 D22	C1 D1	C1 D22	C2 D1	C2 D22				
Scheduling Window (Days)[c]:		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 wks post discon	Every 12 weeks
Nivolumab Administration	X	X	X	X	X	X	X	X				
Ipilimumab Administration		X		X								
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Post-study anticancer therapy status									X			
Survival Status									X	X	X	X
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X	X	X	X	X	X	X	X				
Vital Signs and Weight	X	X	X	X	X	X	X	X				
ECOG Performance Status	X	X	X	X	X	X	X	X				
EORTC QOL C30	X		X		X		X		X	X		
Laboratory Parameters												
CBC with Differential	X	X	X	X	X	X	X	X				
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X				
TSH (reflex T3, T4 if abnormal)	X		X		X		X					
Efficacy Measurement												
Tumor Imaging with CT scan every 12 weeks [c]	X		X		X		X					
CA-125	X		X		X		X					
Circulating tumor cells	X		X		X		X					
Correlative Lab												
Correlative Studies Blood Collection [a,b]	X				X				X			

a. Both tumor imaging and correlative studies to be repeated after every 6 weeks.

b. Serum mesothelin and osteopontin will be obtained at the times of tumor imaging and upon tumor progression.

c. For CT scans, the scheduling window is +/- 7 days

The Trial Flow Chart 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.

7.2 Informed Consent

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

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.

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

7.3 Inclusion/Exclusion Criteria Review

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

7.4 Medical History

A medical history will be obtained by the treating 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.

7.5 Prior and Concomitant Medications Review

7.5.1 Prior Medications

The treating 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.

7.5.2 Concomitant Medications

The treating investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.6 Disease Details and Treatments

7.6.1 Disease Details

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

7.6.2 Prior Treatment Details

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

7.6.3 Subsequent Anti-Cancer Therapy Status

The treating 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 should 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.

7.7 Adverse Event (AE) Monitoring

The treating 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 CTCAE (v5.0). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

7.8 Full Physical Exam

The treating investigator or qualified designee will perform a complete physical exam during the screening period and as indicated in the Trial Flow Chart. Clinically significant abnormal findings should be recorded as medical history.

7.9 Vital Signs

The treating 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. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.10 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.11 Tumor Imaging and Assessment of Disease

CT or MRI scans will be obtained at baseline. After completion of neoadjuvant nivolumab + ipilimumab treatment a CT or MRI imaging will again be repeated after completion of surgery (prior to starting adjuvant immunotherapy), and repeated every 6 weeks while on adjuvant therapy and every 3 months for 1 year after completing treatment.

7.12 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor tissue will be obtained at laparoscopy and at surgical resection. Correlative studies blood sampling for SRMP, osteopontin, CA-125, and circulating tumor cells will be obtained per Trial Flow Chart schedule.

7.13 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 4.

Table 4. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG) †
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	PTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total thriiodothyronine (T3)
Red Blood Cell Count	Carbon Dioxide *(CO_2 or bicarbonate)*	Microscopic exam *(If abnormal results are noted)*	Free thyroxine (T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Total protein		

Hematology	Chemistry	Urinalysis	Other
	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.			

Laboratory tests for screening should be performed within 14 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 treating investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.14 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. 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.

7.15 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 3 months by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.16 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.

7.17 Assessing and Recording Adverse Events

7.17.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **Attribution** of the AE:

- Definite (5) – The AE *is clearly related* to the study treatment.
- Probable (4) – The AE *is likely related* to the study treatment.
- Possible (3) – The AE *may be related* to the study treatment.
- Unlikely (2) – The AE *is doubtfully related* to the study treatment.
- Unrelated (1) – The AE *is clearly NOT related* to the study treatment.

7.17.2 Adverse Event Definitions

7.17.2.1 Adverse Event

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 study treatment, 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.

Adverse events may occur during the course of the use of the study treatment 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 treating 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.

