

Full Inclusion and Exclusion Criteria

1. Inclusion Criteria

Patients may be eligible for inclusion in the study if they meet the following criteria:

1.1. All Patients Entering Trial

All patients entering any part of the trial must meet the following criteria for inclusion:

1. ≥ 18 years of age
2. Life expectancy of ≥ 3 months
3. Histological or cytological evidence of advanced and/or metastatic carcinoma or melanoma or (for Part H only) sarcoma
4. At least 1 measurable disease lesion as defined by RECIST 1.1 or (for patients in expansion cohorts only) irRECIST
5. Serum creatinine clearance ≥ 45 mL/min (≥ 30 mL/min for patients in Part I), as determined by either of the following:
 - Estimation as calculated by Cockcroft-Gault equation
 - Direct measurement by 24-hour urine collection
6. Total bilirubin ≤ 1.5 x upper limit of normal (ULN; unless elevated due to Gilbert's syndrome)
7. Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) < 2.5 x ULN (< 5 x ULN if liver metastasis), with the exception of patients in Part I, for whom AST/SGOT and ALT/SGPT < 3 x ULN
8. Adequate hematologic function, defined as absolute neutrophil count ≥ 1.5 x 10^9 /L, hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100 x 10^9 /L
9. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (corresponds to Karnofsky Performance Status [$\geq 60\%$]), with the exception of patients in Part I, for whom ECOG performance status ≤ 1
10. For women of childbearing potential (WCBP): negative serum β human chorionic gonadotropin (β hCG) pregnancy test within 1 week before first treatment (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 12 consecutive months for women > 55 years of age)
11. Willingness of male and female patients who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control for the duration of the study treatment, including 30 days after the last dose of IPI-549 and for 5 months (for females) or 7 months (for males) after the last dose of nivolumab. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception.

12. Azoospermic males and WCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, female patients must still undergo pregnancy testing as described in this section.
13. Ability to adhere to the study visit schedule and all protocol requirements
14. Signed and dated IRB/independent ethics committee (IEC)-approved informed consent form (ICF) before any Screening procedures are performed

1.2. Patients Entering Parts A, B, C, or D

Patients entering Part A, B, C, or D must meet the following additional criterion:

15. Failure to respond to standard therapy, or for whom no appropriate therapies are available (based on the judgment of the Investigator)

1.3. Patients Entering Parts D, E, F, G, H, or I

Patients entering Part D, E, F, G, H, or I must also meet the following additional criterion:

16. Willing to undergo 1 pre-treatment and 1 on-treatment tumor biopsy

1.4. Patients Entering Part E

Patients entering Part E must also meet the following additional criteria:

17. Histological or cytological evidence of NSCLC, melanoma, human papillomavirus (HPV) positive or HPV negative SCCHN (oral cavity, pharynx, hypopharynx, larynx, nasopharyngeal [including undifferentiated nasopharyngeal carcinoma]), or another tumor type to be determined
18. Failure to respond to standard therapy, or for whom no appropriate therapies are available (based on the judgement of the Investigator)
19. The most recent treatment prior to study entry must be an anti-PD-1 or anti-PD-L1 therapy, given as either monotherapy or in combination, and patient must have evidence (ie, scans, clinical note, laboratory results, photos, et cetera) of progression while on that anti-PD-1 or anti-PD-L1 therapy
20. **Patients with NSCLC:** Tumors that harbor an actionable genetic alteration for which there is a corresponding approved therapy for that specific alteration (including but not limited to alterations in *EGFR*, *ALK*, and *ROS*) should (if deemed appropriate by the Investigator) have progressed on, or had intolerance to, the respective therapy

1.5. Patients Entering Part F

Patients entering Part F must also meet the following additional criteria:

21. Histological or cytological evidence of estrogen-receptor negative (ER-), progesterone receptor negative (PgR-) and human epidermal growth factor-2 receptor negative (HER2-) Breast Cancer by local laboratory testing, based on last available tumor tissue, or another tumor type to be determined
 - ER/PgR negativity to follow local guidelines

- If immunohistochemistry HER2 2+, a negative fluorescence in situ hybridization test is required
 - Inflammatory triple-negative breast cancer is allowed
22. Should have received and failed/progressed a cytotoxic chemotherapy as first-line therapy, per standard of care if deemed appropriate by the Investigator
23. No prior anti-PD-1 or anti-PD-L1 therapy

1.6. Patients Entering Part G

Patients entering Part G must also meet the following additional criteria:

24. Histological or cytological evidence of ACC, mesothelioma, or another tumor type to be determined
- Both pleural and peritoneal mesothelioma are allowed
 - Epithelioid, sarcomatoid, or biphasic mesothelioma subtypes are allowed
25. Progression after at least first-line available therapy but naïve to anti-PD-1 therapy

1.7. Patients Entering Part H

Patients entering Part H must also meet the following additional criteria:

26. High-circulating MDSCs, currently defined for this study as MDSCs $\geq 20.5\%$ as measured by CLIA-certified Seramatrix assay (this cutoff may be revised in the future should new experience and clinical data from use of the assay become available)
27. Microsatellite status of tumor has been determined
28. Patients with tumors that are microsatellite instability-high must have previously received an anti-PD-1/anti-PD-L1 therapy and must have evidence (ie, scans, clinical note, laboratory results, photos, et cetera) of progression while on that therapy
29. Additionally, if patient's tumor type is one for which anti-PD-1/anti-PD-L1 therapy is standard of care, patient must have previously received an anti-PD-1 or anti-PD-L1 therapy and radiologically progressed while on that therapy

1.8. Patients Entering Part I

Patients entering Part I must also meet the following additional criteria:

30. Histological or cytological evidence of locally advanced or metastatic urothelial cancer, with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
31. Patients who have received more than 2 prior lines of chemotherapy must not have liver metastases. Sequential chemotherapy given as a planned sequence to optimize response will count as 1 regimen.

32. No prior anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or anti-CD137 therapy, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
33. Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration. Patients must have measurable disease outside the radiation field to be eligible; patients with progression in a previously radiated field will also be eligible.
34. Evaluable tumor tissue (archived or new biopsy) must be provided for biomarker analysis, including PD-L1 status per central laboratory (DAKO).
35. Blood sample must be provided for evaluation of MDSC levels, as measured by CLIA certified Seramatrix assay. In order to be treated, all patients must have a confirmed result of MDSC content.
36. All toxicities attributed to prior anticancer therapy, with the exception of neuropathy, alopecia, and fatigue, must have resolved to Grade 1 (per NCI-CTCAE version 4.03) or baseline before administration of study drug. Patients with toxicities attributed to prior anticancer therapy that are not expected to resolve and result in long-lasting sequelae, such as neuropathy after platinum-based therapy, are permitted to enroll. Neuropathy must have resolved to Grade 2 (per NCI-CTCAE version 4.03 or higher).

2. Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Severe allergic or anaphylactic reaction to any monoclonal antibody therapy, murine protein, or known hypersensitivity to any excipient in the study drugs
2. Major surgery within 4 weeks prior to Screening
3. Patients who have been treated with chemotherapy, biologic therapy, or other investigational agent within < 5 times the half-life of the agent or < 28 days (whichever is shorter) of starting study drug

NOTE: Patients whose immediate prior treatment was with a PD-1 or PD-L1 inhibitor may start study drug anywhere from 2 to 3 weeks after the last dose of that agent, depending upon the prescribed dosing interval for the PD-1 or PD-L1 inhibitor.

4. Patients who have received radiotherapy within < 2 weeks of starting study treatment, or who have unresolved associated AEs
5. Symptomatic or untreated brain metastases (including leptomeningeal metastases)
6. Primary central nervous system (CNS) malignancy
7. Infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C virus (HCV)
8. Ongoing treatment with chronic immunosuppressants (eg, cyclosporine) or systemic steroids (except for steroid use as cortisol replacement therapy in documented adrenal insufficiency)
9. Ongoing systemic bacterial, fungal, or viral infections at Screening

NOTE: Patients on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met.

10. Administration of a live vaccine within 6 weeks of first dose of study drug
11. Administration of any of the following within 1 week prior to the administration of study drug:
 - a. Strong inhibitors or inducers of CYP3A4, including grapefruit, grapefruit juice and herbal supplements
 - b. P-gp inhibitors
 - c. Warfarin, phenytoin, or other substrates of CYP2C8 or CYP2C9 with a narrow therapeutic range
 - d. Medications associated with QTc interval prolongation or Torsades de Pointes
12. Baseline QT interval corrected with Fridericia's method (QTcF) > 480 ms (average of triplicate readings)

NOTE: criterion does not apply to patients with a right or left bundle branch block.
13. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (eg gastric bypass surgery, gastrectomy)
14. Female patients who are pregnant or breastfeeding
15. Concurrent active malignancy other than nonmelanoma skin cancer, carcinoma in situ of the cervix, or prostate intraepithelial neoplasia
16. Parts C, D-Annex, E, F, G, H, and I only: Patients with active, known, or suspected autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
17. Part F only: Prior anti-PD-1 or anti-PD-L1 therapy
18. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease
19. History of peptic ulcer and/or gastrointestinal bleed within the past 6 months prior to Screening
20. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months prior to Screening
21. Unstable or severe uncontrolled medical condition (eg, unstable cardiac function, unstable pulmonary condition including pneumonitis and/or interstitial lung disease, uncontrolled diabetes) or any important medical illness or abnormal laboratory finding that would, in the

Investigator’s judgment, increase the risk to the patient associated with his or her participation in the study

22. History of any Grade 3 or 4 immune-related AE toxicity from prior immunotherapy that resulted in treatment discontinuation

2.1. Patients Entering Part H

Patients entering Part H must not meet any of the following additional criteria:

23. Any tumor type that meets the specific entry criteria for Part E of this study while enrollment to Part E is ongoing
24. Any tumor type that is being studied in Part F or Part G of this study while enrollment to Part F or Part G is ongoing