TITLE: A Phase II trial of retifanlimab (INCMGA00012) in patients with previously treated unresectable or metastatic adenosquamous pancreatic or ampullary cancer

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1. OBJECTIVES

1.1 Primary Objectives

To determine the disease control rate (DCR) at 4 months using Response Evaluation Criteria for Solid Tumors (RECIST 1.1) in subjects with previously treated unresectable or metastatic adenosquamous pancreatic or ampullary cancer (ASQ) treated with retifanlimab.

1.2 Secondary Objectives

1.2.1 To determine the objective response rate (ORR) using RECIST 1.1.
1.2.2 To assess progression-free survival (PFS).
1.2.3 To characterize the treatment-related adverse events attributable to retifanlimab.

1.3 Exploratory Objectives

1.3.1 To assess overall survival (OS).
1.3.2 To assess duration of response (DOR) and time to progression (TTP).
1.3.3 To assess the DCR, ORR, PFS, and DOR by immune RECIST (iRECIST).
1.3.4 To identify potential biomarker predictors of response versus resistance to retifanlimab and autoimmune toxicity in plasma samples.
1.3.5 To test for predictors of response and resistance and explore changes in the tumor microenvironment (TME) following retifanlimab treatment in collected archived tissue and pre- and post-treatment biopsies via immunohistochemical studies.
1.3.6 Measure tumor marker kinetics (CA 19-9) in subjects receiving treatment and correlate with OS, PFS, and best overall response.
1.3.7 Measure tumor mutation burden, microsatellite instability, and profile genetic abnormalities in treated patients and correlate with response and resistance to therapy.

1.4 Study Design

This is multi-center two stage phase 2 study to evaluate the clinical activity of retifanlimab in patients with unresectable or metastatic ASQ. This study will enroll subjects who have progressed after at least 1 prior chemotherapy regimen, have been deemed unfit for cytotoxic chemotherapy or who have refused cytotoxic chemotherapy. The primary endpoint of this study will be disease control rate (DCR) at 4 months following the start of treatment using RECIST 1.1. Up to 25 subjects will be enrolled to target 21 evaluable patients.

The study will consist of a screening period (within 21 days of first dose), a treatment period per the table below (**Section 10**), and a follow-up period. Subjects will receive a baseline biopsy and then be treated with the anti-PD1 antibody retifanlimab every 4 weeks. After 2 doses (8 weeks), subjects will be assessed for response with imaging and laboratory tests and receive another research biopsy. For patients with stable disease or tumor response and clinical benefit, retifanlimab will be continued until disease progression or unacceptable toxicity. Patients will be evaluated radiographically after every 2 doses of retifanlimab (every 8 weeks). Subjects will come

to the clinic for dosing and assessments on Day 1 of each cycle. Assessment will consist of 1) physician evaluation to assess symptoms of tumor response or progression and potential drug related toxicity, 2) cross sectional imaging (CT scans), 3) CA19-9 blood levels. Additional visits for safety and immune monitoring follow-up will occur per the study calendar in **Section 10**.

No dose escalations or reductions are allowed. Enrollment will continue until 21 subjects have received at least one dose of retifanlimab and completed one cycle of therapy. The null hypothesis that the DCR 4 months following the start of treatment is 5% will be tested against a one-sided alternative (DCR of 30%).

Complete unacceptable toxicity criteria can be found in **Section 5.7**. At the investigator's discretion, subjects may receive additional cycles of treatment if they are clinically stable and meet dosing eligibility criteria. All subjects may continue in the treatment period until the criteria in **Section 5.9** are met. Subjects may continue on treatment with radiographic disease progression if clinically stable and investigator believes the treatment is providing benefit. Subjects will be considered in the treatment period until 28 days after the last dose of study drug.

Patients who have a confirmed complete response by two scans ≥ 4 weeks apart and who have been on retifanlimab treatment for at least 6 months may discontinue retifanlimab treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. Patients with SD, PR or CR that received at least 24 months of retifanlimab may also discontinue retifanlimab at the discretion of the investigator. Retifanlimab may be resumed upon disease recurrence or progression in these patients. Criteria and procedures for retreatment are described in Sections 5.9.2 and 10.0.

After completion of treatment and end of treatment (EOT) visit assessments, all subjects, including those who did not receive treatment, will continue to be followed every three months (± 2 weeks) by telephone, e-mail, or optional clinic visit until death, withdrawal of consent, or closure of study. Subjects will also be contacted at 90 days (+14 day reporting window) from the last dose of therapy. Information on survival and new cancer therapies will be collected. All subjects who discontinue study treatment should continue to be monitored for disease status by radiologic imaging every two months (± 2 weeks) until: 1) the start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) the close of the study, whichever occurs first. All subjects will be followed after their last dose of study drug for the development of adverse events (AEs) and serious adverse events (SAEs) as described in **Section 7.5**.

The primary analysis will be conducted 4 months after the last enrolled subject begins treatment, or all patients have either come off study or have completed 4 months on study. Information on survival may continue to be gathered for supplementary analyses after the completion of the primary analysis.

2. BACKGROUND

2.1 Study Disease

Pancreatic cancer is estimated to be the second leading cause of cancer-related death in the US by 2030[1]. It is one of the deadliest cancers – it has the lowest 5 year survival rate of all cancer types with most patients being diagnosed with advanced disease with a median survival less than 1 year[2]. In unresectable and metastatic patients standard regimens only include cytotoxic chemotherapy. As far as single agents – gemcitabine reports a median survival of 5.65 to 6.8 months and overall tumor response rates are 5.4 to 9.4% [3]. To achieve reasonable response rates multiagent regimens are utilized. The FOLFIRINOX regimen utilizes a combination of oxaliplatin, irinotecan, fluorouracil, and leucovorin. Response rates are 31.6% and estimated median OS is 11.1 months[4]. Another established combination regimen is *nab*-paclitaxel combined with gemcitabine with ORR of 23% and median OS of 8.5 months[5]. As expected these multiagent cytotoxic regimens cause significant toxicity and are often reserved for the fittest patients. This trial involves a targeted approach to treating a subtype of pancreatic adenocarcinoma with the goal to establish immunotherapy in this deadly disease.

ASQ of the pancreas constitutes 1 to 5% of all pancreatic cancers and compared to pancreatic adenocarcinoma has a worse survival. ASQs have glandular and squamous histologic components (>30% squamous component for the diagnosis) and are considered a variant of pancreatic ductal adenocarcinomas. Given its rarity and aggressiveness, systemic therapy has not been well studied in ASQ and in practice a cytotoxic chemotherapy treatment paradigm is pursued in advanced disease with overall poor outcomes[6]. In addition, there is no data regarding the efficacy of immune checkpoint inhibition in ASQ pancreatic cancer, and most clinical trials have excluded them from eligibility.

2.2 Rationale

Immunotherapies in Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is considered an immune quiescent tumor and single agent checkpoint blockade has had an overall disappointing impact on survival (including targeting PD-1, PD-L1 and CTLA-4)[7–9]. Immunotherapeutic approaches have shown some ability to "reprogram" the immune tumor microenvironment (TME) within pancreatic tumors[10–12]. Several studies have also described the clinical and prognostic significance of PD-L1 expression in pancreatic cancer including higher expression levels predicting a poor prognosis further suggesting the immune TME influences pancreatic tumor behavior[13–15]. In an effort to identify patient subgroups most likely to respond to immunotherapy, the immune TME in the rare pancreas cancer histological subtype - adenosquamous carcinoma (ASQ) was evaluated by our team. Indeed a recent article reported high PD-L1 expression in a series of ASQ cases (5 of 6 surgical cases)[16].

Tumor microenvironment of adenosquamous pancreatic cancer subtype

[redacted]

[redacted]

[redacted]

[redacted]

Retifanlimab and its dose selection

[redacted]

[redacted]

Hypothesis

Retifanlimab treatment will have clinical activity in patients with ASQ, a subtype of pancreatic and ampullary cancer that has a dynamic tumor microenvironment.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Age ≥18 years.

3.1.2 Have histologically- or cytologically-proven adenosquamous carcinoma of the pancreas or ampulla by pathologic review. Patients must have squamous component to be included. All pathology will be reviewed by Johns Hopkins or Cedars-Sinai Department of Pathology.

3.1.3 Have unresectable or metastatic disease.

3.1.4 Must have received (or been intolerant to, ineligible for, or refused) at least 1 prior line of cytotoxic chemotherapy and received no more than 2 prior systemic treatments.

3.1.5 Presence of at least one lesion with measurable disease as defined by 10 mm in longest diameter for a soft tissue lesions or 15 mm in short axis for a lymph node by RECIST 1.1.

3.1.6 Patient's acceptance to have a tumor biopsy of an accessible lesion at baseline and on treatment if the lesion can be biopsied with acceptable clinical risk (as judged by the investigator).

3.1.7 ECOG performance status 0 or 1 (**Appendix A**).

3.1.8 If HIV-positive, then all of the following criteria must also be met: CD4+ count ≥ 350/μL, undetectable viral load, and receiving highly active antiretroviral therapy.