7.17.2.2 Serious Adverse Event

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) Life-threatening (e.g. places subject at <u>immediate</u> risk of death, this does not include events that might have caused death if they occurred a greater severity)
3) Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

7.17.2.3 Adverse Reactions

An adverse event is considered to be an adverse reaction if there is evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

7.17.3 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 5.0. 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.

7.17.4 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.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Primary Endpoint

The primary endpoint in this study is Major Pathologic Response (MPR), defined as presence of <=10% residual viable tumor in the resected surgical specimen. The proportion of patients who achieve an MPR will be reported (MPR rate), along with an exact 95% confidence interval.
Sample size considerations: A total of 37 patients will be enrolled, with the goal to enroll 18-19 patients per year in 2 consecutive years. This sample size will provide 80% power to detect a significant increase in MPR rate of at least 40% using the one-sided binomial test with the null hypothesis H_0:p = 0.5 against the alternative hypothesis H_a:p > 0.5 corresponding to an actual MPR rate of ~0.7 or higher.

8.2 Secondary Endpoints

Safety and feasibility will be assessed throughout the trial, especially in discussion with the surgeon performing the cytoreductive surgery. Adverse events will be summarized by type, grade, and relationship to the study drug. The trial will be discontinued if the 30-day mortality occurs in two patients and the cause of death is determined to be related to the investigational agent by the treating medical oncologist and surgeon. Refer to section 6.8 for additional clinical criteria for early trial termination.

Analyses to address the secondary objectives will be primarily descriptive in nature. Progression-free survival (PFS) and overall survival (OS) will be estimated using the Kaplan-Meier method with qualitative assessment of the emergence of a tail at the end of the curve as evidence of long-term survival, which is not seen in this disease despite aggressive multimodality therapy. Median event times will be determined as the time at which the Kaplan-Meier curve falls below 50%.

The objective response rate to neoadjuvant nivolumab + ipilimumab based on cross-sectional imaging pre- and post-treatment will be determined along with an exact 90% confidence interval.

8.3 Exploratory Endpoints

CD8 tumor infiltrating lymphocytes (TILs) will be assessed by % of tumor showing infiltration and calculation of CD8 TIL density in the pre- and post-treatment biopsy specimens. An increase in the TIL density will be termed a TIL-response and correlated with TCIP response using Pearson or Spearman rank correlation coefficients.

Presence of additional pathologic markers, including CD3, CD4, CD68, and CD20 will be assessed in pre- and post-treatment tissue samples. Results will be descriptive and presented in tabular form. Changes in PD-L1 expression compared between the pre- and post-treatment tissue samples will be determined using IHC and mass spectrometry. Ordinal IHC data will be assessed using the

Wilcoxon signed-rank test. Changes in other continuous immune response and biomarker values will be analyzed using paired t-tests.

Analysis of variance for repeated measures will be performed to evaluate changes in serum mesothelin and osteopontin levels over time.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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.

9.2 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. Drug identity (name, strength) is included in the label text.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient’s personal physician or to other appropriate medical personnel responsible for the patient’s welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the Drug Manufacturer’s representatives, by the IRB and the regulatory authorities.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration

Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54) and will be implemented following institutional standards.

10.3 Compliance with Law, Audit and Debarment

The trial will be conducted in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor 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.

10.5 Quality Management System

The Principal Investigator will ensure that trial is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

A quality assurance audit/inspection of this study may be conducted by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this clinical study.

The trial will be monitored in the weekly mesothelioma multidisciplinary conference.

10.6 Data Management

Data management will be provided via the cancer clinical trial infrastructure available at the University of Chicago (eVELOS). It is the responsibility of the investigators to record and verify the accuracy of subject data.

