A Phase 1/2 Open-label, Multi-center Study of the Safety, Pharmacokinetics, and Anti-tumor Activity of LYT-200 as a Single Agent and in Combination with Chemotherapy or Tislelizumab in Patients with Locally Advanced or Metastatic Solid Tumors

Protocol Number: LYT-200-2020-01

Sponsor: PureTech Health LLC

6 Tide Street, 02210, Boston, MA, USA

Development Phase: Phase 1/2
Original Version: Protocol Version 1.0, dated 03 September 2020
Amendment #1: Protocol Version 2.0, dated 16 November 2020
Amendment #2: Protocol Version 2.1, dated 18 November 2020
Amendment #3: Protocol Version 2.2, dated 08 October 2021
Amendment #4: Protocol Version 2.3, dated 01 February 2022
Amendment #5: Protocol Version 3.0, dated 15 November 2022

Number of Pages: 133

IND number 144664

Property of PureTech Health LLC – Confidential

May not be used, divulged, published or otherwise disclosed without the consent of PureTech Health LLC

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Number: LYT-200-2020-01

Protocol Title: A Phase 1/2 Open-label, Multi-center Study of the Safety, Pharmacokinetics, and Anti-tumor Activity of LYT-200 as a Single Agent and in Combination with Chemotherapy or Tislelizumab in Patients with Locally Advanced or Metastatic Solid Tumors

Version #: 3.0

Version Date: 15 November 2022

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately described the planned conduct of the study. I hereby approve this protocol for release to clinical trial sites.

Sponsor Signatory:

DocuSigned by:
Aleksandra Filipovic
Signer Name: Aleksandra Filipovic
Signing Reason: I approve this document
Signing Time: 17-Nov-2022 | 05:04 EST
[illegible]

17-Nov-2022 | 05:04 EST

Aleksandra Filipovic MD, PhD
Head of Oncology, PureTech Health LLC

Date

INVESTIGATOR'S AGREEMENT

Title: A Phase 1/2 Open-label, Multi-center Study of the Safety, Pharmacokinetics, and Anti-tumor Activity of LYT-200 as a Single Agent and in Combination with Chemotherapy or Tislelizumab in Patients with Locally Advanced or Metastatic Solid Tumors

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB), or Human Research Ethics Committee. No changes will be made to the study protocol without the prior written approval of the Sponsor and the appropriate Ethics Committee, except where necessary to avert an immediate hazard to the participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), in accordance with the current version of International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and in accordance with the current version of National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (updated 2018). The conduct of the study will also be in accordance with the integrated Addendum to ICH E6 (R1), Guideline for GCP ICH E6 (R2).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigational Site

Printed name of Investigator

Signature of Investigator

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 3.0, 15 November 2022

Amendment #5.0

The following changes are incorporated into Version 3.0 of the protocol:

Description of change and rationale for change:

Combination treatment of LYT-200 at the planned dose levels of 6.3 mg/kg and 16.0 mg/kg once weekly (QW), combined with chemotherapy (gemcitabine/nab-paclitaxel) or an anti-PD-1 monoclonal antibody (tislelizumab), was added to Part 1 in pancreatic ductal adenocarcinoma (PDAC), head and neck (H/N) and urothelial cancers, to provide additional safety/tolerability data for LYT-200 in combination, for potential further investigation and expansion in Part 2.

Section(s) of the protocol affected:

Synopsis; Section 1.3.4; SoA (Table 2); Section 1.3.3; Section 2.1; Section 3.4.2; Section 4.2; Section 5.2, Table 6; Section 6.4.3; Section 6.7; Section 7.2.1;Section 8.2.1

Description of change and rationale for change:

The Part 2 design was revised to remove single agent administration of LYT-200 and to include tumor types investigated in Part 1, with the option of adding additional tumor types, depending on Part 1 results.

Sections of the protocol affected:

Synopsis; Section 3.4.3; Section 8

Description of change and rationale for change:

Part 3 was deleted.

Sections of the protocol affected:

Synopsis; Section 3.4.3

Description of change and rationale for change:

Estimated date last participant completed changed to from January 2023 to February 2024 to accommodate addition of new Part 1 cohorts.

Section(s) of the protocol affected:

Synopsis

Description of change and rationale for change:

The definition of backfill cohorts was changed to provide additional patients in the event that a preliminary/early efficacy signal is observed during Part 1 combination treatment, or a Part 1 combination treatment fails, and new indication(s)/tumor types are selected for evaluation. Previously the backfill cohort definition was to provide additional galectin-9 positive patients for further evaluation, but this is no longer required.

Section(s) of the protocol affected:

Synopsis; Section 3.4.2.2
Description of change and rationale for change: Part 1 Study Objectives and Endpoints: For the escalation cohort, the Primary Objectives were revised to include assessment of the safety and tolerability of LYT-200 as a single agent treatment and in combination with gemcitabine/nab-paclitaxel or tislelizumab, and to determine the recommended Phase 2 dose (RP2D) for LYT-200. The Exploratory Objective was changed from the evaluation of preliminary efficacy of LYT-200 to include the evaluation of the preliminary efficacy of LYT-200 as a single agent treatment and in combination with gemcitabine/nab-paclitaxel or tislelizumab. **Section(s) of the protocol affected:** Synopsis; Section 2.1
Description of the change and rationale for the change: Part 2 Study Objectives and Endpoints: The Primary Objectives were changed to reflect deletion of single agent administration of LYT-200 from Part 2. The Secondary Objectives were revised to reflect the change in Part 2 to H/N and urothelial cancer. **Section(s) of the protocol affected:** Synopsis; Section 2.2
Description of change and rationale for change: The Safety Monitoring Committee (SMC) rules were revised to accommodate the addition of Part 1 Combination Treatment and the changes to the Part 2 design. **Section(s) of the protocol affected:** Synopsis; Section 3.4; Section 3.8; Section 8.2.1

Description of change and rationale for change: Inclusion/Exclusion Criteria were revised to account for the addition in this amendment of the Part 1 combination treatment and the changes to the Part 2 design. **Section(s) of the protocol affected:** Synopsis; Section 4.1; Section 4.2; Section 4.3
Description of change and rationale for change: Statistical methods were revised to address dose escalation and sample size to accommodate the addition in this amendment of the Part 1 combination treatment and the changes to the Part 2 design. **Section(s) of the protocol affected:** Synopsis; Section 8
Description of change and rationale for change: The Study Schema was revised to accommodate in this amendment the addition of the Part 1 combination treatment and the changes to the Part 2 design. **Section(s) of the protocol affected:** Study Schema
Description of change and rationale for change: LYT-200 will be stored at 2°C to 8°C (liquid) or ≤ 65°C (frozen) and protected from light. **Section(s) of the protocol affected:** Section 5.3; Section 5.3.1; Section 5.3.2
Description of change and rationale for change: Minor grammatical and editorial changes have been made. **Section(s) of the protocol affected:** Changes were made throughout the protocol.

Version 2.3, 01 Feb 2022 Amendment #4
Version 2.2, 08 Oct 2021 Amendment #3
Version 2.1, 18 Nov 2020 Amendment #2
Version 2.0, 16 Nov 2020 Amendment #1

Version 1.0, 03 Sep 2020 Original Version

PROTOCOL SYNOPSIS

Name of Sponsor/Company:

PureTech Health LLC

Name of Investigational Product:

LYT-200

Name of Active Ingredient:

LYT-200, a fully human IgG4 monoclonal antibody targeting galectin-9

Protocol Number:

LYT-200-2020-01

Title of Study: A Phase 1/2 Open-label, Multi-center Study of the Safety, Pharmacokinetics, and Anti-tumor Activity of LYT-200 as a Single Agent and in Combination with Chemotherapy or Tislelizumab in Patients with Locally Advanced or Metastatic Solid Tumors

Study Center(s): Up to 20 sites in the United States

Studied Period (Years):	**Phase of Study:**
Estimated date first Participant enrolled: Dec 2020 Estimated date last Participant completed: Feb 2024	Phase 1/2

Study Description

This is an open-label, non-randomized, multi-center, Phase 1/2 study with a dose escalation phase (Part 1) and a cohort expansion phase (Part 2) in patients with relapsed/refractory, unresectable locally advanced or metastatic solid tumors. This study will be conducted at up to 20 sites in the United States. The study duration is estimated to be 12-24 months. Follow-up for survival will continue for up to 2 years.

Treatment duration: Study drug administration is planned to continue until progression of disease, unacceptable toxicity, or withdrawal from the study. Patients who discontinue the study drug prior to disease progression and are not being treated with other anticancer therapy(ies) will be followed on the study until the time of disease progression.

The study consists of the following periods in both Part 1 and Part 2:

Screening period:	Up to 4 weeks prior to the first dose (Day -28 to Day -1)
Treatment period:	28-day treatment cycles
Post treatment period:	30 days after the last treatment (End of Treatment Visit/Early Termination Visit)

Immune-mediated Adverse Reactions (IMARs) follow-up:

All patients treated with LYT-200 + tislelizumab must return 90 days ± 7 days after the last dose of study drug for an assessment of potential IMARs.

Follow-up Period: long term follow-up for up to 2 years (follow-up every 3 months).

Part 1: Single Agent: Dose Escalation Phase

A dose-finding study will be conducted using a continuous reassessment method (CRM) to establish dose-limiting toxicities (DLTs) and to help evaluate the potential recommended Phase 2 dose (RP2D). Two to 6 patients per treatment Cohorts 1-6 will be assigned to receive sequentially higher intravenous (IV) infusions of LYT-200 every 2 weeks (Q2W) on Day 1 and Day 15 of each 28-day cycle, starting at a dose of 0.2 mg/kg. Patients assigned to a specific dose escalation cohort will receive the corresponding study dose for that cohort. They will receive study drug until progression of disease, unacceptable toxicity, or withdrawal from the study for other reasons. Patients who withdraw for reasons other than toxicity or tolerability issues *during the first treatment cycle only* will be replaced.

For Cohorts 1-6, 2 patients at a time will be dosed under the CRM design. Dose escalations will only be initiated when approval from the Safety Monitoring Committee (SMC) has been received and will be based on analysis of patient safety data focusing on occurrences of DLTs at previous dose levels and other relevant safety and dosing data from previous cohorts. Dose escalations may occur after a minimum of 28 days (1 cycle). No dose level skipping will be allowed.

Following the completion of Cohort 6 under the CRM design, a once weekly (QW) LYT-200 dosing schema will be evaluated, provided the RP2D has not been reached within the CRM design. Cohorts 7 and 8 will not be evaluated with the CRM design. Patients will only be allowed to enter Cohort 7 once the SMC has reviewed the safety data from Cohort 6 and no DLT has been identified.

Four patients per dose level in Cohorts 7 and 8 will be assigned to receive IV infusions of LYT-200 QW on Days 1, 8, 15, and 22 of each 28-day cycle. Starting with the first 4 patients in Cohort 7, dose escalations to the next cohort will only occur if no DLTs are identified. If a single DLT is documented in Cohort 7, no further patients will be dosed within that cohort and Cohort 8 will not be activated.

In Part 1, Cohorts 1-8 will enroll a maximum of approximately 44 patients. A total of 6 dosage levels will be evaluated within the CRM design:

- Dose Escalation Cohort 1 = 0.2 mg/kg Q2W
- Dose Escalation Cohort 2 = 0.63 mg/kg Q2W
- Dose Escalation Cohort 3 = 2 mg/kg Q2W
- Dose Escalation Cohort 4 = 6.3 mg/kg Q2W
- Dose Escalation Cohort 5 = 10.0 mg/kg Q2W
- Dose Escalation Cohort 6 = 16.0 mg/kg Q2W

If the RP2D is not achieved during Cohorts 1-6, an additional 2 dosage levels may be included for the consideration of RP2D:

- Dose Escalation Cohort 7 = 10.0 mg/kg QW
- Dose Escalation Cohort 8 = 16.0 mg/kg QW

CRM Completion within Part 1

The CRM within Part 1 will be completed when up to 6 patients in one of Cohorts 1 to 6 have received the dose that has been identified as RP2D or when Cohort 6 is completed without reaching to RP2D. The RP2D will be based, in part, on the CRM study design, pharmacokinetic (PK) and pharmacodynamic (PD) data parameters, additional safety and efficacy data and any other factors the Sponsor may consider.

Part 1 Combination Treatment: Dose Escalation

For the Part 1 Combination Treatment (Cohorts 9-14), patients will be dosed using a 4+2 design algorithm. Each disease indication (Cohort 9 and 10: Pancreatic ductal adenocarcinoma [PDAC]; Cohorts 11 and 12: Head and Neck [H/N]; Cohorts 13 and 14: Urothelial carcinoma), will be conducted in independent cohorts, as follows:

- Combination Cohort 9 = LYT-200 6.3 mg/kg QW + gemcitabine/nab-paclitaxel (PDAC) (up to n=10)
- Combination Cohort 10 = LYT-200 16.0 mg/kg QW + gemcitabine/nab-paclitaxel (PDAC) (up to n=10)
- Combination Cohort 11 = LYT-200 6.3 mg/kg QW + tislelizumab 300 mg every 4 weeks (Q4W) (H/N) (up to n=6)
- Combination Cohort 12 = LYT-200 16.0 mg/kg QW + tislelizumab 300 mg Q4W (H/N) (up to n=6)
- Combination Cohort 13 = LYT-200 6.3 mg/kg QW + tislelizumab 300 mg Q4W (Urothelial) (up to n=6)
- Combination Cohort 14 = LYT-200 16.0 mg/kg QW + tislelizumab 300 mg Q4W (Urothelial) (up to n=6)

Cohorts 9, 11 and 13 (the 6.3 mg/kg lower dose for PDAC, H/N and urothelial, respectively), can run-in parallel. The higher doses of each of these cohorts (16.0 mg/kg) will open to enrollment only once the SMC has evaluated DLT occurrences and other safety parameters and determined the lower doses to be safe for each tumor type.

Under the 4+2 algorithm, after the first 4 patients in Cohorts 9, 11 and 13, (LYT-200 6.3 mg/kg QW) complete Cycle 1, enrollment will be paused, and an SMC meeting will then be held to review and assess the safety of these first 4 patients.

Dose De-escalation

In the event of DLTs (s) during Cycle 1, the following will occur:

If, during Cycle 1 of Cohort 9, 1 of 4 patients reaches DLT, then 2 additional patients will be added to the same Cohort. If 2 or more patients reach DLT out of 4-6 patients in Cohort 9, then Cohort 10 may be opened at a lower dose of LYT-200. The same procedure will be used for Cohort 11-12 and 13-14, respectively.

Note: the SMC may schedule ad hoc meetings at any time during the study.

Backfill Cohorts

If any signs of clinical benefit are observed in any dosing cohort, based on secondary endpoints, exploratory endpoints, and the treating clinician's assessment, a backfill of up to 4 to 6 additional

patients per that particular dosing cohort may be added. This may be done for more than one dosing cohort. If the backfill cohort is recruiting additional patients after the safety in 4 patients has been cleared for that dose level, the next dose level cohort may enroll in parallel with the previous dose cohort's backfill. With dose escalation cohorts and backfill patients, the study will enroll up to 10 patients per cohort for Cohorts 9-10 and up to 6 patients for Cohorts 11-14, respectively.

Backfill cohorts are not Part 2 expansion cohorts and, if actioned, would serve to further validate combination safety and/or any preliminary efficacy and/or PD signals observed in initially enrolled patients, in the respective cohort which is being considered for a backfill.

Patients treated in early cohorts prior to identification of the RP2D will be allowed to dose escalate up to the highest dose level cleared through the SMC. Dose escalation will be at the discretion of the Investigator in consultation with the Medical Monitor. Patients will only be allowed to dose escalate after completing their current cycle of treatment, and at the beginning of the next treatment cycle. Dose escalations may not occur in the middle of a cycle. Patients can continue to dose escalate to the highest SMC approved dose level until they are discontinued for toxicity or disease progression, or for other reasons (e.g., a patient elects to discontinue from the study).

If a DLT occurs in any patient during the first 28 days of treatment, that patient will be permanently discontinued from study drug administration.

For patients who experience toxicities (including IMARs) outside of the DLT window, dose reduction will be allowed only if the Investigator assesses that clinical benefit is being derived and may continue to be derived with lower doses of LYT-200. The dose of LYT-200 will initially be reduced by 50%, and potentially by a further reduction of 50%, as defined by the dose modification guidance provided in the protocol. No further dose reductions will be allowed. In cases where patients in Part 1 withdraw for reasons other than toxicity or tolerability issues *during the first treatment cycle only*, they will be replaced until the RP2D has been identified.

Part 2: Expansion Phase

Once safety is established in any of the Part 1 cohorts, and a preliminary efficacy and/or PD signal is identified, 1 or more expansion cohorts may be launched to further evaluate the safety and efficacy in that particular tumor type. The sample size for each of the expansion arms will be determined based on the point estimates (1) available with standard of care [null hypothesis] versus (2) anticipated with the proposed combination therapy [alternative hypothesis] for each tumor type investigated in Part 1. A protocol amendment may be submitted with details around the expansion population, treatment regimen, and statistical methods prior to initiating Part 2.

Study Objectives and Endpoints

PART 1 – Dose Escalation

OBJECTIVES	ENDPOINTS
Primary	
To establish the safety and tolerability of LYT-200 as a single agent treatment and in combination with gemcitabine/nab-paclitaxel or tislelizumab To determine the recommended Phase 2 dose (RP2D) for LYT-200	• Evaluation of safety parameters including adverse events, vital sign measurements, clinical safety laboratory tests, 12-lead electrocardiograms (ECG), echocardiography/cardiac ultrasound (ECHO), physical examinations • Evaluation of DLTs • Determination of RP2D
Secondary	
To characterize the pharmacokinetic (PK) profile of LYT-200	Evaluation of PK parameters of LYT-200 (including but not limited to area under the curve from time zero until 336 h [AUC_{0-336h}], maximum observed serum concentration [C_{max}], time to reach C_{max} [T_{max}], estimated half-life [$t_{1/2}$])
To assess the pharmacodynamics (PD) of LYT-200	Samples and assays below are included, but not limited to: • Peripheral blood mononucleocyte (PBMC) immunophenotyping by flow cytometry • Pre-specified cytokine profile (serum) by enzyme-linked immunosorbent assay (ELISA) • Soluble gal-9 levels in blood (serum) by ELISA • Gal-9 tumor tissue expression levels, and pattern of expression by immunohistochemistry (IHC) (expression on tumor cells and immune cells as well as a combined score) • Tumor tissue multiplex immunophenotyping • Programmed death ligand-1 (PD-L1) expression by IHC • Mismatch repair (MMR) status by IHC
To assess the immunogenicity of LYT-200	Evaluation of anti-drug antibodies (ADA)
Exploratory	
To evaluate the preliminary efficacy of LYT-200 as a single agent treatment and in combination with gemcitabine/nab-paclitaxel or tislelizumab	• Evaluation of confirmed objective response rate (ORR) • Evaluation of disease control rate (DCR)

	• Evaluation of duration of response (DoR) • Evaluation of progression-free survival (PFS) • Evaluation of overall survival (OS)
Part 2: Expansion	
Objectives	• **Endpoints**
Primary	•
To establish the safety and tolerability of LYT-200 in combination with gemcitabine/nab-paclitaxel or tislelizumab	• Evaluation of safety parameters including AEs, vital sign measurements, clinical safety laboratory tests, 12-lead ECG, ECHO, physical examinations • Evaluation of DLTs
To assess the ORR in patients with H/N or urothelial cancer treated with LYT-200 as a single agent or in combination with tislelizumab	• Evaluation of the confirmed ORR-3 in patients with H/N or urothelial cancer
To assess PFS in patients with PDAC treated with LYT-200 in combination with gemcitabine/nab-paclitaxel	• Evaluation of PFS-6 in patients with PDAC
Secondary	•
To characterize the pharmacokinetic (PK) profile of LYT-200	• Evaluation of PK parameters of LYT-200
To assess the pharmacodynamics (PD) of LYT-200	• PBMC immunophenotyping by flow cytometry • Cytokine profile (serum) by ELISA • Soluble gal-9 levels in blood (serum) by ELISA • Gal-9 tumor tissue expression levels, and pattern of expression by IHC (expression on tumor cells and immune cells as well as a combined score) • Tumor tissue multiplex immunophenotyping • PD-L1 expression by IHC • MMR status by IHC • TMB in tissue
To assess the immunogenicity of LYT-200	• Evaluation of ADA
To evaluate efficacy of LYT-200	• Confirmed ORR • PFS • DCR • DoR • OS

Safety Monitoring Committee (SMC)

Routine safety monitoring will be performed by the Medical Monitor. Safety monitoring, including analysis of PK, will be performed by a SMC, consisting of the Principal Investigators (and co-Investigators, as needed), Sponsor's representatives, and the study-specific Medical Monitor.

Additional Investigators and study team members will participate in reviews as needed. An Independent Data Monitoring Board will not be utilized for this open-label study.

In Part 1, single agent dose escalation phase (Cohorts 1-8), dose escalation to the next cohort will proceed following review of Cycle 1 data of each cohort. Safety and available PK data will be used to assess DLTs in all patients of each cohort by the SMC. Select DLT safety analysis for each patient will be performed following completion of Cycle 1.

The SMC process for the Part 1 Combination Treatment Phase is described above.

During Part 2, toxicities will be monitored by the SMC. The frequency of SMC meetings may increase as warranted by any increase in toxicity rate. For Part 1 and Part 2, the SMC has the right to recommend terminating or altering the study design of this clinical study at any time, including but not limited to testing of intermediate dose levels or initiation of the intermittent dose schedule.

The SMC will operate per a written charter and minutes will be maintained to include the data used for review and decisions made during the study.

Note: the SMC may schedule ad hoc meetings at any time during the study.

Study Drug Dosage and Mode of Administration

In Part 1, sequentially increasing doses of LYT-200 will be administered by IV infusion either Q2W (Cohorts 1-6) or QW (Cohorts 7-8). Once the SMC has reviewed Cohort 6, Cohorts 7 and 8 may be opened. Cohorts 9, 11, and 13 may open once Cohort 7 is approved by the SMC; Cohorts 10, 12, and 14 may open once Cohorts 9, 11, and 13 are approved by the SMC.

- Dose Escalation Cohort 1 = 0.2 mg/kg Q2W
- Dose Escalation Cohort 2 = 0.63 mg/kg Q2W
- Dose Escalation Cohort 3 = 2 mg/kg Q2W
- Dose Escalation Cohort 4 = 6.3 mg/kg Q2W
- Dose Escalation Cohort 5 = 10.0 mg/kg Q2W
- Dose Escalation Cohort 6 = 16.0 mg/kg Q2W

The following additional 2 dosage levels may be included to evaluate weekly dosing in the single agent setting:

- Dose Escalation Cohort 7 = 10.0 mg/kg QW
- Dose Escalation Cohort 8 = 16.0 mg/kg QW

Combination Treatment with LYT-200 QW:

- Combination Cohort 9 = LYT-200 6.3 mg/kg + gemcitabine/nab-paclitaxel (PDAC) (up to n=10)
- Combination Cohort 10 = LYT-200 16.0 mg/kg + gemcitabine/nab-paclitaxel (PDAC) (up to n=10)
- Combination Cohort 11 = LYT-200 6.3 mg/kg + tislelizumab 300 mg Q4W (H/N) (up to n=6)
- Combination Cohort 12 = LYT-200 16.0 mg/kg + tislelizumab 300 mg Q4W (H/N) (up to n=6)
- Combination Cohort 13 = LYT-200 6.3 mg/kg + tislelizumab 300 mg Q4W (Urothelial) (up to n=6)

- Combination Cohort 14 = LYT-200 16.0 mg/kg + tislelizumab 300 mg Q4W (Urothelial) (up to n=6)

If 2 or more patients reach DLT out of 4 to 6 patients in Cohort 9, then Cohort 10 may be opened at a lower dose of LYT-200. The same procedure will be used for Cohort 11-12 and 13-14, respectively.

Number of Participants (Planned)

In Part 1, an initial total sample size of up to 88 patients is anticipated. Backfill will provide for the enrollment of additional patients if deemed necessary.

In Part 2, the total sample size will depend on the number of disease indications selected as a result of the safety and efficacy findings in the Part 1 combination cohorts.

Eligibility Criteria

Patients are eligible for the study after meeting the following inclusion criteria and not meeting any of the exclusion criteria.

Inclusion Criteria:

Part 1

1. Written Informed Consent (mentally competent patient, able to understand and willing to sign the informed consent form)
2. Age ≥ 18 years, male or non-pregnant female
3. Able to comply with the study protocol, as per Investigator's judgment
4. Histologically confirmed, unresectable locally advanced or metastatic cancer. There are no limits to prior lines of therapies received for the treatment of the cancer condition for which the patient is being enrolled into this study.
    a. For the Part 1 combination urothelial carcinoma Cohorts 13 and 14: histologically or cytologically confirmed diagnosis of unresectable, locally advanced or metastatic urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra (i.e., transitional cell carcinoma).
    b. For the Part 1 combination H/N cancer Cohorts 11 and 12: histologically confirmed, locally advanced or metastatic squamous cell carcinoma of head and neck (SCCHN; oral cavity, oropharynx, hypopharynx, or larynx).
5. For urothelial and H/N combination cancer cohorts, prior exposure to immunotherapy is allowed, with standard of care treatment options and/or within a clinical trial context. If the patient received an anti-PD-1 and/or an anti-PD-L1 containing regimen at any point, they must have demonstrated at least stable disease, as per RECIST 1.1 or iRECIST criteria to one of these treatment regimens, if these measurements are available. If RECIST or iRECIST measurements are not available, then clinical PFS of at least 4 months is required to have been achieved on any of the prior anti-PD-1 and/or anti-PD-L1 containing regimens.
6. There is no PD-L1 expression requirement for the Part 1 combination urothelial and H/N cohorts; however, fresh biopsy or archival tissue is required for assessment of PD-L1 by IHC, or a historical PD-L1 expression by IHC must be available. If PD-L1 expression data are already available, this does not override the protocol preference for obtaining a fresh biopsy whenever feasible.

7. For Part 1 combination cohort H/N cancer patients of oropharynx origin: human papilloma virus (HPV) status needs to be established in the screening period or at any point while patient is on study drug, unless it is historically known. p16+ as a surrogate for HPV+, HPV RNA ISH or DNA PCR are all acceptable. The study accepts both HPV+ and HPV- patients.
8. Life expectancy > 3 months according to Investigator's judgment.
9. ECOG performance status 0-1.
10. Patient able and willing to undergo pre- and on/post treatment biopsies. According to the Investigator's judgment, the planned biopsies should not expose the patient to substantially increased risk of complications. Every effort will be made that the same lesion is biopsied on repeat biopsies. If the patient is eligible according to all other criteria but declines to consent to a biopsy or there are other medical reasons precluding biopsy, this will be discussed with the Sponsor.
11. Measurable disease, according to RECIST v1.1. Note that lesions intended to be biopsied should not be target lesions.
12. Adequate hematologic and end organ function, defined by the following laboratory results obtained prior to first dose of study drug treatment, provided no anticancer treatment was administered within the last 7 days:
    a. neutrophil count $\geq 1 \times 10^9$/L
    b. platelet count $\geq 100 \times 10^9$/L; for hepatocellular carcinoma (HCC) in Part 1 $\geq 50 \times 10^9$/L
    c. hemoglobin ≥ 9.0 g/dL without transfusion in the previous week
    d. creatinine ≤ 1.5 x the upper limit of normal (ULN); or eGFR > 50 mg/mmol
    e. aspartate aminotransferase AST (SGOT) ≤ 3 x ULN (≤ 5 x ULN when HCC or hepatic metastases are present)
    f. alanine aminotransferase (ALT [SGPT]) ≤ 3 x ULN (≤ 5 x ULN when HCC or hepatic metastases present)
    g. bilirubin ≤ 1.5 x ULN (patients with known Gilbert's disease may have a bilirubin ≤ 3.0 x ULN)
    h. albumin ≥ 3.0 g/dL
    i. international normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5 x ULN, unless patient receiving anticoagulant therapy
13. No evidence of active serious infection or infections requiring parenteral antibiotics.
14. Women of childbearing potential must have a negative pregnancy test within 72 h prior to start of treatment. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last study treatment.
    A woman is of childbearing potential if she is post-menarche, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing

intrauterine devices 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, symptom-thermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.

15. Four (4) weeks or 5 half-lives (whichever is shorter) since the last dose of anticancer therapy before the first LYT-200 administration.
16. Bisphosphonate treatment (e.g., zoledronic acid) or denosumab are allowed if previously used prior to commencement of clinical trial.
17. Patients:
    a. who have already received at least one prior line of systemic therapy for metastatic or locally advanced disease, and/or
    b. who have a tumor type for which there are no available standard of care options.
18. Patients who have not previously received a gemcitabine-containing regimen.

Exclusion Criteria

1. Patient unwilling or unable to follow protocol requirements
2. Patient diagnosed with metastatic cancer of an unknown primary
3. Current illicit drug addiction (medical and recreational marijuana/cannabidiol [CBD]/ tetrahydrocannabinol [THC] would not be considered "illicit")
4. Clinically significant, active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease). Prophylactic or therapeutic use of anticoagulants is allowed.
5. Pregnant and/or lactating females
6. Receiving any other investigational agents or participating in any other clinical trial involving another investigational agent for treatment of solid tumors within 3 weeks or 5 half-lives of the administered drug (whichever is shorter) prior to the first dose of study drug, or major surgery or planned surgery within 4 weeks of the first dose of study drug (this includes dental surgery).
7. Radiation therapy within 4 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass, and which does not jeopardize required measurable lesions for response assessment (RECIST v1.1).
8. Patients with fungating tumor masses
9. History or current evidence of any condition, therapy, any active infections, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator
10. Grade 4 immune-mediated toxicities with a prior checkpoint inhibitor. Grade 2 or Grade 3 pneumonitis or any other Grade 3 checkpoint inhibitor-related toxicity that led to immunotherapy treatment discontinuation. Low-grade (< Grade 3) toxicities, such as neuropathy from prior treatments, manageable electrolyte abnormalities and lymphopenia, alopecia and vitiligo are allowed.

11. History of other prior or other concomitant malignancy that requires other active treatment.
12. Active parenchymal brain metastases, patients with carcinomatous meningitis or leptomeningeal metastases. Patients with brain metastases are eligible provided they have shown clinically and radiographically stable disease for at least 4 weeks after definitive therapy and have not used steroids (> 10 mg/day of prednisone or equivalent) for at least 4 weeks prior to the first dose of study drug
13. Evidence of severe or uncontrolled systemic diseases, congestive heart failure > New York Heart Association (NYHA) class 2, myocardial infarction (MI) within 6 months, or laboratory finding that in the view of the Investigator makes it undesirable for the patient to participate in the trial
14. Any medical condition that the Investigator considers significant to compromise the safety of the patient or that impairs the interpretation of LYT-200 toxicity assessment
15. Serious non-healing wound, active ulcer, or untreated bone fracture unless for e.g., a rib fracture for (which does not elicit treatment)
16. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. For the purposes of this study, "recurrent" is defined as ³ 3 drains in the last 30 days.
17. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
18. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of Cycle 1, Day 1
19. History of pulmonary embolism, stroke or transient ischemic attack within 3 months prior to Cycle 1, Day 1
20. Active autoimmune disorder (except type I/II diabetes, hypothyroidism requiring only hormone replacement, vitiligo, psoriasis, or alopecia areata).
21. Requires systemic immunosuppressive treatment, including, but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents. Patients who have received or are receiving acute, low dose systemic immunosuppressant medications (e.g., ≤ 10 mg/day of prednisone or equivalent) may be enrolled. Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy [e.g., ≤ 10 mg/day of prednisone equivalent] for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone), topical steroids, intranasal steroids, intra-articular, and ophthalmic steroids is allowed
22. Severe tumor-related pain (Grade 3, CTCAE v.5.0) unresponsive to broad analgesic interventions (oral and/or patches)
23. Hypercalcemia (defined as ³ Grade 3, per CTCAE v 5.0) despite use of bisphosphonates
24. Any other diseases, 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 or that may affect the interpretation of the results or render the patient at high risk of treatment complications
25. Received organ transplant(s)

26. Patients undergoing dialysis
27. For Part 1, hormonal androgen deprivation therapy is allowed to continue for patients with metastatic castration-resistant prostate cancer
28. Any ablative therapy (Radio Frequency Ablation or Percutaneous Ethanol Injection) for HCC < 6 weeks prior trial entry
29. Hepatic encephalopathy or severe liver adenoma
30. Child-Pugh score ≥ 7

Statistical Methods:

Sample Size

Dose escalations will be based on the presence or absence of DLTs in patients treated at previous dose levels. For each dose cohort, prior DLT probabilities will have been specified from Good Laboratory Practice (GLP)-compliant toxicity studies as well as from preclinical models. For the specified target DLT rate and total number of dose levels, the skeleton for a power model d^exp(a) will be generated according to the approach of Lee and Cheung (2011), using a prior maximum tolerated dose (MTD) adjusted by PK/PD data, located at the median dose level and a spacing measure of delta = 0.05. The prior distribution on the parameter "a" has a mean zero normal distribution with the least informative prior variance. The trial will be stopped for safety if the lower limit of an Agresti and Coull binomial CI for the lowest study dose level exceeds the target DLT rate.

CRM trial simulation analyses with 1000 iterations suggested an average of approximately 20 patients will be needed to inform the selection of RP2D, which is the largest dose that has an estimated probability of a DLT less than or equal to a target toxicity level of 25%.

The CRM used will be based upon the first 6 cohorts, but that itself will not necessarily determine the RP2D, as data from Cohorts 7 to 14 will also be used to determine the RP2D.

A total approximate sample size of 88 patients is anticipated for Part 1 of the study. Backfill will provide for the enrollment of additional patients if deemed necessary.

Part 2 of this study (cohort expansion phase) will adopt a Simon's 2-stage optimal design to establish safety and efficacy for LYT-200 in patients with tumor types that demonstrated safety and preliminary efficacy in Part 1. In Part 2, the total sample size will depend on the number of expansion cohorts selected as a result of the safety and efficacy findings in the Part 1 combination cohorts.

Randomization Stratification:

This is an open-label study. In Part 1, patients will be assigned to treatment according to the CRM design of the study. In Part 2, patients will be assigned to treatment arm at the Investigator's discretion and in line with the inclusion and exclusion criteria.

Analysis Populations

The intent-to-treat (ITT) population will be defined as those patients who received at least one dose of the study drug, unless otherwise specified. The primary efficacy analyses will be performed for the ITT. Patient disposition will be performed for the ITT.

The Efficacy Population will be defined as all patients in the ITT and having at least one measurable ORR-3 or PFS-6 assessment. This population will be used for a sensitivity analysis.

The per-protocol (PP) Population will be defined as any patient who received at least one full cycle of LYT-200 and without major protocol deviations.

The safety population (SAF) will be defined as all patients who receive at least one dose of the study drug. The safety analyses will be performed for the SAF.

The PK/PD population will be defined as those patients who have received at least one full cycle of LYT-200.

General Statistical Plan

A database lock and primary analysis will be performed after the last patient has had their primary endpoint event. A final study analysis will be performed after study completion. All analyses will be descriptive.

Safety Analysis

All safety analyses will be made on the SAF unless otherwise specified and will be analyzed using descriptive statistics

Efficacy Analysis

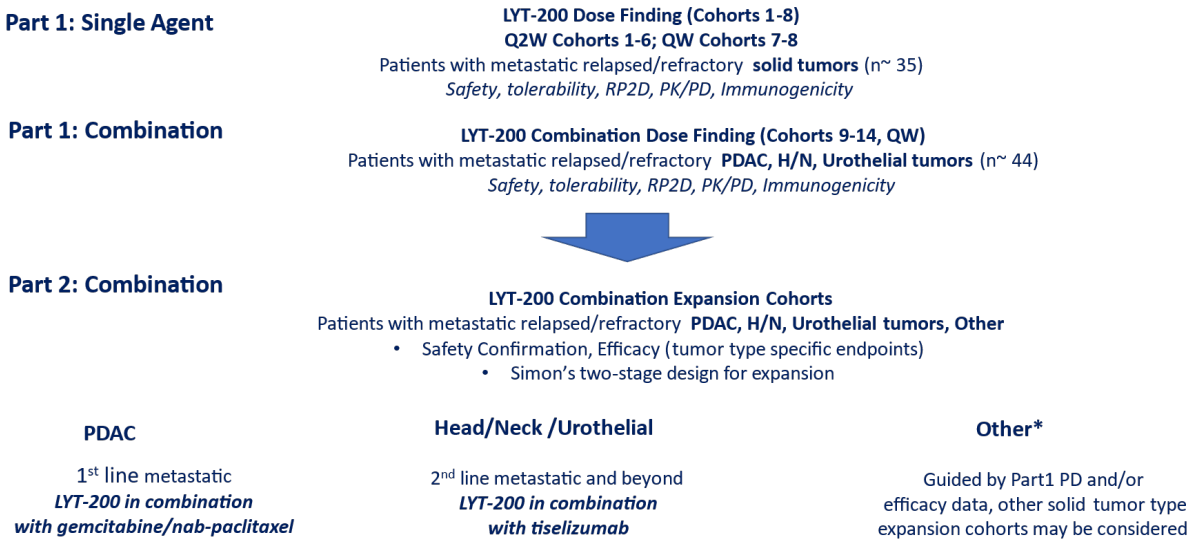
Disease response assessed according to RECIST v1.1 will be summarized descriptively for the ITT and PP. A sensitivity analysis will be performed for the Efficacy Populations.

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

PK, PD, and immunogenicity will be summarized descriptively for the PK/PD population.

STUDY SCHEMA

Figure 1. Study Schema



Abbreviations: H/N = head and neck; PD = pharmacodynamics; PDAC = pancreatic ductal adenocarcinoma; PK = pharmacokinetics; Q2W = every 2 weeks; QW = every week; RP2D = recommended Phase 2 dose.

A protocol amendment may be required to execute expansion cohorts in other tumor types.

SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Assessments for Part 1 Cohorts 1-6

	Pre-Dose	Treatment Phase														Post Treatment	
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)			Cycle 3 (28 days)				Cycle 4 (28 days) and beyond			End of Treatment or Early Termination	Long Term Follow -Up [T] Every 3 mons
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**30 days after last dose**	
Cycle Day		**C1 D1**	**C1 D2**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D2**	**C3 D8**	**C3 D15**	**CX D1**	**CX D8**	**CX D15**	--	--
+/- days allowable			1	1	1	2	1	2	2	1	1	2	2	1	2	3	n/a
Study drug administration [A]		X			X	X		X	X			X	X		X		
Study Procedures & Examinations																	
Eligibility assessment and written informed consent	X																
Demographics [B]	X																
Medical history [C]	X																

	Pre-Dose	Treatment Phase														Post Treatment	
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)			Cycle 3 (28 days)				Cycle 4 (28 days) and beyond			End of Treatment or Early Termination	Long Term Follow -Up [T] Every 3 mons
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**30 days after last dose**	
Cycle Day		**C1 D1**	**C1 D2**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D2**	**C3 D8**	**C3 D15**	**CX D1**	**CX D8**	**CX D15**	--	--
+/- days allowable			1	1	1	2	1	2	2	1	1	2	2	1	2	3	n/a
Previous and concomitant medications [D]	X	X	X	X	X	X		X	X	X	X	X	X		X	X	
Adverse events [E]		X	X	X	X	X		X	X	X	X	X	X		X	X	
ECHO/MUGA [F]	X												X				
12-lead ECG (QTcF)	X	X				X			X				X				
Physical exam [G]	X	X			X	X		X	X			X	X		X	X	
ECOG	X	X			X	X		X	X			X	X		X	X	
Vital Signs[H]	X	X			X	X		X	X			X	X		X	X	

	Pre-Dose	Treatment Phase														Post Treatment	
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)			Cycle 3 (28 days)				Cycle 4 (28 days) and beyond			End of Treatment or Early Termination	Long Term Follow -Up [T] Every 3 mons
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**30 days after last dose**	
Cycle Day		**C1 D1**	**C1 D2**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D2**	**C3 D8**	**C3 D15**	**CX D1**	**CX D8**	**CX D15**	--	--
+/- days allowable			1	1	1	2	1	2	2	1	1	2	2	1	2	3	n/a
Tumor imaging assessment CT with contrast preferred) [N]	X								X							X repeat if end of study is > 8 weeks after last scan	X [U]
Clinical Labs																	
Pregnancy test [I]	X					X			X				X			X	
Hematology [J]	X	X			X	X		X	X			X	X		X	X	
Serum Chemistry [K]	X	X			X	X		X	X			X	X		X	X	
TSH, Free T4, serum lipase, amylase, PTH, FSH, LH, free cortisol	X	X				X			X				X			X	

	Pre-Dose	Treatment Phase														Post Treatment	
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)			Cycle 3 (28 days)				Cycle 4 (28 days) and beyond			End of Treatment or Early Termination	Long Term Follow -Up [T] Every 3 mons
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**30 days after last dose**	
Cycle Day		**C1 D1**	**C1 D2**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D2**	**C3 D8**	**C3 D15**	**CX D1**	**CX D8**	**CX D15**	--	--
+/- days allowable			1	1	1	2	1	2	2	1	1	2	2	1	2	3	n/a
Blood Coagulation [L]	X	X			X	X		X	X			X	X		X	X	
Urinalysis [M]	X	X			X	X		X	X			X	X		X	X	
Pharmacodynamics and Pharmacokinetics																	
Tumor biopsy [O]	X											X ± 7 d					
Tumor type-relevant biomarkers [P]	X	X			X	X		X	X			X	X		X	X	
Blood sampling for biomarker PD analysis [Q]		X	X	X	X	X			X	X	X	X	X			X	
PK blood sampling [R]		X	X	X	X	X			X	X	X	X	X				

	Pre-Dose	Treatment Phase													Post Treatment	
	Screening	Cycle 1 (28 days)				Cycle 2 (28 days)			Cycle 3 (28 days)				Cycle 4 (28 days) and beyond			End of Treatment or Early Termination	Long Term Follow -Up [T] Every 3 mons
Study Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**30 days after last dose**	
Cycle Day		**C1 D1**	**C1 D2**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D2**	**C3 D8**	**C3 D15**	**CX D1**	**CX D8**	**CX D15**	--	--
+/- days allowable			1	1	1	2	1	2	2	1	1	2	2	1	2	3	n/a
Immunogenicity (ADA) [S]		**X**				X			X				X			X	
Survival Follow-up																	X

ADA: anti-drug antibodies; AE: adverse event; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; C: cycle; CPK: creatine phosphokinase; COVID19: Coronavirus SARS-CoV-2; CRP: C-reactive protein; CT: computed tomography; D or d: day(s); ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ECHO: echocardiography/cardiac ultrasound; FSH: follicle-stimulating hormone; IMAR: immune-mediated adverse reaction; INR: international normalized ratio; LDH: lactate dehydrogenase; LH: luteinizing hormone; min: minute(s); MUGA: multigated acquisition scan; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; PTH: parathyroid hormone; PTT: partial thromboplastin time; QTcF: QT interval, Fridericia's Correction Formula; RBC: red blood cell count; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; TSH: thyroid stimulating hormone; WBC: white blood cell count.

A) Study drug administration: LYT-200 treatment will be administered, on C1D1 and C1D15 on every cycle.

B) Demographics: Data include age, gender, race, and ethnicity.

C) Medical history: In addition to general medical history, data collection also includes oncology history, surgical/transplant and radiation therapy history and COVID-19 history and testing.

D) Previous and concomitant medications (including vaccines and complementary treatments/supplements): Data to include name, indication, dose, route, start and end dates for each. Allergies and intolerances, dose modifications while on study, schedule of dosing changes and reasons for them should also be obtained.

E) Adverse events: Any AEs starting or worsening after study drug administration will be recorded. AEs should be followed until resolved to one of the following: baseline, stabilized, or deemed irreversible. All SAEs are to be collected until 30 days after last dose of study medication. All study-procedure-related SAEs must be collected from the date of patient's written consent.

F) ECHO/MUGA: This assessment of heart function is conducted at screening and repeated on Day 1 of Cycle 4; the assessment window is +/- 5 days. It should be conducted more frequently when clinically indicated and once every 3 months.

G) Physical exam: Include height at screening for determination of body surface area. Include weight at all scheduled exam times. A Neurological exam will be conducted only on patients who have stable and/or pre-treated brain metastases.

H) Vital Signs: temperature, heart rate, blood pressure, respiratory rate.

I) Pregnancy test (blood or urine): Only for women of childbearing potential with uterus in situ. Test results must be available before scheduled dosing.

J) Hematology: Analysis includes complete blood count, differential, platelets, hemoglobin. Collect blood samples pre-dose.

K) Serum chemistry: Analysis includes albumin, alkaline phosphatase, bilirubin (total, direct), blood urea nitrogen, calcium, CPK, creatinine, electrolytes (sodium, potassium, chloride, magnesium, phosphorus), gamma glutamyl transferase (gamma GT), glucose, hemoglobin A1c (HgbA1c) (only if history of Type 1 or Type 2 diabetes mellitus), LDH, SGPT (ALT) or SGOT (AST), total protein. Fasting glucose to be assessed only if clinically indicated. Collect blood samples pre-dose.

L) Blood Coagulation: Collect blood samples pre-dose. Analysis includes APTT, PT, PTT, and INR (if on allowable anticoagulants), CRP, and troponin.

M) Urinalysis: Analysis includes color, appearance, dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, pH. (Urine culture and sensitivity to be run only if patient is clinically symptomatic.)

N) Tumor imaging assessment: For screening, the assessment must be performed within the 28-day screening period. On study, assessments are done every 8 weeks ± 7 days (i.e., C3D1, C5D1, C7D1, C9D1, etc.) and at the End of Treatment if not assessed within the previous 4-6 weeks. Assessments may be performed more frequently if clinically indicated. If an objective response is seen on a scan, a confirmation scan will be done 4 weeks (+7 d) later. After this confirmatory scan, the scheduled scans are to be resumed at a frequency of every 8 weeks ± 7 days from the date of the confirmatory scan.

O) Tumor biopsies: If patient MMR/MSI status is unknown at screening, the test should be run at the local laboratory. In Part 2, TMB tissue analysis will be performed. The on-study biopsy is scheduled for C3D15 ± 7 days and should occur only after the tumor imaging scan in Cycle 3. It is recognized that a variety of clinical factors may make it difficult to obtain adequate specimens. Decisions not to perform biopsy on-treatment should be discussed with the Medical Monitor.

P) Tumor type-relevant biomarkers: Blood samples are to be collected at screening and every cycle pre-dose administration as appropriate for the tumor type. Blood sampling may be decreased to every 3rd cycle after 6 months of treatment.

Q) PD blood sampling: Blood samples will be collected pre-dose administration on dosing days. May be decreased to every 3rd cycle after 6 months of treatment.

R) PK blood sampling: Cycle 1 and Cycle 3 Day 1: blood samples will be collected pre-dose and at end of study drug infusion (EOI), 2 and 4 h (± 30 min) post-study drug administration. Cycle 1 and Cycle 3 Day 15, blood samples will be collected pre-dose and at EOI only. Cycle 1 and Cycle 3 Day 2 and 8 (non-dosing days), PK blood samples will be collected at only one time point. Cycle 2 and Cycle 4: blood samples will be collected Day 1 only and should occur pre-dose and at EOI. Blood samples for PK will be collected every 2 cycles thereafter (i.e., C6D1, C8D1, etc.) pre-dose and at EOI.

S) ADA blood sampling: Blood samples will be collected Day 1 of Cycles 1-4, blood samples will be collected Day 1, pre-dose. Thereafter, it will be collected every 2 cycles, Day 1, pre-dose (i.e., C6D1, C8D1, etc.).

T) Long Term Follow-up: Tumor imaging should continue, where possible, for patients discontinuing treatment due to reasons other than progression of disease and not receiving additional systemic anticancer treatments. Survival data will be collected at a minimum every 3 months. It can be collected more frequently to support data cleaning or regulatory submission efforts. Follow-up can be conducted by telephone, electronic messaging or chart review and will continue for up to 2 years after the patient has the End of Treatment/Early Termination visit.

Table 2. Schedule of Assessments for Part 1 Cohorts 7-14 and Part 2

	Pre-Dose	Treatment Phase																		Post Treatment		
	Screening	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)					Cycle 4 (28 days) and beyond				End of Treatment or Early Termination	IMAR Follow-Up[T]	Long Term Follow -Up [U] Every 3 mons
Study Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30 days after last dose**	**90 days after last dose**	
Cycle Day		**C1 D1**	**C1 D3**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D8**	**C2 D15**	**C2 D22**	**C3 D1**	**C3 D3**	**C3 D8**	**C3 D15**	**C3 D22**	**CX D1**	**CX D8**	**CX D15**	**CC D22**	--	--	--
+/- days allowable			1	1	1	1	2	1	2	2	2	1	1	2	2	2	1	2	2	3	7	n/a
Study drug administration [A]		X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X			
Study Procedures & Examinations																						
Eligibility assessment and written informed consent	X																					
Demographics [B]	X																					
Medical history [C]	X																					

	Pre-Dose	Treatment Phase																		Post Treatment		
	Screening	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)					Cycle 4 (28 days) and beyond				End of Treatment or Early Termination	IMAR Follow-Up[T]	Long Term Follow -Up [U] Every 3 mons
Study Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30 days after last dose**	**90 days after last dose**	
Cycle Day		**C1 D1**	**C1 D3**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D8**	**C2 D15**	**C2 D22**	**C3 D1**	**C3 D3**	**C3 D8**	**C3 D15**	**C3 D22**	**CX D1**	**CX D8**	**CX D15**	**CX D22**	--	--	--
+/- days allowable			1	1	1	1	2	1	2	2	2	1	1	2	2	2	1	2	2	3	7	n/a
Previous and concomitant medications [D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AEs [E]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO/MUGA [F]	X															X						
12-lead ECG (QTcF)	X	X					X				X					X						
Physical exam [G]	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
ECOG	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Vital Signs[H]	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Tumor imaging assessment (CT with contrast preferred) [N]	X										X									X repeat if end of study is > 8 weeks after last scan		X [U]

	Pre-Dose	Treatment Phase																		Post Treatment		
	Screening	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)					Cycle 4 (28 days) and beyond				End of Treatment or Early Termination	IMAR Follow-Up[T]	Long Term Follow-Up [U] Every 3 mons
Study Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30 days after last dose**	**90 days after last dose**	
Cycle Day		**C1 D1**	**C1 D3**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D8**	**C2 D15**	**C2 D22**	**C3 D1**	**C3 D3**	**C3 D8**	**C3 D15**	**C3 D22**	**CX D1**	**CX D8**	**CX D15**	**CX D22**	--	--	--
+/- days allowable			1	1	1	1	2	1	2	2	2	1	1	2	2	2	1	2	2	3	7	n/a
Clinical Labs																						
Pregnancy test [I]	X						X				X					X				X		
Hematology [J]	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Serum Chemistry [K]	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
TSH, Free T4, serum lipase, amylase, PTH, FSH, LH, free cortisol	X	X					X				X					X				X	X	
Blood Coagulation [L]	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Urinalysis [M]	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	

	Pre-Dose	Treatment Phase																	Post Treatment		
	Screening	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)					Cycle 4 (28 days) and beyond				End of Treatment or Early Termination	IMAR Follow-Up[T]	Long Term Follow-Up[U] Every 3 mons
Study Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30 days after last dose**	**90 days after last dose**	
Cycle Day		**C1 D1**	**C1 D3**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D8**	**C2 D15**	**C2 D22**	**C3 D1**	**C3 D3**	**C3 D8**	**C3 D15**	**C3 D22**	**CX D1**	**CX D8**	**CX D15**	**CX D22**	--	--	--
+/- days allowable			1	1	1	1	2	1	2	2	2	1	1	2	2	2	1	2	2	3	7	n/a
Pharmacodynamics and Pharmacokinetics																						
Tumor biopsy[O]	X													X ± 7 d								
Tumor type-relevant biomarkers[P]	X	X			X		X		X		X			X		X		X		X		
Blood sampling for biomarker PD analysis[Q]		X	X	X	X		X				X	X	X	X		X				X		
PK blood sampling[R]		X	X	X	X	X	X				X	X	X	X	X	X						
Immunogenicity (ADA)[S]		X			X		X		X		X					X				X		

	Pre-Dose	Treatment Phase																	Post Treatment		
	Screening	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)					Cycle 4 (28 days) and beyond				End of Treatment or Early Termination	IMAR Follow-Up[T]	Long Term Follow-Up [U] Every 3 mons
Study Day	**-28 to -1**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**3**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**30 days after last dose**	**90 days after last dose**	
Cycle Day		**C1 D1**	**C1 D3**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D8**	**C2 D15**	**C2 D22**	**C3 D1**	**C3 D3**	**C3 D8**	**C3 D15**	**C3 D22**	**CX D1**	**CX D8**	**CX D15**	**CX D22**	--	--	--
+/- days allowable			1	1	1	1	2	1	2	2	2	1	1	2	2	2	1	2	2	3	3	n/a
Survival Follow-up																						X [U]

ADA: anti-drug antibodies; AE: adverse event; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; C: cycle; CPK: creatine phosphokinase; COVID19: Coronavirus SARS-CoV-2; CRP: C-reactive protein; CT: computed tomography; D or d: day(s); ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ECHO: echocardiography/cardiac ultrasound; FSH: follicle-stimulating hormone; IMAR: immune-mediated adverse reaction; INR: international normalized ratio; LDH: lactate dehydrogenase; LH: luteinizing hormone; min: minute(s); MUGA: multigated acquisition scan; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; PTH: parathyroid hormone; PTT: partial thromboplastin time; QTcF: QT interval, Fridericia's Correction Formula; RBC: red blood cell count; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; TSH: thyroid stimulating hormone; WBC: white blood cell count.

A) Study drug administration: LYT-200 treatment will be administered, on CXD1, CXD8, CXD15, and CXD22 on every weekly cycle. On Days 1, 8, and 15 in every cycle, gemcitabine and nab-paclitaxel will be administered to PDAC patients on the LYT-200 combination regimen. Tislelizumab will be administered to H/N and urothelial patients on Day 1 of every cycle on the LYT-200 combination regimen. Study drug may be administered on Days 1, 8, 15, and 22 +/- 3 days from C2 onwards.

For PDAC patients, gemcitabine/nab-paclitaxel will be administered as such: gemcitabine is administered as a 1000 mg/m^2 dose over 30 minutes on Days 1, 8 and 15 of each 28-day cycle and nab-paclitaxel is administered as a 125 mg/m^2 dose over 3-40 minutes on Days 1, 8 and 15 of each 28-day cycle). For H/N and Urothelial patients, tislelizumab will be administered at 300 mg administered on Day 1 of every cycle on the LYT-200 combination regimen).

B) Demographics: Data include age, gender, race, and ethnicity.

C) Medical history: In addition to general medical history, data collection also includes oncology history, surgical/transplant and radiation therapy history and COVID-19 history and testing.