3.1.9 Life expectancy of greater than 3 months.

3.1.10 Adequate organ and marrow function as defined below:

- Leukocytes ≥ 3,000/mcL
- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 75×10^3/uL
- Hemoglobin ≥ 8.0 g/dL
- Total bilirubin ≤ upper limit of normal (ULN) except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL
- AST(SGOT) and ALT(SGPT) ≤2.5 × ULN
- Alkaline phosphatase ≤5.0 × ULN
- Creatinine ≤1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

- Albumin ≥2.5 g/dL

3.1.11 Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]). WOCBP is defined in **Section 5.7. NOTE:** If a patient has a positive or indeterminate serum or urine pregnancy test, then an ultrasound must be done to rule out pregnancy to enroll on trial.

- WOCBP must agree to follow instructions for method(s) of contraception from the time of screening, through the duration of treatment with study drug plus 6 months after the last dose of study drug.

- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception from the time of screening, through the duration of treatment with study drug plus 6 months after the last dose of study drug.

- At least one barrier method of contraception must be employed by all sexually active patients (male and female), regardless of other methods, to prevent the transfer of body fluids.

3.1.12 Ability to understand and willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients with known MSI-H / dMMR adenosquamous pancreatic or ampullary cancer

3.2.2 Patient has a known history or evidence of active brain/CNS metastases. Patients with treated brain/CNS metastases by surgery or radiation who are not on steroid therapy for this indication and have a stable MRI brain for 3 months are eligible for the study.

3.2.3 Patient who has had chemotherapy, radiation, or biological cancer therapy within 14 days prior to the first dose of study drug. With the following caveats: 28 days for pelvic radiotherapy, 6 months for thoracic region radiotherapy that is > 30 Gy. Hormonal therapy in the setting of a second, hormone-sensitive malignancy not thought to have impact on longevity (i.e. prostate cancer, early stage breast cancer) are allowed at the discretion of the principal investigator.

3.2.4 Patient has received an antineoplastic investigational agent or used an investigational device within 28 days of the first dose of study drug.

3.2.5 Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study. Exceptions are hormonal therapy in the setting of a second, hormone-sensitive malignancy not thought to have impact on longevity (i.e. prostate cancer, early stage breast cancer)

3.2.6 Patients who have had major surgery within 28 days of dosing of investigational agent, excluding minor procedures (dental work, skin biopsy, port placement, etc.), celiac plexus block, biliary stent placement, etc.

3.2.7 Patients who have received a live vaccine within 28 days prior to the first dose of study drug. Seasonal influenza vaccines for injection are generally killed virus and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.

3.2.8 Patients with a history of prior treatment with immune checkpoint inhibitor therapy including anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4, anti-OX40, and anti-LAG-3 antibodies.

3.2.9 Have used any systemic steroids within 14 days of study treatment.

3.2.10 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.11 Evidence of clinically significant ascites, defined as requiring a paracentesis within the last 3 weeks OR clinical symptoms with palpable ascites on exam

3.2.12 Have clinically significant and/or malignant pleural effusion (pleural effusions that are not clinically significant are allowed, defined as no more than 25% fluid level of the corresponding hemithorax and stable fluid level [non-progressive] over at least 6 weeks documented radiographically).

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14 History of autoimmune disease requiring systemic immunosuppression within the last 2 years.

3.2.15 Presence of any tissue or organ allograft, regardless of need for immunosuppression, including corneal allograft. Patients with a history of allogeneic hematopoietic stem cell transplant will be excluded.

3.2.16 All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 5.0) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long-lasting sequelae, such as neuropathy after chemotherapy, are permitted to enroll.

3.2.17 Known active HAV, HBV, or HCV infection, as defined by elevated transaminases with the following serology: positivity for HAV IgM antibody, anti-HCV, anti-HBc IgG or IgM, or HBsAg (in the absence of serology suggesting prior immunization or achieve immunity). Patients who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening.

3.2.18 Patient has a pulse oximetry of $\leq$92% on room air.

3.2.19 Patient is on supplemental home oxygen.

3.2.20 Patient has an unhealed surgical wound or ulcer, or a bone fracture considered non-healing.

3.2.21 Patient has clinically significant heart disease (such as uncontrolled angina, myocardial infarction within the last 3 months or congestive heart failure of New York Heart Association III or IV).

3.2.22 Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or other substance abuse (including alcohol) that could potentially interfere with adherence to study procedures or requirements.

3.2.23 Patient is unwilling or unable to follow the study schedule for any reason.

3.2.24 Patient has history of non-infectious pneumonitis.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION

4.1 General Guidelines

Eligible patients will be entered on study at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator. All sites should contact the Lead Study Coordinator to verify ongoing study enrollment.

If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

To register a patient, the following de-identified documents should be completed and sent to the Lead Study Coordinator[redacted]

- Registration Form
- Signed patient consent form
- Eligibility Checklist
- Copy of required screening tests and scans

To complete the registration process, the Lead Study Coordinator will:

- Assign a patient study number
- Register the patient on the study

5. TREATMENT PLAN

5.1 Retifanlimab Administration

Treatment will be administered on an outpatient basis. Dosing delays are described in **Section 6.2**. No investigational or commercial agents or therapies other than retifanlimab may be administered with the intent to treat the subject's malignancy.

SUMMARY DESCRIPTION				
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Cycle Length***
Retifanlimab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 5.2**.	500 mg	IV infusion over 30 minutes*	28 days

*Infusion times are approximate (-5/ +15 min) and may need to be adjusted based on subject tolerability.

5.2 General Concomitant Medication and Supportive Care Guidelines

Retifanlimab is a fully human monoclonal immunoglobulin (Ig) G44κ antibody. Subjects should be closely monitored for potential AEs during antibody infusion and potential AEs throughout the study.

5.2.1 Infusion Reactions

Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.

Guidelines for management of suspected infusion reactions are provided in **Table 1**.

Table 1: Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a)]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (e.g., IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue study treatment.	Premedicate at least 30 minutes before infusion with antihistamines (e.g., diphenhydramine 50 mg PO) and acetaminophen/ paracetamol (500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increase by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (e.g., IV fluids, antihistamines NSAIDS, acetaminophen/ paracetamol, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment.

[a)] Per NCI CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration.

Please refer to **Section 6.2** for guidelines to manage treatment delays due to retifanlimab infusion-related reactions.

5.2.2 Retifanlimab Related Adverse Events

Blocking PD-1 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/pruritus, diarrhea/colitis, pneumonitis, hepatitis, and hypothyroidism were drug-related, presumptive autoimmune events noted in previous anti-PD1 studies.

For the purposes of this study, a retifanlimab-related AE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected retifanlimab-related AEs must be documented on an AE or SAE CRF. Identification and treatment of retifanlimab-related AEs can be found in NCCN's guidelines for the management of immunotherapy-related toxicities. Additional guidance can be found in the Retifanlimab Investigator's Brochures (IB).

5.3 Prohibited and/or Restricted Medications and Devices

The following therapies or devices are not permitted during the treatment period (if administered, the subject may be removed from the study):

- Immunosuppressive agents unless they are utilized to treat an AE or as specified in **Sections 5.2** and **5.6**.
- Any non-study anticancer chemotherapy or immunotherapy (approved or investigational) with the exception of subjects in the survival period of the study, with the exception of hormonal therapy in the setting of a second, hormone-sensitive malignancy not thought to have impact on longevity (i.e. prostate cancer, early stage breast cancer)
- Any major surgery or surgical procedure; if required must be discussed with the IND Sponsor to determine if it is appropriate for the subject to continue study treatment
- Another investigational agent
- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Palliative (limited-field) radiation therapy is permitted, but only for pain control and with approval by the IND Sponsor.
- Systemically active steroids can be used but should be reported to the IND Sponsor. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments. Patients requiring adrenal replacement steroid doses $\leq$ 10 mg daily prednisone equivalent (in the absence of active autoimmune disease) may resume treatment if approved by the IND Sponsor.
- Use of growth factors unless prior discussion and agreement with the IND Sponsor.
- Use of allergen hyposensitization therapy

5.4 Other Restrictions and Precautions

Palliative (limited-field) radiation therapy is permitted, but only for pain control to sites present at baseline and with approval by the IND Sponsor.

Medical marijuana for pain or symptom control will be permitted.

5.5 Definition of an Overdose for this Protocol

Overdose of retifanlimab is defined as:
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see **Section 7.5.1** for reporting details). Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose with and without an AE must be reported within 24 hours to the IND Sponsor and Incyte. Incyte contact information can be found in **Section 7.5.1**.

5.6 Unacceptable Toxicity

Toxicities are defined in the Investigator's Brochure and **Table 4**. Unacceptable toxicities for this protocol that will trigger additional review described below are defined as:

1. Any treatment-related ≥ grade 3 AEs. Exceptions include:

    - Asymptomatic laboratory abnormalities (AST, ALT, and bilirubin abnormalities requiring discontinuation as per **Table 4** will be considered unacceptable toxicity)
    - Grade 3 fatigue
    - Grade 3 dermatologic AEs that are considered mild in severity but only considered grade 3 because of >30% body surface involvement including pruritus
    - Diarrhea, nausea, or vomiting that resolves to < grade 3 within 48 hours of maximal intervention
    - Grade 3-4 hyperglycemia or grade 3 endocrinopathies where symptoms are controlled on hormone replacement therapy

2. Treatment related blood bilirubin > 5 x ULN or concurrent blood bilirubin > 2 x ULN and AST or ALT > 3 x ULN

3. Treatment related eye pain ≥ grade 2 or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy is an unacceptable toxicity.

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

The proportion of treated subjects with unacceptable toxicity will be monitored using a Bayesian stopping guideline. A Beta (1.5, 5.5) prior, representing a toxicity rate of 21%, a slightly conservative estimate, was used in the development of our guidelines. We will halt the accrual and re-evaluate the safety if the posterior probability that the toxicity rate exceeds the 33% boundary is greater than 60%. Toxicity will be monitored continuously. **Table 2** summarizes the stopping boundaries for unacceptable toxicities.

Table 2. The number of unacceptable toxicities needed to trigger stopping guidelines throughout the course of the study.

Number of Subjects	**Number of unacceptable toxicities needed to trigger re-evaluation**
2	2
3-5	3
6-7	4
5-10	5
11-13	6
14-16	7
17-19	8
20-22	9
23-25	10

Table 3. Probability of triggering a re-evaluation based upon the proportion with an unacceptable toxicity for a range of true toxicity probabilities.

True probability of unacceptable toxicity	Probability of triggering stopping guidelines
5%	0.4%
10%	1.8%
15%	6%
20%	14%
25%	27.5%
30%	44.9%
35%	62.3%
40%	78%
45%	89.2%

5.7 WOCBP, Contraception, Use in Pregnancy, Use in Nursing

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 62 years must have a documented serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause.

Women treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

5.7.1 Contraception

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 6 months after the end of study treatment.*****

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*

- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in **Section 10**.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 6 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 6 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 6 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 6 months after the end of study treatment.

5.7.2 Use in Pregnancy

The investigational agents used in this protocol may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

Pregnancy in female subjects or in partners of male subjects throughout the study or within 6 months of completing treatment should be reported initially as a serious adverse event (see reporting procedures in **Section 7.5.6**) by the investigator within 24 hours of learning of its occurrence. Pregnancy information must be reported on the Pregnancy Form.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Follow-up information regarding the course of the pregnancy, including any voluntary or spontaneous termination, perinatal and neonatal outcome and where applicable, offspring information must be reported on the Pregnancy Follow-up Form. Pregnancy outcomes must also be collected for the female partners of any males in this trial. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

5.7.3 Use in Nursing Women

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

5.7.4 All Subjects (Male and Female)

All sexually active patients must use at least a barrier method (i.e., condom) to prevent transmission of body fluids.

5.8 Duration of Therapy

Subjects who are clinically stable and meet dosing requirements (per **Section 6.2**) may continue to receive treatment until the criteria in **Section 5.9** are met.

5.9 Criteria for Removal from Treatment

The reason for study removal and the date the subject was removed will be documented in the CRF.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for participation in the study.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable toxicity (see **Section 5.6**). Exceptions for treatment discontinuation are listed in **Section 5.6**,
- Disease progression as defined in **Section 5.9.1,**
- Severe or life-threatening retifanlimab-related AE(s) (see **Section 6.2**),
- Need for >2 dose delays due to the same drug-related toxicity as per the dose delay guidelines (see **Section 6.2**),
- If, in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the subject,
- Noncompliance with trial treatment or procedure requirements,
- Subject is lost to follow-up, or
- Subject becomes pregnant.

A subject may, at the discretion of the Investigator, be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) if they have:

- Completed 6 months of treatment with retifanlimab and has a complete response (CR) by at least two scans ≥ 4 weeks apart AND have received at least two doses of retifanlimab beyond the initial determination of CR.
- Completed 24 months of treatment with retifanlimab and has a response of stable disease, partial response, or complete response at the time of discontinuation

  Note: time on treatment is calculated from the date of first dose.

5.9.1 Disease Progression

Retifanlimab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some subjects may have objective volume increase of tumor lesions or other disease parameters within weeks following the start of immunotherapy. Such subjects may not have had sufficient time to develop the required immune activation or, in some subjects, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 2-4 months of the study would constitute disease progression and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Subjects will be permitted to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assesses that the patient is not clinically deteriorating, and
- Subject is tolerating study drug.

The assessment of lack of deterioration should take into account whether the subject is clinically stable or if they unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- No significant decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

All decisions to continue treatment beyond PD must be discussed with the IND Sponsor and documented in the study records.

Tumor assessments will be made using RECIST 1.1 (**Appendix B**) and iRECIST (**Appendix C**).

5.9.2 Retreatment with Retifanlimab

Patients who stop retifanlimab with SD or better may be eligible for resume therapy if they progress after stopping retifanlimab and they meet the following criteria:

EITHER

- Stopped initial treatment with retifanlimab after attaining an investigator determined confirmed CR according to RECIST 1.1, was treated for at least 6 months with retifanlimab, and received at least two doses of retifanlimab beyond the date when the initial CR was declared.

OR

- Subject had SD, PR or CR and stopped retifanlimab treatment after 24 months of study drug for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic or clinical disease progression after stopping their initial treatment with retifanlimab
- Did not receive any anti-cancer treatment since the last dose of retifanlimab
- Have an ECOG performance status of 0-2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 3 days prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to follow instructions for method(s) of contraception or abstain from heterosexual activity for the course of the study through 6 months after the last dose of study drug.
- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 6 months after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment should resume at the next cycle which they would have received prior to discontinuation. Study visit requirements are outlined in the Study Calendar (Section 10.0).

5.10 End of Treatment (EOT) Visit

All subjects will return to the study site 28 days (± 7 days) after the final study treatment for an EOT evaluation. Procedures and assessments performed at these visits and beyond should follow the respective guidelines described in **Sections 5.11 and 10.0** as appropriate.

If the EOT visit occurs early (e.g., 1 week prior to the expected visit as protocol allows) or if the patient cannot return due to disease progression, an assessment for AEs should be made by telephone or email on day 28 (± 1 day) after last dose of study drug and documented.

For subjects who discontinue study drug after 24 months of SD or better or with a CR after 6 months (see Section 5.9.2), the EOT visit should be completed as described above. If a patient later restarts study drug, they should have a second EOT visit performed when they eventually discontinue study drug for a second time.

5.11 Duration of Follow-Up

5.12.1 Safety Follow-up

Subjects who discontinue treatment should be contacted by telephone or email at 90 days (+14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

5.12.2 Clinical Follow-up

Subjects who discontinue treatment without disease progression should continue to be monitored for disease status by radiologic imaging. Disease monitoring should continue to be assessed every two months (± 2 weeks) for the first 2 years and then every 3 months (± 4 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first.

5.12.3 Survival Follow-up

Subjects who discontinue treatment and have disease progression will enter the survival follow-up portion of the trial. Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

6. DOSE MODIFICATION, DELAYS AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-RELATED AES

6.1 Dose Modifications

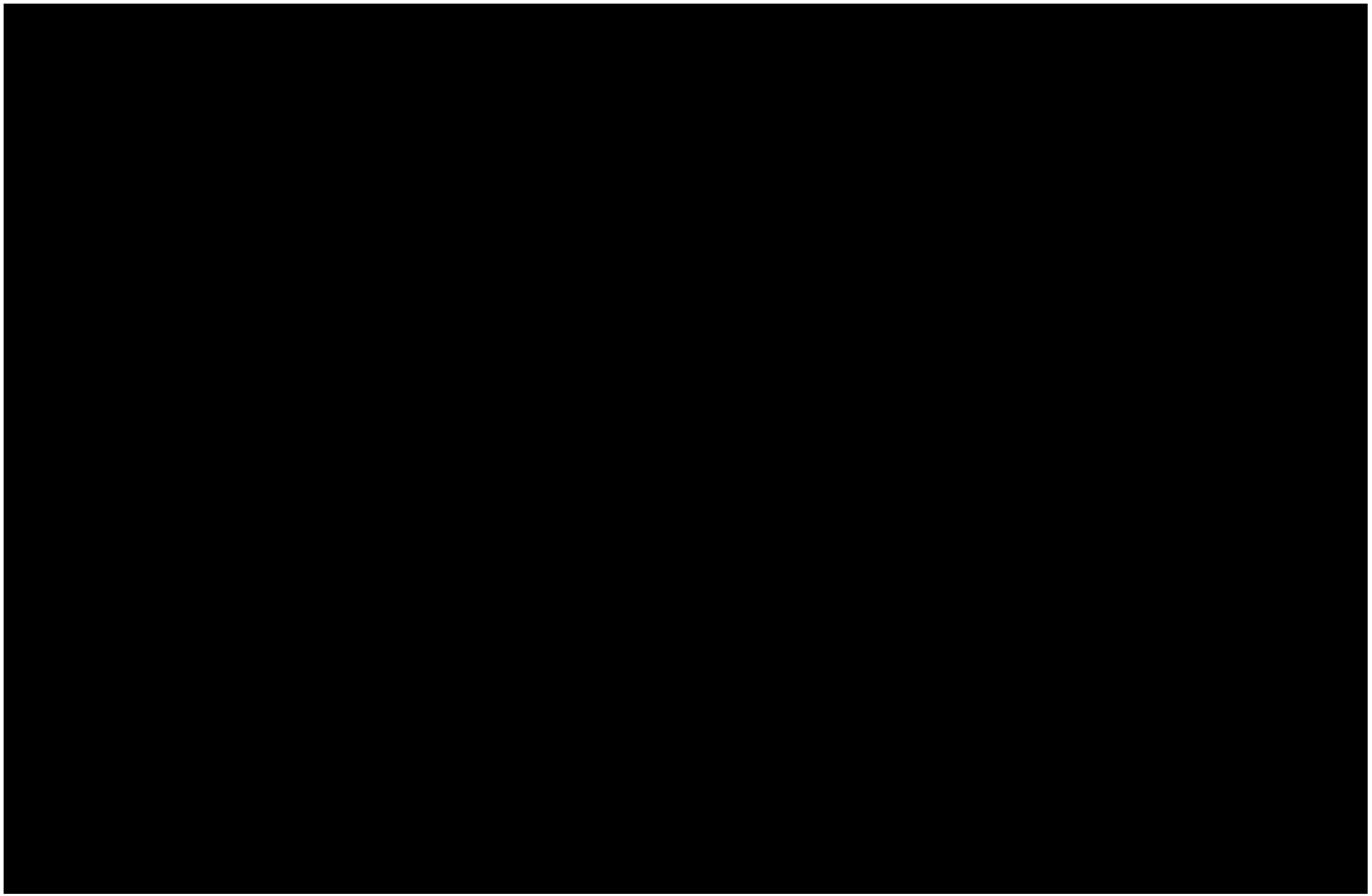
Subjects will be monitored continuously for AEs while on study drug. Subjects will be instructed to notify their physician immediately for any and all AEs. Dose escalations or reductions of retifanlimab will not be allowed.

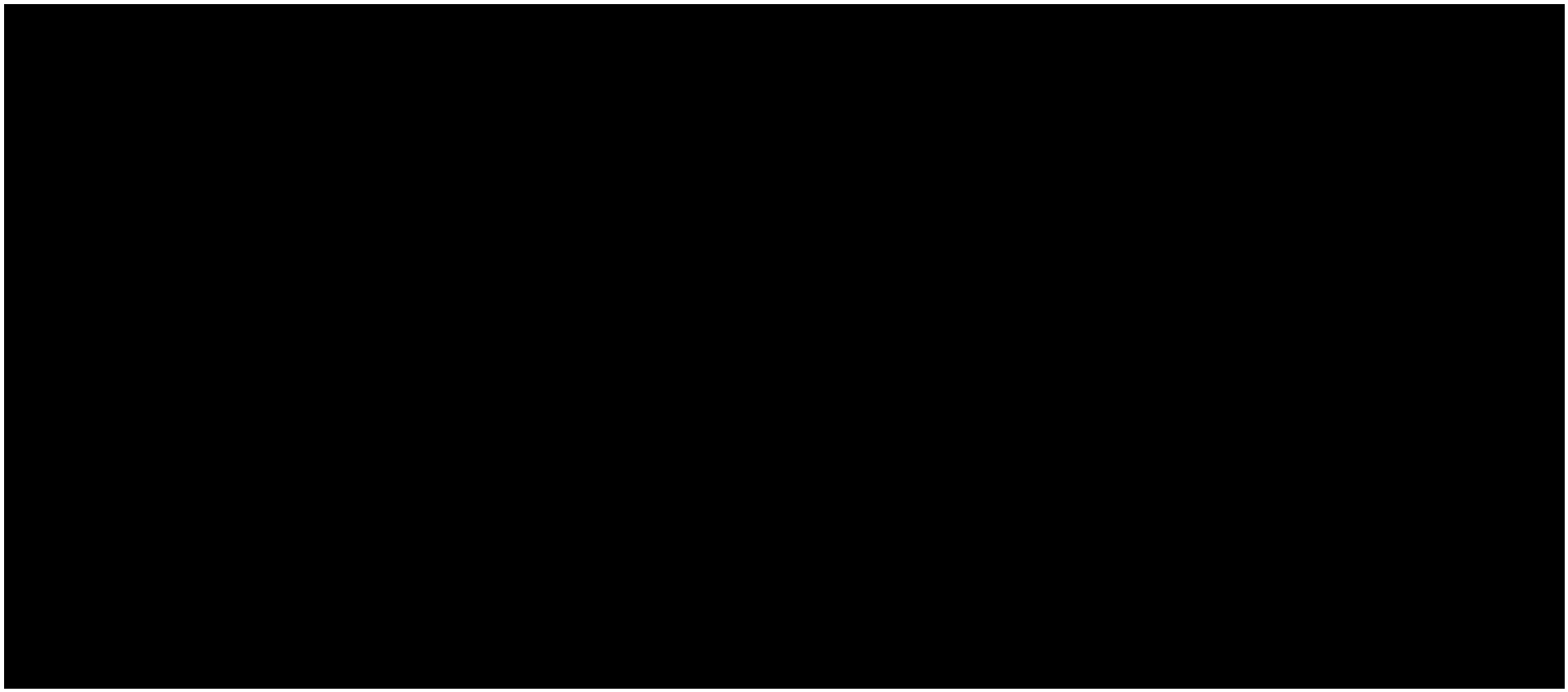
6.2 Dose Delays and Discontinuation

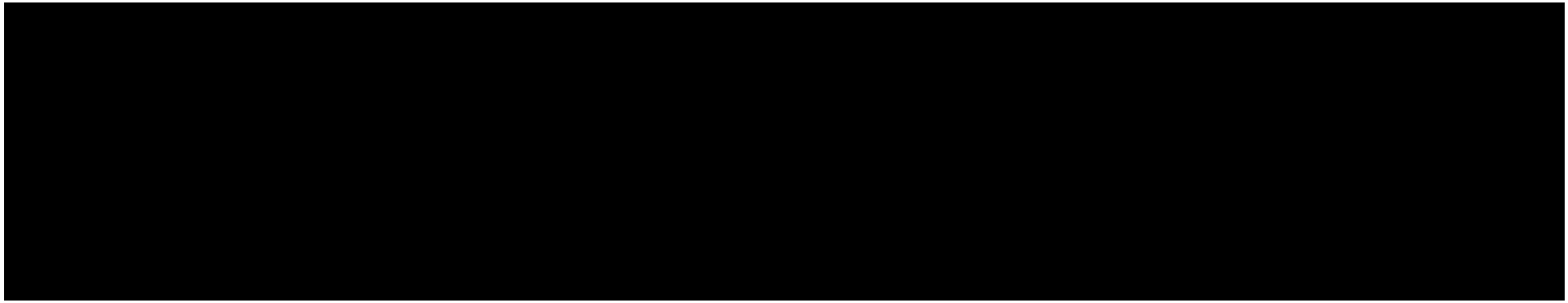
Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. If an irAE is suspected,

efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE.

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (e.g., pembrolizumab, nivolumab) are detailed in **Table 4** (below). Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the Protocol should follow the ASCO or ESMO Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2017).







7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised CTCAE version 5.0 for AE reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

7.1 Definitions

7.1.1 Adverse Event

An AE is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered AEs if they worsen after starting the study treatment (any procedures specified in the protocol). New medical conditions / diseases occurring before starting the study treatment but after signing the informed consent form will not be recorded as AEs. Additionally, expected progression of the disease being studied will not be recorded as an adverse event.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator (induce clinical signs or symptoms or require therapy), meets the definition of an SAE, or requires the participant to have study drug discontinued or interrupted..

7.1.2 Serious Adverse Event

A SAE is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) for >24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon

appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.

Events **not** considered to be SAEs are hospitalizations for:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE.

7.2 Assessment of Causality

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Assessment of Grade:

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experienced by the subject.

7.3 Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered "unexpected". An expected AE with a fatal outcome should be considered unexpected unless the IB specifically states that the AE might be associated with a fatal outcome.

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered "expected", only if it is included in the IB document as a risk.

7.4 Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor (or designee) and Incyte will notify

investigators of all SAEs that are unexpected (i.e., not previously described in the IB), and related to retifanlimab. An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report that is to be e-mailed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the IB and where required by local regulations, the investigator will submit the SUSAR to the appropriate IRB. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

7.5 Reporting

7.5.1 Adverse Events and Serious Adverse Events

All AEs (both related and unrelated) will be captured on the appropriate study-specific CRFs. All AEs experienced by subjects will be collected and reported from the first dose of the investigational agent, throughout the study, and will be followed for 28 days after last dose of study drug unless related to the investigational agent.

Subjects who experience a grade 2 or higher retifanlimab-related AE should be discussed with the IND Sponsor.

Report AEs to the IND Sponsor within 24 hours once identified as an unacceptable toxicity (defined in Section 5.6).

Nilofer Azad: [redacted]

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested

All SAEs (including deaths) occurring from the first dose of the study drug through 90 days (+ 14 day reporting window) after the last dose of retifanlimab or within 7 days prior to initiation of a new antineoplastic treatment (whichever comes first) will be collected and reported. All SAEs (including deaths) that the investigator considers related to study drug occurring after the follow-up period must be reported.

Subjects who have an ongoing AE/SAE related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

All SAEs will be reported promptly to the IND Sponsor and Incyte within 24 hours of initial notification of the SAE using the form found in Appendix D. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments. Medical records (e.g., discharge summary) should not be provided to Incyte, unless specifically requested. If this falls on a weekend or holiday, an email

notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

Nilofer Azad: [redacted]
Incyte:

7.5.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the IND Sponsor and Incyte (per **Section 7.5.9**).

7.5.3 Reconciliation of SAEs

The IND Sponsor (or designee) will reconcile the clinical database SAE cases (case level only) transmitted to the IND Sponsor and Incyte. Frequency of reconciliation should be approximately every 3 months and prior to the database lock or final data summary. Incyte will email, upon request from the Investigator, the reconciliation report. Requests for reconciliation should be sent to [redacted]. The data elements listed on the Incyte reconciliation report will be used for case identification purposes. If the Sponsor determines a case was not transmitted to the IND Sponsor and Incyte, the case should be sent immediately to the IND Sponsor and Incyte.

7.5.4 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

7.5.5 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs under the seriousness category checked as 'other medically important event'. Potential drug induced liver injury

is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.5.6 Pregnancy Reporting

Although pregnancy and lactation are not always serious by regulatory definition, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 6 months of completing the trial. This also includes the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy, which occurs during the trial or within 6 months of completing the trial.

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to the IND Sponsor [redacted] and Incyte ([redacted] within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report" or equivalent must be completed and emailed to the IND Sponsor [redacted] within 30 days after delivery, so that the IND Sponsor and Incyte are provided with information regarding the outcome of the pregnancy. If the pregnancy results in any event(s) which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

7.5.7 Institutional Review Board (IRB)

Serious adverse events will be reported to the IRB per institutional standards. Upon receipt, follow-up information will be given to the IRB (as soon as relevant information is available) per institutional standards.

7.5.8 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the IND Sponsor.

7.5.8.1 Expedited IND Safety Reports

7 Calendar-Day Telephone or Fax Report:
The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly

related to the investigational agent. Such reports are to be emailed to the regulatory project manager and faxed (301-796-9845) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

7.5.8.2 IND Annual Reports

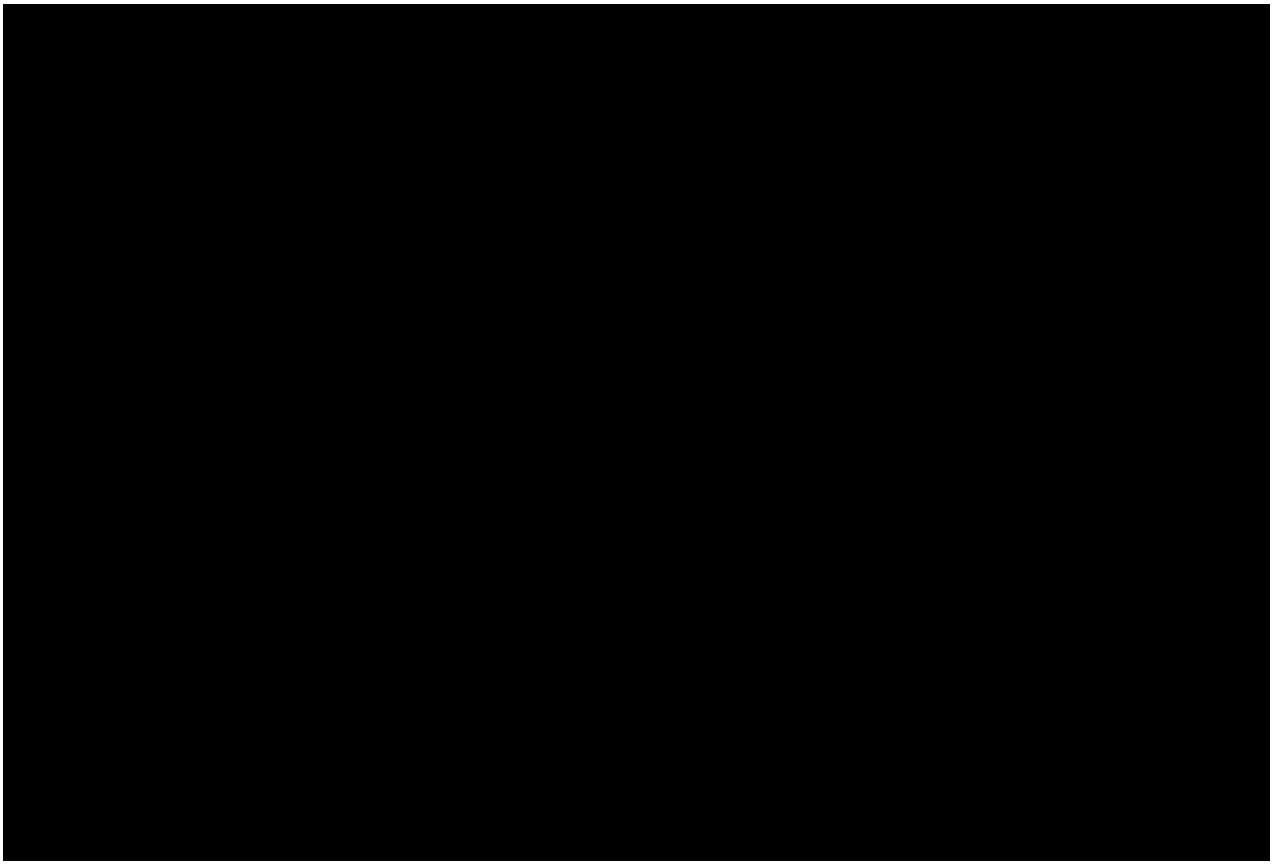
In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

8. PHARMACEUTICAL INFORMATION

[redacted]

8.1.3 Description

[redacted]



8.1.10 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9. CORRELATIVE/SPECIAL STUDIES

We have incorporated numerous correlative studies that will allow us to better understand ASQ anti-PD-1 response and resistance mechanisms. We plan to test tissue pre and post treatment for markers of immunogenicity and susceptibility to immunotherapy. This will be accomplished through immunohistochemical and multiplex immunofluorescence staining studies of tumor cells and TME immune cells and next-generation sequencing of pre and post treatment samples. These results will be correlated with response or resistance to retifanlimab.

We plan to explore:

- Immunosuppressive molecules and immune checkpoint proteins (PD-L1, PD-1, LAG3, TIM3, VISTA and IDO).
- Immune infiltrating pro and anti-inflammatory cells (T cell subsets via IHC for CD4+, CD8+, CD20, FOXP3, and CD68, myeloid-derived suppressor cells, dendritic cells etc.).
- Gene signatures of tumor and immune cells including molecular mutational status and tumor mutation burden.
- Further sequencing of T cell receptor (TCR) genes to evaluate infiltrating T cell repertoire.

Several CLIA-certified laboratories now offer molecular profiling of cancer specimens in commercial and noncommercial settings and provide these results to patients and their physicians (e.g. Foundation Medicine, PGDx, Michigan Center for Translational Pathology, or JHU CLIA Laboratories). It is possible, therefore, that some of our research analyses will be conducted in these CLIA-certified environments. If tissue or cells are evaluated with next generation sequencing strategies to provide a molecular profile of individual cancer specimens in a CLIA-certified facility, these results will be made available to the patient and their physician. Patient confidentiality will be maintained, and the patient's identity will not be publicly linked to any study results. Researchers may use the data set generated in the CLIA assay setting to study genetic alterations across a large number of genes important in cancer. Germline mutations are only identified in punitive cancer genes. Researchers will use the data set for exploratory research to study cancer cell heterogeneity. Some of the sequencing data obtained from the NGS strategies will be uploaded to government sponsored databases, such as GEO and dbGAP. The results of the research studies may be published but subjects will not be identified in any publication.

If a germline alteration of clinical importance (as judged by the Investigator) to the subject and his or her family members is identified by a CLIA-certified test in the course of this analysis, attempts will be made in writing to contact the subject and/or family members for genetic counseling referral. Results from the sequencing studies will not be released to the patients.

For patients whose tumors have not been sent to CLIA-certified sequencing laboratories, sequencing on archival tissue or biopsy tissue collected for the studies are for research purposes only, and the sequencing studies are not using a clinically validated platform and will be performed as batched analysis for research rather than real time. Accordingly, they will not be released to the patients.

9.1 Tumor Tissue Studies

Tumor biopsies will be collected (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at Cycle 3 (4-6 cores per time point). Fine needle aspiration will not be acceptable. Additional optional biopsies may be obtained later in the course of study treatment.

Attempts will be made to obtain archived tissue samples from all subjects. Archived FNA biopsy samples do not contain sufficient tissue and will not be collected.