11.0 REFERENCES

Alexander HR Jr, Bartlett DL, Pingpank JF, Libutti SK, Royal R, Hughes MS, Holtzman M, Hanna N, Turner K, Beresneva T, Zhu Y. Treatment factors associated with long-term survival after cytoreductive surgery and regional chemotherapy for patients with malignant peritoneal mesothelioma. Surgery. 2013 Jun;153(6):779-86.

Alley E, Molife LR, Santoro A, et al. Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma (MPM): Preliminary results from KEYNOTE-028. Proc AACR 2015.

Armato SG, Li P, Husain AN et al. Radiologic-pathologic correlation of mesothelioma tumor volume. Lung Cancer. 2015 Mar;87(3):278-82.

Armato SG 3rd, Nowak AK. Revised Modified Response Evaluation Criteria in Solid Tumors for Assessment of Response in Malignant Pleural Mesothelioma (Version 1.1). J Thorac Oncol. 2018 Jul;13(7):1012-1021.

Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, Mansfield AS, Popat S, Jahan T, Antonia S, Oulkhouir Y, Bautista Y, Cornelissen R, Greillier L, Grossi F, Kowalski D, Rodríguez-Cid J, Aanur P, Oukessou A, Baudelet C, Zalcman G. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet. 2021 Jan 30;397(10272):375-386.

Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, Krijgsman O, van den Braber M, Philips D, Broeks A, van Thienen JV, Mallo HA, Adriaansz S, Ter Meulen S, Pronk LM, Grijpink-Ongering LG, Bruining A, Gittelman RM, Warren S, van Tinteren H, Peeper DS, Haanen JBAG, van Akkooi ACJ, Schumacher TN. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018 Nov;24(11):1655-1661.

Blayney JK, Ceresoli GL, Castagneto B, et al. Response to chemotherapy is predictive in relation to longer overall survival in an individual patient combined-analysis with pleural mesothelioma. Eur J Cancer 2012; 48 (16): 2983-2992.

Bott MJ, Yang SC, Park BJ, Adusumilli PS, Rusch VW, Isbell JM, Downey RJ, Brahmer JR, Battafarano R, Bush E, Chaft J, Forde PM, Jones DR, Broderick SR. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg. 2019 Jul;158(1):269-276.

Burt BM, Cameron RB, Mollberg NM, et al. Malignant pleural mesothelioma and the Society of Thoracic Surgeons Database: an analysis of surgical morbidity and mortality. J Thorac Cardiovasc Surg 2014; 148(1): 30-5.

Campbell N, Kindler HL. Update on malignant pleural mesothelioma. Semin Respir Crit Care Med 2011; 32(1): 102-110.

Chalabi M, Fanchi LF, Dijkstra KK, Van den Berg JG, Aalbers AG, Sikorska K, Lopez-Yurda M, Grootscholten C, Beets GL, Snaebjornsson P, Maas M, Mertz M, Veninga V, Bounova G, Broeks A, Beets-Tan RG, de Wijkerslooth TR, van Lent AU, Marsman HA, Nuijten E, Kok NF, Kuiper M, Verbeek WH, Kok M, Van Leerdam ME, Schumacher TN, Voest EE, Haanen JB. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med. 2020 Apr;26(4):566-576.

Cottrell TR, Thompson ED, Forde PM, Stein JE, Duffield AS, Anagnostou V, Rekhtman N, Anders RA, Cuda JD, Illei PB, Gabrielson E, Askin FB, Niknafs N, Smith KN, Velez MJ, Sauter JL, Isbell JM, Jones DR, Battafarano RJ, Yang SC, Danilova L, Wolchok JD, Topalian SL, Velescu VE, Pardoll DM, Brahmer JR, Hellmann MD, Chaft JE, Cimino-Methews A, Taube JM. Pathologic features of response to neoadjuvant anti-PD-1 resected non-small-cell carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). Ann Oncol 2018 Aug 1;29(8):1853-1860.

Facciabene A, Motz GT, Coukos G. T-regulatory cells: key players in tumor immune escape and angiogenesis. Cancer Res. 2012 May 1;72(9):2162-71.

