A PHASE 2 CLINICAL STUDY OF TJ004309 IN COMBINATION WITH ATEZOLIZUMAB (TECENTRIQ®) IN PATIENTS WITH ADVANCED OR METASTATIC OVARIAN CANCERS AND SELECTED ADVANCED SOLID TUMORS

Protocol Number:	TJ004309STM103
Compound Name:	TJ004309
Study Phase:	Phase 2
Sponsor Name:	I-Mab Biopharma US Limited
Legal Registered Address:	9801 Washingtonian Blvd, Suite 710 Gaithersburg, MD 20878 USA
Regulatory Agency Identifier Number(s):	IND: 156151
Version (Approval Date):	3.0 (30 September 2021)

This study will be conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation Tripartite Guideline.

Sponsor Signatory:

DocuSigned by:
Claire Xu
Signer Name: Claire Xu
Signing Reason: I approve this document
Signing Time: 10/1/2021 | 11:31:34 AM EDT
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10/1/2021 | 11:31:40 AM EDT

Claire (Cong) Xu, MD, PhD
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Date

Sponsor Study Contact Information

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INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

_____
Principal Investigator (Printed)

_____
Principal Investigator (Signature) Date

_____
Clinical Site

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from I-Mab Biopharma US Limited representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

STUDY IDENTIFICATION

Sponsor	I-Mab Biopharma US Limited 9801 Washingtonian Blvd, Suite 710 Gaithersburg, MD, 20878
Sponsor's Study Contact	Claire (Cong) Xu, MD, PhD US Site Head I-Mab Biopharma US Limited 9801 Washingtonian Blvd, Suite 710 Gaithersburg, MD, 20878
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Study Sites	Obtain information from Form FDA 1572
Principal Investigators	Obtain information from Form FDA 1572
Bioanalytical Laboratory	Frontage Laboratory 700 Pennsylvania Drive Exton, PA 19341
Immunogenicity Laboratory	Frontage Laboratory 700 Pennsylvania Drive Exton, PA 19341
Immunohistochemistry Laboratory (Tumor Analyses)	GoPath Laboratories, LLC 1351 Barclay Boulevard Buffalo Grove, IL 60089 WuXi AppTec Co, Ltd 288 Fute Middle Rd Pilot Free Trade Zone Shanghai, China

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: I-Mab Biopharma US Limited

Title of Study:
A PHASE 2 CLINICAL STUDY OF TJ004309 IN COMBINATION WITH ATEZOLIZUMAB (TECENTRIQ®) IN PATIENTS WITH ADVANCED OR METASTATIC OVARIAN CANCERS AND SELECTED ADVANCED SOLID TUMORS

Name of Investigational Product: TJ004309

Principal Investigators: To be determined

Rationale:

TJ004309 is an investigational antibody to CD73, an ectonucleotidase that converts AMP to adenosine and inorganic phosphate. Adenosine inhibits tumor immune surveillance by binding to the A2A and A2B adenosine receptors. TJ004309 non-competitively inhibits CD73-mediated conversion of AMP to adenosine, thereby reversing adenosine mediated immune suppression in T cells. Adenosine mediated by CD73 is implicated as a mechanism of resistance to PD-1/PD-L1 checkpoint inhibitors. TJ004309 inhibits tumor growth and complements the activity of antibody checkpoint inhibitors that target the PD-1/PD-L1 pathway in preclinical models. By targeting the adenosine pathway, TJ004309 has the potential to complement the PD-L1/PD-1 checkpoint inhibitor such as atezolizumab in cancer patients. Atezolizumab is a humanized monoclonal antibody to PD-L1 that is approved for the treatment of locally advanced or metastatic urothelial carcinoma and indicated for the treatment of several other indications, which will be combined with TJ004309 in this trial.

Based on the published database and literature reports, CD73 is highly expressed in head and neck squamous cell carcinoma (60-80%), ovarian (50-70%), gastric (50-69%), and other cancers. To further test the hypothesis that the tumor types with high CD73 expression may better respond to the combination therapy, a tumor biomarker enriched cohort is planned to enroll patients with non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), triple negative breast cancer (TNBC), ovarian carcinoma (OC), and gastric cancers (GC) to assess the relationship between antitumor activity and various tumor biomarkers.

The enrollment of dose escalation of TJ004309 in combination with atezolizumab has been completed in a Phase 1 trial NCT03835949 under IND 141965. In the 3+3 dose escalation study, TJ004309 was administered intravenously at doses of 5, 10 or 15 mg/kg weekly (QW), or 15 or 20 mg/kg every 3 weeks (Q3W) as a monotherapy in the first 21-day treatment cycle followed by combination therapy with atezolizumab (1200 mg Q3W) starting from the second cycle (week 4). No dose limiting toxicity (DLT) was observed and maximum tolerated dose (MTD) was not reached. Among 13 efficacy evaluable patients dosed ≥ 10 mg/kg, a complete response (CR = 1) and partial responses (PR = 2) were observed in 3 patients (ORR = 23%). A PD-(L)1 naïve patient with ovarian carcinoma achieved CR and remained on study for at least 15 months. In addition, higher tumor CD73 and PD-L1 co-expression was found in all responders compared to that in non-responders, indicating a potential correlation that warrants further investigation. This supports further exploration of the efficacy of TJ004309 combination therapy in selected solid tumor types as well as the relationship between the expressions

of PD-L1 and CD73 with responses. This clinical study is designed to evaluate the efficacy and safety of TJ004309 combination therapy in patients with ovarian cancers and selected advanced solid tumors.

Objectives:

The primary objectives of the study are:

- Part 1: To assess the efficacy of TJ004309 combined with atezolizumab in a cohort of patients with platinum-resistant IO naïve ovarian carcinoma and a separate biomarker enriched cohort of subjects with selected tumor types
- Part 2: To further evaluate and confirm the efficacy in targeted patient population based on the efficacy observed in Part 1

The secondary objectives of the study are:

- To evaluate the safety and tolerability of TJ004309 when combined with the standard dose of atezolizumab
- Part 1: To characterize the pharmacokinetic profile of TJ004309 when administered in combination with atezolizumab
- Part 1: To determine the immunogenicity of TJ004309 when administered in combination with atezolizumab

The exploratory objectives of the study are:

- To investigate the expression of PD-L1, CD73, and other immune subset markers (CD8, CD68, CD19 and CD163) in tumor biopsies at baseline and on treatment, and their associations with clinical responses
- To examine the CD73 enzymatic activity of tumor biopsies
- To study the whole genome gene expression profiles in tumor biopsies

Study design:

This is a multicenter, open label, Phase 2 study of TJ004309 in combination with atezolizumab in patients with advanced or metastatic solid tumors. This clinical study will be conducted in two parts. Part 1 of the study will include two cohorts: Cohort 1 will include Immuno-Oncology (IO) treatment naïve ovarian cancer (OC) patients who have progressed on or after platinum therapy; and Cohort 2 will include patients with head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), gastrointestinal cancer (GC), triple negative breast cancer (TNBC), or ovarian carcinoma (OC) with PD-L1 expression ≥ 1% (Table 1). All subjects will be evaluated for antitumor activity on a regular basis as specified in the protocol and their clinical status classified according to RECIST 1.1 and iRECIST. Treatments may continue until clinically significant disease progression, unacceptable toxicity, or subject/Investigator decision to withdraw. Based on the efficacy observation in Part 1, Part 2 of the study will further evaluate the efficacy in selected targeted patient populations and will be initiated after reaching agreement with the regulatory agency.

TJ004309 will be given in combination with atezolizumab 1200 mg every 3 weeks (Q3W) beginning with Cycle 1 Day 1 (C1D1). Premedication will be given prior to the initial infusion of TJ004309 to mitigate infusion related reactions. Each cycle will be 21 days in duration.

Table 1: Study Drug Dosing Schedule – Part 1

Cohort	TJ004309 Q3W	Atezolizumab Q3W	Subjects
Cohort 1: Platinum resistant or refractory IO naïve ovarian carcinoma (OC)	20 mg/kg	1200 mg flat dose	N= 30
Cohort 2: HNSCC, NSCLC, GC, TNBC, OC	20 mg/kg	1200 mg flat dose	N= 30

Up to 30 subjects will be enrolled in each cohort. If two or less responses are observed from the first 15 subjects in Cohort 1, the enrollment may be stopped based on rules from a Simon's 2-stage design. If 3 or more responses are observed from the first 15 subjects in Cohort 1 from Part 1, then Part 2 of the study may be initiated earlier. If any response is observed from Cohort 2, an additional cohort with up to 30 subjects may be opened with a specific tumor type after reviewing all other available data at that time.

Safety Follow-up Period

After the treatment periods, all subjects will enter a safety follow-up period and will be evaluated for safety, tolerability, and tumor response (if applicable) for at least 90 days after the last dose of study drug, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects will be required to return to the study sites for three (3) safety follow-up visits (approximately 30, 60 and 90 days after the last dose of study drug), except those subjects who withdraw consent for study participation. After treatment discontinuation, in the event of continuing serious adverse events (SAEs), subjects will be followed until resolution or stabilization of the SAEs (regardless of the relationship to the IMP). Any subject who has an ongoing non-serious AE that is possibly related or related to the IMP or study procedures at the 90-day post-treatment Follow-up visit will be followed up, where possible, until resolution or until the unresolved non-serious AE is judged by the Investigator (or designee) to have stabilized. Any subject who has an ongoing non-serious AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit, can be closed out as ongoing at the Investigator's discretion. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, one (1) Post-Treatment Safety Follow-Up visit should occur approximately 30 days after the last dose of study drug and therefore subsequent follow-up visits will not be required.

Response/Survival Follow-up Period

Subjects who do not experience progressive disease prior to treatment discontinuation will continue to have radiologic and clinical tumor assessments every 9 weeks for the first year and every 12 weeks during the second year until progression is confirmed, consent withdrawal, start of a new anti-cancer treatment, loss to follow-up, or death, whichever comes first. These subjects will also be followed by telephone every 12 weeks during the second year. The duration for response/survival follow-up is approximately 2 years from the first dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Males or females, age ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
3. In all cohorts, archival tumor tissue in a tissue block or biopsy specimen that allows the preparation of at least 20 slides prior to study entry. Tissue blocks are preferred. Archival tumor tissue is acceptable in either format per site's preference.
4. Cohort 1 - Ovarian Carcinoma (OC):
   a. Histologically confirmed epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer subjects with any high-grade serous component, progressed on or after platinum-containing therapy and not eligible for further platinum containing treatment (platinum-resistant, platinum-refractory disease defined by progression of disease on a platinum-containing regimen or recurrence of disease within 180 days of receiving the last dose of platinum-based treatment).
   b. Prior lines of therapy to include:
      - Patients must have had 1 to 3 prior lines of therapy including at least one bevacizumab-containing regimen or ineligible for all other available therapies;
        Or
      - Patients must be in the 4th or 5th line of treatment, irrespective of bevacizumab or who are ineligible for all therapies with demonstrated clinical benefit;
        Or
      - Patients with known BRCA-positive associated cancer or mutation, prior therapy must include PARP inhibitors (unless contraindicated)
5. Cohort 2 - Patients with selected tumor types that have relapsed or progressed after 2 lines of therapy or who are ineligible for other standard of care (SOC) therapies:
   a. Histologically or cytologically confirmed metastatic NSCLC
   b. Histologically or cytologically confirmed recurrent or metastatic HNSCC (oral cavity, oropharynx, hypopharynx, or larynx)
   c. Histologically or cytologically confirmed metastatic or non-resectable advanced metastatic gastric or gastroesophageal adenocarcinoma
   d. Histologically or cytologically confirmed unresectable, locally advanced or metastatic TNBC (confirmed HER2-negative, estrogen receptor-negative and progesterone receptor-negative)
   e. Histologically confirmed ovarian cancer of all high-grade epithelial types who are IO treatment naïve and have progressed after 3 months on or after platinum-containing therapy
   f. PD-L1 expression Tumor Proportion Score (TPS) ≥ 1% for NSCLC and Combined Proportion Score (CPS) ≥ 1% for all other tumor types
   g. A 28-day washout period after the completion of programmed death-1 (PD-1)/PD-L1 therapy
   h. Patients should have no more than 5 prior lines of therapies
   i. If the patients have progressed on treatment with prior PD-1/L1 inhibitor administered either as monotherapy or in combination with other therapies, additional following criteria must be met:

- have received at least 2 doses of the PD-1/L1 inhibitor;
- have been on a continuous regimen of the PD-1/L1 inhibitor for at least 4 months without disease progression;
- have demonstrated radiographic disease progression after PD-1/L1

j. Patients who have had more than 1 prior PD-1/L1 inhibitor may be considered after discussion with the Sponsor's Medical Monitor

6. Cohort 2 - Pre-treatment fresh tumor biopsies and paired treatment fresh tumor biopsies will be collected from at least 5 patients. Biopsy must be excisional, incisional, or core. Fine needle aspiration is insufficient. Waiver of biopsy samples must be discussed with Sponsor's Medical Monitor. NOTE: CD73 enzymatic activity and assessment of proteins in the adenosine pathway (e.g., CD73, A2A receptor, and whole genome gene expression profiles) will be assessed in fresh tumor biopsies. Samples will be collected prior to dosing and processed and shipped within 24 hours according to a separate laboratory manual. The fresh tumor biopsies require testing for the following infectious diseases: Hepatitis B, Hepatitis C, Tuberculosis, HIV, Syphilis, and COVID-19. Testing must be completed within 28 days of tumor biopsy collection and confirmed to be negative.
7. Willingness and ability to consent for self to participate in study and the ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
8. Patients who received prior PD-1/PD-L1 checkpoint inhibitor or prior CTLA-4 inhibitor therapy may enroll to Cohort 2 if they did not experience Grade 3 immune-related toxicity (applies to all tumor types except ovarian cancer patients)
9. At least one measurable lesion as defined by RECIST 1.1
10. Resolution of all acute adverse events resulting from prior cancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≤ 1 or baseline (except alopecia or neuropathy)
11. Considered by the Investigator to be an appropriate candidate for a clinical study, with a life expectancy of ≥ 12 weeks
12. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥ 1500/μL
    b. Platelets ≥ 100,000/μL without transfusion support within 28 days prior to study treatment
    c. Hemoglobin ≥ 9.0 g/dL without transfusion support within 7 days prior to study treatment (erythropoietin or darbepoetin permitted)
    d. Creatinine clearance > 30 mL/min by Cockcroft-Gault formula
    e. Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 3 times upper limit of normal (ULN) or ≤ 5 times ULN in cases of liver metastases
    f. Total serum bilirubin ≤ 1.5 times the ULN, unless patient has documented Gilbert's disease in which case bilirubin ≤ 3.0 times the ULN
    g. International normalized ratio (INR) from 0.8 to 1.2 unless the INR elevation is related to use of a Factor Xa Inhibitor

h. Activated partial thromboplastin time (aPTT) ≤ 1.5× ULN unless patient is receiving anticoagulant therapy if PT or PTT is within therapeutic range of intended use of anticoagulants

13. No systemic anti-cancer therapy within 4 weeks of starting study treatment or at least 5 half-lives (whichever is shorter) before study drug administration, and all AEs have either resolved or stabilized. Note: Participants who have entered the follow-up phase of an investigational study may participate if it has been 4 weeks after the last dose of the previous investigational agent.
14. Subject with a QT interval corrected for heart rate using Fridericia's formula (QTcF) and/or QT interval corrected for heart rate using Bazett's formula of ≤ 480 msec. NOTE: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (i.e., the patient otherwise has no cardiac abnormalities), the patient may be eligible to participate in the study following discussion with the Sponsor's Medical Monitor.
15. Women of childbearing potential (WOCBP) must:
    a. Agree to use at least 2 effective contraceptive methods (1 highly effective method in combination with a barrier method; oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner), one of which must be barrier. Use of contraceptive methods lasts from date of ICF signature, throughout the study, and for up to 5 months following the last dose of TJ004309.
    b. Have a negative serum pregnancy test (sensitive of at least 25 mIU/ml) at Screening; and have a negative serum or urine pregnancy test within 72 hours prior to Cycle 1 Day 1 of study treatment (note that the screening serum pregnancy test can be used as the test prior to Day 1 study treatment if it is performed within the prior 72 hours)
    c. Avoid conceiving for 5 months after the last dose of TJ004309
    d. Avoid donation of ova from date of ICF signature until 5 months after the last dose of TJ004309
    e. Agree to ongoing urine pregnancy testing, if clinically indicated, during the study
16. Males must agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or a female of childbearing potential, will avoid donation of sperm, or having a female partner conceive from date of ICF signature, while participating in the study, during dose interruptions, and for at least 5 months after the last dose of study treatment, even if he has undergone a successful vasectomy.

Exclusion Criteria:

1. Autoimmune disease requiring active treatment within the past twelve months (Note: vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger are permitted)
2. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment

(Note: inhaled and topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.)

3. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease
4. Current treatment on another therapeutic clinical trial
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX 40 [Tumor necrosis factor receptor superfamily, member 4 (TNFRSF4)], CD137 [tumor necrosis factor receptor superfamily member 9 (TNFRSF9)]) (only applies to ovarian cancer patients in Cohorts 1 and 2)
6. For ovarian patients in both cohorts:
    a. Patients who progressed during or within 3 months of first line of platinum-based therapy
    b. Patients with histologically non-epithelial tumors or ovarian tumors with low malignant potential (i.e., borderline tumors) or mucinous tumors
    c. Patients with evidence of bowel obstruction requiring hospitalization and decompression within the past 30 days
7. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure; and no date of surgery (if applicable) or anticipated need for a major surgical procedure planned within the next 6 months (The following situations are not considered to be major procedures and are permitted up to 7 days prior to study treatment: thoracentesis, paracentesis, port placement, laparoscopy, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, incisional biopsies, and routine dental procedures. Core biopsy and skin biopsy do not require a waiting period prior to dosing.)
8. Chest radiotherapy ≤ 28 days, wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvic bones or equivalent), or limited field radiation for palliation ≤ 14 days prior to study treatment
9. Pleural effusion or ascites that requires therapeutic paracentesis in the last 30 days
10. Brain involvement with cancer, spinal cord compression, carcinomatous meningitis, or new evidence of brain or leptomeningeal disease; unless the lesion(s) have been radiated or resected, are considered fully treated and inactive, are asymptomatic, and no steroids have been administered for CNS disease over the 7 days prior to study treatment
11. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment
12. Thrombolytic use (except to maintain IV catheters) within 10 days prior study treatment
13. Known active or chronic Hepatitis B or Hepatitis C, other hepatitides (non-alcohol steatohepatitis, alcohol or drug-related, autoimmune) serology at screening or cirrhosis

14. Any active infection requiring parenteral treatment
15. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months prior to study treatment
16. Known human immunodeficiency virus (HIV) unless CD4+ T cell count > 350 cells/μL with an undetectable viral load
17. Pregnancy or breastfeeding - Female patients must be surgically sterile (i.e., ≥ 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal for at least one year or must agree to use effective contraception during the study and for 5 months following last dose of TJ004309. All female patients of reproductive potential must have a negative pregnancy test (serum or urine) within 72 hours prior to study treatment. Male patients must be surgically sterile or must agree to use effective contraception during the study and for 5 months following last dose of TJ004309
18. Patients with any severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infections should not be enrolled in the trial. Patients who required IV antibiotics or were treated with antiviral medications within this 4 week period should be discussed with the Sponsor Medical Monitor prior to enrollment
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

Investigational Products, Dose and Mode of Administration:

Each subject will be administered IV infusions of TJ004309 20 mg/kg Q3W in combination with atezolizumab 1200 mg Q3W. The dose of TJ004309 will be calculated based on the actual weight (kg) of each subject.

TJ004309 will be supplied by the Sponsor as 150 mg/3 mL (50 mg/mL) solution in a single use vial.

Atezolizumab will be supplied by the Sponsor as 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial.

All study treatments will be administered at the clinical study site. The pharmacy manual will contain specific instructions for the preparation of TJ004309 and administration of the infusion solution.

Duration of Subject Participation in the Study:

Planned screening duration: approximately 4 weeks.

Planned treatment duration: patients are eligible for treatment until clinically significant disease progression, unacceptable toxicity, or subject/Investigator decision to withdraw.

Planned follow-up safety evaluation: at least 30 days following the last dose of study drug(s).

Response/Survival follow-up duration: approximately 2 years from the first dose of study drug.

Total duration of study participation: approximately 120 weeks (including response/survival follow-up).

Parameters to be Assessed/Endpoints:

Part 1

Efficacy: Anti-tumor activity of the combination of TJ004309 and atezolizumab will be measured by best of response (BOR), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS) based on RECIST 1.1 and iRECIST.

Safety: Treatment-emergent AEs (including serious AEs and immune-related AEs) evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 5.0), changes from baseline in clinical laboratory parameters (complete blood counts [CBC] and serum chemistry), 12-lead electrocardiograms (ECGs), vital sign measurements, physical examinations, ECOG performance status, and use of concomitant medications.

Pharmacokinetics: Serum TJ004309 concentration will be measured using validated methods at the time points specified in the Schedule of Assessments to determine PK parameters including C_{max} and C_{trough}.

Immunogenicity: TJ004309 anti-drug antibodies (ADA) will be measured using validated methods at time points specified in the Schedule of Events.

Exploratory biomarkers:

- Expression of PD-L1, CD73 and other immune subset markers (CD8, CD68, CD19 and CD163)
- CD73 enzymatic activity of tumor biopsies
- Whole genome gene expression profiles in tumor biopsies

Part 2

Efficacy: Based on the efficacy observations in Part 1, further evaluation of anti-tumor activity of the combination of TJ004309 and atezolizumab in selected targeted patient population, measured by best of response (BOR), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS) based on RECIST 1.1 and iRECIST.

Statistical Methods:

Details of the statistical methods will be provided in the Statistical Analysis Plan.

Analysis Populations:

The following populations will be considered for data summaries:

Efficacy Evaluable Population: Population will comprise of all subjects who receive at least 1 dose of study drug and undergo at least 1 post-baseline tumor assessment. Subjects who die before the first scheduled post-baseline tumor assessment will be included in this evaluable population.

Safety Population: Population will comprise of all subjects who receive at least 1 dose of study drug.

Pharmacokinetic Population: Population will comprise of all subjects who receive at least 1 dose of study drug and at least 1 PK parameter can be derived from the collected PK data.

Pharmacodynamic Population: Population will comprise of all subjects who receive at least 1 dose of TJ004309 and have paired fresh pretreatment and on-treatment tumor biopsy specimen for pharmacodynamic evaluation.

Biomarker Population: Population will comprise of all subjects who receive at least 1 dose of study drug and have baseline archival tumor biopsy specimen.

Efficacy:

A listing of tumor measurements will be provided by subject and time. BOR, ORR, DOR, PFS and OS will be listed and summarized by cohort or group if data permits.

Safety:

All recorded AEs will be listed and tabulated by system organ class, preferred terms, cohort/group and coded according to the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Vital signs, ECG, ECOG performance status, and clinical laboratory test results will be listed. Safety events will be summarized overall, and any significant physical examination findings and results of clinical laboratory test will be listed. No formal statistical analysis of safety data is planned.

Pharmacokinetics:

Summary statistics will be tabulated for each PK parameter, if feasible, and wherever applicable, by cohort/treatment. Mean, standard deviation, median, geometric means, and coefficients of variation will be presented for C_{max} and C_{trough}. The exposure of sparse PK samples will be combined with the PK data obtained from Phase 1 trial for population PK analysis and exposure-response analyses.

Immunogenicity:

A listing of all available immunogenicity data will be provided with the incidence of specific anti-drug antibodies (ADA) to TJ004309.

Pharmacodynamics:

Pharmacodynamics effects on CD73 enzymatic activity, immune cell profiles, and whole genome gene expression profiles will be evaluated in paired fresh tumor biopsies at baseline and on-treatment collected from a subset of subjects in Cohort 2.

Biomarker:

Expression of PD-L1, CD73, immune cell subsets, and whole genome gene expression profiles in baseline archival tumor biopsy will be evaluated for their association with clinical responses. These analyses are considered exploratory and will be summarized in a separate technical report.

1.2 Schedule of Assessments

The schedule of assessments (SoA) is presented in Table 2 and Table 3.

Table 2: Schedule of Assessments

Schedule of Assessments							
Cycle Number		Cycle 1 (21 days)	Cycle 2+[a] (21 days)	End of Treatment (EOT)/Early Termination	Safety Follow-up (EOT + 30 days)	Safety Follow-up (EOT + 60 days)	Safety Follow-up (EOT + 90 days)
Cycle Day	Screening	1	1				
Visit Window	(≤ 28 days)	None	±2 days	Within 7 days of EOT/ET Decision	±7 days	±7 days	±7 days
Informed Consent	X						
Medical History[b]	X						
Inclusion/Exclusion Criteria	X						
Demographic Information	X						
HBV, HCV, and HIV[c]	X						
Pregnancy Test[d]	X	X	Q4 Cycles	X			
ECOG Performance Status	X	X	X		X	X	X
Whole blood for genetic analysis (optional)[e]	X						
Archival Tumor Tissue Sample[f]	X						

Schedule of Assessments							
Cycle Number		Cycle 1 (21 days)	Cycle 2+[a] (21 days)	End of Treatment (EOT)/Early Termination	Safety Follow-up (EOT + 30 days)	Safety Follow-up (EOT + 60 days)	Safety Follow-up (EOT + 90 days)
Cycle Day	Screening	1	1				
Visit Window	(≤ 28 days)	None	±2 days	Within 7 days of EOT/ET Decision	±7 days	±7 days	±7 days
Paired Fresh Tumor Biopsy[g]	X		C3D1				
Study Drug Administration							
TJ004309[h]		X	X				
Atezolizumab		X	X				
Safety							
Adverse Events[i]	X	X	X	X	X	X	X
Prior and Concomitant Medications[j]	X	X	X	X	X	X	X
Full Physical Examination[k]	X	X		X			
Abbreviated Physical Examination[l]			X		X	X	X
Height and Body Weight[m]	X	X	X	X			

Schedule of Assessments							
Cycle Number		Cycle 1 (21 days)	Cycle 2+[a] (21 days)	End of Treatment (EOT)/Early Termination	Safety Follow-up (EOT + 30 days)	Safety Follow-up (EOT + 60 days)	Safety Follow-up (EOT + 90 days)
Cycle Day	Screening	1	1				
Visit Window	(≤ 28 days)	None	±2 days	Within 7 days of EOT/ET Decision	±7 days	±7 days	±7 days
Vital Signs[n]	X	X	X	X	X	X	X
12-lead ECG[o]	X			X			
Blood Chemistry[p]	X	X	X	X	X	X	X
Complete Blood Count (with differential and platelets, reticulocytes)[q]	X	X	X	X	X	X	X
Coagulation Assessment[r]	X	X	X	X	X	X	X
TSH, T3, T4 Testing[s]	X	X	X	X	X	X	X
Urinalysis[t]	X	X	X	X	X	X	X
Tumor Assessments[u]	X	Every 9 Weeks					

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase;; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PTT = partial thromboplastin time.

a) Treatment with TJ004309 may continue in accordance with the protocol. Subsequent study cycles should follow the same schedule of assessments as Cycle 2 unless otherwise specified.
b) Relevant medical history including current disease state and prior treatment, including last prior therapy, best response to last prior therapy (partial response, complete response, stable disease, or progressive disease), and either time on last therapy or duration of response. Medical history includes all clinically significant diseases, cardiac history, surgeries, cancer history (which may include, but not limited to prior cancer therapies, procedures, and estrogen receptor and progesterone receptor status, bulky disease status), reproductive status, smoking history, use of alcohol and drugs of abuse.
c) Anti-hepatitis B surface antibody, HBsAg, anti-HCV, HIV-1 and HIV-2 antibodies at Screening only.
d) Serum pregnancy test at Screening, urine pregnancy at pre-dose Cycle 1 Day 1 (within 72 hours prior), Cycle 4 Day 1 and Day 1 of every subsequent 4 cycles (i.e., Cycle 8 Day 1, Cycle 12 Day 1, etc.). The screening serum pregnancy test can be used as the test prior to Day 1 study treatment if it is performed within the prior 72 hours. Additional tests may be ordered at the Investigator's discretion. Positive urine pregnancy tests should be confirmed with a serum pregnancy test. Only a Follicle-stimulating hormone test is required for postmenopausal women.
e) Samples may be collected for genetic testing (i.e., MSI/dMMR, BRCA, HRD, etc) if not previously obtained. Ovarian cancer patients only.
f) Archival tissue is required for both Cohorts 1 and 2. Blocks are preferred but archival tumor tissue that allows the preparation of at least 20 slides prior to study entry is acceptable as well. See lab manual for further instructions. Format of archival tissue is at the site's discretion. Sponsor may request PD-L1 testing at central laboratory.
g) For Cohort 2 only: Pre-treatment and paired on-treatment fresh tumor biopsies will be collected from at least 5 patients. CD73 enzymatic activity and assessment of proteins in the adenosine pathway (e.g., CD73, A2A receptor, and whole genome gene expression profiles) will be assessed in fresh tumor biopsies. Biopsy must be excisional, incisional, or core. Fine needle aspiration is insufficient. Samples will be collected prior to dosing and processed and shipped within 24 hours according to separate laboratory manual. The tumor biopsy samples must complete testing for the following infectious diseases within 28 days of tumor biopsy collection: Hepatitis B, Hepatitis C, Tuberculosis, HIV, Syphilis, and COVID-19 and confirmed to be negative. Testing is to be performed locally.
h) Initially, TJ004309 will be administered over 1 hour (±15 minutes) in Cycles 1 and 2. In the absence of IRRs in patients infused over 1 hour in Cycle 2, the infusion time of TJ004309 may be reduced to 30 minutes (±10 minutes) per Investigator's discretion. Infusion timing should be close to the instructed infusion time as possible.
i) Adverse events should be documented and recorded at each visit using the NCI CTCAE Version 5.0.
j) All medications used by the patient including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies taken from 28 days prior to the first study drug dose are to be documented as prior medications.
k) A full physical examination will be performed at Screening and at pre-dose of Cycle 1 Day 1, unless the screening physical examination was performed within the last 7 days.
l) Abbreviated physical examinations should be performed for all other visits. If indicated, a full physical exam may be performed instead at the Investigator's discretion.
m) Height will only be recorded at Screening. Doses will be calculated based on the actual weight of each subject, as measured at the Screening Visit. The weight used may be revised to a weight collected at a later date if it has changed by more than 10%.
n) Vital signs will include body temperature, pulse rate, blood pressure, and respiratory rate after the subject has rested quietly in the seated position for ≥5 minutes. For the first cycle, vital signs (pulse rate, blood pressure, and respiratory rate) will be collected pre-dose, 30 minutes after the start of infusion, and 2 hours after EOI. Body temperature will be measured singly. At all subsequent cycles (C2+) vital signs will be performed pre-dose singly and repeated once if outside the relevant clinical reference ranges. On Cycle 1 Day 1, subjects should remain at the site for monitoring (with immediate access to medical resuscitation equipment) for at least 1 hour following the end of TJ004309 infusion. Acceptable window for collection of vital signs is ± 15 minutes.
o) Triplicate ECG measurements will be obtained at Screening and as clinically indicated. The average of the 3 Screening ECGs will be used to calculate QTc to determine study eligibility. Measurements should be taken after the subject has been resting quietly in the supine or reclined position for ≥ 5 minutes.
p) Serum chemistry includes sodium, potassium, chloride, cholesterol, total protein, bicarbonate, albumin, calcium, magnesium, phosphorus, glucose, blood urea nitrogen, creatinine, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, amylase, and lipase. CA-125 testing required for ovarian cancer subjects only (both cohorts) and should be collected every cycle. If screening laboratory testing is performed within 72 hours of first dose of study treatment on Day 1, repeat testing is not required.

q) Complete Blood Count and Differential: white blood cells, red blood cells, absolute neutrophil count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, platelets, reticulocytes, and white blood cell differential. If screening laboratory testing is performed within 72 hours of first dose of study treatment on Day 1, repeat testing is not required

r) Coagulation Tests: PT, PTT or aPTT, and INR. Any subject receiving anticoagulant therapy should continue to have coagulation factors monitored closely while on study. If screening laboratory testing is performed within 72 hours of first dose of study treatment on Day 1, repeat testing is not required.

s) Thyroid Function Tests: TSH, free T3, and free T4.

t) Dipstick is acceptable. Microscopic analyses if dipstick is abnormal. No need to repeat on Cycle 1 Day 1 if screening assessment performed within 72 hours prior to that date. If ≥ 2+ protein on urine dipstick, then collect spot urine sample to calculate urine protein to creatinine ratio.

u) Tumor assessments will be performed at Screening, Cycle 4 Day 1, then every 9 weeks for 1 year following the first dose of study drug, and every 12 weeks for the second year. Scans within 28 days of Cycle 1 Day 1, prior to signing the ICF, can be used as the screening scan. On-treatment scans can be obtained +/- 7 days. The same modality (CT, PET/CT or MRI) should be used throughout the study for a given patient. Collection of images will be obtained for retrospective analysis. Central review of scans may be performed during the study.