Detailed instructions for tissue collection, processing, storage, and shipment will be provided in the Laboratory Manual.

9.2 Peripheral Blood Mononuclear Cells (PBMCs)

Whole blood for isolation of PBMCs will be collected prior to dosing on Day 1 of Cycles 1, 2, 3, and 5 as well at the time of progression or off-study. Pre- and post-treatment changes in PBMCs including effector, helper, and regulatory T cells, NK cells, and macrophages through cell phenotyping analysis and gene expression profiling will be measured. Detailed instructions for collection, processing, storage, and shipping are provided in the Laboratory Manual.

9.3 Serum and Plasma Marker and Liquid biopsy/ctDNA Studies

Sera will be collected at the same time points as whole blood sampling, as described above. Potential therapeutic targets, biomarkers, and predictors of response and autoimmune toxicity will be evaluated. Detailed instructions for collection, processing, storage, and shipping are provided in the Laboratory Manual.

9.4 Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnose immune-related toxicities.

10. STUDY CALENDAR

Study Procedures	Screen[17]	Cycle (28 days)[18]		EOT[20]	Safety FU[21]	Clinical FU[22]	Survival FU[23]
		Day 1	Day 15				
Visit Windows (days)[1]	-21 to D1	-	+3	±7	+14	±14	±14
Retifanlimab		X					
Inclusion/ exclusion criteria	X						
Demographics	X						
Medical, Cancer, & Con Med History[2]	X						
Con Meds, Adverse Events[3]		X	X[19]	X	X		
Physical Exam, ECOG PS[3]	X	X		X			
Vitals, Weight, Pulse Ox, & Height[4]	X	X		X			
Hematology, Chemistry[5, 11]	X	X	X	X			
Endocrine[6, 11]		X		X			
Urinalysis[7]	X						
Virology[8]	X						
Coagulation panel[9]	X						
Pregnancy Test[10, 11]	X	X					
CA19-9[11]	X	X		X			
ECG[12]	X						
CT/MRI, RECIST/iRECIST[13]	X	X		X		X	
Whole blood for PBMC[14]		X					
Whole blood for plasma[14]		X					
Whole blood for Serum[14]		X					
Archival Tissue[15]	X						
Tumor Biopsies[16]	X			X			
Survival Follow-up							X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1: If necessary, a scheduled cycle may be delayed for up to 1 week. Longer delays to be approved by the IND Sponsor.

2: Cancer history includes: primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, prior cancer therapy regimens, MSI testing, and tumor mutation testing.

3: Complete physical examination and assessment of ECOG PS will be completed at baseline; focused physical examinations and assessment of ECOG PS will be conducted thereafter. Day 1 Physical examination and ECOG status may be done up to 1 day prior to dosing.

4: Blood pressure, pulse, and temperature are required as indicated. Weight and pulse oximetry will be obtained at baseline and prior to each cycle. Height will be taken at or prior to screening only. Retifanlimab vitals will be collected prior to and at the end of the infusion (-5/+ 15 minutes).

5: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count; Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lipase, total protein, albumin, calcium, magnesium, and phosphate. LDH at baseline only. Any unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours. Grade 3 or greater creatinine, AST, ALT, and bilirubin should be repeated within 24-72 hours as well.

6: TSH (Total T3 and free T4 if TSH abnormal and clinically indicated).

7: Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, color, protein, RBC and WBC count, and specific gravity.

8: Virology screen: HIV antibody, hepatitis B surface antigen and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll. Window for viral screen is -60 days to D1.

9: Coagulation panel: international normalized ratio of prothrombin time, APTT

10: Pregnancy tests will be administered to WOCBP: serum pregnancy test is required at screening; urine pregnancy tests are required before each dose of retifanlimab.

11: Labs may be collected within a window of up to 3 days prior to dosing.

12: ECG should be performed at baseline.

13: Spiral CT of thorax, abdomen and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. 3-D CT scans and RECIST reads will not be used to determine eligibility at baseline. On study radiologic evaluations and tumor measurements (RECIST and iRECIST per **Appendix B** and **Appendix C**) will be performed every 8 weeks (± 1 week; starting from the date of first treatment) including the EOT evaluation (± 4 weeks). If the EOT visit occurs early, scans do not need to be repeated if one has been done within the past 6 weeks. Weeks are in reference to calendar week and should not be adjusted due to dosing delays.

14: Up to 120 mL of whole blood for PBMC isolation will be drawn cycle 1, 2, 3, and 5 and must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen. Approximately 20 mL of whole blood for plasma collection and another approximately 5 mL of blood for serum for immune monitoring. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual. Patients who discontinue retifanlimab with SD or better and later restart after off-treatment progression will have additional research bloods collected (same volume and type as above) at similar intervals as at the start of study: i.e. prior to the 1st, 2nd, 3rd, and 5th cycles of retreatment (though the actual cycle numbers will continue where subject was discontinued).

15: Attempts to obtain surgical or biopsy archival tumor samples will be made for every subject until the sample is obtained or documentation that the sample cannot be obtained. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

16: Tumor biopsies to be taken (if a subject's tumor is thought to be reasonably safe and easy to biopsy) at baseline and at Cycle 3 (4-6 cores per timepoint). The Cycle 3 biopsy has a ± 1 week window. Additional optional biopsies may be obtained later in the course of study treatment or at progression. Fine needle aspiration will not be acceptable. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual. Patients who discontinue retifanlimab with SD or better and later restart after off-treatment progression may have an additional biopsy collected prior to resuming study treatment.

17: Patients who stop retifanlimab with SD or better may be eligible for additional retifanlimab therapy if they progress after stopping study drug, they meet the criteria listed in Section 5.9.2, and undergo the following evaluations: interval medical and cancer history, physical exam, vitals, weight, PS, hematology and chemistry profile, endocrine panel, urinalysis, serum or urine pregnancy test, CA19-9, radiographic evaluations, and tumor measurements. Subjects who restart treatment after relapse should resume at the next cycle which they would have received prior to discontinuation. Additional research samples will also be collected prior to restarting treatment and while on study (see footnotes 14 and 16 for details).

18: Cycle 1 Day 1 evaluations do not need to be repeated if they were conducted within 3 days of the screening evaluations.

19: Day 15 (± 1 day) adverse event assessments may be conducted by telephone or email after cycle 2 day 1.

20: Subjects will return to the study site for an EOT evaluation. EOT follow-up will occur 28 (±7) days after the last dose of study drug. NOTE: CT scan assessment at EOT will occur 28 days (± 4 weeks) after the final dose. If the EOT visit occurs early (or if the patient cannot return due to disease progression), an assessment for AEs should be made by telephone or email on day 28 (±1) after last study dose. Subjects who restart study drug after off-treatment progression should have a second EOT visit performed when they stop study drug a second time.

21: Subjects who discontinue treatment should be contacted by telephone or email at 90 days (+ 14 day reporting window) from their last dose of study drug or within 7 days before initiation of a new antineoplastic treatment (whichever comes first) to assess for treatment related toxicities. In addition, all SAEs occurring during this time should be reported as well.

22: Subjects who discontinue treatment without disease progression should continue to be monitored for disease status by radiologic imaging (**Section 5.12.2**). Disease monitoring should continue to be assessed every two months (± 2 weeks) for the first 2 years and then every 3 months (± 4 weeks) until: 1) start of a new antineoplastic therapy (information of the new cancer therapy will be collected), 2) disease progression, 3) death, 4) withdrawal of consent, or 5) study closure, whichever occurs first.

23: Subjects who discontinue treatment will enter the survival follow-up portion of the trial (**Section 5.12.3**). Subjects should be contacted every 12 weeks (± 2 weeks) to monitor overall survival. Information of other cancer therapies after discontinuation from the study treatment will be collected as well.

11. STUDY ENDPOINTS

11.1 Primary Endpoint

The primary endpoint is DCR at 4 months following the start of treatment with retifanlimab, which is defined as the proportion of subjects with PR or CR or stable disease according to RECIST 1.1 following 4 months from the start of therapy. Subjects who discontinue due to toxicity prior to post-baseline tumor assessments will be evaluable and considered treatment failures. Otherwise, subjects who discontinue or do not have any post-baseline scans for other reasons including withdrawal of consent or being lost to follow-up prior to C2D1 will be replaced and not included in the primary efficacy analysis.