Fiegle E, Doleschel D, Koletnik S, Rix A, Weiskirchen R, Borkham-Kamphorst E, Kiessling F, Lederle W. Dual CTLA-4 and PD-L1 Blockade Inhibits Tumor Growth and Liver Metastasis in a Highly Aggressive Orthotopic Mouse Model of Colon Cancer. Neoplasia. 2019 Sep;21(9):932-944.

Gordon GJ, Rockwell GN, Godfrey PA, et al. Validation of genomics-based prognostic tests in malignant pleural mesothelioma. Clin Cancer Res 2005; 11:4406-14.

Hamid O, Robert C, Daud A, et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med 2013; 369:134-44.

Harlin H. Meng Y, Peterson AC, et al. Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. Cancer Res 2009; 69, 3077–3085.

Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N, Pataer A, Travis WD, Swisher SG, Kris MG; University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol. 2014 Jan;15(1):e42-50.

Helm JH, Miura JT, Glenn JA, Marcus RK, Larrieux G, Jayakrishnan TT, Donahue AE, Gamblin TC, Turaga KK, Johnston FM. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. Ann Surg Oncol. 2015 May;22(5):1686-93.

Henley SJ, Larson TC, Wu M, et al. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003-2008. Int J Occup Environ Health 2013; 19 (1): 1-10.

Hjerpe A, Ascoli V, Bedrossian CWM, et al. Guidelines for the cytopathologic diagnosis of epithelioid and mixed-type malignant mesothelioma: a secondary publication. Cytopathology2015; 26 (3): 142-156.

Huang AC, Orlowski RJ, Xu X, Mick R, George SM, Yan PK, Manne S, Kraya AA, Wubbenhorst B, Dorfman L, D'Andrea K, Wenz BM, Liu S, Chilukuri L, Kozlov A, Carberry M,

Giles L, Kier MW, Quagliarello F, McGettigan S, Kreider K, Annamalai L, Zhao Q, Mogg R, Xu W, Blumenschein WM, Yearley JH, Linette GP, Amaravadi RK, Schuchter LM, Herati RS, Bengsch B, Nathanson KL, Farwell MD, Karakousis GC, Wherry EJ, Mitchell TC. A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma. Nat Med. 2019 Mar;25(3):454-461.

Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2009; 133 (8): 1317-1331.

Kepenekian V, Elias D, Passot G, Mery E, Goere D, Delroeux D, Quenet F, Ferron G, Pezet D, Guilloit JM, Meeus P, Pocard M, Bereder JM, Abboud K, Arvieux C, Brigand C, Marchal F, Classe JM, Lorimier G, De Chaisemartin C, Guyon F, Mariani P, Ortega-Deballon P, Isaac S, Maurice C, Gilly FN, Glehen O; French Network for Rare Peritoneal Malignancies (RENAPE). Diffuse malignant peritoneal mesothelioma: Evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE Database: Multi-Institutional Retrospective Study. Eur J Cancer. 2016 Sep;65:69-79. doi: 10.1016/j.ejca.2016.06.002. Epub 2016 Jul 26. PubMed PMID: 27472649.

Kindler HL, Zuo Z, Khatri A, Keck MK, Vigneswaran W, Husain AN, Seiwert TY. T-cell inflamed phenotype and PDL1 expression in malignant mesothelioma. J Clin Oncol 32:5s, 2014 (suppl, abstr 7589)

Krug L, Pass H, Rusch V et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. J Clin Oncol. 2009; 27(18):3007-13.

Miura JT, Johnston FM, Gamblin TC, Turaga KK. Current trends in the management of malignant peritoneal mesothelioma. Ann Surg Oncol. 2014 Nov;21(12):3947-53. doi: 10.1245/s10434-014-3803-6. Epub 2014 May 20. PubMed PMID: 24841356.