D) Previous and concomitant medications (including vaccines and complementary treatments/supplements): Data to include name, indication, dose, route, start and end dates for each. Allergies and intolerances, dose modifications while on study, schedule of dosing changes and reasons for them should also be obtained.

E) Adverse events: Any AEs starting or worsening after study drug administration will be recorded. AEs should be followed until resolved to one of the following: baseline, stabilized, or deemed irreversible. All SAEs are to be collected until 30 days after last dose of study medication. All study-procedure-related SAEs must be collected from the date of patient's written consent.

F) ECHO/MUGA: This assessment of heart function is conducted at screening and repeated on Day 1 of Cycle 4; the assessment window is +/- 5 days. It should be conducted more frequently when clinically indicated and once every 3 months.

G) Physical exam: Include height at screening for determination of body surface area. Include weight at all scheduled exam times. A Neurological exam will be conducted only on patients who have stable and/or pre-treated brain metastases.

H) Vital Signs: temperature, heart rate, blood pressure, respiratory rate.

I) Pregnancy test (blood or urine): Only for women of childbearing potential with uterus in situ. Test results must be available before scheduled dosing.

J) Hematology: Analysis includes complete blood count, differential, platelets, hemoglobin. Collect blood samples pre-dose.

K) Serum chemistry: Analysis includes albumin, alkaline phosphatase, bilirubin (total, direct), blood urea nitrogen, calcium, CPK, creatinine, electrolytes (sodium, potassium, chloride, magnesium, phosphorus), gamma glutamyl transferase (gamma GT), glucose, hemoglobin A1c (HgbA1c) (only if history of Type 1 or Type 2 diabetes mellitus), LDH, SGPT (ALT) or SGOT (AST), total protein. Fasting glucose to be assessed only if clinically indicated. Collect blood samples pre-dose.

L) Blood Coagulation: Collect blood samples pre-dose. Analysis includes APTT, PT, PTT, and INR (if on allowable anticoagulants), CRP, and troponin.

M) Urinalysis: Analysis includes color, appearance, dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, pH. (Urine culture and sensitivity to be run only if patient is clinically symptomatic.)

N) Tumor imaging assessment: For screening, the assessment must be performed within the 28-day screening period. On study, assessments are done every 8 weeks ± 7 days (i.e., C3D1, C5D1, C7D1, C9D1, etc.) and at the End of Treatment if not assessed within the previous 4-6 weeks. Assessments may be performed more frequently if clinically indicated. If an objective response is seen on a scan, a confirmation scan will be done 4 weeks (+7 d) later. After this confirmatory scan, the scheduled scans are to be resumed at a frequency of every 8 weeks ± 7 days from the date of the confirmatory scan.

O) Tumor biopsies: If patient MMR/MSI status is unknown at screening, the test should be run at the local laboratory. In Part 2, TMB tissue analysis will be performed. The on-study biopsy is scheduled for C3D15 ± 7 days and should occur only after the tumor imaging scan in Cycle 3. It is recognized that a variety of clinical factors may make it difficult to obtain adequate specimens. Decisions not to perform biopsy on-treatment should be discussed with the Medical Monitor.

P) Tumor type-relevant biomarkers: Blood samples are to be collected at screening and every cycle pre-dose administration as appropriate for the tumor type. Blood sampling may be decreased to every 3rd cycle after 6 months of treatment.

Q) PD blood sampling: Blood samples will be collected pre-dose administration on dosing days. May be decreased to every 3rd cycle after 6 months of treatment.

R) PK blood sampling: Cycle 1 and Cycle 3 Day 1: blood samples will be collected pre-dose, end of study drug infusion (EOI) and 1 h (± 15 min) post-study drug administration. Cycle 1 and Cycle 3 Day 3, blood samples will be collected at one time point, any time. Cycle 1 and Cycle 3 Day 8, Day 15, and Day 22,

blood samples will be collected pre-dose and at EOI only. Cycle 2 and every even cycle there after: blood samples will be collected Day 1 only and should occur pre-dose and at EOI. Blood samples for PK will not be collected on every odd cycle after Cycle 3.

S) ADA blood sampling: Blood samples will be collected Day 1 and Day 15 of Cycles 1 and 2, pre-dose. Thereafter, it will be collected every cycle, Day 1, pre-dose (i.e., C3D1, C4D1, etc.).

T) All patients treated with LYT-200 + tislelizumab must return 90 days +/- 7 days after last dose of study drug for an assessment of potential immune-mediated adverse reactions (IMARs).

U) Long Term Follow-up: Tumor imaging should continue, where possible, for patients discontinuing treatment due to reasons other than progression of disease and not receiving additional systemic anticancer treatments. Survival data will be collected at a minimum every 3 months. It can be collected more frequently to support data cleaning or regulatory submission efforts. Follow-up can be conducted by telephone, electronic messaging or chart review and will continue for up to 2 years after the patient has the End of Treatment/Early Termination visit.

TABLE OF CONTENTS

1. Introduction and Background 44
1.1. Study Rationale 44
1.2. Background 44
1.3. Role of Galectin-9 in Specific Tumor Types 46
1.3.1. Pancreatic Cancer 46
1.3.2. Colorectal Cancer 46
1.3.3. Urothelial Cancer 47
1.3.4. Head and Neck Cancer 47
1.4. Summary of Nonclinical Studies 47
1.4.1. Pharmacology 47
1.4.2. Pharmacokinetics 50
1.4.3. Toxicology 51
1.5. Summary of Clinical Studies 51
1.5.1. Summary of Potential Risks and Benefits of LYT-200 52

2. Objectives and Endpoints 53
2.1. Part 1: Dose Escalation 53
2.2. Part 2: Cohort Expansion 54

3. Study Design 55
3.1. Overall Design 55
3.2. Treatment Duration and Treatment Periods 55
3.2.1. Treatment Duration 55
3.2.2. Treatment Periods 55
3.3. Determination of Clinical Starting Dose 55
3.4. Study Design 56
3.4.1. Part 1: Single Agent Dose Escalation Phase 56
3.4.2. Part 1: Combination Treatment Phase 58
3.4.3. Part 2: Cohort Expansion Phase 59
3.4.4. Dose-limiting Toxicity Criteria 61
3.5. Scientific Rationale for Study Design 62
3.6. End of Study Definition 62
3.7. Trial Stopping Rules 62
3.8. Safety Monitoring Committee 63

4. Study Population 64
4.1. General Considerations 64
4.2. Inclusion Criteria 64
4.3. Exclusion Criteria 66
4.4. Lifestyle Considerations 68
4.5. Screen Failures 68
4.6. Participant Discontinuation/Withdrawal from the Study 69
4.7. Lost to Follow-up 69

4.8. Replacement of Patients 69

5. Study Drugs 70
5.1. Agents Administered in Combination with LYT-200 70
5.1.1. Tislelizumab 70
5.1.2. Gemcitabine plus Nab-Paclitaxel 73
5.2. Study Drug Administration 74
5.3. Preparation/Handling/Storage/Accountability 78
5.3.1. Preparation of LYT-200 78
5.3.2. Storage of LYT-200 78
5.4. Study Drug Compliance 78
5.5. Dose Modification 79
5.5.1. Dose Administration 79
5.5.2. Dose Delay 80
5.5.3. Dose Reduction 80
5.5.4. Dose Continuation for LYT-200 for Patients in the LYT-200+gemcitabine/Nab-paclitaxel Cohort 80
5.5.5. Dose Modifications for Specific AEs Related to Administration of Tislelizumab 80
5.5.6. Dose Modifications for Specific AEs Related to Administration of Gemcitabine + Nab-Paclitaxel 81
5.5.7. Dose Modification for IMARs 81
5.5.8. Discontinuation of Study Drug 81
5.6. Continued Access to Study Drug After the End of the Study 82
5.7. Concomitant Therapy 82
5.7.1. Permitted Medications 82
5.7.2. Prohibited Medications 82
5.7.3. Supportive Care 83

6. Study Assessments and Procedures 84
6.1. Assessments by Visit 84
6.2. Efficacy Assessments 85
6.2.1. RECIST v1.1 Criteria for Tumor Assessment 85
6.3. Safety Assessments 85
6.3.1. Physical Examinations 86
6.3.2. Vital Signs 86
6.3.3. Electrocardiograms 86
6.3.4. Clinical Safety Laboratory Assessments 86
6.3.5. Pregnancy Testing 87
6.4. Pharmacokinetics Assessments 87
6.4.1. PK Schedule for Cohorts 1-6: 88
6.4.2. PK Schedule for Cohorts 7 and 8: 88
6.4.3. PK Schedule for Cohorts 9-14: 89
6.5. Genetics 89
6.6. Pharmacodynamic Biomarkers 90

6.7. Immunogenicity Assessments 90
6.8. Other Assessments 91
6.8.1. Demographics 91
6.8.2. Medical History 91
6.8.3. Prior and Concomitant Medications 92
6.8.4. Tumor Imaging Assessments 92
6.8.5. Tumor Biopsies 92
6.8.6. ECHO/MUGA 93
6.8.7. ECOG 93

7. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting 94
7.1. Definitions 94
7.1.1. Adverse Events 94
7.1.2. Serious Adverse Events 94
7.1.3. Relatedness 94
7.2. Adverse Event Management 95
7.2.1. Immune-mediated Adverse Reactions 95
7.2.2. Dose Reduction Procedure for Adverse Event Management 96
7.2.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs 96
7.3. Reporting Adverse Events 96
7.3.1. General Considerations 96
7.3.2. Prompt Reporting of SAEs 97
7.3.3. Time Period and Frequency for Collecting AE and SAE Information 98
7.3.4. Follow-up of AEs and SAEs 99
7.3.5. Regulatory Reporting Requirements for SAEs 99
7.3.6. Pregnancy 99
7.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 100

8. Statistical Considerations 101
8.1. Statistical Hypotheses 101
8.2. Sample Size Determination 101
8.2.1. Part 1 101
8.2.2. Part 2 102
8.3. Analysis Sets 102
8.4. Statistical Analyses 103
8.4.1. General Considerations 103
8.4.2. Primary Endpoint(s) 103
8.4.3. Secondary Endpoint(s) 104
8.4.4. Exploratory Endpoints 105
8.4.5. Other Analysis 105
8.5. Interim Analysis 105

9. References 106
10. Appendices 109

LIST OF TABLES

Table 1. Schedule of Assessments for Part 1 Cohorts 1-6 22
Table 2. Schedule of Assessments for Part 1 Cohorts 7-14 and Part 2 29
Table 3. Adverse Events (non-IMAR-Related) Reported for Tislelizumab According to Frequency 71
Table 4. Adverse Events Reported for Tislelizumab to be Treated as IMARs* 72
Table 5. Adverse Events Reported for Gemcitabine + Nab-Paclitaxel in the Treatment of Pancreatic Cancer, According to Frequency 74
Table 6. Summary Characteristics of Study Drugs 76

LIST OF FIGURES

Figure 1. Study Schema 21

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-TNF	Anti-tumor necrosis factor
APTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}168h}$	Area under the curve from time zero until 168 h
$AUC_{0\text{-}336h}$	Area under the curve from time zero until 336 h
C or Cx	Cycle or cycle number
CA15-3, CA-125, CA19-9	Tumor markers (blood)
CBD	Cannabidiol
CCA	Cholangiocarcinoma
CD	Cluster of differentiation markers
CEA	Carcinoembryonic antigen
CFR	Code of federal regulations
cGMP	Current good manufacturing practice
CI	Confidence interval
C_{max}	Maximum observed serum concentration
COVID-19	Coronavirus SARS-CoV-2
CPK	Creatine phosphokinase
CR	Complete response
CRC	Colorectal cancer
CRD2	Cysteine-rich domain 2
CRF	Case report form
CRM	Continuous reassessment method
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYFRA(-21)	Cytokeratin-fragment (-21)
D/d or Dx	Day or day number
DCR	Disease control rate
DLT	Dose-limiting toxicity
dMMR/MSI-H	Mismatch-repair-deficient and microsatellite-instability-high
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiography/cardiac ultrasound
ECOG	Eastern Cooperative Oncology Group

Abbreviation or Specialist Term	Explanation
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOI	End of infusion
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FIH	First-in-human
FOXP3	Forkhead-box-protein P3
FSH	Follicle-stimulating hormone
fT4	Free T4 or thyroxine
gal-9	Galectin-9
gamma GT	Gamma glutamyl transferase
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVHD	Graft versus host disease
HCC	Hepatocellular carcinoma
HED	Human equivalent dose
HgbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN-γ	Interferon gamma
IHC	Immunohistochemistry
IL	Interleukin
IMAR	Immune-mediated adverse reaction
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
irAE	Immune related adverse event
ITT	Intent-to-treat
IV	Intravenous
KPC	LSL-Kras(G12D/+); LSL-Trp53(R172H/+); Pdx-1-Cre
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
mAb	Monoclonal antibody
MABEL	Minimum acceptable biological effect level
MedDRA®	Medical Dictionary for Regulatory Activities
MCP-1	Monocyte chemoattractant protein 1
MDSC	Myeloid derived suppressor cell
MI	Myocardial infarction
MIP	Macrophage inflammatory protein
min	Minute(s)
MMR	Mismatch repair

Abbreviation or Specialist Term	Explanation
mo	Month(s)
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximal tolerated dose
MUGA	Multigated acquisition scan
n	Number
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Non-evaluable
NOAEL	No observed adverse effect level
NPC	Nasopharyngeal carcinoma
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NSE	Neurone-specific enolase
NYHA	New York Heart Association
ORR	Objective response rate
ORR-3	Objective response rate at 3 months
OS	Overall survival
PAN-CK	Pan cytokeratin
PARP	Poly adenosine diphosphate ribose polymerase
PBMC	Peripheral blood mononucleocyte
PDAC	Pancreatic ductal adenocarcinoma
PD	Pharmacodynamics
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PDOT	Patient-derived organoid model
PET	Positron emission tomography
PFS	Progression-free survival
PFS-6	Progression-free survival at 6 months
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PT	Prothrombin time
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
Q1WX5	Once weekly for 5 weeks
QW	Every week
Q2W	Every 2 weeks
QT	QT interval, distance in time on the ECG tracing from the start of the QRS complex to the end of T-wave
QTL	Quality tolerance limit
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell (count)s
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or Specialist Term	Explanation
RP2D	Recommended Phase 2 Dose
RP2D-1	Dose in the cohort that immediately preceded the RP2D dose cohort
RT-qPCR	Real time quantitative polymerase chain reaction
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SD	Stable disease
SJS	Stevens-Johnson syndrome
SMC	Safety Monitoring Committee
SoA	Schedule of Assessments
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Estimated half-life
TBD	To be determined
TBL	Serum total bilirubin
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TGF-β(1)	Transforming growth factor beta (1)
THC	Tetrahydrocannabinol
Th	T-helper cell
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TK	Toxicokinetic
T_{max}	Time to reach C_{max}
TMB	Tumor Mutational Burden
TNF	Tumor necrosis factor
Treg	T regulatory
TSH	Thyroid stimulating hormone
TTL	Target toxicity level
ULN	Upper limit of normal
WBC	Leukocytes (white blood cell [count])
WOCBP	Woman of childbearing potential

1. Introduction and Background

1.1. Study Rationale

LYT-200 is a fully human IgG4 monoclonal antibody (mAb) targeting galectin-9 (-gal-9) protein. Gal-9 functions as an immuno-suppressor, conferring immune privilege to tumor cells and disabling immune-mediated cancer attack by regulating macrophages, T -cells, myeloid derived suppressor cells as well as cancer cell susceptibility to cytotoxic T -cell-induced death. Based on the data produced by the Sponsor, LYT-200 blockade of gal-9 interferes with the immunosuppressive functions of gal-9 resulting in effective immune activation and tumor growth inhibition across multiple preclinical models.

Gal-9 can be overexpressed and/or secreted in many solid tumor types including pancreatic adenocarcinoma, cholangiocarcinoma (CCA), CRC, breast cancer, bladder cancer, ovarian cancer, non-small cell and small cell lung cancer, nasopharyngeal cancer, malignant melanoma, ovarian cancer etc., and high levels of tissue and/or circulating gal-9 correlate with aggressive tumor features and adverse survival outcome.

Therefore, the target indications of LYT-200 are relapsed or refractory, metastatic solid and advanced tumors, where LYT-200 will be investigated both as a single agent and in combination with chemotherapy (gemcitabine/nab-paclitaxel) or a checkpoint inhibitor (a programmed cell death 1 [PD-1] antibody).

Dose escalation (Part 1) will be conducted in all comer solid tumors types in order to establish the safety and tolerability profile of LYT-200, assess its immunogenicity potential, establish the pharmacokinetic (PK) and pharmacodynamic (PD) profile, and arrive at the recommended Phase 2 dose (RP2D). This may be the MTD. Part 2 expansion cohorts are planned in: first line metastatic pancreatic ductal adenocarcinoma (PDAC), in combination with gemcitabine/nab-paclitaxel; as well as H/N and urothelial cancer, in combination with tislelizumab.

No other therapies targeting gal-9 are currently known to be approved or in clinical trials for any indication.

1.2. Background

Gal-9 functions through multiple pathways by binding to carbohydrate motifs on cell surface molecules/receptors. It plays a critical regulatory role in immune cell response and homeostasis and mediates immunoregulatory activities in several ways. Binding of gal-9 to T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) for example, induces cell death of terminally differentiated TIM-3+ T -helper cell (Th) 1 and cluster of differentiation (CD)8+ T -cells (Wu et al., 2014), as well as apoptosis of CD4+ Th1 cells (Zhu et al., 2005; Gooden et al., 2013; Lhuillier et al., 2015). Gal-9 binds to CD44 and cooperates with transforming growth factor beta (TGF-β) to promote T regulatory (Treg) cell differentiation (Zhu et al., 2005), and favors expansion of immunosuppressive myeloid derived suppressor cells (MDSCs) (Rabinovich and Conejo-Garcia, 2016), in the overall promotion of Th2/M2 differentiation, that ultimately favors tumor progression. Gal-9 also functions to reduce the development of Th17 cells (Seki et al., 2008; Lv et al., 2012; Oomizu et al., 2012a; Oomizu et

al., 2012b; Kared et al., 2013; Wu et al., 2014; Madireddi et al., 2017), and is immunomodulatory on tumor-associated macrophages (Lv et al., 2017). Taking all this into consideration, gal-9 is considered a potent mediator of cancer-associated immunosuppression.

High levels of tissue and/or circulating gal-9 correlate with aggressive tumor features and adverse survival outcome in many tumor types. For example, gal-9 levels are significantly increased in metastatic melanoma patient plasma (Enninga et al., 2016; Seifert et al., 2020), correlating with Th2 systemic bias and less favorable 2-year clinical survival outcome. Gal-9 is also highly expressed in human PDAC compared with normal pancreas tissue and present on both tumor and intra-tumoral immune cells. Moreover, high serum concentration of gal-9 may be able to discriminate PDAC from benign pancreatic disease and healthy individuals and is potentially prognostic for stage IV patients (Seifert et al., 2020). Plasma levels of gal-9 are associated with a worse overall and disease-free survival, as well as chemoresistance, in ovarian cancer patients (Labrie et al., 2017). In gastric cancer, patients with gal-9 positive tumors have significantly lower overall and gastric cancer-specific mortalities (Choi et al., 2017). In yet another gastrointestinal tumor type, CRC, gal-9 markedly inhibits the cytotoxicity of the gamma delta T -cells toward colon cancer cells (Li et al., 2020), indicating its immune-suppressive mechanism of action. In muscle invasive bladder cancer, tumor-associated macrophages expressing gal-9 are associated increasing numbers of Treg cells and decreasing numbers of CD8 T and dendritic cells, indicating an immunosuppressed microenvironment, that in turn translates to increased tumor grade/stage and gal-9 positive tumors with poor prognosis (Qi et al., 2019).

In nasopharyngeal carcinoma (NPC), significant increase in the expression of gal-9 positive tumor cells, with concomitant increase in Treg cells and decrease in CD8 T -cells, is observed in recurrent tumor tissues, indicating that gal-9 confers immunologic escape in NPC.

High gal-9 expression is highly correlated with expression of immune checkpoint molecules, M2 tumor-associated macrophages in the mesenchymal subtype of glioblastoma multiforme and in small cell lung cancer correlates with high levels of neuron-specific enolase and shorter survival. In breast cancer, surface gal-9 protects carcinoma cells against cytotoxic T-cell-induced death (Yasinska et al., 2019), while in non-small cell lung cancer (NSCLC), there is a co-expression between gal-9 and programmed cell death ligand 1 (PD-L1), with high gal-9 expression on immune cells correlating with early disease relapse. Moreover, early accumulation of MDSCs expressing gal 9 in NSCLC, is associated with primary and secondary resistance to anti-PD-1 treatment (Limagne et al., 2019).

Collectively, these data, across multiple solid tumor types, support the use of LYT-200 in relapsed/refractory, metastatic solid and advanced tumors.

In basal physiological conditions, gal-9 is weakly expressed in most tissues, with some abundance in the thymus and kidney (Lhuillier et al., 2018).

1.3. Role of Galectin-9 in Specific Tumor Types

Tumor types planned for expansion cohorts are currently underserved by approved immunotherapy agents, while response rates and survival benefits remain suboptimal even with non-immunotherapy standard of care anticancer agents.

1.3.1. Pancreatic Cancer

PDAC immunotherapy trials have largely shown disappointing, limited activity with single agent checkpoint inhibitors, and only a small number of studies on combination therapy showed promise with regards to response (Henriksen et al., 2019).

Pancreatic cancer remains a disease that is difficult to treat due to a typically late presentation, relatively high resistance to chemotherapy, and lack of effective immune and targeted therapies (Adel, 2019). 57,600 new cases are estimated in the United States in 2020 and 47,050 estimated deaths (Pancreatic Cancer Stats). Approximately 355,000 new cases are estimated to occur annually until 2040, and almost as many deaths are reported as new cases on a yearly basis. It is projected to be the second leading cause of cancer-related deaths in the United States by the year 2030 (Rawla et al., 2019). Despite intervention, the median life expectancy for patients with metastatic pancreatic cancer is less than 1 year with current treatment (Stadinski, 2019), while most patients (as many as ~80%) present at an advanced/metastatic stage, when the disease is beyond curative resection. The 5-year survival rate in 2019 reached double digits for the first time and stands at 10% for patients with metastatic disease (Pancreatic Cancer Stats).

The current standard of care for metastatic pancreatic cancer is predominantly chemotherapy (e.g., gemcitabine/nab-paclitaxel or FOLFIRINOX, used as standard of care in the first and second lines in the metastatic setting) (von Hoff et al., 2013; Lambert et al., 2019), while a distinct minority of patients (under 10%) with breast cancer genes 1 and 2 mutations and even fewer with mismatch repair (MMR)-deficient tumors may benefit from poly adenosine diphosphate ribose polymerase (PARP) inhibitors and potentially anti-PD-1 therapy, respectively. However, PDAC immunotherapy trials have largely shown disappointing, limited activity with single agent checkpoint inhibitors, and only a small number of studies on combination therapy showed any promise with regards to response (Henriksen et al., 2019).

1.3.2. Colorectal Cancer

CRC presents one of the largest cancer burdens in the world. Nowadays, it is the world's fourth most deadly cancer with almost 900,000 deaths annually globally (Dekker et al., 2019). In the United States, 147,950 cases are predicted in 2020 with 53,200 estimated deaths (Colorectal Cancer Stats). Despite significant advances in standard of care therapies, the 5-year survival rate for metastatic CRC remains around < 20% (Parmar et al., 2019). Death from CRC is expected to nearly double within the next 20 years. The current standard of care for CRC are chemotherapy regimens, combined and/or sequenced with anti-angiogenic therapy and anti-epidermal growth factor receptor modalities in selected patients. In addition, current immunotherapies are only efficacious (albeit producing profound and durable responses) in the small subset of patients whose tumors are mismatch-repair-deficient and microsatellite-instability-high (dMMR/MSI-H) (Dekker et al., 2019).

Outcomes on immunotherapy in microsatellite stable CRC, which are the majority of patients with CRC are suboptimal and this represent a significant unmet medical need for active immunotherapy. CRC, the small subset that is dMMR/MSI-H derive benefit from immunotherapy (Huyghe et al., 2019), but the vast majority of patients with proficient mismatch repair or with microsatellite stable CRC, do not.

The silent presentation of these tumors combined with their highly aggressive nature and refractoriness to chemotherapy contribute to their alarming mortality where the 5-year survival for patients with distant disease remains at a dismal 2% (Banales et al., 2020; Bile Duct Cancer Survival, 2020).

1.3.3. Urothelial Cancer

In muscle invasive bladder cancer, tumor-associated macrophages expressing gal-9 are associated increasing numbers of Treg cells and decreasing numbers of CD8 T and dendritic cells, indicating an immunosuppressed microenvironment, that in turn translates to increased tumor grade/stage and gal- 9 positive tumors with poor prognosis (Qi et al., 2019).

1.3.4. Head and Neck Cancer

In nasopharyngeal carcinoma (NPC), significant increase in the expression of gal-9 positive tumor cells, with concomitant increase in Treg cells and decrease in CD8 T cells, is observed in recurrent tumor tissues, indicating that gal-9 confers immunologic escape in NPC.

1.4. Summary of Nonclinical Studies

Nonclinical studies conducted in support of first-in-human (FIH) Phase 1/2 clinical development of LYT-200 were designed to demonstrate:

1. LYT-200 binding and specificity to gal-9
2. LYT-200-mediated *in vitro* and *in vivo* PD effects
3. Assessment of LYT-200 safety pharmacology
4. LYT-200 PK and exposure in nonclinical toxicology species
5. Assessment of LYT-200 safety profile in rats and cynomolgus monkeys, pharmacologically relevant species
6. Basis for calculating the FIH clinical dose for the Phase 1/2 study.

A brief overview of the nonclinical testing strategy and a summary of the pharmacology, PK and safety results follow with additional details provided in the IB.

1.4.1. Pharmacology

1.4.1.1. In vitro Pharmacology

In vitro pharmacology data has been generated to support the clinical development of LYT-200. The key findings are provided below with additional details in the IB.

1. LYT-200 binding to the gal-9 target was conducted by several orthogonal methods in non-cell-based (bead-based flow cytometry, ELISA, surface plasmon resonance) and cell-based assays (flow cytometry). LYT-200 bound to the cysteine-rich domain 2 (CRD2) domain of human, non-human primate, mouse, and rat CRD2 domain of gal-9 in non-cell-based assays with similar low nanomolar affinity. LYT-200 also bound cell surface gal-9 on human colon cancer cells at low nanomolar affinity. This confirms desirable binding characteristics of LYT-200, both for executed *in vitro* and *ex vivo* preclinical assays as well as for clinical testing
2. LYT-200 function was evaluated in a non-cell-based competition ELISA which confirmed that LYT-200 potently blocks interaction of gal-9 to its binding partner CD206 protein. This serves as an example of the expected and desired blocking function of LYT-200 as a fully human IgG4 mAb and confirms that LYT-200 can inhibit gal-9 interactions which elicit immunosuppression.
3. LYT-200 function was next evaluated in a T -cell-based apoptosis assay. In this experiment, gal-9 elicits T -cell apoptosis while addition of LYT-200 potently, and in a dose-dependent manner prevented T -cell death mediated by gal-9. Function of LYT-200 was also assessed in cell-based antibody-dependent cell-mediated cytotoxicity (ADCC) assays using human Jurkat T-cells and in antibody-dependent cellular phagocytosis assays using THP-1 cells. LYT-200 does not show any ADCC activity while it does elicit moderate ADCP activity with an EC50 of ~0.9 μg/mL.
4. LYT-200 was next evaluated for its ability to induce cytokines in human peripheral blood mononucleocytes (PBMCs) from normal donors and from donors with non-hematologic cancer. Both the soluble and wet-coated stimulation formats were evaluated. Cytokines (interleukin [IL]-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, IL-17A, tumor necrosis factor [TNF]-α, IFN-γ) were assessed using the MultiCyt QBeads PlexScreen Secreted Protein Assay. In normal donors, LYT-200 did not induce a cytokine response at any tested concentration with any dose response trend under either soluble or wet-coated stimulation formats relative to the IgG4 isotype matched control. In PBMCs from cancer patients, a few donors exhibit some IL-1β, IL-6, IL-10 and TNF-α release in response to LYT-200 stimulation, although no dose response was evident. Baseline IL-8 levels were variable and LYT-200 stimulation led to a trend of dose-dependent increase in the levels of IL-8 production in wet-coated stimulation format. However, some donors demonstrated a dose-dependent increase in IL-8 production in response to isotype control treatment as well.
5. The ability of LYT-200 to inhibit macrophage polarization toward the M2 phenotype and to induce repolarization of M2 macrophages from immune tolerogenic to immune active phenotype, was evaluated using human macrophages isolated from PBMCs. Specifically, TGF-β1 and IL-10 secretion was evaluated in M2 macrophages that were generated using polarization cocktails containing IL-3/IL-14 or gal-9. LYT-200 treatment of M2-polarized macrophages led to a reduction of secreted IL-10 and TGF-β1 levels in all donors compared to untreated and IgG4 Isotype Control antibody-treated controls.

6. LYT-200 was evaluated for both gal-9 and off target protein binding using the Retrogenix protein array. This assay evaluated binding interactions of LYT-200 to 5484 full-length human plasma membrane proteins and secreted proteins and demonstrated specificity to gal- 9.
7. The presence of soluble gal-9 was evaluated in human serum samples from healthy donors and metastatic cancer patients. Serum from cancer patients with various tumor types was used (CRC, PDAC, CCA, breast cancer, NSCLC). Gal-9 was found to be significantly increased in the serum of cancer patients across all analyzed tumor types, compared to healthy controls. This is consistent with the known tumor biology.
8. Expression of gal-9 in various solid tumor types was evaluated by immunohistochemistry (IHC). Cancer types of interest for this clinical study were included, such as PDAC (n = 141 cases) and CCA (n = 99 cases). Breast cancer tissues (n > 1000 cases) were assessed as well. Gal-9 expression was detected at high levels both on tumor cells and on intra-tumoral immune cells. High gal-9 expression correlated with worse patient outcome.
9. *Ex vivo* mode of action of LYT-200 was assessed in patient-derived organoid models (PDOTs) obtained from fresh excisional tumor specimens of various cancer types, including CRC, PDAC and CCA, which contain representative immune tumor microenvironment. LYT-200 induced activation of intra-tumoral T -cells across all tumor type PDOTs assessed, confirming desired mode of action of LYT-200, to ultimately release immunosuppression and enable effector T -cell activity against tumors.
10. *In vivo* activity of LYT-200 was assessed by utilizing a mouse IgG1 clone of LYT-200, i.e., a mAb which binds the exact same CRD2 domain of gal-9 but has the mouse IgG1 backbone (mIgG1-200). This antibody shares similar binding affinity like LYT-200 to gal-9 across all tested species. mIgG1-200 was used a as a single agent as well as in combination with gemcitabine/nab-paclitaxel and anti-PD-1, in orthotopic pancreatic cancer KPC mouse models (LSL-Kras(G12D/+); LSL-Trp53(R172H/+); Pdx-1-Cre), as well as in the B16F10 melanoma models. In the KPC models and in the B16F10 models, single agent mIgG1-200 significantly inhibits tumor growth starting at dose levels equivalent to ~0.8 mg/kg human dose. mIgG1-200 used as a single agent induced intra-tumoral T -cell activation in the KPC model as well. In combination with gemcitabine/nab-paclitaxel, mIgG1-200 was well tolerated in the KPC model, produced a complete responder animal and increased survival compared to chemotherapy alone. In the B16F10 model, mIgG1-200 in combination with anti-PD-1 was well tolerated, was equally effective to inhibit tumor growth like single agent mIgG1-200, which was superior to anti-PD-1 alone, but the combination was superior to either single agent treatment in augmenting intertumoral presence of effector CD8 T -cells. This suggests that anti-gal-9 therapy is well tolerated, effective and can be combined safely with chemotherapy and anti-PD-1, which is the approach the Sponsor will undertake in this clinical trial. Moreover, the B16F10 model data of intra-tumoral T cell content provide a mechanistic and a molecular synergy rational for combining LYT-200 and an anti-PD1 agent, i.e. tislelizumab.

1.4.1.2. Safety Pharmacology

Safety pharmacology was evaluated as part of the repeat-dose Good Laboratory Practice (GLP)-compliant toxicity studies in rats and monkeys. Effect on the central nervous system was assessed by evaluation of clinical observations throughout the study and the use of a functional observation battery assessment. Cardiovascular, respiratory and ocular evaluations were conducted in monkeys and included electrocardiograms (ECGs), blood pressure, heart rate, respiratory rate and ocular evaluations. No LYT-200-related changes were observed in any of the safety pharmacology endpoints at doses up to 300 mg/kg/dose once weekly for 5 weeks (Q1WX5) in either species.

1.4.2. Pharmacokinetics

Both rats and monkeys were identified as relevant species for toxicity testing and toxicokinetic (TK) analyses based on gal-9 sequence homology and binding studies. The TK of LYT-200 was evaluated in single-dose and repeat-dose (Q1WX5) toxicity studies in both rats and cynomolgus monkeys. Tissue distribution, metabolism and excretion studies have not been conducted for this protein therapeutic.

The GLP-compliant, repeat-dose rat and monkey studies used validated assays to measure serum concentrations of LYT-200. ADA were evaluated in rats using a validated assay. Consistent with ICH S6, ADA was not evaluated in the cynomolgus monkey since there was no evidence of altered PD activity, no safety findings suggesting immunogenicity and no unexpected changes in exposure after repeat-dose administration.

The main findings from the nonclinical TK studies in both rats and monkeys presented in this module are summarized as follows:

- Systemic exposure to LYT-200 was independent of sex.
- Following intravenous (IV) infusion of LYT-200, maximum observed serum concentration (C_{max}) and area under the curve (AUC) values increased with increasing dose in an approximately dose proportional manner.
- In rats and monkeys, systemic exposure (area under the curve from time zero until 168 h [$AUC_{0\text{-}168h}$]) to LYT-200 did not appear to consistently change (< 2-fold) following repeated administration of LYT-200 at 100 and 300 mg/kg.
- $t_{1/2}$ values for LYT-200 were approximately 10-14 days in rats and 8-9 days at in monkeys.
- In rats, systemic exposure did not appear to be influenced by ADA. In monkeys, no change in exposure was observed after repeat-dose administration and ADA evaluations were not performed.

Additional details are provided in the IB.

1.4.3. Toxicology

Toxicity testing followed the recommendations in ICH S6 and ICH S9. Rats and cynomolgus monkeys were identified as relevant species for toxicity testing based on gal-9 sequence homology and binding studies. However, in both species, gal-9 expression in healthy animals is very low or undetectable. No additional toxicity studies in other species were conducted. The IV route and 5 weekly dose administrations were selected based on the planned clinical dose route and schedule. Non-GLP-compliant, single-dose iv range finding studies were conducted in rats and cynomolgus monkeys and were used to inform the dose levels in the GLP-compliant repeat-dose (Q1WX5) IV studies.

Based on the lack of toxicologic findings in the single-dose studies, the high-dose level selected for the repeat-dose studies was the maximal feasible dose based on iv dose volume limitations and stock test article concentrations. The GLP-compliant, repeat-dose studies administered LYT-200 on a more frequent schedule (Q1WX5) than the planned clinical schedule (every 2 weeks [Q2W]) and went to the maximal feasible dose based on stock drug substance concentration and maximal feasible volume for each species and the IV route (300 mg/kg/dose; Human Equivalent Dose (HED) on a mg/kg basis of the monkey dose~100 mg/kg/dose). This dose level is 500-fold higher than the proposed FIH starting dose of 0.2 mg/kg. A complete set of toxicity, local tolerability and safety pharmacology endpoints were collected in both the rat and monkey studies and systemic exposure was confirmed throughout the 29-day dosing period. Despite the attempt to demonstrate toxicity in rats and monkeys, 300 mg/kg/dose was not associated with any LYT-200-related findings in either species in any endpoint evaluated. Toxicity study endpoints included clinical observations, body weights, food consumption, cytokine assessment, immunophenotyping of peripheral blood mononuclear cells, gal- 9 concentrations, clinical pathology (hematology, serum chemistry, coagulation, urinalysis), eye exams, central nervous system evaluations, ECGs, blood pressure, heart rate, respiratory rate and histopathology. Both rats and monkeys had low levels of soluble gal-9 in serum and levels did not change with LYT-200 treatment. As anticipated in normal monkeys, the levels of gal-9 detected on circulating peripheral blood mononuclear cells was very low and not reliably detectable. In agreement with ICH S9, neither carcinogenicity, mutagenicity, nor the effects of LYT-200 on fertility, early embryonic development or pre- and post-natal development have been assessed.

Additional toxicity information can be found in the IB.

1.5. Summary of Clinical Studies

This study, LYT-200-2020-01, initiated in December 2020, is the first clinical study with LYT-200. As of November 2022**,** preliminary safety results showed no apparent trends in adverse event (AE) frequency between dosing groups, and no DLTs were observed. Of the 17 total subjects, 7 subjects (41.2%) had 11 serious AEs (SAEs), none of which were assessed as related to LYT-200 by the Investigator and Sponsor. The only SAE term reported for more than 1 subject was pleural effusion, which was reported for 1 subject each in the 10.0 mg/kg QW and 16.0 mg/kg Q2W groups. One subject in the 16.0 mg/kg Q2W group had a Grade 5 SAE of intestinal perforation that was unrelated to LYT-200.

At dose levels ranging from 0.2 to 16.0 mg/kg Q2W and at 10.0 mg/kg QW, no immune-mediated adverse reactions (IMARs) nor any cytokine release/tumor lysis-type side effects have been observed.

Two patients treated with LYT-200 have experienced IRRs. Both patients had CRC, and both had prior IRRs on prior lines of therapy (chemotherapy for 1 patient and an anti-PD-1 mAb for the other patient). Neither patient had ADAs to LYT-200.

1.5.1. Summary of Potential Risks and Benefits of LYT-200

In nonclinical studies conducted to date, no significant toxicities have been observed at doses that are ~500-fold above those intended for human administration. Furthermore, LYT-200 has been shown to be highly specific for gal-9 and has been demonstrated to be efficacious in multiple animal models of cancer. The patient populations targeted for enrollment are at late stages in their disease and will have failed at standard of care treatments prior to enrollment in this study. Thus, the potential benefits to the patients who will receive LYT-200 likely exceed the potential risks.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LYT-200 may be found in the IB.

2. Objectives and Endpoints

2.1. Part 1: Dose Escalation

OBJECTIVES	ENDPOINTS
Primary	
To establish the safety and tolerability of LYT-200 as a single agent treatment and in combination with gemcitabine/nab-paclitaxel or tislelizumab To determine the recommended Phase 2 dose (RP2D) for LYT-200	• Evaluation of safety parameters including AEs, vital sign measurements, clinical safety laboratory tests, 12-lead ECG, echocardiography/cardiac ultrasound (ECHO), physical examinations • Evaluation of dose-limiting toxicities (DLTs) • Determination of RP2D
Secondary	
To characterize the pharmacokinetic (PK) profile of LYT-200	Evaluation of PK parameters of LYT-200 (including but not limited to area under the curve from time zero until 336 h [AUC_{0-336h}], maximum observed serum concentration [C_{max}], time to reach C_{max} [T_{max}], estimated half-life [$_{t1/2}$])
To assess the pharmacodynamics (PD) of LYT-200	Samples and assays below are included, but not limited to: • Peripheral blood mononucleocyte (PBMC) immunophenotyping by flow cytometry • Pre-specified cytokine profile (serum) by ELISA • Soluble gal-9 levels in blood (serum) by ELISA • Gal-9 tumor tissue expression levels, and pattern of expression by IHC (expression on tumor cells and immune cells as well as a combined score) • Tumor tissue multiplex immunophenotyping • Programmed death ligand-1 (PD-L1) expression by IHC • Mismatch repair (MMR) status by IHC
To assess the immunogenicity of LYT-200	Evaluation of ADA
Exploratory	
To evaluate the preliminary efficacy of LYT-200 as a single agent treatment and in combination with gemcitabine/nab-paclitaxel or tislelizumab	• Evaluation of confirmed objective response rate (ORR) • Evaluation of disease control rate (DCR) • Evaluation of duration of response (DoR) • Evaluation of progression-free survival (PFS)

	• Evaluation of overall survival (OS)

2.2. Part 2: Cohort Expansion

Objectives	Endpoints
Primary	
To establish the safety and tolerability of LYT-200 in combination with gemcitabine/nab-paclitaxel or tislelizumab	• Evaluation of safety parameters including AEs, vital sign measurements, clinical safety laboratory tests, 12-lead ECG, ECHO, physical examinations • Evaluation of DLTs
To assess the ORR in patients with H/N or urothelial cancer treated with LYT-200 as a single agent or in combination with tislelizumab	Evaluation of the confirmed ORR-3 in patients with H/N or urothelial cancer
To assess PFS in patients with PDAC treated with LYT-200 in combination with gemcitabine/nab-paclitaxel	Evaluation of PFS-6 in patients with PDAC
Secondary	
To characterize the pharmacokinetic (PK) profile of LYT-200	Evaluation of PK parameters of LYT-200
To assess the pharmacodynamics (PD) of LYT-200	• PBMC immunophenotyping by flow cytometry • Cytokine profile (serum) by ELISA • Soluble gal-9 levels in blood (serum) by ELISA • Gal-9 tumor tissue expression levels, and pattern of expression by IHC (expression on tumor cells and immune cells as well as a combined score) • Tumor tissue multiplex immunophenotyping • PD-L1 expression by IHC • MMR status by IHC • TMB in tissue
To assess the immunogenicity of LYT-200	Evaluation of ADA
To evaluate efficacy of LYT-200	• Confirmed ORR • PFS • DCR • DoR • OS

3. Study Design

3.1. Overall Design

This is an open-label, uncontrolled, multi-center Phase 1/2 study with a dose escalation phase (Part 1) and a cohort expansion phase (Part 2) in patients with relapsed/refractory unresectable locally advanced or metastatic solid tumors. This study will be conducted at up to 20 sites in the United States. The study duration is estimated to be 12-24 months. Follow-up for survival will continue for up to 2 years. A study schema is presented in Figure 1.

3.2. Treatment Duration and Treatment Periods

3.2.1. Treatment Duration

Study drug administration is planned to continue until progression of disease, unacceptable toxicity, or withdrawal from the study. Patients who discontinue the study drug prior to disease progression and are not being treated with other systemic anticancer therapy(ies), will be followed on the study until the time of disease progression.

3.2.2. Treatment Periods

The study consists of the following periods in both Part 1 and Part 2:

Screening period:	Up to 4 weeks prior to first dose (Day -28 to Day -1)
Treatment period:	28-day treatment cycles as presented in the Schedule of Assessments (SoA; Table 1 and Table 2)
Post treatment period:	30 days after last treatment (End of Treatment Visit/Early Termination Visit)
IMAR follow-up period:	All patients treated with LYT-200 + tislelizumab must return 90 days ± 7 days after the last dose of study drug for an assessment of potential IMARs
Follow-up period	Long term follow-up for up to 2 years (visits every 3 months) for patients discontinuing treatment due to reasons other than progression of disease, and not receiving additional systemic anticancer treatments

3.3. Determination of Clinical Starting Dose

Various potential approaches to clinical starting dose selection were evaluated by integrating guidance from ICH S9 ‘Nonclinical Evaluation for Anticancer Therapeutics’ and the available nonclinical data for toxicity and efficacy. Although LYT-200 is not an immune agonist, it does have immunological activity. Therefore, the Sponsor is using the “minimum acceptable biological effect level” (MABEL) approach for selecting the starting dose.

The pharmacology and toxicology data for LYT-200 indicate the following:

- By way of example: a dose of 2 mg/kg in humans is anticipated to result in a C_{max} of 28 ug/mL.
- LYT-200 is an immune activating agent with cytokine release potential based on in vitro assays: At 4 µg/mL, there is a signal for IL-8 release. This concentration is approximately 1/7th (14%) of the anticipated C_{max} in humans at a dose of 2 mg/kg.
- LYT-200 resulted in inhibition of T cell apoptosis with an IC_{50}= 8.9 µg/mL which is approximately 1/3rd the estimated C_{max} at a dose of 2 mg/kg.
- The ADCP activity has an EC_{50}= 0.89 µg/mL, approximately 1/30th (3%) the estimated C_{max} of a 2 mg/kg dose.
- In an in vivo anti-tumor study, a dose of 50 µg was determined to be the lowest dose with biological activity. The HED would result in an anticipated human C_{max} of 2.24 µg/mL, and an exposure of approximately 12.5% the anticipated human exposure at a dose of 2 mg/kg.

Taken together, these data suggest that an appropriate starting dose for LYT-200 based on MABEL is 0.2 mg/kg.

3.4. Study Design

3.4.1. Part 1: Single Agent Dose Escalation Phase

A dose-finding study will be conducted using a CRM (O'Quigley et al., 1990) to establish DLTs and the RP2D. Two to 6 patients per treatment Cohorts 1-6 will be assigned to receive sequentially higher intravenous (IV) infusions of LYT-200 Q2W on Day 1 and Day 15 of each 28-day cycle, starting at a dose of 0.2 mg/kg. Patients assigned to a specific dose escalation cohort will receive the corresponding study dose for that cohort. They will receive study drug until progression of disease, unacceptable toxicity, or withdrawal from the study for other reasons. Patients who withdraw for reasons other than toxicity or tolerability issues *during the first treatment cycle only* will be replaced.

For Cohorts 1-6, 2 patients at a time will be dosed under the CRM design. Dose escalations will only be initiated when approval from the Safety Monitoring Committee (SMC) has been received and will be based on analysis of patient safety data focusing on occurrences of DLTs at previous dose levels and other relevant safety and dosing data from previous cohorts. Dose escalations may occur after a minimum of 28 days (1 cycle). No dose level skipping will be allowed.

Following the completion of Cohort 6 under the CRM design, a once weekly (QW) LYT-200 dosing schema will be evaluated, provided the RP2D has not been reached within the CRM design. Cohorts 7 and 8 will not be evaluated with the CRM design. Patients will only be allowed to enter Cohort 7 once the SMC has reviewed the safety data from Cohort 6 and no DLT has been identified.

Four patients per dose level in Cohorts 7 and 8 will be assigned to receive IV infusions of LYT-200 QW on Days 1, 8, 15, and 22 of each 28-day cycle. Starting with the first 4 patients in Cohort 7, dose escalations to the next cohort will only occur if no DLTs are identified. If a single DLT is

documented in Cohort 7, no further patients will be dosed within that cohort and Cohort 8 will not be activated.

Part 1, Cohorts 1-8 will enroll approximately 44 patients. A total of 6 dosage levels will be evaluated within the CRM design:

- Dose Escalation Cohort 1 = 0.2 mg/kg Q2W
- Dose Escalation Cohort 2 = 0.63 mg/kg Q2W
- Dose Escalation Cohort 3 = 2 mg/kg Q2W
- Dose Escalation Cohort 4 = 6.3 mg/kg Q2W
- Dose Escalation Cohort 5 = 10.0 mg/kg Q2W
- Dose Escalation Cohort 6 = 16.0 mg/kg Q2W

If the RP2D is not achieved during Cohorts 1-6, an additional 2 dosage levels will be included for the consideration of RP2D:

- Dose Escalation Cohort 7 = 10.0 mg/kg QW
- Dose Escalation Cohort 8 = 16.0 mg/kg QW

Patients treated in early cohorts prior to identification of the RP2D will be allowed to dose escalate up to the highest dose level cleared through the SMC. Dose escalation will be at the discretion of the Investigator in consultation with the Medical Monitor. After a complete cycle, dose escalations may occur after a minimum of 28 days (1 cycle). Dose escalations may not occur in the middle of a cycle. Patients can continue to dose escalate to the highest SMC approved dose level until they are discontinued for toxicity or disease progression, or for other reasons (e.g., a patient elects to discontinue from the study).

Dose escalations will be based on the presence or absence of DLTs in patients treated at previous dose levels. For each dose cohort, prior DLT probabilities will have been specified from GLP-compliant toxicity studies as well as from preclinical models. For the specified target DLT rate and total number of dose levels, the skeleton for a power model d^exp(a) will be generated according to the approach of Lee and Cheung, using a prior MTD adjusted by PK/PD data, located at the median dose level and a spacing measure of delta = 0.05 (Lee and Cheung, 2011). The prior distribution on the parameter “a” has a mean zero normal distribution with the least informative prior variance. The trial will be stopped for safety if the lower limit of an Agresti and Coull binomial CI for the lowest study dose level exceeds the target DLT rate (Agresti and Coull, 1998). The RP2D will be the MTD dose derived from Part 1.

If a DLT occurs in any patient during the first 28 days of treatment, that patient will be permanently discontinued from study drug administration.

For patients who experience toxicities (including IMARs) outside of the DLT window, dose reduction will be allowed only if the Investigator assesses that clinical benefit is being derived and may continue to be derived with lower doses of LYT-200. The dose of LYT-200 will initially be reduced by 50%, and potentially by a further reduction of 50%, as defined by the dose modification guidance provided in the protocol. No further dose reductions will be allowed, See Appendix 8 for detailed instructions on dose modifications.

3.4.1.1. Part 1 CRM Completion

The CRM within Part 1 will be completed when up to 6 patients in one of Cohorts 1 to 6 have received the dose that has been identified as RP2D or when Cohort 6 is completed without reaching to RP2D. The RP2D will be based, in part, on the CRM study design, PK and PD data parameters, additional safety and efficacy data and any other factors the Sponsor may consider.

3.4.2. Part 1: Combination Treatment Phase

For the Part 1 combination treatment phase, Cohorts 9-14 will enroll approximately 44 patients:

- Combination Cohort 9 = LYT-200 6.3 mg/kg QW/gemcitabine/nab-paclitaxel (PDAC) (up to n=10)
- Combination Cohort 10 = LYT-200 16.0 mg/kg QW/gemcitabine/nab-paclitaxel (PDAC) (up to n=10)
- Combination Cohort 11 = LYT-200 6.3 mg/kg QW/tislelizumab (head and neck [H/N]) (up to n=6)
- Combination Cohort 12 = LYT-200 16.0 mg/kg QW/tislelizumab (H/N) (up to n=6)
- Combination Cohort 13 = LYT-200 6.3 mg/kg QW/tislelizumab (urothelial) (up to n=6)
- Combination Cohort 14 = LYT-200 16.0 mg/kg QW/tislelizumab (urothelial) (up to n=6)

Cohorts 9, 11 and 13 (the 6.3 mg/kg lower dose for PDAC, H/N and urothelial, respectively), can run-in parallel. The higher doses of each of these cohorts (16.0 mg/kg) will open to enrollment only once the SMC has evaluated DLT occurrences and other safety parameters and determined the lower doses to be safe for each tumor type.

If 2 or more patients reach DLT out of 4 to 6 patients in Cohort 9, then Cohort 10 may be opened at a lower dose of LYT-200. The same procedure will be used for Cohort 11-12 and 13-14, respectively.

Under the 4+2 algorithm, after the first 4 patients in Cohorts 9, 11 and 13, (LYT-200 6.3 mg/kg QW) complete Cycle 1, enrollment will be paused and an SMC meeting will then be held to review and assess the safety of these first 4 patients.

3.4.2.1. Dose De-escalation

In the event of DLTs (s) during Cycle 1, the following will occur:

If, during Cycle 1 of Cohort 9, 1 of 4 patients reaches DLT, then 2 additional patients will be added to the same Cohort. If 2 or more patients reach DLT out of 4-6 patients in Cohort 9, then Cohort 10 may be opened at a lower dose of LYT-200. The same procedure will be used for Cohort 11-12 and 13-14, respectively.

Note: the SMC may schedule ad hoc meetings at any time during the study.

3.4.2.2. Backfill Cohorts

If any signs of clinical benefit are observed in any dosing cohort, based on secondary endpoints, exploratory endpoints, and the treating clinician's assessment, a backfill of up to 4 to 6 additional

patients per that particular dosing cohort may be added. This may be done for more than one dosing cohort. If the backfill cohort is recruiting additional patients after the safety in 4 patients has been cleared for that dose level, the next dose level cohort may enroll in parallel with the previous dose cohort's backfill. With dose escalation cohorts and backfill patients, the study will enroll up to 10 patients per cohort for Cohorts 9-10 and up to 6 patients for Cohorts 11-14, respectively.

Backfill cohorts are not Part 2 expansion cohorts and, if actioned, would serve to further validate combination safety and/or any preliminary efficacy and/or PD signals observed in initially enrolled patients, in the respective cohort which is being considered for a backfill.

Patients treated in early cohorts prior to identification of the RP2D will be allowed to dose escalate up to the highest dose level cleared through the SMC. Dose escalation will be at the discretion of the Investigator in consultation with the Medical Monitor. Patients will only be allowed to dose escalate after completing their current cycle of treatment, and at the beginning of the next treatment cycle. Dose escalations may not occur in the middle of a cycle. Patients can continue to dose escalate to the highest SMC approved dose level until they are discontinued for toxicity or disease progression, or for other reasons (e.g., a patient elects to discontinue from the study).

If a DLT occurs in any patient during the first 28 days of treatment, that patient will be permanently discontinued from study drug administration.

For patients who experience toxicities (including IMARs) outside of the DLT window, dose reduction will be allowed only if the Investigator assesses that clinical benefit is being derived and may continue to be derived with lower doses of LYT-200. The dose of LYT-200 will initially be reduced by 50%, and potentially by a further reduction of 50%, as defined by the dose modification guidance provided in the protocol. No further dose reductions will be allowed. In cases where patients in Part 1 withdraw for reasons other than toxicity or tolerability issues during the first treatment cycle only, they will be replaced until the RP2D has been identified.

3.4.2.3. Part 1 Patient Replacement

In cases where patients in Part 1 withdraw for reasons other than toxicity or tolerability issues *during the first treatment cycle only*, they will be replaced until the RP2D has been identified.

3.4.3. Part 2: Cohort Expansion Phase

The second part of the protocol will adopt a Simon's 2-stage optimal design and plans to include approximately TBD patients. The Sponsor plans expansion cohorts for PDAC, H/N and urothelial cancer and/or potentially other solid and advanced tumor types from Part 1. The rationale behind this approach is to ensure recruitment feasibility, as well as to capture the clinical need for specific indications.

- H/N and urothelial cancer patients will receive LYT-200 + tislelizumab
- PDAC patients will receive LYT-200 in combination with gemcitabine/nab-paclitaxel

For all patients receiving a combination treatment (either tislelizumab + LYT-200 or gemcitabine/nab-paclitaxel + LYT-200), treatments can be administered on the same day. Tislelizumab or gemcitabine/nab-paclitaxel should be administered prior to LYT-200. If for any

reason same-day administration cannot be accomplished, tislelizumab or gemcitabine/nab-paclitaxel should be administered on the first day, and LYT-200 on the subsequent day.

Patients with H/N and Urothelial Cancer

Treatment with combination agent cohorts for H/N and urothelial cancer patients may be executed in parallel.

3.4.3.1. LYT-200+Tislelizumab Combination Treatment: H/N and Urothelial Cancer

The dose of LYT-200 in the combination treatment with tislelizumab will be the RP2D identified in Part 1. The optimal 2-stage design will also be used to test the null hypothesis that the ORR-3 is ≤ 10% versus the alternative hypothesis that the ORR-3 is ≥ 25%.

For patients who experience toxicities outside of the DLT window, dose reduction will be allowed only if the Investigator assesses that clinical benefit is being derived and may continue to be derived with lower doses of LYT-200. The dose of LYT-200 will initially be reduced by 50%, and potentially by a further reduction of 50%, as defined by the dose modification guidance provided in the protocol. No further dose reductions will be allowed. Dose modifications for tislelizumab will also be allowed as defined by the guidance in Section 5.5 and Appendix 6.

If an IMAR occurs/recurs that is not managed by dose reduction of either agent, both study medications must be discontinued.

After testing the combination on 18 patients in the first stage, the respective trial arm will be terminated if ≤ 2 patients respond. If the trial goes on to Stage II of Simon's optimal design, approximately 25 patients will be treated additionally in each of the combination arms. If the total number of responding patients is ≤ 7, the combination within that arm will be rejected. If ≥ 8 patients have a confirmed ORR-3, the expansion cohort for that arm will be activated and described in an amendment to the protocol.

3.4.3.2. LYT-200+Gemcitabine/nab-paclitaxel Combination Treatment: PDAC

The Part 2 cohort for patients with metastatic PDAC will entail combination treatment of LYT-200 and gemcitabine/nab-paclitaxel in the first line metastatic setting.

For patients who experience toxicities outside of the DLT window, dose reduction will be allowed only if the Investigator assesses that clinical benefit is being derived and may continue to be derived with lower doses of LYT-200. The dose of LYT-200 will initially be reduced by 50%, and potentially by a further 50% as defined by the dose modification guidance in Section 5.5. and Appendix 8. No further dose reductions will be allowed. Dose modifications of gemcitabine and/or nab-paclitaxel will also be allowed as defined by guidance in Section 5.5 and Appendix 7. Any dose modifications are at the Investigator's discretion and in agreement with the Medical Monitor/Sponsor.

If an IMAR occurs/recurs that is not managed by dose reduction of either agent, both study medications must be discontinued.

The primary efficacy endpoint will be patient PFS6. In the 1st line metastatic setting using gemcitabine/nab-paclitaxel, the PFS6 was reported to be 50% (von Hoff et al., 2013). After testing the LYT-200/chemotherapy combination in 11 patients in the first stage of the Simon 2-stage design, the trial will be terminated if 6 or fewer patients exhibit PFS ≥ 6 months. If the trial goes on to the second stage of the Simon's 2-stage design, approximately 14 patients will be treated additionally. If the total number of responding patients with PFS-6 is ≤ 16, the study arm will be rejected.

Part 2 Completion

Completion of Part 2 will be dependent upon patient ORR-3 for H/N and urothelial cancer patients, and PFS-6 for PDAC.

3.4.4. Dose-limiting Toxicity Criteria

DLTs assessed in this trial are defined as a clinically significant hematologic and/or non-hematologic AE or abnormal laboratory value assessed as unrelated to metastatic tumor disease progression, intercurrent illness, or concomitant medications and is possibly related or related to the study drug and occurring during the first cycle (28 days) on study. Any patient that experiences a DLT in Part 1 or Part 2 during the first 28 days of treatment will be permanently discontinued from study drug administration.

A DLT is a toxicity that meets any of the following criteria:

- Any death not clearly due to the underlying disease or extraneous causes
- Indications of potential drug induced liver injury (Hy's Law cases) as follows:
    - ALT or AST >3 x the upper limit of normal (ULN) with confirmation by repeat testing 24 hours later, AND
    - Serum total bilirubin (TBL) > 2 x ULN with confirmation by repeat testing 24 hours later
    - No other explanation can be found for the elevated TBL and/or aminotransferases (Ats), such as viral hepatitis (A, B or C), alcoholic or autoimmune hepatitis, pre-existing or acute liver disease, gall bladder obstruction or bile duct disease, Gilbert syndrome, disease progression, or another medication capable of causing the observed effect
- All Grade 4 non-hematologic and hematological toxicities of any duration
- All Grade 3 non-hematologic and hematological toxicities. Exceptions are as follow:
    - Grade 3 nausea, vomiting and diarrhea that does not require hospitalization or total parenteral nutrition support and can be managed with supportive care to ≤ Grade 2 within 48 h.
    - Grade 3 electrolyte abnormalities that are corrected to ≤ Grade 2 within 24 h.
    - Grade 3 electrolyte abnormality that lasts <24-72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
    - ≥ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.

3.5. Scientific Rationale for Study Design

The current Phase 1/2 study is using a multifaceted approach to identify the MTD in the initial Phase 1 component, and then seamlessly transition into a Phase 2 design in 3 tumor types to assess the efficacy and safety of LYT-200 as a single agent or in combination. During both the CRM approach in Part 1 and Simon's 2-stage optimal design in Part 2, patients will be protected for untoward toxicity. Indeed, the CRM approach with cohort sizes of 2 patients at each dose level will ensure that drug toxicity is promptly acted upon with dose reductions. Furthermore, the 2-stage optimal design using the RP2D identified in Part 1 (RP2D-1 for the combination arms) will discontinue treatment arms that do not achieve a minimum threshold of drug efficacy. Hence, new patients will be protected by not enrolling them into ineffective treatment arms. In summary, the proposed Phase 1/2 study will efficiently allow LYT-200 to be tested for safety and efficacy, all within one trial design and patient drug exposure will be limited to trial arms where a minimum threshold of drug activity has been achieved.

3.6. End of Study Definition

End of study for Part 1 of the study will be defined at the point when the RP2D has been identified and all patients have been treated with LYT-200 until confirmed disease progression.

End of study for Part 2 of the study will be defined for each tumor type following the completion of Simon's 2-stage optimal design and all enrolled patients have been treated with LYT-200 (alone or in combination) until confirmed disease progression.

In both Part 1 and Part 2 patients will also be followed for OS for up to 2 years following the last dose of LYT-200 if they discontinue treatment due to reasons other than progression of disease and they not receiving additional systemic anticancer treatments.

The end of the study is defined as the date of the last patient's last visit.

3.7. Trial Stopping Rules

Part 1

The trial will be stopped for safety if the lower limit of an Agresti and Coull binomial CI for the lowest study dose level exceeds the target DLT rate (Agresti and Coull, 1998).

Part 2

For the LYT-200 + tislelizumab combination in H/N and urothelial cancer patients, Simon's optimal design will guide trial stopping. After testing the combination on 18 patients in Stage I, the respective trial arm will be stopped if ≤ 2 patients respond. If the trial goes on to Stage II, a trial arm will be stopped if the total number of responding patients is ≤ 7 within that arm.

For the PDAC LYT-200 + gemcitabine/nab-paclitaxel combination treatment arm, Simon's optimal design will guide trial stopping as well. After testing the LYT-200/chemotherapy combination on 11 patients in Stage I, the trial arm will be stopped if ≤ 6 patients exhibit PFS ≥ 6 months. If the trial

goes on to Stage II, the trial arm will be stopped if the total number of responding patients with PFS of ≥ 6 months is ≤ 16.

For each cancer type enrollment will continue only if ≤ 2 patients develop a DLT, which will be below the target toxicity level (TTL) of 25%. If 3 or more patients with a given cancer type develop a DLT in a combination treatment arm, enrollment for that cancer type in that arm will be terminated.

3.8. Safety Monitoring Committee

Routine safety monitoring will be performed by the Medical Monitor. Safety monitoring, including analysis of PK, will be performed by a SMC, consisting of the Principal Investigators (and co-Investigators, as needed), Sponsor's representatives, and the study-specific Medical Monitor. Additional Investigators and study team members will participate in reviews as needed. An Independent Data Monitoring Board will not be utilized for this open-label study.

In Part 1, single agent dose escalation phase (Cohorts 1-8), dose escalation to the next cohort will proceed following review of Cycle 1 data of each cohort. Safety and available PK data will be used to assess DLTs in each cohort by the SMC, according to the schedule in Section 3.4.2. Select DLT safety analysis for each patient will be performed following completion of Cycle 1.

Following the completion of the CRM to identify the maximum tolerated dose (MTD) or RP2D, 6 additional patient cohorts will be activated to evaluate the safety and tolerability of LYT-200 in combination with chemotherapy or anti-PD-1. In the cohort evaluating LYT-200 in combination with chemotherapy at LYT-200 dose 6.3 mg/kg (Cohort 9), the SMC will convene to review the safety data and provide a recommendation on continuing to full enrollment after the first 4 patients have completed Cycle 1. In the 2 cohorts where LYT-200 6.3 mg/kg will be combined with tislelizumab (Cohorts 11 and 13), the SMC will convene to review the safety data and provide a recommendation on continuing to full enrollment after the first 2 patients have completed Cycle 1.

During Part 2, toxicities will be monitored by the SMC. The frequency of SMC meetings may increase as warranted by any increase in toxicity rate. For Part 1 and Part 2, the SMC has the right to recommend terminating or altering the study design of this clinical study at any time, including but not limited to testing of intermediate dose levels or initiation of the intermittent dose schedule.

The SMC will operate per a written charter and minutes will be maintained to include the data used for review and decisions made during the study.

Note: the SMC may schedule ad hoc meetings at any time during the study.

4. Study Population

4.1. General Considerations

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

For the dose escalation Part 1, patients with relapsed/refractory with relapsed/refractory, unresectable locally advanced or metastatic solid tumors, irrespective of tumor type, will be eligible using the CRM as described in Section 3.4.1.

For the dose expansion Part 2, patients with PDAC, H/N and urothelial cancer and/or potentially other solid tumor types based on data from Part 1 will be eligible.

4.2. Inclusion Criteria

Patients are eligible for the study after meeting the following inclusion criteria and not meeting any of the exclusion criteria:

Part 1 and Part 2:

1. Written Informed Consent (mentally competent patient, able to understand and willing to sign the informed consent form)
2. Age ≥ 18 years, male or non-pregnant female
3. Able to comply with the study protocol, as per Investigator's judgment
4. Histologically confirmed, unresectable locally advanced or metastatic cancer. There are no limits to prior lines of therapies received for the treatment of the cancer condition for which the patient is being enrolled into this study.
    a. For Part 1 combination urothelial carcinoma Cohorts 13 and 14: histologically or cytologically confirmed diagnosis of unresectable, locally advanced or metastatic urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra (i.e., transitional cell carcinoma).
    b. For Part 1 combination H/N cancer Cohorts 11 and 12: histologically confirmed, locally advanced or metastatic squamous cell carcinoma of head and neck (SCCHN; oral cavity, oropharynx, hypopharynx, or larynx).
5. For urothelial and H/N combination cancer cohorts, prior exposure to immunotherapy is allowed, with standard of care treatment options and/or within a clinical trial context. If the patient received an anti-PD-1 and/or an anti-PD-L1 containing regimen at any point, they must have demonstrated at least stable disease, as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or iRECIST criteria to one of these treatment regimens, if these measurements are available. If RECIST or iRECIST measurements are not available, then clinical PFS of at least 4 months is required to have been achieved on any of the prior anti-PD-1 and/or anti-PD-L1 containing regimens.
6. There is no PD-L1 expression requirement for the Part 1 combination urothelial and H/N cohorts; however, fresh biopsy or archival tissue is required for assessment of PD-L1 by IHC,

or a historical PD-L1 expression by IHC must be available. If PD-L1 expression data are already available, this does not override the protocol preference for obtaining a fresh biopsy whenever feasible.

7. For Part 1 combination cohort H/N cancer patients of oropharynx origin: HPV status needs to be established in the screening period or at any point while patient is on study drug, unless it is historically known. p16+ as a surrogate for HPV+, HPV RNA ISH or DNA PCR are all acceptable. The study accepts both HPV+ and HPV- patients.
8. Life expectancy > 3 months according to Investigator's judgment.
9. ECOG performance status 0-1.
10. Patient able and willing to undergo pre- and on/post treatment biopsies. According to the Investigator's judgment, the planned biopsies should not expose the patient to substantially increased risk of complications. Every effort will be made that the same lesion is biopsied on repeat biopsies. If the patient is eligible according to all other criteria but declines to consent to a biopsy or there are other medical reasons precluding biopsy, this will be discussed with the Sponsor.
11. Measurable disease, according to RECIST v1.1. Note that lesions intended to be biopsied should not be target lesions.
12. Adequate hematologic and end organ function, defined by the following laboratory results obtained prior to first dose of study drug treatment, provided no anticancer treatment was administered within the last 7 days:
    a. neutrophil count $\geq 1 \times 10^9$/L
    b. platelet count $\geq 100 \times 10^9$/L; for hepatocellular carcinoma (HCC) in Part 1 $\geq 50 \times 10^9$/L
    c. hemoglobin ≥ 9.0 g/dL without transfusion in the previous week
    d. creatinine $\leq 1.5 \times$ ULN; or eGFR > 50 mg/mmol
    e. aspartate aminotransferase AST (SGOT) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN when HCC or hepatic metastases are present)
    f. alanine aminotransferase (ALT [SGPT]) $\leq 3 \times$ ULN ($\leq 5 \times$ ULN when HCC or hepatic metastases present)
    g. bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's disease may have a bilirubin $\leq 3.0 \times$ ULN)
    h. albumin ≥ 3.0 g/dL
    i. international normalized ratio (INR) and partial thromboplastin time (PTT) $\leq 1.5 \times$ ULN, unless patient receiving anticoagulant therapy
13. No evidence of active serious infection or infections requiring parenteral antibiotics.
14. Women of childbearing potential must have a negative pregnancy test within 72 h prior to start of treatment. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last study treatment.

A woman is of childbearing potential if she is post-menarche, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices 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, symptom-thermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists.

15. Four (4) weeks or 5 half-lives (whichever is shorter) since the last dose of anticancer therapy before the first LYT-200 administration.
16. Bisphosphonate treatment (e.g., zoledronic acid) or denosumab are allowed if previously used prior to commencement of clinical trial.
17. Patients:
    a. who have already received at least one prior line of systemic therapy for metastatic or locally advanced disease, and/or
    b. who have a tumor type for which there are no available standard of care options.
18. Patients who have not previously received a gemcitabine-containing regimen.

4.3. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Patient unwilling or unable to follow protocol requirements
2. Patient diagnosed with metastatic cancer of an unknown primary
3. Current illicit drug addiction (medical and recreational marijuana/cannabidiol [CBD]/ tetrahydrocannabinol [THC] would not be considered "illicit")
4. Clinically significant, active uncontrolled bleeding, and any patients with a bleeding diathesis (e.g., active peptic ulcer disease). Prophylactic or therapeutic use of anticoagulants is allowed.
5. Pregnant and/or lactating females
6. Receiving any other investigational agents or participating in any other clinical trial involving another investigational agent for treatment of solid tumors within 3 weeks or 5 half-lives of the administered drug (whichever is shorter) prior to the first dose of study drug, or major surgery or planned surgery within 4 weeks of the first dose of study drug (this includes dental surgery).

7. Radiation therapy within 4 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass, and which does not jeopardize required measurable lesions for response assessment (RECIST v1.1).
8. Patients with fungating tumor masses
9. History or current evidence of any condition, therapy, any active infections, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator
10. Grade 4 immune-mediated toxicities with a prior checkpoint inhibitor. Grade 2 or Grade 3 pneumonitis or any other Grade 3 checkpoint inhibitor-related toxicity that led to immunotherapy treatment discontinuation. Low-grade (< Grade 3) toxicities, such as neuropathy from prior treatments, manageable electrolyte abnormalities and lymphopenia, alopecia and vitiligo are allowed.
11. History of other prior or other concomitant malignancy that requires other active treatment.
12. Active parenchymal brain metastases, patients with carcinomatous meningitis or leptomeningeal metastases. Patients with brain metastases are eligible provided they have shown clinically and radiographically stable disease for at least 4 weeks after definitive therapy and have not used steroids (> 10 mg/day of prednisone or equivalent) for at least 4 weeks prior to the first dose of study drug.
13. Evidence of severe or uncontrolled systemic diseases, congestive heart failure > New York Heart Association (NYHA) class 2, myocardial infarction (MI) within 6 months, or laboratory finding that in the view of the Investigator makes it undesirable for the patient to participate in the trial
14. Any medical condition that the Investigator considers significant to compromise the safety of the patient or that impairs the interpretation of LYT-200 toxicity assessment
15. Serious non-healing wound, active ulcer, or untreated bone fracture unless for e.g., a rib fracture for (which does not elicit treatment)
16. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures. For the purposes of this study, "recurrent" is defined as 3 drains in the last 30 days.
17. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
18. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of Cycle 1, Day 1
19. History of pulmonary embolism, stroke or transient ischemic attack within 3 months prior to Cycle 1, Day 1
20. Active autoimmune disorder (except type I/II diabetes, hypothyroidism requiring only hormone replacement, vitiligo, psoriasis, or alopecia areata).

21. Requires systemic immunosuppressive treatment, including, but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor (anti-TNF) agents. Patients who have received or are receiving acute, low dose systemic immunosuppressant medications (e.g., ≤ 10 mg/day of prednisone or equivalent) may be enrolled. Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy [e.g., ≤ 10 mg/day of prednisone equivalent] for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone), topical steroids, intranasal steroids, intra-articular, and ophthalmic steroids is allowed
22. Severe tumor-related pain (Grade 3, CTCAE v.5.0) unresponsive to broad analgesic interventions (oral and/or patches)
23. Hypercalcemia (defined as Grade 3, per CTCAE v 5.0) despite use of bisphosphonates
24. Any other diseases, 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 or that may affect the interpretation of the results or render the patient at high risk of treatment complications
25. Received organ transplant(s)
26. Patients undergoing dialysis
27. For Part 1, hormonal androgen deprivation therapy is allowed to continue for patients with metastatic castration-resistant prostate cancer
28. Any ablative therapy (Radio Frequency Ablation or Percutaneous Ethanol Injection) for HCC < 6 weeks prior trial entry
29. Hepatic encephalopathy or severe liver adenoma
30. Child-Pugh score ≥ 7

4.4. Lifestyle Considerations

No lifestyle restrictions are required.

4.5. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

4.6. Participant Discontinuation/Withdrawal from the Study

In accordance with the Declaration of Helsinki, ICH GCP Guidelines, and the FDA regulations, a patient has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution.

The Investigator and Sponsor also have the right to withdraw patients from the study treatment, as described below or for safety, behavioral, or administrative reasons.

If the patient withdraws consent for continued follow-up, the Investigator must make every effort to perform the End of Treatment/Early Termination assessments 30 days following the last dose of treatment according to the SoA, even if the patient has initiated other anticancer treatment.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

4.7. Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study drug. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up.

4.8. Replacement of Patients

In Part 1 and Part 2 of the study, only patients who withdraw for reasons other than toxicity or tolerability issues *during the first treatment cycle only* will be replaced.

5. Study Drugs

Study drug(s) is/are defined as any investigational agent(s), marketed product(s), placebo, or medical device(s) intended to be administered/used to/in a study participant according to the study protocol.

5.1. Agents Administered in Combination with LYT-200

5.1.1. Tislelizumab

Tislelizumab is a PD-1 inhibiting mAb drug being developed for the treatment of cancer. Tislelizumab is formulated for IV injection in a single-use glass vial (20R glass, USP type I) with a rubber stopper containing a total of 100 mg of tislelizumab mAb in 10 mL of buffered isotonic solution. Tislelizumab is administered as an intravenous infusion over approximately 30 minutes (unless guided otherwise) at 300 mg every 4 weeks, in a 28-day cycle.

The active ingredient of tislelizumab is a humanized IgG4 variant mAb against PD-1, binding to the extracellular domain of human PD-1 with high specificity and affinity (KD = 0.15 nM). The excipients of tislelizumab include: sodium citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate-20, and water for injection. Tislelizumab competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signaling and enhancing the functional activity in T cells in in vitro cell-based assays. In addition, tislelizumab demonstrated anti-tumor activity in several human cancer allogeneic xenograft models and a human PD-1 transgenic mouse model.

The IgG4 variant antibody has very low binding affinity to Fcγ RIIIA and C1q by in vitro assays, suggesting a low or no ADCC and CDC effect in humans. Unlike natural IgG4 antibody, tislelizumab has no observable Fab-arm exchange activity by the in vitro assay, predicting the antibody would be stable in vivo, unlikely forming bispecific antibodies.

Exposure-response (E-R) relationships between tislelizumab exposure and efficacy across a variety of advanced solid tumors support the 300 mg Q4W regimens. 300 mg Q4W regimen is not expected to be clinically different from the 200 mg Q3W in terms of safety or efficacy outcomes.

The safety profile of tislelizumab is consistent with the therapeutic class of the drug with a relatively low rate of treatment-related Grade 3 or above toxicity.

Tislelizumab AEs are presented below in Table 3 according to their frequency of occurrence. Reported AEs that may be IMAR-related are summarized in Table 4.

Refer to Appendix 5 for dose modifications and management of IMARs related to tislelizumab when given in combination with LYT-200.

Refer to Appendix 6 for management of non-IMAR-related AEs.

Table 2. Adverse Events (non-IMAR-Related) Reported for Tislelizumab According to Frequency

ORGAN SITE	ADVERSE EVENT
blood and lymphaticsystem/ febrile	anemia (8-21%, severe 1-8%)
	leukopenia (5-12%, severe 2%)
neutropenia	lymphopenia (<1%)
	neutropenia (3-9%, severe 1-3%)
	thrombocytopenia (1-9%, severe 1%)
gastrointestinal	*emetogenic potential:* low[3]
	constipation (13%, severe <1%)
	diarrhea (5-13%, severe 1%)
	nausea (4-13%, severe <1%)
	stomatitis, aphthous ulcer (3%, severe <1%)
	vomiting (10%, severe 1%)
general disorders and administration site conditions	*extravasation hazard:* none[4]
	chills (1%, severe 0%)
	fatigue, asthenia (1-23%, severe 2%)
	pyrexia (5-33%, severe 1%)
infections and infestations	pneumonia (3%)
injury, poisoning, and procedural complications	***infusion-related reactions*** (2-29%, severe <2%)
investigations	alkaline phosphatase increase (6%, severe 1%)
	ALT increase (1-16%, severe 2%)
	AST increase (1-17%, severe 3%)
	bilirubin increase (5-12%, severe 2%)
	creatine phosphokinase increase (1-6%, severe 1%)
	hyperglycemia (2-5%, severe 1%)
	hyponatremia (1%, severe 1%)
	lipase increase (1%, severe 1%)

ORGAN SITE	ADVERSE EVENT
Clinically important side effects are in ***bold, italics***	
	proteinuria (1-6%)
	thyroid hormone (free triiodothyronine and thyroxine) decrease (1%)
	thyroid stimulating hormone (TSH) increase (1-7%)
metabolism and nutrition	appetite decrease (1-15%, severe <1%)
	diabetes mellitus, type 1 (1%, severe 1%)
	diabetic ketoacidosis (<1%)
musculoskeletal and connective tissue	arthralgia (2-6%)
respiratory, thoracic and mediastinal	cough (13%)
	dyspnea (6%, severe 1%)
	pruritus (8-14%, severe <1%)
	rash (6-18%, severe 1%)
	skin reaction, undefined (1%, severe <1%)

By disrupting PD-1-mediated signaling, tislelizumab acts to restore anti-tumor immunity and halt progression of tumor growth. This restoration of immune system activity may result in immune related adverse reactions involving 1 or more body systems, which can be life-threatening or fatal in rare cases. While these events usually become manifest during treatment with tislelizumab, they can also occur after discontinuation of tislelizumab therapy.

Table 3. Adverse Events Reported for Tislelizumab to be Treated as IMARs*

ORGAN SITE	ADVERSE REACTION
cardiac	immune-mediated myocarditis (1%, severe <1%)
endocrine	immune-mediated adrenal insufficiency (<1%)
	immune-mediated hyperthyroidism (3-4%, severe <1%)
	immune-mediated hypothyroidism (6-21%, severe 1%)
	immune-mediated thyroiditis (1%)
eye	immune-mediated uveitis (<1%)
gastrointestinal	immune-mediated colitis (1%, severe 1%)
	immune-mediated pancreatitis (1%, severe 1%)
	immune-mediated hepatitis (1-3%, severe 1-2%)
musculoskeletal and connective tissue	arthralgia (2-6%)
	immune-mediated myositis/rhabdomyolysis (1%, severe 1%)
	immune-mediated nephritis, renal dysfunction (1%, severe 1%)
immune system	immune-mediated adverse events (21-22%, severe 5-11%)

respiratory, thoracic and mediastinal	cough (13%)
	dyspnea (6%, severe 1%)
	immune-mediated pneumonitis, interstitial lung disease (2-7%, severe 1-6%)
skin and subcutaneous tissue	immune-mediated dermatitis (1%, severe <1%)
	immune-mediated pruritus (2-4%)
	immune-mediated rash (3%, severe <1%)
	immune-mediated vitiligo (1%)

5.1.2. Gemcitabine plus Nab-Paclitaxel

Gemcitabine is a nucleoside metabolic inhibitor indicated for treatment of multiple cancer types, both as a single agent and in combination with other therapies. Nab-paclitaxel (Abraxane®; a protein-bound form of paclitaxel) is a microtubule inhibitor also indicated for treatment of multiple tumor types. Specifically, Nab-paclitaxel is indicated as a first line treatment for metastatic PDAC in combination with gemcitabine. Gemcitabine is administered as a 1000 mg/m^2 dose over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. Nab-paclitaxel is administered as a 125 mg/m^2 dose over 3-40 minutes on Days 1, 8 and 15 of each 28-day cycle. (The package insert for Gemzar® (brand name of gemcitabine) is located in Appendix 10, and the package insert for Abraxane is in Appendix 9.)

The AEs that are attributed to the combination of gemcitabine + nab-paclitaxel are shown below in Table 5.

Table 4. Adverse Events Reported for Gemcitabine + Nab-Paclitaxel in the Treatment of Pancreatic Cancer, According to Frequency

Common: AEs occurring in >30% of patients			
Neutropenia	Thrombocytopenia	Peripheral neuropathy	Nausea
Alopecia	Peripheral edema	Diarrhea	Vomiting
Pyrexia	Decreased appetite	Rash	Fatigue
Less Common: AE's occurring in 10-29% of patients			
Asthenia	Mucositis	Dysgeusia	Headache
Dehydration	Hypokalemia	Cough	Epistaxis
Urinary tract infections	Pain in extremity	Arthralgia	Myalgia
Depression			
Rare AEs occurring in <10% of patients			
Oral candidiasis	Hypertension	Pneumonitis	
Cystoid macular edema	Pneumonia	Tachycardia	
Congestive cardiac failure			
Most Common Serious Adverse Reactions (>1%)			
Pyrexia (6%)	Dehydration (5%)		
Pneumonia (4%)	Vomiting (4%)		

Source: Section 6.3 Abraxane Package Insert. See Appendix 9.

Limiting infusion of nab-paclitaxel to 30 minutes reduces the likelihood of infusion-related reactions.

Premedication to prevent hypersensitivity reactions is generally not needed prior to administration of nab-paclitaxel. Gemcitabine is contraindicated in patients with a hypersensitivity to gemcitabine.

Abraxane causes myelosuppression and should not be used when neutrophil counts are <1,500 cells/mm^3. Severe hypersensitivity reactions have been known to occur with Abraxane. Gemcitabine should not be administered to patients with known sensitivity to gemcitabine.

5.2. Study Drug Administration

All patients will receive LYT-200. LYT-200 will be administered via IV infusion, QW, or Q2W, until progression of disease, unacceptable toxicity, or withdrawal of consent.

In **Part 1**, patients will receive LYT-200 as a single agent at sequentially increasing doses starting at 0.2 mg/kg, in accordance with the CRM design (see Section 3.4.1).

In the **Part 1** combination treatment phase, patients with PDAC, H/N, and urothelial tumors will receive LYT-200 at sequentially increasing doses of 6.3 mg/kg QW and 16.0 mg/kg QW, in combination with gemcitabine/nab-paclitaxel or tislelizumab (Cohorts 9-14: see Section 3.4.2). Cohorts 9-14 will enroll approximately 44 patients.

In **Part 2**, patients will receive the RP2D of LYT-200 (as determined in Part 1) in combination with tislelizumab or gemcitabine/nab-paclitaxel as follows:

- Patients with H/N or urothelial cancer
  - LYT-200 + tislelizumab in H/N
  - LYT-200 + tislelizumab in urothelial cancer
- Patients with PDAC
  - LYT-200 + gemcitabine/nab-paclitaxel
- Other solid tumor types (based on data from Part 1)
  - LYT-200 in combination with tislelizumab or gemcitabine/nab-paclitaxel that will be determined based on each tumor type

See Table 6 for a summary description of each study drug. Details are presented in the IB.

Patients who experience a DLT in Part 1 will not resume treatment. Patients who experience a DLT in Part 2 will have their treatment interrupted. Their treatment may resume at the same or reduced dose of LYT-200 if they are experiencing a clinical benefit, per Investigator's judgment and following a discussion with the Study Medical Monitor.

See Section 5.5 for details on dose modifications.

Table 5. Summary Characteristics of Study Drugs

Arm Name	**LYT-200**	**LYT-200 + tislelizumab**	**LYT-200 + gemcitabine/nab-paclitaxel (Abraxane)**
Drug Name	LYT-200	tislelizumab	gemcitabine/nab-paclitaxel
Drug Type	Biologic	Biologic	Drugs
Dose Formulation	Vial	Vial	Vial(s)
Unit Dose Strength(s)	30 mg/mL	100 mg/10mL vial	Nab-paclitaxel: 5 mg/mL powder for suspension for infusion. Gemcitabine: 200 mg or 1 g lyophilized powder in single-dose vials for reconstitution
Dosage Level(s)	**Part 1**: increasing doses starting at Q2W 0.2 mg/kg with a maximum dose of QW 16.0 mg/kg **Part 2:** RP2D-1 for LYT-200 in combination with tislelizumab or chemotherapy	**Part 1 and Part 2** : tislelizumab: 300 mg	**Part 2 only:** Nab-paclitaxel: 125 mg/m² Gemcitabine: 1000 mg/m²
Frequency of Administration	Q2W: Days 1 and 15 of each 28-day cycle (Part 1, Cohorts 1-6) QW: Days 1, 8, 15, and 22 of each 28-day cycle (Part 1, Cohorts 7-8)	Days 1 of each 28-day cycle	Days 1, 8, and 15 of each 28-day cycle
Route of Administration	IV infusion	IV infusion	IV infusion
Use	experimental	experimental	standard of care
IMP and non-IMP	IMP	IMP	non-IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided locally by the trial site, subsidiary, or designee

Packaging and Labeling	Study Drug will be provided in appropriate configurations; each will be labeled as required per country requirement	Study Drug will be provided in appropriate configurations; each will be labeled as required per country requirement	Study Drug will be provided locally according to approved label

IMP: investigational medicinal product, IV: intravenous, mAb: monoclonal antibody, RP2D: recommended Phase 2 dose; RP2D-1: dose level in cohort immediately preceding the RP2D

5.3. Preparation/Handling/Storage/Accountability

LYT-200 may be supplied as a liquid or frozen formulation. Refer to the Pharmacy Manual for details.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

5.3.1. Preparation of LYT-200

Manufacture and packaging of the investigational medicinal product (IMP) LYT-200 will be in accordance with applicable current Good Manufacturing Practice (cGMP) and the product will meet applicable criteria for use in humans.

LYT-200 liquid drug product will be diluted to the target dose prior to administration. See Pharmacy Manual for dilution instructions. All dilutions should be performed in a controlled and sterile environment (patient dose is prepared for and delivered via an approximately 60 minutes IV infusion per the Pharmacy Manual).

Refer to the Pharmacy Manual for preparation of the frozen formulation of LYT-200.

5.3.2. Storage of LYT-200

LYT-200 will be stored at 2°C to 8°C (liquid) or ≤ 65°C (frozen) and protected from light.

5.4. Study Drug Compliance

When patients are dosed at the site, they will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug and study patient identification

will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

In accordance with all applicable regulatory requirements, the Investigator or designated site staff (e.g., investigational drug pharmacist) must maintain current investigational product accountability records throughout the course of the study. These records will contain the following information:

- Date, quantity, and vial number(s) received from and returned to the Sponsor (as applicable)
- Patient Study ID number, date, quantity, and vial number(s) of agent dispensed
- Date, quantity, and vial number(s) of accidental loss of study agent (if applicable)
- Date, quantity, and vial number(s) investigational product destroyed per institutional guidelines (if applicable)
- Documentation of storage conditions

These inventories must be made available for inspection by the study monitor. The Investigator or designee will be responsible for ensuring that all used and unused trial supplies are accounted for. At the end of the trial the study monitor will also collect the original investigational agent dispensing record. A copy of the dispensing record should be kept at the site and maintained with the study records.

5.5. Dose Modification

The decision to proceed to the next dose level of LYT-200 in Part 1 will be made by the SMC based on safety, tolerability, and preliminary PK data obtained in at least 2 patients at the prior dose level.

The dosing schedule may also be adjusted based on PK data obtained.

Detailed dose modification instructions are available as follows:

Appendix 4: Management of Immune-mediated Adverse Reactions (IMARs) caused by LYT-200

Appendix 5: Management of Immune-mediated Adverse Reactions (IMARs) caused by LYT-200 + tislelizumab Combination Treatment

Appendix 6: Recommended Dose Modifications for tislelizumab for AEs (other than IMARs)

Appendix 7: Recommended Dose Modifications for Gemcitabine + Nab-Paclitaxel in PDAC Patients

Appendix 8: Recommended Dose Modifications for LYT-200 (for AEs outside the DLT window and other than IMARs)

5.5.1. Dose Administration

If an infusion-related reaction is encountered, interrupt the infusion and if clinically indicated, administer relevant medication(s) (e.g., anti-histamine, anti-emetic, steroids, anti-pyretics,

beta- blocker(s) etc.). If it is deemed appropriate to resume the infusion, resume at a slower infusion rate.

For subsequent cycles for the same patient, apply the appropriate pre-medications (anti- histamine, anti-emetic, steroids, anti-pyretics, beta-blocker(s) etc., as clinically indicated needed) and consider utilizing a slower infusion rate.

5.5.2. Dose Delay

If any clinically meaningful AE ≥ Grade 3 possibly related or related to one or more study drugs occurs, it will be discussed with the Medical Monitor before continuing with dosing. Where judged appropriate by the Investigator (after discussion with the Medical Monitor) a dose delay may be necessary for ≥ Grade 3 AE.

5.5.3. Dose Reduction

No dose reductions will be allowed for any patient that is being evaluated for DLTs (within the 28-day DLT window). In case a dose reduction is necessary, the study drug will be administered as follows:

For Parts 1 LYT-200 single-agent patients: Dose reduction will be allowed only if the Investigator assesses that clinical benefit is being derived and may continue to be derived under dose reduced conditions, see Appendix 4 (for IMARs) or Appendix 8 (for other AEs).

For Part 2 combination treatment cohorts of LYT-200 + gemcitabine/nab-paclitaxel or LYT-200 + tislelizumab, see Appendix 5, Appendix 6, and Appendix 7.

5.5.4. Dose Continuation for LYT-200 for Patients in the LYT-200+gemcitabine/Nab-paclitaxel Cohort

If a patient is experiencing clinical benefit from LYT-200 as per Investigator's judgment, and protocol efficacy assessment criteria, and the patient is experiencing adverse reactions that are not attributed to LYT-200, then treatment with LYT-200 as a single agent may continue while the gemcitabine/nab-paclitaxel is modified/discontinued. For guidance on AEs that can be attributed gemcitabine/nab-paclitaxel, see Section 5.5.7 and Appendix 7.

LYT-200 may be continued if:

- the Investigator determines the patient's clinical status is not deteriorating rapidly; AND
- the combination agent is discontinued due to AEs that are attributed to the combination agent only.

Recommended LYT-200 dose modifications in response to any of these potential AEs (outside of DLT windows) are located in Appendix 8.

If an IMAR occurs/recurs that is not managed by dose reduction of either agent, both study medications must be discontinued. Please refer to Appendix 4.

5.5.5. Dose Modifications for Specific AEs Related to Administration of Tislelizumab

Recommendations for tislelizumab modifications based on specific AEs are provided in Appendix 5 (for IMARs) and Appendix 6 (for other AEs).

5.5.6. Dose Modifications for Specific AEs Related to Administration of Gemcitabine + Nab-Paclitaxel

The recommended dose modifications in response to specific AEs are provided in Appendix 7.

Nab-paclitaxel is not recommended in patients who have total bilirubin >5 x ULN or AST >10 x ULN. In addition, Nab-paclitaxel is not recommended in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN). The starting dose should be reduced for patients with moderate or severe hepatic impairment.

5.5.7. Dose Modification for IMARs

If an IMAR occurs, refer to Appendix 4 and Appendix 5 for guidance on dose management of LTY-200 and/or tislelizumab.

Investigator should carry out all relevant medical exam(s)/test(s) in order to confirm that the adverse event is an IMAR.

5.5.8. Discontinuation of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue study drug. If study drug is permanently discontinued due to reasons other than disease progression, and the patient is not being treated with other anticancer therapy(ies), the patient will continue to be evaluated for disease progression for up to 2 years. See the SoA for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

Every effort must be made by study personnel to keep patients on study treatment until one of the reasons for study treatment termination are met (disease progression, toxicity related to the study drug, withdrawal of consent). If the patient has radiographic progression but no unequivocal clinical progression and alternate treatment is not initiated, the patient may continue on study treatment at the Investigator's discretion. However, if patients have unequivocal clinical progression without radiographic progression, study treatment should be stopped as per Investigator's judgment and patients advised regarding available treatment options.

A patient may be discontinued prior to disease progression for any of the following reasons:

- A DLT per definition in Section 3.4.4.
- An AE occurs/recurs outside of the DLT window that requires discontinuation of study treatment(s)
- An IMAR occurs/recurs that requires discontinuation of study treatment(s)
- Termination of the study by PureTech Health LLC
- Intercurrent illness or medical condition that prevents further administration of treatment or may jeopardize the patient's safety if they continue on study treatment
- Due to patient's or Investigator's decision
- Pregnancy
- Use of a non-protocol anticancer therapy

Patients may also be discontinued prior to disease progression for any of the following reasons:

- Significant deviation from protocol on the part of the patient (includes lack of compliance)
- Significant protocol violation on the part of the Investigator

The explanation of why the patient is discontinuing study treatment should be documented in the case report form (CRF). If the patient discontinues study treatment due to toxicity, "Dose-Limiting Toxicity" or "Adverse Event" will be recorded as the primary reason for withdrawal. If a patient is prematurely discontinued from the study at any time due to an AE or SAE, the patient must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of the underlying disease.

5.6. Continued Access to Study Drug After the End of the Study

Continued access to study drug is not planned after study end.

5.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.7.1. Permitted Medications

The following concomitant medications are allowed:

- Any standard of care premedication for patients on a combination treatment regimen.
- Continuation of bisphosphonate treatment (e.g., zoledronic acid) or denosumab for bone metastases, which have been stable for at least 6 months before treatment (C1D1).
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone), topical steroids, intranasal steroids, intra-articular, and ophthalmic steroids.
- Prophylactic or therapeutic use of anticoagulants.
- Vaccination for COVID-19, common flu and/or other common clinically required indications (e.g. tetanus, pneumococcus, HBV, etc.) is allowed before or during the study period. The timing and type of vaccine must be recorded.

See Section 5.7.3 for supportive care.

5.7.2. Prohibited Medications

Following medications are not allowed while on this study:

- Concomitant administration of other investigational agents, other than LYT-200, for any indication.

- Systemic immunosuppressive treatment, including, but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents. However, patients are allowed to take acute, low dose systemic immunosuppressant medications (e.g., ≤ 10 mg/day of prednisone or equivalent).
- Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy [e.g., ≤ 10 mg/day of prednisone equivalent] for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

5.7.3. Supportive Care

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with institutional guidelines.

6. Study Assessments and Procedures

A signed, written ICF approved by an IRB must be obtained from the potential patient before he/she can participate in any study-specific procedures, including study-specific screening procedures.

Patients will be entered in the study once all screening procedures have been completed and it is determined that they meet all eligibility criteria.

- Study procedures and their respective timing for Part 1, Cohorts 1-6 are summarized in the SoA (Table 1). Study procedures and their respective timing for Part 1, Cohorts 7-14, and Part 2 are summarized in the SoA (Table 2). Protocol waivers or exemptions are not allowed.
- Adherence to all study requirements, including those specified in the SoA, is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Medical Monitor/Sponsor immediately upon occurrence or awareness to determine the need for drug or study discontinuation.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

6.1. Assessments by Visit

The SoA (Table 1 and Table 2) provides a list of assessments to be performed during the screening period (up to 28 days), the treatment period (presented as 28-day cycles), the End of Treatment/Early Termination period, IMAR follow-up and the long term follow-up period. Optional visits are allowed during each treatment cycle if medically indicated, during which any of the study assessments may be performed at the discretion of the Investigator.

During the COVID-19 pandemic many governments require citizens to practice social distancing, and more vulnerable populations are advised to self-isolate. These types of constraints may affect the ability to run this clinical study as originally intended. Planned site visits can be adapted so that the study can safely continue during the pandemic. Possible modifications as approved by the Sponsor may include:

- visit and/or study procedure postponement
- replacement with telephone/video call(s)
- replacement with home visits
- visits performed at an alternative clinical location
- visits performed by a health care provider outside the study team
- visit and/or study procedure completely cancelled.

6.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Table 1 and Table 2).

6.2.1. RECIST v1.1 Criteria for Tumor Assessment

At the screening tumor assessment, tumor lesions/lymph nodes will be categorized as measurable or non-measurable with measurable tumor lesions recorded according to the longest diameter in the plane of measurement (except for pathological lymph nodes, which are measured in the shortest axis). When more than one measurable lesion is present at screening all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter). A sum of the diameters for all target lesions will be calculated and reported as the baseline sum diameters.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at screening. Measurements are not required, and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'.

Tumor target lesions will be assessed according to the RECIST v1.1 Guidelines (Eisenhauer et al., 2009) using the following disease response measures:

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease

Definitions of these categories are provided in Appendix 3.

The disease response measures at different timepoints will allow for the calculation of the following:

- Disease control rate (DCR), defined as percentage of patients who have achieved CR, PR and SD.
- Objective response rate (ORR), defined as the proportion of patients with tumor size reduction of a predefined amount (tumor shrinkage of ≥ 30%).
- Progression-free survival (PFS), defined as the time from study drug treatment initiation to disease progression (tumor growth by ≥ 30%).
- Duration of response (DoR), defined as the length of time that a tumor continues to respond to treatment without the cancer growing or spreading.
- Overall survival (OS) defined as the time from study drug treatment initiation to death from any cause.

6.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

6.3.1. Physical Examinations

Medical and physical examinations must be performed by a qualified physician, nurse practitioner, or physician assistant, and should include a thorough review of all body systems. Additionally, height (at screening only) and weight are measured.

6.3.2. Vital Signs

Vital signs will be measured in a post-supine position after 5 minutes rest and will include temperature, blood pressure (systolic and diastolic), heart rate, and respiratory rate.

6.3.3. Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (see Table 1 and Table 2) using an ECG machine that automatically calculates the heart rate and measures heart rate, PR interval, QRS duration, distance in time on the ECG tracing from the start of the QRS complex to the end of T- wave (QT) interval, and QTcF intervals.

6.3.4. Clinical Safety Laboratory Assessments

Patients will have blood samples collected for routine clinical laboratory testing (approximately 5 mL at each timepoint), according to the SoA (Table 1 and Table 2); additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 4 of the protocol.

The clinical laboratory parameters will be analyzed at the site's local laboratory. Laboratory assessments to be completed will include hematology and serum chemistry and will be defined as following:

- **Serum Chemistry:** To include glucose, total protein, albumin, electrolytes [sodium, potassium, chloride, magnesium, phosphorus], calcium, bilirubin (total, direct), SGPT (ALT) or SGOT (AST), alkaline phosphatase, gamma glutamyl transferase (gamma GT), lactate dehydrogenase (LDH), creatinine, hemoglobin A1c (HgbA1c) (only if history of Type 1 or Type 2 diabetes mellitus), blood urea nitrogen, creatine phosphokinase (CPK)
    - TSH, fT4, lipase, amylase, parathyroid hormone (PTH), FSH, LH, free cortisol additionally at specified visits
    - Fasting glucose will be assessed only if clinically indicated
- **Hematology**: To include complete blood count, differential, platelets, hemoglobin
- **Coagulation**: To include prothrombin time (PT) and PTT, activated partial thromboplastin time (APTT) and INR (if on allowable anticoagulants) C- reactive protein (CRP), and troponin
- **Urinalysis**: Patients will have urine samples collected for routine urinalysis. The urinalysis will include color, appearance, and dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, white blood cell count (WBC), red blood cell count (RBC), and pH, and urine culture (if patient is clinically symptomatic).

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline or Grade 1 within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA (Table 1 and Table 2).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

6.3.5. Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.

Additional pregnancy testing should be performed during the treatment period and at the End of Treatment/Early Termination visit according to the SoA (Table 1 and Table 2), and as required locally.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

If the patient has prior history of bilateral salpingo-oophorectomy and/or hysterectomy, record these surgical procedures; a pregnancy test is not required for these patients.

6.4. Pharmacokinetics Assessments

The following serum PK parameters will be calculated for LYT-200, if possible:

- $AUC_{0\text{-}336h}$
- C_{max}
- T_{max}
- $t_{1/2}$
- serum concentration vs. time profiles

Blood samples of approximately 5 mL will be collected and processed to serum at each timepoint as specified in the SoA (Table 1 and Table 2).

6.4.1. PK Schedule for Cohorts 1-6:

Cycle 1 and Cycle 3 Day 1

- Pre-dose
- At the EOI
- 2 h (± 30 min) after EOI
- 4 h (± 30 min) after EOI

Cycle 1 and Cycle 3 Day 15

- Pre-dose
- At EOI

Cycle 1 and Cycle 3 Day 2 and 8 (non-dosing days)

- One timepoint, any time during the visit

Cycle 2 and Cycle 4 Day 1

- Pre-dose
- At EOI

Every 2 Cycles beyond Cycle 4 on Day 1 (i.e., C6D1, C8D1 etc.)

- Pre-dose
- At EOI

6.4.2. PK Schedule for Cohorts 7 and 8:

Cycles 1 and 3 Day 1 (i.e., C1D1, C3D1)

- Pre-dose
- At the EOI
- 1 h (± 15 min) after EOI

Cycles 1 and 3 Day 3 (i.e., C1D3, C3D3)

- One timepoint, any time during the visit

Cycles 1 and 3 Days 8, 15, and 22 (i.e. C1D8, C3D8)

- Pre-dose
- At EOI

Even numbered Cycle Day 1 (i.e., C2D1, C4D1, etc.)

- Pre-dose
- At EOI

6.4.3. PK Schedule for Cohorts 9-14:

Cycles 1 and 3 Day 1 (i.e., C1D1, C3D1)

- Pre-dose
- At the EOI
- 1 h (± 15 min) after EOI

Cycles 1 and 3 Day 3 (i.e., C1D3, C3D3)

- One timepoint, any time during the visit

Cycles 1 and 3 Days 8, 15, and 22 (i.e. C1D8, C3D8)

- Pre-dose
- At EOI

Even numbered Cycle Day 1 (i.e., C2D1, C4D1, etc.)

- Pre-dose
- At EOI

If the Investigator determines that the dose of study drug should be interrupted, additional PK and safety assessments will be collected upon resumption of dosing; additional PK assessments may be performed during the interruption at the discretion of the Investigator. If the dose of study drug is reduced, additional PK assessments will be collected pre-administration of the reduced dose (within 2 h pre-dosing), and 2 to 4 h after starting the reduced study drug dose. Additional PK, and other blood assessments may be taken if clinically indicated at the discretion of the Investigator. Centers that are not able to hold patients more than 2 h post-dose due to COVID-19 restrictions, will contribute samples at EOI and 2 h post-dose only.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-h clock time) of each sample will be recorded.

Samples will be used to evaluate the serum concentration levels of total LYT-200 and free/partially free LYT-200 by a Sponsor-designated laboratory. Concentrations will be determined using validated assays. A minimum of 2 50 µL aliquots of serum are needed to determine total LYT-200 concentrations. A minimum of 2 100 µL aliquots of serum are needed to determine free and partially free LYT-200 concentrations and residual serum in a third aliquot. Samples collected for analyses of LYT-200 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained. At visits during which blood samples for the determination of PD, ADA, safety lab of LYT-200 will be taken, one sample of sufficient volume can be used.

PD biomarkers are evaluated in this study and are described in Section 6.6.

6.5. Genetics

Genetics are not evaluated in this study.

6.6. Pharmacodynamic Biomarkers

Planned time points for biomarker assessments are provided in the SoA (Table 1 and Table 2); sampling may be decreased to every 3rd cycle after 6 months of treatment.

Collection of biological samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Blood samples, to be collected prior to study drug administration (approximately 15 mL pre-dose)
- Tumor biopsy (tissue sample)

Samples will be tested for PD biomarkers (by flow cytometry, ELISA, IHC, or multiplex phenotyping) to evaluate their association with the observed clinical responses to LYT-200 using validated assays.

The following biomarkers are planned to be assessed for this study, but not limited to:

- Tumor markers (blood): CA15-3, CA-125, carcinoembryonic antigen (CEA), CA19-9, alpha fetoprotein, neuron-specific enolase (NSE), cytokeratin-fragment-21 (CYFRA-21) to be assessed every cycle pre-dose administration as needed per tumor type. This may be decreased to every 3 cycles after 6 months of treatment, following the same schedule as tumor imaging assessments, as appropriate
- PBMC phenotype (blood): e.g., CD3, CD4, CD8, CD45RO, forkhead-box-protein P3 (FOXP3), CD11B, CD14, CD15, CD16, CD33, CD68, human leukocyte antigen (HLA) DR, CD163, arginase 1, granzyme B, KI67, PD-1, PD-L1, pan cytokeratin (PAN-CK)
- Cytokines (blood): e.g., interferon gamma (IFN-γ), IL-10, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-6, IL-8, TNF-α, MIP-1b, monocyte chemoattractant protein 1 (MCP-1), MIP-1a, IL-17a, IL-5, TGF-β
- Gal-9 in blood and tumor tissue
- PD-L1 (tissue)
- Mismatch repair status (tissue)
- Tumor Mutational Burden (TMB)

Exploratory biomarker changes, if any, will be correlated with safety and response outcomes.

Samples may be stored for a maximum of 2 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of the effect of LYT-200 on PD biomarkers.

6.7. Immunogenicity Assessments

Blood samples (approximately 3 mL) will be collected from all participants according to the SoA (Table 1 and Table 2) and processed to serum. Additionally, serum samples should also be collected at the End of Treatment/early termination visit from patients who discontinued study drug or were withdrawn from the study.

Cohorts 1-6: Cycle 1 to Cycle 4 Day 1

- Pre-dose

Cohorts 1-6: Every 2 cycles beyond Cycle 4 on Day 1 (i.e., C6D1, C8D1 etc.):

- Pre-dose

Cohorts 7 and 8: Every Cycle Day 1

- Pre-dose

Cohorts 7 and 8: Cycle 1 Day 15 and Cycle 2 Day 15 only

- Pre-dose

Cohorts 9-14: Every Cycle Day 1

- Pre-dose

Cohorts 9-14: Cycle 1 Day 15 and Cycle 2 Day 15 only

- Pre-dose

A minimum of 2 aliquots of 500 µL serum each, with residual serum in a third tube will be obtained. Samples will be shipped to a lab designated by the Sponsor for analysis using a validated assay. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to LYT-200 (ADA) and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to LYT-200 and/or further characterize the immunogenicity of LYT-200.

The detection and characterization of antibodies to LYT-200 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study drug will also be evaluated for LYT-200 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug. Samples may be stored for a maximum of 2 years (or according to local regulations) following the last patient’s last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to LYT-200.

6.8. Other Assessments

6.8.1. Demographics

At screening, patient demographic data will be collected. These include age, gender, race, and ethnicity.

6.8.2. Medical History

The medical history will include oncology history, surgical/transplant history radiation therapy history, and COVID-19 history and testing.

- Personal medical history, including prior treatments/surgeries, record of any implants in situ or past implants, prior and/or current use of medical devices, concomitant medications (name, indication, dose, route, start and end dates dose modifications if any and reason), pre-existing symptoms, and AEs), hereditary diseases at risk of based on family history and complete family history to the best knowledge of the patient
- Record of any dental work performed in the past 12 months
- For patients with previously resected pancreatic adenocarcinoma, record whether the primary tumor was localized to the head of pancreas, pancreatic body or the pancreatic tail
- Bowel habits/ typical frequency and consistency
- Record any dietary requirements or preferences (for example, practice of a particular diet regimen: intermittent fasting, keto diet etc.)
- Record and allergies past and present (allergen, severity)

6.8.3. Prior and Concomitant Medications

Prior and concomitant medications, including vaccines and complementary treatments/supplements, will be documented for each patient at each scheduled visit (Table 1 and Table 2).

6.8.4. Tumor Imaging Assessments

Tumor assessments will be performed using CT or MRI with or without contrast; a PET-CT will be performed if requested by the Investigator.

CT with contrast is the preferred modality (MRI, PET-CT, or other imaging modalities instead of, or in addition to, the CT scan, if CT is not feasible or appropriate, given location of the disease). Assessment should include the chest/abdomen/pelvis at a minimum and should include other anatomic regions as indicated, based on the patient's tumor type and/or disease history. Imaging scans must be de-identified and archived in their native format as part of the patient study file. While the type of scan obtained is at the discretion of the Investigator, as appropriate for the disease, the same method should be used for the duration of the study.

On study, assessments are done every 8 weeks ± 7 days according to the SoA (i.e., C3D1, C5D1, C7D1, C9D1, etc.) and at the End of Treatment if not assessed within the last 4-6 weeks. Assessments may be performed more frequently if clinically indicated. For Part 2 only, if an objective response is seen on a scan, a confirmation scan will be done 4 weeks (+7 days) later. After a confirmatory scan, the scheduled scans are to be resumed at a frequency of every 8 weeks (± 7 days) from the date of the confirmatory scan.

6.8.5. Tumor Biopsies

Pre- and on-treatment biopsies are collected. A pre-treatment biopsy is to be collected during screening. If a pre-treatment biopsy is unobtainable as per the reasons outlined in the inclusion criteria, and the patient is enrolled in the study, an archival tumor tissue specimen from that patient will be collected from a primary tumor and/or a metastatic deposit. Excisional or core biopsy (FFPE tissue block(s) OR fresh tissue in formalin) obtained currently or within 5 years before study start from the primary tumor lesion or a metastatic deposit. If both primary and

metastatic tissues are available, use of metastatic deposit tissue will be prioritized. If information of treatment(s) received before and after tissue acquisition are available, this will be collected as well.

The on-treatment biopsy is scheduled for C3D15 ± 7 days and should occur only after the tumor imaging scan in Cycle 3. In instances where the procedure cannot be performed within the protocol-specified timeframe, alternatives may be permitted but must be discussed with the Study Director/Medical Monitor. It is recognized that a variety of clinical factors may make it difficult to obtain adequate specimens. Decisions not to complete biopsy on-treatment should be discussed with the Medical Monitor.

6.8.6. ECHO/MUGA

ECHO and/or MUGA will be obtained at the timepoints indicated in the SoA (Table 1 and Table 2). If clinically indicated, the assessment is to be repeated once every 3 months.

6.8.7. ECOG

ECOG performance status will be assessed at the timepoints indicated in the SoA (Table 1 and Table 2) using the following grading (Oken et al., 1982).

- Grade 0: Fully active, able to carry on all pre-disease performance without restriction
- Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
- Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- Grade 5: Dead

7. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

7.1. Definitions

7.1.1. Adverse Events

An AE is defined in the ICH Guideline for GCP as "any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment."

This definition of AEs is broadened in this study to include any such occurrence (e.g., sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a patient has signed informed consent to the time of initiation of the investigational drug. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches, gout, hypertension, etc.) has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

7.1.2. Serious Adverse Events

A SAE is defined as an AE that:

- Results in death;
- Is life-threatening (places the patient at immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
  A hospitalization meeting the definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Inpatient admission does not include rehabilitation facilities, hospice facilities, skilled nursing facilities, nursing homes, routine emergency room admissions, same-day surgeries (as outpatient/same day/ambulatory procedures), or social admission (e.g., patient has no place to sleep).
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical drug to prevent one of the outcomes listed in this definition. Examples of such medical events include anaphylaxis and allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.1.3. Relatedness

For all AEs, enough information should be obtained by the Investigator to determine the causality of the AE (e.g., study drug or other illness). The relationship of the AE to the study treatment will be assessed following the definitions below:

- **Unrelated**: any event that does not follow a reasonable temporal sequence from administration of study drug AND that is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- **Unlikely Related**: any event that does not follow a reasonable temporal sequence from administration of study drug OR that is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- **Possibly Related**: any reaction that follows a reasonable temporal sequence from administration of study drug OR that follows a known response pattern to the suspected drug AND that could not be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
- **Related**: any reaction that follows a reasonable temporal sequence from administration of study drug AND that follows a known response pattern to the suspected drug AND that recurs with re-challenge, AND/OR is improved by stopping the drug or reducing the dose.

7.2. Adverse Event Management

AEs will not be recorded prior to the administration of the first dose of study medication. AEs that start, or symptoms related to medical history that worsen after study drug administration will be recorded. AEs should be followed until they are either resolved, have returned to baseline, or are determined to be a stable or chronic condition. All SAEs are to be collected until 30 days after the last dose of study medication. All study-procedure-related SAEs must be collected from the date of patient's written consent.

7.2.1. Immune-mediated Adverse Reactions

IMARs are identified for tislelizumab.

7.2.1.1. Tislelizumab.

The specific IMARs noted are:

- Immune-mediated Hepatitis
- Immune-mediated Nephritis
- Immune-mediated Pneumonitis
- Immune-mediated Pneumonitis
- Immune-mediated Colitis and Diarrhea Immune-Mediated Endocrinopathies
- Immune-mediated Skin Reactions
- Other IMARs: arthritis, encephalitis, rhabdomyolysis, myositis, myocarditis, pancreatitis, and uveitis

- The monitoring plan is intended to limit the severity and duration of IMARs that occur during combination drug development, and encompass: scheduled visits for a physical exam, vital signs, safety laboratory assessments including blood hematology, biochemistry, assessing endocrine functions each Day 1 of a new dosing cycle (pre-dose), assessing coagulation status and urine analyses. The SoA (Table 1 and Table 2) also

encompasses assessing the ejection fraction once every 3 months and conducting regular ECGs.

The Investigator should carry out all relevant medical exam(s)/test(s) in order to confirm that the adverse event is an IMAR.

Instructions for the management of these IMARs are included in Appendix 4 for LYT-200 as a single agent, and Appendix 5 for the LYT-200 + tislelizumab combination treatment.

7.2.2. Dose Reduction Procedure for Adverse Event Management

In the event where dose reduction is used for AE management in Part 2 of the study, 2 dose reductions of 50% each are allowed. Dose reductions will be pursued only if the Investigator assesses that clinical benefit is being and may continue to be derived. Refer to Section 5.5 for additional details.

7.2.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs and SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at screening and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

Laboratory measurements that deviate clinically significantly from previous measurements (as determined by the Investigator) may be repeated. If warranted, additional or more frequent testing than is specified in the protocol should be done to provide adequate documentation of AEs and the resolution of AEs.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.3. Reporting Adverse Events

7.3.1. General Considerations

The Investigator will record all observed or volunteered AEs regardless of treatment group or causal relationship to study drug will be recorded on the AE page(s) of the CRF. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE), see Appendix 2.

For all AEs, the Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE

requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. For AEs with a causal relationship to the investigational product, follow-up by the Investigator is required until the event resolves or stabilizes at a level acceptable to the Investigator and the Sponsor clinical monitor or his/her designated representative.

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. When there is a safety evaluation during the study, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs, as detailed in this section of the protocol. Refer to definitions in protocol Section 7.1.

The CRF should include the following information: start and stop dates, CTCAE v. 5.0 grading, relationship to study medication, action taken, and outcome. AEs should be recorded from time of first dose up to 30 days following the last dose of study medication regardless of the causal relationship to the study medication. AEs considered related or possibly related to study medication should be recorded at any time regardless of when they occurred.

The Investigator will also assess the possible relationship between the AE and any of the study medications as well as any concomitant medications according to the criteria presented in Section 7.1.3.

Event outcomes will be recorded using the following categories:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

7.3.2. Prompt Reporting of SAEs

All SAEs, whether or not considered related to study drug, must be reported by completing the SAE form electronically in the electronic data capture (EDC) system for the study.

In the event EDC is unavailable, the paper SAE form must be filled out and sent via email within 24 h of awareness of the event to Clinipace Pharmacovigilance Department via email to safetygroup@clinipace.com. As soon as EDC is available, the Investigator or site personnel should enter the event from the paper SAE report form, including any updated information into EDC.

The following patient information is required:

- Patient identification including patient study number, and sex
- Date of first study drug dose
- Total dose and number of doses administered
- Date and amount of last study drug dose
- Whether the patient was taking study drug at the time of the AE

- Date, duration, and description of AE
- Events and symptoms leading up to the AE
- Action taken, including whether patient was withdrawn from study
- Concomitant therapy (including doses, routes, and regimens)
- Pertinent laboratory data
- Medical history (including time on study prior to AE and history that might be related to the AE)
- Study drug status (e.g., interrupted, discontinued, dose changed)

In addition to the above information, the Medical Monitor will require the Investigator's assessment of the following:

- Severity of the AE
- Investigator's assessment of the relationship of the AE to study treatment
- Outcome of the AE

Any oral report of SAEs must be followed within 48 h by a detailed, written report signed by the Investigator. Any necessary follow-up must be submitted within a reasonable time thereafter. The Sponsor will promptly report SAEs related to LYT-200 to the FDA and other applicable regulatory agencies in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 312.32 (21 CFR 312.32) and local regulatory requirements. The Investigator should also comply with any applicable requirements related to the reporting of SAEs to the IRB.

The Investigator will provide an SAE follow-up report to the Sponsor. In this report, the Investigator is to assess and record the SAE in detail, including the date and time of onset, description, intensity, duration, outcome, etiology, relationship to study drug, and action taken. Any SAEs that continue at the patient's last study visit must be followed until the event resolves or follow-up is agreed to be adequate by the Investigator, Medical Monitor, and Sponsor.

7.3.3. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the start of drug until the follow-up visit at the time points specified in the SoA (Table 1 and Table 2).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 h. The Investigator will submit any updated SAE data to the Sponsor within 24 h of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

7.3.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 4.7).

7.3.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

7.3.6. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 180 days after last treatment.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 h of learning of the [female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner)] pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor as described in Section 7.3.5. While the Investigator is not obligated to actively seek this information in former study

participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

7.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Disease progression will not be recorded as AE; however, symptoms of disease progression may be recorded at the Investigator's discretion.

8. Statistical Considerations

The study will be completed when the last patient has had their last visit. The database will be locked for the primary analysis after the last patient has had their primary endpoint event. A final study analysis will be performed after study completion.

8.1. Statistical Hypotheses

The current study is designed to identify the MTD of LYT-200 (Part 1) by assessing DLTs, followed by an assessment of drug activity (as a single agent or in combination) in each disease type using Simon's 2-stage optimal design. Study hypotheses for Part 2 are detailed below.

H/N and urothelial cancer LYT-200 + tislelizumab combination treatment arms

- Null hypothesis: ORR-3 is ≤ 10%
- Alternative hypothesis: ORR-3 is ≥ 25%.

PDAC LYT-200 + gemcitabine/nab-paclitaxel combination treatment

In the 1st line metastatic setting using gemcitabine/nab-paclitaxel, the PFS-6 was reported to be 50% (Von Hoff et al., 2013). This study will test the following:

- Null hypothesis: PFS-6 is ≤ 50%
- Alternative hypothesis: PFS-6 is 75%.

8.2. Sample Size Determination

8.2.1. Part 1

Part 1 of this study (dose escalation phase) will establish DLTs, the MTD, and the RP2D for LYT-200 using a CRM (O'Quigley et al., 1990), a model-based design that informs how the dosage of LYT-200 should be adapted for the next patient cohort based on past trial data.

Dose escalations will be based on the presence or absence of DLTs in patients treated at previous dose levels. For each dose cohort, prior DLT probabilities will have been specified from Good Laboratory Practice (GLP)-compliant toxicity studies as well as from preclinical models. For the specified target DLT rate and total number of dose levels, the skeleton for a power model d^exp(a) will be generated according to the approach of Lee and Cheung (2011), using a prior MTD adjusted by PK/PD data, located at the median dose level and a spacing measure of delta = 0.05 (Lee and Cheung, 2011). The prior distribution on the parameter "a" has a mean zero normal distribution with the least informative prior variance. The trial will be stopped for safety if the lower limit of an Agresti and Coull binomial CI for the lowest study dose level exceeds the target DLT rate (Agresti and Coull, 1998).

CRM trial simulation analyses with 1000 iterations suggested an average of approximately 20 patients will be needed to inform the selection of RP2D, which is the largest dose that has an estimated probability of a DLT less than or equal to a TTL of 25%.

The patients in Cohorts 7 to 14 will not be evaluated using the CRM. The CRM used will be based upon the first 6 cohorts, but that itself will not necessarily determine the RP2D, as data from Cohorts 7 to 14 will also be used to determine the RP2D. Among the 4 patients in Cohort 7, if there is not a single DLT, dosing will continue with Cohort 8. If there is at least 1 DLT (25%

DLT threshold) among the 4 patients, the study will not proceed to the next cohort. For Cohorts 9 and 10 (PDAC), initially 4 patients will be dosed in cohort 9 at the 6.3 mg/kg dose in combination with gemcitabine/nab-paclitaxel. A SMC meeting will then be held to review and assess the safety of these first 4 patients prior to enrolling the additional 6 patients in this cohort and proceed to dose escalation with enrollment of the firsts 4 patients at the 16.0 mg/kg dose in Cohort 10. Once again, a SMC meeting will be held to determine the safety of the first 4 patients dosed in Cohort 10 prior to enrolling the additional 6 patients at the 16.0 mg/kg combination dose.

The same sequence of events must occur for Cohorts 11 and 12 (H/N) and Cohorts 13 and 14 (urothelial). Initially, 4 patients will be dosed in each of Cohorts 11 (LYT-200 6.3 mg/kg QW/tislelizumab) and 13 (LYT-200 6.3 mg/kg QW/tislelizumab). A SMC meeting will be held, and safety reviewed prior to dose escalation to LYT-200 16.0 mg/kg QW in combination with tislelizumab for both Cohorts 12 and 14. As in the previous combination cohorts, the SMC will evaluate the safety of the initial 4 patients in each of the 6.3 mg combination Cohorts 11 and 13 prior to initiating enrollment of the initial 4 patients in Cohorts 12 and 14.

8.2.2. Part 2

Part 2 of this study (cohort expansion phase) will adopt a Simon's 2-stage optimal design with (one-sided) $\alpha = 0.05$ and 80% power to establish safety and efficacy for LYT-200 in patients with H/N, urothelial cancer, and PDAC. Approximately TBD patients will be treated in Part 2, of whom approximately TBD will be treated in Simon's Stage I and about TBD in Simon's Stage II.

H/N and Urothelial Cancer Combination Treatment Arms

It is estimated that approximately 18 patients are needed per combination treatment arm in Simon's Stage I to reject the null hypothesis that ORR-3 is $\leq 10\%$ and to continue to Simon's Stage II.

If the trial goes on to Stage II of Simon's optimal design, approximately 25 patients will be treated additionally in each of the combination arms to test the alternative hypothesis that ORR-3 is $\geq 25\%$. If the alternative hypothesis is not met, the respective arm will be stopped.

PDAC Combination Treatment Arm

It is estimated that approximately 11 patients are needed in the PDAC combination treatment arm in Simon's Stage I to reject the null hypothesis that PFS6 is $\leq 50\%$ and to continue to Simon's Stage II.

If the trial goes on to Stage II of Simon's optimal design, approximately 14 patients will be treated additionally to test the alternative hypothesis that PFS6 is 75%. If the alternative hypothesis is not met, the respective arm will be stopped.

8.3. Analysis Sets

The intent-to-treat (ITT) population will be defined as those patients who received at least one dose of the study drug, unless otherwise specified. The primary efficacy analyses will be performed for the ITT. Patient disposition will be performed for the ITT.

The Efficacy Population will be defined as all patients in the ITT and having at least one measurable ORR-3 or PFS-6 assessment. This population will be used for a sensitivity analysis.

The per-protocol (PP) Population will be defined as any patient who received at least one full cycle of LYT-200 and without major protocol deviations.

The safety population (SAF) will be defined as all patients who receive at least one dose of the study drug. The safety analyses will be performed for the SAF.

The PK/PD population will be defined as those patients who have received at least one full cycle of LYT-200.

8.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to data base lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

8.4.1. General Considerations

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of patients (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages, with 95% CI. The screening measurement will be the last value on or before the date of first study treatment. Survival curves for, PFS and OS will be generated by the method of Kaplan-Meier from the day treatment was initiated, but there will be no comparative analysis between study arms in any part of the trial. Waterfall and Swimmers plots will be used to graphically present the ORR and DoR for all patients in each study arm, within each tumor type evaluated in Part 2. All statistical analyses will be performed using SAS®, version 9.2. (SAS, Cary, NC).

Protocol Deviations

In general, a protocol deviation is an inadvertent excursion to, or non-compliance with the IRB approved protocol. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures described in this protocol and should not implement any changes to the protocol unless it is required to eliminate an immediate hazard to the patient.

If the deviation affects the safety of the patient, the Sponsor must be notified immediately. Other deviations outside of these categories will be reported to the IRB in accordance with local requirements, as applicable. Deviations will be captured electronically.

Whether a protocol deviation is major or minor will be determined at a data review meeting prior to database lock.

8.4.2. Primary Endpoint(s)

8.4.2.1. Safety Analysis – Part 1 and Part 2

All safety analyses will be made on the SAF unless otherwise specified.

8.4.2.1.1. Adverse Events

Treatment-emergent AEs (TEAEs) will be defined as events that occur on or after the first dose of study medication. The MedDRA coding dictionary will be used for the coding of AEs. TEAEs, serious or CTCAE Grade 3 or Grade 4 TEAEs, and TEAEs related to treatment will be summarized overall and by system organ class and preferred term by treatment group. These will summarize the number of events and the number and percent of patients with a given event. In addition, the number and percent of patients with TEAEs will be provided by maximum severity. A summary of all TEAEs by system organ class and preferred term occurring in ≥ 5% of patients in either treatment group will be provided.

DLTs, the MTD and the RP2D will be summarized.

8.4.2.1.2. Laboratory Assessments

All laboratory-based data will be presented as listings of all values as well as of abnormal results judged to be clinically significant, which will also be reported as AEs. Numeric summaries of all observed findings and changes from baseline screening laboratory evaluations will be provided by visit and treatment group, including chemistry, hematology, and urinalysis results. No inferential comparisons are planned.

8.4.2.1.3. Vital Signs

Numeric summaries of all observed findings and changes from baseline screening vital signs will be provided by time point and treatment group, including blood pressure, heart rate, respiratory rate, and temperature. No inferential analyses are planned for vital signs.

8.4.2.1.4. ECGs, ECHO/MUGA, and Physical Examination

Physical examination data and changes will be presented as listings. ECG results will be presented as listings and summarized by treatment group and visit, based on incidence of clinically significant abnormalities. No inferential comparisons across treatment groups are planned.

8.4.2.2. Primary Efficacy Analysis - Part 2

Disease response is assessed according to RECIST v1.1 and will be summarized descriptively for the ITT, PP, and Efficacy Populations.

The primary efficacy endpoints are:

- ORR-3 for H/N and urothelial cancer
- PFS-6 for PDAC

8.4.3. Secondary Endpoint(s)

8.4.3.1. Pharmacokinetics, Pharmacodynamics, and Immunogenicity

PK, PD, and immunogenicity will be summarized descriptively for the PK/PD population in both Part 1 and Part 2.

8.4.3.2. Secondary Efficacy Analysis - Part 2

Disease response (ORR, PFS, DCR, DoR, and OS) is assessed according to RECIST v1.1 and will be summarized descriptively for the ITT, PP, and Efficacy Populations.

8.4.4. Exploratory Endpoints

Analysis of exploratory endpoints will be detailed in the SAP.

8.4.5. Other Analysis

Other collected data not specifically mentioned will be presented in patient listings.

8.4.5.1. Disposition, Demographics, Baseline Characteristics, and Medical History

Disposition information will be summarized including the number of enrolled patients, screening failures, treated patients, and the number of patients withdrawn by reason.

Demographics, baseline characteristics, and medical history will be summarized by treatment group and overall using descriptive statistics for the ITT and PP.

8.4.5.2. Prior and Concomitant Medications

Number and percentage of patients taking prior and concomitant medications will be summarized by treatment group and overall for the ITT and PP.

8.4.5.3. Protocol Deviations

Number and percentage of patients with protocol deviations will be summarized by treatment group and overall for the ITT.

8.5. Interim Analysis

No interim analysis is planned.

9. References

Adel N. Current Treatment Landscape and Emerging Therapies for Pancreatic Cancer. The American Journal of Managed Care. 2019;25:-S0

Agresti A, Coull BA. Approximate is Better than "Exact" for Interval Estimation of Binomial Proportions. The American Statistician 1998;52(2):119-26.

Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nature Reviews Gastroenterology & Hepatology 2020;17: 557-88.

Bile Duct Cancer Survival. Last revised 2020. Available from: https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html (Accessed 09 Sep 2020)

Choi SI, Seo KW, Kook MC, Kim CG, Kim YW, Cho SJ. Prognostic value of tumoral expression of galectin-9 in gastric cancer. The Turkish Journal of Gastroenterology: the Official Journal of Turkish Society of Gastroenterology. 2017;28(3):166-70.

Ciombor KK, Goff LW. Advances in the management of biliary tract cancers. Clinical Advances in Hematology & Oncology: H&O. 2013;11(1):28-34.

Colorectal Cancer Stats. National Cancer Institute. Cancer Stat Facts: Colorectal Cancer. Available from: https://seer.cancer.gov/statfacts/html/colorect.html (Accessed 09 Sep 2020)

Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. The Lancet 2019 Oct 19;394(10207):1467-80.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45(2):228-47.

Enninga EA, Nevala WK, Holtan SG, Leontovich AA, Markovic SN. Galectin-9 modulates immunity by promoting Th2/M2 differentiation and impacts survival in patients with metastatic melanoma. Melanoma Research 2016 Oct;26(5):429-41.

Gooden MJ, Wiersma VR, Samplonius DF, Gerssen J, van Ginkel RJ, Nijman HW, et al. Galectin-9 activates and expands human T-helper 1 cells. PloS one. 2013;8(5):e65616.

Henriksen A, Dyhl-Polk A, Chen I, Nielsen D. Checkpoint inhibitors in pancreatic cancer. Cancer Treatment Reviews. 2019;78:17-30.

Huyghe N, Baldin P, Van den Eynde M. Immunotherapy with immune checkpoint inhibitors in colorectal cancer: what is the future beyond deficient mismatch-repair tumours? Gastroenterology Report. 2019;8(1):11-24.

Kared H, Fabre T, Bédard N, Bruneau J, Shoukry NH. Galectin-9 and IL-21 mediate cross-regulation between Th17 and Treg cells during acute hepatitis C. PLoS Pathog. 2013;9(6):e1003422.

Labrie M, De Araujo LOF, Communal L, Mes-Masson A-M, St-Pierre Y. Tissue and plasma levels of galectins in patients with high grade serous ovarian carcinoma as new predictive biomarkers. Scientific Reports. 2017;7(1):13244.

Lambert A, Schwarz L, Borbath I, Henry A, Van Laethem J-L, Malka D, et al. An update on treatment options for pancreatic adenocarcinoma. Therapeutic Advances in Medical Oncology. 2019;11:1758835919875568.

Lee SM, Cheung YK. Calibration of prior variance in the Bayesian continual reassessment method. Statistics in Medicine. 2011;30(17):2081-9.

Lhuillier C, Barjon C, Niki T, Gelin A, Praz F, Morales O, Souquere S, Hirashima M, Wei M, Dellis O, Busson P. Impact of Exogenous Galectin-9 on Human T Cells: Contribution of the T Cell Receptor Complex to Antigen-independent Activation but not to Apoptosis Induction. The Journal of Biological Chemistry. 2015;290(27):16797-811.

Lhuillier C, Barjon C, Baloche V, Niki T, Gelin A, Mustapha R, et al. Characterization of neutralizing antibodies reacting with the 213-224 amino-acid segment of human galectin-9. PLoS One. 2018;13(9):e0202512.

Li X, Lu H, Gu Y, Zhang X, Zhang G, Shi T, et al. Tim-3 suppresses the killing effect of Vγ9Vδ2 T cells on colon cancer cells by reducing perforin and granzyme B expression. Experimental Cell Research. 2020;386(1):111719.

Limagne E, Richard C, Thibaudin M, Fumet JD, Truntzer C, Lagrange A, et al. Tim-3/galectin-9 pathway and mMDSC control primary and secondary resistances to PD-1 blockade in lung cancer patients. Oncoimmunology. 2019;8(4):e1564505.

Lv K, Zhang Y, Zhang M, Zhong M, Suo Q. Galectin-9 ameliorates Con A-induced hepatitis by inducing CD4(+)CD25(low/int) effector T-Cell apoptosis and increasing regulatory T cell number. PLoS One. 2012;7(10):e48379.

Lv R, Bao Q, Li Y: Regulation of M1-type and M2-type macrophage polarization in RAW264.7 cells by Galectin-9. Molecular Medicine Reports 2017;16:9111-9.

Madireddi S, Eun SY, Mehta AK, et al. Regulatory T Cell-Mediated Suppression of Inflammation Induced by DR3 Signaling Is Dependent on Galectin-9. The Journal of Immunology. 2017;199(8):2721-2728.

NCI Common Terminology Criteria for Adverse Events Version 5.0. 2017. Available from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (Accessed 09 Sep 2020)

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology. 1982;5(6):649-55.

Oomizu S, Arikawa T, Niki T, Kadowaki T, Ueno M, Nishi N, Yamauchi A, Hirashima M. Galectin-9 suppresses Th17 cell development in an IL-2-dependent but Tim-3-independent manner. Clinical Immunology. 2012;143(1):51-8. (2012a)

Oomizu S, Arikawa T, Niki T, Kadowaki T, Ueno M, Nishi N, Yamauchi A, Hattori T, Masaki T, Hirashima M. Cell surface galectin-9 expressing Th cells regulate Th17 and Foxp3+ Treg development by galectin-9 secretion. PLoS One. 2012;7(11):e48574. (2012b)

O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics. 1990;46(1):33-48.

Pancreatic Cancer Stats. National Cancer Institute. Cancer Stat Facts: Pancreatic Cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html (Accessed 09 Sep 2020)

Parmar A, Chan KKW, Ko YJ. Metastatic colorectal cancer: therapeutic options for treating refractory disease. Current Oncology. 2019;26(Suppl 1):S24-S32.

Qi Y, Chang Y, Wang Z, et al. Tumor-associated macrophages expressing galectin-9 identify immunoevasive subtype muscle-invasive bladder cancer with poor prognosis but favorable adjuvant chemotherapeutic response. Cancer Immunology Immunotherapy. 2019;68:2067-80.

Rabinovich GA, Conejo-García JR. Shaping the Immune Landscape in Cancer by Galectin-Driven Regulatory Pathways. Journal of Molecular Biology. 2016;428(16):3266-81.

Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World Journal of Oncology. 2019;10(1):10-27.

Seifert AM, Reiche C, Heiduk M et al. Detection of pancreatic ductal adenocarcinoma with galectin-9 serum levels. Oncogene. 2020;39:3102-13.

Seki M, Oomizu S, Sakata KM, et al. Galectin-9 suppresses the generation of Th17, promotes the induction of regulatory T cells, and regulates experimental autoimmune arthritis. Clinical Immunology. 2008;127(1):78-88.

Stadinski B. Novel Treatment Strategies Are Explored in Pancreatic Cancer. 2019. Available from: https://www.targetedonc.com/view/novel-treatment-strategies-are-explored-in-pancreatic-cancer (Accessed 09 Sep 2020)

von Hoff D, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. The New England Journal of Medicine. 2013;369:1691-703.

Wu C, Thalhamer T, Franca RF, Xiao S, Wang C, Hotta C, et al. Galectin-9-CD44 Interaction Enhances Stability and Function of Adaptive Regulatory T Cells. Immunity. 2014;41(2):270-82. ISSN 1074-7613.

Yasinska IM, Sakhnevych SS, Pavlova L, Teo Hansen Selnø A, Teuscher Abeleira AM, Benlaouer O, et al. The Tim-3-Galectin-9 Pathway and Its Regulatory Mechanisms in Human Breast Cancer. 2019;10(1594).

Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, Zheng XX, Strom TB, Kuchroo VK. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nature Immunology. 2005 Dec;6(12):1245-52.

10. Appendices

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR

50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

When required by applicable regulations, the Investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, PureTech Health LLC, will provide the Investigator with a full summary of the study results. The Investigator is encouraged to share the summary results with the patients, as appropriate. In addition, the Investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at the PureTech Health LLC, site or other mutually agreeable location.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

- Quality tolerance limits (QTLs) will be predefined in the study-specific data review manual to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Record Retention

Following closure of the study, the Investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

These records should be retained for not less than 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of a clinical development of the investigational produce. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor. Thereafter, records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records.

The Investigator must notify PureTech Health LLC, of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the Investigator leaves the site.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication of Results

The publication, presentation or other public disclosure of study results (each, a "Publication") will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by the Sponsor.

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor; the Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation or other disclosure.

The clinical trial will be posted to a clinical trial registry as required by legal agreement, local law or regulation.

