PROTOCOL

TITLE:	**A MULTICENTER, SINGLE ARM STUDY TO EVALUATE THE PRELIMINARY EFFICACY AND SAFETY PROFILE OF INAVOLISIB IN PREVIOUSLY TREATEDPANCREATIC DUCTAL ADENOCARCINOMA PATIENTS**
PROTOCOL NUMBER:	ML46544
VERSION NUMBER:	1.2
NCT NUMBER:	
INVESTIGATIONAL MEDICATION PRODUCT::	Inavolisib（RO7113755）
SPONSOR:	Fudan University Shanghai Cancer Center
DATE FINAL:	See electronic signature and date stamp on the final page of this document.

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– PROTOCOL ACCEPTANCE FORM

TITLE:	**A MULTICENTER, SINGLE ARM STUDY TO EVALUATE THE PRELIMINARY EFFICACY AND SAFETY PROFILE OF INAVOLISIB IN PREVIOUSLY TREATEDPANCREATIC DUCTAL ADENOCARCINOMA PATIENTS**
PROTOCOL NUMBER:	ML46544
VERSION NUMBER:	1.0
INVESTIGATIONAL MEDICATION PRODUCT::	Inavolisib (RO7113755)
SPONSOR:	Fudan University Shanghai Cancer Center

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form by the local study monitor.

- PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, SINGLE ARM STUDY TO EVALUATE THE PRELIMINARY EFFICACY AND SAFETY PROFILE OF INAVOLISIB IN PREVIOUSLY TREATEDPANCREATIC DUCTAL ADENOCARCINOMA PATIENTS**
PROTOCOL NUMBER:	
VERSION NUMBER:	1.0
INVESTIGATIONAL MEDICATION PRODUCT::	Inavolisib
PHASE:	Phase II
INDICATION:	Pancreatic ductal adenocarcinoma
SPONSOR:	Fudan University Shanghai Cancer Center
INVESTIGATOR:	Xianjun Yu

Objectives and Endpoints

This study aims to evaluate the preliminary efficacy and safety of Inavolisib monotherapy in ≥2L pancreatic ductal adenocarcinoma（PDAC）patients. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
To evaluate the efficacy of Inavolisib	● Objective response rate (ORR)(INV): defined as the proportion of patients with a complete response (CR) or partial response (PR). Response will be assessed by the investigator according to RECIST v1.1. CR and PR require confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response.
Secondary Efficacy Objective	**Corresponding Endpoints**

To evaluate the efficacy of Inavolisib	● Progression free survival（PFS）(INV), defined as the time between the date of first dose of Inavolisib and the date of disease progression assessed by **investigator** according to RECIST v1.1 or death due to any cause (whichever occurs first). Subjects who are alive and have not progressed, whether on-study or lost to follow-up will be censored at their last evaluable tumor assessment date. ● Overall survival（OS）： defined as the time from treatment starting with Inavolisib to death due to any cause. Subjects without events will be censored at the date last known to be alive. ● Disease control rate（DCR）（INV）: defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) and status last >= 4 weeks.Response will be assessed by the investigator according to RECIST v1.1 ● Duration of response (DOR): The duration of response is defined as time from first evidence of PR or CR to disease progression or death due to any cause. DOR will be calculated only for subjects who achieve a **confirmed** response of PR or CR. ● Time to response (TTR): defined as the time from the start of first dose of Inavolisib until the first evidence of PR or CR. TTR will be calculated only for subjects who achieve a response of **confirmed** PR or better.
Safety Objectives	**Corresponding Endpoints**

To evaluate the safety and tolerability of inavolisib	● Incidence and nature of select treatment-related toxicities (Safety run in stage only) ● Incidence, type, and severity of adverse events (based on the NCI CTCAE v5.0), including serious adverse events (SAEs) ● Change from baseline in targeted vital signs ● Change from baseline in targeted clinical laboratory test results, including electrocardiograms (ECGs)
Biomarker Objective	**Corresponding Endpoints** （will be performed with permission of HGRAC）
To identify and/or evaluate biomarkers that are associated with acquired resistance to study treatment, can provide evidence of study treatment activity (i.e., predictive biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	● E-cadherin testing by Immunohistochemistry（IHC） E-cadherin status will be assessed by Immunohistochemistry (IHC) staining on tumor samples in the local laboratory of each site. • Tumor markers Serum CEA, CA19-9 testing will be performed every 8 weeks to evaluate the study treatment activity.

NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; RESICT v1.1 = Response Evaluation Criteria in Solid Tumor, Version 1.1. HGRAC = Human Genetic Resources Administration of China.

Study Design

Description of Study

This is a phase II, multicenter, single arm study designed to evaluate the efficacy and safety of Inavolisib in second line pancreatic ductal adenocarcinoma（PDAC） patients. This study will be conducted in two stages and expected to enroll up to approximately 62 patients. In the safety run in stage, approximately up to 12 patients will be enrolled to receive Inavolisib under 3+3 design. After safety run-in, if the tolerability allows, an additional 50 patients will be enrolled.（expansion stage）. Eligible patients will receive one of the treatments as outlined below:

Table 2 Treatment Regimens

Study stage	Study treatment
Safety run in stage	Inavolisib 9mg P.O. QD under 3+3 design If Inavolisib 9mg is not tolerable Inavolisib 6mg P.O. QD under 3+3 design
Expansion stage	Inavolisib 9mg P.O. QD or Inavolisib 6mg P.O. QD follow the results in safety run in stage

Dose Modification Guidelines for Inavolisib-Related Adverse Events: Inavolisib started at dose 9 mg QD, first reduction to 6 mg QD, second reduction to 3 mg QD. If the patient continues to experience specified drug-relate d adverse events after the second dose reduction, Inavolisib should be permanently discontinued.

Tumor assessments will be performed every 8 weeks, including enhanced chest CT, abdominal CT / MRI and pelvic CT / MRI.Head CT/MRI also can be performed if necessary. Additional scans will be performed as clinically indicated.

Tumor specimens acquired from biopsy will be collected for E-cadherin testing by IHC at each site. Tumor tissue (via biopsies and/or surgical resection) and blood samples from eligible patients will be provided to a local laboratory and tested and analyzed for biomarkers that might be associated with clinical benefit, tumor immunobiology, mechanisms of resistance, et al.

Patients will be closely monitored for adverse events throughout the study, including the incidence, nature and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE 5.0).

Definition of Select Treatment-Related Toxicity (TRT) Criteria

Any of the following events will be considered as a treatment-related toxicity criteria if it occurs during the initial safety evaluation window (Day 1 of Cycle 1 to Day 1±2 of Cycle 2) and is assessed by the investigator to be related to study treatment. If **select treatment-related toxicities (TRTs)** occur in **2 out of 3** or **2 out of 6** patients, the safety run-in for the **6 mg** QD dose of **Inavolisib** will be conducted. Adverse events meeting toxicity criteria as defined below and observed within the safety evaluation window must be reported to the Sponsor within 24 hours:

- Fasting Grade 4 hyperglycemia
- Fasting Grade 3 hyperglycemia that does not respond to insulin therapy within 3 days, or fasting Grade 3 hyperglycemia that requires hospitalization
- Grade 3 metabolic AEs (hypercholesterolemia or triglyceridemia) lasting 14 days despite appropriate intervention with SOC therapy
- Grade 4 diarrhea
- Grade 3 diarrhea lasting for 7 days with optimal supportive care
- Grade 3 colitis
- Grade 3 or Grade 2 pneumonitis not manageable with corticosteroids
- Grade 4 neutropenia (ANC 500/mm^3) lasting 7 days with G-CSF support
- Grade 3 febrile neutropenia for 7 days or Grade 4 febrile neutropenia of any duration
- Grade 4 thrombocytopenia (platelet count 25,000/mm^3) or Grade 3 thrombocytopenia associated with severe bleeding that requires invasive intervention or transfusion
- Grade 4 anemia

- Grade 3 elevation of total bilirubin or serum hepatic transaminase (ALT or AST) lasting 7 days

  For participants with liver metastases or Gilbert's disease, total bilirubin 5 the upper limit of normal (ULN) lasting for 7 days will be considered a treatment-limiting toxicity. For participants with elevated hepatic transaminase at baseline due to documented liver metastases, hepatic transaminase 8 ULN for 48 hours will be considered a treatment-limiting toxicity.
- Any Grade 3 clinically significant non-hepatic, non-metabolic (e.g., hyperglycemia, hyperlipidemia), non-hematologic adverse event, with the following exceptions:
  – Grade 3 nausea or vomiting that improves to Grade 1 in 3 days with standard-of-care therapy
  – Grade 3 fatigue lasting 3 days or less than two grade changes from baseline
  – Treatment emergent Grade 3 laboratory abnormalities that are asymptomatic or not clinically significant
  – Grade 3 arthralgia that can be adequately managed with supportive care or resolves to Grade 2 within 7 days
  – Grade 3 rash that resolves to Grade 2 within 7 days with appropriate supportive care
- Grade 5 treatment-related adverse event

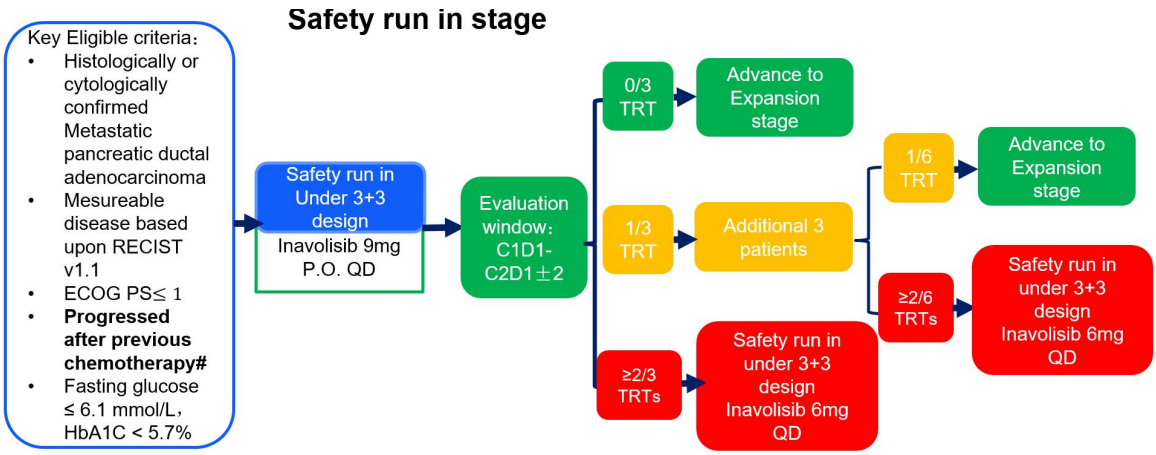
The safety run in stage will follow the flow chart as below under 3+3 design. It will start with Inavolisib 9mg QD. If it is not tolerable, repeat safety run in with Inavolisib 6mg QD under 3+3 design. The expansion stage will not begin until the safety run in stage is completed. The dose in the expansion stage will follow the tolerable dose selected throughsafety run in. Patients enrolled in safety run in stage will be pooled with the cohort in expansion stage for final analysis.

Patients who withdraw or discontinue from the study prior to completing the safety evaluation window for reasons other than a select TRT will be considered non-evaluable for dose decisions and assessments, and will be replaced by an additional patient at that same dose level. Patients who receive at least 75% of planned inavolisib doses and remain in the study through the safety evaluation window will be considered evaluable. Patients who do not receive at least 75% of planned inavolisib doses and during the safety evaluation window will be replaced to ensure that at least 3 patients have been assessed for the full TRT assessment period of 28 days prior to moving to the expansion stage. During expansion stage, patients who withdraw from the study will not be replaced.

Patients who discontinue study treatment as a result of disease progression will be managed per local practice. Patients who receive non-protocol anti-cancer therapy during the study treatment period will be considered as protocol deviation. The investigator should document and explain it for evaluating. These patients will remain in study for survival follow-up. Patients who discontinue study treatment due to toxicity will be subsequently treated according to local practice. Study treatment will continue until unequivocal disease progression as determined by the investigator, unacceptable toxicity, patient withdrawal of consent, or study termination by sponsor, whichever occurs first.

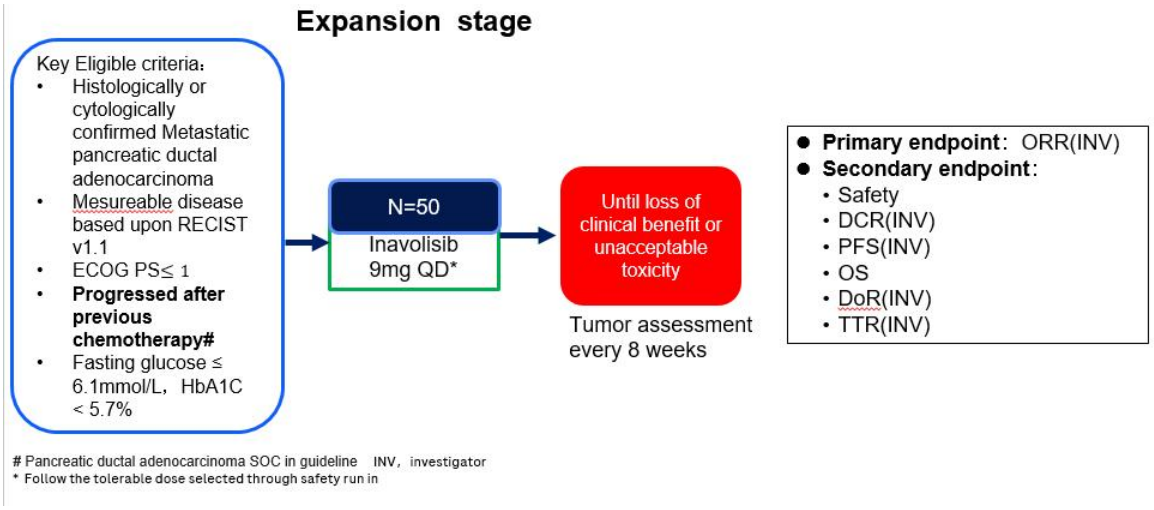
Following treatment discontinuation, follow-up information will be collected by telephone, patient medical records, and/or clinic visits every 3 months until death, loss to follow-up, withdrawal of informed consent or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up.

Study Flow



- Safety run in will perform under 3+3 design start with Inavolisib 9mg QD.
- If it is not tolerable with Inavolisib 9mg QD, repeat safety run in with Inavolisib 6mg QD under 3+3 design. The cohort will be terminated if Inavolisib 6mg QD is still not tolerable

Pancreatic ductal adenocarcinoma SOC in guideline



Pancreatic ductal adenocarcinoma SOC in guideline INV, investigator
* Follow the tolerable dose selected through safety run in

Number of Patients

Up to 12 patients will be enrolled in safety run in stage under 3+3 design. During the expansion stage, an additional 50 patients will be enrolled in this study. Thus，up to 62 patients will be enrolled in this study. All patients will be enrolled in China.

Target Population

Inclusion Criteria

Patients must meet all the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 years at time of signing Informed Consent Form
3. Ability to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically confirmed diagnosis of pancreatic ductal adenocarcinoma.
5. The disease must have progressed after previous chemotherapy given in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), 1st line therapy of locally advanced, or metastatic setting.
6. Availability of a representative tumor specimen that is suitable for pathological evaluation and biomarker expression analysis.
   - A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in approximately 8-10 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization.
   - If fewer than 8 slides are obtained, but there are enough slides for E-cadherin testing by local lab of each site patients are still eligible.
7. ECOG Performance status (PS) of 0 or 1 within 7 days prior to initiation of study treatment.
8. At least one measurable lesion per RECIST v1.1
9. Adequate hematologic and organ function, defined by the following laboratory test results, obtained within 7 days prior to initiation of study treatment:
   - ANC ≥ 1.5 × 10^9/L (1500/μL) without granulocyte colony-stimulating factor support
   - Lymphocyte count ≥ 0.5 × 10^9/L (500/μL)
   - Platelet count ≥ 100 × 10^9/L (100,000/μL) without transfusion
   - Hemoglobin ≥ 90 g/L (9 g/dL)

     Patients may be transfused to meet this criterion, but must not have been transfused within 2 weeks prior to screening
   - Fasting glucose < 6.1.mmol/L and HbA1c < 5.7%
   - AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN).
   - Total bilirubin ≤ 1.5 × ULN with the following exception:

     Patients with known Gilbert disease: total bilirubin ≤ 3 × ULN
   - Serum creatinine ≤ 1.5 × ULN or Creatinine clearance ≥ 60 mL/min (calculated using the Cockcroft-Gault formula)
   - Albumin ≥ 25 g/L (2.5 g/dL)
   - For patients not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 × ULN
   - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
10. Negative HIV test at screening

11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

    Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 1 week after the final dose of study treatment. Women must refrain from donating eggs during this same period.

    A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

12. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

    With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 1 week after the final dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

1. Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway.
2. Prior treatment with any RAS inhibitor or BRCA inhibitor.
3. Known hypersensitivity to any of the components of study treatments.
4. Histology consistent with small cell carcinoma, Neuroendocrine carcinoma, or mixed carcinoma.
5. Type 2 diabetes requires ongoing systemic treatment at the time of study entry;or pre-diabetes, or any history of Type 1 diabetes；or any other type of diabete; or any other type of diabetes.
6. Inability or unwillingness to swallow pills
7. Malabsorption syndrome or other condition that would interfere with enteral absorption
8. Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:
   – Measurable disease outside the CNS
   – No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases
   – Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic assessments
   – Screening CNS radiographic assessments ≥ 4 weeks since completion of radiotherapy
   – No history of intracranial hemorrhage or spinal cord hemorrhage
9. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently
   Indwelling pleural or abdominal catheters may be allowed, provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved, and has prior approval from the Medical Monitor.
10. Serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1
11. Any concurrent ocular or intraocular condition excluding cataracts (e.g. , diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition.

12. Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
13. Requirement for daily supplemental oxygen
14. Symptomatic active lung disease, including pneumonitis
15. History of or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)

    Patients currently receiving immunosuppressants for inflammatory bowel disease (e.g., sulfasalazines) are considered to have active disease and are therefore ineligible.
16. Any active bowel inflammation (including diverticulitis)
17. Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in and completion of the study
18. Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

    Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
19. Clinically significant and active liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
20. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that renders the patient at high risk from treatment complications
21. Chemotherapy, radiotherapy, or any other anti-cancer therapy within 2 weeks before study treatment
22. Investigational drug(s) within 4 weeks before study treatment
23. Prior radiotherapy to ≥ 25% of bone marrow, or hematopoietic stem cell or bone marrow transplantation
24. Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade ≤ 2 peripheral neuropathy
25. History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
26. History of or active clinically significant cardiovascular dysfunction, including the following:

    – History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment

    – History of myocardial infarction within 6 months prior to first dose of study treatment

    – New York Heart Association Class III or IV cardiac disease or congestive heart failure requiring medication

    – Uncontrolled arrhythmias, history of or active ventricular arrhythmia requiring medication

    – Coronary heart disease that is symptomatic or unstable angina

    – Congenital long QT syndrome or QT interval corrected through use of Fridericia's formula > 470 ms demonstrated by at least two ECGs > 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
27. Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)

28. Chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
29. Treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
30. Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of study treatment.
    Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment or negative urine pregnancy test if serum pregnancy test is not available.
31. Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
32. Minor surgical procedures <7 days prior to first dose of study treatment.
    Patients must have sufficiently recovered from surgery, including adequate wound healing.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 8 months after the LPI. In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 32 months.

Investigational Medicinal Product

The investigational medicinal product for this study is Inavolisib that is administered for the target 2L PDAC population.

Test Product (Investigational Drug)

Inavolisib will be supplied by Roche as an immediate release tablet formulation (3-mg and 9-mg). The 3-mg tablet is a greyish orange to brownish orange, round film-coated tablet and the 9-mg tablet is a greyish orange to brownish orange, oval film-coated tablet. The 3-mg and 9-mg tablets should be stored at or below 86°F (30°C) and protected from light. Inavolisib will be administered orally QD on Days 1-28 of each 28-day cycle at a starting dose of 9 mg. Inavolisib should be taken at approximately the same time each day without regard to the timing of administration of food. If a dose is missed (not taken within 9 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose.

Non-Investigational Medicinal Products

There are no non-investigational medicinal products.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of Inavolisib based on objective response rate (ORR). ORR is defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions>=4 weeks apart（confirmed response）during investigation treatment, as determined by the investigator according to RECIST v1.1. Patients who did not achieve a confirmed response and patients with no response assessments (for whatever reason) will be considered non-responders. An estimate of the response rate and its 95% CI will be provided. The 95% CI will be calculated with the Clopper Pearson method (Clopper and Pearson 1934).

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, changes in vital signs and ECGs.

Determination of Sample Size

This study is not designed to account for statistical power and Type I error considerations but rather aims to obtain preliminary safety and efficacy data for Inavolisib as a second-line treatment for patients with pancreatic ductal adenocarcinoma (PDAC).

The planned enrollment for this study (both safety run-in stage and expansion stage) is up to approximately 62 patients. The sample size for safety run-in stage is based on a 3+3 design, with up to 12 patients to be enrolled. In the expansion stage, an additional 50 patients will be enrolled. With a targeted ORR>=26%, a sample size of 53 patients would be able to produce a lower bound of the associated 95% CI (calculated using Clopper-Pearson method) to exclude a 15% threshold. Different scenarios with their associated 95% CI are presented in Table 3 below. With the sample size of 53 and a two-sided 95% CI, the probability of detecting an improvement in ORR compared with a historical ORR of 15% is shown in Table 4.

Table 3 Objective Response Rate Scenarios

	N=53		N=56	
Expected Objective Response Rate	Expected Number of Patients with a Response	95% CI for Objective Response Rate	Expected Number of Patients with a Response	95% CI for Objective Response Rate
23%	12	（12.3，36.2）	13	（13.0，36.4）
26%	14	（15.3，40.3）	15	（15.8，40.3）
30%	16	（18.3，44.3）	17	（18.8，44.1）

Table 4 Probability of Detecting ORR Improvement (Reference:15% ORR)

	N=53
True ORR difference compared to 15%	Probability (%) of Detecting ORR Improvement
8%	33%
11%	53%
15%	76%

Interim Analyses

The assessment committee will oversee futility analyses performed and based on the ORR analysis set. The interim futility analyses will be conducted in a continuous manner using Bayesian predictive probability (Lee and Liu, 2008) to evaluate monotherapy. It will begin after approximately 25 response-evaluable subjects, defined as received at least 1 dose of Inavolisib and have had at least one post-baseline tumor assessment. Subjects who stopped disease assessments prior to 8 weeks will be included in this analysis if the data cutoff is at least 8 weeks after their first dose date. Following the initial interim analysis, a second interim analysis will be conducted after an additional 15 response-evaluable subjects are enrolled.

The futility analyses will be based on Inv-assessed disease response. Subjects with unconfirmed PR or CR will be counted as responders for this futility analysis if they are still in study at the time of data cutoff and potential for future confirmation scan.

The success criterion will be met if the probability that the true ORR exceeds the benchmark

ORR is ≥ to a high probability of:

- Success Criterion : probability [ORR > 0.10] ≥ 80%

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a success criterion if the treatment group is enrolled and evaluated to the planned maximum final sample size of 56 subjects. The success criterion is for interim futility analysis purpose only.

Futility will be met if it is predicted that there is a small probability of reaching a success criterion upon full enrollment of subjects given the existing observed data. A noninformative prior distribution of beta (1, 1) will be used.

- Futility Criterion: Predictive probability < 5%

The decision rules and operating characteristics for continuous monitoring of ORR are provided in table 5.

Table 5 Stopping Boundary and Operating Characteristics

Number of Subjects	Considered Futile If Observing Number of Responses	Cumulative Probability of Futility					
		True ORR=0.02	True ORR=0.05	True ORR=0.1	True ORR=0.2	True ORR=0.3	True ORR=0.4
25	**<=1**	**91.1%**	**64.2%**	**27.1%**	**2.7%**	**0.2%**	**0.0%**
40	**<=3**	**99.3%**	**87.7%**	**46.4%**	**4.4%**	**0.2%**	**0.0%**
56	<=7	100%	97.9%	74.0%	9.7%	0.3%	0.0%
Average Number of Subjects		27	33	45	55	56	56

LIST OF ABBREVIATIONS AND DEFINITIONs OF TERMS

Abbreviation	Definition
AC	Assessment committee
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ANC	Absolute neutrophil count
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FDA FFPE	Food and Drug Administration Formalin-fixed, paraffin-embedded
HGRAC	Human Genetics Resources Administration of China
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committees
IMP	Investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
LPLV	Last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI *CTCAE*	National Cancer Institute *Common Terminology Criteria for Adverse Events*
NGS	Next generation sequencing
ORR	objective response rate
OS	overall survival
PDAC	Pancreatic ductal adenocarcinoma

PFS	progression-free survival
PR	Partial Response
PS	Performance status
SD	Stable disease
TRT	Treatment related toxicity
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON PANCREATIC CANCER

Pancreatic cancer is globally recognized as one of the most lethal malignancies, characterized by an insidious onset, late clinical presentation, and limited therapeutic options, leading to exceptionally high case-fatality ratios and stagnant survival rates worldwide. In China, the disease burden of pancreatic cancer has escalated substantially over the past three decades, outpacing global trends. In 2021 alone, China reported 118,665 new cases and over 2.9 million Disability-Adjusted Life Years (DALYs), with a disproportionately higher burden among males.

Age-standardized rates of incidence, prevalence, and DALYs have markedly increased between 1990 and 2021, with accelerated increases identified after 2015. The burden is concentrated in older age groups and driven primarily by years of life lost due to premature mortality. Projections indicate a continued rise in incidence, prevalence, and DALY rates through 2030, underscoring the growing public health challenge in China. This escalating burden is attributed to factors such as urbanization, aging, and lifestyle changes, including dietary shifts and smoking. The escalating burden of PDAC in China, with its growth outpacing global trends, highlights an increasingly severe public health challenge posed by this disease. This dire situation indicates that targeted research and resource allocation are critically important for advanced pancreatic cancer, where therapeutic options are particularly scarce. Therefore, conducting clinical trials in China is not only globally relevant but also decisively important for developing tailored treatment strategies and optimizing healthcare resource allocation to address the rapidly increasing challenge of pancreatic cancer within the Chinese population.

1.2 CURRENT STANDARD OF CARE FOR SECOND-LINE PDAC AND ITS LIMITATIONS

The prognosis for PDAC remains dismal, with a 5-year survival rate of approximately 10%, largely due to advanced clinical manifestation at diagnosis. Surgical resection, the only potential curative measure, is feasible in only 10–20% of patients. For patients with advanced, unresectable, metastatic, or recurrent disease, systemic chemotherapy is the primary palliative measure. Upon progression after first-line therapy, subsequent second-line treatment typically involves gemcitabine or 5-fluorouracil (5-FU) based chemotherapy, depending on the prior regimen and timing of progression.

The efficacy of current second-line chemotherapy regimens is generally limited. Notably, the NAPOLI-1 Phase III clinical trial evaluated liposomal irinotecan (nal-IRI) in combination with 5-FU/leucovorin (LV) in patients with metastatic PDAC who had progressed after gemcitabine-based therapy. Results showed that the nal-IRI + 5-FU + LV arm had a median OS of 8.65 months and a median PFS of 5.25 months, compared to 6.70 months OS and 3.55 months PFS in the control arm (5-FU + LV).The ORR was significantly improved in the nal-IRI arm (odds ratio of 1.50).[8] Based on these results, liposomal irinotecan in combination with 5-FU and leucovorin was approved for patients with metastatic pancreatic adenocarcinoma who had progressed after gemcitabine-based therapy. Other second-line chemotherapy study efficacy data are summarized in table 1 with ORR about 15%，PFS 4-6 months and OS 6-8 months.

Table 6. Efficacy of Second line chemotherapy in PDAC

Study Name	Study Type	Sample size	mPFS (months)	mOS (months)	ORR (%)
NAPOLI-1	Phase III	117 (Nal-IRI+5-FU+LV arm)	5.25	8.65	16%
NAPOLI-1 (Control Arm)	Phase III	119 (5-FU+LV arm)	3.55	6.70	1%
Korean Retrospective Study	Retrospective Study	104	4.5	6.4	/
Korean perspective study	Phase II	40	5.8	9.9	15%
USA Retrospective Study	Retrospective Study	59	3	3.9	10%

Beyond chemotherapy, the exploration of other treatment modalities has also been slow. While immunotherapy (ICIs) has brought revolutionary breakthroughs in other cancers, it is less effective for pancreatic cancer, showing higher resistance and does not improve the survival rates of patients with advanced pancreatic cancer. This indicates that the unique biological challenges of PDAC (e.g., tumor microenvironment, CAFs, ILs) render it an "immuno-cold" tumor, emphasizing the need for non-immunotherapy or combination approaches that target distinct oncogenic pathways.

In terms of targeted therapies, the pancreatic cancer field also faces challenges. Although *KRAS* mutations are highly prevalent in PDAC (over 90%), targeted agents for *KRAS* G12D (the most common *KRAS* mutation, accounting for approximately 45% of *KRAS* mutations) are still in exploratory stages, with no FDA-approved therapies specifically targeting *KRAS* G12D currently available. For example, VS-7375, a *KRAS G12D* inhibitor, has received FDA Fast Track designation but remains in clinical trials. In addition to selective RAS inhibitors, PanRAS inhibitors are also under development. Phase 1 study data showed that in patients with ***KRAS G12X*-mutant PDAC** treated with RMC-6236 as a second-line therapy, the **ORR** was **29%**, the **DCR** was **91%**, the median **PFS** was **8.5 months**, and the median **OS** was **14.5 months**. The percentage of patients achieving 6-month OS was **89%**. Furthermore, in **PDAC patients with any *RAS* mutation** treated with RMC-6236 as a second-line therapy, the median PFS was **7.6 months**, the median OS was **14.5 months**, and the percentage of patients achieving 6-month OS was **91%**. This showed encouraging results and potential breakthroughs in targeted therapies for pancreatic cancer in the future. But now we still lack mature, widely applicable targeted therapy options in pancreatic cancer. Given the **upstream-downstream relationship** between the RAS and PI3K signaling pathways, PI3K inhibitors hold significant potential as future combination agents with RAS inhibitors, or as a strategy to overcome acquired

resistance. Therefore, it is warranted to explore the efficacy and safety of PI3K inhibitors in pancreatic cancer.

Given the limited means to significantly improve survival in the second-line setting and the scarcity of existing treatment options, there is an urgent need for more effective and tolerable therapeutic choices for PDAC patients who have progressed on initial systemic therapy. Any improvement in efficacy or new treatment types would be of great significance to this disease area. Consequently, multiple guidelines, including those from the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology（CSCO）, explicitly recommend that patients with advanced pancreatic cancer consider participating in clinical trials.[15] Participation in clinical trials not only offers patients access to innovative therapies but also advances the understanding and treatment of this highly aggressive disease, with the aim of achieving clinically meaningful improvements in survival .

1.3 BACKGROUND ON PI3K/AKT/MTOR PATHWAY IN PDAC

The PI3K/AKT/mTOR pathway is a crucial intracellular signaling cascade that regulates fundamental cellular processes, including cell cycle progression, proliferation, growth, survival, motility, and metabolism. Dysregulation and hyperactivation of this pathway are frequently observed in a wide variety of human cancers, contributing to tumorigenesis, reduced apoptosis, increased proliferation, and therapeutic resistance.

Activation of the PI3K pathway can occur through various mechanisms, including mutations in the *PIK3CA* gene itself, or downstream activation by other oncogenes such as *KRAS*. The *PIK3CA* gene encodes the p110α catalytic subunit of PI3K. Activating mutations in this gene are among the most common genetic alterations in various solid tumors. Hotspot mutations, such as E542K and E545K in exon 9 and H1047R in exon 20, lead to constitutive activation of the PI3K pathway. These mutations cause hyperactivation of downstream PI3K pathways by altering domains and disrupting inhibitory interactions between p110α and p85α.

While the PI3K/AKT pathway is frequently activated in PDAC (often due to *KRAS* mutations present in over 90% of tumors), mutations in the *PIK3CA* gene itself are found in only a "few subsets" of conventional PDAC patients, with reported prevalence ranging from 3% to 5%. This indicates that although the PI3K pathway is highly relevant and activated in PDAC, *PIK3CA* mutations are not the primary drivers of this activation in the majority of cases. This implies that while *PIK3CA* inhibitors might be effective for a small subset of PDAC patients with *PIK3CA* mutations, broader PI3K pathway inhibitors or combination therapies targeting *KRAS* and its downstream effectors (like PI3K) might have more universal applicability in PDAC. The focus should be on pathway activation rather than solely on *PIK3CA* mutation status to select a broader patient population for PDAC.

1.4 BACKGROUND ON METABOLISM DYSREGULATION IN PDAC

Patients with PDAC often present with metabolic fragility due to the high prevalence of **Pancreatic Cancer-Associated Diabetes (PCAD)**, a paraneoplastic phenomenon induced by the tumor, frequently accompanied by severe insulin resistance and impaired islet function. Given that the PI3K/AKT signaling pathway is a key axis controlling

glucose metabolism, PI3K inhibitors like Inavolisib produce **hyperglycemia** as a defined on-target adverse event by inhibiting glucose transport. The superimposition of pre-existing metabolic instability in PDAC patients and drug-induced hyperglycemic effects significantly elevates the risk of severe metabolic complications. In the clinical experience with other PI3K inhibitors, hyperglycemia has been established as a Dose-Limiting Toxicity (DLT) and a major cause of dose reduction/discontinuation. Direct evidence comes from the pan-PI3K inhibitor Buparlisib (BKM120), where a Phase I combination chemotherapy trial enrolling gastrointestinal malignancies, including **pancreatic cancer**, reported **Grade 3 hyperglycemia** as a DLT, alongside increased overall toxicity. Therefore, in this trial, rigorous metabolic monitoring and proactive anti-diabetic drug management (including baseline HbA1c screening and optimization) are essential elements for ensuring patient safety and maintaining optimal drug intensity (to mitigate the risk of resistance driven by hyperinsulinemia).And dose interruption or reduction of inavolisib will be performed if necessary.

1.5 BACKGROUND ON INAVOLISIB

- **1.4.1 <u>Detailed Description of Inavolisib mechanism as a Selective PI3Kα Inhibitor</u>**

Inavolisib (also known as GDC-0077, Itovebi, RG6114, RO7113755) is an orally available, highly potent, and selective inhibitor of phosphatidylinositol 3-kinase (PI3K). Inavolisib specifically binds to p110α, the catalytic subunit of the PI3K complex encoded by the *PIK3CA* gene, to inhibit downstream signaling through PI3K-AKT pathway effector proteins, thereby blocking tumor cell growth and survival. Beyond direct inhibition, inavolisib also promotes the degradation of mutated p110αThis degradation property, combined with its enhanced selectivity for p110α, may contribute to a wider therapeutic window and sustained pathway inhibition compared to earlier PI3K inhibitors. Dysregulation of the PI3K signaling pathway is frequently associated with tumorigenesis and tumor resistance to a variety of antineoplastic agents and radiotherapy.

- **1.4.2 <u>Summary of Inavolisib's Clinical Efficacy and Safety in Other Indications (Breast Cancer)</u>**

Inavolisib has demonstrated significant clinical efficacy in patients with *PIK3CA*-mutated, hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer. The Phase III INAVO120 trial showed that adding Inavolisib to palbociclib and fulvestrant significantly improved overall survival (OS) and progression-free survival (PFS).

Key findings from INAVO120 include:

- At primary PFS analysis: median PFS of 15.1 months in the Inavolisib group versus 7.3 months in the placebo group (stratified HR 0.43, 95%CI 0.32-0.59)
- At primary analysis: median OS in the Inavolisib group versus in the placebo group is NE vs 31.1 months (stratified HR 0.67, 95%CI 0.48-0.94), representing a 33% reduction in the risk of death.

- Objective response rate (ORR) of 62.7% for Inavolisib versus 28.0% for placebo.

- The Inavolisib combination delayed the time until patients who needed to start the first chemotherapy (35.6 months vs. 12.6 months).

Based on these results, Inavolisib in combination with palbociclib and fulvestrant was approved by the U.S. Food and Drug Administration (FDA) in 2024 and approved by the China National medical products administration (NMPA) in 2025 for this specific breast cancer population. Inavolisib's demonstrated efficacy in *PIK3CA*-mutated breast cancer (INAVO120 trial) provides strong clinical validation for targeting the PI3Kα pathway, establishing a clear precedent for its potential in other cancers driven by this pathway, even if direct PDAC data is absent. Inavolisib as a "highly potent and selective PI3Kα inhibitor that also promotes mutated p110α degradation" suggests a more favorable therapeutic window than earlier PI3K inhibitors, which is crucial for combination therapies.

The safety profile of Inavolisib, when combined with palbociclib and fulvestrant, while generally manageable, includes a higher incidence of hyperglycemia (63.4% any grade vs. 13.5% placebo), stomatitis or mucosal inflammation, gastrointestinal side effects (e.g., diarrhea, nausea, vomiting), and ocular side effects (e.g., dry eye, blurred vision) compared to placebo. Serious adverse events occurred in 27.3% of the Inavolisib group vs. 13.5% of placebo, with discontinuation rates due to AEs being low (6.8% vs. 0.6%).

Inavolisib is also under investigation in other clinical trials for various solid tumors, including metastatic colorectal cancer, *KRAS G12C* mutated solid tumors, and other *PIK3CA*-mutated cancers, including tumor-agnostic platform studies. Inavolisib's ongoing exploration in "Tumor-agnostic Precision Immuno-oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study" for "*PIK3CA*-Mutated Cancers" implies a recognition of *PIK3CA* as a pan-cancer target. This further supports the exploration of Inavolisib in PDAC, even if its *PIK3CA* mutation frequency is relatively low, as long as the PI3K pathway is activated.

1.6 RATIONALE FOR INAVOLISIB IN PANCREATIC DUCTAL ADENOCARCINOMA

1.6.1 Preclinical Evidence Supporting PI3K Inhibition in PDAC

Preclinical studies have demonstrated that targeted inhibition of the PI3K/AKT/mTOR pathway leads to a significant reduction of tumor burden and improvement of overall survival in aggressive mouse models of pancreatic cancer. Specifically, blocking the class I p110α isoform of the PI3K complex (the target of Inavolisib) in the presence of mutant K-Ras significantly attenuated the transition of exocrine acinar cells towards pancreatic preneoplastic ductal lesions after pancreatic injury. This highlights the critical role of p110α in early PDAC development and progression. These findings provide strong preclinical justification for evaluating Inavolisib, a selective PI3Kα inhibitor, in PDAC, both as a monotherapy and in combination with other agents. Preclinical data showing "targeted inhibition of PI3K/Akt/mTOR together led to a significant reduction of tumor burden and improvement of overall survival" and "blocking specific class I p110alpha PI3K isoform... significantly attenuated the transition of exocrine acinar cells towards pancreatic preneoplastic ductal lesions" provides strong preclinical justification for Inavolisib, a selective PI3Kα inhibitor, in PDAC. This supports both monotherapy and combination approaches, as it targets a fundamental oncogenic dependency.

1.6.2 Challenges in PI3K inhibition Therapy for PDAC

As previously noted, *PIK3CA* mutations are found in only a small subset of conventional PDAC patients (3%-5%), making it a less common driver mutation compared to *KRAS*, which is mutated in over 90% of PDACs. The overall effectiveness of PI3K inhibitors is limited by compensatory mechanisms or feedback loops that reactivate the pathway following inhibition, leading to insufficient target engagement. For example, compensatory ERK activation was observed in *PIK3CA*-mutated PDAC models treated with Alpelisib. Epithelial-mesenchymal transition (EMT) is associated with drug resistance and can rewire the PI3K pathway, leading to acquired resistance. Other factors include inactivation or loss of PTEN activity, PI3K mutations and amplifications, and drug-related toxicities. So far, there is little clinical study data on PI3K inhibitors (including Inavolisib and other PI3K inhibitors) in PDAC patients. In a phase 1 trial, BYL719 in combination with gemcitabine and nab-paclitaxel in locally advanced and metastatic pancreatic cancer, only 8 pts were evaluable for response. Two had stable disease, 5 had partial responses and 1 had progression with mPFS 5.36 months and mOS 8.74 months. The efficacy data is similar to MPACT study that AG regimen achieve ORR 23%, mPFS 5.5m and mOS 8.5months. So, directly exploring the efficacy and safety of PI3K inhibitor monotherapy in PDAC patients can we directly answer whether it has anti-tumor activity in PDAC patients.

1.7 E-CADHERIN: ITS ROLE IN CANCER AND POTENTIAL AS A PREDICTIVE BIOMARKER FOR PI3K INHIBITOR EFFICACY

1.7.1 E-cadherin's Function in Cell Adhesion and Tumor Biology (EMT)

E-cadherin is a crucial cell adhesion molecule and a well-known tumor suppressor protein, integral to maintaining epithelial phenotype and regulating tissue homeostasis. It mediates cell-cell adhesion through calcium-dependent homophilic interactions. Loss or downregulation of E-cadherin expression is frequently observed in malignant epithelial cancers and is considered a hallmark of the epithelial-mesenchymal transition (EMT). EMT is a critical process in cancer metastasis, where cancer cells lose epithelial characteristics and gain mesenchymal features, facilitating detachment from the primary tumor, invasion, and migration.

However, the role of E-cadherin in metastasis is complex and context-dependent. While E-cadherin loss promotes EMT and invasion, many metastases retain E-cadherin expression, and EMT is not always required for metastasis; tumor cell clusters can also metastasize. E-cadherin can also be involved in collective cell behaviors that facilitate invasion and metastasis. Interestingly, E-cadherin re-expression can occur in new organ environments (e.g., liver) and has been shown to confer chemo resistance and a survival advantage to metastatic breast and prostate cancer cells.

The prevalence of E-cadherin positive in PDAC patients varies with the disease stage. It is about 80-95% in resectable patients and about 40-60% in locally advanced or metastatic 1L patients. The prevalence in 2L patients has not yet been found but it is estimated to be similar to that in first-line patients, because first-line chemotherapy does not significantly change the biological characteristics of the tumor.

1.7.2 Review of Available Literature on the Interplay between E-cadherin, PI3K Pathway, and Sensitivity/Resistance to PI3K Inhibitors

The relationship between E-cadherin and the PI3K/AKT pathway is intricate and context-dependent across different cancer types:

- E-cadherin Activating PI3K: E-cadherin has been shown to directly contribute to PI3K/AKT activation by engaging the PI3K-p85 regulatory subunit to adherens junctions, particularly in ovarian carcinoma cells. Formation of E-cadherin-mediated cell-cell adhesion can activate AKT via PI3K.

- E-cadherin Loss Activating PI3K: Conversely, loss of E-cadherin can induce ovarian cancer growth and constitutive activation of PI3K/AKT signaling by inhibiting PTEN transcription through downregulation of Egr1. This suggests E-cadherin negatively regulates PI3K/AKT signaling in some contexts.

- E-cadherin and PI3K Inhibitor Sensitivity:

  - In ovarian cancer cell lines, higher E-cadherin expression was associated with poorer resistance to cell death (implying greater sensitivity) compared to cell lines with higher N-cadherin expression.

  - Studies in breast cancer have shown that upregulation of miRNA-200c, which increases E-cadherin expression, leads to inactivation of Akt signaling (via PTEN upregulation) and increased sensitivity to doxorubicin. Conversely, E-cadherin knockdown can reactivate PI3K/Akt signaling. This suggests that maintaining E-cadherin expression or an epithelial state might enhance sensitivity to PI3K pathway inhibition.

  - EMT (often characterized by E-cadherin loss) has been associated with drug resistance, including PI3K inhibitor resistance. Tumors showing EMT can rewire signaling pathways, and loss of ERBB3 after EMT can be rescued by reactivating PI3K (e.g., through enhanced p110α signaling), contributing to resistance.

  - In paclitaxel-resistant, *PIK3CA*-mutated endometrial cancer, both PI3K/AKT and EMT pathways were significantly upregulated. Combination of a PI3K inhibitor (alpelisib) with eribulin enhanced anti-tumor activity by inhibiting both pathways, suggesting a link between EMT and PI3K-mediated resistance.

  - In prostate cancer, loss of E-cadherin led to impaired primary and metastatic tumor formation in vivo, suggesting a tumor promoter role for E-cadherin in some contexts, and transient repression of E-cadherin may be mediated by the PI3K/AKT signaling pathway.

  - Mutations in CDH 1 (E-cadherin) and *PIK3CA* have been shown to cooperate in inducing immune-related invasive lobular carcinoma of the breast.

The relationship between E-cadherin expression and PI3K pathway activity/inhibitor sensitivity is highly complex and context-dependent, presenting seemingly contradictory findings in the literature. While some studies suggest that E-cadherin positive cells might be sensitive to PI3K inhibitors, other literature indicates that E-cadherin loss can activate PI3K, or that EMT (often associated with E-cadherin loss) is linked to PI3K inhibitor

resistance. Conversely, the E-cadherin expression itself can also activate PI3K. This complexity highlights the critical need for empirical validation in PDAC.

1.7.3 Hypothesis for E-cadherin as a Potential Predictive Biomarker for Inavolisib in PDAC

Given the complex yet mechanistically plausible interplay between E-cadherin and the PI3K pathway in tumor biology, and preliminary findings in other cancers linking E-cadherin expression to PI3K inhibitor sensitivity, we hypothesize that E-cadherin expression may serve as a predictive biomarker for Inavolisib efficacy in PDAC patients. The retrospective analysis of E-cadherin expression in this study aims to validate this hypothesis in a clinical setting, potentially identifying a subgroup of PDAC patients most likely to benefit from Inavolisib therapy. This could lead to a more personalized treatment approach in a disease with high unmet needs.

E-cadherin re-expression can lead to chemo resistance, while EMT (E-cadherin loss) may be associated with PI3K inhibitor resistance. This suggests that modulating E-cadherin expression or targeting EMT pathways could be a strategy to overcome resistance to PI3K inhibitors or chemotherapy. This provides a broader context for E-cadherin research, indicating its role may extend beyond a predictive biomarker to a potential therapeutic target or a target for combination strategies.

1.8 Clinical Exploration of Inavolisib in Beyond Second-Line PDAC: Study Design Rationale and Future Direction

1.8.1 Justification for Evaluating Inavolisib as Monotherapy in PDAC ≥2L patients

Given the complete absence of prior clinical data for Inavolisib in PDAC, a monotherapy cohort is essential to rigorously evaluate the intrinsic efficacy and safety profile of Inavolisib in this patient population. This approach will allow for a direct assessment of the drug's activity against PDAC, particularly in the context of the well-established dysregulation of the PI3K pathway in this malignancy, independent of confounding factors from combination partners.

The prognosis remains extremely poor for patients in the second-line and beyond 2L setting, and there is a critical lack of effective, standardized treatment options. This represents a major clinical challenge that urgently needs to be addressed. Current approved or commonly used second-line regimens (such as liposomal irinotecan-based therapy or platinum/fluorouracil-based regimens) offer limited efficacy as mentioned above, typically showing low objective response rates (ORR) poor survival, and are associated with cumulative toxicities. Many 2L patients may be unable to receive or benefit from these standard treatments due to deteriorated performance status or reduced tolerance to chemotherapy agents. Therefore, this study selects patients who have failed prior chemotherapy setting to directly address this stage with the most pressing clinical need and weakest standard treatment efficacy. Furthermore, evaluating the monotherapy efficacy of Inavolisib in these patients can minimize potential confounding factors from chemotherapy agents, allowing for a clearer, independent assessment of the anti-tumor activity of this novel targeted agent.

1.8.2 Importance of Retrospective Analysis of E-cadherin Expression and its Correlation with Clinical Outcomes

Given the complex yet mechanistically plausible interplay between E-cadherin and the PI3K pathway in tumor biology, and preliminary findings in other cancers linking E-cadherin expression to PI3K inhibitor sensitivity, we hypothesize that E-cadherin expression may serve as a predictive biomarker for Inavolisib efficacy in PDAC patients. Considering the low frequency of *PIK3CA* mutations in PDAC (3%-5%), directly screening for *PIK3CA* mutated patients would significantly limit patient recruitment, especially in a first exploratory study. However, the PI3K/AKT pathway is broadly activated in PDAC, often driven by *KRAS* mutations even without *PIK3CA* mutations suggesting that Inavolisib may be effective in a broader patient population. Given the conflicting relationship between E-cadherin and the PI3K pathway and EMT in the literature, this study will not pre-screen patients for *PIK3CA* mutation status or E-cadherin expression. Instead, all eligible ⩾2L PDAC patients will be enrolled, and E-cadherin expression will be retrospectively analyzed to explore its value as a potential predictive biomarker for Inavolisib efficacy. This approach allows for the exploration of E-cadherin's predictive value without pre-selecting patients, potentially leading to the discovery of novel biomarkers to guide future precision medicine.

2. OBJECTIVES AND ENDPOINTS

This study aims to evaluate the preliminary efficacy and safety of Inavolisib monotherapy in 2L pancreatic ductal adenocarcinoma（PDAC） patients. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the Inavolisib assigned to patients.

2.1 EFFICACY OBJECTIVES

Response will be assessed according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (see Appendix 3). Response will be assessed by the investigator.

2.1.1 Primary Efficacy Objective

To evaluate the efficacy of Inavolisib monotherapy of the following endpoint:

Objective response rate (ORR)(INV): defined as the proportion of patients with a best response of complete response (CR) or partial response (PR). Response will be assessed by the investigator according to RECIST v1.1. CR and PR require confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response.

2.1.2 Secondary Efficacy Objective

To evaluate the efficacy of Inavolisib monotherapy:

- Progression free survival（PFS）(INV), defined as the interval between the date of first dose of Inavolisib and the date of disease progression assessed by investigator according to RECIST v1.1 or death due to any cause (whichever comes first). Subjects who are alive and have not progressed, whether on-study or lost to follow-up will be censored at their last evaluable tumor assessment date.

- Overall survival（OS）： defined as the time from treatment starting with Inavolisib until the event of death due to any cause. Subjects without events will be censored at their last contact date.
- Disease control rate（DCR）（INV）: defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) >= 4 weeks. Response will be assessed by the investigator according to RECIST v1.1.
- Duration of response (DOR): The duration of response is defined as time from first evidence of PR or CR to disease progression or death due to any cause. DOR will be calculated only for subjects who achieve a **confirmed** best overall response of PR or CR.
- Time to response (TTR): defined as time from the start of treatment until the first evidence of PR or CR. TTR will be calculated only for subjects who achieve a best overall response of confirmed PR or better.

ORR, PFS will be additionally assessed in subgroup population with E-cadherin expression in baseline.

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of Inavolisib monotherapy:

- Incidence and nature of select treatment-related toxicities (Safety run in only)
- Incidence, type, and severity of adverse events (based on the NCI CTCAE v5.0), including serious adverse events
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results, including ECGs

2.3 BIOMARKER OBJECTIVE

The biomarker objective for this study is to identify and/or evaluate biomarkers that are associated with acquired resistance to study treatment, can provide evidence of study treatment activity (i.e., predictive biomarkers), or can increase the knowledge and understanding of disease biology and drug safety:

Biomarker objective	Corresponding Endpoints （will be performed with permission of HGRAC）

To identify and/or evaluate biomarkers that are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, can provide evidence of study treatment activity (i.e., predictive biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	● E-cadherin testing by Immunohistochemistry（IHC） E-cadherin status will be assessed by Immunohistochemistry (IHC) staining on tumor samples in the local laboratory of each site. • Tumor markers Serum CEA, CA19-9 testing will be performed every 8 weeks to evaluate the study treatment activity.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a phase II, multicenter, single arm study designed to evaluate the efficacy and safety of Inavolisib in second line pancreatic ductal adenocarcinoma（PDAC） patients.

There are two stages in this study:

- Safety run-in stage: approximately up to 12 patients will be enrolled under 3+3 dose de-escalation design treated with Inavolisib monotherapy.

- Expansion stage: 50 patients will be enrolled and treated with Inavolisib monotherapy.

3.1.1.1 Safety run-in stage

Patients will first be accrued into the safety run-in stage. Patients enrolled in the safety run-in stage will receive Inavolisib under 3+3 dose de-escalation design. Upon determination of the safety of the treatment regimen, the study will proceed to the expansion stage. All safety results from the safety run-in stage will be reviewed by the Assessment Committee (AC). The safety run in stage will be conducted only in the leading site.

The first 3 patients will be enrolled in the safety run-in stage consecutively. The study schedule is presented in Figure 1. After signing informed consent, patients will undergo screening procedures that include laboratory tests (e.g., hematology, chemistries, liver function tests); contrast−enhanced computed tomography (CT) scan, or magnetic resonance imaging (MRI) of the chest, abdomen, pelvis and head; assessments; and tumor biopsies the same as expansion stage. A schedule of activities is provided in Appendix 1.

Patients in safety run-in stage will receive Inavolisib monotherapy at a dose of 9mg P.O. QD for 1 cycle. (Table 2, Safety Run-in).

The safety run-in stage will follow the “3+3” approach and we define the stopping rule of AEs to refer to Inavolisib safety profile. It is **Select Treatment-Related Toxicity (TRT) Criteria**. The first 3 patients enrolled in this stage will be closely monitored by the assessment

committee (AC) for all safety events during the initial safety evaluation window (Day 1 of Cycle 1 to Day 1±2 of Cycle 2).

Safety run in stage AC Review Charter

Planned first AC Review:

- The first planned AC review will be conducted for the first 3 patients during the initial safety evaluation window (Day 1 of Cycle 1 to Day 1±2 of Cycle 2). All safety data of these patients will be reviewed. Enrollment will be stopped during the AC review.

- If AC recommends another 3 patients to be enrolled in the safety run-in stage, the second planned AC review will be scheduled and conducted for the 3 patients safety evaluation window. All safety data of all 6 patients will be reviewed

After the **first planned AC review**, the AC may recommend

- Enroll additional three patients in safety run-in stage without study modification at the same dose level（Inavolisib 9mg P.O. QD）,

- Enroll additional three patients in safety run-in stage with study modification at the same dose level（Inavolisib 9mg P.O. QD）,

- Begin the expansion stage without study modification at the same dose level（Inavolisib 9mg P.O. QD）,

- Begin the expansion stage with study modification at the same dose level（Inavolisib 9mg P.O. QD）,

- Stop the trial.

After the **second planned AC review** if applicable, the AC may recommend

- Begin the expansion stage without study modification at the same dose level（Inavolisib 9mg P.O. QD）,

- Begin the expansion stage without study modification at the same dose level（Inavolisib 9mg P.O. QD）

- Enroll additional three patients in safety run-in stage without study modification at a lower dose level（Inavolisib 6mg P.O. QD）, and the third planned AC review will be scheduled and conducted for the 3 pateints（Inavolisib 6mg P.O. QD） safety evaluation window

- Enroll additional three patients in safety run-in stage with study modification at a lower dose level（Inavolisib 6mg P.O. QD）, and the third planned AC review will be scheduled and conducted for the 3 pateints（Inavolisib 6mg P.O. QD） safety evaluation window

- Stop the trial.

After the **third planned AC review** if applicable, the AC may recommend to

- Begin the expansion stage without study modification at the dose level（Inavolisib 6mg P.O. QD）,
- Begin the expansion stage without study modification at the dose level（Inavolisib 6mg P.O. QD）
- Enroll additional three patients in safety run-in stage without study modification at the same dose level（Inavolisib 6mg P.O. QD）, and the fourth planned AC review will be scheduled and conducted for the 3 pateints（Inavolisib 6mg P.O. QD） safety evaluation window
- Enroll additional three patients in safety run-in stage with study modification at a the same dose level（Inavolisib 6mg P.O. QD）, and the fourth planned AC review will be scheduled and conducted for the 3 pateints（Inavolisib 6mg P.O. QD） safety evaluation window
- Stop the trial.

After the **fourth planned AC review** if applicable, the AC may recommend

- Begin the expansion stage without study modification at the dose level（Inavolisib 6mg P.O. QD）,
- Begin the expansion stage with study modification at the dose level（Inavolisib 6mg P.O. QD）
- Stop the trial.

Definition of Select Treatment-Related Toxicity (TRT) Criteria

Any one of the following events will be considered as a treatment-related toxicity criterion if it occurs during the initial safety evaluation window (Day 1 of Cycle 1 to Day 1±2 of Cycle 2) and is assessed by the investigator to be related to study treatment. Adverse events meeting toxicity criteria as defined below and observed within the safety evaluation window must be reported to the Sponsor within 24 hours:

- Fasting Grade 4 hyperglycemia
- Fasting Grade 3 hyperglycemia that does not respond to insulin therapy within 3 days, or fasting Grade 3 hyperglycemia that requires hospitalization
- Grade 3 metabolic AEs (hypercholesterolemia or triglyceridemia) lasting 14 days despite appropriate intervention with SOC therapy
- Grade 4 diarrhea
- Grade 3 diarrhea lasting for 7 days with optimal supportive care
- Grade >=3 colitis

- Grade 3 or Grade 2 pneumonitis not manageable with corticosteroids within 7 days
- Grade 4 neutropenia (ANC 500/mm^3) lasting 7 days with G-CSF support
- Grade 3 febrile neutropenia for 7 days or Grade 4 febrile neutropenia of any duration
- Grade 4 thrombocytopenia (platelet count 25,000/mm^3) or Grade 3 thrombocytopenia associated with severe bleeding that requires invasive intervention or transfusion
- Grade 4 anemia
- Grade 3 elevation of total bilirubin or serum hepatic transaminase (ALT or AST) lasting 7 days.
  For participants with liver metastases or Gilbert's disease, total bilirubin 5 the upper limit of normal (ULN) lasting for 7 days will be considered a treatment-limiting toxicity. For participants with elevated hepatic transaminase at baseline due to documented liver metastases, hepatic transaminase 8 ULN for 48 hours will be considered a treatment-limiting toxicity.

- Any Grade 3 clinically significant non-hepatic, non-metabolic (e.g., hyperglycemia, hyperlipidemia), non-hematologic adverse event, with the following exceptions:
  – Grade 3 nausea or vomiting that improves to Grade 1 in 3 days with standard-of-care therapy
  – Grade 3 fatigue lasting 3 days or less than two grade changes from baseline
  – Treatment emergent Grade 3 laboratory abnormalities that are asymptomatic or not clinically significant
  – Grade 3 arthralgia that can be adequately managed with supportive care or resolves to Grade 2 within 7 days
  – Grade 3 rash that resolves to Grade 2 within 7 days with appropriate supportive care
- Grade 5 treatment-related adverse event

Patients who withdraw or discontinue from the study prior to completing the select TRT assessment window for reasons other than a select TRT will be considered non-evaluable for dose decisions and assessments, and will be replaced by an additional patient at that same dose level. Patients who receive at least 75% of planned inavolisib doses and remain in the study through the TRT assessment window will be considered evaluable. Patients who do not receive at least 75% of planned inavolisib doses during the TRT assessment window will be replaced to ensure that at least 3 patients in each cohort have been assessed for the full TRT assessment period of 28 days prior to moving to the expansion stage. During the expansion stage, patients who withdraw from the study will not be replaced.

3.1.1.2 Expansion stage

This stage will enroll an additional 50 patients. Eligible patients will receive one of the treatments as described in Table 2. Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Table 2 Treatment Regimens

Study stage	Study treatment

Safety run in stage	Inavolisib 9mg P.O. QD under 3+3 design If Inavolisib 9mg is not tolerable Inavolisib 6mg P.O. QD under 3+3 design
Expansion stage	Inavolisib 9mg P.O. QD or Inavolisib 6mg P.O. QD follow the safety run in result

Inavolisib will be administered orally QD on Days 1-28 of each 28-day cycle at a starting dose of 9mg or 6mg following the safety run in result. Dose Modification Guidelines for Inavolisib-Related Adverse Events Inavolisib：Starting dose 9 mg QD, first reduction 6 mg QD, second reduction 3 mg QD. If the patient continues to experience specified drug-related adverse events after the second dose reduction, inavolisib should be discontinued.

Patients who discontinue study treatment as a result of disease progression will be managed per local practice. Patients who receive non-protocol anti-cancer therapy during the study treatment period will be considered as protocol deviation. The investigator should document and explain it for evaluating. These patients will remain in study for survival follow-up. Patients who discontinue study treatment due to toxicity will be subsequently treated according to local practice. Study treatment will continue until unequivocal disease progression as determined by the investigator, unacceptable toxicity, patient withdrawal of consent, or study termination by sponsor, whichever occurs first.

Tumor assessments will be performed every 8 weeks, including enhanced chest CT, abdominal CT / MRI and pelvic CT / MRI，head CT/MRI if necessary. Additional scans will be performed as clinically indicated.

Tumor specimens acquired from biopsy will be collected for E-cadherin testing by IHC at each site. Tumor tissue (via biopsies and/or surgical resection) and blood samples from eligible patients will be provided to a local laboratory and tested and analyzed for biomarkers that might be associated with clinical benefit, tumor immunobiology, mechanisms of resistance, et al.

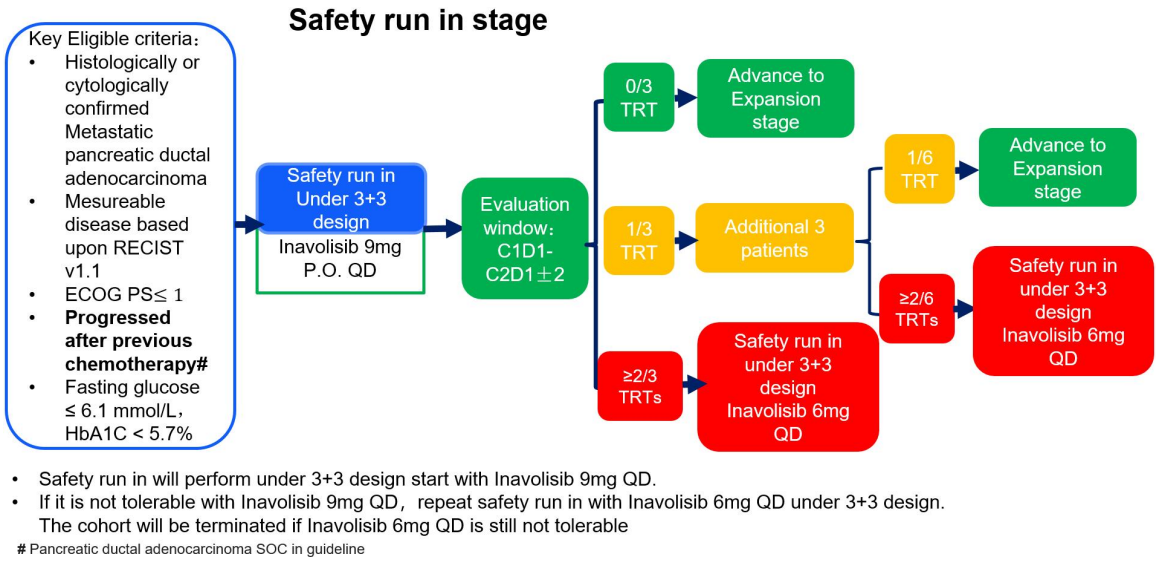
Patients will be closely monitored for adverse events throughout the study, including the incidence, nature and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE 5.0).

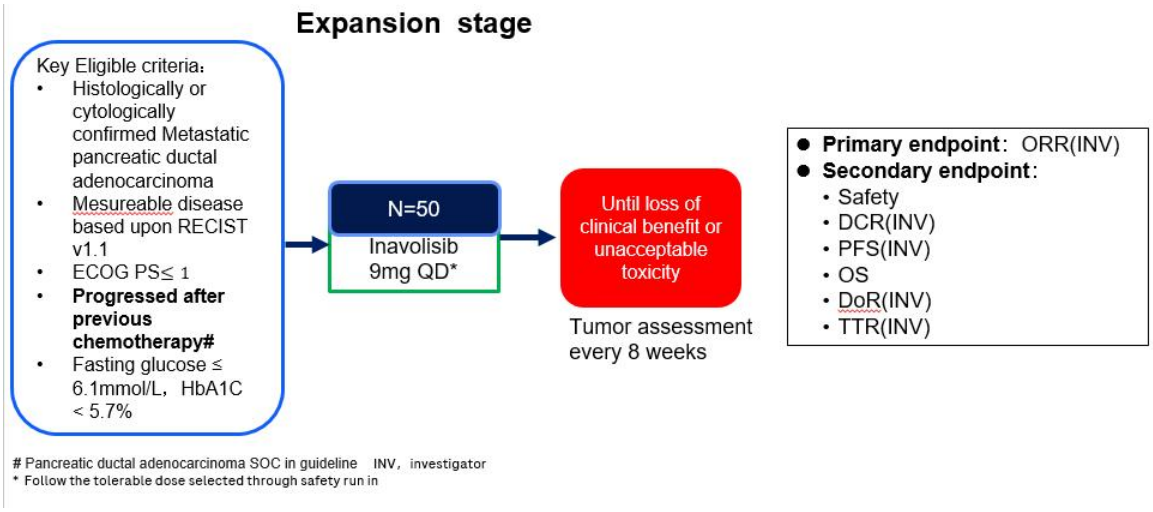
In the expansion stage, an interim AC review will be performed twice when 25 patients and 40 patients are response-evaluable. All safety data and tumor response data of these patients by this timepoint will be reviewed by AC in order to provide a recommendation whether to continue, modify or terminate the study. The final decision will be based on the totality of the benefit-risk profile. An AC charter will outline roles and responsibilities of the AC members as well as the policies and procedures to be followed by the AC. Any safety outcome that may affect the study conduct will be informed in a timely manner to investigators for notification of the Institutional Ethics Committees (IECs).

Following treatment discontinuation, follow-up information will be collected by telephone, patient medical records, and/or clinic visits every 3 months until death, loss to follow-up, withdrawal of informed consent or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up.

During the expansion stage, patients who withdraw from the study will not be replaced.

Figure 1 Study Flow





3.1.2 Assessment Committee

An Assessment Committee (AC) will evaluate safety and tumor response data during the study. The Assessment Committee(AC) should be comprised of multidisciplinary experts, including an **independent clinical oncologist/pancreatic cancer specialist** to serve as the Chairperson, a **biostatistician** experienced in interim analysis, a **pharmacology/toxicology expert, and an endocrinologist/diabetes specialist** to focus on hyperglycemia management, all of whom should be independent of the study team. Representatives from other Sponsor functional areas may be included as ad hoc members.

All safety data will be dynamically monitored during the safety run-in stage, and all available safety data will be collected and reviewed *during the treatment* period of each patient. AC will review all safety data at specific time points (refer to Section 3.1.1.1). The safety data may include, but are not limited to, demographic, study conduct, adverse events (including serious adverse events and adverse events of special interest), and relevant laboratory data. After reviewing the data, the AC will provide a final decision of the study according to the AC Charter. The expansion stage will be initiated by AC based on the safety profile of the safety run-in phase. The dose of Inavolisib in the expansion stage will follow the safety run in result. All available safety data and tumor response data will be reviewed twice as interim futility analysis, scheduled to occur when there are 25 and 40 response-evaluable patients to provide a recommendation whether to continue, modify or terminate the study (see Section 6.5).

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is planned 8 months after LPI. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 15 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Safety run-in phase

The phase I study GO39374 has explored escalating doses of Inavolisib monotherapy. Inavolisib monotherapy has shown to be safe and tolerable in patients with advanced/metastatic *PIK3CA*-mutated solid tumors patients, but there are no PDAC patients.

In this study, inavolisib will be administered to patients with >=2L PDAC patients. Although inavolisib has been approved for breast cancer indications in China and GO39374 has shown Inavolisib monotherapy is safe and tolerable in advanced/metastatic *PIK3CA*-mutated solid tumors patients, there is still a lack of data on pancreatic cancer patients, including dosage. The study will start a safety run-in phase under a “3+3” design to closely monitor the patients safety and tolerability as well as help to better understand possible risk of the treatment setting. It will refer to the dose that has been approved for marketing and conduct a dose de-escalation design. A “3+3” design could limit the number of patients exposed to Inavolisib and collect comprehensive safety data.

3.3.2 Rationale for Inavolisib Dose and Schedule

Inavolisib will be administered at a fixed dose of 9 mg P.O. QD, which is an approved dosage for Inavolisib, as outlined in the prescribing information. In Study GO39374, the MTD for inavolisib as a single agent was considered to be exceeded at the 12 mg QD dose level, and the inavolisib 9 mg QD dose level was identified as the MTD. The exposure

response analyses, preliminary longitudinal TGI analysis, high-dose intensity (＞90%) seen across all exposure quartiles of inavolisib at 9 mg QD, low discontinuation rate of inavolisib due to AEs (6.2% in INAVO120), and substantial clinical benefit observed with 9 mg QD dose in INAVO120 altogether indicate that inavolisib 9 mg QD dose has a favorable risk-benefit profile and is considered as the optimal dose for further studies as a single agent or in combination with other anti-cancer therapies.

3.3.3 Rationale for Dosing beyond Cycle 1

The ethical conduct of a study of cancer therapy requires that patients have the opportunity to continue study treatment provided that the treatment is active and tolerable, and that patients comply with the requirements of the protocol. Therefore, dosing beyond Cycle 1 will be allowed in the absence of unacceptable toxicity or clinically compelling disease progression, at the investigator's discretion, following a careful assessment and thorough discussion of the potential risks and benefits with the patient.

3.3.4 Rationale for Patient Population

This study will enroll ≥2L PDAC patients, regardless of *PIK3CA* mutation status、E-cadherin expression and other biomarker selection. This target population has been chosen to address their limited treatment options, unsatisfied outcome and unmet medical needs for improved treatment strategy. If Inavolisib shows clinically significant anti-tumor activity in this population, it can enrich the treatment options for this population and provide a chemo-free treatment option without having to prove that it is more effective than chemotherapy.

3.3.5 Rationale for Objective Response Rate as Primary Endpoint

In this study, the primary efficacy endpoint will be investigator-assessed objective response rate. This study is not designed to account for statistical power and Type I error considerations but rather aims to obtain preliminary safety and efficacy data for Inavolisib as a second-line treatment for patients with pancreatic ductal adenocarcinoma (PDAC).

Objective response rate was chosen as the primary endpoint for this study, as ORR rate is a clinical meaningful and the most direct indicator of the drug's anti-tumor activity. By observing the ORR of Inavolisib monotherapy in the PDAC population, we can directly understand the anti-tumor activity of Inavolisib in the PDAC population without indirect comparison, which is the basis for future follow-up exploration of Inavolisib in PDAC.

3.3.6 Rationale for Biomarker Assessments

The PI3K/AKT pathway is frequently activated in PDAC， mainly caused by *KRAS* mutation（prevalence about 90%）rather than *PIK3CA* mutations（prevalance ranging from 3% to 5%）. *PIK3CA* mutations might be a predictive biomarker for Inavolisib in PDAC but only a few subsets. Review of the literature shows the relationship between E-cadherin and the PI3K/AKT pathway is intricate and appears bidirectional across different cancer types. And the prevalence of E-cadherin is higher than *PIK3CA* mutations. E-cadherinmay serve as a potential predictive biomarker for Inavolisib efficacy in PDAC patients.

Tissue samples will be collected at baseline and retrospectively analyzed by IHC for E-cadherin expression to explore its value as a potential predictive biomarker for Inavolisib efficacy.

4. MATERIALS AND METHODS

4.1 PATIENTS

Up to 62 patients with PDAC will be enrolled in this study.

Approximately 3-12 patients with PDAC will be enrolled during the study safety run-in phase under the "3+3" approach at the study leading site. After completion of the safety run-in phase, 50 additional patients may be enrolled at study sites. All patients will be enrolled in China.

4.1.1 Inclusion Criteria

Patients must meet all the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 years at time of signing Informed Consent Form
3. Ability to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically confirmed diagnosis of pancreatic ductal adenocarcinoma.
5. The disease must have progressed after previous chemotherapy given in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), 1st line therapy of locally advanced, or metastatic setting.
6. Availability of a representative tumor specimen that is suitable for pathological evaluation and biomarker expression analysis.
   - A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in approximately 8-10 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization.
   - If less than 8 slides are obtained, but there are enough slides for E-cadherin testing by local lab at each site, patients are still eligible.
7. ECOG Performance status (PS) of 0 or 1 within 7 days prior to initiation of study treatment.
8. At least one measurable lesion per RECIST v1.1
9. Adequate hematologic and organ function, defined by the following laboratory test results, obtained within 7 days prior to initiation of study treatment:
   - ANC ≥ 1.5×10^9/L (1500/μL) without granulocyte colony-stimulating factor support
   - Lymphocyte count ≥ 0.5×10^9/L (500/μL)
   - Platelet count ≥ 100×10^9/L (100,000/μL) without transfusion
   - Hemoglobin ≥ 90 g/L (9 g/dL)

     Patients may be transfused to meet this criterion, but must not have been transfused within 2 weeks prior to screening
   - Fasting glucose < 6.1 mmol/L and HbA1c < 5.7%
   - AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN).

- Total bilirubin ≤ 1.5 × ULN with the following exception:

  Patients with known Gilbert disease: total bilirubin ≤ 3 × ULN
- Serum creatinine ≤ 1.5 × ULN or Creatinine clearance ≥ 60 mL/min (calculated using the Cockcroft-Gault formula)
- Albumin ≥ 25 g/L (2.5 g/dL)
- For patients not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 × ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen

10. Negative HIV test at screening
11. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

    Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 1 weeks after the final dose of study treatment. Women must refrain from donating eggs during this same period.
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
    - Women can consider egg banking prior to enrolling in the clinical trail to preserve the potential for future fertility.
12. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 1 weeks after the final dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.
    - Men can consider sperm banking prior to enrolling in the trial to preserve potential for future fertility.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway.
2. Prior treatment with any RAS inhibitor or BRCA inhibitor.
3. Known hypersensitivity to any of the components of study treatments.
4. Histology consistent with small cell carcinoma, Neuroendocrine carcinoma, or mixed carcinoma.
5. Type 2 diabetes requires ongoing systemic treatment at the time of study entry; or pre-diabetes, or any history of Type 1 diabetes； or any other type of diabetes; or any other type of diabetes.
6. Inability or unwillingness to swallow pills
7. Malabsorption syndrome or other condition that would interfere with enteral absorption
8. Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:
   – Measurable disease outside the CNS
   – No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases
   – Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic assessments
   – Screening CNS radiographic assessments ≥ 4 weeks since completion of radiotherapy
   – No history of intracranial hemorrhage or spinal cord hemorrhage
9. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently
   Indwelling pleural or abdominal catheters may be allowed, provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved, and has prior approval from the Medical Monitor.
10. Serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1
11. Any concurrent ocular or intraocular condition excluding cataracts (e.g. diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition.
12. Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye

13. Requirement for daily supplemental oxygen
14. Symptomatic active lung disease, including pneumonitis
15. History of or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)

    Patients currently receiving immunosuppressants for inflammatory bowel disease (e.g., sulfasalazines) are considered to have active disease and are therefore ineligible.
16. Any active bowel inflammation (including diverticulitis)
17. Any serious medical condition or abnormality in clinical laboratory tests that precludes an individual's safe participation in and completion of the study
18. Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

    Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.
19. Clinically significant and active liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
20. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that renders the patient at high risk from treatment complications
21. Chemotherapy, radiotherapy, or any other anti-cancer therapy within 2 weeks before study treatment
22. Investigational drug(s) within 4 weeks before study treatment
23. Prior radiotherapy to ≥ 25% of bone marrow, or hematopoietic stem cell or bone marrow transplantation
24. Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade ≤ 2 peripheral neuropathy
25. History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
26. History of or active clinically significant cardiovascular dysfunction, including the following:

    – History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment

    – History of myocardial infarction within 6 months prior to first dose of study treatment

    – New York Heart Association Class III or IV cardiac disease or congestive heart failure requiring medication

    – Uncontrolled arrhythmias, history of or active ventricular arrhythmia requiring medication

    – Coronary heart disease that is symptomatic or unstable angina

    – Congenital long QT syndrome or QT interval corrected through use of Fridericia's formula > 470 ms demonstrated by at least two ECGs > 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
27. Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
28. Chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease

29. Treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
30. Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within the time frame in which contraception is required
    Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment or negative urine pregnancy test if serum pregnancy test is not available.
31. Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
32. Minor surgical procedures <7 days prior to first dose of study treatment.
33. Patients must have sufficiently recovered from surgery, including adequate wound healing.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a multicenter single arm study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number.

Patients will be assigned to receive Inavolisib monotherapy treatment.

4.2.2 Blinding

NA

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is Inavolisib.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Inavolisib

Inavolisib will be supplied by Roche as an immediate release tablet formulation (3-mg and 9-mg). The 3-mg tablet is a greyish orange to brownish orange, round film-coated tablet and the 9-mg tablet is a greyish orange to brownish orange, oval film-coated tablet. The 3-mg and 9-mg tablets should be stored at or below 86°F (30°C) and protected from light. Inavolisib will be administered orally QD on Days 1-28 of each 28-day cycle at a starting dose of 9 mg. Inavolisib should be taken at approximately the same time each day without regard to the timing of food administration. If a dose is missed (not taken within 9 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose.

The excipients in inavolisib Drug Product include microcrystalline cellulose, lactose, magnesium stearate, and sodium starch glycolate. In addition, the 3 mg and 9 mg tablets include Opadry® II brown film coating.

For further details, see the Inavolisib IB.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1 (see Table 2). Patients will receive study treatment until unacceptable toxicity or loss of benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status.

It is recommended that patients keep a daily medication diary to assist them with inavolisib compliance. Patients will be asked to record the time and date that they take each dose in a medication diary. Patients should return daily dosing diaries and unused inavolisib tablets at every visit for assessment of inavolisib compliance and accountability.

If a patient misses an inavolisib dose by more than 9 hours or vomits up a tablet, he or she should be instructed to skip that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring their medication diary and unused inavolisib tablets at the end of the cycle for accountability.

Patients who experience a selected TRT during the safety run in assessment window should have inavolisib dosing suspended. Inavolisib should be permanently discontinued, except when the selected TRT is reversible and monitorable and the benefit-risk ratio suggests a reasonable rationale for the patient to continue study treatment, with approval by the Investigator. In such cases, if the selected TRT improves to Grade ≤1 within 21 days, inavolisib dosing may resume at one dose level lower. Dose Modification Guidelines for Inavolisib-Related Adverse Events Inavolisib：Starting dose 9 mg QD, first reduction 6 mg QD, second reduction 3 mg QD. If the patient continues to experience specified drug-related adverse events after the second dose reduction, inavolisib should be discontinued.

Patients who withdraw or discontinue from the study prior to completing the select TRT assessment window for reasons other than a select TRT will be considered non-evaluable for dose decisions and assessments, and will be replaced by an additional patient at that same dose level. Patients who receive at least 75% of planned inavolisib doses and remain in the study through the TRT assessment window will be considered evaluable. Patients who do not receive at least 75% of planned inavolisib doses during the TRT assessment window will be replaced to ensure that at least 3 patients in each cohort have been assessed for the full TRT assessment period of 28 days prior to moving to the expansion stage. During the expansion stage, patients who withdraw from the study will not be replaced.

4.3.3 Supportive medication

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided b y Roche. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by Roche. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Roche-supplied IMPs must be agreed to by Roche. The site must obtain written authorization from Roche before any Roche-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the applicable Investigator's Brochure or local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Inavolisib

Currently, the Sponsor does not have any plans to provide Roche IMPs (Inavolisib) to patients who have completed the study.

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience toxicities should be treated symptomatically as clinically indicated.

Anti-emetic and anti-diarrheal medications should not be administered prophylactically before initial treatment with study treatment. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drug.

To reduce the risk of stomatitis, dexamethasone 0.5 mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) may be started concurrently with study treatment. No food or drink should be consumed for at least 1 hour after swishing and spitting the dexamethasone mouthwash.

Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study and are to be recorded on the Analgesic Concomitant Medications eCRF.

Bisphosphonate or denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed. Multivitamins, calcium, and vitamins C, D, and E as supplements are allowed. However, due to the potential for drug-supplement interactions, and variability among suppliers and batches, the use of other dietary supplements is cautioned and should be discussed with the Medical Monitor in advance.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

In vitro data suggest that both inavolisib and paclitaxel are substrates of the efflux transporter P-gp. Therefore, concomitant use of inhibitors of P-gp is not recommended in this study.

Inhibitors of P-gp: ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar, and valspodar.

Inavolisib has been shown to have the potential to induce CYP3A4 in human hepatocyte culture. Therefore, DDIs with co-administered CYP3A4 substrates cannot be excluded at this point. Moderate/strong inhibitors or inducers of CYP3A4 as listed below should be used with caution during study treatment.

- Strong/moderate CYP3A4 inhibitors, including, but not limited to, the following: atazanavir, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, troleandomycin, fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, aprepitant, conivaptan, fluvoxamine, diltiazem, nefazodone, mibefradil, verapamil, and grapefruit juice or grapefruit supplements.
- Strong/moderate CYP3A4 inducers, including, but not limited to, the following: rifampin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital, efavirenz, nevirapine, etravirine, modafinil, hyperforin (St. John's Wort), and cyproterone

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is strongly discouraged because the pharmacokinetics, safety profiles, and potential drug-drug interactions (DDI) are generally unknown.

4.4.3 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 7 days prior to initiation of study treatment, unless otherwise specified below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, herbal and traditional Chinese medicine therapy), whether health authority−approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Radiotherapy for unequivocal progressive disease with the exception of new brain metastases in the setting of systemic response as follows: patients who have demonstrated control of their systemic disease (defined as having received clinical benefit [i.e., a PR, CR, or SD for ≥3 months]), but who have developed brain metastases that are treatable with radiation, will be allowed to continue to receive therapy with inavolisib in the study until they either experience systemic progression of their disease and/or further progression in the brain (based on investigator assessments). Patients should not miss more than one cycle of study treatment due to radiation treatment and must meet eligibility requirements to continue receiving treatment.
- Quinidine or other anti-arrhythmic agents.
- Primary prophylactic use of hematopoietic growth factors (e.g., erythropoietins, granulocyte colony-stimulating factor [G-CSF], and granulocyte-macrophage colony stimulating factor [GM-CSF]) is not permitted from 7 days before Cycle 1, Day 1 until completion of the safety run in assessment window in absence of a selected TRT. However, they may be used to treat treatment-emergent neutropenia or anemia indicated by the current ASCO guidelines or per standard clinical practice.
- Patients who require the use of any prohibited therapies will be discontinued from study treatment and followed for safety outcomes for 30 days after their last dose of inavolisib, or until they receive another anti-cancer therapy, whichever occurs first.

4.4.4 Lifestyle Restrictions

Consumption of grapefruit, grapefruit juice, or Seville oranges (potent CYP3A4 enzyme inhibitors) is prohibited for at least 14 days prior to initiation of study treatment and during study treatment.It is advisable for participants at high risk of hyperglycemia (age ≥ 35 years, family history of Type 2 diabetes, history of gestational diabetes, body mass index [BMI] ≥ 24) to adopt lifestyle changes; that is, dietary advice (e.g., small frequent meals, low carbohydrate diet (carbohydrates $<$ 130 g/day or $<$ 26% of a 2000 kcal/day diet), high fiber, balanced carbohydrate intake over the course of the day, three small meals and two small snacks rather than one large meal) and exercise. Consultation with an endocrinologist or diabetologist is highly recommended.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

All patients will be closely monitored for safety and tolerability during the course of therapy and at the study treatment discontinuation visit. Patients will be assessed for toxicity at all study visits; continued dosing will occur only if the clinical assessments and local laboratory test values are acceptable.

Every effort should be made to adhere to the protocol-mandated visits and procedures. For patients receiving study treatment beyond the safety run in assessment window, if the timing of a protocol-mandated visit coincides with a holiday and/or other scheduling conflict that causes the visit to fall outside of the protocol-defined visit windows, the visit should be scheduled on the nearest date, which may be earlier or later than the originally scheduled visit.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, dysglycemia (prediabetes or diabetes),and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g. prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

As part of the tumor assessment, physical examinations should include evaluation of the presence and degree of enlarged lymph nodes.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Tumor and Response Evaluations

Imaging studies will include a computed tomography (CT) scan of the chest, abdomen, and pelvis. A bone scan or other institutional standard bone imaging to assess for extent of disease should be performed as clinically indicated. Subsequent bone scans or other institutional standard bone imaging are optional if the patient does not have bone metastases. At screening, a CT scan of the neck and CT or magnetic resonance imaging (MRI) brain should be obtained if clinically indicated.

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. A documented standard-of-care tumor assessment performed within 28 days prior to Cycle 1 Day 1 may be used for the required screening assessment provided it meets the above requirements.

Tumor response assessment will be performed every 8 weeks± 1 week. Response will be assessed by the investigator on the basis of physical examinations, CT scans and other imaging modalities as clinically indicated, which may include brain imaging (CT or MRI), MRI scans, or bone scan, using RECIST v1.1 criteria. An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Special considerations regarding the measurability and assessment of bone lesions are outlined in RECIST v1.1.

At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Positive areas on bone scans should be assessed by either CT scan with bone windows, MRI, or X-ray. Bone lesions identified at baseline by CT scan, MRI or X-ray should be assessed using the same modality (CT scan, MRI, or X-ray) throughout the study. Additional bone scans or skeletal surveys should be performed if clinically indicated. If a bone scan cannot be performed during the course of the study due to, for example, a Technetium-99m shortage, alternative imaging options should be discussed with the Medical Monitor (e.g., sodium fluoride [NaF]).

For metformin-treated patients undergoing CT scans with contrast, metformin should be held as per institutional standard of care.

4.5.6 Laboratory, Biomarker, and Tissue Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis. When noted, fasting samples should be collected after a minimum 8-hour fast.

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate and LDH
- Fasting glucose (may be obtained by glucometer [fingerstick] or 24 hours continuous fasting glucose measure
- Fasting Insulin and C-peptide
- HbA1c
- Fasting lipid profile: total cholesterol, HDL, LDL, triglycerides, amylase, and lipase
- Serum CEA 、Serum CA19-9
- C-Reactive Protein (CRP) Test
- Coagulation: INR, and aPTT
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- HIV serology

The following samples sent to the study site's local laboratory for analysis with the permission by Human Genetic Resources Administration of China (HGRAC):

- Archival or newly collected tumor tissue sample obtained at baseline for efficacy objective analysis and exploratory research on biomarkers

  A representative FFPE tumor specimen in approximately 8-10 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report within 4 weeks of randomization. If fewer than 8 slides are obtained, but there are enough slides for biomarker analysis by the the local laboratory of each site, the patient may still be eligible for the study, after Medical Monitor confirmation has been obtained.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Samples should be from primary tumor tissue, and Tumor tissue from lymph node metastases are not acceptable.

Exploratory biomarker research includes analysis of E-cadherin and/or genomic signatures to further understand whether and why E-cadherin can be a predictor biomarker. E-cadherin will be tested by Immunohistochemistry. Guided by clinical and nonclinical data, additional exploratory research to evaluate potential predictive biomarkers, to understand mechanism of action of the drug, and of disease biology using assays for analysis of proteins and/or genes may be performed with the permission by HGRAC.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The leftover biological samples will be returned to the site as per the site requirement or destroyed when the final Clinical Study Report has been completed, with the following exceptions:

Tumor tissue and blood samples collected for exploratory biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed or earlier depending on local regulations. However, the storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Electrocardiograms

Triplicate 12-lead ECG will be performed at screening. For triplicate ECG, three individual ECG tracings should be obtained as closely as possible in succession, at least 2 minutes apart but no more than 5 minutes apart.

Single 12-lead ECG recordings will be obtained at specified timepoints (see Schedule of activities) and may be obtained at unscheduled timepoints as indicated.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Post-Treatment Hyperglycemia Follow-Up Assessment

Participants who, at the end of the 30-day safety follow-up, are still receiving antihyperglycemic agents for the treatment of hyperglycemia, and those participants with events of hyperglycemia ongoing at the end of the 30-day safety follow-up, will undergo additional safety follow-up assessments for hyperglycemia monthly until resolution of their fasting glucose to baseline levels, complete down titration of their antihyperglycemic medications, or up to approximately 3 months after the final dose of study treatment, even if the participant initiates another anti-cancer therapy subsequent to study treatment discontinuation.

The investigators must collect data to support the following assessments (antihyperglycemic medication, fasting FBG, fasting insulin , C-peptide and HbA1c per SOA) :

- Time taken for complete resolution of participants' fasting blood glucose, fasting insulin, and HbA1c to baseline levels or better; baseline levels refer to the FBG values at screening before they have started any prophylactic anti-hyperglycemic medication.

- Time taken for the complete down-titration of participants' anti-hyperglycemic medications; complete down-titration refers to complete stopping of the antihyperglycemic medication or down-titrating to the baseline dose of antihyperglycemic medication given as prophylaxis.

- Status of the ongoing adverse events of hyperglycemia and any additional information associated with the events.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Unequivocal disease progression (defined using RECIST v1.1; see Appendix 3)
- Symptomatic deterioration attributed to disease progression as determined by the investigator
- Intolerable toxicity related to study treatment determined by the investigator to be unacceptable given the potential for treatment benefit and the severity of the event
- Any medical condition that the investigator and/or Sponsor determines may jeopardize the patient's safety if he or she continues on study treatment
- Use of non-protocol systemic anti-cancer therapy (see Section 4.4.2)

- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced..

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study (verbally or in writing) at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Any AE that requires treatment discontinuation per the guidelines outlined (if any);
- Severe non-compliance with the study protocol;
- Patients that for any reason interrupt treatment for more than 28 days;
- Occurrence of other malignancies that required systemic treatments;
- Any medical condition that may jeopardize the patient's safety if she continues study treatment;
- Disease Progression per RECIST v 1.1 as assessed by the Investigator;
- Pregnancy.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

Following treatment discontinuation, follow-up information will be collected by telephone, patient medical records, and/or clinic visits every 3 months until death, loss to follow-up, withdrawal of informed consent or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up.

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients

- Patient enrollment is unsatisfactory
- The futility criteria is met or the decision based on the totality of the benefit-risk profile
- Data recording is inaccurate or incomplete.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

This is the first study in which Inavolisib will be administered to PDAC patients. Meanwhile, due to the specialty of PDAC in metabolism dysregulation, safety profile of Inavolisib in breast cancer, especially hyperglycemia cannot be directly referenced. Therefore, the safety profile in PDAC patients is not known at this time. The following information is based on the anticipated mechanism of action, nonclinical data (in vitro and in vivo), preliminary clinical data, and published data on similar PI3K/AKT/mTOR pathway inhibitor molecules. The safety of participating patients will be addressed through appropriate inclusion/exclusion criteria, the implementation of appropriate dose-modification and treatment guidelines, and real-time safety monitoring and assessments. Please refer to the Inavolisib Investigator's Brochure and prescribing information for a complete summary of safety information.

The study will start a safety run-in phase under a ‘3+3’ design to closely monitor the patients safety and tolerability as well as help to better understand possible risk of the treatment setting. A ‘3+3’ design could both limit the number of patients exposed to Inavolisib and collect comprehensive safety data of Inavolisib. An AC has also been incorporated into the study design to periodically review safety data and determine whether to continue, modify or terminate the study. (see the AC Charter for a detailed monitoring plan).

Safety will be evaluated through the monitoring of all serious and non-serious adverse events, with severity graded according to NCI CTCAE v5.0. Safety assessments will include interval history since the previous assessment, physical examinations, and specific laboratory studies, including CBCs and a serum chemistry panel. Patients will be monitored as outlined in Appendix 1 until the end of the adverse event reporting period.

All serious adverse events, selected TRTs, and adverse events of special interest (AESI) will be reported in "real time" (within 24 hours of the event) via the electronic data capture (EDC) system (for more details, see Section 5.4.2) to sponsor.

As this is the first study in which Inavolisib will be administered to PDAC patients., there is the potential for toxicities that cannot be predicted from animal studies. To mitigate potential unknown risks, at least in part, dosing beyond Cycle 1 will be limited to patients who are tolerating Inavolisib treatment and not exhibiting signs or symptoms of disease progression, as previously described in Section 3.3.3. In addition, complete recovery from any clinically relevant toxicities from prior chemotherapy, radiotherapy, or surgical procedures will be a requirement for study entry.

Dose determination of the expansion stage will occur following a review of available safety data after the last patient completes safety run in stage.

5.1.1 Identified and Potential Risks Associated with Inavolisib

On the basis of the established class effects of PI3K and mTOR inhibitors in patients with cancer, as well as nonclinical data and clinical experience , hyperglycemia and associated complications (including ketoacidosis), gastrointestiicities, stomatitis/oral mucositis, and rash are considered as identified risks for inavolisib. Potential risks including pneumonitis, immunosuppressant effects, ocular toxicities, reproductive toxicity, embryo-fetal toxicity and colitis. Given that these adverse events may require either dose interruptions and/or dose reductions or may have the potential to cause life-threatening conditions, close monitoring and a robust risk-mitigation strategy are warranted during the conduct of this Phase II study. Refer to the Inavolisib IB for details.

5.1.1.1 Hyperglycemia and associated complications (including ketoacidosis)

Effects on glucose and/or insulin metabolism are a known effect with PI3K inhibitors. Increased glucose was observed in rat and dog toxicology studies at all doses tested and appeared to be dose dependent. Severe cases of hyperglycemia, including complications such as life-threatening ketoacidosis, have been reported in participants receiving inavolisib and is an identified risk of inavolisib. Meanwhile, patients with pancreatic cancer are more likely to have impaired islet function. Hence, only fasting glucose ≤ 6.1mmol/L （110mg/dl） or HbA1C < 5.7% patients without any anti-diabetes medications will be included in the study. Fasting glucose levels will be assessed at baseline, and fasting glucose, insulin levels and C-peptide will be monitored during the study, as outlined in Appendix 1. Participants should be advised to report symptoms associated with hyperglycemia such as polydipsia, polyuria, polyphagia, blurry vision, or symptoms associated with acidosis such as rapid or shallow breathing, confusion, fatigue, headache, or drowsiness.

The preferred first-line agent for the management of hyperglycemia is metformin or in the investigator’s discretion; more detailed guidelines for study treatment dose modification, interruption or discontinuation, and medical management for patients who experience hyperglycemia are provided in Section 5.1.2.3.

5.1.1.2 Stomatitis and Oral Mucositis

Treatment related stomatitis/oral mucositis has been reported with the use of Inavolisib. Patients should be advised to report symptoms immediately. Intervention should begin at the earliest signs of oral mucosal inflammation. A compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment, and/or used reactively with the first appearance of symptoms. Patients should avoid alcohol, hydrogen peroxide, iodine, or thymecontaining products, as they may exacerbate the condition. They should also avoid harsh mouthwashes (e.g., Listerine). Diet should be modified (e.g., avoidance of spicy foods). Guidelines for managing stomatitis and oral mucositis are provided in Section 5.1.2.4.

5.1.1.3 Gastrointestinal Toxicities

In the 4-week toxicology study in dogs of Inavolisib, gastrointestinal inflammation was observed. Thus, patients with inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, and active bowel inflammation (e.g., diverticulitis) will be excluded from this study. Gastrointestinal effects will be closely monitored by interval history and physical examination (see Appendix 1). Development of abdominal pain, nausea, vomiting, clinically significant changes in stool (e.g., diarrhea, bloody stools), and stomatitis/oral mucositis may necessitate more frequent monitoring, and study drug may be held if symptoms are prohibitive for normal function. Clinical evaluation for infectious (e.g., Clostridium difficile, enteric bacteria, and cytomegalovirus) or inflammatory (e.g., inflammatory colitis) etiologies for diarrhea should be conducted. Guidelines for managing gastrointestinal toxicities are provided in Section 5.1.2.6.

5.1.1.4 Rash

Treatment-related rash has been reported for other PI3K inhibitors in clinical studies and is commonly manifested as a maculo-papular rash with or without pruritus. Rash and other dermatologic events should be closely monitored and managed per standard of care. Guidelines for management of rash, including dosage modification, are provided in Section 5.1.2.5.

5.1.1.5 Potential Lung Inflammation/Pneumonitis

Lung inflammation was observed in the 4-week dog study at the highest dose tested. This finding was observed only at a dose level considered not tolerable in this species. Interstitial lung inflammation/pneumonitis has been observed in clinical studies with other PI3K inhibitors. Specific management guidelines and guidance for holding or discontinuing therapy for symptomatic and asymptomatic pneumonitis based on the severity of pneumonitis are provided in Section 5.1.2.8.

5.1.1.6 Potential Immunosuppressant Effects

Immunosuppression and increased risk of infections are known to be associated with marketed PI3K-mTOR pathway inhibitors. Toxicology studies demonstrated decreases in reticulocytes, leukocytes, and absolute lymphocyte counts in animals treated with

Inavolisib. Thus, patients who are immunocompromised as the result of HIV or receiving immunosuppressive therapies will be excluded from this study. Patients will be monitored routinely for changes in circulating blood counts, including white cell differential, and should be monitored for fever and signs of infection.

5.1.1.7 Potential Reproductive Effects

Potential adverse effects on male reproductive function, including focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis, were observed in one or more dogs in the 4-week repeat-dose toxicity study. Focal inspissation of seminiferous tubule contents persisted in one animal at the end of the 4-week recovery period.

Patients should be notified of the possibility of permanent reproductive sterility. Measures might be taken for sperm banking to preserve the potential for future fertility. Because of the unknown effects on human reproductive organs and gonadal cells, all male and female patients should use an effective means of contraception (e.g., abstinence, double-barrier method, surgical sterilization of partner) while taking Inavolisib.

5.1.1.8 Potential Embryo-Fetal Toxicity

The embryo-fetal development study in Sprague Dawley rats identified inavolisib-related dose dependent effects on embryo-fetal development that included decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, and teratogenicity (fetal external, visceral, and skeletal malformations).

No embryo or fetus should be exposed to inavolisib. Please refer to the Inavolisib Investigator's Brochure for a complete summary of safety information about embryo-fetal toxicity.

5.1.1.9 Potential Ocular Toxicities

In the 4-week toxicology study in rats, lens degeneration was observed in the highest inavolisib dose group (10 mg/kg; 4 of 30 rats). This finding was characterized by minimal-to-mild lens fiber swelling, separation of lens fibers, and/or accumulation of subcapsular proteinaceous material. Dry eye and blurred vision were the most common ocular AEs reported in WO41554 study. Please refer to the Inavolisib Investigator's Brochure for a complete summary of safety information of ocular toxicities. *Participants* will undergo ophthalmic examinations at baseline during the screening period, and based on any ocular disturbances.

5.1.1.10 Potential Colitis Toxicity

Colitis is considered to be an immune-mediated toxicity of PI3K inhibitors, especially the PI3K delta isoform inhibitors such as idelalisib, duvelisib and umbralisib.

Review of the nonclinical toxicology studies for inavolisib revealed dose-dependent and reversible microscopic inflammation in the GI tract (including esophagus and rectum) in beagle dogs administered inavolisib for three months at a dose of 0.5−1.5 mg/kg/day (10 times the recommended human dose), and the inflammation correlated with pathological

changes in inflammatory markers. Please refer to the Inavolisib Investigator's Brochure for a complete summary of safety information of colitis.

Based on these findings and expectedness owing to class effect, participants with active inflammatory gastrointestinal disease are excluded from inavolisib clinical studies, and all study protocols involving inavolisib specify dose modification and management guidelines for gastrointestinal toxicities (diarrhea and nausea/vomiting) and colitis to mitigate the risks.

5.1.1.11 Drug-Drug Interactions

Inavolisb has been shown to have the potential to induce CYP3A4 in human hepatocyte culture. Therefore, DDIs with co-administered CYP3A4 substrates cannot be excluded at this point. In addition, in vitro data suggest that Inavolisibis a substrate of the efflux transporter P-glycoprotein (P-gp). As such, care should be taken with co-administered drugs that are metabolized by this enzyme system, especially if those drugs have a narrow therapeutic index, because their systemic concentrations could be decreased when co-administered with Inavolisib (See Section 4.4.3).

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications of Inavolisib

The Inavolisib dose reduction instructions provided in Table 7 are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while monitoring patient safety.

These guidelines are intended to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the investigator in managing individual cases. In addition to these guidelines, more conservative drug interruptions or dose reductions for the management of adverse events are permitted at the discretion of the investigator when deemed to be in the best interest of the patient.

Table 7 **Overall Dose Modification Guidelines for Inavolisib-Related Adverse Events**

	Inavolisib
Starting dose	9mg QD
First reduction	6mg QD
Second reduction	3mg QD[a]

QD = once daily.
[a] If the patient continues to experience specified drug-related adverse events after the second dose reduction, inavolisib should be discontinued.

5.1.2.2 Treatment Interruption of Inavolisib

The investigator may temporarily suspend inavolisib dosing due to inavolisib-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression.

Dose interruptions of study treatment should not exceed one cycle (i.e., approximately 28 days); participants withheld from treatment beyond 30 continuous days are expected to be withdrawn from study treatment unless in the investigator's assessment the participant may benefit from continuing study treatment in such an instance. Inavolisib treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The investigator will determine the acceptable length of treatment interruption in such cases.

Dose re-challenge or re-escalation of inavolisib is permitted only after a thorough benefit-risk evaluation by the investigator and should be documented by the investigator.

During safety run in stage, patients who withdraw or discontinue from the study prior to completing the safety evaluation window for reasons other than a select TRT will be considered non-evaluable for dose decisions and assessments, and will be replaced by an additional patient at that same dose level. Patients who receive at least 75% of planned inavolisib doses and remain in the study through the safety evaluation window will be considered evaluable. Patients who do not receive at least 75% of planned inavolisib doses and during the safety evaluation window will be replaced to ensure that at least 3 patients have been assessed for the full TRT assessment period of 28 days prior to moving to the expansion stage. During expansion stage, patients who withdraw from the study will not be replaced.

5.1.2.3 Management of Hyperglycemia

The anti-hyperglycemic agent metformin preferably extended release metformin or long-acting metformin should be used as first-line for the management of sustained fasting glucose > 160 mg/dL or > 8.9 mmol/L or anytime fasting glucose is > 250 mg/dL or > 13.9 mmol/L. Metformin should be up-titrated to the maximum allowed dose as per local prescribing information and may be given in divided doses as tolerated. Metformin will start lowering fasting blood glucose levels in the first week of treatment, but it may take 2-3 months to exert its full effect. Metformin should not be discontinued upon improvement or resolution of hyperglycemia but maintained throughout the duration of inavolisib treatment. Investigators should exercise caution in the dosing and management of participants receiving metformin in combination with inavolisib and must be vigilant for signs of renal impairment and metformin toxicity.

Participants administered metformin should be cautioned and monitored for signs of intolerance or toxicity, including lactic acidosis, which may occur in the setting of acute worsening of renal function or cardiorespiratory illness or sepsis and can be life-threatening. The most frequently reported adverse events with metformin are nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. Metformin does not produce hypoglycemia, but it may occur with a missed meal, alcohol consumption, heavy exercise, or when it is taken with another type of diabetes medicine.In the event metformin is not tolerated or not sufficient, or not deemed suitable, another anti-hyperglycemic medication(s) may be added to or used in place of metformin. Preferred

agents include sodium glucose co-transporter 2 (SGLT2) inhibitors, pioglitazone, and dipeptidyl peptidase-4 inhibitors, where available and considered appropriate by investigators. If SGLT2 inhibitors are prescribed, ensure adequate hydration and monitor for vaginal yeast infections. Participants administered pioglitazone should be monitored closely for signs of heart failure including fluid retention or edema. Participants administered insulin or sulfonylureas should be treated with caution when these agents are used to manage hyperglycemia and inavolisib is subsequently interrupted or discontinued: this can lead to rapid escalation of insulin levels and risk of hypoglycemia. Short-term insulin is allowed to control blood glucose levels, but goal should be to maintain participants on oral agents once acute episode resolves. Long-term insulin use is not recommended. For each of these agents, refer to the local prescribing information for additional information.

Participants at risk for developing hyperglycemia (e.g., clinical diagnosis of pre-diabetes, BMI ≥ 24 kg/m^2,, ≥ 35 years of age, family history of diabetes, history of gestational diabetes, and any other factor that may lead to increased risk of developing hyperglycemia [e.g. certain ethnicities, inactive lifestyle etc.]) should initiate treatment with metformin by Day 1 of the study, where allowed by local regulations.

Table Management of Hyperglycemia

Grade(NCI CTCAE v5.0) or Condition Fasting Glucose Values	**Action to be Taken with Inavolisib**	**Adverse Event Management and Monitoring**	**Action with next dose (as applicable)**
All Values	Not applicable	● Encourage participants to adopt a diabetic diet (low carbohydrate diet) ● Consider consultation with endocrinologist or diabetologist	Not applicable
>ULN to 160 mg/dL (8.9 mmol/L)	Continue current dose level of Inavolisib	● Provide home glucose monitoring to high-risk participants and	Not applicable

		educate to check fasting glucose at home [a] ● *O*ral anti-diabetic medications (e.g., metformin) *should be initiated* for highrisk participants [a] ● Recheck in 3 days and adjust medications as needed [b]	
>160 to 250 mg/dL (>8.9-13.9 mmol/L)	Interrupt Inavolisib dose	● Start or increase dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor)[c] ● Recheck in 3 days and adjust or add anti-diabetic medications as needed [b] ● Initiate fasting home glucose monitoring	● Inavolisib dose interruption until hyperglycemia resolves to < 160 mg/dL *(*8.9 mmol/L*)*; then resume current dose level [d] ● If fasting blood glucose persists > 200-250 mg/dL*(* > 11.1-13.9 mmol/L*)* for 7 days despite above interventions, discuss with the Medical Monitor [d]

>250 to 500 mg/dL (>13.9-27.8 mmol/L)	Interrupt Inavolisib	• Manage hyperglycemia as per standard of care [c, e] • Start or increase dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor)[c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed [b] • Initiate fasting home glucose monitoring	• *Interrupt inavolisib.* • *If hyperglycemia resolves to ≤ 250 mg/dL (≤ 13.9 mmol/L) within 7 days, may resume at current dose level of inavolisib after hyperglycemia further resolves to ≤ 160 mg/dL (≤ 8.9 mmol/L).* • *If hyperglycemia resolves to ≤ 250 mg/dL (≤ 13.9 mmol/L) in ≥ 8 days, reduce inavolisib dose by one dose level when treatment resumes after hyperglycemia further resolves to ≤ 160 mg/dL (≤ 8.9 mmol/L). [f]* • *If hyperglycemia > 250–500 mg/dL (> 13.9-27.8 mmol/L)*

			recurs within 30 days, reduce inavolisib dose by one dose level. [f]
>500 mg/dL (>27.8 mmol/L)	Interrupt Inavolisib	• Manage hyperglycemia as per standard of care [c, e] • Assess for volume depletion and ketosis and administer appropriate intravenous or oral hydration • Start or increase the dose for an oral anti-diabetic medication (e.g., metformin, SGLT2 inhibitor) [c] • Recheck in 3 days and adjust or add anti-diabetic medications as needed [d] • Initiate fasting home glucose monitoring	• *Interrupt inavolisib.* • *When hyperglycemia resolves to ≤ 160 mg/dL (≤ 8.9 mmol/L), reduce inavolisib dose by one dose level when treatment resumes.* [f] • *If hyperglycemia > 500 mg/dL (> 27.8 mmol/L) recurs within 30 days, permanently discontinue inavolisib.*

SGLT2 = sodium-glucose transport protein 2; ULN = upper limit of normal.

[a] High-risk factors for diabetes include pre-diabetes, body mass index greater or equal to 24 kg/m2, ≥35 years of age, family history of diabetes, history of gestational diabetes and any other factors that increases the risk of hyperglycemia (like certain ethnicities, sedentary lifestyle etc.).

[b] Fasting glucose should be checked by finger stick or lab value (if patient has scheduled appointment) PRIOR to dosing. Oral anti-diabetic medications should be titrated to the maximum allowed dosages to achieve control of blood glucose to ≤160 mg/dL or 8.9 mmol/L. For example, metformin may be administered to a maximum dose allowed as per local prescribing information, given in divided doses, as tolerated. Please see local prescribing information of individual oral anti-diabetic agents for dosing guidelines.

[c] There is a risk of hypoglycemia if insulin or sulfonylureas are used, particularly if these agents are started during periods of Inavolisib exposure and doses are not adjusted appropriately during periods of treatment interruption, during which patients' insulin sensitivity may increase rapidly. Short term insulin is allowed to control blood glucose levels, but the goal should be to maintain oral agents once acute episodes resolve.

[d] If, in the investigator's opinion, the benefit-risk assessment favors continued inavolisib dosing without interruption, inavolisib may be continued without interruption upon discussion with Medical Monitor once participants are managed on anti-diabetic agent(s) and fasting glucose≤200 mg/dL [≤11.1 mmol/L]. It is recommended that participants be instructed to utilize a home glucometer to monitor fasting glucose and to call the clinic if fasting glucose＞*160* mg/dL [＞*8.9* mmol/L] prior to inavolisib dosing at home.

[e] It is recommended that the participant is reassessed within 24 hours and preferably the same day for assessments of hydration status and renal function..

[f] A maximum of two dose reductions will be allowed.

Additional Management Guidelines for Participants at High Risk of Hyperglycemia

Patient Characteristics	Guidelines

• Body mass index ≥ 24 kg/m^2 • Age ≥ 35 years • Family history of diabetes • History of gestational diabetes • Any other factor that increases the risk of hyperglycemia (e.g., certain ethnicities such as African American, South Asian; sedentary lifestyle)	Participant*s should* be instructed to monitor fasting glucose at home on a daily basis*, as needed. The investigator should instruct the patient in the use of a glucometer to perform home glucose monitoring.* Consultation with an endocrinologist or diabetologist is highly recommended. *P*rophylactic treatment with metformin (by Day 1 of Cycle 1) *should be initiated* in participants with more than one risk factor, where allowed by local regulations. Recommend moderate lifestyle changes such as: • Dietary advice (e.g., small frequent meals, low carbohydrate content, high fiber, balanced carbohydrate intake over the course of the day, three small meals and two small snacks rather than one large meal, avoiding drinking sugar-sweetened beverages and switch to water whenever possible. • Increase daily physical activity and exercise.

5.1.2.4 Management of Stomatitis/Oral Mucositis

For any grade stomatitis/mucosal inflammation, aggressive mouth care should be implemented early to help manage or prevent symptoms. A compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis. As per the SWISH study (Rugo et al. 2017), patients may use 4 times daily for 8 weeks (10 mL swished for 2 minutes and spat) started concurrently with study treatment, and/or used reactively with the first appearance of symptoms. No food or drink should be consumed for at least 1 hour after swishing and spitting the dexamethasone mouthwash. Additional mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) or topical corticosteroids (e.g., triamcinolone acetonide 0.05-0.5%, fluocinolone acetonide 0.025-0.05%, clobetasol propionate 0.025%) may be implemented. Diet should be modified (e.g., avoidance of spicy foods) and harsh mouth washes (e.g., Listerine®) should be avoided.

Grade(NCI CTCAE v5.0) or Condition	Action to Be Taken with Inavolisib	Adverse Event Management and Monitoring	Action with next dose (as applicable)
Any grade	● See grade-specific guidance	● Intervene early ● For management, please refer to Section5.1.2.4	● Not applicable
Grade 1	Continue current dose level of inavolisib	● Initiate management as above ● Monitor symptoms and compliance with oral regimen ● Re-evaluate within 48–72 hours	● Not applicable
Grade 2	● Interrupt Inavolisib and manage as above until Grade ≤ 1	● Manage per institutional guidelines	● When stomatitis/oral mucositis improves to Grade ≤ 1, resume *inavolisib* dosing at the same dose or one dose level lower per investigator evaluation ● For recurrent Grade 2 stomatitis or oral mucositis within 30 days, resume

			inavolisib dosing at one dose level lower
Grade 3	● Interrupt Inavolisib and manage until Grade ≤ 1	● Manage per institutional guidelines	● When stomatitis/oral mucositis improves to Grade ≤1, resume inavolisib dosing at one dose level lower.
Grade 4	● Permanently discontinue Inavolisib	● Manage per institutional guidelines	● Not applicable for inavolisib

5.1.2.5 Management of Rash

Grade (NCI CTACE v5.0) or Condition	Action to be Taken with Inavolisib	Adverse Event Management and Monitoring	Action with next dose (as applicable)
Grade 1	● Continue current dose level of Inavolisib and monitor for changes in severity	● Consider prescribing topical corticosteroids [a] and/or antihistamines	● Not applicable
Grade 2	● Interrupt Inavolisib treatment	● Treat rash per standard of care, including topical and/or oral corticosteroids,[b] and/or antihistamines	● When rash resolves to Grade ≤1 and steroids have been downtitrated to ≤10 mg prednisone equivalent, resume inavolisib at the same dose or one dose level lower per

			investigator evaluation
Grade 3	• Interrupt Inavolisib treatment	• Treat rash with topical and/or systemic corticosteroids (oral or IV) and antihistamines • Consider dermatologist consultation and skin biopsy	• If rash resolves to Grade ≤1 within 30 days and steroids have been downtitrated to ≤ 10 mg prednisone equivalent, reduce inavolisib/placebo by one dose level when treatment resumes • If rash does not resolve to Grade ≤ 1 within 30 days, discontinue Inavolisib
Grade4	• Permanently discontinue inavolisib	• Manage per institutional guidelines	• Not applicable

[a] Suggested topical steroids include hydrocortisone 2.5% to face 2times daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body 2times daily.

[b] Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by taper (e.g., 60 mg x 2 days, 40 mg x 2 days, 20 mg x 2 days, etc.)

Patients with severe rash should also be monitored for associated signs and symptoms, such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. Permanently discontinue treatment for any rash with concurrent signs/symptoms strongly suggestive of a severe Type I hypersensitivity or anaphylactic/anaphylactoid reaction or with painful desquamation or mucosal involvement suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis or with other life-threatening complications. Dermatological consultation is recommended.

5.1.2.6 Management of Diarrhea

Grade **(NCI CTACE**	Action to be Taken with Inavolisib	**Adverse Event Management and Monitoring**	**Action with next dose (as applicable)**

v5.0) or Condition			
Grade1	● Continue current dose level of Inavolisib	● Adequate treatment with anti-diarrheals [a] and maximum supportive care [b]	● Not applicable
Grade2	● Interrupt Inavolisib	• Adequate treatment with anti-diarrheals [a] and maximum supportive care [b] ● Close monitoring	● Interrupt Inavolisib until recovery to Grade ≤1, may resume at the same dose ● If recurs within 30 days, reduce Inavolisib by one dose level
Grade3	● Interrupt Inavolisib	● Manage as per Grade 2 diarrhea guidelines	● Interrupt Inavolisib until recovery to Grade ≤1, then reduce by one dose level ● If recurs within 30 days after initiation of the first dose reduction, reduce inavolisib by one dose level.

			If recurs within 30 days from the second dose reduction, permanently discontinue inavolisib
Grade4	● Permanently discontinue Inavolisib	● Manage per institutional guidelines	● Not applicable

[a] Initiate loperamide (Imodium®) dose with 4 mg, then 2 mg every loose stool up to 16 mg/day. May consider using a combination of loperamide and Lomotil® (diphenoxylate and atropine) or codeine phosphate. Monitor closely for dehydration or constipation. May initiate second-line therapy (e.g., octreotide) if Grade ≥ 2 diarrhea persists after 48 hours of treatment with loperamide and/or Lomotil®.

[b] Supportive care: initiate appropriate dietary modification, hydration therapy, and electrolyte supplements when clinically indicated. Dietary modification includes: stop all lactose-containing products and eat small meals; encourage adequate hydration with salt-containing liquids such as broth or Gatorade®.

5.1.2.7 Management of Inflammatory Colitis

Grade **(NCI CTACE v5.0) or Condition**	Action to be Taken with Inavolisib	**Adverse Event Management and Monitoring**	**Action with next dose (as applicable)**
Grade1	● Continue current dose level of inavolisib	● Close monitoring and treat as appropriate	Not applicable
Grade2	● Interrupt Inavolisib	● If colitis-related symptoms do not improve to Grade ≤ 1 after 48 hours of anti-diarrheals,	● Interrupt Inavolisib until recovery to Grade ≤ 1, then may resume at the same dose or one dose level lower

		start treatment with oral corticosteroid [a] •	per investigator evaluation • If recurs within 30 days, reduce Inavolisib by one dose level
Grade3	Interrupt Inavolisib	• Treat with high dose corticosteroids (IV solumedrol or PO prednisone) [b] • Consider colonoscopy	• Interrupt inavolisib/placebo until recovery to Grade ≤ 1 and steroids have been downtitrated to ≤ 10 mg prednisone equivalent, then reduce by one dose level • If Grade 3 recurs, permanently discontinue inavolisib
Grade4	Permanently discontinue Inavolisib	Manage per institutional guidelines	Not applicable

[a] 20-40 mg prednisone PO QD (starting dose).

[b] For severe grades, may also consider IV solumedrol 16-20 mg every 8 hours, or prednisone 60-80 mg PO QD equivalent to start.

5.1.2.8 Management of Pneumonitis

Grade **(NCI CTACE v5.0) or Conditio n**	**Actions to be Taken with Inavolisib**	**Adverse Event Management and Monitoring**	**Action with next dose (as applicable)**

Grade 1	• Continue Inavolisib without any dose modification .	• No specific therapy required • Chest CT scan • Repeat CT at least every 8 weeks until return to baseline • Consider pulmonologist/ respirologist consult • Advise participant to promptly report new or worsening respiratory symptoms	Not applicable
Grade 2	• Interrupt Inavolisib	• Prescribe corticosteroids if	• Hold Inavolisib and until any corticosteroids have been downtitrated to ≤ 10 mg prednisone equivalent and pneumonitis improves to Grade ≤ 1. Resume Inavolisib dosing at the same dose or one dose level lower per

		infectious etiology is ruled out ● Taper as clinically indicated ● Obtain a chest CT scan ● Repeat CT at least every 8 weeks until return to baseline ● Consider PFTs ● Obtain pulmonologist/respirologist consult	investigator evaluation ● For recurrent Grade 2 event, resume Inavolisib dosing at one dose level lower
Grade 3	● Interrupt Inavolisib	● Prescribe corticosteroids if infectious etiology is ruled out ● Taper as clinically indicated ● Obtain a chest CT scan ● Repeat CT at least every 8 weeks until return to baseline ● Consider PFTs and bronchoscopy ● Obtain pulmonologist/respirologist consult	● Hold Inavolisib until any corticosteroids have been down titrated to ≤ 10mg prednisone equivalent and pneumonitis improves to Grade ≤ 1. Resume Inavolisib dosing one dose level lower.
Grade 4	● Permanently discontinue Inavolisib	● Prescribe corticosteroids if infectious etiology is ruled out	● Not applicable

		• Taper as clinically indicated • Obtain a chest CT scan • Repeat CT at least every 8 weeks until return to baseline. • Consider PFTs • Obtain pulmonologist/respirologist consult • Bronchoscopy is recommended	

CT = computed tomography (scan); PFTs = pulmonary function tests

5.1.2.9 Management of Other Clinically Significant Adverse Events

Inavolisib may be continued without interruption for uncomplicated Grade 3 hematologic toxicities with the exception of neutropenic fever where Inavolisib should be interrupted until neutrophil count recovers to Grade ≤ 2. Inavolisib then may resume at the same dose.

For uncomplicated Grade 4 neutropenia, Inavolisib may be continued without interruption. Interrupt Inavolisib for all other Grade 4 hematologic toxicities until recovery to Grade ≤ 2, and then resume Inavolisib at the same dose.

See Table 8 for Inavolisib dose modifications for other clinically significant adverse events attributed to Inavolisib.

Table 8 Inavolisib Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events Attributed to Inavolisib

Grade	Inavolisib
Grade3，first event	Hold Inavolisib until Grade ≤ 1 Resume Inavolisib at the same dose or one dose level lower per investigator evaluation
Grade3, recurrent or Grade4, non-life-threatening	Hold Inavolisib until Grade ≤ 1. Resume Inavolisib dosing at one dose level lower.

Grade4, life-threatening	Permanently discontinue Inavolisib

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including SAE,AESI and Select Treatment-Related Toxicity (TRT) in safety run in stage（Section 3.1.1.1）， serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
    - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Grade≥ 3 hyperglycemia
- Grade≥3 rash
- Grade≥3 diarrhea
- Grade≥2 pneumonitis
- Grade≥2 colitis or enterocolitis
- Grade≥3 stomatitis or mucosal inflammation
- Grade≥3 ALT or AST elevation

Adverse events of special interest for general：

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4−5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.1 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment regardless of initiation of any new systemic anti-cancer therapy (see Section 5.4.1.2 for instructions).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.1 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.1 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 9 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

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

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.1 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should

be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

Cases of potential drug-induced liver injury, as defined by Hy's Law below:

When baseline ALT or AST values are within the normal range, the finding of an elevated ALT or AST ($>$3 ×ULN) in combination with either an elevated total bilirubin ($>$ 2× ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

When baseline ALT or AST are above the normal range, the finding of an elevated ALT or AST ($>$ 3 ×baseline) in combination with either an elevated total bilirubin ($>$2 ×ULN of which ≥35% is direct bilirubin) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of rectal cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor(see Section 5.4.2). An internal monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Pancreatic ductal adenocarcinoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event. Cases of clinical/symptomatic progression will not be considered as objective disease progression per RECIST v1.1, and should be reported only as a reason for End of Treatment, when appropriate. The Overall Tumor Assessment at such a timepoint should be reported strictly per RECIST v1.1.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Medication Error and Other Special Situations

Medication error and other special situations and any associated adverse events will be recorded and reported

- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, wrong dosing schedule, incorrect route of administration)

- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm

- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.1 for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.1 for details on reporting requirements)
- Pregnancies (see Section 5.4.2 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Reporting Requirements for all Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.1.2 Events That Occur after Study Treatment Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 30 days after the final dose of study drug, or until initiation of another anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to sponsor by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the reporting period are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 60 days after the final dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.2.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 98 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.2.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.2.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the patient is lost to follow-up, or the patient withdraws consent.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined in Section 5.3.1), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situation Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Inavolisib	Inavolisib Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An IMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

5.8 SAFETY REPORTING TO STUDY FUNDER

The Sponsor will submit safety reports to the Study Funder within the timeframe specified in the Safety Data Exchange Agreement (SDEA).

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to evaluate the preliminary efficacy and safety of Inavolisib monotherapy in 2L pancreatic ductal adenocarcinoma（PDAC） patients.

The analysis sets are defined as follows:

The Safety Run-in Analysis Set (SRAS) will consist of all patients who enrolled in the safety run-in phase and received at least one dose of study drug. The analysis of all safety run-in endpoints will be conducted on the SRAS.

The Full Analysis Set (FAS) will consist of all patients (combining the expansion phase and those from the safety run-in phase who received the same dose as in the expansion phase) who received at least one dose of the study drug and have one or more measurable lesions at baseline. The analysis for tumor response and other efficacy-related endpoints will be performed on the FAS.

The Safety Analysis Set (SAS) will consist of all patients (combining the expansion phase and those from the safety run-in phase who received the same dose as in the expansion phase) who received at least one dose of study drug. If the study successfully progresses to the expansion phase, the analysis of all safety endpoints, unless noted otherwise, will be conducted on the SAS.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to account for statistical power and Type I error considerations but rather aims to obtain preliminary safety and efficacy data for Inavolisib as a second-line treatment for patients with pancreatic ductal adenocarcinoma (PDAC).

The planned enrollment for this study (both safety run-in stage and expansion stage) is up to approximately 62 patients. The sample size for safety run-in stage is based on a 3+3 design, with up to 12 patients to be enrolled. In the expansion stage, an additional 50 patients will be enrolled. With a targeted ORR>=26%, a sample size of 53 patients would be able to produce a lower bound of the associated 95% CI (calculated using Clopper-Pearson method) to exclude a 15% threshold. Different scenarios with their associated 95% CI are presented in Table 2 below. With the sample size of 53 and a two-sided 95% CI, the probability of detecting an improvement in ORR compared with a historical ORR of 15% is shown in Table4.

Table 3 Objective Response Rate Scenarios

	N=53		N=56	
Expected Objective Response Rate	Expected Number of Patients with a Response	95% CI for Objective Response Rate	Expected Number of Patients with a Response	95% CI for Objective Response Rate
23%	12	（12.3，36.2）	13	（13.0，36.4）
26%	14	（15.3，40.3）	15	（15.8，40.3）
30%	16	（18.3，44.3）	17	（18.8，44.1）

Table 4 Probability of Detecting ORR Improvement (Reference:15% ORR)

	N=53
True ORR difference compared to 15%	Probability (%) of Detecting ORR Improvement
8%	33%
11%	53%
15%	76%

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study drug administration, reasons for study drug discontinuation, and reasons for discontinuation from the study will be summarized. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics (including age, sex, etc.) and baseline characteristics (， e.g., ECOG Performance Status, disease history, and stage at study entry) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary endpoint for this study is objective response rate (ORR). ORR is defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions >=4 weeks apart during investigation treatment, as determined by the investigator according to RECIST v1.1. Patients not meeting this criterion will be considered non-responders. ORR will be analyzed in the FAS. An estimate of the response rate and its 95% CI will be provided. The 95% CI will be calculated with the Clopper Pearson method (Clopper and Pearson 1934) .

6.4.2 Secondary Efficacy Endpoints

Progression free survival (PFS) Assessed by Investigators

Investigator-assessed PFS (INV-assessed PFS), defined as the time from the first day of study treatment to the first occurrence of disease progression assessed by investigator according to RECIST v1.1 or death due to any cause (whichever comes first). Data for patients who have not experienced disease progression or death at the time of the analysis data cutoff will be censored at the time of last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of Inavolisib initiation. PFS will be analyzed in the FAS.

The Kaplan-Meier method will be used to estimate the median PFS and PFS rate at the selected time points (e.g. 6months,12 months), and a Kaplan-Meier curve will be constructed to provide a visual description. The 95% confidence intervals for the median PFS will be calculated according to Brookmeyer and Crowley (1982) and 95% confidence intervals for the survival function estimates at above defined timepoints will be derived using the log-log transformation according to Kalbfleisch and Prentice (2011).

Overall Survival (OS)

OS, defined as the time from the first day of study treatment to death from any cause. Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of Inavolisib initiation.

Analysis methodology is as outlined for the PFS.

Disease control rate（DCR）

DCR, defined as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) >= 4 weeks. Response will be assessed by the investigator according to RECIST v1.1.

Analysis methodology is as outlined for the primary endpoint ORR.

Duration of response (DOR)

DoR, defined as time from first evidence of PR or CR to disease progression or death due to any cause. DOR will be calculated only for subjects who achieve a confirmed response of PR or CR. Data for patients without the occurrence of disease progression or death at the time of the analysis data cutoff will be censored at the time of the last tumor assessment.

Analysis methodology is as outlined for the PFS.

Time to Response (TTR)

TTR, defined as time from the first day of study treatment to the first evidence of PR or CR. TTR will be calculated only for subjects who achieve a best overall response of confirmed PR or better. TTR will be summarized with descriptive statistics.

6.4.3 Biomarker Endpoints

Biomarker analyses will be performed in an effort to understand the association of these markers with study treatment response, efficacy, and/or adverse events. The tumor biomarkers from tissue include but are not limited to E-cadherin.

Biomarker analyses are exploratory and will be presented in a separate report.

6.5 SAFETY ANALYSES

The safety analyses for the safety run-in stage will be performed on the *SRAS.*

If the study successfully progresses to the expansion stage, the safety analyses will be performed on the SAS.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, Vital Sign, and 12-lead ECG Data

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0**.** All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment

discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 INTERIM ANALYSIS

Interim futility analysis is planned for the primary endpoint ORR rate in this study.

The assessment committee will oversee futility analyses performed and based on the ORR analysis set. The interim futility analyses will be conducted in a continuous manner using Bayesian predictive probability (Lee and Liu, 2008) to evaluate monotherapy. It will begin after approximately 25 response-evaluable subjects, defined as having received at least 1 dose of Inavolisib and have had at least one post-baseline tumor assessment. Subjects who stopped disease assessments prior to 8 weeks will be included in this analysis if the data cutoff is at least 8 weeks after their first dose date. Following the initial interim analysis, a second interim analysis will be conducted after an additional 15 response-evaluable subjects are enrolled.

The assessment committee may recommend stopping the trial if the futility criteria is met. The final decision will be based on the totality of the benefit-risk profile beyond the ORR futility stopping rule.

The futility analyses will be based on Inv-assessed disease response. Subjects with unconfirmed PR or CR will be counted as responders for this futility analysis if they are still in study at the time of data cutoff and potential for future confirmation scan.

The success criterion will be met if the probability that the true ORR exceeds the benchmark

ORR is ≥ to a high probability of:

- Success Criterion : probability [ORR > 0.10] ≥ 80%

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability is obtained by calculating the probability of reaching a success criterion if the treatment group is enrolled and evaluated to the planned maximum final sample size of 56 subjects. The success criterion is for interim futility analysis purpose only.

Futility will be met if it is predicted that there is a small probability of reaching a success criterion upon full enrollment of subjects given the existing observed data. A noninformative prior distribution of beta (1, 1) will be used.

- Futility Criterion: Predictive probability < 5%

The decision rules and operating characteristics for continuous monitoring of ORR are provided in table 5.

Table 5 Stopping Boundary and Operating Characteristics

Number of Subjects	Considered Futile If Observing Number of Responses	Cumulative Probability of Futility					
		True ORR=0.02	True ORR=0.05	True ORR=0.1	True ORR=0.2	True ORR=0.3	True ORR=0.4
25	**<=1**	**91.1%**	**64.2%**	**27.1%**	**2.7%**	**0.2%**	**0.0%**
40	**<=3**	**99.3%**	**87.7%**	**46.4%**	**4.4%**	**0.2%**	**0.0%**
56	<=7	100%	97.9%	74.0%	9.7%	0.3%	0.0%
Average Number of Subjects		27	33	45	55	56	56

6.7 EXPLORATORY BIOMARKER ANALYSIS

Exploratory biomarker analysis will be performed in an effort to understand the association of these markers with study treatment response, efficacy, and/or adverse events. The tumor biomarkers from tissue include, but are not limited to E-cadherin. Results from these exploratory analyses may be reported separately from the Clinical Study Report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An

acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC−approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study,, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Fudan University Shanghai Cancer Center. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 4 sites in China will participate to enroll up to *62* patients.

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An AC will monitor and evaluate patient safety throughout the study. Tumor response and progression will be evaluated by investigators.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Activities

Assessment	Screening [a]	Study Treatment（28days per cycle）					Study Treatment Discontinuation Visit[b]	Hyperglycemia F/U[c]	Survival Follow-Up [d]
Day	-28 to -1	1	4	7	15	22	≤ 30 days from last dose	Monthly up to 3 months	every 3 months (±2 weeks)
(Window)		D1[f]	(±1d)	(±1d)	(±1d)	(±1d)			
Informed consent [e]	X								
Demographic data	X								
Medical history and baseline conditions	X								
Vital signs [f]	X	X	C1	C1	X	C1	X		
Weight	X	X					X		
Height	X								
Complete physical examination [g]	X						X		
Limited physical examination [h]		X	C1	C1	X	C1			
ECOG performance status	X	X	C1	C1	X	C1	X		
12-lead ECG [i]	X	X					X		
Hematology [j]	X	X	C1	C1	X	C1	X		

Fasting serum or plasma Chemistry [k]	X	X	C1	C1	X	C1	X		
Serum or urine pregnancy test [l]	X	X					X		
Glycosylated hemoglobin （HbA1c） [m]	X	Every 3 cycles					X	X	
Fasting glucose [n]	X	X	C1	C1	X	C1	X	X	
Fasting insulin and C-peptide [n]	X	X	C1	C1	X	C1	X	X	
Fasting lipid profile plus amylase, and lipase [o]	X	C1D28，then every 3 cycles					X		
Urinalysis [p]	X	X	C1	C1	X	C1	X		
Serum CEA	X	X					X		
Serum CA19-9	X	X					X		
C-reactive protein	X	X					X		
Serum fibrinogen, Coagulation (aPPT, INR, PT)	X	X					X		
STUDY TREATMENTS									
Inavolisib		QD							
IMAGING ASSESSMENT [q]									
Radiological imaging （CT/MRI） and Tumor assessment	X	every 8 weeks							

Appendix 1: Schedule of Activities

Bone scan	X	Investigator assessment if necessary							
MRI brain	X	Investigator assessment if necessary							
Pre-treatment tumor tissue sample（fresh or archival） for biomarkers [r]	X								
E-cadherin testing by Immunohistochemistry（IHC）	Complete the test before the end of the study								
pre-treatment blood sample for NGS[s]	X								
Concomitant medications [t]	X	X	C1	C1	X	C1	X		
Adverse events [u]	X	X	C1	C1	X	C1	X		
Survival [v]									X
Post-treatment assessment of ongoing hyperglycemia and management								X	
Post-treatment anti-cancer therapy [w]							X		X

[a] **SCREENING PERIOD** - Perform within 28 days prior to Cycle 1, Day 1, with the exception of laboratory assessments, which must be obtained within 14 days prior to Cycle 1, Day 1. Written informed consent is required before performing any study-specific tests or procedures and may be obtained at any time prior to such tests or procedures. Results of standard-of-care tests or examinations

performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening. Unless otherwise stated, screening assessments that are done within 2 days prior to Cycle 1, Day 1 do not need to be repeated on Cycle 1, Day 1.

[b] STUDY TREATMENT DISCONTINUATION VISIT - Participants who discontinue study treatment permanently should return to the clinic for a treatment discontinuation visit within 30 days after their final dose of study drug. While multiple assessments are expected at this visit, and follow up of adverse events is expected until 30 days after the final dose of study treatment, or until initiation of another anti-cancer therapy, whichever occurs first. Thus, for practicality, the need for the treatment discontinuation visit should ideally be discussed with the participant at the time the decision is made to discontinue the last study drug, and the treatment discontinuation visit should ideally be scheduled for 30 days after the final dose of study treatment.

[c] POST-TREATMENT HYPERGLYCEMIA FOLLOW-UP - Patients on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment and those patients with events of hyperglycemia ongoing at the end of the 30-day safety follow-up, will undergo additional safety follow-up assessments monthly until resolution of their fasting glucose to baseline levels, complete down-titration of their anti-hyperglycemic medications, or up to approximately 3 months after the final dose of study treatment, even if the patient initiates another anti-cancer therapy subsequent to study treatment discontinuation.

[d] SURVIVAL FOLLOW-UP PERIOD - After study treatment discontinuation and post-treatment follow-up, all patients will be followed for survival and all subsequent anti-cancer therapies. These data will be collected approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

[e] INFORMED CONSENT - Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] VITAL SIGNS - Includes height, weight, respiratory rate, pulse rate, blood oxygenation (pulse oximetry), and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[g] COMPLETE PHYSICAL EXAMINATION - Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[h] LIMITED PHYSICAL EXAMINATION - Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[i] ECG - Triplicate 12-lead ECG recordings will be obtained at baseline to determine eligibility; otherwise, single 12-lead ECG recordings will be performed.

[j] HEMATOLOGY- Hematology panel includes: RBC count, hemoglobin, hematocrit, reticulocyte count, platelet count, WBC count with differential count (neutrophils, bands [optional], eosinophils, basophils, monocytes, lymphocytes, other cells; i.e., must be sufficient for

the determination of ANCs, lymphocytes). Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess prior to dosing.

[k] FASTING CHEMISTRY - Fasting (≥ 8-hour fast) blood chemistry panel (serum or plasma) includes: sodium, potassium, chloride, bicarbonate (or total carbon dioxide if considered standard of care for the region), BUN or urea, creatinine, glucose, calcium, magnesium, phosphorus, total protein, albumin, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), total and direct bilirubin, and alkaline phosphatase (ALP). Laboratory samples should be drawn within 48 hours prior to study drug administration ; results for glucose, bilirubin, ALP, AST, and ALT should be available prior to dosing.

[l] PREGNANCY TEST - Women of childbearing potential must have a negative serum pregnancy test result within 14 days of first dose of study treatment and serum or urine pregnancy tests will be performed on Day 1 of Cycles ≥ 2 and at study treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential

[m] **HbA1c** - Assess at screening, every 3 cycles starting on Day 1 of Cycle 3 (e.g., Day 1 of Cycles 1, 3, 6, etc.), at treatment discontinuation visit, and monthly during the hyperglycemia safety follow-up.

[n] FASTING GLUCOSE AND INSULIN - Fasting (≥8-hour fast) insulin and glucose sample. Glucose levels may be obtained by glucometer (fingerstick) or via 24-hour continuous glucose monitoring (CGM), with the specific method to be jointly decided by the investigator and the participant. Finger test result or 24h continuous glucose result are based on the subcutaneous data, it is only reference rather than precise values. All the reads from fingers or 24h continuous test should be reviewed by the physicians before dosing. Samples should be drawn within 48 hours prior to study drug administration; glucose results must be available and reviewed prior to dosing. In addition, patients may be instructed to monitor fasting glucose more frequently via use of home glucometer.

[o] FASTING LIPID PROFILE PLUS AMYLASE AND LIPASE - Fasting (≥ 8-hour fast) lipid profile (includes total cholesterol, HDL, LDL, and triglycerides), amylase and lipase will be assessed at screening, every 3 cycles (e.g., Day 1 of Cycles 1, 3, 6, etc.), and at treatment discontinuation visit.

[p] URINALYSIS - Urinalysis (dipstick allowed) includes pH, specific gravity, glucose, protein, ketones, and blood; if clinically indicated, microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria.

[q] TUMOR ASSESSMENT - Tumor assessments are performed according to RECIST v1.1. Post-baseline tumor assessments should be performed every 8 weeks (± 7 days) from Cycle 1, Day 1, regardless of dose delay, treatment interruption or early treatment discontinuation, and until disease progression. At screening, bone scans or other institutional standard bone imaging should be acquired in all patients. The method used for a patient (CT or MRI scan or photographic measurements) must be the same throughout

the study. A missed tumor assessment should be rescheduled as soon as possible. Patients who discontinue study treatment for reasons other than disease progression or death will continue onto the “post-treatment tumor assessment follow-up”.

[r] PRE-TREATMENT TUMOR TISSUE SAMPLE (FRESH OR ARCHIVAL) FOR BIOMARKERS - Pre-treatment tumor tissue samples for biomarkers are mandatory and are to be collected fresh (preferred) within the study screening period or a recent archival tumor tissue sample can be submitted. If only an archival tumor tissue sample is available, the sample should preferably be from the patient’s primary disease. If none of these options are possible, please contact the Medical Monitor. 8-10 4-5 µm sections of FFPE will be applied for NGS if possible.

[s] BLOOD SAMPLE FOR BIOMARKER NGS - Blood sample for NGS is to be collected prior to dosing on Day 1 of Cycle 1.

[t] CONCOMITANT MEDICATIONS - Medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until 30 days after the final dose of study treatment. In addition, an Analgesics eCRF will be utilized to collect specific information regarding pain management at specific timepoints.

[u] ADVERSE EVENTS - After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment, or until initiation of another anti-cancer therapy, whichever occurs first. After the end of treatment and the 30-day safety follow-up visit, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to study drug treatment.

[v] SURVIVAL - After study treatment discontinuation and post-treatment follow-up, all patients will be followed for survival. These data will be collected via telephone calls and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

[w] POST-TREATMENT ANTI-CANCER THERAPY - After study treatment discontinuation, all patients will be followed for subsequent anti-cancer therapies. These data will be collected via telephone calls and/or clinic visits during the post-treatment follow-up and survival follow-up, approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Appendix 2 American Joint Committee on Cancer（AJCC） TNM Staging of Pancreatic Cancer (8th ed., 2017)

T stage

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma *in situ,*

This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with highgrade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia

T1: Tumor ≤2 cm in greatest dimension

T1a Tumor ≤0.5 cm in greatest dimension

T1b Tumor >0.5 cm and <1 cm in greatest dimension

T1c Tumor 1–2 cm in greatest dimension

T2: Tumor >2 cm and ≤4 cm in greatest dimension

T3: Tumor >4 cm in greatest dimension

T4: Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

N stage

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastases

N1: Metastasis in one to three regional lymph nodes

N2: Metastasis in four or more regional lymph nodes

M stage

M0: No distant metastasis

M1: Distant metastasis

Appendix 2 American Joint Committee on Cancer（AJCC） TNM Staging of Pancreatic Cancer (8th ed., 2017)

stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2, T3	N1	M0
III	T1, T2, T3	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Appendix 3 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)

10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Cystic Lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scans have slice thickness of >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation .

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two

sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm · 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non−lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non−lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non−lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

Complete response (CR): Disappearance of all target lesions

Any pathological lymph nodes must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in 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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228−47.