Table 3: Schedule of Assessments – Pharmacokinetic, Anti-Drug Antibody, Pharmacodynamic Sampling Schedule

Pharmacokinetic, Anti-Drug, Pharmacodynamic Antibody Testing							
Cycle Number		Cycle 1 (21 days)	Cycle 2+ (21 days)	End of Treatment (EOT)/Early Termination	Safety Follow-up (EOT + 30 days)	Safety Follow-up (EOT + 60 days)	Safety Follow-up (EOT + 90 days)
Cycle Day	Screening	1	1				
Visit Window	(≤ 28 days)	None	±2 days	Within 7 days of EOT/ET Decision	±7 days	±7 days	±7 days
TJ004309 PK pre-dose[a]		X	X				
TJ004309 PK EOI (+5mins) post-dose[b]		X	X	X	X		
TJ004309 ADA pre-dose[a]		X	X	X	X		
PBMC biomarker pre-dose[a]		X	Cycles 2-4	X			
PBMC biomarker 3 hours post-EOI[b]		X	Cycle 2				
Serum biomarker pre-dose[a]		X	Cycles 2-4	X			X

Abbreviations: ADA = anti-drug antibody; EOI = end of infusion; PK = pharmacokinetic; SC = Screening.

a) Acceptable window for pre-dose sampling is within 30 minutes prior to dose.
b) Post-dose blood draws should be performed after TJ004309 infusion. Timepoints for post-dose blood draws should be measured from EOI.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ASCC	Antibody-dependent T-cell-mediated cytotoxicity
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMP	Adenosine Monophosphate
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity
AUC_{0-t}	Area under the curve from time 0 to time t
AUC_{τ}	Area under the curve during a dosing interval
BOR	Best objective response
C	Cycle
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
Cmax	Maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
DLT	Dose-limiting toxicity
DOR	Duration of response
DRC	Data Review Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	Electronic case report form
EOS	End-of-Study
FFPE	Formalin fixed, paraffin-embedded
FOCBP	Females of childbearing potential
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HNSCC	head and neck squamous cell carcinoma
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
kg	kilogram
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	milliliter
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
OC	Ovarian carcinoma
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival

Abbreviation	Definition
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SoA	Schedule of Activities
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein-creatinine ratio
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution

2 INTRODUCTION

2.1 Overview

Traditionally, metastatic cancer is treated with chemotherapy or other treatments that directly target the tumor. However, toxicities can limit the effectiveness of chemotherapy and resistance can develop as well. Cancer immunotherapy is one method of treatment that has been used successfully to treat various types of tumors by harnessing the body's immune system to fight cancer. Data suggest that tumors suppress T-cell activity by activating pathways and inhibitory checkpoints that restrict antitumor activity. Checkpoint inhibitors are a class of immunotherapy treatments that inhibit checkpoints mediated by the CTLA-4 and PD-1 pathways, to re-establish antitumor activity[1]. Multiple types of cancers have responded to PD-1 checkpoint inhibitor therapy including non-small cell lung cancer, renal cell carcinoma, bladder cancer, and head and neck cancer[2]. However, only a minority of cancer patients respond to single agent immunotherapy treatment. New methods of treatment are needed to continue to improve long-term survival for patients with metastatic cancer.

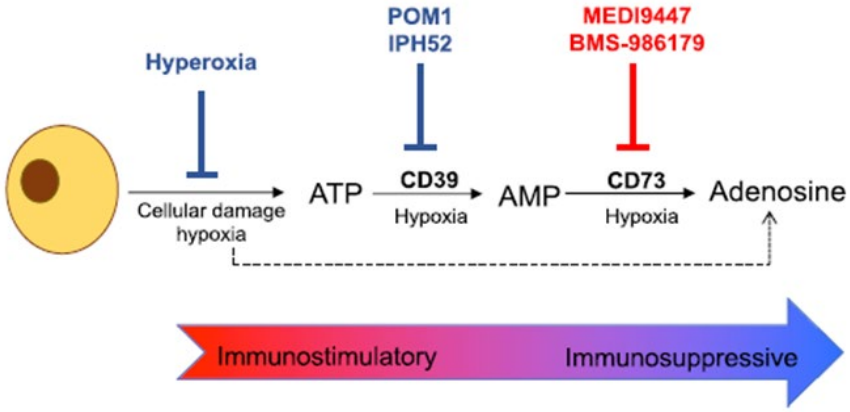
One strategy that tumor cells employ to counter effective immune responses is the generation of high levels of the immunosuppressant adenosine[3]. Adenosine is produced at elevated levels within the tumor microenvironment through the CD73 ectonucleotidase and new immunotherapy treatments are being studied to target this antitumor pathway.

2.2 Background

The adenosine signaling pathway regulates tumor immune evasion. Extracellular adenosine and ATP levels are typically very low. However, inflammation, ischemia and tissue disruption can lead to the release of high levels of ATP that is enzymatically hydrolyzed to produce extracellular adenosine that inhibits antitumor T cell activity through binding to the A2A and A2B adenosine receptors expressed on immune cells[4, 5, 6].

Extracellular ATP is dephosphorylated to produce adenosine by the ectonucleotidases CD39 and CD73. Ectonucleotidases are highly expressed on cells within the tumor microenvironment and are upregulated in states of hypoxia. Ectonucleotidases are upregulated on regulatory T cells in response to adenosine, which establishes a positive feedback loop, causing additional increases in adenosine production in solid tumors and further suppression of antitumor immune responses[3,7.] .

Figure 1: Extracellular Adenosine Signaling Pathway[3]



Work has been done to explore whether the adenosine signaling pathway could be exploited to enhance the immune system response to cancer. Since tumors exhibit many factors that influence adenosine production, including hypoxia, inflammation, CD39 and CD73 upregulation, and tissue disruption, the adenosine pathway therefore became a prime candidate for intervention. Tumor growth is suppressed in CD73 deficient mice suggesting that tumor CD73-mediated immune suppression significantly contributes to cancer immune evasion. Zhang et al. found that adenosine generated by tumor CD73 in vitro and in vivo inhibited the activation phase and effector phase of the antitumor T cell response and promoted T cell apoptosis. Moreover, knockdown of CD73 on tumor cells by siRNA completely restored the efficacy of T cell therapy and led to long-term tumor free survival of tumor-bearing mice[8]. Stagg et al. additionally demonstrated that inhibiting CD73 with a selective monoclonal antibody significantly reduced the growth and metastatic capability of CD73-negative tumors[9].

Medimmune (MEDI9447) and Bristol Myers Squib have studied monoclonal antibodies that inhibit CD73 in early phase trials. MEDI9447 was dosed with or without the PD-1 checkpoint inhibitor durvalumab. The trial enrolled 42 monotherapy and 95 combination therapy patients without the development of dose limiting toxicity. Sustained decreases in free soluble CD73 and CD73 expressed on peripheral T cells was demonstrated at all dose levels. Partial responses were observed in 1 of 21 colorectal cancer patients and 2 of 34 pancreatic cancer patients; stable disease was observed in 2 of 21 colorectal cancer patients and 5 of 34 pancreatic cancer patients from the dose expansion phase. The most commonly reported adverse events in patients treated with the CD73 and PD-1 antibodies (N=71) were diarrhea (5 patients (7.0%)), fatigue (5 patients (7.0%)), pyrexia (4 patients (5.6%)), and increases in AST (4 patients (5.6%))[7].

The CD73 antibody BMS-986179 was tested in a phase 1/2 study as a monotherapy and in combination with the PD-1 checkpoint inhibitor nivolumab in patients with advanced solid tumors. Drug-related adverse events were observed in 30 of 52 patients (58%) who received the combination, without a clear dose dependent relationship. Eight patients (15%) experienced grade 3 drug-related adverse events, and one patient discontinued treatment due to a drug-related

adverse event of grade 3 increased ALT. Both the monotherapy and the combination treatments were well tolerated, without grade 4 drug-related adverse events. BMS-986179 efficiently inhibited CD73 enzymatic activity in tumor biopsies at all doses and produced dose dependent reductions in soluble CD73. Overall, 7 patients with head and neck, pancreatic, prostate, anal, and renal cancer achieved confirmed partial responses and 10 patients had stable disease[11]. These data suggest that CD73 could be a novel target for cancer treatment with encouraging signs of activity and limited toxicity.

2.3 Description of TJ004309 Investigational Product

TJ004309 is a humanized IgG1 to CD73 containing a N297A mutation that prevents antibody glycosylation. TJ004309 inhibits CD73 through a non-competitive mechanism and does not possess ADCC or CDC effector function. TJ004309 is formulated at 50 mg/mL in a 20 mM histidine buffer containing trehalose.

2.4 Summary of Nonclinical Data

TJ004309 is a non-competitive inhibitor of CD73 with a K_D of 14 nM by Biacore testing that binds human and cynomolgus, but not rodent, CD73. TJ004309 binds CD73 on cell lines with an EC_{50} of 0.12-0.29 µg/mL and inhibits CD73 enzymatic activity with IC_{50} of 0.6-3.3 ug/ml. Maximal CD73 receptor occupancy reaching over 80% was observed in vitro at a mean concentration of 33.86 µg/mL.

TJ004309 reversed CD73+ tumor cell mediated T cell immunosuppression that was maximal at 30 ug/mL. TJ004309 at a dose of 5 mg/kg and 10 mg/kg increased the activity of PD-L1 antibody in immunodeficient mice reconstituted with human PBMCs engrafted with palpable melanoma xenografts (Figure 2 and Figure 3).

Figure 3: Mean Tumor Volume of A375 Bearing Mice

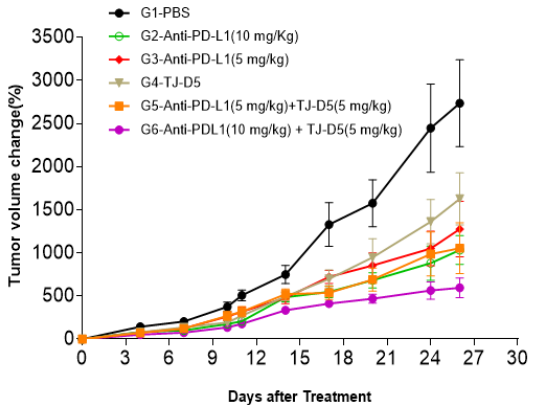
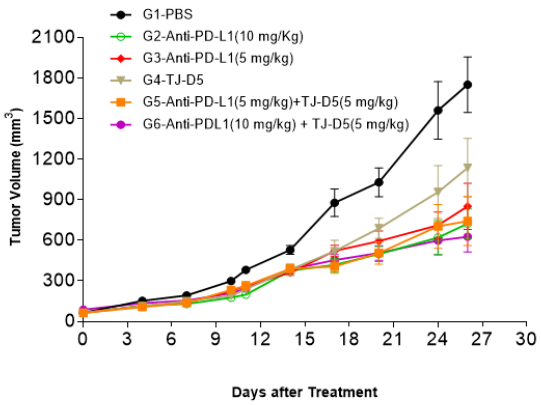


Figure 2: Mean Tumor Volume Change of A375 Bearing Mice



2.4.1 Nonclinical Pharmacology

Safety Pharmacology studies of TJ004309 have not been performed.

2.4.2 Nonclinical Pharmacokinetics

The pharmacokinetics of TJ004309 was determined in cynomolgus monkeys after bolus intravenous injection of single doses of 5, 25, and 50 mg/kg and after 4 weekly repeated doses of 25 mg/kg.

TJ004309 was administered as a single dose of 5, 25, and 50 mg/kg via bolus intravenous injection to cynomolgus monkeys (3 animals/sex/group). Blood samples were collected at pre-dose and for up to 28 days post dose. Following a single intravenous injection at 5 mg/kg, 25 mg/kg, and 50 mg/kg of TJ004309, mean peak concentrations (C_{max}) of TJ004309 were 136 µg/mL, 682 µg/mL, and 1430 µg/mL, respectively. Mean area under the concentration time curve from hour 0 to the time of the last measurable concentration ($AUC_{0\text{-last}}$) values of TJ004309 were 4020 hr*µg/mL, 50400 hr*µg/mL and 135000 hr*µg/mL, respectively. Mean half-life ($T_{1/2}$) was 44.9 hr, 61.5 hr and 104 hr, respectively. C_{max} increased proportionally with increasing dose; while exposure increased in a non-linear manner. The elimination rate of TJ004309 was decreased in cynomolgus monkeys as dosage increased. The detection of antibody against TJ004309 did not meaningfully influence pharmacokinetics of single dose administration.

Toxicokinetics of TJ004309 were also determined as part of dose-range finding (DRF), where the antibody was administered at doses of 0, 5, 30 and 200 mg/kg once weekly over 15 days (total 3 doses) via bolus intravenous injection to cynomolgus monkeys (1 animal/sex/group). Exposure to TJ004309, based on C_{max} and $AUC_{0\text{-last}}$, increased in proportion to dose level from 5 to 200 mg/kg/day in both sexes on Days 1 and 8. The $AUC_{0\text{-last}}$ values on Day 8 were similar to those on Day 1.

TJ004309 was also administered at doses of 0, 20, 60 and 200 mg/kg once weekly for 29 days (total 5 doses) via bolus intravenous injection to cynomolgus monkeys (5 animals/sex/group). The $AUC_{0\text{-last}}$ values on Day 22 were generally higher than that on Day 1 of the dosing phase, with mean accumulation ratios (AR) ranging from 1.65 to 2.19. Mean AR in male and female animals who received 20 mg/kg and 60 mg/kg were higher than 2-fold. Generally, the exposure of males, based on C_{max} and $AUC_{0\text{-last}}$, was similar to that of females, with ratios ranging from 0.894 to 1.19. Anti-TJ004309 antibody (ADA) were observed in 10 of 10 animals administered 20 mg/kg, 10 of 10 animals administered 60 mg/kg, and 8 of 10 animals administered 200 mg/kg.

TJ004309 was also administered weekly at 25 mg/kg on days 0, 7, 14 and 21 (total 4 doses) via bolus intravenous injection to cynomolgus monkeys (3 animal/sex/group). Blood samples were collected prior to dosing and for up to 7 days following dosing for each dose. After multiple administrations of TJ004309 at 25 mg/kg, in week 4, mean C_{max} of TJ004309 were 714 µg/mL and 791 µg/mL in male and female monkeys, respectively. Mean $AUC_{0\text{-}168}$ of TJ004309 were

52900 hr*µg/mL and 92400 hr*µg/mL in male and female monkeys, respectively. Mean $AUC_{0\text{-}last}$ of TJ004309 were 90000 hr*µg/mL and 111000 hr*µg/mL in male and female monkeys, respectively. Mean $T_{1/2}$ calculated using data from 0 to 168 hours were 128 hr and 125 hr in male and female monkeys, respectively and were 69.0 hours and 112 hours, respectively, when extrapolated to infinity. Mean trough concentrations were approximately 254 µg/mL in week 4.

After multiple doses of TJ004309 C_{max} observed in male and female monkeys was comparable to single administration at the same dose level. Mean concentration-time curves were higher in week 4 compared to week 1 following multiple administrations at 25 mg/kg (AUC > 2-fold), indicating accumulation following multiple dose administration.

Antibody against TJ004309 was observed in nearly all animals by day 14 following dosing and did not influence pharmacokinetics of multiple doses of TJ004309 except in a single male animal who demonstrated pronounced immunogenicity, whose PK data was excluded from summary data calculations.

2.4.3 Toxicology

The toxicology program to support this initial Phase 1 study included a dose range finding study (DRF) and a GLP 28-day repeat dose toxicology study in cynomolgus monkeys. Toxicity of TJ004309 was assessed in a GLP-compliant repeat-dose definitive toxicology study in cynomolgus monkeys that received 5 weekly doses of TJ004309 at the following dose levels: 0 mg/kg (vehicle control), 20 mg/kg, 60 mg/kg and 200 mg/kg. Animals were dosed by IV bolus injection in a volume of 4 ml/kg. The vehicle was used as control.

All animals survived to their scheduled sacrifices. TJ004309-related clinical or histopathologic findings were not observed at terminal or recovery sacrifices. TJ004309 related alterations in cytokine parameters included decreased monocyte chemoattractant protein 1 (MCP-1) observed on Day 1 of the dosing phase in animals administered ≥ 20 mg/kg approximately 24 hours following dosing, and male animals administered 20 and 60 mg/kg approximately 48 hours following dosing.

Based on the collective findings, the no observed adverse effect level (NOAEL) was determined to be 200 mg/kg. This dose level produced to mean peak concentration (C_{max}) and area under the concentration time curve (AUC) values of 6890 ug/mL and 594000 ug*hr/mL, respectively, in males and 6450 ug/mL and 501000 ug*hr/mL, respectively, in females, on Day 22 of the dosing phase.

Refer to the Investigator's Brochure for additional nonclinical data with TJ004309.

2.5 Summary of Clinical Data

TJ004309 was evaluated in the first-in-human (FIH) Study 4309ST101 sponsored by Tracon in the US, and Study TJ004309STM102 sponsored by I-Mab Biopharma in China. Study 4309ST101, was an open label, nonrandomized, Phase 1 dose escalation study of TJ004309 in combination with standard dose atezolizumab in patients with advanced or metastatic solid

tumors who are refractory to or intolerant to all available therapy. Study TJ004309STM102 is a Phase 1/2 dose-escalation and cohort expansion study of TJ004309 in combination with toripalimab in patients with advanced or metastatic solid tumors to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary evidence of efficacy of TJ004309 as a single agent and in combination with toripalimab in the Chinese patient population. As of 17 January 2021, 20 patients had been treated in Study 4309ST101 and 6 patients have been treated in Study TJ004309STM102.

In Study 4309ST101, TJ004309 was well-tolerated with no dose limiting toxicity up to 20 mg/kg Q3W and 15 mg/kg QW. The most common treatment-related adverse events were first dose infusion related reactions (65%, n=13) most commonly comprising chills/rigors, nausea, and vomiting (Grade 1 or 2) that resolved in subsequent infusions. One complete response and two partial responses were observed in 3 patients together with 3 stable disease (SD) patients. Refer to the Investigator's Brochure (IB) for additional data with TJ004309.

2.6 Benefit/Risk Assessment

2.6.1 Potential Benefit

TJ004309 is an investigational product, and its efficacy has not been fully established. Atezolizumab is approved for the treatment of appropriately selected patients who progress following treatment with chemotherapy. It is possible that the administration of TJ004309 and/or atezolizumab may result in clinical benefit (i.e., tumor response or prolonged stable disease) beyond that expected for treatment with atezolizumab alone. More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) associated with TJ004309 may be found in the Investigator's Brochure.

2.6.2 Potential Risk

TJ004309 is an investigational product, and its safety profile has not been fully established. The occurrence of adverse events associated with TJ004309 treatment from the US dose escalation portion of the study (NCT04322006) includes infusion related reactions, fatigue, pruritis, and diarrhea.

All therapeutic mAb used for cancer treatment have the potential to cause infusion reactions. Symptoms vary with a wide spectrum of severity, ranging from mild fever and chills to life-threatening anaphylaxis with bronchospasm, and hypotension. Typically, infusion reactions to mAb develop within 30 to 120 minutes after the initiation of drug infusion, although symptoms may not show up until 24 hours. The majority of reactions occur after the first or second exposure to drug, although it can also occur during subsequent treatments. The risk of an infusion reaction declines with each subsequent course of therapy.

The most common symptoms of infusion-related reactions are fever/chills, nausea, vomiting, diarrhea, itching/flushing, rash, changes in blood pressure and pulse rate, dyspnea, chest discomfort, back and abdominal pain. Although the exact mechanism of infusion-related

reactions caused by mAb is not fully clear, most likely it is a result of antibody-antigen interactions resulting in cytokine release.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives:

The primary objectives of the study are:

- Part 1: To assess the efficacy of TJ004309 combined with atezolizumab in a cohort of patients with platinum-resistant IO naïve ovarian carcinoma and a separate biomarker enriched cohort of subjects with selected tumor types
- Part 2: To further evaluate and confirm the efficacy in targeted patient population based on the efficacy observed in Part 1

3.1.2 Secondary Objective:

The secondary objectives of the study are:

- To evaluate the safety and tolerability of TJ004309 when combined with the standard dose of atezolizumab
- Part 1: To characterize the pharmacokinetic profile of TJ004309 when administered in combination with atezolizumab
- Part 1: To determine the immunogenicity of TJ004309 when administered in combination with atezolizumab

3.1.3 Exploratory Objective:

The exploratory objectives of the study are:

- To investigate the expression of PD-L1, CD73, and other immune subset markers (CD8, CD68, CD19 and CD163) in tumor biopsies at baseline and on treatment, and their associations with clinical responses
- To examine the CD73 enzymatic activity of tumor biopsies
- To study the whole genome gene expression profiles in tumor biopsies

3.2 Endpoints

3.2.1 Primary Endpoints

Primary endpoints are:

- Efficacy within each tumor type: ORR by RECIST v1.1

3.2.2 Secondary Endpoints

Secondary endpoints are:

- The safety and tolerability of TJ004309 when combined with the standard dose of atezolizumab

- ORR by iRECIST
- Duration of response (DOR) by RECIST v1.1 and iRECIST
- Disease control rate (DCR) by RECIST v1.1 and iRECIST
- Progression-free-survival (PFS) by RECIST v1.1 and iRECIST
- Overall survival (OS)
- Immunogenicity and pharmacokinetic profiles of the combination treatment

3.2.3 Exploratory Endpoints

The exploratory endpoints are:

- CD73 enzymatic activity of tumor biopsies at baseline and on-treatment tumor biopsies;
- Expression of PD-L1, CD73 and other immune subset markers (CD8, CD68, CD19 and CD163);
- Whole genome gene expression profiles in tumor biopsies at baseline and on-treatment tumor biopsies;

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, open label, Phase 2 study of TJ004309 in combination with atezolizumab in patients with advanced or metastatic solid tumors. This clinical study will be conducted in two parts. Part 1 of the study will include two cohorts: Cohort 1 will include Immuno-Oncology (IO) treatment naïve ovarian cancer patients who have progressed on or after platinum therapy; and Cohort 2 will include patients with head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), gastric cancer (GC), triple negative breast cancer (TNBC), or ovarian carcinoma with PD-L1 expression ≥ 1% (Table 1). All subjects will be evaluated for antitumor activity on a regular basis as specified in the protocol and their clinical status classified according to RECIST 1.1 and iRECIST. Treatments may continue until clinically significant disease progression, unacceptable toxicity, or subject/Investigator decision to withdraw. Based on the efficacy observation in Part 1, Part 2 of the study will further evaluate the efficacy in selected targeted patient populations and will be initiated after reaching agreement with the regulatory agency.

TJ004309 will be given in combination with atezolizumab 1200 mg every 3 weeks (Q3W) beginning with Cycle 1 Day 1 (C1D1). Premedication will be given prior to the initial infusion of TJ004309 to mitigate infusion related reactions. Each cycle will be 21 days in duration.

Table 1: Study Drug Dosing Schedule – Part 1

Cohort	TJ004309 Q3W	Atezolizumab Q3W	Subjects
Cohort 1: Platinum resistant or refractory IO naïve ovarian carcinoma (OC)	20 mg/kg	1200 mg flat dose	N= 30
Cohort 2: HNSCC, NSCLC, GC, TNBC, OC	20 mg/kg	1200 mg flat dose	N= 30

Up to 30 subjects will be enrolled in each cohort. If two or less responses are observed from the first 15 subjects in Cohort 1, the enrollment might be stopped based on rules from a Simon's 2-stage design. If 3 or more responses are observed from the first 15 subjects in Cohort 1 from Part 1, then Part 2 of the study may be initiated earlier. If any response is observed from Cohort 2, an additional cohort with up to 30 subjects may be opened with a specific tumor type after reviewing all other available data at that time.

4.2 Study Rationale

TJ004309 is an investigational antibody to CD73 that non-competitively inhibits CD73 mediated conversion of AMP to adenosine, thereby reversing adenosine mediated immune suppression on T cells. This mechanism of action is distinct from that inhibited by antibodies to PD-1/PD-L1, and CD73 is implicated as a mechanism of resistance to PD-1/PD-L1 antibody treatment. TJ004309 inhibited tumor growth in preclinical models and complemented the activity of antibodies targeting the PD-1/PD-L1 pathway. Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with PD-1 and B7.1 receptors. While single agent activity of TJ004309 was limited, by targeting the adenosine pathway, TJ004309 has the potential to complement atezolizumab and improve clinical efficacy over that seen with single agent atezolizumab.

4.3 Justification for Dose

The proposed dosing regimen for the Phase 2 trial is 20 mg/kg of TJ004309 administered as a 1 hour intravenous infusion every three weeks (Q3W) in combination with atezolizumab (1200 mg Q3W) starting from Cycle 1 Day 1. This dosing regimen is based on the preliminary safety, PK, biomarker, and antitumor activities observed in the first-in-human study 4309ST101 under IND 141965.

Study 4309ST101 was an open label, non-randomized, Phase 1 dose escalation study of TJ004309 in combination with standard dose atezolizumab in patients with advanced or metastatic solid tumors who are refractory to or intolerant to all available therapy. In this 3+3 dose escalation study, TJ004309 was administered intravenously at doses of 5, 10, or 15 mg/kg weekly (QW), or 15 or 20 mg/kg every 3 weeks (Q3W) as a monotherapy in the first 21-day treatment cycle followed by combination therapy with atezolizumab (1200 mg Q3W) starting from the second cycle (week 4).

At the time of 29 April 2021, the safety, PK, and PD from dose levels of 5 mg/kg, 10 mg/kg, 15 mg/kg once weekly (QW), and 15 mg/kg and 20 mg/kg once every 3 weeks (Q3W) have been evaluated. Serum TJ004309 concentrations were measured using validated methods and the PK was analyzed by noncompartmental analysis (NCA) and population PK analysis. The immunogenicity was evaluated by measuring the anti-drug antibodies (ADA) to TJ004309 using validated methods. Furthermore, the following exploratory biomarkers were evaluated: receptor occupancy assessment of soluble CD73 and CD73 expression on CD19+ B cells; CD73, A2A receptor, and whole genome gene expression profiles in tumor specimens; CD73 enzymatic activity in fresh tumor biopsies.

The proposed dosing regimen is supported by the observed clinical data, as summarized below.

Safety:

In Study 4309ST101, TJ004309 was well-tolerated. No dose limiting toxicity (DLT) was observed and maximum tolerated dose (MTD) was not reached at dose levels up to 20 mg/kg Q3W and 15 mg/kg QW. The most common treatment-related adverse events (TRAE) were infusion related reactions (65%, n=13) following the first dose, most commonly comprising chills/rigors, nausea, and vomiting (Grade 1 or 2). All these TRAEs were well managed and resolved in subsequent infusions.

Table 4: 4309ST101 Most Common AEs (Excluding Symptoms of IRR) (>1 Patient) by Preferred Term and Grade, Suspected Related to TJ004309 (N = 20)

Preferred Term[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infusion related reaction	2 (10.0%)	11 (55.0%)	0	0	0	13 (65.0%)
Diarrhoea	4 (20.0%)	1 (5.0%)	0	0	0	5 (25.0%)
Fatigue	2 (10.0%)	3 (15.0%)	0	0	0	5 (25.0%)
Pruritus	3 (15.0%)	2 (10.0%)	0	0	0	5 (25.0%)
Nausea	3 (15.0%)	0	0	0	0	3 (15.0%)
Vomiting	3 (15.0%)	0	0	0	0	3 (15.0%)
Angioedema	2 (10.0%)	0	0	0	0	2 (10.0%)
Arthralgia	2 (10.0%)	0	0	0	0	2 (10.0%)
Decreased appetite	2 (10.0%)	0	0	0	0	2 (10.0%)
Dry skin	1 (5.0%)	1 (5.0%)	0	0	0	2 (10.0%)
Hyperthyroidism	1 (5.0%)	1 (5.0%)	0	0	0	2 (10.0%)
Malaise	1 (5.0%)	1 (5.0%)	0	0	0	2 (10.0%)
Myalgia	1 (5.0%)	1 (5.0%)	0	0	0	2 (10.0%)
Rash	2 (10.0%)	0	0	0	0	2 (10.0%)
Vision blurred	2 (10.0%)	0	0	0	0	2 (10.0%)

Antitumor activity:

Among 13 efficacy evaluable patients dosed ≥ 10 mg/kg, complete response (CR = 1) and partial response (PR = 2) were observed in 3 patients (ORR = 23%). A PD-L1 naïve patient with ovarian carcinoma achieved CR and remained on study for at least 15 months. Refer to the Investigator's Brochure (IB) for additional data with TJ004309.

Pharmacokinetics:

Systemic exposure to TJ04309 (C_{max} and AUC) increased in a dose proportional manner over a range from 5 mg/kg to 20 mg/kg following single dose or multiple doses. Power model tests suggested a slope of 0.986 and 1.00 for C_{max} and AUC, respectively. The linear PK over the tested dosing range indicated target saturation. Following multiples doses once every three weeks, the accumulation ratio at the steady state over the first dose was approximately 2.

Preliminary population PK analysis suggested that the best model was a two-compartment model with first order linear clearance. Body weight was found to be predictive of central volume of distribution, but not predictive of clearance. The population PK model estimated an effective half-life of 19 days (range: 11.6 to 43.9 days), which supported the dosing interval of three weeks.

Figure 4: Serum PK of TJ004309 Following a Single Dose and Multiple Doses

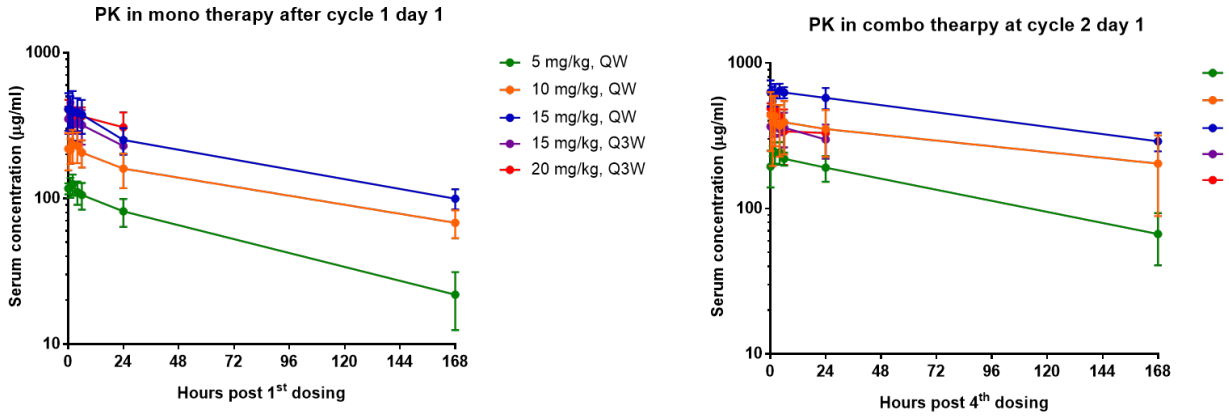
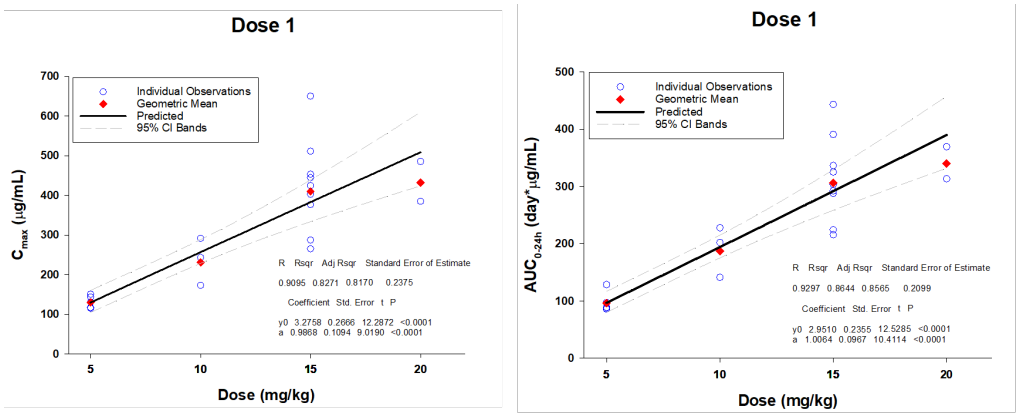


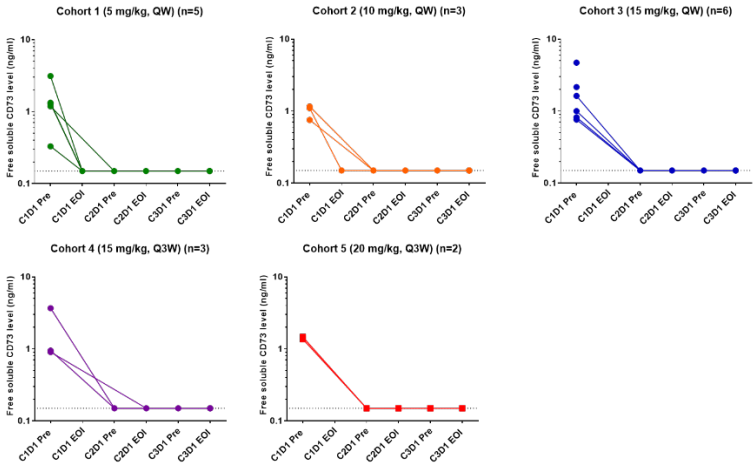
Figure 5: Dose Proportionality Analysis After the First Dose



Pharmacodynamic:

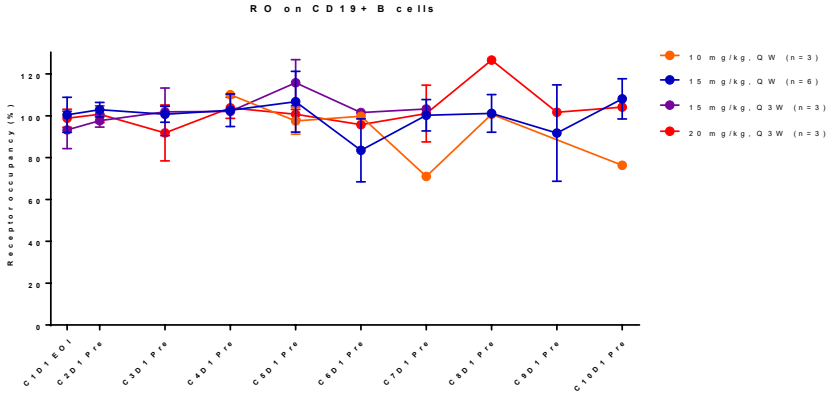
Soluble CD73: Treatment of TJ004309 achieved a sustained decrease in free soluble CD73 level in monotherapy stage (Cycle 1) or in combination with Atezolizumab (starting at Cycle 2) at each of dose cohorts (5, 10, and 15 mg/kg QW; 15 mg/kg and 20 mg/kg Q3W).