Panou V, Gadiraju M, Wolin A, Weipert CM, Skarda E, Husain AN, Patel JD, Rose B, Zhang SR, Weatherly M, Nelakuditi V, Knight Johnson A, Helgeson M, Fischer D, Desai A, Sulai N, Ritterhouse L, Røe OD, Turaga KK, Huo D, Segal J, Kadri S, Li Z, Kindler HL, Churpek JE. Frequency of Germline Mutations in Cancer Susceptibility Genes in Malignant Mesothelioma. J Clin Oncol. 2018 Oct 1;36(28):2863-2871.

Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study. J Clin Oncol 2013; 31 (suppl; abstr 3001).

Ray M, Kindler HL. Malignant pleural mesothelioma: an update on biomarkers and treatment. Chest 2009; 136(3): 888-896.

Ribas A, Robert C, Hodi FS, et al Association of response to programmed death receptor 1 (PD-1) blockade with pembrolizumab (MK-3475) with an interferon-inflammatory immune gene signature. J Clin Oncol 33, 2015 (suppl; abstr 3001)

Rusch VW, Giroux D. Do we need a revised staging system for malignant pleural mesothelioma? Analysis of the IASLC database. Ann Cardiothoracic Surg 2012; 1(4): 438-448.

Saloura, V, Zuo, Z, Koeppen, H, et al. Correlation of T-cell inflamed phenotype with mesenchymal subtype, expression of PD-L1, and other immune checkpoints in head and neck cancer. J Clin Oncol 2014; 32:5s, (suppl; abstr 6009)

Seiwert TY, McGregor, S, Zuo Z, Khattri A, Hasina R, Vigneswaran W, Salgia R, Husain A, Kindler H. T-cell inflamed phenotype, PD-L1, and ICOS expression identify a subgroup of malignant mesotheliomas amenable to immunotherapy approaches. Proc IMIG 2014.

Seiwert TY, Burtness, B, Weiss J, Eder JP, Yearly J, Murpy E, Nebozhyn M, McClanahan M, Ayers M, Lunceford J, Mehra R,Heath K, Cheng J, Chow LQ, Inflamed-phenotype gene expression signatures, and in particular a γ-Interferon signature predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ HNC, ASCO Annual Meeting 2015, abstract 6017.

Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science 2020;367(6477).

Turaga KK, Deraco M, Alexander HR. Current management strategies for peritoneal mesothelioma. Int J Hyperthermia. 2017 Aug;33(5):579-581. doi: 10.1080/02656736.2017.1320591. PubMed PMID: 28664790.

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21 (14): 2636-2644.

White MG, Schulte JJ, Xue L, Berger Y, Schuitevoerder D, Vining CC, Kindler HL, Husain A, Turaga KK, Eng OS. Heterogeneity in PD-L1 expression in malignant peritoneal mesothelioma with systemic or intraperitoneal chemotherapy. Br J Cancer. 2021 Feb;124(3):564-566.

Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013; 369:122-33.

Wolchok JD, Hoos A, O'day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune related response criteria. Clin Cancer Res 2009; 15: 7412

Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P, Mohamed F, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol. 2009 Dec 20;27(36):6237-42. doi: 10.1200/JCO.2009.23.9640. Epub 2009 Nov 16. PubMed PMID: 19917862

Yang Z, Liu M, Yu Y, Chen T, Han Y, Zhu L, Zhao J, Fu X, Cai X. Treatment of stage III non-small cell lung cancer in the era of immunotherapy: pathological complete response to neoadjuvant pembrolizumab and chemotherapy. Transl Lung Cancer Res 2020; 9(5):2059-2073.

12.0 APPENDIX

12.1 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.	

12.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60)

12.3 Prescribing Information

12.3.1 Nivolumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf

12.3.2 Ipilimumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s110lbl.pdf

12.4 EORTC QOL-C30 Quality of Life Survey

https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf