MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2020-0296
Protocol Title	An Open-label, Single-center, Phase 1b/2 Study to Evaluate the Safety of Plinabulin in Combination with Radiation/Immunotherapy in Patients with Select Advanced Malignancies after progression on PD-1 or PD-L1 Targeted Antibodies
Protocol Phase	Phase 1b/2
Protocol Version	6.0
Version Date	10 May 2023
Protocol PI	Dr. Siqing Fu
Department	Investigational Cancer Therapeutics
IND Sponsor	MD Anderson Cancer Center
IND #	**154404**

CLINICAL STUDY PROTOCOL

An Open-label, Single-center, Phase1b/2 Study to Evaluate the Safety of Plinabulin in Combination with Radiation/Immunotherapy in Patients with Select Advanced Malignancies after progression on PD-1 or PD-L1 Targeted Antibodies

Study Number: 2020-0296

Study Phase: 1b/2

IND Number: 154404

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	Version Number	Amendment	Date
Original Protocol	4.0		08 June 2021
	5.0		16 November 2021
	6.0		10 May 2023

PROTOCOL SYNOPSIS

Name of Study Institute: MD Anderson Cancer Center
Protocol Number: 2020-0296
Name of Investigational Product: Plinabulin
Name of Active Ingredient: Plinabulin+ Anti-PD-1/PD-L1 Antibodies + Radiation Therapy
Study Title: A Single-Center, Phase1b/2 Study to Evaluate the Safety and Efficacy of Plinabulin in Combination with Radiation/Immunotherapy in Subjects with Select Advanced Solid Malignancies after progression on PD-1 or PD-L1 Targeted Antibodies
Study Phase: 1b/2
Indication Under Investigation: Advanced Solid Malignancies
Study Objectives: **Primary Objective:** • To assess the safety and tolerability of plinabulin when administered in combination with a radiation/immunotherapy regimen in subjects with select advanced solid malignancies after progression on anti-PD-1/PD-L1 mAb • To assess the objective tumor response rate (ORR) (complete response + partial response) **Secondary Objectives**: • To assess disease control rate (complete response, partial response + stable disease) • To determine progression-free survival (PFS) • To assess overall survival (OS) **Exploratory Objectives:** • To determine the gene mutation density for the evaluable samples • To assess TCR immune repertoire by sequencing in peripheral blood, pre- and post- treatment. • To perform Imaging CyTOF and/or single cell RNAseq analysis on tumor tissue: Immune Phenotyping, including DC, T cells, TAMs, pre and post treatment • To conduct phenotyping analysis of immune cells from peripheral blood using multicolor flow cytometry • To evaluate dendritic cell activation from whole blood upon the treatment • To utilize collected blood and tumor biopsy samples to discover novel response biomarkers
Study Design:

This is a single center study with a Phase 1b and a Phase 2 component.

Phase 1b:

This is an open label, single-center study to assess the safety and tolerability of plinabulin when administered in combination with radiation/immunotherapy regimens in subjects with one of several metastatic or locally advanced cancers who had disease progression on anti-PD-1/PD-L1 mAb treatment as standard of care, and to assess objective response rate of the study regimen.

The targeted cancer types for this study are as follows:

1. Bladder Cancer
2. Melanoma
3. Merkel Cell Cancer
4. MSI-H Cancers (of any histology)
5. Non-small Cell Lung Cancer
6. Renal Cell Cancer
7. Small Cell Lung Cancer
8. Any tumor type that has a checkpoint inhibitor approval

The study cohort is tumor type specific. There are 8 study cohorts as mentioned above for this study. Anti-PD-1/PD-L1 mAb treatment cycle will define subject's treatment cycle for the study.

All subjects in Phase 1b will receive a triple combo treatment of Radiation Therapy (RT) + Plinabulin + anti-PD-1/PD-L1 mAb in Cycle 1, followed by anti-PD-1/PD-L1 mAb and plinabulin combo regimen in Cycle 2 and beyond until disease progression or development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study (see table below). A short course of local consolidative RT will be administered in Cycle 1 starting from Day 1. Optional sequential RT may be administered to target other untreated lesions at discretion of the treating doctor in Cycle 2 of any regimens. Plinabulin will be dosed on Day 1 and Day 4 of Cycle 1 of any anti-PD-1/PD-L1 regimen, and if optional RT is given in Cycle 2, Plinabulin will also be given on Day 4 of Cycle 2. Plinabulin will be given on Day 1 of Cycle 3 and thereafter. Anti-PD-1/PD-L1 mAb will be dosed on Day 1 of every treatment cycle (also on Day 15 [Q4W] in case of regimen containing Avelumab or Durvalumab or Nivolumab as Anti-PD-1/PD-L1 mAb). Subjects must receive the same anti-PD-1/PD-L1 mAb they failed in the prior treatment.

Phase 1b/Phase 2: Study Drugs/Regimen

Phase 1b/Phase 2: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin** **30 mg/m^2 (Starting dose) or 20 mg/m^2**	**Anti-PD-1/PD-L1 mAb**	**DLT Window After 2 doses of Anti-PD-1/PD-L1 mAb**
RTX + Plinabulin + Avelumab	1 Cycle = 4 weeks	C1D1-3 (8 Gy x 3 fractions) or C1D1-4 (12.5 Gy x 4 fractions)	C1D1, 4 C2D1 C2D4 (optional if RT on C2D1)	Avelumab (800 mg): D1, 15 of every cycle	C1 = 4 weeks
RTX + Plinabulin + Durvalumab	1 Cycle = 4 weeks			Durvalumab (10 mg/kg): D1, 15 of every cycle	

RTX + Plinabulin + Nivolumab	1 Cycle = 4 weeks	or C1D1-5 (4 Gy x 5 fractions) C2D1 (optional)	C3 onward D1	Nivolumab (240 mg): D1, 15 of every cycle	
RTX + Plinabulin + Atezolizumab	1 Cycle = 3 weeks			Atezolizumab (1200 mg): D1 of every cycle	C1-2 = 6 weeks
RTX + Plinabulin + Pembrolizumab	1 Cycle = 3 weeks			Pembrolizumab (200 mg): D1 of every cycle	

C = cycle, D = day, DLT = dose limiting toxicity, mAb = monoclonal antibody, PD = progression disease, RT = radiation therapy.

The determination of maximum tolerated dose (MTD)

The study will begin with 30 mg/m^2 plinabulin in combination with a full dose of anti-PD-1/PD-L1 mAb and RT. Lower dose level at 20 mg/m^2 of plinabulin will be explored as necessary depending on observed toxicity. Anti-PD-1 or PD-L1 antibody dose according to FDA drug inserts will not change in Phase 1b.

The dose-limiting toxicity (DLT) is calculated after two doses of PD1/PDL1. Due to variability of the frequency of dosing, there is a range when the DLT is assessed. When PD1/PDL1 is Q2weeks, DLT period is 4 weeks. When PD1/PDL1 is Q3weeks, the DLT period is 6 weeks.

A DLT is defined as any of the following plinabulin-related adverse events (AEs) or laboratory abnormalities, graded according to NCI CTCAE version 5.0:

- Febrile neutropenia
- Grade 4 hypertension
- Grade 4 anemia unrelated to underlying disease
- Grade 3 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia lasting more than 7 days and/or requiring a platelet transfusion
- Grade 4 neutropenia lasting more than 7 days
- ≥Grade 3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting >48 hours despite optimal prophylactic and curative treatment
- ≥Grade 3 hypersensitivity reaction (unless first occurrence and resolves within 6 hours with appropriate clinical management)
- Treatment delay >21 days secondary to recovery from study drugs-related AEs.
- ≥Grade 3 non-hematologic AEs, except for the exclusions listed below.

The following events will be excluded from the DLT definition:

- Any AE ≥grade 3 clearly determined to be unrelated to study drug(s) (e.g., disease progression)
- ≥Grade 3 isolated alkaline phosphatase laboratory abnormality of any duration
- ≥Grade 3 isolated, asymptomatic amylase or lipase laboratory abnormality of any duration
- ≥Grade 3 endocrinopathies controlled by corticosteroids or hormone replacement
- Vitiligo or Alopecia of any grade
- Grade 3 fatigue.

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan et al., 2016) to find the MTD based on all comers, including the targeted cancer types. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou, Yuan and Nie, 2018). The two dose levels are 20 mg/m^2

and 30 mg/m^2 and the starting dose is 30 mg/m^2. The target DLT rate for the MTD is $\phi = 0.25$ and the maximum sample size is 12. We will enroll and treat patients in cohorts of size 3.

Once we determine the MTD, an additional 10 patients will be enrolled for additional experience with safety and efficacy in each of the eight cancer cohorts and to determine the recommended Phase 2 dose (RP2D). The RP2D will be selected based on both safety and totality of clinical evidence (e.g., PK/PD data), and is not necessarily the MTD. Patients treated at the MTD/RP2D in the dose finding will roll over into the cohort expansion. Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the expansion.

Selection of cohort that will advance into Phase 2 will be based on the following consideration:

1. The cohort with the best response rate, within a 9-week window after RT plus plinabulin with 2 cycles (3 weeks Anti-PD-1/PD-L1 mAb dosing) of Anti-PD-1/PD-L1 mAb, will advance into Phase 2, if deemed well-tolerated. Upon sponsor's discretion and totality of clinical evidence, other cohort(s) instead may be selected to advance into Phase 2. The final selection of the group to go into Phase 2 will be determined by a Safety Monitoring Committee. Please see charter for details.
2. The response evaluation will be based on a minimum of 5 subjects and up to 10 subjects per cohort, unless enrollment of a given cohort is very slow and incomplete at the time sufficient response data is available on other cohorts, in which case that given cohort could be closed for further patient accrual.

Phase 2:

Subjects with the selected tumor type will be accrued to receive the plinabulin MTD/RP2D in combination with RT and anti-PD-1/PD-L1 mAb. Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the study. They will be randomized to one of two treatment arms in a 1:1 ratio. The randomization will be stratified by the number of mets (oligo (<=3 vs > 3) and ECOG 0-1 vs 2.

Arm A: Radiation Therapy + Plinabulin + anti-PD-1/PD-L1 mAb (experimental)

Arm B: Radiation Therapy + anti-PD-1/PD-L1 mAb (control)

Subjects in Arm A will receive triple combo in Cycle 1, followed by plinabulin and anti-PD-1/PD-L1 mAb double combo for Cycle 2 and beyond (see table below).

Subjects in arm B will receive combo regimen of RT and anti-PD-1/PD-L1 mAb in Cycle 1, followed by anti-PD-1/PD-L1 mAb alone for Cycle 2 and beyond (see table below).

Treatment will continue until disease progression, development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study. Because the experimental combination arm is not expected to be worse than the control arm, no futility monitoring is planned.

A short course of local consolidative RT will be administered in Cycle 1 starting from Day 1. An optional sequential RT to other untreated lesions at discretion of the treating doctor is allowed (Cycle 2 Q4W; Cycle 2 Q3W). Plinabulin will be dosed on Day 1 of every treatment cycle and/ or anti-PD-1/PD-L1 mAb will be dosed on Day 1 of every treatment cycle ((also on Day 15 [Q4W] in case of regimen containing Avelumab or Durvalumab or Nivolumab as Anti-PD-1/PD-L1 mAb) to subjects based on their treatment assignment.

Assuming the ORR is 5% in control arm and 15% in experimental arm, based on Chi-squared test, a

sample size of 51 evaluable patients in each group is required to detect the difference with one sided type I error 0.2 and power 80% (nQuery 4.0). The BOIN elimination rule will be used to monitor toxicity in both arms independently. The monitoring will start from the 11thpatient and carried out every 10 patients.

For subjects in Phase 1b and Phase 2, toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation in accordance with prespecified dose modification instructions.

Phase 2 Only: Study Drugs/Regimen

Phase 2 only: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin 30 mg/m^2 (Starting dose) or 20 mg/m^2**	**Anti-PD-1/PD-L1 mAb**	**DLT Window**
RTX + Avelumab	1 Cycle = 4 weeks	C1D1-3 (8 Gy x 3 fractions) or C1D1-4 (12.5 Gy x 4 fractions) or C1D1-5 (4 Gy x 5fractions) C2D1 (optional)	N/A[a]	Avelumab (800 mg): D1, 15 of every cycle	N/A
RTX + Durvalumab	1 Cycle = 4 weeks			Durvalumab (10 mg/kg): D1, 15 of every cycle	
RTX + Nivolumab	1 Cycle = 4 weeks			Nivolumab (240 mg): D1, 15 of every cycle	
RTX + Atezolizumab	1 Cycle = 3 weeks			Atezolizumab (1200 mg): D1 of every cycle	
RTX + Pembrolizumab	1 Cycle = 3 weeks			Pembrolizumab (200 mg): D1 of every cycle	

C = cycle, D = day, DLT = dose limiting toxicity, mAb = monoclonal antibody, N/A = not applicable, PD = progression disease, RT = radiation therapy.
a. Plinabulin marked N/A only applies to Arm B for Phase 2, not Arm A. Plinabulin will be administered to subjects in Arm A on days listed in Phase 1b/Phase 2: Study Drugs/Regimen table above.

The Study Treatments:

Radiation Therapy (RT) Administration

Radiation therapy will be delivered using external beam radiation, with either 2D/conventional techniques, three-dimensional conformal therapy, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS) or proton beam therapy (PBT), at the discretion of the treating radiation oncologist.

Radiation Therapy (RT) will be administered with one of three regimens: 8 Gy x 3 fractions, 12.5 Gy x 4 fractions, and/or 4 Gy x 5 fractions from Days 1 to 3 (3 fractions), Days 1 to 4 (4 fractions), or Days 1 to 5 (5 fractions) in Cycle 1. The choice of RT regimens for tumors and lesions is at the discretion of the treating radiation oncologist. RT will target up to a maximum of 5 tumor lesions, and any of the radiation regimens could be use simultaneously or sequentially. Optional sequential RT is at the discretion of the treating radiation oncologist is warranted to target other untreated lesions with same regimens described above (Cycle 2 Q4W; Cycle 2 Q3W). Treatment could be for any lesions in nodes and organs including brain and bone. Please always leave at least one measurable lesion untreated for disease assessment during the study. Assessment of responses however should not be reliant on RT treated tumor lesions and bony lesions. Brain metastasis should be treated and not be used for irRECIST response assessment.

If patients develop toxicity attributable to radiation after receiving at least one dose of radiation, the rest of the radiation treatment may be discontinued if deemed by treating radiation oncologist to be in the best

interest of the patient, and the AEs will be documented. Since the number of fractions are between 3-5 fractions, patients could receive at least 1 fraction up to 5 fractions. The initially prescribed dose per fraction will not change, but it is possible to simply reduce the total dose delivered. The patient will have a visit with the treating radiation oncologist at the end of every cycle of radiation treatment.

PD-1 or PD-L1 Administration:

Subjects must be given the same anti-PD-1/PD-L1 mAb on which they have failed in prior treatment. Anti-PD-1/PD-L1 mAb will be dosed according to FDA recommendations as specified under Phase 1b and Phase 2 above. Anti-PD-1/PD-L1 mAb treatment cycle will define subject's treatment cycle for the study. The list of anti-PD-1/PD-L1 mAb approved to date for the following indications is provided here:

1) Merkel cell cancer: Avelumab, Pembrolizumab
2) Renal cell cancer: Pembrolizumab, Nivolumab
3) Bladder cancer: Durvalumab
4) MSI-H cancers (of any histology): Pembrolizumab, Nivolumab
5) Non-small cell lung cancer: Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab
6) Small cell lung cancer: Pembrolizumab, Nivolumab, Atezolizumab
7) Melanoma: Nivolumab or Pembrolizumab single agent
8) Any tumor type that has any approved immune checkpoint inhibitors

Please note any approved anti-PD-1/PD-L1 mAb can be used for the study.

Anti-PD-1/PD-L1 mAb dose and administration route:

1. Avelumab 800 mg IV over 1 hr on Day 1 and Day 15 in Q4W
2. Atezolizumab 1200 mg Q3W IV 1 hr in 1st dose, may infuse over 30 min in subsequent doses if tolerated well
3. Durvalumab 10 mg/kg IV over 1 hr on Day 1 and Day 15 in Q4W
4. Nivolumab 240 mg IV over 30-60 min on Day 1 and Day 15 in Q4W
5. Pembrolizumab 200 mg Q3W IV over 30 min

Anti-PD-1/PD-L1 mAb will be administered after the rest period (at least 3 hours, but no later than 12 hours) of RT, if applicable, and before plinabulin infusion. Please follow FDA product insert for the instructions of treatment dosing and toxicity management of each approved anti-PD-1 or PD-L1 mAb.

Plinabulin Administration. Plinabulin will be administered on Day 1 and Day 4 in Cycle 1 intravenously, and if optional RT is given in Cycle 2, Plinabulin will also be given on Day 1 and Day 4 of Cycle 2. Optional RT will always be given in Cycle 2 on Day 1. Plinabulin will always be given on Day 1 of Cycle 3 and after.

Two plinabulin dose levels may be explored in Phase 1b trial. Plinabulin dose level at 30 mg/m^2 will be first tested in Phase 1b trial. If it is not deemed tolerable during the DLT observation, then the dose at 20 mg/m^2 will be explored.

For plinabulin at 30 mg/m^2 dose level a 60-minute infusion through IV with ± 10 min window is recommended. For plinabulin at 20 mg/m^2 dose level a 30-minute infusion through IV with ± 5 min window is recommended. For patients with a body surface area (BSA) greater than 2.4 m^2, dosing should be calculated using the maximum BSA of 2.4 m^2 for Plinabulin.

Plinabulin should always be administered at 1-2 hours after completion of anti-PD-1 or PD-L1 mAb

infusion when applicable, or at least 3 hours (but not longer than 12 hours) after the radiotherapy.

Schedule of Assessments

The Schedule of Assessments for the study is shown in Table 7.

Safety & Efficacy Assessments

Safety and tolerability are assessed throughout the study according to NCI-CTCAE version 5.0

Vital signs, physical examination, and safety lab test result review (hematology, chemistry & urinalysis) will have to be performed prior to the study treatment to make sure the study treatment is safe to be administered.

Tumor assessments will be performed by the investigators based on both immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Treatment decisions by the investigator will be based on irRECIST.

Tumor assessments will be carried out during the Screening, and every 9 weeks (± 1 week) for 27 weeks (during Q3W dosing) or every 8 weeks (± 1 week) for 24 weeks (during Q4W dosing), then every 12 weeks during treatment cycles in the Treatment Phase regardless of treatment cycles and follow up period. Computed tomography (CT)/magnetic resonance imaging (MRI) scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1/ Day 1), at all tumor assessment time points, and as indicated clinically. RT treated lesions will not be used for response assessment. Please keep at least one measurable tumor lesion untreated by RT for disease response assessment across the treatment.

The tumor assessment schedule should not be affected by interruptions in study treatment. The same method of assessment used at screening must be used at all time points.

Subjects going off treatment without disease progression will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.

If the time point tumor assessment is progressive disease (PD), treatment should continue, and tumor assessments repeated at least 4 weeks later in order to confirm immune-related progressive disease (irPD).

Study Population: Advanced staged cancer subjects who are either unresponsive or relapsed following prior standard PD-1 or PD-L1 regimen +/- chemotherapy or anti-CTLA4, for one of the following cancers: non-small cell lung cancer, small cell lung cancer, renal cell cancer, bladder cancer, Merkle cell cancer, MSI-H cancer (any history), melanoma, and any other tumor type that has a checkpoint inhibitor approval.

Treatment Duration: Treatment will continue until disease progression, development of unacceptable toxicity (i.e., DLTs), withdrawal from study treatment, or discontinuation of this study.

Duration of Study:

Screen period: up to 28 days

Treatment period: Study treatment continues until disease progression (estimate 2-6 months), development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study.

Follow-up period: Study Follow-up consists of the End of Treatment Visit and the Follow-up Visits. The End of Treatment Visit will occur within 30 days following the last dose of study treatment, then transit to the Follow-up visit period. The Follow-up Visit at every 12 weeks (±1 week) continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. In the Follow-up Period, Subjects who discontinued for reasons other than progression of disease (and withdrawal from study treatment) will continue to visit the clinic for study assessments and evaluation of their disease by CT, MRI, or positron emission tomography (PET)/CT scan approximately every 12 weeks until progression of disease is determined, the patient receives additional anti-neoplastic medication, or for a maximum of 5 years. Subjects who stopped treatment due to disease progression will be followed up for survival status.

Subject Eligibility Criteria:

Inclusion Criteria:

1. Subjects must have one of several histologically or cytologically confirmed malignant neoplasms (non-small cell lung cancer, small cell lung cancer, renal cell cancer, bladder cancer, Merkle cell cancer, MSI-H cancer (any history), melanoma, and any other tumor type with checkpoint inhibitor approval that may or may not have progressed on previous anti-PD-1/PD-L1 mAb treatment +/- chemotherapy or anti-CTLA4 requiring further treatment.
2. At least one lesion is amenable to radiation
3. At least one additional non-contiguous lesion that has not been irradiated amenable to radiographic evaluation
4. Have measurable disease based on irRECIST.
5. Tissue must be newly obtained as a core needle biopsy (not FNA) of the lesion being evaluated
6. Age ≥ 18 years.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Subjects must be recovered from any prior major surgery. The major surgery must be performed at least 4weeks prior to consent date.
9. Adequate hematologic function defined as:
    i. platelets≥100×10^9/L,
    ii. hemoglobin ≥ 9 g/dL
    iii. absolute neutrophil count (ANC) ≥1.5×10^9/L,
    iv. white blood cell (WBC) ≥ 3×10^9/L.

    Transfusions and growth factors are allowed.
10. Adequate liver function defined as:
    i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×upper limit of normal (ULN) (≤1.5×ULN if alkaline phosphatase is >2.5×ULN) (In the expansion cohort, subjects with known liver involvement may have ALT ≤5×ULN),

ii. Alkaline phosphatase < 4×ULN,
iii. Total Bilirubin ≤1×ULN (In the expansion cohort, subjects with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3×ULN),
iv. Albumin ≥ 3g/dL.

11. Renal function defined as a calculated or measured glomerular filtration rate (GFR) ≥30 mL/min and Cockcroft-Gault equation.
12. The patient has recovered to Grade ≤ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI-CTCAE v5.0) from the effects of recent surgery, radiotherapy, chemotherapy, hormonal therapy, or other targeted therapies, with the exception of alopecia. The exceptions for such effects are allowed lab values of ≤ Grade 2 specified elsewhere in these inclusion criteria.
13. Subjects must give informed consent according to the rules and regulations of the individual participating sites.
14. Negative urine pregnancy test in women of childbearing potential within 7 days of first dose of treatment and subjects of child-bearing potential must agree to use effective contraception during and for 5 months following the last dose of atezolizumab or nivolumab, for 4 months after the last dose of pembrolizumab, and for 3 months after last dose of Durvalumab and Avelumab, and for 3 months after your last dose of plinabulin. A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable or mechanical contraception; women who are single and women whose male sexual partners have been vasectomized or whose male sexual partners have received or are utilizing mechanical contraceptive devices.

Exclusion Criteria:

1. Evidence of complete or partial bowel obstruction.
2. Subjects with primary central nervous system (CNS) tumor or CNS tumor involvement. However, subjects with metastatic CNS tumors may participate in this study if the patient is:
   - >4 weeks from prior therapy completion
   - Clinically stable with respect to the CNS tumor at the time of study entry
   - Not receiving steroid therapy in treating CNS tumor or CNS tumor involvement
   - Not receiving anti-convulsive medications (that were started for brain metastases).
3. Need of Total Parenteral Nutrition.
4. Allergic to any of PD1/ PDL1 agents intended to receive.
5. Prior exposure to plinabulin.
6. Pregnancy or lactation.
7. Radiation (except planned or ongoing palliative radiation to bone outside of the region of measurable disease) ≤3 weeks prior to study drug administration date.
8. Chemotherapy, or immunotherapy or any other systemic anticancer therapy ≤ 3 weeks prior to study drug administration date except anti-PD-1/PD-L1 mAb mono or combination therapy.
9. Diagnosis or recurrence of invasive cancer other than the present cancer within 3 years (except basal or squamous cell carcinoma of the skin that has been definitively treated).
10. Major surgery within four weeks before consent date.
11. Unstable cardiovascular function or active cardiac disease:
    - Symptomatic ischemia (chest pain of cardiac origin), or
    - Uncontrolled clinically significant conduction abnormalities (e.g. ventricular tachycardia on antiarrhythmics are excluded; 1st degree AV

block or asymptomatic left anterior fascicular block (LAFB)/ right bundle branch block (RBBB) will not be excluded), or
- Congestive heart failure (CHF) of NYHA Class ≥3, or
- Myocardial infarction (MI) within 3 months of consent date.

12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to the first dose. Active infection with concurrent treatment is acceptable only if the patient is clinically stable.
13. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C.
14. Significantly diseased (as determined by the Principal Investigator [PI] or treating physician) or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea. Presence of ileus or other significant gastrointestinal disorder known to predispose to ileus or chronic bowel hypomotility
15. Treatment with an investigational anti-cancer study drug within 3 weeks prior to study drug administration date.
16. Concurrent therapy with approved or investigational anticancer therapeutics except PD-1/PD-L1 associated treatments.
17. Medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
18. Men whose partner is a woman of child-bearing potential, (i.e., biologically able to conceive), and who is not employing two forms of highly effective contraception. Highly effective contraception (e.g., male condom with spermicide, diaphragm with spermicide, intra-uterine device) must be used by both sexes during the study and must be continued for 5 months following the last dose of atezolizumab or nivolumab, and 4 months after the last dose of pembrolizumab, and for 3 months after last dose of Durvalumab and Avelumab, and for 3 months after your last dose of plinabulin. Women of child-bearing potential is defined as sexually mature women who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (e.g., who has had menses any time in the preceding 12 consecutive months).

Study Endpoints:

Primary Endpoint:

1. Safety and Tolerability: AEs will be evaluated according to NCI-CTCAE version 5.0
2. The objective tumor response rate (complete response + partial response), assessed according to irRECIST criteria

Secondary Endpoints:

1. Disease control rate (complete response, partial response+ stable disease) assessed according to irRECIST criteria)
2. Progression-free survival (PFS).
3. Overall Survival (OS)

Exploratory Endpoints:

1. Gene mutation density
2. Immune repertoire TCR sequencing change in peripheral blood
3. Immune phenotypes in tumor tissue, including DC, T cells, TAMs, pre- and post-treatment
4. Phenotypes of Immune cells in peripheral blood
5. Dendritic cell activation in peripheral blood
6. To explore predictive and response biomarkers for treatment response based on the

collected biomarkers

Statistical Methods:

Statistical Considerations:

Pre-planned analysis population

Safety Population: All subjects who received at least one dose of study medication.

Modified Intent-to-Treat population (mITT Population): All safety subjects who provide post treatment tumor assessments or present clinical disease progression post treatment without any formal post treatment tumor assessments. The efficacy analysis will be based on the mITT population.

Per Protocol Population (PP Population) will include all mITT population without major protocol deviation. The criteria for PP Population exclusion will be documented before data base is locked.

PK Population: All the subjects who have received at least 1 dose of plinabulin and have evaluable concentration data.

Sample Size

In the initial Phase 1b portion of the study, 12 all-comers patients will be recruited for the dose determination and up to 80 subjects are expected to be recruited in 8 tumor specific cohorts. In the Phase 2 portion, 102 will be recruited in two arms. A maximum number of 194 patients will be enrolled. Screen failures will be replaced with the next eligible patient.

Safety Analysis

All AEs occurring during the course of the study and for up to 30 Days after the last dose of study medication will be captured, documented and reported. Toxicity is graded according to NCI-CTCAE version 5.0.

Vital signs and safety blood tests including complete blood count and clinical chemistry (including liver/renal function tests) will be checked at screening, every treatment Cycle and end of treatment. A physical examination will be performed at screening, Day 1 of each Cycle, end of study, and at follow-up; a symptom-directed examination will be performed at other visits. Urinalysis will be performed at screening, and the end of treatment. Coagulation and will be performed at the screening, Cycle 1 Day 1, and end of Treatment, and will be additionally monitored when clinically indicated. Electrocardiogram (EKG) will be performed at Screening, Cycle 1 Day 1, and as clinically indicated.

Pregnancy test for childbearing potential subjects will be performed within 7 Days of the 1st study treatment, on Day 1 of each Cycle afterward.

In Phase 1, BOIN study design is used to determine the MTD. In Phase 2, the BOIN elimination rule is used for toxicity monitoring.

Efficacy Analysis

ORR will be defined as percent of subjects achieved complete response (CR) or partial response (PR).

Disease control rate defined as percent of subjects achieved CR, PR, and stable disease

PFS is defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurs first).

OS is measured from the start date of the treatment period until date of death from any cause. Subjects

who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive.

The mITT Subjects without any post treatment tumor assessments will be treated as non-responders.

Chi-square or Fisher's exact test is used to compare ORR and disease control rate between two arms in phase 2. ORR and disease control rate are estimated with 95% confidence interval.

The time-to-event endpoints including overall survival, progression free survival will be analyzed using Kaplan-Meier method or Cox regression.

Companion Translational Study

Gene Mutation Evaluation:

We expect most patients enrolled will have had hot spot mutation testing or targeted exome profiling performed prior to enrollment. If there is evidence of clinical activity, targeted exome sequencing on a 200-400 gene platform or larger will be performed in those patients with objective responses and prolonged stable disease >6 months as well as any patients with rapid progression (this could be done as part of an Institute of Personalized Cancer Therapy Unusual Responder Program). In addition, patients who have a response with subsequent progression will be approached for optional biopsies for molecular characterization as well as generation of patient derived xenografts and conditionally reprogrammed cells. This evaluation will determine the evolution of mutations with treatment under this protocol.

Biomarker Testing

The following immune regulatory cells and markers will be studied to better understand the plinabulin's mechanisms of action and to identify potential predictors of responsive subjects that can be utilized to enrich for responders in subsequent clinical studies.

- The Imaging-guided core needle tumor biopsy samples (at least 2 to 4 research cores) will be collected at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1 of immunotherapy with Plinabulin. The biopsied lesion should not have been targeted by radiation. If there has been a complete response in the pre-treatment biopsied lesion, another non-irradiated lesion could be biopsied with any response (partial, stable, or progressive), but should be documented clearly. Multiple lesions could be biopsied if it is safe to do and has clear biologic or clinical rationale to do so.
- The whole blood samples will be collected at screening (<1 week prior to triple combo), and Cycle 1 Day 4, then pre-treatment Day 1 of every 2 cycles and End of treatment (EOT) (2 – 10 mL EDTA/purple top (processed for peripheral blood mononuclear cell [PBMC], plasma, whole blood DNA), 1 – 10 mL Heparin/Green top (for flow cytometry and DC activation assay), 1 – 10 mL Streck tube (for plasma and germline DNA).

Minimum measurements on core needle tumor biopsies

- Imaging CyTOF analysis and/or single cell RNAseq: Immune phenotypes of tumor phenotypes including DC, T cells, TAMs

Minimum measurements on whole blood PBMC collected for biomarker evaluation

- Phenotyping analysis of immune cells from peripheral blood using multicolor flow cytometry (Purple top tube)
- Immune repertoire TCR sequencing on whole blood or PBMCs (Purple top tube)
- Dendritic Cell activation assay from whole blood (Green cap tube)

Exploratory Biomarker Research including Pharmacogenomic Study

Blood samples for the development of exploratory predictive biomarkers will be collected prior to the first dose of study drug, on Cycle 1 Day 4, then on Day 1 of every 2 cycles (C3, 5, etc.) for both Q4W and Q3W during Treatment Phase, and at the End-Of-Treatment assessment. Subjects will be required to provide a fresh biopsy of tumor before treatment, and within 7 days prior to Cycle 3 Day 1 of the study treatment for biomarker analyses. Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers which may be useful to predict subject response to the study treatment, as determined by evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples from subjects receiving study treatment may be analyzed using RNAseq, Flow cytometry, multiplex bead-based immunoassay, or other assays/methods or new technology. In addition, biomarkers identified in other plinabulin studies may also be assessed in the biomarker samples collected from subjects enrolled in this study.

A blood sample for PBMCs and plasma isolation will be collected from enrolled subjects. Cell free nucleic acid isolated from plasma samples may be used to obtain circulating tumor DNA (ctDNA) and explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Any leftover samples from the translational study will be stored for up to 15 years from the study closure for future research. The samples may be used to study the mechanism of the study treatment or to explore the predictive and response biomarkers for the diseases or the treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HBs	Hepatitis B surface antibody
AOC	Area over the curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BOIN	Bayesian optimal interval
BSA	Body surface area
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRM	Continual reassessment method
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Cell free circulating tumor DNA
CTV	Clinical Target Volume
D5W	Dextrose 5% in distilled water
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal

Abbreviation or Specialist Term	Explanation
GTV	Gross Tumor Volume
HIV	Human Immunodeficiency Virus
HPF	High power field
ICF	informed consent form
ICH	International Council on Harmonisation
ICI	Immune checkpoint inhibitor
IEC	Independent Ethics Committee
iGTV	Internal Gross Tumor Volume
IL	interleukin
INR	International normalized ratio
IMRT	Intensity modulated radiation therapy
IND	Investigational New Drug
IRB	Institutional Review Board
irCR	Immune-related complete response
irPR	Immune-related partial response
irPD	Immune-related progressive disease
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
irSD	Immune-related stable disease
ITT	intent-to-treat
IV	Intravenous
LAFB	Left anterior fascicular block
mAb	Monoclonal Antibody
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mITT	Modified Intent-to-Treat
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OAE	Other adverse event
OAR	Organ at Risk
ORR	Overall response rate

Abbreviation or Specialist Term	Explanation
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PBT	Proton beam therapy
PET	Positron emission tomography
PFS	Progression-free survival
PG	Pharmacogenomic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per Protocol
PR	Partial response
PT	Prothrombin time
PTV	Planning Target Volume
RBBB	Right bundle branch block
RECIST	Response Evaluation Criteria In Solid Tumors
RT	Radiation Therapy
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SOC	System organ class
SOP	Standard Operating Procedure
t½	Half-life
ULN	Upper limit of normal
V_z	Volume of distribution
WHO	World Health Organization

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Investigational Product(s)

1.1.1. Plinabulin

Plinabulin (BPI-2358) is a synthetic, low molecular weight, new chemical entity that belongs to the diketopiperazine class of compounds. The chemical name of plinabulin is 2,5-piperazinedione, 3-[[5-(1,1-dimethylethyl)-1H-imidazol-4-yl] methylene]-6-(phenylmethylene)-, (3Z,6Z).

Plinabulin, which inhibits the polymerization of tubulin monomers, is a differentiated tubulin binder, in binding pocket and binding kinetics, with other tubulin binders (La Sala et al., 2019). It has multiple mechanisms of action that inhibit tumor growth. Plinabulin targets angiogenesis and the existing tumor vasculature and also directly induces cancer cell apoptosis via the JNK pathway (Nicholson et al., 2006, Singh et al., 2011, Kennedy et al., 2003). Plinabulin stimulates the tumor-related immune system by means of dendritic cell maturation and enhances the antitumor activity of checkpoint inhibitors in an immune-competent mouse model (Lloyd et al., 2016, Kashyap et al., 2019). The safety profile of plinabulin appears to be superior to that of other agents with immune- oncology effects, such as checkpoint inhibitors (e.g., nivolumab), providing a potential safety advantage. Thus, plinabulin may prove to be efficacious in the management of cancers such as advanced non-small cell lung cancer (NSCLC). A Phase 3 global trial with plinabulin in combination with docetaxel is underway in NSCLC patients. (Study NPI-2358-103).

Preclinical evidence shows that plinabulin induces maturation of dendritic cells, resulting in the release of the cytokines interleukin (IL)-1β, IL-6, and IL-12 from monocytes/dendritic cells (Lloyd et al, 2016). In particular tissue level IL-6 is implicated in the prevention of neutrophil apoptosis (Asensi et al., 2004) and IL-1β with increased neutrophil count (Dinarello, 2011).

1.2. Background Information

1.2.1. Immune checkpoint inhibitors (ICI) as first line therapy for advanced cancers

Immune checkpoint inhibitors (ICIs), most prominently are anti-PD-1 and PD-L1 agents, are first line indication for a number of tumor types, with responses that range from 15-60%. For cancers like lung cancer, ICI responses are augmented when combined with chemotherapy. These strategies have substantially enhanced survival of advanced cancer patients. However, many patients become refractory to ICI after which limited options are available. There is a significant need to identify strategies that could help reverse ICI resistance and prolong the utilization of ICI.

1.2.2. Plinabulin as an immune modulatory agent by stimulating dendritic cells

Plinabulin (BPI-2358) is derived from a molecule produced by a marine-fungus and is a unique molecular class of agents that reversibly bind to β-tubulin within the colchicine pocket,

preventing polymerization into microtubules. Following microtubule disruption, plinabulin causes diverse cellular effects include direct killing of cancer cells and increase dendritic cell maturation (Kashyap et al., 2019), leading to tumor antigen specific T cell activation, as well as reducing chemotherapy induced neutropenia in cancer patients. Plinabulin demonstrates a favorable safety profile and encouraging anti-tumor responses in two early phase clinical trials. Based on these results, plinabulin is currently in Phase 3clinical development in combination with docetaxel and in Phase 1/2 trials in combination with nivolumab in NSCLC as well as with nivolumab and ipilimumab combo in advanced Small Cell Lung Cancer.

1.2.3. Radiation

Radiation therapy has also been shown to promote a potent immunogenic release of tumor antigen and local cytokines, priming the adaptive immune system towards tumor control. Such immune education has been shown to promote distal disease control (also known as the abscopal effect) both in pre-clinical models, clinical cases, and early clinical trials. Clinical descriptions of this phenomenon have been predominately limited and most often in sporadic case reports where unexpected yet pronounced distal tumor regression are observed outside of radiation fields. The effect has become reproducible and robust when it is given concomitantly with immunotherapies (Kaminski et al., 2005). So far, most of the proof comes from preclinical studies showing synergy of radiation and immunotherapies, and some case reports or small clinical trials in metastatic melanoma showing that adding high dose ablative radiotherapy to a single site disease with either ipilimumab (Postow et al., 2012) or IL-2 (Seung et al., 2012) can generate systemic response rates that are much bigger than given drug alone. While trials in lung cancer are being planned, most of these trials are still being planned for the metastatic setting.

1.3. Study Rationale

Non-clinical studies demonstrated the efficacy of anti-PD-L1 combined with radiotherapy in preclinical models of lung cancer. One study (Deng et al., 2014), showed that combining anti-PD-L1 enhanced the efficacy of radiation through a CD8+ T cell dependent mechanism. The anti-tumor effect was seen both locally in the primary tumor, but also in a contralateral, non-irradiated tumor, supporting the role of radiation inducing a “distant”, or abscopal, anti-tumor effect, that is synergistic with anti-PD-L1. In a second study (Deng et al., 2014), the authors discovered that radiation induced PD-L1 expression, and by combining radiation with anti-PD-L1 antibody therapy induces a T-cell mediated depletion of myeloid-derived suppressor cells (MDSC) via TNF-mediated signaling. A third study (Dovedi et al., 2014), also demonstrated that conventional fractionated radiotherapy led to upregulation of PD-L1 expression on a number of syngeneic mouse tumor models. By administering an anti-PD-L1 antibody along with conventional fractionated radiotherapy, the authors demonstrated significant improvement in CD8+ T cell infiltration into tumors, and generated significantly improved local tumor control, long term survival, and a protection against tumor rechallenge. It is however unknown in the setting of immunotherapy resistance, how radiation could resensitize tumor response when combined with ICI alone, or may require an additional pathway such as dendritic cell activation to help promote immunotherapy response in the context of resistance.

Hypothesis: The central hypothesis of this study is that radiation with plinabulin could help reverse ICI resistance in ICI-refractory tumors and generate responses that are greater than radiation with ICI alone.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To assess the safety and tolerability of plinabulin when administered in combination with radiation/immunotherapy regimen in subjects with select advanced solid malignancies after progression on anti-PD-1/PD-L1 monoclonal antibody (mAb)
- To assess the objective tumor response rate (complete response + partial response)

2.2. Secondary Objectives

- To assess disease control rate (complete response, partial response + stable disease)
- To determine progression-free survival (PFS)
- To assess overall survival

2.3. Exploratory Objectives

- To analyze the gene mutation density within each sample
- To assess TCR sequencing in tumor tissue and peripheral blood, pre- and post- treatment.
- To perform Imaging CyTOF and/or single cell RNAseq analysis on tumor tissue: Immune phenotyping, including DC, T cells, TAMs, pre- and post-treatment.
- To conduct phenotyping analysis of immune cells from peripheral blood using multicolor flow cytometry.
- To evaluate dendritic cell activation from whole blood upon the treatment.
- To explore general predictive and response biomarker measurements from the collected biomarkers

2.4. Overall Study Design and Plan

This is a single center study with a Phase 1b and a Phase 2 component.

Phase 1b:

This is an open label, single-center study to assess the safety and tolerability of plinabulin when administered in combination with Radiation/Immunotherapy regimens in subjects with one of several metastatic or locally advanced cancers who had disease progression on anti-PD-1/PD-L1 mAb treatment as standard of care. The targeted cancer types for this study are as follows:

1. Bladder Cancer
2. Melanoma
3. Merkel Cell Cancer
4. MSI-H Cancers (of any histology)
5. Non-small Cell Lung Cancer
6. Renal Cell Cancer
7. Small Cell Lung Cancer

8. Any other tumor type that has a checkpoint inhibitor approval

Anti-PD-1/PD-L1 mAb treatment cycle will define subject's treatment cycle for the study.

All subjects in Phase 1b will receive a triple combo treatment of Radiation Therapy (RT) + plinabulin + anti-PD-1/PD-L1 mAb in Cycle 1, followed by anti-PD-1/PD-L1 mAb and plinabulin combo regimen in Cycle 2 and beyond until disease progression or development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study (Table 1). A short course of local consolidative RT will be administered in Cycle 1 starting from Day 1. Optional sequential RT to other untreated lesions at discretion of the treating doctor is allowed in Cycles 2 of any anti-PD-1/PD-L1 regimen. Plinabulin will be dosed on Day 1 and Day 4 of Cycle 1 of any anti-PD-1/PD-L1 regimen, and if optional RT is given in Cycle 2 Day 1, Plinabulin will also be given on Day 4 of Cycle 2. If optional RT is not given on Cycle 2 Day 1, then Plinabulin will be administered on Day 1 of Cycle 3 and after. Anti-PD-1/PD-L1 mAb will be dosed on Day 1 of every treatment cycle (also on Day 15 [Q4W] in case of regimen containing Avelumab or Durvalumab or Nivolumab as Anti-PD-1/PD-L1 mAb). Subjects must receive the same anti-PD-1/PD-L1 mAb they failed in the prior treatment.

The two dose levels of plinabulin are 20 mg/m^2 and 30 mg/m^2 and the starting dose is 30 mg/m^2. Lower dose level at 20 mg/m^2 of plinabulin will be explored as necessary depending on observed toxicity. We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan et al., 2016) to find the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou et al., 2018).

Once we determine the MTD, an additional 10 patients will be enrolled for additional experience with safety and efficacy in each of the eight cancer cohorts. Patients treated at the MTD in the dose finding will roll over into the cohort expansion. We will use the elimination boundaries for dose-limiting toxicity (DLT) monitoring.

Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the study.

Table 1: Phase 1b/Phase 2: Study Drugs/Regimen

Phase 1b/Phase 2: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin** 30 mg/m^2 (Starting dose) Or 20 mg/m^2	**Anti-PD-1/PD-L1 mAb**	**DLT Window** **After 2 doses of Anti-PD-1/PD-L1 mAb**
RTX + Plinabulin + Avelumab	1 Cycle = 4 weeks	C1D1-3 (8 Gy x 3 fractions) or C1D1-4 (12.5 Gy x 4 fractions)	C1D1, 4 C2D1 C2D4 (optional if RT on C2D1) C3 onward D1	Avelumab (800 mg): D1, 15 of every cycle	C1 = 4 weeks
RTX + Plinabulin + Durvalumab	1 Cycle = 4 weeks			Durvalumab (10 mg/kg): D1, 15 of every cycle	

Phase 1b/Phase 2: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin** 30 mg/m^2 (Starting dose) Or 20 mg/m^2	**Anti-PD-1/PD-L1 mAb**	**DLT Window** **After 2 doses of Anti-PD-1/PD-L1 mAb**
RTX + Plinabulin + Nivolumab	1 Cycle = 4 weeks	or C1D1-5 (4 Gy x 5 fractions) C2D1 (optional)		Nivolumab (240 mg): D1, 15 of every cycle	
RTX + Plinabulin + Atezolizumab	1 Cycle = 3 weeks			Atezolizumab (1200 mg): D1 of every cycle	C1-2 = 6 weeks
RTX + Plinabulin + Pembrolizumab	1 Cycle = 3 weeks			Pembrolizumab (200 mg): D1 of every cycle	

C = cycle, D = day, DLT = dose-limiting toxicity, mAb = monoclonal antibody, PD = progression disease, RT = radiation therapy.

Selection of cohort that will advance into Phase 2 will be based on the following consideration:

1. The cohort with the best response rate, within a 9-week window after RT plus plinabulin with 2 cycles (3 weeks Anti-PD-1/PD-L1 mAb dosing) of Anti-PD-1/PD-L1 mAb, will advance into Phase 2, if deemed well-tolerated.
2. The response evaluation will be based on a minimum of 5 subjects and up to 10 subjects per cohort, unless enrollment of a given cohort is very slow and incomplete at the time sufficient response data is available on other cohorts, in which case that given cohort could be closed for further patient accrual.
3. The final selection of the group to go into Phase 2 will be determined by a Safety Monitoring Committee.

Phase 2:

The cohort which is selected by the Safety Monitoring Committee will be selected for the Phase 2 portion of the study. Subjects with the selected tumor type will be accrued to receive the plinabulin MTD in combination with RT and anti-PD-1/PD-L1 mAb. Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the study. They will be randomized to one of two treatment arms in a 1:1 ratio. The randomization will be stratified by the number of mets (oligo (<=3 vs > 3) and Eastern Cooperative Oncology Group (ECOG) 0-1 vs 2.

Arm A: Radiation Therapy + Plinabulin + PD-1 or PD-L1 (experimental)

Arm B: Radiation Therapy + PD-1 or PD-L1 (control)

Subjects in Arm A will receive triple combo in Cycle 1, followed by plinabulin and anti-PD-1/PD-L1 mAb double combo for Cycle 2 and beyond (Table 2).

Subjects in Arm B will receive combo regimen of RT and anti-PD-1/PD-L1 mAb in Cycle 1, followed by anti-PD-1/PD-L1 mAb alone for Cycle 2 and beyond (Table 2).

Assuming the overall response rate (ORR) is 5% in control arm and 15% in experimental arm, based on Chi-squared test, a sample size of 51 evaluable patients in each group is required to detect the difference with one sided type I error 0.2 and power 80% (nQuery 4.0). The BOIN elimination rule will be used to monitor toxicity in both arms. The toxicity monitoring will start from the 11th patient and carried out every 10 patients.

The study treatment continues until disease progression or development of unacceptable toxicity, withdrawal from study treatment, or discontinuation of this study.

A short course of local consolidative RT will be administered in Cycle 1 starting from Day 1. An optional sequential RT to other untreated lesions at discretion of the treating doctor is allowed (Cycle 2 Q4W; Cycle 2 Q3W). Plinabulin and/or anti-PD-1/PD-L1 mAb will be dosed on Day 1 of every treatment cycle to subjects based on their treatment assignment.

Table 2: Phase 2 Only: Study Drugs/Regimen

Phase 1b/Phase 2: Study Drugs/Regimen	**Cycle Length**	**Radiation Therapy (RT)**	**Plinabulin 30 mg/m^2 (Starting dose) Or 20 mg/m^2**	**Anti-PD-1/PD-L1 mAb**	**DLT Window**
RTX + Avelumab	1 Cycle = 4 weeks	C1D1-3 (8 Gy x 3 fractions) or C1D1-4 (12.5 Gy x 4 fractions) or C1D1-5 (4 Gy x 5fractions) C2D1 (optional)	N/A	Avelumab (800 mg): D1, 15 of every cycle	N/A
RTX + Durvalumab	1 Cycle = 4 weeks			Durvalumab (10 mg/kg): D1, 15 of every cycle	
RTX + Nivolumab	1 Cycle = 4 weeks			Nivolumab (240 mg): D1, 15 of every cycle	
RTX + Atezolizumab	1 Cycle = 3 weeks			Atezolizumab (1200 mg): D1 of every cycle	
RTX + Pembrolizumab	1 Cycle = 3 weeks			Pembrolizumab (200 mg): D1 of every cycle	

C = cycle, D = day, DLT = dose-limiting toxicity, mAb = monoclonal antibody, N/A = not applicable, PD = progression disease, RT = radiation therapy.
a. Plinabulin marked N/A only applies to Arm B for phase 2, not Arm A. Plinabulin will be administered to subjects in Arm A on days listed in Table 1 above.

For entire study all efficacy endpoints, other than overall survival (OS), will be based on the tumor assessments performed by the investigators using both immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Treatment decisions by the Investigator will be based on irRECIST.

Safety and tolerability are assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Vital signs, physical examination, and safety lab test result review (hematology, chemistry & urinalysis) will have to be performed prior to the study treatment to make sure the study treatment is safe to be administered.

2.5. Study Endpoints

2.5.1. Primary Endpoint

1. Safety and tolerability, adverse events (AEs) according to NCI CTCAE version 5.0
2. The objective tumor response rate (complete response + partial response), assessed according to irRECIST criteria

2.5.2. Secondary Endpoints

1. Disease control rate (complete response, partial response + stable disease) assessed according to irRECIST criteria
2. Progression-free survival (PFS)
3. Overall Survival (OS)

2.5.3. Exploratory Endpoints

1. Gene mutation density for each patient
2. Immune repertoire TCR sequencing change in peripheral blood
3. Immune phenotypes in tumor tissue, including DC, T cells, TAMs, pre and post treatment
4. Phenotypes of immune cells in peripheral blood
5. Dendritic cell activation in peripheral blood
6. Additional exploratory measurements on Blood or Tumor Biopsy samples, with the goal of developing Predictive and Response Biomarkers

2.5.4. Number of Patients

In the initial Phase 1b portion of the study, 12 patients will be recruited for the dose determination and up to 80 subjects are expected to be recruited in 8 tumor specific cohorts. In the Phase 2 portion, 102 will be recruited in two arms. A maximum number of 194 patients will be enrolled. Screen failures will be replaced with the next eligible patient.

2.5.5. Study Duration

Screen period: up to 28 days.

Treatment period: Study treatment continues until disease progression (estimate 2-6 months), development of unacceptable toxicity, withdrawal of consent, or discontinuation of this study.

Follow-up period: Follow-up consists of the End of Treatment Visit and the Follow-up Visits. The End of Treatment Visit will occur within 30 days following the last dose of study treatment, then transit to the Follow-up visit period. The Follow-up Visit at every 12 weeks (±1 week)

continue as long as the study subject is alive unless the subject withdraws consent or until the study is terminated. In the Follow-up Period, Subjects who discontinued for reasons other than progression of disease (and withdrawal of consent for participation in the study) will continue to visit the clinic for study assessments and evaluation of their disease by computed tomography (CT), magnetic resonance imaging (MRI) scan approximately every 12 weeks until progression of disease is determined, the patient receives additional anti-neoplastic medication, or for a maximum of 5 years.

2.5.6. Study Discontinuation

MD Anderson and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, MD Anderson and the Investigator will assure that adequate consideration is given to the protection of the patient's interests. Subjects will be followed up for survival status.

The study treatment will continue until any one of the following occurs:

- Drug related AEs which prevent further dosing
- Initiation of a protocol-prohibited concomitant medication or non-protocol chemo/biological therapy for treatment of their disease.
- Development of a serious adverse event (SAE)/AE, illness, or condition that may interfere with the patient's participation or require treatment discontinuation.
- Investigator opinion.
- Voluntary withdrawal of consent.

2.6. Selection of Doses

2.6.1. Experimental Treatments

The determination of maximum tolerated dose (MTD)

Based on other plinabulin study data, the 30 mg/m^2 plinabulin dose appeared to have more anti-cancer activity than the 20 mg/m^2 plinabulin dose, when combined with Docetaxel, in NSCLC patients. The safety profile of the 30 mg/m^2 dose was favorable as obtained from more than 250 patients exposed to the 30 mg/m^2 plinabulin dose to-date. The most frequent safety events observed were nausea, vomiting and diarrhea, and transient hypertension around the time of infusion.

The study will begin with 30 mg/m^2 plinabulin in combination of full dose of anti-PD-1/PD-L1 mAb according to FDA package inserts and RT. Lower dose level at 20 mg/m^2 of plinabulin will be explored as necessary depending on observed toxicity. Anti-PD-1/PD-L1 mAb dose will not change in the study. For determination of MTD, only DLTs during the initial 4 or 6 weeks (dependent on study drug) of the treatment will be assessed. The DLT is calculated after two doses of PD1/PDL1. Due to variability of the frequency of dosing, there is a range when the

DLT is assessed. When PD1/PDL1 is Q2weeks, DLT period is 4 weeks. When PD1/PDL1 is Q3weeks, the DLT period is 6 weeks.

A DLT is defined as any of the following plinabulin-related AEs or laboratory abnormalities, graded according to NCI CTCAE version 5.0:

- Febrile neutropenia
- Grade 4 hypertension
- Grade 4 anemia unrelated to underlying disease
- Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia lasting more than 7 days and/or requiring a platelet transfusion
- Grade 4 neutropenia lasting more than 7 days despite the use of granulocyte colony-stimulating factor (G-CSF)
- ≥Grade 3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting >48 hours despite optimal prophylactic and curative treatment
- ≥Grade 3 hypersensitivity reaction (unless first occurrence and resolves within 6 hours with appropriate clinical management)
- Treatment delay >21 days secondary to recovery from study drugs-related AEs
- ≥Grade 3 non-hematologic AEs, except for the exclusions listed below.

The following events will be excluded from the DLT definition:

- Any AE ≥Grade 3 clearly determined to be unrelated to study drug(s) (e.g., disease progression)
- ≥Grade 3 isolated alkaline phosphatase laboratory abnormality of any duration
- ≥Grade 3 isolated, asymptomatic amylase or lipase laboratory abnormality of any duration
- ≥Grade 3 endocrinopathies controlled by corticosteroids or hormone replacement
- Vitiligo or Alopecia of any grade
- Grade 3 fatigue.

We will employ the BOIN design (Liu and Yuan, 2015, Yuan et al., 2016) to find the MTD/RP2D. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as CRM (Zhou et al., 2018).The target DLT rate for the MTD is $\phi = 0.25$ and the maximum sample size is 12. We will enroll and treat patients in cohorts of size 3.

In order to be evaluable for DLT assessment, subjects must complete first cycle treatment. Subjects who experience a DLT within the first 4 or 6 weeks (dependent on study drug) of

treatment and drop out of the study will be considered evaluable for DLT and will not be replaced. Patients who drop out of the study for reasons other than DLT during the first 4 or 6 weeks (dependent on study drug) will be considered not evaluable and will be replaced.

Once plinabulin MTD/RP2D is confirmed, it will be considered as the recommended dose for the Phase 1b expansion of the eight cancer cohorts and Phase 2.

Anti-PD-1/PD-L1 mAb dose will follow FDA recommendations to each indication and will not change in the study.

2.6.2. Dose Delay or Dose Adjustment Criteria

The NCI CTCAE v5.0 will be used to grade AEs. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for AEs (all grades), SAEs, and AEs requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

In the event of multiple toxicities, dose delays and modifications should occur in accordance with the highest grade of AEs observed. All patients with dose interruptions for 28 consecutive days due to toxicity that does not resolve to grade 1 or less, with or without treatment, will be discontinued from study treatment. All patients with evidence of radiographically confirmed progressive disease or clinical evidence of disease progression or global deterioration of health unrelated to progressive disease, as defined by irRECIST, will be discontinued from study treatment.

Plinabulin

The general approach to dose delay and modification of plinabulin are shown below (Table 3). Two dose levels of plinabulin (30 mg/m^2 and 20 mg/m^2) are suggested for dose modification. Plinabulin dose reduction to below 20 mg/m^2 is not recommended. In that case plinabulin should be discontinued. Plinabulin dosing must be withheld if the patient has evidence or signs of any medical conditions that would prevent dosing (such as an infection, grade 4 neutropenia or unacceptable medical condition).

At the discretion of the Investigator, the dose may be delayed for up to 28 consecutive days for any toxicity possibly or probably related to plinabulin that does not meet DLT criteria. Dosage interruptions to assess or treat intercurrent illnesses are allowed and should be clearly described in the study eCRF. A delay greater than 28 consecutive days will require the patient to be removed from the study (except in case of potential patient benefit, which must be approved by the Investigator).

If plinabulin is withheld, anti-PD-1/PD-L1 mAb will be withheld as well.

As well as the adverse reactions described in Table 3, dose modifications and treatment discontinuation may also occur as a result of hematologic and other non-hematologic AEs and/or laboratory abnormalities ≥Grade 2. In the case of dose delay or modification, assigned treatment may be resumed once the relevant AE is classified as Grade 1. If a DLT would occur, a lower dose level at 20 mg/m^2 of plinabulin will be explored as necessary depending on the observed toxicity.

Table 3: Dose Modifications or Dose Discontinuation for Plinabulin

Adverse Reaction	Provide Supportive Care for:	Withhold Plinabulin for:	Permanently Discontinue Plinabulin for:
Infusion related reaction	**Grade 2**: Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve. Monitor subject closely. If symptoms recur, then no further plinabulin will be administered at that visit. Administer diphenhydramine 50 mg IV, remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).	N/A	**Grade 3 or 4**: Immediately discontinue infusion of plinabulin Begin an IV infusion of normal saline and treat the subject as follows. • Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
Cytokine release syndrome	Management of symptoms such as fever and muscle pain with acetaminophen or other analgesic. Consider oxygen therapy, fluids and antihypotensive agents (if hypotensive) for Grade 2 or higher. For Grade 2 symptoms that do not resolve or for Grade 3 or higher symptoms, high-dose steroids should be initiated, and patient should be admitted for management and observation.	**Grade 2:** May restart plinabulin at one dose level lower once symptoms resolve.	**Grade 3 or 4** Permanently discontinued

Adverse Reaction	Provide Supportive Care for:	Withhold Plinabulin for:	Permanently Discontinue Plinabulin for:
Hypertension	**For BP > 160**: oral amlodipine 10 mg or an equivalent calcium channel blocker should be administered before each subsequent dose. Increases in systolic blood pressure above 200 mmHg should be managed with nitroprusside or similar regimen per institutional practice	• First occurrence of BP >140 and <160 with the use of anti-hypertensives. • May restart plinabulin at one dose level lower with anti-hypertensive prophylaxis once BP returns to grade 1 or better	• Second occurrence of BP >140 and <160 with use of antihypertensive and one dose reduction **OR** First occurrence of BP ≥ 160in spite of anti-hypertensives.
Diarrhea	Grade 1 or 2 diarrhea. Institute symptomatic treatment including hydration, electrolyte replacement, dietary changes, and loperamide or other per institutional guidelines.	• First occurrence of grade 3 event. Withhold plinabulin and institute symptomatic treatment. Plinabulin may be restarted at the same dose level once toxicity resolved to grade 1 or better if SYMPTOMATIC treatment-controlled diarrhea. • Grade 3 event in patients on optimal symptomatic treatment: Withhold plinabulin and restart at one dose level lower once event resolves to Grade 1 or better.	• Any grade 4 event. • Recurrence of Grade 3 diarrhea after one dose reduction and optimal symptomatic treatment

BP: Blood pressure; eCRF: Electronic case report form; IV: Intravenous

Anti-PD-1/PD-L1 mAb

Please follow the instructions in FDA package inserts or institutional policies for dose modification and/or dose delay guidelines for anti-PD-1/PD-L1 mAbs.

If anti-PD-1/PD-L1 mAb is withheld, plinabulin will be withheld too.

Criteria for Re-Treatment

In the absence of disease progression, laboratory tests are required prior to Day 1 of each cycle as per the schedule of assessments. The follow criteria must be met:

a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×upper limit of normal (ULN) (≤1.5×ULN if alkaline phosphatase is >2.5×ULN) (In the expansion cohort, subjects with known liver involvement may have ALT ≤5×ULN),
b. Alkaline phosphatase <4×ULN,
c. Total Bilirubin ≤1×ULN (In the expansion cohort, subjects with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤3×ULN),
d. Albumin ≥ 3g/dL,
e. Hematological parameters have returned to within grade 1 levels

Radiation

If patients develop toxicity attributable to radiation after receiving at least one dose of radiation, the rest of the radiation treatment may be discontinued if deemed by the treating radiation oncologist to be in the best interest of the patient, and the AEs will be documented. Since the number of fractions are between 3-5 fractions, patients could receive at least 1 fraction up to 5 fractions. The initially prescribed dose per fraction will not change, but it is possible to simply reduce the total dose delivered. The patient will have a visit with the treating radiation oncologist at the end of every cycle of radiation treatment.

3. STUDY POPULATION

3.1. Enrollment

3.1.1. Inclusion Criteria

1. Subjects must have one of several like histologically or cytologically confirmed malignant neoplasms (non-small cell lung cancer, small cell lung cancer, renal cell cancer, bladder cancer, Merkle cell cancer, MSI-H cancer (any histology), Melanoma and any other tumor type that has an approval for checkpoint inhibitor who may or may not have progressed on previous anti-PD-1/PD-L1 mAb treatment +/- chemotherapy or anti-CTLA4 requiring further treatment.
2. At least one lesion is amenable to radiation
3. At least one additional non-contiguous lesion that has not been irradiated amenable to radiographic evaluation
4. Have measurable disease based on immune-related response criteria (irRECIST).
5. Tissue must be newly obtained as a core needle biopsy (not FNA) of the lesion being evaluated
6. Age ≥ 18 years.
7. Eastern Cooperative Oncology Group (ECOG) performance status of0-2.
8. Subjects must be recovered from any prior major surgery. The major surgery must be performed at least 4 weeks prior to consent date.
9. Adequate hematologic function defined as:
    i. Platelets≥100×10^9/L,
    ii. Hemoglobin ≥ 9 g/dL
    iii. Absolute neutrophil count (ANC) ≥1.5×10^9/L,
    iv. White blood cell (WBC) ≥ 3×10^9/L.

    Transfusions and growth factors are allowed.
10. Adequate liver function defined as:
    i. AST and ALT ≤2.5×ULN (≤1.5×ULN if alkaline phosphatase is >2.5×ULN) (In the expansion cohort, subjects with known liver involvement may have ALT ≤5×ULN),
    ii. Alkaline phosphatase <4×ULN,
    iii. Total Bilirubin≤1xULN (In the expansion cohort, subjects with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤3×ULN),
    iv. Albumin ≥3 g/dL.
11. Renal function defined as a calculated or measured glomerular filtration rate (GFR) ≥ 30mL/min and Cockcroft-Gault equation.
12. The patient has recovered to Grade ≤ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) from the effects of recent surgery, radiotherapy, chemotherapy, hormonal therapy, or other targeted therapies, with the exception of alopecia. The exceptions for such effects are allowed lab values of ≤ Grade 2 specified elsewhere in these inclusion criteria.

13. Subjects must give informed consent according to the rules and regulations of the individual participating sites.
14. Negative urine pregnancy test in women of child bearing potential within 7 Days of first dose of treatment and subjects of child-bearing potential must agree to use effective contraception during and for 5 months following the last dose of atezolizumab or nivolumab, and for 4 months after the last dose of pembrolizumab, and for 3 months after last dose of Durvalumab and Avelumab, and for 3 months after your last dose of plinabulin. A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable or mechanical contraception; women who are single and women whose male sexual partners have been vasectomized or whose male sexual partners have received or are utilizing mechanical contraceptive devices.

3.1.2. Exclusion Criteria

1. Evidence of complete or partial bowel obstruction.
2. Subjects with primary central nervous system (CNS) tumor or CNS tumor involvement. However, subjects with metastatic CNS tumors may participate in this study if the patient is:
    - >4 weeks from prior therapy completion
    - Clinically stable with respect to the CNS tumor at the time of study entry
    - Not receiving steroid therapy in treating CNS tumor or CNS tumor involvement
    - Not receiving anti-convulsive medications (that were started for brain metastases).
3. Need of Total Parenteral Nutrition.
4. Allergic to any of anti-PD-1/PD-L1 mAb intended to receive.
5. Prior exposure to plinabulin.
6. Pregnancy or lactation.
7. Radiation (except planned or ongoing palliative radiation to bone outside of the region of measurable disease) ≤3weeks prior to study drug administration date.
8. Chemotherapy, or immunotherapy or any other systemic anticancer therapy ≤ 3 weeks prior to study drug administration date except anti-PD-1/PD-L1 mAb mono or combination therapy.
9. Diagnosis or recurrence of invasive cancer other than the present cancer within 3 years (except basal or squamous cell carcinoma of the skin that has been definitively treated).
10. Major surgery within four weeks before consent date.
11. Unstable cardiovascular function or active cardiac disease:
    - Symptomatic ischemia (chest pain of cardiac origin), or
    - Uncontrolled clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded; 1st degree AV block or asymptomatic Left anterior fascicular block (LAFB)/ right bundle branch block (RBBB) will not be excluded), or
    - Congestive heart failure (CHF) of NYHA Class≥3, or
    - Myocardial infarction (MI) within 3 months of consent date.

12. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to the first dose. Active infection with concurrent treatment is acceptable only if the patient is clinically stable.
13. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C
14. Significantly diseased (as determined by the PI or treating physician) or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea. Presence of ileus or other significant gastrointestinal disorder known to predispose to ileus or chronic bowel hypomotility
15. Treatment with an investigational anti-cancer study drug within 3 weeks prior to study drug administration date.
16. Concurrent therapy with approved or investigational anticancer therapeutics.
17. Medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
18. Men whose partner is a woman of child-bearing potential, (i.e., biologically able to conceive), and who is not employing two forms of highly effective contraception. Highly effective contraception (e.g., male condom with spermicide, diaphragm with spermicide, intra-uterine device) must be used by both sexes during the study and must be continued for 5 months following the last dose of atezolizumab or nivolumab, for 4 months after the last dose of pembrolizumab, and for 3 months after last dose of Durvalumab and Avelumab, and for 3 months after your last dose of plinabulin. Women of child-bearing potential is defined as sexually mature women who are not surgically sterile or who have not been naturally postmenopausal for at least 12 consecutive months (e.g., who has had menses any time in the preceding 12 consecutive months).

3.2. Removal of Subjects

3.2.1. Reasons for Withdrawal/Early Discontinuation

A patient may decide to withdraw from the study at any time, for any reason, without prejudice to subsequent care or treatment by the Investigator. The Investigator also has the right to withdraw patients from the study if it is in the best interest of the patient. The MD Anderson Cancer Center may also decide to withdraw a patient. All efforts should be made to complete and report the observations as thoroughly as possible. Patients who discontinue the treatment due to AEs should remain under observation until the resolution or stabilization of the AEs.

A patient may be discontinued from the study drug treatment before completion for any of the following reasons:

- Patient death
- Patient experiences an AE(s)/SAEs that warrants discontinuation, as judged by the Investigator and/or the MD Anderson Cancer Center
- A major protocol deviation, which, in the opinion/discretion of the Investigator and/or the MD Anderson Cancer Center compromises the data integrity of the study.
- Patient is noncompliant with the study drug treatment

- Drug related AEs as associated with the study treatment regimen which can prevent further dosing
- Need for a dose reduction below protocol-defined recommendations or study drug delay greater than 28 consecutive days
- Initiation of a protocol-prohibited concomitant medication or non-protocol chemo/biological therapy for treatment of their disease
- Investigator discretion
- MD Anderson Cancer Center terminates the study
- Patient withdraws consent
- Patient decision to discontinue treatment.

Every reasonable effort should be made to determine as completely as possible the reason for the withdrawal, including contacting the patient either by telephone or through a personal visit, or contacting a responsible relative. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

If the reason for removal of a patient from the study is an AE or an abnormal laboratory test result, the principal specific event or test will also be recorded on the electronic case report form (eCRF).

Patients with clearly confirmed progressive disease will be taken off the study treatment.

4. STUDY TREATMENTS

4.1. Investigational Products

4.1.1. Investigational Product

Plinabulin is supplied as a solution in 40% Kolliphor HS 15 (formerly known as polyoxyl 15 hydroxystearate, or Solutol HS-15®)/60% propylene glycol in an amber vial containing 80 mg in 20 mL (4 mg/mL) or 40 mg in 10 mL (4 mg/mL). Each vial is designated for single use.

Plinabulin is an investigational drug that will be supplied by BeyondSpring Pharmaceuticals or designee. Vials of plinabulin should be stored at room temperature (between 15°C and 25°C [59°F and 77°F]) and must be protected from light. Protection from light must be maintained throughout the drug administration process.

Plinabulin is given to all subjects in Phase 1b study and subjects on Arm A in Phase 2 study on Day 1 of every treatment cycle and day 4 of cycle 1 until disease progression. If an optional RT is administered on Cycle 2 Day 1, then plinabulin dose will be infused on Cycle 2 Day 4. Plinabulin will be given on Day 1 of Cycle 3 and after.

4.1.2. Anti-PD-1/PD-L1 mAbs

Subjects must be given the same anti-PD-1/PD-L1 mAb on which they have failed in prior treatment and keep the dose and treatment cycle unchanged. Anti-PD-1/PD-L1 mAb will be dosed according to recommendations until disease progression as specified in Table 1 and Table 2 for Phase 1b and Phase 2, respectively. Anti-PD-1/PD-L1 mAb treatment cycle defines subject's treatment cycle for this study.

The list of anti-PD-1/PD-L1 mAbs approved to date for the following indications is provided here: Please note any approved anti-PD-1/PD-L1 mAbs can be used for the study.

1. Merkel cell cancer: Avelumab, Pembrolizumab
2. Renal cell Cancer: Pembrolizumab, Nivolumab
3. Bladder cancer: Durvalumab
4. MSI-H cancers (of any histology): Pembrolizumab, Nivolumab
5. Non-small cell lung cancer: Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab
6. Small cell lung cancer: Pembrolizumab, Nivolumab, Atezolizumab
7. Melanoma: Nivolumab or Pembrolizumab single agent
8. Any other tumor type that has any approved immune checkpoint inhibitors

Anti-PD-1/PD-L1 mAb dose and administration route:

1. Avelumab 800 mg intravenous (IV) over 1 hr on Day 1 and Day 15 in Q4W
2. Atezolizumab 1200 mg Q3W IV 1 hr in 1st dose, may infuse over 30 min in subsequent doses if tolerated well
3. Durvalumab 10 mg/kg IV over 1 hr on Day 1 and Day 15 in Q4W

4. Nivolumab 240 mg IV over 30-60 min on Day 1 and Day 15 in Q4W
5. Pembrolizumab 200 mg Q3W IV over 30min

Anti-PD-1/PD-L1 mAbs will be covered under subject's medical plan as part of standard of care. The site investigator shall take responsibility and all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of those medications in accordance with the protocol and any applicable laws and regulations.

Anti-PD-1/PD-L1 mAb will be administered after the rest period (3-12 hours) of RT and before plinabulin dosing. Please follow the instructions from FDA package insert of each drug for drug storage, preparation, infusion, and treatment cycle etc. The anti-PD-1/PD-L1 mAb treatment cycle should maintain the same throughout the study.

Please follow PD-1 or PD-L1 dose modification instructions per FDA package insert. If the PD-1 or PD-L1 dose is withheld due to toxicity the plinabulin treatment should also be withheld.

4.1.3. Radiation Therapy

Radiation therapy will be delivered using external beam radiation, with either 2D/conventional techniques, three-dimensional conformal therapy, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS) or proton beam therapy (PBT), at the discretion of the treating radiation oncologist. For implanted devices, such as pacemakers, MD Anderson Standard Operating Procedure (SOP) will be followed.

Radiation Therapy (RT) will be administered with one of three regimens: 8 Gy x 3 fractions, or 12.5 Gy x 4 fractions, and/or 4 Gy x 5 fractions from Days 1 to 3 (3 fractions), Days 1 to 4 (4 fractions), or Days 1 to 5 (5 fractions). The choice of RT regimens for tumors and lesions is at the discretion of the treating radiation oncologist. RT will target up to a maximum of 5 tumor lesions, and any of the radiation regimens could be use simultaneously or sequentially. Optional sequential RT may be administered in Cycle 2 of any anti-PD-1/PD-L1 regimens at the discretion of the treating doctor to target the other untreated lesions with the regimens described in this protocol. Optional RT will always be given in Cycle 2 on Day 1.

If patients develop toxicity attributable to radiation after receiving at least one dose of radiation, the rest of the radiation treatment may be discontinued, and the AEs will be documented. Since the number of fractions are between 3-5 fractions, patients could receive at least 1 fraction up to 5 fractions. The initially prescribed dose per fraction will not change, but it is possible to simply reduce the total dose delivered. The patient will have a visit with the treating radiation oncologist at the end of every cycle of radiation treatment.

Please always leave at least one measurable lesion untreated for disease assessment monitoring. There should be at least a 3-hour (but not longer than 12 hours) rest period after RT before any study drug infusion. Treatment could be for any lesions in organs including in nodes, brain, and bone. Assessment of responses however should not be reliant on bony lesions. Brain metastasis should be treated and not be used for irRECIST response assessment.

Radiation Simulation

Patients will be simulated on a CT scanner and immobilized based on the site of disease. Immobilization devices will be at the discretion of the treating radiation oncologist. Typical immobilization devices include a head and neck mask for metastatic sites in this region, an upper body cradle for disease in the thorax, and a lower body cradle for disease in the abdomen, pelvis, or lower extremities. Four-dimensional CT scanning will be utilized at the treating radiation oncologist's discretion, to assess for internal motion.

Definition of Radiation Target Volumes

Target volumes will be approved by the treating radiation oncologist, using the information obtained through clinical examination, radiologic images, the simulation planning study, and histologic specimens. When feasible and necessary, the patient's diagnostic images (CT scan, MRI study, or positron emission tomography [PET]/CT imaging) will be fused with the simulation scan to delineate the suggested target volumes below.

Gross Tumor Volume (GTV) – All known disease detected by the above methods, including nodal disease.

Internal Gross Tumor Volume (iGTV) – GTV plus internal motion, if 4D scanning is obtained at the time of simulation.

Clinical Target Volume (iCTV) – iGTV plus the region at risk for microscopic spread. This target volume will be added at the physician's discretion, given that all patients in this study will have metastatic disease and thus the utility of accounting for microscopic spread is limited.

Planning Target Volume (PTV) – iGTV or iCTV plus a margin to account for patient movement and daily setup error.

Organ at Risk Volumes (OAR) – Delineation of the pertinent organs at risk, to include the lung, heart, esophagus, spinal cord, kidney, and liver.

Contouring atlases are used standardly at MD Anderson contoured by the physicians and dosimetrists based on established atlases available through RTOG/NRG websites. These atlases are available for review at: https://www.nrgoncology.org/ciro-contouring-atlases-templates-and-tools. All organs within a body site (thoracic site will include lung, great vessels, trachea, esophagus, heart, and spinal cord; for gastrointestinal (GI) sites, liver, small bowel, kidneys (right and left), and spinal cord) are contoured regardless of where the tumor being treated is situated. Due to dose scatter of radiation, if an OAR is within 5 cm from the PTV, that organ should be contoured. If outside superiorly or inferiorly by 5 cm, those OARs need not be contoured.

The dose constraints for hypofractionated regimens will be adjusted based on the number of fractions. Normal tissue dose constraints will not vary between photons and protons. Suggested dose constraints for three, four, and five fraction regimens are shown in Table 4, Table 5, and Table 6.

Table 4: Summary of Suggested OAR Dose Constraints for three-fraction regimens

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**
Spinal Cord and medulla	<0.35 cc	15.9 Gy	22.5 Gy

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**
	<1.2 cc	13 Gy	
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	15.9 Gy (changed from 18Gy on original form)	22.5 Gy
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy
Sacral Plexus	<5 cc	22.5 Gy	24 Gy
Esophagus*	<5 cc	17.7 Gy	25.2 Gy
Brachial Plexus	<3 cc	22 Gy	26 Gy
Heart/Pericardium	<15 cc	24 Gy	30 Gy
Great vessels	<10 cc	39 Gy	45 Gy
Trachea and Large Bronchus*	<5 cc	25.8 Gy	30 Gy
Bronchus- smaller airways	<0.5 cc	18.9 Gy	23.1 Gy
Rib	<5 cc	40 Gy	50 Gy
Skin	<10 cc	31 Gy	33 Gy
Stomach	<5 cc	22.5 Gy	30 Gy
Bile duct			36 Gy
Duodenum*	<5 cc <10 cc	15.6 Gy 12.9 Gy	22.2 Gy
Jejunum/Ileum*	<30 cc	17.4 Gy	27 Gy
Colon*	<20 cc	24 Gy	34.5 Gy
Rectum*	<3.5 cc <20 cc	45 Gy 27.5 Gy	49.5 Gy
Ureter			40 Gy
Bladder wall	<15 cc	17 Gy	33 Gy
Penile bulb	<3 cc	25 Gy	
Femoral Heads	<10 cc	24 Gy	
Renal hilum/vascular trunk	15 cc	19.5 Gy	
Parallel Tissue	Critical Volume (cc)	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	1500 cc	10.5 Gy	
Lung (Right & Left)	1000 cc	11.4 Gy	V-11Gy<37%
Liver	700 cc	17.1 Gy	
Renal cortex (Right & Left)	200 cc	15 Gy	

OAR: Organ at Risk
*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

Table 5: Summary of Suggested OAR Dose Constraints for four-fraction regimens

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**
Brainstem (not medulla)	<0.5 cc	20.8 Gy	27.2 Gy
Spinal Cord and medulla	<0.35 cc <1.2 cc	18 Gy 14.6 Gy	25.6 Gy
Spinal Cord Subvolume (5-6 mm above and below level treated per	<10% of subvolume	18 Gy	25.6 Gy

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****
Ryu)			
Cauda Equina	<5 cc	26 Gy	28.8 Gy
Sacral Plexus	<5 cc	26 Gy	28 Gy
Esophagus*	<5 cc	18.8 Gy	30 Gy
Brachial Plexus	<3 cc	24.8 Gy	29.6 Gy
Heart/Pericardium	<15 cc	28 Gy	34 Gy
Great vessels	<10 cc	43 Gy	49 Gy
Trachea and Large Bronchus*	<5 cc	28.8 Gy	34.8 Gy
Bronchus- smaller airways	<0.5 cc	20 Gy	28 Gy
Rib	<5 cc	43 Gy	54 Gy
Skin	<10 cc	33.6 Gy	36 Gy
Stomach	<5 cc	25 Gy	33.2 Gy
Bile duct			38.4 Gy
Duodenum*	<5 cc <10 cc	17.2 Gy 14 Gy	24.4 Gy
Jejunum/Ileum*	<30 cc	18.8 Gy	30 Gy
Colon*	<20 cc	26 Gy	37.2 Gy
Rectum*	<3.5 cc <20 cc	47.2 Gy 30 Gy	52.4 Gy
Ureter			43 Gy
Bladder wall	<15 cc	18.5 Gy	35.6 Gy
Penile Bulb	<3 cc	27 Gy	
Femoral Heads	<10 cc	27 Gy	
Renal hilum/vascular trunk	15 cc	21.5 Gy	
Parallel Tissue	Critical Volume (cc)	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	1500 cc	11.6 Gy	
Lung (Right & Left)	1000 cc	12.4 Gy	V-13Gy<37%
Liver	700 cc	19.2 Gy	
Renal cortex (Right & Left)	200 cc	17 Gy	

OAR: Organ at Risk
*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

Table 6: Summary of Suggested OAR Dose Constraints for five-fraction regimens

Serial Tissue	**Volume**	**Volume Max (Gy)**	**Max Point Dose (Gy)****
Brainstem (not medulla)	<0.5 cc	23 Gy	31 Gy
Spinal Cord and medulla	<0.35 cc <1.2 cc	22 Gy 15.6 Gy	28 Gy
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	22 Gy	28 Gy
Cauda Equina	<5 cc	30 Gy	31.5 Gy
Sacral Plexus	<5 cc	30 Gy	32 Gy

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**
Esophagus*	<5 cc	19.5 Gy	35 Gy
Brachial Plexus	<3 cc	27 Gy	32.5 Gy
Heart/Pericardium	<15 cc	32 Gy	38 Gy
Great vessels	<10 cc	47 Gy	53 Gy
Trachea and Large Bronchus*	<5 cc	32 Gy	40 Gy
Bronchus- smaller airways	<0.5 cc	21 Gy	33 Gy
Rib	<5 cc	45 Gy	57 Gy
Skin	<10 cc	36.5 Gy	38.5 Gy
Stomach	<5cc	26.5 Gy	35 Gy
Bile duct			41 Gy
Duodenum*	<5 cc <10 cc	18.5 Gy 14.5 Gy	26 Gy
Jejunum/Ileum*	<30 cc	20 Gy	32 Gy
Colon*	<20 cc	28.5 Gy	40 Gy
Rectum*	<3.5 cc <20 cc	50 Gy 32.5 Gy	55 Gy
Ureter			45 Gy
Bladder wall	<15 cc	20 Gy	38 Gy
Penile Bulb	<3 cc	30 Gy	
Femoral Heads	<10 cc	30 Gy	
Renal hilum/vascular trunk	15 cc	23 Gy	
Parallel Tissue	Critical Volume (cc)	**Critical Volume Dose Max (Gy)**	
Lung (Right & Left)	1500 cc	12.5 Gy	
Lung (Right & Left)	1000 cc	13.5 Gy	V-13.5Gy<37%
Liver	700 cc	21 Gy	
Renal cortex (Right & Left)	200 cc	18 Gy	

OAR: Organ at Risk
*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

4.1.4. Study Drug Preparation

The plinabulin dose should be calculated based on the baseline body surface area (BSA). If BSA subsequently varies from baseline by more than ±10%, then the newer BSA value should be used for calculation of subsequent doses. For patients with a BSA greater than 2.4 m^2, dosing should be calculated using a maximum BSA of 2.4 m^2 for Plinabulin. Plinabulin will be diluted with dextrose 5% in water (D5W) for infusion. Please refer to plinabulin pharmacy manual for the Instructions of the drug preparation.

Please refer to the instructions from FDA package inserts or local hospital guidance for the preparation of anti-PD-1/PD-L1 mAbs in the study.

4.1.5. Methods of Assigning Patients to Study Cohorts

The Phase 1b trial is an open-label study. Subject in Phase 1b trial is assigned to the study cohort based on the type of cancers confirmed by pathology tests.

The Phase 2 trial is an open-label study with two treatment cohorts. Subject in Phase 2 trial will be randomized 1:1 between two treatment arms.

Arm A: Radiation Therapy + Plinabulin + anti-PD-1/PD-L1 mAb

Arm B: Radiation Therapy + anti-PD-1/PD-L1 mAb

The randomization will be stratified by (i) the number of mets (oligo (<=3 vs > 3) and (ii) ECOG 0-1 vs 2. The block size of 6 will be used for randomization. Randomization will be carried out using the CTC website.

4.1.6. Study Drug Administration

Plinabulin

Plinabulin is intended for intravenous (IV) infusion diluted with dextrose 5% in water (D5W) over 30 to 60 minutes. Plinabulin 30 mg/m^2 will be administered intravenously over 60 minutes ± 10 min. Plinabulin 20 mg/m^2 will be infused through IV over 30 minutes ± 5 min. Plinabulin must be protected from light at all times (storage, prior to, during, and after dilution).

Plinabulin should always be administered at 1-2 hour after completion of PD-1 or PD-L1 inhibitor infusion on Day 1of treatment cycle. When required on Day 4, it will be given at least 3 hours (but not longer than 12 hours) after the 4th fraction of radiotherapy if applicable.

4.1.7. Method of Assessing Treatment Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Patients will receive all study drug administrations under the supervision of the Investigator.

Accountability for study drug administration during the study is the responsibility of the Investigators or designees.

4.1.8. Packaging and Labeling Information

Labels will be prepared in accordance with Good Manufacturing Practice Annex 13 requirements and local regulatory guidelines. The study drug label on the bottle specifies the appropriate storage.

Plinabulin is supplied as a solution in 40% Kolliphor HS 15 (formerly known as Solutol HS-15®)/60% propylene glycol in amber vials containing 80 mg in 20 mL (4 mg/mL), or in amber vials containing 40 mg in 10 ml (4 mg/ml). Each vial is designated for single use. The labeled storage condition for the drug product is stored between 15°C and 25°C (59°F and 77°F). Vials are labeled with other information as per local regulatory requirements. The contents of the label will be in accordance with all applicable regulatory requirements.

4.1.9. Study Drug Storage

Vials of plinabulin should be stored at room temperature (between 15°C and 25°C [59°F and 77°F]) and must be protected from light. Protection from light must be maintained throughout the drug administration process. Vials should be stored upright. Drug supplies must be kept in an appropriate secure area (e.g., locked cabinet) and drug storage temperature must be monitored and recorded. Refer to the Pharmacy Manual for further information.

4.1.10. Study Drug Accountability

Plinabulin will be provided by BeyondSpring Pharmaceuticals or its designee and shipped directly to the Investigator or the designated pharmacist.

The Investigator or designated pharmacist will acknowledge receipt of the shipment and note content and condition of the shipment on the clinical material shipping form.

The pharmacist or person responsible for dispensing the study drug at the site will maintain an accurate and current record of all drug supplies received from the repository and dispensed to study patients. The dispensing record should contain the protocol number and information regarding the amount/vial(s) dispensed; date dispensed, lot #, patient identifier number, patient initials, and the initials of the person dispensing the medication.

4.1.11. Study Drug Handling and Disposal

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

At the end of the study, all expired or unused medication will be returned to the BeyondSpring contract repository or destroyed on site according to site procedures. Refer to the Pharmacy Manual for further information.

4.2. Concomitant Medications

4.2.1. Permitted Medications

All concomitant medications will be recorded from the time the subject signs the informed consent form. Concomitant medication will only be collected after end of treatment (EOT) if it is associated with an on ongoing AE.

Prior medications of all cancer treatments will be collected for this study.

Medications considered necessary for the patient's welfare, which are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

Prophylactic anti-emetics and early symptomatic treatment to prevent GI AEs are encouraged. A 5-HT_3 blocker (palonosetron) is preferred, and if not available, ondansetron or granisetron could be considered as an alternative. Physicians should also provide patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed. On cycle 1or 2 day 4, plinabulin is

administered without PD-1 or PD-L1 agents, and a 5-HT3 blocker must be given as an emesis prophylaxis.

If diarrhea occurs, it must be treated. Anti-diarrheas such as loperamide must be prescribed for diarrhea. Suggested loperamide use: 4 mg orally after first loose stool or frequent bowel movement, then 2 mg every 2 hours (4 mg every 4 hours at night) until 12 hours have passed without a bowel movement. Do not exceed 16mg in 24 hours. The Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. Appropriate dietary interventions should be advised to patients. Patients should also be cautioned to avoid dehydration, and of the importance to drink water and electrolyte containing fluids throughout the day when diarrhea occurs. If IV fluids are needed, their administration must be recorded on the eCRF.

Non-steroidal anti-inflammatory drugs are permitted for the treatment of AEs and as pre-medication.

Corticosteroid use for nausea is to be avoided.

Other pre-medications may be administered as appropriate and diphenhydramine with acetaminophen may be administered in the event of an infusion reaction. Institutional guidelines should be followed in the event of infusion/hypersensitivity reaction.

Increases in systolic blood pressure above 200 mm Hg should be managed with nitroprusside or similar regimen per institutional practice. Blood pressure should be closely monitored. Please follow the plinabulin dose modification table (Table 3) for instructions.

All medications will be recorded in an appropriate section of the CRF.

4.3. Prohibited Medications or Cancer Therapies

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies, such as chemotherapy, hormone therapy, palliative radiotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and continuation of the study medication and further participation in the study must be discussed with the Investigator.

5. STUDY PROCEDURES

A complete Schedule of Assessments for the Study can be seen in Table 7 for any Anti-PD-1/PD-L1 mAb regimen.

Table 7: Schedule of Assessments for Anti-PD-1/PD-L1 mAb Treatment (1 Cycle = 3 or 4 Weeks)

Cycle	Screen	Cycle 1 & 2				Cycle 3 & Onwards	End of Treatment (EOT)	Follow-Up Visits
Day	**Days -28 to -1**	**Day 1**	**Days 2 & 3**	**Day 4**	**Day 5**	**Day 1**	**30 Days after last dose of Plinabulin**	**Every 12 weeks**
Window		**±3d**				**± 3 Days**	**± 7 Days**	**± 7 Days**
Informed consent[1]	X							
Verify eligibility criteria[2]	X	X						
Medical history[3]	X							
Urine beta- hCG[4]	X	X				X		
Protocol/Safety Evaluation								
Physical Exam and ECOG[5]	X	X				X	X	X
Height[6]	X							
Vital Signs[6]	X	X		X		X	X	X
12-lead ECG[7]	X	X	As Clinically Indicated					
AE/SAE Assessment	X	X		X		X	X	X
Concomitant Medications	X	X		X		X	X	X
Survival Status[8]								X
Safety Laboratory Evaluation								
Hematology[9]	X	X		X		X	X	X
Serum Chemistry[10]	X	X		X		X	X	X
Urine analysis[11]	X						X	
Coagulation test[12]	X	X	As Clinically Indicated				X	

	Screen	Cycle1 & 2				Cycle 3&Onwards	End of Treat	Follow-Up Visits
	-28 to -1 Day	Day 1	Day 2, 3	Day 4	Day 5	Day 1	30 Days after last dose of Plinabulin	Every 12 weeks
Window		±3d				± 3 Days	± 7 Days	± 7 Days
Translational Study & Sample Collection								
Phenotyping analysis of immune cells from peripheral blood[13]	X			X		X	X	
Imaging guided core needle tumor biopsy[14]	X					X		
Cancer related Gene Mutation test[15]	X							
TCR sequencing peripheral blood[16]	X			X		X	X	
TCR sequencing tumor tissue[17]	X					X		
Immune repertoire Imaging CyTOF analysis and/or single cell RNAseq[18]	X					X		
Dendritic cell activation assay[19]	X			X		X	X	
T cell activation assay[20]	X			X		X	X	
RNAseq including Phosphorylated GEF-H1-dependent immune signature[20]	X			X		X	X	
Targeted cytokine panel assay[20]	X			X		X	X	
ctDNA[20]	X			X		X	X	
Study Treatment								
Radiation Therapy (RT)[21]		X	X	X	X			
Plinabulin Administration[22]		X		X		X		
Anti-PD-1/PD-L1 mAb Administration[23]		X				X		
Tumor Measurement								
CT, MRI or PET/CT[24]	X					X	X	X

Footnote:

[1] Prior to the first study-specific measures. May include optional biobank study consent and pregnancy consent.

[2] Prior to Cycle 1 Day 1.

[3] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[4] Applicable for women of childbearing potential. Urine B-HCG within 7 Days before the first dose of study treatment, and on Day 1 of every Cycle. Positive results to be confirmed by serum pregnancy testing.

[5] ECOG performance status will be performed at screening, Day 1 of every cycle, end of study treatment (EOT) and follow-up visits. A full physical examination will be performed at screening, on Day 1of every cycle,EOT, and follow-up visits. Symptom-directed physical examinations will be performed at other visits.

[6] Vital signs including temperature, pulse, respiratory, blood pressure, body surface area (BSA) and body weight will be measure (body surface area (BSA) and body weight on D1 of each cycle). Subjects will have vital signs performed at screening, pre-dose on Days they receive infusion, EOT, and Follow-up. Additional vital signs should be measured on Day 1 of every cycle and when the optional RT in C2D4 is administered at immediately before and after Plinabulin infusions, and 30 (± 5 min) and 60 (± 10 min) minutes following Plinabulin infusion.

[7] 12-lead ECG(single) will be performed at screening, Cycle 1 Day 1 pre-dose, and as clinically indicated.

[8] Survival Status: Investigators will continue to collect survival data for subjects every 12 weeks after progression of disease or start of additional anti-neoplastic medication using information from a chart review, patient visit, or telephone call unless patient fully withdrew consent to participate in the study. The telephone call will be less than five minutes to obtain information regarding survival status.

[9] Hematology: White blood cell (WBC) count with differential, hhemoglobin, platelet count, red blood cell count, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC). Subjects will have hematology lab performed on screening, pre-dose on Day 1 of every cycle, Day 4 of Cycle 1 or 2 prior to plinabulin dose when applicable, EOT, Follow-up Visits. Labs may be performed more frequently at the physician's discretion.

[10] Chemistry: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, LDH, total protein, albumin, uric acid. Subjects will have labs at screening, Pre-dose on Day 1 of every cycle, Day 4 of Cycle 1 or 2 prior to plinabulin dose when applicable, EOT, Follow-up Visits. Amylase, lipase, and creatine kinase will only be performed in Cycle1 and as clinically indicated. Labs may be performed more frequently at the physician's discretion.

[11] Urine analysis will include Color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin and microscopy including WBC/high powerfield (HPF), RBC/HPF if clinically indicated. Urine analysis will be at screening, and EOT.

[12] Coagulation tests include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT).Coagulation tests will be performed at screening, Cycle 1 Day 1, EOT, and as clinically indicated.

[13] Phenotyping analysis of immune cells from peripheral blood is performed on blood samples collected at baseline (<1 week prior to triple combo treatment), Cycle 1 Day 4, then pre-dose for every 2 cycles (C3, 5, etc.), and EOT

[14] Imaging-guided core needle tumor biopsy samples (at least 2 to 4 research cores) will be collected at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1of immunotherapy with Plinabulin. The biopsied lesion should not have been targeted by radiation. If there has been a complete response in the pre-treatment biopsied lesion, another non-irradiated lesion could be biopsied with any response (partial, stable, or progressive), but should be documented clearly. Multiple lesions could be biopsied if it is safe to do and has clear biologic or clinical rationale to do so.

[15] Cancer related gene mutation information will be collected from the patient medical records. If not available, the biopsied tumor samples will be used to test the gene mutations (<1 week prior to any study treatment).

[16] TCR sequencing peripheral blood is performed on blood samples collected at baseline (<1 week prior to triple combo treatment), Cycle 1 Day 4, then pre-dose for every 2 cycles (C3, 5, etc.) and EOT.

[17] TCR sequencing tumor tissue will be collected at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1 of immunotherapy with Plinabulin. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

[18] Immune repertoire Imaging CyTOF analysis and/or single cell RNAseq will be performed in tumor biopsies at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1 of immunotherapy with Plinabulin.

[19] Dendritic cell activation assay is performed on blood samples collected at baseline (<1 week prior to triple combo treatment), Cycle 1 Day 4, then pre-dose for every 2 cycles (C3, 5, etc.) and EOT.

[20] These Assays are performed on blood samples collected at baseline (<1 week prior to triple combo treatment), Cycle 1 Day 4, then pre-dose for every 2 cycles (C3, 5, etc.) and EOT. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

[21] Radiation Therapy (RT), one of three regimens: 8 Gy x 3 fractions, 12.5 Gy x 4 fractions, and/or 4 Gy x 5 fractions from Days 1 to 3 (3 fractions), Days 1 to 4 (4 fractions), or Days 1 to 5 (5 fractions) in Cycle 1 should be prescribed. The choice of RT regimens for tumors and lesions is at the discretion of the treating radiation oncologist. RT will treat or target a maximum of 5 tumor lesions. Optional sequential RT in Cycle 2 is at the discretion of the treating doctor to `target other

untreated lesions with same regimens for the study. At least one measurable lesion untreated should be left for disease assessment monitoring. Each cycle, a radiation-related AE assessment will occur on the last day of the radiation treatment, and 1 week following (may be a telehealth visit). If acute RT-related toxicities of specified grades (i.e., Grade 3 or higher) develop, you should indicate that patients will be assessed at least weekly (may be a telehealth visit) until the AE(s) resolve to Grade ≤1 or baseline.

[22] Plinabulin will be administered intravenously on Cycle 1 Day 1 and Day 4. If optional RT is given in Cycle 2 Day 1, then Plinabulin will be dosed on Cycle 2 Day 1 and Day 4. Otherwise, Plinabulin will be administered only on Cycle 2 Day 1 if no RT is given, then Plinabulin will always be given on Day 1 of Cycle 3 and after.

[23] Atezolizumab or Pembrolizumab (Anti-PD-1/PD-L1 mAb) is infused on Day 1 of every cycle according to FDA approved indications and dosing instructions. The Anti-PD-1/PD-L1 mAb will always be administered at least 3 hours (but not longer than 12 hours) after the radiotherapy. The same PD-1 or PD-L1 which patient failed prior to the study must be administered in this study. Avelumab or Durvalumab or Novilumab (Anti-PD-1/PD-L1 mAb) is infused on Day 1 and 15 of every cycle according to FDA approved indications and dosing instructions.

[24] For Q3W regimens, CT, MRI or PET-CT Scans will be performed at screening, then every 9 weeks (3 Cycles) (± 7 days) for 27 weeks (9 cycles), and then every 12 weeks (4 cycles) (± 7 days) during the treatment, at EOT and follow up period (Q12W). For Q4W regiments, CT, MRI, or PET-CT Scans will be performed at screening, then every 8 weeks (2 Cycles) (± 7 days) for 24 weeks (6 cycles), and then every 12 weeks (3 cycles) (± 7 days) during the treatment, at EOT and follow up period (Q12W). A repeat CT in 1 month should be conducted if there is evidence of progression but for confirmation that there is no "pseudoprogression". Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable. Subjects who discontinued for reasons other than progression of disease or withdrawal from study treatment will continue to visit the clinic for study assessments and evaluation of their disease by CT, MRI, or PET/CT scan approximately every 12 (± 7 days) weeks until progression of disease is determined, the subject receives additional anti-neoplastic medication, or for a maximum of 5 years. A brain scan must be performed at screening to assess potential CNS disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment timepoints. For all subjects, a follow-up brain scan must be performed to confirm irCR within 1 week of response confirmation, or if clinically indicated.

5.1. Screening Period (-28 to -1 Days)

At the screening visit, information will be collected, and patients will have clinical evaluations as follows:

- Informed consent: main study and future research
- Medical history: Present and past medical events, demographics; cancer gene mutation status, smoking history; prior cancer treatments)
- Cancer diagnosis and staging
- Tumor assessments and measurement by irRECIST (Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable)
- Concomitant medications (starting from the time the patient signs the informed consent)
- Complete physical examination, including height (screen only) and weight
- Vital sign measurements
- ECOG performance status.
- Baseline electrocardiogram (ECG)
- Hematology, serum chemistry and urinalysis, endocrine labs, and coagulation tests
- Research blood and biopsy at screening will be as described in Section 6.1
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing).

5.2. Treatment Period

5.2.1. Day 1 of all Treatment Cycles

On Day 1 of treatment cycle, information will be collected, and patients will have clinical evaluations as follows:

- Physical examination (within the past 48 working hours)
- Vital sign measurements, Vital signs include temperature, blood pressure, heart rate, respiratory rate, weight, and BSA. Vital signs should be measured prior to the study treatment, immediately before and after plinabulin infusions, and 30 and 60 minutes following plinabulin infusion during Day 1
- ECOG performance status
- ECG (Cycle 1 mandatory, other cycles as clinically indicated)
- Hematology and serum chemistry
- Coagulation test (Cycle 1 only)
- Urine pregnancy test, if applicable (positive results to be confirmed by serum pregnancy testing)
- Tumor assessment and measurement: For Q3W regimens the assessment will be conducted every 9 weeks (3 cycles) (± 7 days) for 27 weeks (9 cycles), and then every 12 weeks (4 cycles) (± 7 days) during the treatment. For Q4W regimens the assessment will be conducted every 8 weeks (2 cycles) (±7 day) for the first 24 weeks (6 cycles), then every 12 weeks (±7 day) for post 24 weeks duration treatment, or as clinically indicated
- Imaging-guided core needle tumor biopsy samples (at least 2 to 4 research cores) will be collected at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1of immunotherapy with Plinabulin.
- Research laboratory tests collected before plinabulin administration, as described in Section 6.1
- RT (Cycle 1 Day 1 out of 3 to 5 days, and also in Cycle 2 which is optional per treating physician's discretion)
- Anti-PD-1/PD-L1 mAb infusion
- Plinabulin infusion (in Phase 2, only for patients in the RT+PD-1/PD-L1+Plinabulin arm)
- Concomitant medications
- Assessment of AEs on days of plinabulin administration.

5.2.2. Day 4 of Cycle 1& 2 for Immune Checkpoint Inhibitors with Q3W Regimens

On Days 4 of Cycle1 and Cycle 2, information will be collected, and patients will have the procedures performed as follows:

- Vital signs including weight, BSA, temperature, blood pressure, heart rate, and respiratory rate. Vital signs should be measured immediately before and after plinabulin infusions, and 30 and 60 minutes following plinabulin infusion during Day 4 if optional RT is given in Cycle 2 Day 1.
- Hematology, serum chemistry. (on cycle 1 Day 4 and only when Plinabulin is given on C2D4)
- Research laboratory tests collected before plinabulin administration, as described in Section 6.1
- Plinabulin infusion
- RT given to complete 3 to 5 fraction regimen (Cycle 1 mandatory, Cycle 2 optional per treating physician's discretion). If given in Cycle 2, RT will be given on the same days as it was given in Cycle 1.
- Assessment of AEs on days of plinabulin administration.
- Concomitant medications (on Cycle 1 Day 4 and only when Plinabulin is given on C2D4)

5.2.3. Day 4 of Cycle 1 & Cycle 2 for Immune Checkpoint Inhibitors with Q4W Regimens

On Days 4, of Cycle 1& Cycle 2, information will be collected, and patients will have the procedures performed as follows:

- Vital signs including weight, BSA, temperature, blood pressure, heart rate, and respiratory rate. Vital signs should be measured immediately before and after plinabulin/placebo infusions, and 30 and 60 minutes following plinabulin/ infusion during Day 4 if optional RT is given in Cycle 2 Day 1.
- Hematology, serum chemistry (on Cycle 1 Day 4 and only when Plinabulin is given on C2D4)
- Research laboratory tests collected before plinabulin administration, as described in Section 6.1
- Plinabulin infusion
- RT given to complete 3 to 5 fraction regimen (Cycle 1 mandatory, Cycle 2 optional per treating physician's discretion). If given in Cycle 2, RT will be given on the same days as it was given in Cycle 1.
- Assessment of AEs on days of plinabulin administration.
- Concomitant medications (on Cycle 1 Day 4 and only when Plinabulin is given on C2D4)

5.2.4. End of Study

At the end of study, information will be collected, and patients will have clinical evaluations as follows:

- Vital signs

- Physical examination
- ECOG performance status
- Hematology, serum chemistry, and urine analysis
- Coagulation test
- Tumor assessments and measurement
- Research laboratory tests collected before plinabulin administration, as described in Section 6.1
- Concomitant medications
- Assessment of AEs

5.2.5. Follow-up (Every 12 Weeks)

At the Follow up visit, information will be collected, and patients will have clinical evaluations as follows:

- Vital signs
- Physical examination
- ECOG performance status
- Hematology, serum chemistry
- Concomitant medications
- Assessment of AEs
- Tumor assessments and measurement (every 12 weeks until progression of disease is determined, the patient withdraws from study treatment, or the patient receives additional anti-neoplastic medication)
- Survival follow-up (every 12 weeks after progression of disease, the subjects starts additional anti-neoplastic medication, or for a maximum of 5 years).

6. STUDY VARIABLES AND METHODS OF ASSESSMENTS

6.1. Blood Sampling

Subjects will only have hematology labs performed on Screening, pre study treatment on day 1 of every cycle (RT or drug treatment) Day 4 of Cycle 1 or 2 prior to plinabulin dose when applicable, EOT, and Follow-up Visit. Labs may be performed more frequently at the physician's discretion.

Subjects will have chemistry labs at screening, Pre-dose on Day 1 of every cycle, Day 4 of Cycle 1 or 2 prior to plinabulin dose when applicable, EOT, Follow-up Visits. Amylase, lipase, and creatine kinase will only be performed in Cycle 1 and as clinically indicated. Labs may be performed more frequently at the physician's discretion.

Coagulation tests include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation tests will be performed at screening, Cycle 1 Day 1, EOT, and as clinically indicated.

Blood sampling for the following translational studies is performed on blood samples collected at baseline (<1 week prior to triple combo treatment), Cycle 1 Day 4, then pre-dose for every 2 cycles (C3, 5, etc.) and EOT.

- Immune repertoire TCR sequencing
- Phenotyping analysis of immune cells from whole blood using multicolor flow cytometry
- Dendritic Cell activation assay from whole blood

The decision to perform additional exploratory biomarker analysis (including but not limited to the tests listed below) may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

- TCR sequencing for tumor tissue
- T Cell activation assay from whole blood
- RNAseq, including GEF-H1 immune signature evaluation
- Cell free circulating tumor DNA (ctDNA) sequencing
- Multiplex cytokine panel including, but not limited to: IL-2, IFNγ, IL-6, IL-12p70, IL-12p40, IL-13, IL-17A, IL-23, G-CSF, IL-8 and IFN-β

Serum pregnancy test will be needed if urine pregnancy test is positive.

6.2. Urine Sampling

Urine analysis will include color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, and microscopy including WBC/high power field (HPF), RBC/HPF if clinically indicated. Urine analysis will be at screening, and EOT.

6.3. Tumor biopsy

The Imaging-guided core needle tumor biopsy samples (at least 2 to 4 research cores) will be collected at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1 of immunotherapy with Plinabulin. The biopsied lesion should not have been targeted by radiation. If there has been a complete response in the pre-treatment biopsied lesion, another non-irradiated lesion could be biopsied with any response (partial, stable, or progressive), but should be documented clearly. Multiple lesions could be biopsied if it is safe to do and has clear biologic or clinical rationale to do so. If there has been a complete response without targetable lesions to biopsy, then the biopsy of this second time point will be optional and documented as such.

6.4. Assessment of Efficacy

6.4.1. Criteria for Disease Evaluation

All efficacy endpoints, other than OS, will be based on the tumor assessments performed by the investigators using both irRECIST and modified RECIST 1.1. Treatment decisions by the Investigator will be based on irRECIST. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice.

Tumor assessments will be carried out during the Screening, and then every 9 weeks (± 1 week) for 27 weeks (during Q3W dosing) or every 8 weeks (± 1 week) for 24 weeks (during Q4W dosing), then every 12 weeks during treatment cycles in the Treatment Phase regardless of treatment cycles and follow up period. CT/MRI scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1/ Day 1), at all tumor assessment time points, and as indicated clinically. RT treated lesions will not be used for response assessment. Please keep at least one measurable tumor lesion untreated by RT for disease response assessment across the treatment. Color photographs containing a millimeter scale must be taken of all skin lesions being used as target lesions. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable.

The CT scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated IV contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with non-contrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner is not acceptable. Ultrasound should not be used for radiographic tumor assessment. Chest disease may not be followed using chest x-ray.

A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at screening to assess potential CNS disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment timepoints. For all subjects, a follow-up brain scan must be performed to confirm irCR within 1 week of response confirmation, or if clinically indicated. Brain metastasis should be treated by RT and not be used for irRECIST response assessment.

The tumor assessment schedule should not be affected by interruptions in study treatment.

Subjects going off treatment without disease progression will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.

The same method of assessment used at screening must be used at all time points. Throughout the study it is critical that the same imaging methodology be applied, and contrast be consistently provided unless IV contrast becomes medically contraindicated during the course of treatment or the dose of contrast needs to be adjusted based on the subject's health status.

In order for immune-related stable disease (irSD) to be considered the best overall response, it must occur ≥5 weeks following the first dose of study drug.

The first radiological assessment of tumor response status will be performed at Week 8(±1 week), unless there is clinical indication warranting earlier radiologic imaging. If imaging at Week 8 shows stable disease (irSD), treatment will be continued and tumor assessments will be conducted at the next regularly scheduled imaging time point, i.e., at Week 16 (±1 week). Responses (irPR [immune-related partial response] or irCR [immune-related complete response]) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point.

If the time point tumor assessment is PD, treatment should continue, and tumor assessments repeated at least 4 weeks later in order to confirm immune-related progressive disease (irPD). If repeat imaging shows a reduction in the tumor burden compared to the initial tumor assessment demonstrating PD, treatment may be continued as per treatment schedule. If repeat imaging confirms irPD, subjects will be discontinued from study treatment. In determining the tumor time point response, investigators should consider all target lesions as well as non-target lesions and new lesions.

The decision to continue study treatment after the first evidence of PD is at the Investigator's discretion based on the clinical status of the subject as described in Table 8 below.

Subjects may continue receiving study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must discuss continuing treatment.

Tumor assessments per modified RECIST 1.1 will follow Eisenhauer et al., 2009, however, instead of the maximum of 5 target lesions (up to 2 per organ), up to 10 target lesions, (up to 5 per organ) may be selected.

Table 8: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scans	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Subsequent scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Subsequent scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

CR = complete response, PR = partial response, SD = stable disease, PD = progression disease, N/A = not applicable.

Assessment of responses however should not be reliant on bony lesions. A bone scan or PET/CT will only be performed in patients with known bone metastasis at study entry to monitor the status of metastatic disease in bone. If radiologic imaging shows progressive disease (PD), tumor assessment may be repeated approximately 4-6 weeks later in order to confirm continued PD (as compared to the initial scan). Treatment may continue at the discretion of the treating physician while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar.

Brain metastasis should be treated and not be used for irRECIST response assessment. Irradiated lesion(s) should not be used in disease assessment. Please always keep one lesion untreated by RT for the clinical efficacy assessment. Please refer to irRECIST guidance in Section 13 (Appendix B).

7. ASSESSMENT OF SAFETY

Details are provided in Table 7.

7.1. Safety Parameters

Safety assessments should be performed at all visits to the study center and throughout the study.

7.1.1. Demographic/Medical History

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All clinically significant medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Demographic data will include gender, date of birth (or age), and race/ethnicity. Medical history findings (i.e., previous diagnoses, diseases, or surgeries) started before signing the informed consent, information of all medications and cancer treatment used within 30 days of signing the informed consent, as well as the relevant information needed for checking study eligibility will be collected and captured in the eCRF.

Information will also be collected regarding child-bearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, hematology and blood chemistry, urinalysis, pregnancy test, and electrocardiogram [ECG]).

7.1.2. Vital Signs

The following measurements for vital signs must be performed: systolic/diastolic blood pressure, heart rate, and respiratory rate. Vital signs will be measured per standard of care and documented on the vital signs CRF.

Subjects will have vital signs performed at screening, pre-dose on Days they receive infusion, EOT, and Follow-up. Additional vital signs should be measured immediately before and after plinabulin infusions, and 30 and 60 minutes following plinabulin infusion during Day 1 and Day 4 when plinabulin is given.

If abnormalities are found and they are considered an AE, record on the AE summary page. If an isolated elevated temperature is not clinically significant, it should not be reported as an AE. If an elevated temperature is part of an AE that is reported elsewhere, elevated temperature (fever) should not be reported as an AE.

7.1.3. Weight and Height

Height will be measured in centimeters once at screening. Weight will be measured at every drug dosing visit and BSA will be calculated.

7.1.4. Physical Examination

Physical examinations will be performed. A comprehensive (including neurological) examination will be performed at screening, Day 1 of each cycle, end of treatment, and follow-up, as detailed in Table 7, and a symptom-directed examination will be performed at other visits. A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the screening visit will be recorded on the eCRF. Changes from the screening physical examination findings that meet the definition of an AE will be recorded on the eCRF.

7.1.5. Electrocardiogram (ECG)

ECGs are to be performed using a standardized method within 1 hour before the start of chemotherapy administration. The patient must be in a supine position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. If the patient is unable to be in the supine position, the patient should be in most recumbent position as possible.

Single safety ECGs will be obtained on screening visit and Day 1 of Cycle 1, and then as clinically indicated.

7.1.6. Laboratory Assessments

7.1.6.1. Clinical Laboratory Assessments

Hematology: White blood cell (WBC) count with differential, hemoglobin, platelet count, red blood cell count, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC). Subjects will only have labs performed on Screening, pre study treatment on day 1 of every cycle (RT or drug treatment) Day 4 of Cycle 1 or 2 prior to plinabulin dose when applicable, EOT, and Follow-up Visit. Labs may be performed more frequently at the physician’s discretion.

Chemistry: Sodium, potassium, chloride, bicarbonate, bun, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, LDH, total protein, albumin, uric acid, amylase, lipase and creatine kinase. Subjects will have Chemistry labs at screening, Pre-dose on Day 1 of every cycle, Day 4 of Cycle 1 or 2 prior to plinabulin dose when applicable, EOT, Follow-up Visits. Amylase, Lipase, and Creatine Kinase will only be performed in Cycle 1 and as clinically indicated. Labs may be performed more frequently at the physician’s discretion.

Coagulation tests include PT, INR, and aPTT. Coagulation tests will be performed at screening and Day 1 of Cycle 1, end of treatment, and as clinically indicated.

7.1.6.2. Pregnancy Testing

Pregnancy tests will be done using urine samples in women of childbearing potential. Patients must have a negative urine pregnancy test documented within 7 days of the first dose of treatment. Urine pregnancy tests will also be performed on Day 1 of each cycle. Confirm with serum testing (local or central laboratory) if urine sample is positive.

7.1.6.3. Companion Translational Study

Gene Mutation Evaluation:

We expect most patients enrolled will have had hot spot mutation testing or targeted exome profiling performed prior to enrollment. If there is evidence of clinical activity, targeted exome sequencing on a 200-400 gene platform or larger will be performed in those patients with objective responses and prolonged stable disease >6 months as well as any patients with rapid progression (this could be done as part of a Institute of Personalized Cancer Therapy Unusual Responder Program). In addition, patients who have a response with subsequent progression will be approached for optional biopsies for molecular characterization as well as generation of patient-derived xenografts and conditionally- reprogrammed cells. This evaluation will determine the evolution of the mutation.

7.1.6.4. Biomarker Testing

Biomarker testing will be performed during the study. Dr. James Reuben, Professor of Hematopathology at MD Anderson Cancer Center will perform the specific measurements for biomarker testing mentioned below.

The following immune regulatory cells and markers will be studied to better understand the plinabulin's mechanisms of action and to identify potential predictors of responsive subjects that can be utilized to enrich for responders in subsequent clinical studies.

*Imaging-guided core needle tumor biopsy samples (at least 2 to 4 research cores) will be collected at Pre-dose (<2 week prior to radiation therapy) and within 7 days prior to Cycle 3 Day 1 of immunotherapy with Plinabulin. The biopsied lesion should not have been targeted by radiation. If there has been a complete response in the pre-treatment biopsied lesion, another non-irradiated lesion could be biopsied with any response (partial, stable, or progressive), but should be documented clearly. Multiple lesions could be biopsied if it is safe to do and has clear biologic or clinical rationale to do so.

*The whole blood samples will be collected at Pre-dose (<1 week prior to triple combo), and Cycle 1 Day 4, then pre-treatment Day 1 of every 2 cycles & EOT. (2 – 10 mL EDTA/purple top (processed for peripheral blood mononuclear cell [PBMC], plasma, whole blood DNA), 1 – 10 mL Heparin/Green top (for flow cytometry and DC activation assay), 1 – 10 mL Streck tube (for plasma and germline DNA).

<u>Minimum measurements on core needle tumor biopsies</u>

Immune phenotyping analysis by CyTOF and/or single cell RNAseq

<u>Minimum measurements on whole blood PBMC collected for biomarker evaluation</u>

Dendritic Cell activation assay
Phenotyping analysis of immune cells using multicolor flow cytometry
Immune repertoire TCR sequencing

Exploratory Biomarker Research including Pharmacogenomic Study

Blood samples including pharmacogenomic samples (PG samples) for the development of exploratory predictive biomarkers will be collected prior to the first dose of study drug, on Cycle 1 Day 4, then on Day 1 of every cycle for Q4W, or every 2 cycles for Q3W during Treatment Phase, and at the EOT assessment. Subjects will be required to provide a fresh biopsy of tumor before treatment, and within 7 days prior to Cycle 3 Day 1 of the study treatment for biomarker analyses. Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers which may be useful to predict subject response to the study treatment, as determined by evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples from subjects receiving study treatment may be analyzed using RNAseq, Flow cytometry, multiplex bead-based immunoassay, or other assays/methods or new technology. In addition, biomarkers identified in other plinabulin clinical studies may also be assessed in the biomarker samples collected from subjects enrolled in this study.

A blood sample for peripheral blood mononuclear cells (PBMCs) and plasma isolation will be collected from enrolled subjects. Cell free nucleic acid isolated from plasma samples may be used to obtain ctDNA and explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Any leftover samples from the translational study will be stored for up to 15 years from the study closure for future research. The samples may be used to study the mechanism of the study treatment or to explore the predictive and response biomarkers for the diseases or the treatment.

7.2. Adverse and Serious Adverse Events

7.2.1. Definition of Adverse Events

7.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include

an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs encountered during the clinical study will be reported in the electronic CRF MOCLIA. All SAEs will be reported on eSAE. Disease progression or deterioration of the malignancy under study (including new sites of metastasis due to disease progression) will be recorded as part of the subject's disease status and should not be reported as an AE/SAE.

The MD Anderson Cancer Center will collect all deaths on study regardless of its potential relationship to disease progression.

The Investigator is responsible for assessing the severity of the AE and/or the adverse drug reaction, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution.

Attribution - the determination of whether an AE is related to a medical treatment or procedure will be as follows:

- **Definite** - the AE is clearly related to the investigational agent(s)
- **Probable** - the AE is likely related to the investigational agent(s)
- **Possible** - the AE may be related to the investigational agent(s)
- **Unlikely** - The AE is doubtfully related to the investigational agent(s)
- **Unrelated** - The AE is clearly NOT related to the investigational agent(s).

7.2.1.2. Serious Adverse Event (SAE)

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered SAEs. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the Investigational New Drug (IND) Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the Institutional Review Board (IRB) in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".
- Serious Adverse Events will be captured from the time of the first protocol-specific intervention, through 90 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anti-cancer therapy, whichever is earlier; unless the subject withdraws consent.
- Serious Adverse Events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution.
- Death or life-threatening events that are unexpected, possibly, probably, or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**.
- Additionally, any Serious Adverse Events that occur after the 90-day time period or 30 days following the last dose if the subject initiates new anticancer therapy, that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office.

Reporting to FDA:

- SAEs will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the Principal Investigator and the research team to ensure Serious Adverse Events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2.1.3. Other Adverse Event (OAE)

OAEs will be identified by the Drug Safety Physician from the sponsor and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report (CSR). Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient/subject from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the CSR.

7.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related, Probably Related or Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

7.4. Recording Adverse Events

AEs spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the first administration of study drug (Study Day 1) until 30 days after the last infusion of study treatment, or initiation of another anti-cancer therapy. SAE information will be collected from time of signing of the informed consent through 90 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy. The AE term should be reported in standard CTCAE v5.0terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Whenever possible, the intensity of clinical AEs will be graded according to NCI CTCAE (v5.0) grading system. AEs not listed on the NCI-CTCAE grading system will be graded on a 3-point scale (mild, moderate, severe) as described below, and reported in detail as indicated on the CRF (Study Manual).

Severity Grading for AEs not listed in NCI-CTCAE (v5.0):

- **Grade 1: Mild** (awareness of sign or symptom, but easily tolerated)
- **Grade 2: Moderate** (discomfort sufficient to cause interference with normal activities)
- **Grade 3: Severe** (incapacitating, with inability to perform normal activities, hospitalization may be indicated)
- **Grade 4: Life Threatening** (extreme limitation in activity; significant assistance required; significant medical intervention or therapy required; hospitalization indicated)
- **Grade 5: Death**

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 7.2.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur to female participants or female partners of a male participant during the study treatment or within 3 months of last plinabulin dose, it must be reported to the MD Anderson Cancer Center safety group within 24 hours of awareness using the MD Anderson Cancer Center's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

This Phase 1b/2 study will follow the recommended AE data collection guidelines as indicated in Table 9.

Table 9: Recommended Adverse Event Reporting Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.5. Reporting Serious Adverse Events

All SAEs are collected from the time of signing of the consent form through 90 days after the subject's last dose, or 30 days following the last dose if the subject initiate's new anticancer therapy. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should

be reported to the MD Anderson Cancer Center and BeyondSpring Pharmaceuticals regardless of the length of time that has passed since study completion.

All SAEs must be reported to The MD Anderson Cancer Center BeyondSpring Pharmaceuticals within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by email or fax to:

BeyondSpring Pharmaceuticals:

SAE Email Address: ICON-Safety-CentralReceipt@iconplc.com

or by fax to 215-616-3096 (ICON- PV)

8. STATISTICAL METHODS

All statistical analyses will be performed by the MD Anderson Cancer Center or designee after the study is completed. Details of the analyses will be included in a separate Statistical Analysis Plan (SAP).

8.1. Study Endpoints and Analysis

8.1.1. Primary Endpoint and Analysis

1. Safety and tolerability; AEs will be evaluated according to CTCAE version 5.0
2. The objective tumor response rate (complete response + partial response), assessed according to irRECIST criteria

8.1.2. Secondary Endpoints and Analysis

1. Disease control rate (complete response, partial response + stable disease) assessed according to irRECIST criteria)
2. Progression-free survival (PFS)
3. Overall Survival (OS)

8.1.3. Exploratory Endpoints and Analysis

1. Gene mutation density
2. Immune repertoire TCR sequencing change in peripheral blood
3. Immune phenotypes in tumor tissue, including DC, T cells, TAMs, pre and post treatment
4. Phenotypes of immune cells in peripheral blood
5. Dendritic cell activation in peripheral blood
6. Predictive and Response Biomarker analysis taking account of the collected biomarkers

8.2. Statistical Analysis Sets and Considerations

8.2.1. Analysis Sets

Modified Intent-to-Treat Analysis Set

Modified Intent-to-Treat population (mITT Population): All safety subjects who provide post treatment tumor assessments or present clinical disease progression post treatment without any formal post treatment tumor assessments. The efficacy analysis will be based on the mITT population.

Safety Analysis Set

The safety analysis set comprises all patients who received at least one dose of study medication.

Per Protocol Analysis Set

Per Protocol Population (PP Population) will include all mITT population without major protocol deviation. The criteria for PP Population exclusion will be documented before data base is locked.

8.2.2. Patient Disposition

Descriptive summaries will be generated to describe the disposition of all enrolled patients.

8.2.3. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be described.

8.2.4. Study Treatment Exposure

Study treatment exposure will be summarized.

8.2.5. Efficacy Analyses Displays

Data will be tabulated by treatment sequence, with data listings provided for all data captured in the eCRF as well as laboratory data. On treatment data, will be assessed descriptively as both observed values and as changes from pretreatment. When tabulated, data will be presented using descriptive statistics (e.g., mean, median, standard deviation, and range for continuously scaled parameters, and as number and percent for categorically scaled parameters). Statistical Analysis System Version 9.4 or higher will be used to perform the majority of the analyses; other software (e.g., NCSS) may be utilized to generate graphics or perform other analysis. Analyses will be performed based on observed data, and missing values will not be imputed unless otherwise stated in the SAP.

ORR will be defined as percent of subjects achieved complete response (CR) or partial response (PR).

Disease control rate defined as percent of subjects achieved CR, PR, and stable disease

PFS is defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurs first).

OS is measured from the start date of the treatment period until date of death from any cause. Subjects who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive.

Chi-square or Fisher's exact test is used to compare ORR and disease control rate between two arms in phase 2. ORR and disease control rate are estimated with 95% confidence interval.

The time-to-event endpoints including overall survival, progression free survival will be analyzed using Kaplan-Meier method or Cox regression.

The mITT Subjects without any post treatment tumor assessments will be treated as non-responders.

Additional details are provided in the SAP.

8.3. Safety Analyses

Medical history and AE data will be graded by system organ class (SOC) and NCI CTCAE v5.0 terminology.

All treatment emergent adverse events (TEAEs) will be graded according to NCI CTCAE version 5.0 and summarized by worst grade severity per patient.

Treatment emergent AEs are those events that occur after first administration of any study therapy through 30 days post last dose of any study therapy, and/or any treatment-related AEs, regardless of the onset date. Dose delays, dose modifications and/or dose discontinuation of plinabulin due to safety concerns will be summarized.

In Phase 1, BOIN study design is used to determine the MTD. In Phase 2, Bayesian toxicity monitoring is used.

8.3.1. Deaths

Treatment emergent deaths are those deaths within 30 days of last dose of any study therapy. Early deaths are those deaths within 60 days of the first dose of study therapy.

Treatment emergent and/or early deaths will be tabulated and summarized by treatment sequences.

8.3.2. Extent of Exposure

Refer to the SAP for details.

8.3.3. Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized CTCAE v5.0 terminology.

8.3.4. Laboratory Analyses

Continuous variables will be analyzed using t-tests with unequal variances. Proportions for comparing independent treatment arms will be analyzed using the Wilson score test. Other categorical data will be analyzed using non-parametric statistical methods.

8.3.5. Vital Signs

Descriptive statistics and shift tables will be used for the evaluations.

8.3.6. Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described in Table 10 and per the timings presented in Table 7.

Table 10: ECOG Performance Status

ECOG Scale	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., office work or light housework)
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot perform any self-care; totally confined to bed or chair

ECOG = Eastern Cooperative Oncology Group

8.4. Sample Size Considerations

Phase 1:

We will employ the BOIN design (Liu and Yuan, 2015, Yuan et al., 2016) to find the MTD/RP2D. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou et al., 2018).

The target DLT rate for the MTD is $\phi = 0.25$ and the maximum sample size is 12. We will enroll and treat patients in cohorts of size 3. DLTs are defined in Section 2.6.1, and only those DLTs that occur within the first cycle will be used for dose finding. As shown in Figure 1, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment under the alternatives $\phi 1 = 0.6\phi$ and $\phi 2 = 0.6\phi$, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level.
- if it is ≥ 0.298, de-escalate the dose to the next lower dose level.
- otherwise, stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further consideration if $\Pr(p_j > 0.25 \mid \text{data}) > 0.95$ and at least 3 patients have been treated at dose level j, where p_j is the true DLT rate of dose level j, $j = 1, \ldots, 2$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0, 1)$, where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate $\phi \leq 1/6$, a dose with 2/3 patients experiencing DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 11, which will be used to conduct the trial.

The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort are treated at dose level 2. There are only 2 doses (30 mg/m^2 and 20 mg/m^2) specified in the protocol, and we will begin at the higher dose, dose level 2 = 30 mg/m^2.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 11. When using Table 11, please note the following:
    a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, treat the new patients at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
    e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size of 12 is reached, or stop the trial early if the number of patients treated at the current dose ≥ 9 and the decision according to Table 11 is to stay at the current dose.

Table 11: Dose escalation/De-escalation Rule for the BOIN Design

Actions*	The number of patients treated at the current dose								
	1	2	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	0	0	0	0	1	1	1	1
De-escalate if # of DLT ≥	1	1	1	2	2	2	3	3	3
Eliminate if # of DLT ≥	NA	NA	3	3	3	4	4	4	5

* When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. Note that "# of DLT" is the number of patients with at least 1 DLT, and "NA" means that a dose cannot be eliminated before treating 3 patients.

After the trial is completed, select the MTD based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program (Venier et al., 2020). Specifically, select as the MTD the dose for which the isotonic estimate of the DLT rate is closest to the target DLT rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target DLT rate and select the lower dose level when the isotonic estimate is greater than or equal to the target DLT rate.

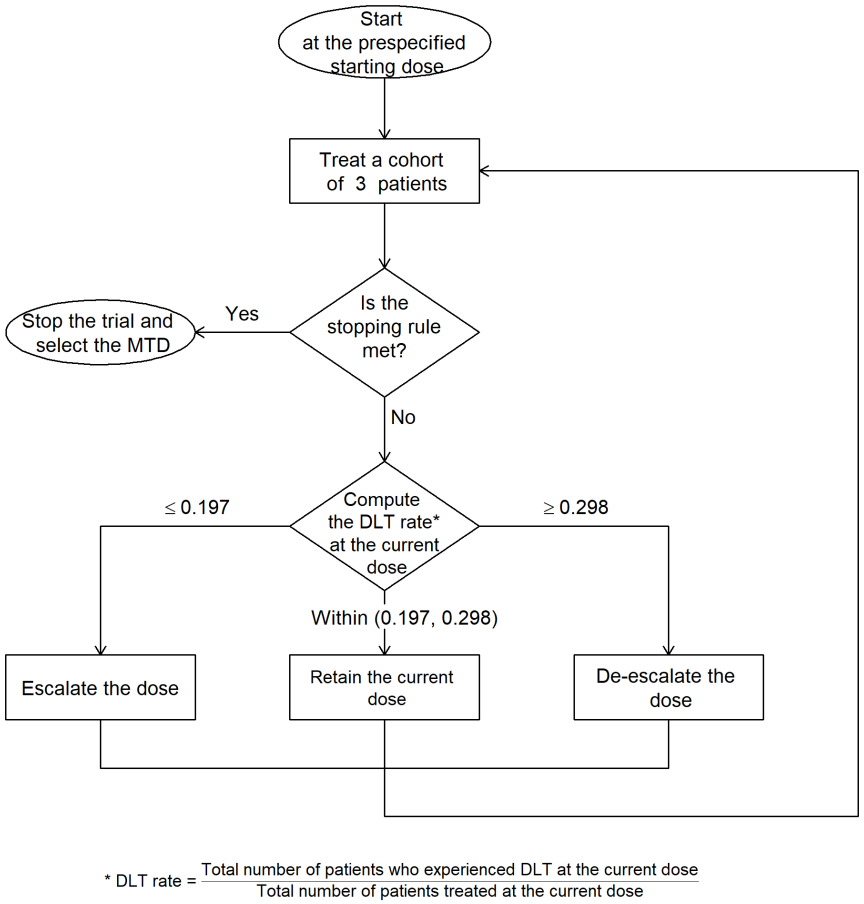

Figure 1 Flowchart for trial conduct using the BOIN design.

Once we determine the MTD, an additional 10 patients will be enrolled for additional experience with safety and efficacy in each of the eight cancer cohorts and to determine the recommended Phase 2 dose (RP2D). The RP2D will be selected based on both safety and totality of clinical evidence (e.g., PK/PD data), and is not necessarily the MTD. We will use the elimination boundaries in Table 12 for DLT monitoring.

Selection of cohort that will advance into Phase 2 will be based on the following consideration:

1. The cohort with the best response rate, within a 9-week window after RT plus plinabulin with 2 cycles (3 weeks Anti-PD-1/PD-L1 mAb dosing) of Anti-PD-1/PD-L1 mAb, will advance into Phase 2, if deemed well-tolerated. In consultation with the sponsor and using the totality of clinical evidence, other cohort(s) instead may be selected to advance into Phase 2. The final selection of the group to go into Phase 2 will be determined by a Safety Monitoring Committee
2. The response evaluation will be based on a minimum of 5 subjects and up to 10 subjects per cohort, unless enrollment of a given cohort is very slow and incomplete at the time sufficient response data is available on other cohorts, in which case that given cohort

could be closed for further patient accrual.

Table 12 shows the operating characteristics of the dose finding based on 1000 simulations of the trial using the BOIN Design Desktop Program (Venier et al., 2020). The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.

Table 12: BOIN Operating Characteristics Table

	Dose Level		Number of patients	% Early stopping
	-1	1 (starting)		
Scenario 1				
True DLT Rate	0.2	0.25	11	2.4
Selection %	40.5	57.1		
% Pts Treated	36.7	63.3		
Scenario 2				
True DLT Rate	0.25	0.3	11.1	5
Selection %	52.3	42.7		
% Pts Treated	43	57		
Scenario 3				
True DLT Rate	0.3	0.35	11.2	8.8
Selection %	60.6	30.6		
% Pts Treated	48.9	51.1		

DLT: dose-limiting toxicity

Phase 2:

102 Patients will be 1:1 randomized to the control and experimental arms.

Arm A: Radiation Therapy + Plinabulin + anti-PD-1/PD-L1 mAb (experimental)

Arm B: Radiation Therapy + anti-PD-1/PD-L1 mAb (control)

Because the experimental combination arm is not expected to be worse than the control arm, no futility monitoring is planned. Assuming the ORR is 5% in control arm and 15% in experimental arm, based on Chi-squared test. A sample size of 51 evaluable patients in each group is required to detect the difference with one sided type I error 0.2 and power 80%.

The BOIN elimination rule, e.g., if Pr(DLT rate >0.25 | interim data) > 0.95, then stop the accrual, will be used to ensure patient safety in both arms. The posterior probability calculation is based on the uniform prior for the DLT rate. The monitoring will start from the 11th patient and carried out every 10 patients. The target toxicity (DLT) rate is 25%.

Table 13: Toxicity Stopping Boundaries

Number of patients	**Number of toxicities are considered too toxic**
11	6–11

Number of patients	Number of toxicities are considered too toxic
21	9– 21
31	12– 31
41	15– 41
51	18– 51

Below shows the operating characteristics of the safety monitoring rule based on 10000 simulations.

	True DLT rate				
	0.1	**0.2**	**0.3**	**0.4**	**0.5**
Pr(stopping)	0	0.03	0.31	0.78	0.98
Average sample size	51	50	42.9	28.8	18.6

The Investigator is responsible for completing an efficacy/safety summary report and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval.

Phase 1b:

A Cohort summary will be submitted after the first 3 evaluable patients complete two doses of PD1/PDL1 and every 3 evaluable patients thereafter. Approval from IND office is required prior to expanding/changing dose levels.

Ph1b expansion:

A Cohort summary will be submitted after the first 3 evaluable patients per cohort complete two doses of PD1/PDL1, and every 3 evaluable patients, per cohort thereafter. During every submission, response assessed at 9 weeks will be included in the summary.

Phase 2:

Efficacy/safety summary will be submitted after the first 11 evaluable patients per arm, complete two doses of PD1/PDL1, and every 10 evaluable patients per arm, thereafter. During every submission, the response assessment (done at 8 weeks) of previously submitted patients will be provided.

A copy of the summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.5. Withdrawal

If a patient discontinues treatment due to any other reason than disease progression/death/withdrawal of informed consent, the disease evaluations shall continue until disease progression. This includes subjects who wish to discontinue treatment but agree that further data is captured for the purpose of the study (partial withdrawal).

9. DATA INTEGRITY AND QUALITY ASSURANCE

9.1. Source Documents

Study data will be collected on source documents. The Investigator is responsible for assuring that collected data are complete and accurate. Source documentation (the point of initial recording of a piece of data) should support data collected on the eCRF. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study.

9.2. Data Collection and Case Report Form Monitoring

All subjects will be registered in the Clinical Oncology Research System (CORe).

All data obtained for this study will be entered in a Code of Federal Regulations Title 21 (21 CFR) Part 11-compliant Data Management System provided by MD Anderson Cancer Center or its designee. These data will be recorded with an electronic data capture (EDC) system (Moclia). The Investigator will ensure the accuracy and completeness of the data reported to the MD Anderson Cancer Center. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from the MD Anderson Cancer Center to verify the proper transcription of data. Data reported in the eCRFs should be consistent with and substantiated by the subject's medical record and original source documents. The eCRF data will be monitored by the MD Anderson Cancer Center or designee. The MD Anderson Cancer Center will retain the final eCRF data and audit trail. A copy of all completed eCRFs will be provided to the investigator.

9.3. Study Records Retention

Study documents should be retained indefinitely. No records will be destroyed without the written consent of MD Anderson Cancer Center.

9.4. Audits and Inspections

Authorized representatives of the MD Anderson Cancer Center, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a MD Anderson Cancer Center audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the MD Anderson Cancer Center immediately if contacted by a regulatory agency about an inspection.

9.5. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

10. ETHICAL CONSIDERATIONS, COMPLIANCE STATEMENT ND REGULATORY COMPLIANCE

10.1. Ethical Considerations

A copy of the protocol, informed consent forms (ICFs), other information to be completed by subjects, such as questionnaires and any proposed advertising or recruitment materials, will be submitted to the regulatory authority(ies) and ECs.

All subsequent amendments to the protocol, informed consent documents, and other study documentation referenced above must be submitted and approved in accordance with country specific requirements.

Periodic study status reports, as applicable, will be submitted to the ECs in accordance with country specific regulations. The PI will be responsible for obtaining EC approval of the annual continuing review throughout the duration of the study.

The PI will notify the local ECs of violations from the protocol and SAEs.

Subjects will be informed that medical care will not be affected by their agreement or refusal to participate in this study, and that they are free to withdraw from the study at any time without prejudice to the clinician patient relationship.

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the MD Anderson Cancer Center before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The MD Anderson Cancer Center will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

10.2. Good Clinical Practice

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (October 2013), the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and FDA GCP Regulations: C21 CFR, Parts 11, 50, 54, 56 and 312 as appropriate.

The MD Anderson Cancer Center will ensure that the study complies with all local, federal, or country regulatory requirements as applicable. Throughout the study, the MD Anderson Cancer Center and its designee will work with the Investigator(s) to ensure proper study protocol implementation and adherence to regulatory requirements as listed in the study protocol.

10.3. Delegation of Investigator Duties

The PI should ensure that all persons assisting with the study are adequately qualified, trained, and informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions.

The PI should maintain a list of sub-investigators and other appropriately qualified persons to whom he/she has delegated significant study related duties.

10.4. Subject Confidentiality

The Investigators and the MD Anderson Cancer Center will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals regarding the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the CRF/eCRF or other documents submitted to MD Anderson Cancer Center, subjects should be identified by a unique subject identifier as designated by the MD Anderson Cancer Center. Documents that are not for submission should be kept in strict confidence by the Investigator.

In compliance with federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the MD Anderson Cancer Center, of the regulatory agency(s), and the EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

10.5. Written Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject, or legally acceptable representative, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject, or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

10.6. Regulatory Compliance

MD Anderson has a legal responsibility to notify the FDA as well as all sites, about the safety of the drug.

The study protocol, subject information and consent form, the IB, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., advertisements), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the EC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the EC for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the EC of deviations from the protocol or SAEs occurring at the site, in accordance with local procedures.

As required by local regulations, MD Anderson Cancer Center will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

The Investigator(s)/institution(s) will permit study related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents. Copies of the notification to the EC must be sent to the MD Anderson Cancer Center.

11. STUDY ADMINISTRATIVE INFORMATION

11.1. Financial Disclosure

The disclosed financial interest of the PI must be collected before screening of the first study subject. The PI should promptly update this information if any relevant changes occur during the study period and 1 year following overall study completion.

11.2. Study Registration and Results Disclosure

The MD Anderson Cancer Center may provide study information for inclusion in national registries per local regulatory requirements.

Results of this study will be disclosed per the relevant national regulatory requirements.

11.3. Use of Stored Samples and Data

Stored samples will be labeled with study and subject information and kept in a locked room with limited access. Electronic data will be kept in password protected computers at the laboratory at MD Anderson Cancer Center or designee as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's tracking system.

Prior MD Anderson Cancer Center and IRB approval are required before using or sharing study samples or data in ways not specified in the study protocol.

Any loss or unanticipated destruction of samples (e.g., freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to the MD Anderson Cancer Center and the IRB.

Unless otherwise directed by the subject, at the completion (termination) of the study, samples will continue to be stored indefinitely. In all cases, samples will be stored until the completion (termination) of the study. At any time, subjects may inform the Investigator that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will request that all known remaining samples be destroyed to MD Anderson Cancer Center and report the disposition of samples to the requesting subjects and the IRB.

11.4. Disposition of Stored Samples and Data

Access to stored samples will be limited by using a locked room. Data will be kept in password protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, other Investigators may wish to study these samples and/or data. In that case, IRB approval and MD Anderson Cancer Center approval must be obtained before any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior MD Anderson Cancer Center and IRB approval.

Any loss or unanticipated destruction of samples (e.g., due to freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to the MD Anderson Cancer Center and the IRB.

At the completion (termination) of the study, samples will continue indefinitely.

Additionally, subjects may decide at any point not to have their samples stored for a period of up to 15 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol.

11.5. Subject Identification and Confidentiality

A subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the MD Anderson Cancer Center. All records will be kept confidential to the extent provided by federal, state, and local laws. The subjects will be informed that representatives of the MD Anderson Cancer Center, EC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The PI will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6. Protocol Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by the MD Anderson Cancer Center, before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies), central ECs, and local IRBs/ECs. Copies of the applicable written approvals must be given to the site monitor or their designee.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by the MD Anderson Cancer Center in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the study MD Anderson Cancer Center or its agent should be notified and the applicable regulatory authority(ies)/central ECs/local IRBs/ECs should be informed within 10 working days. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/central EC/local IRB/IEC approval, but the regulatory authority(ies)/central ECs/local IRBs/ECs must be kept informed of such administrative changes in accordance with country specific requirements.

11.7. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the MD Anderson Cancer Center may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support always for these activities. Medical records and other study documents may be copied during audit or inspection if subject names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform the study MD Anderson Cancer Center, immediately that this request has been made.

The MD Anderson Cancer Center will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

12. REFERENCES

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13. APPENDICES

APPENDIX A. CTCAE VERSION 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX B. IMMUNE-RELATED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Investigators should follow the guidelines provided here which are an adaptation of RECIST and irRC. The following guide represents a summary of irRECIST and is meant to help investigators in providing more objective and reproducible immune therapy related tumor response assessments in solid tumors.

The key changes for irRECIST are:

- irRECIST allows the site to select up to ten (10) target lesions at baseline, five (5) per organ, if clinically relevant via CT/MRI scans or by electronic calipers for skin lesions. The ability to continue treatment, if clinically stable, until repeat imaging scans ≥4 weeks later (in most cases at the next scanning time point 6 weeks later) to confirm Progressive Disease(irPD)

irRECIST Lexicon	
1. Baseline Assessments	
Measurable (Target) lesions	Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter (LDi) by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis (SDi) for nodal lesions • 10 mm in LDi for clinical lesions (must be measured using electronic calipers) • Identify up to 10 lesions, not more than 5 from one organ system. Lymph nodes are considered one organ system • Likely to be reproducible across all time points • Representative of tumor burden • May include lesions in previously irradiated areas ONLY if there is demonstrated progression in that lesion after irradiation • Sum of diameters (SOD) of all target lesions including nodal and non-nodal are reported as baseline SOD, which is used for assessing tumor response at follow-up time points
Bone lesions	Regardless of the imaging modality, blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.

Cystic and Necrotic Lesions as Target Lesions	Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the SOD of all target lesions at baseline. If other lesions with a nonliquid/nonnecrotic component are present, those should be preferred.
Lesions with Prior Local Treatment	During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (eg, previous irradiation, RF-ablation, TACE, surgery). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progression in the lesion.
Nonmeasurable (Nontarget) lesions	Nontarget lesions will include: • Measurable lesions not selected as target lesions. There is no limit to the number of nontarget lesions that can be recorded at baseline • Other types of lesions that are confidently felt to represent neoplastic tissue but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc. • Multiple non target lesions from the same organ may be captured as a single item on the eCRF (e.g., multiple liver metastases) Nontarget lesions should be reported as present at baseline
SOD baseline	Sum of diameters at baseline = LDi of all non-nodal + SDi of all nodal target lesions
2. Time point Assessments After Baseline	
Target lesion measurements	Locate image that optimizes the LDi of the non-nodal target lesion or short axis of target node(s). There is no need to go to an identical slice from baseline. Measure the respective LDi and SDi for all target lesions and calculate time point SOD (SOD timepoint). Special consideration for target lesions: • If target lesion is too small to measure, a default value of 5mm should be entered on eCRF. • If target lesion is 5-10mm, actual diameter should be entered in the eCRF. • If target lesion splits into 2 or more lesions, then the LDi of split lesions will be added and entered in place of that lesion.

	• If two target lesions merged to form one lesion than LDi of one should be entered as "0mm" while the other lesion should have the diameter of the merged lesion.
Nontarget Lesion Assessment	Nontarget lesions are evaluated qualitatively as present, absent, not evaluable (NE) or unequivocal progression. The response of nontarget lesions primarily contributes to the overall response assessments of irCR. Nontarget lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of nontarget lesions alone, even in the presence of stable disease or a partial response in the target lesion is indicative of irPD. irCR is not possible unless all nontarget lesions are absent
3. irRECIST Overall Tumor Assessment	
irCR	• Complete disappearance of all measurable and non-measurable lesions (from baseline) and there are no unequivocal new lesions (unconfirmed irCR). • Lymph nodes must decrease to <10 mm in short axis. • Confirmation of response is required ≥4 weeks later, preferably at next time point, to be considered a confirmed irCR.
irPR	• If the **$SOD_{timepoint}$** of TLs decreases by ≥30 % compared to $SOD_{baseline}$ and there are no unequivocal new lesions, and no progression of nontarget disease, it is an irPR (unconfirmed). • Confirmation is required ≥4 weeks later, preferably at next time point, to be considered a confirmed irPR.
irSD	Failure to meet criteria for irCR or irPR in the absence of irPD. • If the sum of the TLs and the status of the nontarget lesions do not reach the criteria to meet irPR or irPD (increase ≥20% and at least 5 mm absolute increase in SOD compared to nadir†) the response is irSD. • **irSD** = neither 30% decrease compared to $SOD_{baseline}$ or 20% increase and at least 5 mm absolute change compared to nadir. • **†SOD_{nadir}:** Lowest measure SOD of TLs at any time point from baseline onward.
irPD	Minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or irPD for nontarget lesion(s) or unequivocal new lesion(s). • Confirmation of progression is recommended at a minimum of 4 weeks after the first irPD assessment (preferably at next tumor assessment time point). • The decision to continue study treatment after the first evidence of PD is at the investigator's discretion based on the clinical status of the subject as described in table below

<table>
<tr><td></td><td>
<table>
<tr><th></th><th colspan="2">Clinically Stable</th><th colspan="2">Clinically Unstable</th></tr>
<tr><td></td><td>Imaging</td><td>Treatment</td><td>Imaging</td><td>Treatment</td></tr>
<tr><td>1st radiologic evidence of PD</td><td>Repeat imaging at ≥4 weeks (next TA time point) to confirm PD</td><td>May continue study treatment at the Investigator's discretion while awaiting confirmatory scans</td><td>Repeat imaging at ≥4 weeks to confirm PD per physician discretion only</td><td>Discontinue treatment</td></tr>
<tr><td>Subsequent scan confirms PD</td><td>No additional imaging required</td><td>Discontinue treatment</td><td>No additional imaging required</td><td>N/A</td></tr>
<tr><td>Subsequent scan shows SD, PR or CR</td><td>Continue regularly scheduled imaging assessments</td><td>Continue study treatment at the Investigator's discretion</td><td>Continue regularly scheduled imaging assessments</td><td>May restart study treatment if condition has improved and/or clinically stable per investigator's discretion</td></tr>
</table>
Subjects may continue receiving study treatment while waiting for confirmation of irPD if they are clinically stable as defined by the following criteria:
• Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
• No decline in ECOG performance status
• Absence of rapid progression of disease
• Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact sponsor to discuss continuing treatment</td></tr>
<tr><td>irNE</td><td>Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure</td></tr>
</table>

Derivation of irRECIST overall responses			
Measurable response	**Non-measurable response**		
Target Lesions (% change in SOD)[a]	**Nontarget Lesions Status**	**New Lesions Status**	**Overall Response (irRECIST)**
↓100	Absent	Absent	irCR[b]
↓100	Present/NE	Absent	irPR[b]
↓≥30	Present/Absent/NE	Absent	irPR[b]
↓<30 to <20	Present/Absent/NE	Absent	irSD
↓100 ↓≥30 ↓<30 to <20 NE	Present/Absent/NE	Present	irPD[b]
↓100 ↓≥30 ↓<30 to <20 NE	Unequivocal Progression	Any	irPD[b]
≥20 from nadir	Any	Any	irPD[b]
NE	Present/Absent/NE	Absent	irNE[b]

irNE = immune-related not evaluable, irPD = immune-related progression disease, NE = Not evaluable
a: Decreases assessed relative to baseline, including measurable lesions only.
b: Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.