Figure 6: Sustained Decrease in Free Soluble CD73 with TJ004309 QW or Q3W Dosing



CD73 Target Occupancy on Peripheral B cells:

Figure 7: Saturated CD73 Target Occupancy on Peripheral B Cells



Treatment of TJ004309 reached a complete saturation of receptor occupancy (RO) on peripheral CD19+ B cells throughout the whole dosing period at all dose levels following either QW or

Q3W dosing regimens, over the treatment period of monotherapy or in combination with atezolizumab.

Immunogenicity:

Three subjects were confirmed positive for anti-drug antibodies (ADA) during the treatment. No impacts of ADA were observed on safety or PK up to date.

In summary, TJ004309 demonstrated a well-tolerated safety profile with only mild to moderate treatment-related adverse events that were managed well, promising antitumor activity with an ORR of 23.1% observed in three patients among 13 evaluable patients, a complete target saturation suggested by 100% target occupancy on the peripheral B-cells and sustained decrease of soluble CD73, and a linear PK with an effective half-life of approximately 19 days over the dosing range from 5 mg/kg to 20 mg/kg. Therefore, the proposed dosing regimen of 20 mg/kg in combination with atezolizumab (1200 mg/kg Q3W starting from Day 1 of Cycle 1) to be further tested in the Phase 2 trial is therefore supported.

4.4 End of Study Definition

A patient is considered to have completed the study treatment period if they complete the End-of-Study (EOS) visit and, as required, any further follow-up of ongoing serious adverse events (SAEs) regardless of relationship to study drug and/or non-serious adverse events (AEs) considered to be possibly, probably or definitely related to study drug until either resolution or determined by the Investigator to be chronic or stable.

4.5 Safety Follow-up Period

After the treatment periods, all subjects will enter a safety follow-up period and will be evaluated for safety, tolerability, and tumor response (if applicable) for at least 90 days after the last dose of study drug, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects will be required to return to the study sites for three (3) safety follow-up visits (approximately 30, 60 and 90 days after the last dose of study drug), except those subjects who withdraw consent for study participation. After treatment discontinuation, in the event of continuing serious adverse events (SAEs), subjects will be followed until resolution or stabilization of the SAEs (regardless of the relationship to the IMP). Any subject who has an ongoing non-serious AE that is possibly related or related to the IMP or study procedures at the 90-day post-treatment Follow-up visit will be followed up, where possible, until resolution or until the unresolved non-serious AE is judged by the Investigator (or designee) to have stabilized. Any subject who has an ongoing non-serious AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit, can be closed out as ongoing at the Investigator's discretion. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, one (1) Post-Treatment Safety Follow-Up visit should occur approximately 30 days after the last dose of study drug and therefore subsequent follow-up visits will not be required.

4.6 Response/Survival Follow-up Period

Subjects who do not experience progressive disease prior to treatment discontinuation will continue to have radiologic and clinical tumor assessments every 9 weeks for the first year and every 12 weeks during the second year until progression is confirmed, consent withdrawal, start of a new anti-cancer treatment, loss to follow-up, or death, whichever comes first. These subjects will also be followed by telephone every 12 weeks during the second year. The duration for response/survival follow-up is approximately 2 years from the first dose of study drug.

5 STUDY POPULATION

5.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

1. Males or females, age ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
3. In all cohorts, archival tumor tissue in a tissue block or biopsy specimen that allows the preparation of at least 20 slides prior to study entry. Tissue blocks are preferred. Archival tumor tissue is acceptable in either format per site's preference.
4. Cohort 1 - Ovarian Carcinoma (OC):
    a. Histologically confirmed epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer subjects with any high-grade serous component, progressed on or after platinum-containing therapy and not eligible for further platinum containing treatment (platinum-resistant, platinum-refractory disease defined by progression of disease on a platinum-containing regimen or recurrence of disease within 180 days of receiving the last dose of platinum-based treatment).
    b. Prior lines of therapy to include:
        - Patients must have had 1 to 3 prior lines of therapy including at least one bevacizumab-containing regimen or ineligible for all other available therapies;
          Or
        - Patients must be in the 4th or 5th line of treatment, irrespective of bevacizumab or who are ineligible for all therapies with demonstrated clinical benefit;
          Or
        - Patients with known BRCA-positive associated cancer or mutation, prior therapy must include PARP inhibitors (unless contraindicated)
5. Cohort 2 - Patients with selected tumor types that have relapsed or progressed after 2 lines of therapy or who are ineligible for other standard of care (SOC) therapies:
    a. Histologically or cytologically confirmed metastatic NSCLC
    b. Histologically or cytologically confirmed recurrent or metastatic HNSCC (oral cavity, oropharynx, hypopharynx, or larynx)
    c. Histologically or cytologically confirmed metastatic or non-resectable advanced metastatic gastric or gastroesophageal adenocarcinoma
    d. Histologically or cytologically confirmed unresectable, locally advanced or metastatic TNBC (confirmed HER2-negative, estrogen receptor-negative and progesterone receptor-negative)
    e. Histologically confirmed ovarian cancer of all high-grade epithelial types who are IO treatment naïve and have progressed after 3 months on or after platinum-containing therapy
    f. PD-L1 expression Tumor Proportion Score (TPS) ≥ 1% for NSCLC and Combined Proportion Score (CPS) ≥ 1% for all other tumor types

g. A 28-day washout period after the completion of programmed death-1 (PD-1)/PD-L1 therapy
h. Patients should have no more than 5 prior lines of therapies
i. If the patients have progressed on treatment with prior PD-1/L1 inhibitor administered either as monotherapy or in combination with other therapies, additional following criteria must be met:
   - have received at least 2 doses of the PD-1/L1 inhibitor;
   - have been on a continuous regimen of the PD-1/L1 inhibitor for at least 4 months without disease progression;
   - have demonstrated radiographic disease progression after PD-1/L1
j. Patients who have had more than 1 prior PD-1/L1 inhibitor may be considered after discussion with the Sponsor's Medical Monitor.

6. Cohort 2 - Pre-treatment fresh tumor biopsies and paired treatment fresh tumor biopsies will be collected from at least 5 patients. Biopsy must be excisional, incisional, or core. Fine needle aspiration is insufficient. Waiver of biopsy samples must be discussed with Sponsor's Medical Monitor. NOTE: CD73 enzymatic activity and assessment of proteins in the adenosine pathway (e.g., CD73, A2A receptor, and whole genome gene expression profiles) will be assessed in fresh tumor biopsies. Samples will be collected prior to dosing and processed and shipped within 24 hours according to a separate laboratory manual. The fresh tumor biopsies require testing for the following infectious diseases: Hepatitis B, Hepatitis C, Tuberculosis, HIV, Syphilis, and COVID-19. Testing must be completed within 28 days of tumor biopsy collection and confirmed to be negative.
7. Willingness and ability to consent for self to participate in study and the ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
8. Patients who received prior PD-1/PD-L1 checkpoint inhibitor or prior CTLA-4 inhibitor therapy may enroll to Cohort 2 if they did not experience Grade 3 immune-related toxicity (applies to all tumor types except ovarian cancer patients)
9. At least one measurable lesion as defined by RECIST 1.1
10. Resolution of all acute adverse events resulting from prior cancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≤ 1 or baseline (except alopecia or neuropathy)
11. Considered by the Investigator to be an appropriate candidate for a clinical study, with a life expectancy of ≥ 12 weeks
12. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) $\geq 1500/\mu L$
    b. Platelets $\geq 100{,}000/\mu L$ without transfusion support within 28 days prior to study treatment
    c. Hemoglobin ≥ 9.0 g/dL without transfusion support within 7 days prior to study treatment (erythropoietin or darbepoetin permitted)
    d. Creatinine clearance > 30 mL/min by Cockcroft-Gault formula

e. Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 3 times upper limit of normal (ULN) or ≤ 5 times ULN in cases of liver metastases
f. Total serum bilirubin ≤ 1.5 times the ULN, unless patient has documented Gilbert's disease in which case bilirubin ≤ 3.0 times the ULN
g. International normalized ratio (INR) from 0.8 to 1.2 unless the INR elevation is related to use of a Factor Xa Inhibitor
h. Activated partial thromboplastin time (aPTT) ≤ 1.5× ULN unless patient is receiving anticoagulant therapy if PT or PTT is within therapeutic range of intended use of anticoagulants

13. No systemic anti-cancer therapy within 4 weeks of starting study treatment or at least 5 half-lives (whichever is shorter) before study drug administration, and all AEs have either resolved or stabilized. Note: Participants who have entered the follow-up phase of an investigational study may participate if it has been 4 weeks after the last dose of the previous investigational agent.
14. Subject with a QT interval corrected for heart rate using Fridericia's formula (QTcF) and/or QT interval corrected for heart rate using Bazett's formula of ≤ 480 msec. NOTE: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (i.e., the patient otherwise has no cardiac abnormalities), the patient may be eligible to participate in the study following discussion with the Sponsor's Medical Monitor.
15. Women of childbearing potential (WOCBP) must:
    a. Agree to use at least 2 effective contraceptive methods (1 highly effective method in combination with a barrier method; oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner), one of which must be barrier. Use of contraceptive methods lasts from date of ICF signature, throughout the study, and for up to 5 months following the last dose of TJ004309.
    b. Have a negative serum pregnancy test (sensitive of at least 25 mIU/ml) at Screening; and have a negative serum or urine pregnancy test within 72 hours prior to Cycle 1 Day 1 of study treatment (note that the screening serum pregnancy test can be used as the test prior to Day 1 study treatment if it is performed within the prior 72 hours)
    c. Avoid conceiving for 5 months after the last dose of TJ004309
    d. Avoid donation of ova from date of ICF signature until 5 months after the last dose of TJ004309
    e. Agree to ongoing urine pregnancy testing, if clinically indicated, during the study
16. Males must agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or a female of childbearing potential, will avoid donation of sperm, or having a female partner conceive from date of ICF signature, while participating in the study, during dose interruptions, and for at least 5 months after the last dose of study treatment, even if he has undergone a successful vasectomy.

5.2 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study participation:

1. Autoimmune disease requiring active treatment within the past twelve months (Note: vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger are permitted)
2. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment (Note: inhaled and topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.)
3. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease
4. Current treatment on another therapeutic clinical trial
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX 40 [Tumor necrosis factor receptor superfamily, member 4 (TNFRSF4)], CD137 [tumor necrosis factor receptor superfamily member 9 (TNFRSF9)]) (only applies to ovarian cancer patients in Cohorts 1 and 2)
6. For ovarian patients in both cohorts:
    a. Patients who progressed during or within 3 months of first line of platinum-based therapy
    b. Patients with histologically non-epithelial tumors or ovarian tumors with low malignant potential (i.e., borderline tumors) or mucinous tumors
    c. Patients with evidence of bowel obstruction requiring hospitalization and decompression within the past 30 days
7. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure; and no date of surgery (if applicable) or anticipated need for a major surgical procedure planned within the next 6 months (The following situations are not considered to be major procedures and are permitted up to 7 days prior to study treatment: thoracentesis, paracentesis, port placement, laparoscopy, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, incisional biopsies, and routine dental procedures. Core biopsy and skin biopsy do not require a waiting period prior to dosing.)
8. Chest radiotherapy ≤ 28 days, wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvic bones or equivalent), or limited field radiation for palliation ≤ 14 days prior to study treatment
9. Pleural effusion or ascites that requires paracentesis in the last 30 days

10. Brain involvement with cancer, spinal cord compression, carcinomatous meningitis, or new evidence of brain or leptomeningeal disease; unless the lesion(s) have been radiated or resected, are considered fully treated and inactive, are asymptomatic, and no steroids have been administered for CNS disease over the 7 days prior to study treatment
11. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment
12. Thrombolytic use (except to maintain IV catheters) within 10 days prior study treatment
13. Known active or chronic Hepatitis B or Hepatitis C, other hepatitides (non-alcohol steatohepatitis, alcohol or drug-related, autoimmune) serology at screening or cirrhosis
14. Any active infection requiring parenteral treatment
15. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months prior to study treatment
16. Known human immunodeficiency virus (HIV) unless CD4+ T cell count > 350 cells/µL with an undetectable viral load
17. Pregnancy or breastfeeding - Female patients must be surgically sterile (i.e., ≥ 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal for at least one year or must agree to use effective contraception during the study and for 5 months following last dose of TJ004309. All female patients of reproductive potential must have a negative pregnancy test (serum or urine) within 72 hours prior to study treatment. Male patients must be surgically sterile or must agree to use effective contraception during the study and for 5 months following last dose of TJ004309
18. Patients with any severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infections should not be enrolled in the trial. Patients who required IV antibiotics or were treated with antiviral medications within this 4 week period should be discussed with the Sponsor Medical Monitor prior to enrollment
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

5.3 Lifestyle Considerations

There are no lifestyle restrictions in this study.

5.4 Meals and Dietary Restrictions

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

5.5 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

One additional rescreening may be performed for individuals who initially do not meet the criteria for participation in this study (screen failure). Rescreened patients should be assigned the same participant number as for the initial screening.

6 STUDY TREATMENT

The study drug(s) being administered in this study are TJ004309 and atezolizumab.

6.1 Description, Storage, Packaging and Labeling

TJ004309 is a recombinant humanized IgG1 antibody that binds to and inhibits the biologic activity of CD73. TJ004309 is produced in CHO cells. TJ004309 will be supplied by the Sponsor as 150 mg/3 mL (50 mg/mL) solution in a sterile single-use vial.

The study drug will be stored according to the instructions on the label or according to instructions provided in a separate document. TJ004309 vials are stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light. Study drug will be stored at the study site in a location that is locked with restricted access. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drug and only authorized study site personnel may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

The treatment to be used in this study is outlined in Table 5.

Table 5: Study Drug Treatments

Study Treatment	Formulation	Unit Dose Strengths	Dose Levels	Route of Administration	Regimen/Treatment Period	Sourcing
TJ004039	Solution for infusion	150 mg vial	20 mg/kg	IV infusion	Q3W until clinically significant disease progression, unacceptable toxicity, or subject/Investigator decision to withdraw	Provided by the Sponsor
Atezolizumab (Tecentriq®)	Solution for infusion	1200 mg vial	1200 mg flat dose			

6.2 Dose Preparation

The preparation, handling, and safe disposal of the study drug should only be prepared by qualified and experienced personnel. TJ004309 will be diluted using aseptic technique. The required dose of TJ004309 will be diluted with 0.9% sodium chloride (normal saline) and administered via an IV infusion pump. TJ004309 dose preparations will be administered with a low protein binding 0.2µm in-line filter. TJ004309 should not be administered as an IV push or bolus. Any unused portion in the vial should be discarded.

The physicochemical in-use stability has been demonstrated for 4 hours at ambient room temperature. Detailed instructions on the preparation and dispensing of TJ004309 are provided in the Pharmacy Manual.

Note that the use of closed system transfer devices (CSTD) for preparation or administration of TJ004309 is not permitted.

For preparation of atezolizumab, see the most recent version of the atezolizumab package insert.

6.3 Drug Accountability

The Investigator must maintain an accurate accounting of TJ004309 and atezolizumab supplies. During the study, the following information must be recorded:

- Date of receipt, quantity, and lot number of the study drug received
- Identification number of the patient to whom the product is dispensed
- The date(s) and quantity of the product dispensed
- Dates and quantity of product returned, lost, or accidentally or deliberately destroyed

Investigational Drug Accountability Logs should be maintained by the site and must be readily available for inspection.

6.4 Treatment Administration

Intravenous hydration prior to and during therapy is left to the discretion of the Investigator but should be considered for patients that may be volume depleted.

The following premedication will be administered on Cycle 1 Day 1, to be administered within 30 minutes to 2 hours prior to the start of the initial TJ004309 infusion:

- Antipyretic (i.e., acetaminophen 650 mg PO)
- Antihistamine (i.e., diphenhydramine 25 to 50 mg PO/IV, cetirizine 10 mg, etc.)

Premedication is not required for subsequent infusions unless a given patient experiences Grade > 2 infusion related reaction with the immediate prior dose of TJ004309.

TJ004309 will be administered by IV utilizing an infusion pump. TJ004309 is required to be administered with a 0.2 micron downstream filter. The attachment of the infusion pump administration set to the IV bag and transport of the TJ004309 study drug to the patient will be performed as per standard study site procedures. Priming may be done using normal saline. Initially, TJ004309 will be administered over 1 hour (±15 minutes) in Cycles 1 and 2. In the absence of IRRs in patients infused over 1 hour in Cycle 2, the infusion time of TJ004309 may be reduced to 30 minutes (± 10 min) per Investigator's discretion.

When the IV bag containing TJ004309 is empty, flush the IV line with sufficient normal saline to clear the tubing at the same infusion rate as the study drug infusion. The infusion is considered complete when the bag containing TJ004309 is empty including the flush. The dose level, time

of transfer to IV bag, and the infusion start and stop times must be recorded in the source documents. TJ004309 has been demonstrated to be compatible with polyethylene lined, non-DEHP infusion sets and polyvinyl chloride, non-DEHP infusion sets.

Administer atezolizumab 1200 mg IV over 60 minutes on Cycle 1 Day 1. If the patient does not experience any infusion related reactions, the infusion may be administered over 30 minutes starting with Cycle 2. Atezolizumab will be administered on Day 1 of each 21-day cycle until progression according to the package insert, with any dose modifications done per the package insert beginning with Cycle 2 Day 1. Atezolizumab should be administered at least 15 minutes following the completion of TJ004309 administration.

Please refer to the Pharmacy Manual for detailed information.

6.5 Dose Assignment

All subjects will be given the combination treatment of TJ004309 20 mg/kg and atezolizumab 1200 mg Q3W. All subjects will be evaluated for antitumor activity on a regular basis as specified in the protocol and their clinical status classified according to RECIST 1.1 and iRECIST. Treatments may continue until clinically significant disease progression, unacceptable toxicity, or subject/Investigator decision to withdraw.

6.6 Measures to Minimize Bias: Randomization and Blinding

Part 1 of this study is a single arm non-randomized study.

6.7 Study Intervention Compliance

The United States Food and Drug Administration (US FDA) and other applicable regulatory authorities require accounting of all investigational drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug.

Each study center is to use a study drug accountability log to document study drug disposition. All items on this form are to be completed in full. The Sponsor's Clinical Research Associate (CRA) is to approve the area where study drug is to be stored and accountability records are to be maintained.

The Investigator identification number and patient initials (as allowed by local regulations) and identification number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, he or she is to record the date dispensed, amount of study drug dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The CRA is to review study drug accountability records and remaining drug supplies during routine monitoring visits.

6.8 Concomitant Therapy

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 28 days prior to the first study drug dose are to be documented as *prior* medications. Medications taken from the time of the first study drug dose on C1D1 through 30 days after the last study drug dose are to be recorded as *concomitant* medications in the electronic case report form (eCRF). All therapies for primary diagnosis should be recorded regardless of when they were taken.

6.8.1 Prohibited Concomitant Medications

The following medications and treatments are prohibited during study participation:

- Any commercially available or investigational anti-cancer therapy other than the study treatment
- Radiation therapy is prohibited within 2 weeks prior to study Cycle 1 Day 1 and during study treatment. NOTE: Palliative radiation therapy to a small field outside of the target lesion area >1 week prior to Day 1 of the study treatment may be allowed at the discretion of the Investigator or palliative radiation therapy during the protocol may be permitted after discussion with the Sponsor's Medical Monitor.
- Prophylactic granulocyte colony-stimulating factor (GCSF) or GM-CSF is not permitted. The use of these may only be permitted after discussion with the Sponsor's Medical Monitor if indicated.
- Chronic or systemic corticosteroid use (prednisone ≥10 mg/day or dexamethasone ≥1.5 mg/day) for supportive care is not permitted. (However, acute use to manage suspected immune-related AEs is allowed; however, in such cases, systemic steroid should be stopped at least 24 hours prior to the next dose of the study drug and the use of such needs to be clearly documented in the applicable source docs and CRF). Acute use of topical corticosteroid preparations, inhaled sprays, eye drops, or local injections of corticosteroids are acceptable. Use of a corticosteroid due to a confirmed allergy to IV contrast is also permitted.
- Live vaccines administered within 30 days prior to the initially dose of study drug and while participating in the study are not permitted. Seasonal influenza vaccines for injection that are killed virus vaccines are allowed; live attenuated vaccines such as the intranasal influenza vaccine (e.g., FluMist®) are not allowed. Other types of vaccines (mRNA) may have exemptions, such as the SARS-CoV-2 (COVID-19) vaccine; Sponsor will provide up-to-date guidance based on current practices.
- Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the last Follow-up visit.

6.8.2 Permitted Concomitant Medications

Medications and treatments other than those specified in, including palliative and supportive care for disease-related symptoms, are permitted during the study. Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

- All prior medications and non-drug interventions received by subjects within 28 days (4 weeks) prior to the initially dose of study treatment and up to 30 days after the last dose of study treatment will be recorded on the CRF, including the name of the procedure or medication, dose, route, indication and duration of treatment. Concomitant treatment and supportive care considered necessary for the subject's well-being may be given at the discretion of the treating physician using his or her clinical judgment in consultation with the Sponsor.
- Medications (antihistamines, H2-blockers, anti-pyretics, bronchodilators, corticosteroids, and other medically indicated medications) to treat infusion-related reactions are acceptable.
- Medications to treat anemia, thrombocytopenia, and other TJ004309-related adverse effects are permitted.
- Hormone replacement therapy, oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications.
- Antiemetic treatments may be used at the Investigator's discretion and in accordance with the American Society of Clinical Oncology guidelines or equivalent after documented nausea or vomiting has occurred without medications having been used.

6.8.3 Premedication

On Cycle 1 Day 1, the following premedication will be administered within 30 minutes to 2 hours prior to the start of the initial TJ004309 infusion:

- Antipyretic (i.e., acetaminophen 650 mg PO)
- Antihistamine (i.e., diphenhydramine 25 to 50 mg PO/IV, cetirizine 10 mg, etc.)

Premedication is not required for subsequent infusions unless a given patient experiences Grade > 2 infusion related reaction with the immediate prior dose of TJ004309.

6.9 Dose Modification and Dose Delays

The treatment management guidelines including dose delay and dose modification of TJ004309 for hematological and non-hematological toxicities are provided in Table 6 and Table 7 respectively. Treatment management guidelines for Immune-Related Adverse Events (irAEs) are provided in Table 8.

Dose delay up to 4 weeks is allowed for subjects with manageable AEs at the Investigator's discretion, e.g., Grade 4 or Grade 3 thrombocytopenia with Grade ≥ 2 bleeding, uncomplicated Grade 3 febrile neutropenia, and Grade 4 neutropenia. The Investigator can continue to withhold treatment for up to 12 weeks after the last dose based on the Investigator's medical judgement. If the subject has recovered to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. Dose modification or withholding of doses other than as described in this section is not permitted.

If a Grade ≥ 2 toxicity recurs for the second time, the Investigator may discuss with the Sponsor whether resuming TJ004309 is appropriate considering the type and grade of the toxicity. If the agreement is to resume TJ004309, treatment can continue to be withheld for up to 12 weeks to allow the subject to recover to Grade ≤ 1 or baseline at the Investigator's discretion. If the subject recovers to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. If the subject does not recover within 12 weeks, permanently discontinue TJ004309. The Investigator should always manage their subjects according to their medical judgment based on the clinical circumstances.

All dose modifications must be clearly documented in the subjects' source notes and Case Report Form (CRF).

Study treatment dose delays are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., surgery, unrelated medical events, patient vacation, and/or holidays). Participants should be placed back on study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record. All dose delays must be clearly documented in the patients' source notes and the eCRF.

Table 6: TJ004309 Treatment Management Guidelines for Adverse Events (Hematological Toxicities)

Adverse Event	Grade	Management Actions*
Neutropenia	Grade ≥ 4	• If the subject has recovered to Grade ≤ 1 or baseline within 4 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 4 weeks, the Investigator can continue to withhold for up to 12 weeks after the last dose based on the Investigator's medical judgement. • Monitor absolute neutrophil count weekly until recovered or stable. • Conduct adequate evaluation to confirm etiology and/or exclude other causes. • Initiate broad spectrum antibiotics. • Consider initiating Granulocyte-colony stimulating factor (G-CSF) such as filgrastim or pegylated filgrastim. • If the event recurs for the second time, withhold treatment for up to 12 weeks while giving appropriate medical treatment at the Investigator's discretion. If the subject has recovered to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 12 weeks, permanently discontinue TJ004309.
Febrile Neutropenia	Grade ≥ 3	See above
Other hematological toxicities[1]	Grade ≥ 3	• If the subject has recovered to Grade ≤ 1 or baseline within 4 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 4 weeks, the Investigator can continue to withhold for up to 12 weeks after the last dose based on the Investigator's medical judgement. • Monitor hematological toxicities weekly until recovered or stable. • Conduct adequate evaluation to confirm etiology and/or exclude other causes. • If the event recurs for the second time, withhold treatment for up to 12 weeks while giving appropriate medical treatment at the Investigator's discretion. If the subject has recovered to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 12 weeks, permanently discontinue TJ004309.

[1] With the exception of Grade 3 or 4 lymphopenia.
*Treating physicians' assessment and judgement are critical, and all the management actions should be taken with physician's discretion

Table 7: TJ004309 Treatment Management Guidelines for Adverse Events (Non-Hematological Toxicities)

Adverse Event	Grade	Management Actions*
Infusion Related Reactions (IRR)[1]	Grade 2	• Interrupt or slow the rate of infusion. Monitor and if the reaction worsens, stop infusion. • Administer institutional standard medications for hypersensitivity reaction as medically indicated. Monitor symptoms until stable. Re-initiate infusion if patient is stable at a 50% slower rate. Prophylactic medications indicated for ≤ 24 hours. • For subsequent infusions, administer premedication with the following or per institutional standard: o H-1 antihistamine: Diphenhydramine 25-50 mg PO or IV 30 minutes prior to infusion o Acetaminophen 500-1000 mg PO 30 minutes prior to infusion o Corticosteroids such as dexamethasone (or equivalent) or anti- emetics such as ondansetron (or equivalent) may be administered based on clinical presentation of previous IRR • For subsequent infusions, may administer TJ004309 at a 50% slower rate.
	Grade ≥ 3	• Stop infusion immediately and discontinue TJ004309. • Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressors, oxygen, etc. as medically indicated. Contact sponsor to report SAE. • Increase monitoring of vital signs as medically indicated until stable.
Chills	Grade 3	• Stop the infusion. • Administer aggressive symptomatic therapy per institutional standard. • After resolution of all symptoms, treatment can be resumed at slower rate, unless severe reaction. If severe reaction, then withhold TJ004309 per Investigator's discretion of clinical presentation of the subject.

Diarrhea/Colitis	Grade 2 or 3 that persists for ≥ 7 days despite adequate steroid therapy	• Withhold. • Should consult with gastroenterology for Grade ≥ 2. • Administer corticosteroids starting with initial dose of 1- 2 mg/kg/day prednisone or equivalent. Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance. When symptoms improve to Grade ≤ 1, taper corticosteroids over at least 4 - 6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits. • Monitor subject for signs and symptoms of enterocolitis and/or bowel perforation and advise patient to increase oral fluids or IV infusion if needed. • If the subject has recovered to Grade ≤ 1 or baseline within 4 weeks, and treatment is restarted during corticosteroid taper, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 4 weeks, the Investigator can continue to withhold for up to 12 weeks after the last dose based on the Investigator's medical judgement. • If recurrent Grade ≥ 3 permanently discontinue TJ004309.
Nausea, vomiting, fatigue, or electrolyte abnormalities	Grade 3 if persisting despite optimal medical treatment	• If the subject has recovered to Grade ≤ 1 or baseline within 4 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 4 weeks, the Investigator can continue to withhold for up to 12 weeks after the last dose based on the Investigator's medical judgement. • Monitor toxicities weekly until recovered or stable. • Give supportive care based on Investigator discretion. • Conduct adequate evaluation to confirm etiology and/or exclude other causes. • If recurs for the second time, withhold treatment for up to 12 weeks while giving appropriate medical treatment at the Investigator's discretion. If the subject has recovered to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered up to 12 weeks, permanently discontinue TJ004309.

	Grade 4	• Give supportive care based on Investigator discretion. • If the subject has recovered to Grade ≤ 1 or baseline within 4 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 4 weeks, the Investigator can continue to withhold for up to 12 weeks after the last dose based on the Investigator's medical judgement. • If recurs for the second time, withhold treatment for up to 12 weeks while giving appropriate medical treatment at the Investigator's discretion. If the subject has recovered to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered up to 12 weeks, permanently discontinue TJ004309.
Other non-hematological adverse reactions	Grade 3	• If the subject has recovered to Grade ≤ 1 or baseline within 4 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered within 4 weeks, the Investigator can continue to withhold for up to 12 weeks after the last dose based on the Investigator's medical judgement. • Monitor toxicities weekly until recovered or stable. • Give supportive care based on Investigator discretion. • Conduct adequate evaluation to confirm etiology and/or exclude other causes. • If recurs for the second time, withhold treatment for up to 12 weeks while giving appropriate medical treatment at the Investigator's discretion. If the subject has recovered to Grade ≤ 1 or baseline within 12 weeks, continue treatment of TJ004309 at the same dose level. If the subject has not recovered up to 12 weeks, permanently discontinue TJ004309.
	Grade 4	• Discontinue TJ004309.

[1]For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov
*Treating physicians' assessment and judgement are critical, and all the management actions should be taken with physician's discretion.

Table 8: TJ004309 Treatment Management Guidelines for Immune-Related Adverse Events (irAEs)

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroid followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. TJ004309 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue tapering at least 4 weeks.
4. If TJ004309 has been withheld, TJ004309 may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE V5.0)	Action with TJ004309	Corticosteroid and/or other therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for participants with T1DM Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Persistent Grade 2	Withhold		Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 3	Withhold or discontinue based on the event [e]	Based on severity of AE administer corticosteroids	
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a AST/ALT: > 3.0 - 5.0 x ULN if baseline normal; > 3.0 5.0 x baseline, if baseline abnormal; bilirubin: > 1.5 3.0 x ULN if baseline normal; > 1.5 - 3.0 x baseline if baseline abnormal

b AST/ALT: > 5.0 to 20.0 x ULN, if baseline normal; > 5.0 20.0 x baseline, if baseline abnormal; bilirubin: > 3.0 10.0 x ULN if baseline normal; > 3.0 - 10.0 x baseline if baseline abnormal

c AST/ALT: > 20.0 x ULN, if baseline normal; > 20.0 x baseline, if baseline abnormal; bilirubin: > 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal

d The decision to withhold or permanently discontinue TJ004309 is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, TJ004309 may be resumed.

e Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

6.10 Treatment after Disease Progression

A patient who is deriving clinical benefit despite radiological evidence of progressive disease, defined by RECIST 1.1 and iRECIST criteria, may continue study treatment at the Investigator's discretion after discussion with the Sponsor. The patient must meet all of the following criteria:

- ECOG status of 0 or 1
- Absence of signs/symptoms (including laboratory values) indicating unequivocal progression of disease.
- Absence of tumor progression at specific anatomical sites that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing. These anatomical sites include the CNS, and other organs/tissues where compromised function secondary to tumor progression would be expected to result in severe and/or irreversible disability or death.
- Must provide consent to acknowledge discussion with the Investigator of the benefit-risk of continuing on study beyond radiographic progression.

6.11 Intervention after the End of the Study

No intervention following the completion of study participation is planned.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Patients will be informed that they have the right to discontinue study drug at any time for any reason, without prejudice to their medical care. At the time of discontinuation, all study procedures outlined for the EOS visit should be completed (see Table 2). The primary reason for study drug discontinuation is to be recorded in the eCRF.

7.1.1 Reasons for Discontinuation of Study Intervention

The Investigator has the right to discontinue study drug for any of the following reasons:

- Progression of disease that, in the opinion of the Investigator, precludes further study treatment. (After consultation with the Study Responsible Physician, study drug may be continued for a patient who has met the criteria for progressive disease (PD) but, in the Investigator's opinion, is receiving benefit)
- Occurrence of an unacceptable AE per the Investigator medical judgement
- Pregnancy (see Section 8.4.8)
- Non-compliance
- Lost to follow-up
- Patient withdrawal of consent
- Sponsor request

7.2 Replacement of Patients

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor.

7.3 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

At the time of withdrawal from the study, if possible, an EOS visit should be conducted, as shown in the SoA (Table 2). See Table 2 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent, the patient will be permanently discontinued from the study drug and withdrawn from the study at that time. The Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4 Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a patient fails to return to the clinic for a required study visit or following the site's standard procedures:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole will be handled as described in Section 7.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 2 and Table 3).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that a potential patient meets all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The patient/patient's health proxy must provide written informed consent before the performance of any study-specific procedures.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 2).

8.1 Efficacy Assessments

Tumors will be assessed for anti-tumor activity of TJ004309 at times indicated in the SoA (Table 3). Assessments will be measured by BOR, ORR, DOR, PFS, and OS and will be based on RECIST 1.1 and iRECIST for solid tumors.