11.2 Secondary Endpoints

The secondary endpoints are as follows:

- ORR is defined as the proportion of subjects with PR or CR according to RECIST 1.1. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Otherwise, subjects who discontinue or do not have any post-baseline scans for other reasons including withdrawal of consent or being lost to follow-up prior to C2D1 will be replaced and not included in the primary efficacy analysis.
- Progression-free survival (PFS) is defined as the number of months from the first dose of retifanlimab to radiographic disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria), documented clinical progression as assessed by the treating provider, or death due to any cause. PFS will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
- Safety assessed by the following measures:
  - Number of patients who have grade 3 or above drug-related toxicities
  - Frequency of drug-related toxicity by grade
  - Retifanlimab-related infusion reactions
  - Immune-related AEs
  - Unacceptable toxicities
  - Vital signs: BP, pulse, temperature
  - Physical examination
  - Changes in ECG readings
  - Clinical hematology: complete blood count (CBC) with differential ANC, ALC, AEC, and platelet count
  - Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), ALT, AST, alkaline phosphatase, lipase, bilirubin (total), total protein, albumin, calcium, magnesium and phosphate

11.3 Exploratory Endpoints

- OS, DOR, TTP.
  - Overall survival (OS) is defined as the number of months from the first dose of retifanlimab until death or end of follow-up (OS will be censored on the date the subject was last known to be alive for subjects without documentation of death at the time of analysis).
  - Duration of Response (DOR) is defined as the number of months from the first documentation of a response to date of disease progression.
  - Time to-progression (TTP) is defined as the number of months from the first dose of retifanlimab to the date of documented disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria). It differs from PFS in that it does not include death in the definition of an event. TTP will be censored at the date of the last scan for subjects without documentation of disease progression at the time of analysis.
  - Disease control rate (DCR) is defined as the proportion of subjects with complete response, partial response and stable disease
- Disease control rate, objective response rate, progression-free survival, and duration of response measured by iRECIST
- Immune subset analyses by IHC, next generation sequencing and gene expression profiling of tumor tissue
- Immune subset analyses in PBMCs including effector, helper, and regulatory T cells, NK cells, and macrophages
- Circulating cytokine analysis in patient sera
- Immune checkpoint analysis by IHC and gene expression profiling
- Tumor marker kinetics measured by change in serum CA19-9 concentrations from baseline

12. DATA REPORTING / REGULATORY REQUIREMENTS

AE guidelines and instructions for AE reporting can be found in **Section 7.0 (Adverse Events: List and Reporting Requirements)**.

Dr. Nilofer Azad will be holding the IND for this study. She will comply with all regulated reporting requirements to the FDA, local regulations, including ICH E6 guidelines for Good Clinical Practices.

12.1 Data Collection and Processing

All information will be collected on study-specific CRFs by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator at each site.

CRFs will be used to capture study results and data. The study coordinator or other authorized

study personnel will transcribe data from source documents onto eCRFs. Before or between visits, the IND Sponsor, or designee may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF.

Protocol Chair

The Protocol Chair and/or designee is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of SAE
- Reviewing data from all sites.

Coordinating Center (Johns Hopkins University)

The Coordinating Center (or its representative) is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first subject registration at that site, and maintaining copies of IRB approvals from each site.
- Monitoring subject registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Consent subjects promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

Collecting and submitting data according to the schedule specified by the protocol.

12.2 Safety Meetings

Scheduled meetings will take place weekly (or as needed based on enrollment) and will include the protocol principal investigator, study coordinator(s), research nurse(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings, matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

Monthly teleconferences will be scheduled (or as needed based on enrollment) to include the Coordinating Center and the clinical trial site(s). During these meetings, the Coordinating Center and clinical trial sites shall discuss the following: study protocol updates, safety data, enrollment status, and progress of data for objectives.

12.3 Monitoring

This is a medium risk study under the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC) Data Safety Monitoring Plan (DSMP, 2/21/2019). Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Eligibility for all sites will be monitored by the Protocol Chair. The IND Sponsor and PI at each site shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation. Additional data and safety monitoring oversight will also be performed by the SKCCC Safety Monitoring Committee (SMC - as defined in the DSMP). External monitoring will occur according to the following guidelines:

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating site(s): The protocol will be monitored by authorized representatives of the coordinating center. A report of the reviews will be submitted to the IND Sponsor and the SKCCC CRO.

Authorized representatives of the Coordinating Center may visit the satellite site(s) to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

12.4 Study Documentation

12.4.1 Informed Consent and Authorization for use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information (PHI) must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by the IND Sponsor, the study monitor (if applicable), and the site's IRB before the initiation of the study.

12.4.2 Investigator Study Files

The IND Sponsor or designee will be responsible for maintaining original and backup of all CRF data. Investigator will maintain backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic data will be performed periodically. Backup records will be stored at a secure location on site and backup and recovery logs will be maintained to facilitate data recovery.

Changes to any electronic records require an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification and deletion of an electronic record. Audit trails must be created incrementally, in chronological order and in a manner that does not allow new audit trail information to overwrite existing data. Audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for eCRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

12.4.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of the IND Sponsor (or designee) and to the appropriate regulatory authority inspectors.

12.4.4 Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of an individual product. Longer retention periods may apply.

Audit trails for electronic documents will be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator will retain either the original or a certified copy of audit trails.

12.4.5 Data Confidentiality and Subject Anonymity

All information about the nature of the proposed investigation provided by the IND Sponsor or their representative to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the IND Sponsor, study monitor, Incyte, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, IND Sponsor or their representative.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Sample Size calculation and justification

Simon's two-stage optimal design will be used [18]. The null hypothesis that the true disease control rate at 4 months is 5% will be tested against a one-sided alternative of 30% disease control rate at 4 months. In the first stage, 7 patients will be accrued. If there are zero patients with disease control by 4 months, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 21 patients. The null hypothesis (disease control rate of 5%) will be rejected if 3 or more patients with disease control at 4 months are observed in stage 1 and 2 combined. This design yields a type I error rate of 0.064 (target type I error 0.1) and power of 90% when the true disease control rate is 30%. The probability of stopping the trial early for futility is 70% if the true DCR is 5%.

We plan to enroll 25 subjects to ensure 21 would be evaluable for DCR. As this is a rare tumor subtype patients will be recruited at several sites including Johns Hopkins Hospital, Memorial Sloan Kettering Cancer Center and the Mayo Clinic. We do not anticipate any difficulties in trial enrollment. We expect an accrual rate of at least 2 patients per month across the sites, completing trial enrollment in 12 months.

Patients are evaluable for DCR if they receive at least one dose of retifanlimab, and have at least one post-baseline tumor assessments or discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments. The study plans to enroll 25 subjects to ensure 21 would be evaluable for the primary efficacy endpoint.

There is no reliable historical control data documenting response rates and disease control rates with chemotherapy or any other agent in ASQ. Previous clinical trials of single agent checkpoint inhibitors in pancreatic cancer have reported 0% ORR (anti-PD1, PDL1, CTLA4)[2–6]. A recent trial investigating anti-PDL1 combined with anti-CTLA4 therapy or anti-PD-L1 alone in metastatic PDAC reported ORR of 3.1% and 0% with the combination and single agent, respectively. This trial also reported a median PFS of 1.5 months in both cohorts, DCR at 3 months of 9.4% and 6.1% and PFS rate at 6 months of 9.4% and 3.6% in the combination and single agent cohorts, respectively[5]. Given the results of these trials, the phenomenon that immunotherapy often has a delayed effect compared to chemotherapy and ASQ being an aggressive disease with limited treatment options the primary endpoint of this study will be a 30% DCR at four months.

13.2 Data and Analysis Plan

Analysis of Primary Endpoint

The primary endpoint of the study will be disease control (DC) at four months using RECIST 1.1. DC is defined as complete response, partial response and stable disease at 4 months, per RECIST 1.1. Disease control rate (DCR) will be estimated as the proportion of patients who achieve DC at 4 months, along with 95% confidence interval

Analysis of Secondary Clinical Endpoint

The objective response rate defined as the proportion of response evaluable subjects who have a complete response (CR) or partial response (PR) using RECIST 1.1 criteria at any time during the study. The evaluable population includes all subjects who have completed at least one dose of retifanlimab and have received at least one follow-up scan or discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments. Response rate will be reported with exact 95% confidence interval.

Progression-free Survival (PFS) is defined as the time from cycle 1, day 1 of retifanlimab until first documented local progression or death due to any cause. Disease progression will be assessed using RECIST (version 1.1) and/or documented clinical progression as assessed by the treating provider. Due to the expectation that some patients may experience delayed clinical responses to therapy, patients with disease progression by radiographic imaging or laboratory parameters during a 12-week evaluation period but without rapid clinical deterioration or significant change in performance status that requires additional immediate therapy may continue to receive treatment on study. Subjects that meet the above criteria and continue on study therapy must discontinue treatment upon documentation of disease progression on the second scan. The date of progression will be backdated to the time of first RECIST criteria progression. Tumor assessments will be made using RECIST 1.1 and immune RECIST (iRECIST). Individuals will be censored at the date of the last scan prior to initiation of an alternative therapy for PFS if no event occurs before the start of the alternative therapy.

PFS will be summarized descriptively using the Kaplan-Meier method. Analysis of PFS will be restricted to evaluable individuals who complete at least one dose of retifanlimab.

Analysis of Safety Endpoints

The safety analysis will be performed in all subjects who receive at least one dose of study drug. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after at least 1 dose of study treatment may be required for inclusion in the analysis of a specific safety parameter (e.g., lab shifts from baseline). A complete list of all AE data will be provided along with an assessment of NCI CTCAE grade and relationship to study drug. The incidence of AEs will be tabulated by subgroups of interest (e.g. grade 3 or higher, organ class, relationship to study drug). For analyses at the individual level, the highest grade and relationship to study drug will be assumed if multiple events have occurred. Toxicity will be tabulated by type and grade and will be summarized with descriptive statistics. Other safety data will be assessed in terms of

physical examination, clinical chemistry, hematology, vital signs, and ECGs. Negative binomial regression and Cox proportional hazards models will be used to assess the rate of AE and time to first toxicity, respectively.

Exploratory Clinical Analysis

Overall survival is defined as the duration of time from start of study treatment to time of death. For subjects lost to follow-up or whose vital status is unknown, every effort will be made to determine the date such subjects were last known to be alive. Such efforts may include phone calls, certified mail, and the checking of public records. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right-censored. The censoring date will be determined from the date the subject was last known to be alive.

OS will be summarized descriptively using the Kaplan-Meier method. Analysis of OS will be restricted to evaluable individuals who complete at least one dose of retifanlimab. Median event-free survival will be reported and the associated 95% confidence interval will be estimated.

DOR and TTP were defined in second 11.3.

Exploratory Biomarker Analysis

To specifically evaluate the impact of therapy on the tumor microenvironment, we will compare biopsies obtained at baseline vs. after two cycles of retifanlimab (refer to section on Trial Design). In addition, immune effector cell phenotype circulating in peripheral blood will be assessed. Exploratory data analyses will include plots and summary statistics of these immunologic correlative markers at baseline as well as at the various time points. Patterns of change in the longitudinal data on these markers will be evaluated in this manner for each of the correlative outcomes of interest. Exploratory analyses can also be conducted to examine potential differences in various immune biomarkers between patients who have disease control (prolonged SD or any response vs. those with progressive disease). Linear mixed models can also be used to explore differences in these markers between the two outcome groups along with graphical analyses that plot marker values across time for the two groups to assess potentially different patterns of change between these groups. Appropriate transformations of the various correlative markers will be used in the presence of skewed data distributions.

13.3 Safety Analysis

The safety analysis will be performed in all treated subjects. AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by CTCAE version 5.0) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If 2 or more AEs are reported as a unit, the individual terms will be reported as separate experiences.

Changes in vital signs, hematology and clinical chemistry parameters from baseline to the end of the study will be examined. Toxicity will be tabulated by type and grade. Toxicities will be

characterized according to the CTCAE version 5.0. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

13.4 Safety monitoring and stopping guidelines

Adverse events will be monitored during the trial. The occurrence of unacceptable AEs, as defined in **Section 5.6**, at any time during the treatment will be the endpoint for safety monitoring. If the events of unacceptable AEs appear to be higher than 33%, we will temporarily halt the study pending safety evaluation. A Beta (1.5, 5.5) prior, representing a toxicity rate of 21%, a slightly conservative estimate, was used in the development of the stopping guidelines. The therapy will be re-evaluated if the posterior probability that the toxicity rate exceeds the 33% boundary is greater than 60%. **Table 5** summarizes the stopping boundaries for unacceptable toxicities.

Table 5. The number of unacceptable toxicities needed to trigger stopping guidelines throughout the course of the study.

Number of Subjects	**Number of unacceptable toxicities needed to trigger re-evaluation**
2	2
3-5	3
6-7	4
5-10	5
11-13	6
14-16	7
17-19	8
20-22	9
23-25	10

Operating characteristics of the stopping rule based on 10000 simulations are shown below.

True probability of unacceptable toxicity	Probability of triggering stopping guidelines
5%	0.4%
10%	1.8%
15%	6%
20%	14%
25%	27.5%
30%	44.9%
35%	62.3%
40%	78%
45%	89.2%

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	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. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	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 the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is evidence of progression in the irradiated site. 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.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

> Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
>
> 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the 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. (Note: the appearance of one or more new lesions is also considered progressions).

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

Evaluation of Non-Target Lesions

Complete Response (CR):Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

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):Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects 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.

Reference

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

APPENDIX C: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using the criteria outlined in **Section 5.9.1**.

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
    - Please 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 scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan 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.

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 had 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, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their 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.

Additional details about iRECIST are provided in the iRECIST publication[20].

Table 6: Comparison between RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of disease: numbers, sites and target or non	Measurable are diameters greater than 10 mm (15 for nodes maximum of 5 (2 per organ)	No change from RECIST 1.1
CR, PR or SD	Cannot have met criteria for progression	Can have had iUPD (more than once) but not iCPD before iCR, iPR or iSD
Confirmation of CR or PR	Only in non-randomized studies	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1
New lesions	Progression: recorded but not measured	iUPD but only becomes iCPD if on the next scan there are new lesions or the size increases by greater than 5 mm
Confirmation of progression	Not required	Required
Consideration of clinical status	Not required	Clinical stability considered at iUPD to decide treatment continuation

Table 7: Trajectory of progression in iRECIST

Target Lesions: iCR, Non-target: iCR, no new lesions	iCR	iCR
Target lesions: iCR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target Lesions: iPR, Non-target: non iCR/non iUPD, no new lesions	iPR	iPR
Target lesions: iSD, Non-target: non iCR/non iUPD, no new lesions	iSD	iSD
Target lesions: iUPD with no change or with a decrease from the last time point, Non-target: iUPD with no change or decrease from last time point, new lesions	NA	New lesions confirm iCPD if new lesions previously identified and increased in size (≥ 5 mm in sum of measures for new lesions or any increase for new lesion non-target) or increase in number. If no change is seen in new lesions assignment remains iUPD
Target lesions: iSD, iPR, iCR, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD is confirmed by increase in the size of non-targets (does not need to meet RECIST 1.1 criteria)
Target lesions: iUPD, non-target: non iCR/non iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on the basis of further increase ≥ 5 mm; otherwise stays as iUPD
Target lesions: iUPD, non-target: iUPD, no new lesions	iUPD	Remains iUPD unless iCPD confirmed on previously identified targets iUPD ≥ 5 mm or non-target iUPD
Target lesions: iUPD, non-targets: iUPD, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase of ≥ 5 mm previously identified target, or non-target or an increase in size or number of new lesions
Target lesions non iUPD or progression, non-targets: non iUPD or progression, new lesions	iUPD	Remains iUPD unless iCPD confirmed by increase in size or number of new lesions previously identified.

Target lesions, non-target lesions and new lesions are defined according to RECIST 1.1 criteria: if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD are the same. * Previously identified in the assessment prior to this time point. 'I' indicates immune responses assigned using iRECIST

APPENDIX D: SAE Reporting Form

Serious Adverse Event Reporting Form

Please notify: Dr. Azad within 24 hours [redacted]
Incyte within 24 hours (email: [redacted]

<table>
<tr><td>Protocol Title:</td><td colspan="4">A Phase II trial of retifanlimab (INCMGA00012) in patients with previously treated unresectable or metastatic adenosquamous pancreatic or ampullary cancer</td></tr>
<tr><td>Protocol #:
I-0012-19-07
J19106</td><td>Principal Investigator:</td><td colspan="2">Signature of PI:</td><td>Date:</td></tr>
<tr><td rowspan="2">Report Type:
☐Initial
☐Follow-up
☐Final Follow-up
☐Death
☐Addendum to:</td><td colspan="2" rowspan="2">Serious Criteria (check all that apply):
☐Death
☐Life-threatening
☐ Hospitalization or Elongation of Hospitalization
☐ Other Important Medical Event
☐ Cancer
☐ Overdose
☐ Other:_____</td><td>Hospital Admission Date:</td><td>Date Event Discovered:</td></tr>
<tr><td>Hospital Discharge Date:</td><td>SAE ID:</td></tr>
<tr><td colspan="5">Section A: Subject Information</td></tr>
<tr><td colspan="2">Subject ID:</td><td>Subject Gender:
☐Male
☐Female</td><td colspan="2">Subject Age:</td></tr>
<tr><td colspan="5">Section B: Event Information</td></tr>
<tr><td>Event diagnosis or symptoms:</td><td>Event Grade:</td><td>Cause of death (if applicable):</td><td colspan="2">Event Outcome:
☐ Not Recovered
☐ Recovering
☐ Recovered
☐ Recovered with sequelae
☐ Death
☐ Unknown</td></tr>
<tr><td colspan="2">Event Onset Date (or Date of Death):</td><td colspan="3">Event End Date:</td></tr>
<tr><td colspan="5">Section C: Study Drug Information</td></tr>
<tr><td colspan="5">Investigational Product: Retifanlimab (500mg, IV, Q28 days)
Indication: Previously treated unresectable or metastatic adenosquamous pancreatic or ampullary cancer</td></tr>
</table>

Number of Total Doses Given:		Action taken with the study drug: ☐ None ☐ Interrupted ☐ Delayed ☐ Discontinued
Date of First Dose:	**Date of Last Dose prior to Event:**	
Relationship to:	**Retifanlimab**	**Underlying Disease**
Unrelated	☐	☐
Related	☐	☐

Section D: Brief Description of the Event:

Section E: Relevant Tests/Laboratory Data

Section F: Relevant Medical History

Section G: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section H: Comments

Additional Documents: ☐ Please specify