8.2 Baseline and Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.1 Demographics

Patient demographics, including age, sex, race, and ethnicity, are to be documented during Screening.

8.2.2 Medical History, Including Cancer History

A complete medical history is to be documented during Screening and updated at Baseline, prior to administration of the first study drug dose.

The medical history is to include cancer history, including the patient's primary diagnosis, date of diagnosis, method of diagnosis, and all previous treatments, including radiation therapy, and response to such treatment.

8.2.3 Physical Examinations, Height, and Weight

A full physical examination will be performed at Screening and at pre-dose of Cycle 1 Day 1, unless the screening physical examination was performed within the last 7 days. The full physical examination includes general appearance, head/ears/eyes/nose/throat, lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, extremities and neurological examinations. The genitourinary examination is considered optional unless indicated by medical history or report of current condition.

Starting with Cycle 2, abbreviated physical examinations should be performed as appropriate at each visit in which completed physical examinations are not required, and on an as needed basis for assessment of AEs. Abbreviated physical examinations should be targeted to specific symptoms or complaints and be consistent with local standard of care (brief physical examination will be symptom-directed and include assessment of cardiac, respiratory, and gastrointestinal systems).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Height (cm) is to be measured for all patients at Screening only.

Weight (kg) is to be measured for all patients at the designated time points in the SoA (Table 2). The dose of each study drug will be calculated based on the actual weight of each subject, as measured at the screening visit. The weight used may be revised to a weight collected at a later date if it has changed by more than 10%.

8.2.4 Vital Signs

Seated blood pressure, seated pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Table 2.

For the first cycle, vital signs (seated blood pressure, seated pulse rate, respiratory rate) will be collected pre-dose, 30 minutes after the start of infusion, and 2 hours after EOI. Body temperature will be measured singly. The median value will be used as the baseline value in the data analysis. For treatment in Cycle 1, subjects should remain at the site for monitoring (with immediate access to medical resuscitation equipment) for at least 1 hour following the end of the initial infusion.

At all subsequent cycles vital signs will be performed pre-dose singly and repeated once if outside the relevant clinical reference ranges. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

Subjects must be seated for at least 5 minutes before blood pressure and pulse rate measurements.

8.2.5 Performance Status

Performance status is to be assessed using the Eastern Cooperative Oncology Group (ECOG) performance status scale for all patients at the time points designated in the SoA (Table 2). The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Table 9.

Table 9: Eastern Cooperative Oncology Group Performance Status Scale, with Equivalent Karnofsky Performance Status Scores

ECOG[a]		Karnofsky[b]	
Score	**Criterion**	**%**	**Criterion**
0	Normal activity	100	Normal; no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms but ambulatory	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self; unable to carry on normal activity or do active work
2	In bed <50% of time	60	Requires occasional assistance but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed >50% of time	40	Disabled, requires special care and assistance
		30	Severely disabled; hospitalization is indicated though death is not imminent
4	100% bedridden	20	Very sick; hospitalization is necessary
		10	Moribund; fatal processes progressing rapidly
5	Dead	0	Dead

a Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

b Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002-2007.

8.2.6 Electrocardiograms

At Screening, 12-lead electrocardiograms (ECGs) are to be performed in triplicate, with each measurement separated by 2 minutes. The average of the 3 Screening ECGs will be used to calculate QTc to determine study eligibility. The Investigator (or designee) will perform a clinical assessment of each 12 lead ECG.

ECGs are to be performed at the designated time points in the SoA (Table 2). ECG measurements should be taken after the patient has been resting in the supine or reclined position.

Additional 12 lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required.

8.2.7 Clinical Safety Laboratory Assessments

See Section 10.5 for the list of clinical laboratory tests to be performed and the SoA (Table 2) for the timing and frequency. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required (e.g., repeat testing as required to confirm results).

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.5, must be conducted in accordance with the laboratory manual and the SoA.

8.3 Safety Parameters and Definitions

Adverse events observed or discovered by the Investigator in this study, as well as information on AEs reported by the patient, whether or not there is a suspicious causal association with the study medication, are required to be reported in accordance with the following requirement.

8.3.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any of the following:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., but not related to progression of underlying disease).
- Worsening of signs and symptoms of the malignancy under study drug treatment.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.

- Related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT meeting the AEs definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or its progression, signs, or symptoms, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen overall.

8.3.2 Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose meets any of the following criteria:

- Results in death
- Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a patient's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect
- Is a significant medical event in the Investigator's judgement

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to the NCI CTCAE, version 5.0.

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

8.3.2.1 Hospitalization

Some events that require inpatient hospital care or prolongation of existing hospitalization may not be considered as SAE. When hospitalization is not associated with an AE as supported by evidence, the hospitalization will not be considered as SAE, the following "hospitalizations" should not per se constitute a SAE:

- Inpatient hospital care or prolongation of existing hospitalization is a result of other factors rather than an SAE (e.g., pre-existing conditions)
- Inpatient hospital care appointed or scheduled prior to the study (e.g., hospitalization for routine physical examination, patient education and planned medical operations, social causes etc.).

The causes of the above hospitalization events must be clearly documented in the medical records.

8.3.2.2 Disease Progression

Progression of the malignancy under study (including signs and symptoms of progression) should not be recorded as an AE or SAE. If the Investigator believes that the progression of malignancy under study is related to the study drug or the progression of the malignancy led to death, the progression should be reported as an SAE.

8.4 Safety Reporting Requirement

The Investigator is responsible for ensuring that all AEs are detected, documented, and recorded on the Adverse Event eCRF.

Each study patient will be questioned about AEs at each clinic visit following initiation of treatment. Open-ended and non-leading verbal questioning of the patient/patient's legal guardian is the preferred method to inquire about AE information. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment for seriousness, severity and causality (see Section 8.4.2).

8.4.1 Adverse Event Reporting Time Period

All AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from the time the ICF is signed until study completion, 30 days after the last dose of study drug or 30 days following cessation of study treatment if the subject initiates new anti-cancer therapy, whichever is earlier. The event name, date of onset, duration, and severity will be documented, together with an Investigator's (or designee's) opinion of the relationship to study drug.

Before initiation of study drug, only the AEs which regarded as have relationship to study procedure will be collected as AE.

All SAEs (regardless of relationship to study drug) and/or non-serious AE considered to be possibly, probably or definitely related to study drug recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Medical occurrences that begin before the start of study drug, but after obtaining informed consent, will be recorded on the Medical History/Current Medical Conditions section of the eCRF rather than in the Adverse Event section.

8.4.2 Assessment of Severity of Adverse Event

To report AEs on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE, version 5.0. Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE, version 5.0, then severity of mild, moderate, severe, life-threatening, or fatal may be used to describe the maximum intensity of the AE, as guided by Table 10. Note that the selection of the most appropriate verbatim term for AEs is not restricted to only those toxicities represented in NCI CTCAE. For purposes of consistency, these intensity grades are defined in Table 10.

Table 10: Adverse Event Severity Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate	Minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental ADL[b]
3	Severe	Medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care ADL[c]
4	Life-Threatening	Urgent intervention indicated
5	Fatal	Results in patient's death

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
ADL= Activities of Daily Living
[b] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[c] Self -care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden

8.4.3 Assessment of Causality of Adverse Event

The Investigator is obligated to assess the relationship between study drug(s) and each occurrence of each AE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, and not that a relationship cannot be ruled out. The Investigator (or designee) will determine the relationship of AE to the study and use 5-category system according to the following guidelines, the "definitely related, probably related, and possibly related" are classified into related to the study drug, and "unlikely related, definitely unrelated" are classified into unrelated to the study drug:

- **Definitely unrelated**: there is no temporal relationship; there is reasonable evidence to suggest that AE is caused by other factors such as concomitant medications or concomitant diseases.
- **Unlikely Related**: AE is more likely to be caused by other factors such as concomitant medications or concomitant diseases; the temporal relationship indicates that is unlikely to be causally related to the study drug.
- **Possibly Related**: There is a reasonable temporal relationship but could have been caused by other factors such as concomitant medications or concomitant diseases.
- **Probably Related**: There is a reasonable temporal relationship and unlikely to be caused by other factors such as concomitant medications or concomitant diseases; there is indicative de-challenge information.

- **Definitely related**: There is an obvious reasonable temporal relationship; the AE is a possible adverse reaction and cannot be explained by other factors such as concomitant medications or concomitant diseases; there is indicative information of de-challenge and re-challenge.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.4.4 Procedure for Recording Adverse Event

When an AE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigators should use correct medical terminology/concepts when recording AEs in the eCRF.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE term. Only one AE term should be recorded in the event field on the AE eCRF.

8.4.5 Reporting of Serious Adverse Event

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The Investigator must report such events to the Sponsor immediately (no later than 24 hours). The Investigator must report all SAEs to the Sponsor no later than 24 hours after awareness of the event, regardless of relationship to study drug.

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information).

Investigators must also comply with local requirements for reporting SAEs to the Institutional Review Board (IRB).

Report SAEs to the Sponsor's PV service vendor, dMed Biopharma via email:

- On discovery, all SAEs should be immediately reported (no later than 24 hours after awareness of the event) to dMed Biopharma by completing the SAE reporting form and email the documents to dMed Biopharma Drug Safety:

DrugSafety-imab@dmedglobal.com

- Please note that this email address is for the reporting of SAE and pregnancy information only.

8.4.6 Follow-up of AE and SAE

Every reasonable effort will be made to follow up with subjects who have AEs. Any subject who has an ongoing SAE (regardless of relationship to study drug) and/or non-serious AE that is possibly, probably or definitely related to the IMP or study procedures at the 30-day post-treatment, follow-up visit or last study visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing non-serious AE that is not related or unlikely related to the IMP or study procedures at the Follow up visit or last study visit, can be closed out as ongoing at the Investigator's discretion. If a subject initiates new anti-cancer therapy during the follow-up period, new AEs are not required to be reported.

New or updated information will be recorded in the originally completed eCRF.

8.4.7 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other applicable regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.4.8 Pregnancy Reporting Requirement

A pregnancy event refers to a pregnancy of a female subject or a maternal pregnancy of a male patient during a clinical study or within 5 months after the patient's last dose of study drug. The Investigator will collect pregnancy information via the Pregnancy Reporting Form within 24 hours after becoming aware of the information.

Study drug must be discontinued immediately in the event of a pregnancy in a patient. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the patient /patient's partner until completion of the pregnancy and provide this follow-up information using the same procedures as the initial reporting. Generally, the follow-up will be within 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (Section 8.3.2), then the Investigator should report it as such, and the Investigator needs to fill out an SAE reporting form and report to the Sponsor within 24 hours. Furthermore, all neonatal deaths that occurs within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

Any post-study pregnancy related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor or designee. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.5 Treatment of Overdose

There is no defined overdose of TJ004309. Signs and symptoms of an overdose should be reported as AEs. Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria (see Section 8.3.2).

In the event of an overdose, the Investigator should:

1. Contact the Study Responsible Physician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis if requested by the Study Responsible Physician (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

No specific information is available on the treatment of overdose of TJ004039. In the event of overdose, the subject should have immediate interruption of their infusion and be observed closely for signs of toxicity. Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Study Responsible Physician based on the

clinical evaluation of the patient. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Safety Management Team (SMT)

A dedicated internal Safety Management Team (SMT) for TJ004309 will be formed for continuous safety monitoring. According to the safety management charter, the dedicated TJ004309 SMT is a cross functional team, composed of a safety physician, clinical physician, regulatory representative, biostatistician, and ad hoc members. From the program level, the team will review and evaluate the safety data mentioned above during the lifecycle of TJ004309, periodically and/or ad hoc. The charter guides the team to review all safety data including all lab tests, nonserious AEs, SAEs, nonclinical data, and the published same class drug safety data. Based on the nature of the safety issue with the team consensus, the team will provide the appropriate recommendations as well as communications to the appropriate stakeholders, including but not limited to health authorities, Investigators, subjects, and ethical committees.

8.7 Pharmacokinetics

Blood samples of approximately 5 mL each will be collected for measurement of serum concentrations of study drug as specified in the SoA (Table 3). Serum samples will be prepared per lab manual.

The following pharmacokinetic parameters of TJ004309 will be obtained by direct measurement of PK samples or derived by population PK modeling and simulations:

- C_{max} (maximum observed concentration)
- T_{max} (time of the maximum observed concentration)
- AUC_{0-t} (from time zero to the time of the last quantifiable concentration), AUC_{τ} (AUC over a dosing interval), $AUC_{0-\infty}$ (AUC from time zero to infinity), $t_{1/2}$ (terminal elimination half-life)
- C_{trough} (trough concentration)
- CL (clearance)
- V_{ss} (volume of distribution at steady-state)
- V_z (volume of distribution associated with terminal phase)

8.8 Pharmacodynamics

Paired fresh pre-treatment and on-treatment tumor biopsy specimens will be collected from at least 5 subjects in Cohort 2, for the measurement of CD73 enzymatic activity with enzyme-histochemistry, infiltrating immune cells using multiplex-immunohistochemistry and the whole genome gene expression profiles using RNA sequencing. Samples will be processed, stored, and shipped according to a separate laboratory manual.

8.9 Biomarkers

For both cohorts, baseline archival tumor biopsy specimens will be collected for the expression of PD-L1 and CD73 by immunohistochemistry, measurement of infiltrating immune cells using multiplex-immunohistochemistry and whole genome gene expression profiles using RNA sequencing to explore the predictive biomarkers.

For Cohort 2, PD-L1 expression at baseline archival tumor biopsy will be used to pre-select the patients for the inclusion criteria. Archival tumor biopsy samples are preferred in block format but archival tumor tissue that allows the preparation of at least 20 slides prior to study entry is acceptable.

For both cohorts, approximately 15 mL and 5 mL of blood will be collected as specified in the SoA (Table 3), for peripheral blood mononuclear cell (PBMC) and serum preparation, respectively. After processing the PBMC and serum samples will be cryopreserved for future immunophenotyping, gene expression and protein expression analysis. PBMC and serum samples will be processed, stored, and shipped according to a separate lab manual.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

For Part 1 of the study, the sample size is not based on formal statistical considerations. Rather, it is based on a desire to obtain sufficient safety, tolerability, PK, pharmacodynamic, and preliminary efficacy information while exposing as few patients as possible to the investigational treatment. With up to 30 patients per cohort, Part 1 of the study provides an opportunity to further investigate the safety profile and explore tumor activities in a more selective patient population and helps to make decision for the Part 2 design.

For purposes of analysis, the following populations are defined:

Population	Description
Efficacy Evaluable	The efficacy evaluable population will comprise all subjects who receive at least 1 dose of study drug and undergo at least 1 post-baseline tumor assessment. Subjects who die before the initially scheduled post-baseline tumor assessment will be included in this evaluable population.
Safety	The safety population will include all subjects who receive at least 1 dose of study drug.
Pharmacokinetics	The PK population will include all subjects who receive at least 1 dose of study drug and have sufficient information to estimate at least 1 of the PK parameters of interest (C_{max} or AUC).
Pharmacodynamic	The pharmacodynamic population will include all subjects who receive at least 1 dose of TJ004309 and have sufficient information for pharmacodynamic evaluation.
Biomarker	The biomarker population will include all subjects who receive at least 1 dose of study drug and have baseline archival tumor biopsy specimen.

9.2 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP).

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data. The 95% CI for the estimates will be calculated when applicable. The statistical analyses will be performed using SAS® version 9.4 or later (SAS Institute Inc, Cary NC).

9.2.1 Disposition

The number of patients included in each analysis set will be summarized, along with the reason for any exclusions. Patients discontinuing from study treatment and/or withdrawing from study participation the primary reason for discontinuation will be summarized.

9.2.2 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be tabulated. No statistical tests will be performed on these characteristics.

9.2.3 Exposure

The overall duration of study treatment administration and number of cycles initiated will be summarized. For each patient, the cumulative administered dose of study drug will be calculated. These data will be further summarized for each cohort by calculating the mean, standard deviation, median, and range of these values. The number and proportion of patients with 1 or more dose modifications (i.e., dose reduction) will be tabulated along with the reason for modification.

9.2.4 Efficacy Analyses

A listing of tumor measurements will be provided by subject and time. BOR, ORR, DOR, PFS and OS will be listed and summarized by cohort/group based on efficacy evaluable population if data permits.

9.2.5 Safety Analyses

All safety analyses will be performed on the Safety Analysis Population. The safety assessment will be based on the frequency of AEs, on the observation of clinically significant abnormalities of laboratory values, concomitant medication use, vital signs, ECGs, ECOG performance status, and physical examination data in the Safety Analysis Population.

AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or higher. Adverse events will be graded by the Investigator according to the CTCAE, version 5.0.

Analyses of AEs will be based on the principle of treatment emergence. Treatment-emergent AEs are defined as having onset after study drug dosing or a sign, symptom, or diagnosis that worsens after study drug dosing. Henceforth, whenever an analysis or summary of AEs is mentioned, it is intended that this is in reference to treatment-emergent adverse events (TEAEs), unless it is stated otherwise.

TEAEs will be summarized based on the number and percentage of patients experiencing the event by system organ class (SOC) and preferred term (PT). The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator on the basis of his or her clinical judgment (i.e., Related, Possibly Related, Probably Related, Unlikely Related, and Not Related). In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study drug will be used for purposes of incidence tabulations.

9.2.6 Pharmacokinetic Analyses

Summary statistics will be tabulated for each PK parameter, if feasible, and wherever applicable, by cohort/treatment. Mean, standard deviation, median, geometric means, and coefficients of variation will be presented for C_{max} and C_{trough}. The exposure of sparse PK samples will be combined with the PK data obtained from Phase 1 trial for population PK analysis and exposure-response analyses.

9.2.7 Pharmacodynamics and Biomarker Analyses

Pharmacodynamics effects on CD73 enzymatic activity, immune cell profiles, and whole genome gene expression profiles will be evaluated in paired fresh tumor biopsies at baseline and on-treatment collected from a subset of subjects in Cohort 2.

Expression of PD-L1, CD73, immune cell subsets, and whole genome gene expression profiles in baseline archival tumor biopsy will be evaluated for their association with clinical responses. These analyses are considered exploratory and will be summarized in a separate technical report.

9.3 Interim Analyses

A futility analysis with 15 patients based on rules from a Simon's 2-stage design for Cohort 1 is planned for this study. In addition, analyses of the data may be performed for publication and regulatory reporting purposes.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Data Record and Management

Standard clinical monitoring and data management practices will be used to ensure the integrity of the data. As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each subject. The completed original CRFs are the sole property of I-Mab and should not be made available in any form to third parties, except for authorized representatives of I-Mab or appropriate regulatory authorities, without written permission from I-Mab.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary.

Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

Data will be entered into a validated database. Data Management will be responsible for data review and processing, in accordance with the Sponsor’s data management procedures. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the study.

10.2 Protocol Deviations and Amendments

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol. The Investigator should document and explain any protocol deviations in source. The Investigator should promptly report any deviations to the Sponsor or designee, and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor or designee will review all protocol deviations and conduct impact assessments as needed. As per the Sponsor's standard operating procedures, prospective requests

to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed and will not be granted.

All protocol revisions (amendments) must originate with and be documented by the Sponsor. The Investigator must submit all amendments to his/her IRB for review and approval prior to implementation; documentation of approval signed by the chairperson or designee must be sent to the Sponsor.

10.3 Record Retention

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements. Essential documents include, but are not limited to, the following: signed informed consent documents for all subjects; subject identification code list, screening log (if applicable), and enrollment log; record of all communications between the Investigator and the IRB; composition of the IRB; record of all communications between the Investigator, Sponsor, and their authorized representative(s); list of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures; copies of CRFs (if paper) and of documentation of corrections for all subjects; investigational product accountability records; record of any body fluids or tissue samples retained; and all other source documents (subject records, hospital records, laboratory records, etc.).

ICH requires that patient identification codes be retained for at least 15 years after the completion or discontinuation of the study.

10.4 Regulatory, Ethical, and Study Oversight Considerations

10.4.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The Protocol, Protocol Amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.4.2 Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.4.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her healthcare proxy and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their healthcare proxy will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's healthcare proxy.

10.4.4 Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the participant identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.4.5 Dissemination of Clinical Study Data

A clinical study report (CSR) will be written after completion of the study.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The basic principles regarding publication of study results are as follows:

Both positive and negative study results will be disclosed. In general, the results of research will be submitted for publication to peer-reviewed scientific journals. These journals often do not consider negative results for publication. However, results will be otherwise disclosed on www.clinicaltrials.gov as per regulatory requirement.

10.4.6 Data Quality Assurance

All patient data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB review and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organization).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified immediately by telephone or e-mail and the notification confirmed in writing if a custodial change occurs.

10.4.7 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Any electronic study data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic study data will be documented.

10.4.8 Study and Site Closure

The Sponsor designee reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.

- Discontinuation of further study drug development.

10.4.9 Publication Policy

All information regarding study drug supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of I-Mab. It is understood that there is an obligation to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used towards the development of study drug and may be disclosed by I-Mab to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of Investigators participating in the study and representatives from I-Mab as appropriate, will be formed to oversee any publication or presentation of the study results, which will reflect the experience of all participating study centers. All publications and presentations must be approved in advance by I-Mab, in its sole discretion. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

A pre-publication manuscript is to be provided to I-Mab at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher. All publications and presentations must be approved in writing by I-Mab before public disclosure.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.5 Clinical Laboratory Tests

The tests detailed in Table 11 will be performed by the local/central laboratory. Investigators must document their review of each laboratory safety report.

Protocol-specific laboratory requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 11: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	WBC count with differential	Red blood cell count and reticulocytes
	Platelet count	Hemoglobin
	Mean corpuscular hemoglobin	Hematocrit
	Mean corpuscular volume	Absolute neutrophil count
HBV, HCB, HIV (Screening Only)	Anti-hepatitis B surface antibody	HIV-1
	HBsAg	HIV-2
	Anti-HCV	
Coagulation Studies	International normalized ratio (INR)	
	Prothrombin time	
	Activated partial thromboplastin time or Partial thromboplastin time	
Serum Chemistry	Alanine aminotransferase (ALT)	Bicarbonate
	Aspartate aminotransferase (AST)	Glucose
	Amylase	Lipase
	Albumin	Phosphorus
	Alkaline phosphatase	Total bilirubin
	Blood urea nitrogen	Total protein
	Calcium	Magnesium
	Cholesterol	Potassium
	Creatinine	Chloride
	Gamma-glutamyl transferase	CA125 (ovarian cohorts only)
	Lactate dehydrogenase	Uric Acid
	Sodium	
Urinalysis	A dipstick urinalysis is to be performed for:	
	Color	Protein
	pH	Glucose
	Specific gravity	Ketones
	Blood	

Laboratory Assessments	Parameters
	If dipstick findings are abnormal, a microscopic examination is to be performed
Pregnancy Testing	Serum pregnancy test at Screening, Cycle 1 Day 1 (within 72 hours prior), Cycle 4 Day 1 and Day 1 of every subsequent 4 cycles (i.e., Cycle 8 Day 1, Cycle 12 Day 1, etc.). The screening serum pregnancy test can be used as the test prior to Day 1 study treatment if it is performed within the prior 72 hours. Additional tests may be ordered at the Investigator's discretion. Positive urine test should be confirmed with a serum pregnancy test. Follicle stimulating hormone (FSH) test is required for postmenopausal women only.

10.6 Contraceptive Guidance

10.6.1 Definitions

10.6.1.1 Females of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

10.6.1.2 Postmenopausal Female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L is required.

Females on HRT whose menopausal status is not confirmed will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.2 Fertile Males

A man is considered fertile after puberty (Tanner Stage II) unless permanently sterile by bilateral orchidectomy or vasectomy with medical assessment of surgical success.

10.6.3 Highly Effective Contraception

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods (Clinical Trials Facilitation Group 2014[12]). Such methods include:

- Combined (estrogen and progestin containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progestin-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner, provided that partner is the sole sexual partner of the female study participant and that the vasectomized partner has received medical assessment of the surgical success.

- Sexual abstinence- only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

10.6.4 Acceptable Birth Control Methods that are not Highly Effective Contraception

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestin-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also acceptable, but not highly effective, birth control methods.

10.6.5 Unacceptable Contraception Methods

- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicides only.
- Lactational amenorrhea method.
- Combination of male and female condoms.

10.6.6 Female Contraception Guidance

Females of childbearing potential (FOCBP) may only be enrolled after confirming a negative highly sensitive serum pregnancy test during Screening and a urine or serum pregnancy test within 72 hours prior to receiving the first study drug administration.

It is required that FOCBP agree to use at least 2 effective contraceptive methods (1 highly effective method in combination with a barrier method; oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner), one of which must be barrier, from signing the ICF date of ICF signature, throughout the study, and for up to 5 months following the last dose of TJ004309.

10.6.7 Male Contraception Guidance

Males must agree to use a condom (a latex condom is recommended) during sexual contact with a pregnant female or a female of childbearing potential and will avoid donation of sperm or having a female partner conceive from the time of date of ICF signature, while participating in the study, during dose interruptions, and for at least 5 months after the last dose of study

treatment, even if he has undergone a successful vasectomy. Consider contraception for the FOCBP partner.

10.6.8 Collection of Pregnancy Information

Pregnancy testing should be performed at monthly intervals in female participants. Female partners of male patients are also recommended to have pregnancy testing performed at monthly intervals.

10.6.8.1 Female Participants who Become Pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the Pregnancy Reporting form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.

Any female patient who becomes pregnant while participating in the study must immediately discontinue study drug.

10.6.8.2 Male Patients with Female Partners who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male participant is in this study. This applies only to male patients who receive study drug.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.

11 SUMMARY OF CHANGES (SOC)

List of Minor/Administrative Changes:

- Table of Contents was updated to reflect changes in protocol.
- List of Tables and Figures was updated to reflect changes in protocol.
- Minor changes were made to correct inconsistencies, typographical and grammatical errors.
- Updated References

Detailed Summary of Changes Version 2:

Changes made from Protocol v2.0	Rationale	Relevant Section(s)
Updated safety follow-up period to 90 days.	Per FDA request the safety follow up period has been extended to 90 days.	- Changes made throughout - Table 3: Schedule of Assessments
Added term IMP to list of abbreviations	The abbreviation IMP is used in the body of the protocol and was not included in the past list of abbreviations	- List of Abbreviations
Updated IC #4a to include 'any' high-grade serous component	This is to clarify that any high-grade serous component is acceptable for IC #4a.	- Synopsis – Inclusion Criteria - Section 5.1 – Inclusion Criteria
Removed language "such patients must have recovered adequately from any side effects of such therapy"	This is an exclusion criterion so the language is not necessary.	- Synopsis – Exclusion Criteria - Section 5.2 – Exclusion Criteria
Updated pleural ascites drainage language	Removed (<1 drainage) language to be definitive	- Synopsis – Exclusion Criteria - Section 5.2 – Exclusion Criteria
Added TSH to SOC	Atezo single agent does not seem to affect thyroid functions vs combo therapy with atezo, where hypo/hyperthyroidism is more prevalent.	- Schedule of Assessments
Removed language for no protocol waivers or exemptions	Removed: "Protocol waivers or exemptions to the inclusion and exclusion criteria are not permitted." as IC #6 allows discussion with Medical	- Section 5: Study Population

Changes made from Protocol v2.0	Rationale	Relevant Section(s)
	Monitor.	
Added section 4.5 Safety Follow-up Period to body of protocol	This is included in the Synopsis but was previously not included in the body of the protocol.	- Section 4.5
Added Section 4.6 Response/Survival Follow-up Period	This is included in the Synopsis but was previously not included in the body of the protocol	- Section 4.6
Clarified disease progression SAE requirement	The previous language was not clear that progression of leading to death should be reported as an SAE.	- 8.3.2.2

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13 APPENDICES

Appendix 1: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and Immune-related RECIST

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST 1.1 and iRECIST.

Tumor evaluation must include thoracic, abdominal, and pelvic imaging. This anatomic coverage is appropriate for both baseline imaging and on-treatment imaging.

Contrast-enhanced computed tomography (CT) is the preferred method to measure lesions selected for response assessment. This protocol has defined measurability of lesions when CT slice thickness is 5 mm or less. Magnetic resonance imaging (MRI), typically with gadolinium-based intravenous (IV) contrast, is also acceptable in certain situations, positron emission tomography (PET)-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of the same diagnostic quality to a diagnostic CT (with IV and oral contrast).

RECIST

Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1. Rules described in the following for CT are equally valid for MRI.

Measurable disease

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan
- 10 mm caliper measurement by clinical exam
- 20 mm by chest x-ray

Computed tomography is strongly recommended.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion,

inflammatory breast disease, lymphangitic involvement of skin or lung. Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions, or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet radiographic criteria for simple cysts should not be considered malignant lesions (neither measurable nor non-measurable).
- "Cystic lesions" thought to be cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. However, if non-cystic lesions are present in the same participants, these should be preferably selected for assessment.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes (with short axis ≥10 mm and <15 mm) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response Criteria: The BOR is the best response recorded from the start of the study treatment until the end of treatment. The subject's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have decreased in size to have a short axis of <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, unequivocal progression (see comments below) of existing lesions represents PD. Note: the appearance of one or more new lesions is also considered progression.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

To achieve unequivocal progression in participants with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

In the absence of measurable disease, the same general concepts apply here as noted above.

Target and Non-target Lesion Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration."
Every effort should be made to document the objective progression even after discontinuation of treatment.

Response duration

The duration of OS is measured from the time measurement criteria are initially met for CR/PR (whichever is initially recorded) until the initially date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are initially met for CR until the initially date that recurrent disease is objectively documented.

Stable disease (SD) duration

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective.

CT/MRI - CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm which requires a slice thickness. An MRI is also acceptable in certain situations.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about the radiation exposure at CT, MRI may be used instead of CT in selected instances.

Tumor markers: tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a participant to be considered in CR.

When effusions are known to be a potential adverse effect of treatment (e.g., angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

iRECIST

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using iRECIST for participant management. This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 13 and may be submitted to a central imaging vendor during the study per Sponsor's request.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.

- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

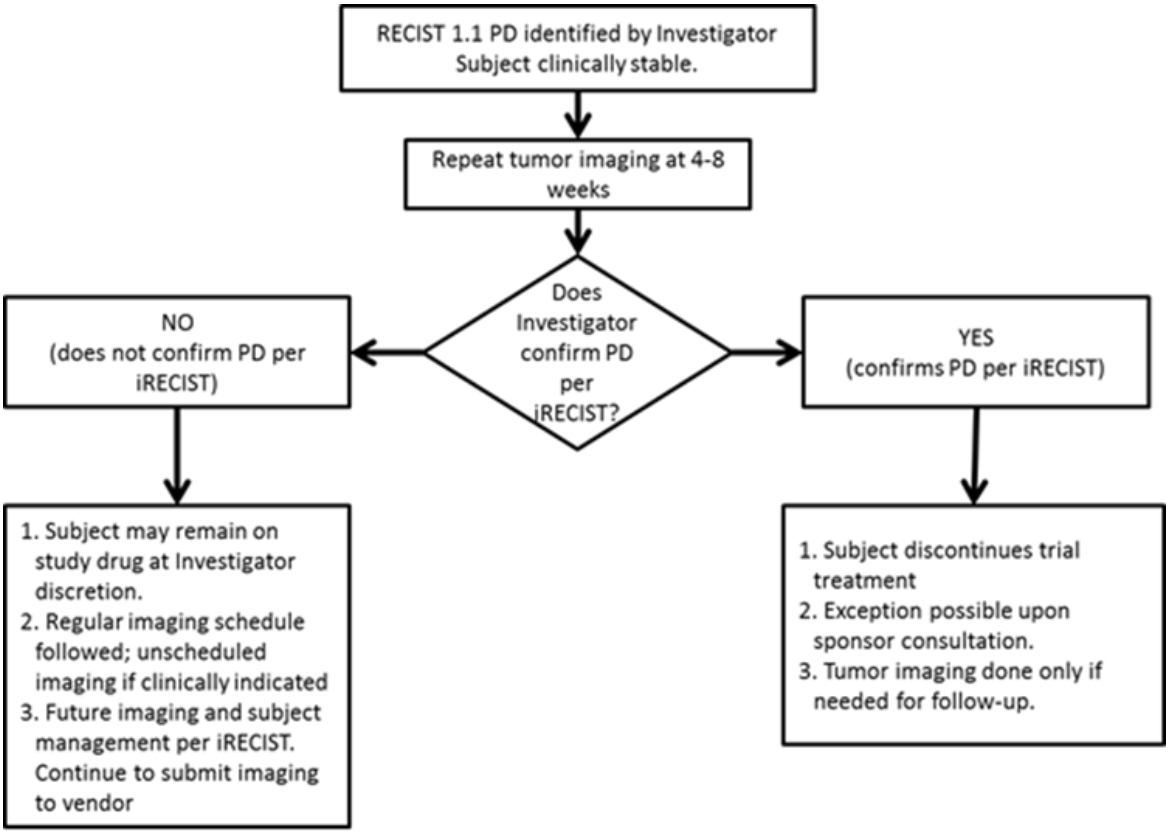
The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 [For those studies in which PFS is the primary endpoint, add the following: that has been verified by BICR]	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	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. Next tumor imaging should occur according to the regular imaging schedule.

BICR = Blinded Independent Central Review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.; VOP=verification of progression

Imaging and Treatment for Clinically Stable Participants Treated with TJ004309 after First Radiologic Evidence of PD Assessed by the Investigator



Comparison of RECIST 1.1 and iRECIST Criteria

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances —eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Sources:

Eisenhauer EA, Therassse P, Boggaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247. doi: 10.1016/j.ejca.2008.10.026.

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-e152. doi: 10.1016/S1470-2045(17)30074-8.