Appendix 2: National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (27 November 2017)

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

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

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

Appendix 3: The RECIST version 1.1) Guidelines

The overall response according to RECIST v1.1 is derived from time point response assessments based on tumor burden as follows below (Eisenhauer et al., 2009).

Evaluation of target lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions:

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of Overall Timepoint Response for Patients with Measurable Disease at Baseline

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

CR: Complete Response, Non-PD: Non-progressive Disease, PR: Partial Response, SD: Stable Disease, NE: Non-evaluable

*When target lesions show SD/PR and some subset of non-target lesions is non-evaluable, a careful decision must be made whether to call the overall response at this timepoint SD/PR or NE. This is based on whether the non-evaluable lesions, if they showed growth, could cause an overall response of progressive disease in the context of

the other lesion responses seen. If the non-evaluable non-target lesions comprise a significant proportion of the overall disease burden, the appropriate timepoint response is NE.

Appendix 4: Management of Immune-mediated Adverse Reactions (IMARs) Caused by LYT-200

IMAR	Guidance for Management
Immune-mediated pneumonitis	• Monitor patients for signs with radiographic imaging and for clinical symptoms of pneumonitis. • Withhold LYT-200 for moderate and permanently discontinue for severe or life-threatening pneumonitis. • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. • Withhold LYT-200 until resolution to < Grade 2. For moderate (Grade 2) pneumonitis. Resume treatment at a 50% dose reduction. • Upon recurrence of Grade 2 pneumonitis at the reduced dose of LYT-200, permanently discontinue LYT-200.
Immune-mediated colitis	• Monitor patients for signs and symptoms of colitis. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration. • If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. • When initial Grade 2 colitis resolves to < Grade 2, resume LYT-200 at a 50% dose reduction. • If ≥ Grade 2 colitis recurs, withhold LYT-200 until colitis resolves to < Grade 2. Resume LYT-200 at an additional 50% dose reduction. No further dose reductions for LYT-200 are allowed. • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. • When Grade 3 colitis resolves to ≤ Grade 2, resume LYT-200 at a 50% dose reduction. • Permanently discontinue LYT-200 for life-threatening (Grade 4) or for recurrent colitis of ≥ Grade 2 upon re-initiation of LYT-200.
Immune-mediated hepatitis	• Monitor for changes in liver function. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. • Withhold LYT-200 for moderate (Grade 2) immune-mediated hepatitis. When resolved to <Grade 2 resume LYT-200 at a 50% dose reduction. • If ≥ Grade 2 hepatitis recurs, permanently discontinue LYT-200. • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin.

IMAR	Guidance for Management
	• Permanently discontinue LYT-200 for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis.
Immune-mediated endocrinopathies: Hypophysitis	• Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. • Withhold LYT-200 for moderate (Grade 2) or severe (Grade 3) and when resolved to < Grade 2, resume LYT-200 at a 50% dose reduction. • If ≥ Grade 2 toxicity recurs, permanently discontinue LYT-200. • Permanently discontinue LYT-200 for life-threatening (Grade 4) hypophysitis.

Adrenal insufficiency	• Monitor patients for signs and symptoms of adrenal insufficiency.
	  • Withhold LYT-200 for moderate (Grade 2) and once resolved to < Grade 2, resume LYT-200 at a 50% dose reduction.
	  • If ≥ Grade 2 toxicity recurs, permanently discontinue LYT-200.
	  • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency.
	  • Permanently discontinue LYT-200 for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency, or for recurrent colitis of ≥ Grade 2 upon re-initiation of LYT-200.

Hypothyroidism and Hyperthyroidism	• Monitor thyroid function prior to and periodically during tislelizumab treatment. • Administer hormone replacement therapy for hypothyroidism. • Initiate medical management for control of hyperthyroidism. • There are no recommended dose adjustments of LYT-200 for < Grade 3 hypothyroidism or hyperthyroidism. • Discontinue LYT-200 for ≥ Grade 3 hypothyroidism or hyperthyroidism.
Type 1 Diabetes Mellitus	• Withhold LYT-200 in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. • Upon resolution to ≤ Grade 2, resume LYT-200 at a 50% dose reduction. • If ≥ Grade 2 toxicity recurs, permanently discontinue LYT-200. • Permanently discontinue LYT-200 for life-threatening (Grade 4) hyperglycemia.

IMAR	Guidance for Management
Immune-mediated nephritis and renal dysfunction (Defined as renal dysfunction or ≥ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology)	• Monitor patients for elevated serum creatinine prior to and periodically during treatment. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. • Withhold LYT-200 for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. When resolved to < Grade 2, resume LYT-200 at a 50% dose reduction. • If ≥ Grade 2 toxicity recurs, permanently discontinue LYT-200. • Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. • Permanently discontinue LYT-200 for life-threatening (Grade 4) increased serum creatinine.
Immune-mediated skin adverse reactions (Immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN))	• Withhold for severe and permanently discontinue for life-threatening rash. • For symptoms or signs of SJS or TEN, withhold LYT-200 and refer the patient for specialized care for assessment and treatment. • If SJS or TEN is confirmed, permanently discontinue LYT-200. • For immune-mediated rash ≥ Grade 2, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. • Withhold LYT-200 for moderate (Grade 2) and severe (Grade 3) rash and when resolved to < Grade 2, resume LYT-200 at a 50% dose reduction. • If ≥ Grade 2 rash recurs, withhold LYT-200 until resolved to < Grade 2 and resume LYT-200 at an additional 50% dose reduction. No further dose reductions are allowed. • Permanently discontinue LYT-200 for life-threatening (Grade 4) rash.
Immune-mediated encephalitis	• Monitor for changes in neurologic function. • Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. • Withhold LYT-200 in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. • Permanently discontinue LYT-200 for immune-mediated encephalitis.

IMAR	Guidance for Management
Other IMARs (May include: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.)	• If uveitis occurs in combination with other IMARs, consider a Vogt-Koyanagi-Harada-like syndrome, and may require treatment with systemic steroids to reduce the risk of permanent vision loss. • For any suspected IMARs, exclude other causes. • Based on the severity (Grade) of the adverse reaction, permanently discontinue or withhold LYT-200, administer high-dose corticosteroids, and if appropriate, initiate hormone replacement therapy. • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. • Consider restarting LYT-200 after completion of corticosteroid taper based on the severity of the event, resuming at a 50% dose reduction.

Appendix 5: Management of Immune-mediated Adverse Reactions (IMARs) Caused by LYT-200 + Tislelizumab Combination Treatment

- For IMAR(s) occurring in the LYT-200 + gemcitabine/nab-paclitaxel cohort, follow the recommended LYT-200 IMAR dose modification instructions in Appendix 4.
- For non-IMAR, hematological and non-hematological AEs that occur in combination arms, upon assessment of causality:
  - If LYT-200 related, follow AE management instructions for LYT-200 (Appendix 8)
  - If combination agent related (tislelizumab or gemcitabine/nab-paclitaxel), follow management instructions in Appendix 6 for tislelizumab and Appendix 7 for gemcitabine/nab-paclitaxel.

IMAR	Guidance for Management
Immune-mediated pneumonitis	• Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. • Grade 1, consider holding no change to tislelizumab until there is significant improvement in patient's signs and symptoms. • Withhold tislelizumab and LYT-200 for moderate (Grade 2) and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2). For more severe (Grade 3-4) pneumonitis, permanently discontinue LYT-200 and tislelizumab and treatment in a hospital setting with IV methylprednisolone 2 to 4 mg/kg/day is recommended, followed by corticosteroid taper. • Withhold tislelizumab and LYT-200 until resolution to < Grade 2 for moderate (Grade 2) pneumonitis. Resume LYT-200 at a 50% dose reduction. • Tislelizumab may be restarted only if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Withhold tislelizumab for Grade 2 pneumonitis, and only restart if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Permanently discontinue treatment with tislelizumab if symptoms persist with the use of corticosteroids. • Upon recurrence of ≥ Grade 2 pneumonitis, permanently discontinue treatment with both the study medication and tislelizumab.
Immune-mediated colitis and diarrhea	• Monitor patients for signs and symptoms of colitis. • Withhold treatment with tislelizumab and LYT-200 for Grade 2 diarrhea or colitis and start oral prednisolone 0.5 mg/kg/day (nonenteric coated). If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. • Taper steroids over 2 to 4 weeks with resolving signs and symptoms. Resume treatment with tislelizumab when signs and symptoms improve or resolve to baseline. Administer prednisolone 1 to 2 mg/kg/day for colitis Grade 3 or Grade 4, converting to oral prednisolone and tapering this dose over at least 4 weeks when improvement is evident. Permanently discontinue tislelizumab and

IMAR	Guidance for Management
	LYT-200 for recurrent severe (Grade 3) or life-threatening Grade 4 diarrhea or colitis. • Resume LYT-200 at a 50% dose reduction when signs and symptoms improve or resolve to baseline. Any dose modifications for tislelizumab are at the Investigator's discretion. • If ≥ Grade 3 recurs, then permanently discontinue treatment with both the study medication and tislelizumab. • If ≥ Grade 2 colitis recurs, withhold LYT-200 and tislelizumab until colitis resolves to baseline. Apply treatment regimen outlined above. Resume LYT-200 at an additional 50% dose reduction. No further dose reductions for LYT-200 are allowed. • If ≥ Grade 2 colitis recurs, permanently discontinue treatment with both study medications. • Permanently discontinue LYT-200 and tislelizumab for life-threatening (Grade 4).
Immune-mediated hepatitis	• Monitor for changes in liver function. • Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. • Withhold tislelizumab and LYT-200 for moderate (Grade 2) immune-mediated hepatitis. When resolved to <Grade 2, and prednisolone tapered to ≤ 10 mg, resume tislelizumab and LYT-200. LYT-200 is to be resumed at a 50 % dose reduction. • If ≥ Grade 2 hepatitis recurs, permanently discontinue treatment with both LYT-200 and tislelizumab. • Administer corticosteroids at a dose of 0.5 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (grade 2), severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. • Permanently discontinue treatment with both LYT-200 and tislelizumab for severe (Grade 3) or life-threatening (grade 4) immune-mediated hepatitis.
Immune-mediated endocrinopathies: Hypophysitis	• Administer hormone replacement as clinically indicated and corticosteroids. Withhold LYT-200 and tislelizumab for moderate (Grade 2) hypophysitis. First administer oral prednisolone 0.5 to 1 mg/kg/day and add hormone replacement as clinically indicated until resolved/improved to ≤ Grade 2. Taper corticosteroids over at least 1 month. Resume LYT-200 at a 50% dose reduction when resuming. Discontinuation is usually not necessary for asymptomatic and manageable patients who are treated by an endocrinologist. • If ≥ Grade 2 toxicity recurs, permanently discontinue treatment with both LYT-200 and tislelizumab. • Permanently discontinue treatment LYT-200 and tislelizumab for severe (grade 3) and life-threatening (Grade 4) hypophysitis.
Adrenal insufficiency	• Monitor patients for signs and symptoms of adrenal insufficiency. • Withhold LYT-200 and tislelizumab for moderate (Grade 2) adrenal insufficiency. First administer oral prednisolone 0.5 to 1 mg/kg/day as clinically indicated until resolved/improved to ≤ Grade 2. Taper corticosteroids over at least 1 month. Resume

IMAR	Guidance for Management
	LYT-200 at a 50% dose reduction when resuming. Discontinuation is usually not necessary for asymptomatic and manageable patients who are treated by an endocrinologist. • If ≥ Grade 2 toxicity recurs, permanently discontinue treatment with both LYT-200 and tislelizumab. • Permanently discontinue treatment LYT-200 and tislelizumab for severe (grade 3) and life-threatening (Grade 4) adrenal insufficiency.
Hypothyroidism and Hyperthyroidism	• Monitor thyroid function prior to and periodically during tislelizumab treatment. • Administer hormone replacement therapy for hypothyroidism. • Initiate medical management for control of hyperthyroidism. Administer oral prednisolone 0.5 mg/kg/day in patients with thyroid pain. • Thyrotoxic patients should be treated with a beta-blocker and may require additional treatment with a carbimazole. • Hold tislelizumab for thyroiditis Grade 3 or 4 until this condition resolves to a Grade 0-1, then consider resuming treatment. • Discontinue LYT-200 and tislelizumab for ≥ Grade 3 and 4 hypothyroidism or hyperthyroidism.
Type 1 Diabetes Mellitus	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes. • Withhold LYT-200 and tislelizumab in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved, until blood glucose has been stabilized to baseline or Grade 0 to 1 and the patient is hyperglycemia symptom-free. Administer insulin as clinically indicated for type 1 diabetes. • Follow LYT-200 IMAR guidance for Type 1 Diabetes Mellitus when resolved to ≤ Grade 2. Permanently discontinue treatment with both study medications for life-threatening (Grade 4) hyperglycemia.
Immune-mediated nephritis and renal dysfunction (Defined as renal dysfunction or ≥ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology)	• Monitor patients for renal function prior to and periodically during treatment. In the event of immune-mediated nephritis, the frequency of renal function tests should be increased. • Withhold LYT-200 and tislelizumab for moderate (Grade 2) or severe (Grade 3) increased nephritis. When resolved to < Grade 2, resume LYT-200 at a 50% dose reduction. If ≥ Grade 2 toxicity recurs, permanently discontinue treatment with both LYT-200 and tislelizumab. • Ensure hydration and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) nephritis. • Permanently discontinue treatment with both LYT-200 and tislelizumab for life-threatening (Grade 4) nephritis and recurrent Grade 3 nephritis as well.
Immune-mediated skin adverse reactions (Tislelizumab can cause immune-mediated rash, including Stevens-Johnson syndrome	• For ≤ Grade 2 rashes, treatment that can be controlled or resolved with moderate strength topical or oral steroids while continuing tislelizumab and LYT-200. • Monitor patients for suspected severe skin reactions and exclude other causes.

IMAR	Guidance for Management
(SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome.)	• Withhold both medications for severe (Grade 3) until signs and symptoms become mild, and permanently discontinued for moderate (Grade 2) to severe (Grade 3) rashes that do not improve or worsen while treated with oral or IV prednisolone, and permanently discontinue for life-threatening (Grade 4) rash. • For symptoms or signs of SJS or TEN, permanently discontinue tislelizumab and LYT-200 and refer the patient for specialized care for assessment and treatment. • The recommended dose of oral prednisolone is 0.5 to 1 mg/kg/day for 3 days with tapering over 2 to 4 weeks (moderate rashes) and using methyl prednisolone 0.5 to 1 mg/kg/day with converting to oral prednisolone and tapering over at least 4 weeks (severe rashes). • When resolved to < Grade 2, resume LYT-200 at a 50% dose reduction.
Immune-mediated encephalitis	• Monitor for changes in neurologic function. • Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. • Withhold LYT-200 and tislelizumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. • Permanently discontinue treatment with LYT-200 and tislelizumab for immune-mediated encephalitis.
Other Immune-mediated Adverse Reactions The following immune-mediated adverse reactions occurred in less than 1% of patients treated with tislelizumab: arthritis, encephalitis, rhabdomyolysis, myositis, myocarditis, pancreatitis, and uveitis.	• For any suspected immune-mediated adverse reactions, exclude other causes. • Based on the severity of the adverse reaction, permanently discontinue or withhold LYT-200 and tislelizumab, administer high-dose corticosteroids, and if appropriate, initiate hormone replacement therapy. • Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. • Consider restarting LYT-200 and tislelizumab after completion of corticosteroid taper based on the severity of the event. Resume LYT-200 at a 50% dose reduction. Immune-mediated adverse reactions may occur after discontinuation of tislelizumab therapy.
Infusion reactions (Reported in less than 1.0% of patients in clinical trials.)	• The symptoms of infusion-related reactions that may be observed with tislelizumab include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. • Patients should be closely monitored for these signs and symptoms during the infusion. • For Grade 1 reactions, decrease infusion rate by 50%; for Grade 2 reactions, stop infusion and only resume with caution at 50% of previous rate if infusion-related reaction has resolved or decreased to Grade 1 in severity. For Grade 3 or Grade 4 infusion-related reactions, stop infusion and permanently discontinue tislelizumab.

IMAR	Guidance for Management
	Subsequent infusions should be given after premedication and at the reduced infusion rate.
Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) (Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1 receptor blocking antibody.)	• Transplant-related complications include hyperacute graft versus host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). • These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. • Follow patients closely for evidence of transplant-related complications and intervene promptly. • Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.
Embryo-Fetal Toxicity (Based on its mechanism of action and data from animal studies, tislelizumab can cause fetal harm when administered to a pregnant woman.)	• Advise pregnant women of the potential risk to a fetus. • Advise females of reproductive potential to use effective contraception during treatment with a tislelizumab-containing regimen and for at least 5 months after the last dose of tislelizumab.

Source: Tislelizumab Highlights of Prescribing Information, Revised April 2019.

Appendix 6: Recommended Dose Modifications for Tislelizumab for AEs (other than IMARs)

Adverse Reaction	Severity*	Dose Modification
AEs	Probably related Grade 3 adverse events	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	

* Toxicity was graded per NCI-CTCAE V5.

Appendix 7: Recommended Dose Modifications for Gemcitabine + Nab-Paclitaxel in PDAC Patients

Table I. Dose Level Reductions for Gemcitabine and Nab-Paclitaxel

Dose Level	Nab-Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Source: Table 3, Abraxane Highlights of Prescribing Information, August, 2018. See Appendix 9.

Table II. Dose Recommendations and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Source: Table 4, Abraxane Highlights of Prescribing Information, August, 2018. See Appendix 9. ANC= absolute neutrophil count

Table III. Dose Modifications for Other Adverse Reactions

		Dose Modification	
Adverse Reaction	**Severity***	**Nab-Paclitaxel**	**Gemcitabine**
Neutropenia	Grade 3 or 4	Withhold until fever resolves and ANC≥1,500 Resume at next lower dose level.	
Peripheral Neuropathy	Grade 3 or 4	Withhold until improves to ≤ Grade 1; Resume at next lower dose level	No dose reduction
Cutaneous toxicity	Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists.	
Gastrointestinal toxicity	Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; Resume at next lower dose level	
Sepsis	Fever, regardless of ANC	Initiate treatment with broad spectrum antibiotics; Withhold until fever resolves and ANC≥1,500; Resume at next lower dose level.	
Pneumonitis	Any	Withhold during evaluation. Upon diagnosis of pneumonitis, permanently discontinue treatment	
Hypersensitivity	Severe	Permanently discontinue	

* Toxicity was graded per NCI-CTCAE V5.
Source: Table 5, Abraxane Highlights of Prescribing Information, August, 2018. See Appendix 9.

Appendix 8: Recommended Dose Modifications for LYT-200

(AEs outside the DLT window and other than IMARs)

Adverse Reaction	Severity	LYT-200 Dose Modification
Non-hematologic and hematologic toxicities	≥ Grade 4	• Permanently discontinue treatment with LYT-200.
Hematologic toxicities	Grade 3	• Withhold treatment until toxicity resolves to ≤ Grade 2. • Resume LYT-200 at 50% reduction from previous dose. • If recurs again at ≥ Grade 3 severity, hold until resolved to ≤ Grade 2 and implement a further 50% dose reduction in agreement with the Investigator and Medical Monitor. • No further dose reductions are allowed.
Non-hematologic toxicities (except those listed in Appendix 4, Management of IMARs Caused by LYT-200)	Grade 3	• Withhold treatment until toxicity resolves to ≤ Grade 2. • Resume LYT-200 at 50% reduction from previous dose. • If recurs again at ≥ Grade 3 severity, hold until resolved to ≤ Grade 2 and implement a further 50% dose reduction in agreement with the Investigator and Medical Monitor. • No further dose reductions are allowed.
Gastrointestinal (Nausea, Vomiting)	Grade 3 Not requiring hospitalization or parenteral nutrition support; managed by supportive care	• Withhold LYT-200 until toxicity reverses to ≤ Grade 2 • Resume LYT-200 with no dose reduction • If recurrent, withhold LYT-200 until toxicity reverses to ≤ Grade 2 • Then resume LYT-200 at a 50% reduction from the previous dose • If recurrent, withhold LYT-200 until toxicity reverses to ≤ Grade 2 • Resume LYT-200 at an additional 50% dose reduction • No further dose reductions are allowed
Electrolyte Abnormalities	Grade 3 corrected to ≤ Grade 2 within 24 hours	
Electrolyte Abnormalities	≥ Grade 3 lasting <24-72 hours Not clinically complicated; resolves spontaneously or responds to conventional medical interventions	
Amylase or Lipase Elevation	≥ Grade 3 Not associated with symptoms or clinical manifestations of pancreatitis	

Appendix 9: Package Insert for ABRAXANE® (Nab-Paclitaxel)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABRAXANE safely and effectively. See full prescribing information for ABRAXANE.

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound), for intravenous use
Initial U.S. Approval: 2005

WARNING: SEVERE MYELOSUPPRESSION

See full prescribing information for complete boxed warning.

- **Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. (4)**
- **Monitor for neutropenia, which may be severe and result in infection or sepsis. (5.1, 5.3)**
- **Perform frequent complete blood cell counts on all patients receiving ABRAXANE. (5.1, 5.3)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 2.7)	8/2020
Contraindications (4)	8/2020
Warnings and Precautions (5.1, 5.2)	8/2020

---------- INDICATIONS AND USAGE ----------

ABRAXANE is a microtubule inhibitor indicated for the treatment of:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. (1.1)
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. (1.2)
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- **Do not substitute ABRAXANE for other paclitaxel products. (2.1)**
- Extravasation: Closely monitor the infusion site for extravasation and infiltration. (2.1)
- Metastatic Breast Cancer (MBC): Recommended dosage of ABRAXANE is 260 mg/m^2 intravenously over 30 minutes every 3 weeks. (2. 2)
- Non-Small Cell Lung Cancer (NSCLC): Recommended dosage of ABRAXANE is 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE. (2.2)
- Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m^2 intravenously over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8, and 15 of each 28-day cycle immediately after ABRAXANE. (2.4)
- Use in Patients with Hepatic Impairment: ABRAXANE is not recommended for use in patients with AST > 10 x ULN; or bilirubin > 5 x ULN or with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment. For MBC or NSCLC, reduce starting dose in patients with moderate to severe hepatic impairment. (2.5)
- Dose Reductions for Adverse Reactions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

For injectable suspension: white to yellow, sterile, lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-dose vial for reconstitution. (3)

---------- CONTRAINDICATIONS ----------

- Neutrophil counts of < 1,500 cells/mm^3. (4)
- Severe hypersensitivity reactions to ABRAXANE. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. (5.2)
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine; interrupt ABRAXANE and gemcitabine until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels. (5.3)
- Pneumonitis occurred with the use of ABRAXANE in combination with gemcitabine; permanently discontinue treatment with ABRAXANE and gemcitabine. (5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not rechallenge with this drug. (4, 5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, consider dose reduction and closely monitor patients with hepatic impairment. (2.5, 5.6)
- ABRAXANE contains albumin derived from human blood, which has a theoretical risk of viral transmission. (5.7)
- ABRAXANE can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.8, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)
- The most common adverse reactions (≥ 20%) in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.1)
- The most common (≥ 20%) adverse reactions of ABRAXANE in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: NEUTROPENIA
1 INDICATIONS AND USAGE
- 1.1 Metastatic Breast Cancer
- 1.2 Non-Small Cell Lung Cancer
- 1.3 Adenocarcinoma of the Pancreas

2 DOSAGE AND ADMINISTRATION
- 2.1 Important Administration Instructions
- 2.2 Recommended Dosage for Metastatic Breast Cancer
- 2.3 Recommended Dosage for Non-Small Cell Lung Cancer
- 2.4 Recommended Dosage for Adenocarcinoma of the Pancreas
- 2.5 Dosage Modifications for Hepatic Impairment
- 2.6 Dosage Modifications for Adverse Reactions
- 2.7 Preparation for Intravenous Administration
- 2.8 Stability

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Severe Myelosuppression
- 5.2 Severe Neuropathy
- 5.3 Sepsis
- 5.4 Pneumonitis
- 5.5 Severe Hypersensitivity
- 5.6 Use in Patients with Hepatic Impairment
- 5.7 Albumin (Human)
- 5.8 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Metastatic Breast Cancer
- 14.2 Non-Small Cell Lung Cancer
- 14.3 Adenocarcinoma of the Pancreas

15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION
ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

WARNING: SEVERE MYELOSUPPRESSION

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm^3. *[see Contraindications (4)].***
- **Monitor for neutropenia, which may be severe and result in infection or sepsis, it is recommended that frequent *[see Warnings and Precautions (5.1, 5.3)].***
- **Perform frequent complete blood cell counts on all patients receiving ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1, 5.3)].***

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer
ABRAXANE is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

1.2 Non-Small Cell Lung Cancer
ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas
ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions
DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS. **ABRAXANE** has different dosage and administration instructions from other paclitaxel products.

Closely monitor the infusion site for extravasation or drug infiltration during administration. Limiting the infusion of ABRAXANE to 30 minutes may reduce the risk of infusion-related reactions *[see Adverse Reactions (6.2)]*.

Consider premedication in patients who have had prior hypersensitivity reactions to ABRAXANE. Do not re-challenge patients who experience a severe hypersensitivity reaction to ABRAXANE *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

2.2 Recommended Dosage for Metastatic Breast Cancer
After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

2.3 Recommended Dosage for Non-Small Cell Lung Cancer
The recommended dose of ABRAXANE is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE *[see Clinical Studies (14.2)]*.

2.4 Recommended Dosage for Adenocarcinoma of the Pancreas
The recommended dose of ABRAXANE is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Administer gemcitabine immediately after ABRAXANE on Days 1, 8, and 15 of each 28-day cycle *[see Clinical Studies (14.3)].*

2.5 Dosage Modifications for Hepatic Impairment
For patients with moderate or severe hepatic impairment, reduce the starting dose of ABRAXANE as shown in Table 1.

Table 1: Recommendations for Starting Dose in Patients with Moderate and Severe Hepatic Impairment

	AST Levels		Bilirubin Levels	ABRAXANE Dose[a]		
				MBC	NSCLC[c]	Adenocarcinoma of Pancreas[c]
Moderate	< 10 x ULN	AND	> 1.5 to ≤ 3 x ULN	200 mg/m^2 [b]	80 mg/m^2 [b]	not recommended
Severe	< 10 x ULN	AND	> 3 to ≤ 5 x ULN	200 mg/m^2 [b]	80 mg/m^2 [b]	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

AST = Aspartate Aminotransferase; MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer; ULN = Upper limit of normal.

[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

[b] A dose increase to 260 mg/m^2 for patients with metastatic breast cancer or 100 mg/m^2 for patients with non-small cell lung cancer in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles.

[c] Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.6 Dosage Modifications for Adverse Reactions

Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophils less than 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

Non-Small Cell Lung Cancer

- Do not administer ABRAXANE on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3 *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce ABRAXANE and carboplatin doses as outlined in Table 2.
- Withhold ABRAXANE for Grade 3-4 peripheral neuropathy. Resume ABRAXANE and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Reactions in NSCLC

Adverse Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas

Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Reaction	ABRAXANE	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

2.7 Preparation for Intravenous Administration

ABRAXANE is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1] The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning, and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use.

Read the entire preparation instructions prior to reconstitution.

1.	Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2.	Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL. 
3.	DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4.	Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5.	Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6.	If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient and slowly withdraw the dosing volume of the reconstituted suspension from the vial(s) into a syringe: Dosing volume (mL)=Total dose (mg)/5 (mg/mL).

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of medical devices containing silicone oil as a lubricant (i.e., syringes and intravenous bags) to reconstitute and administer ABRAXANE may result in the formation of proteinaceous strands.

Visually inspect the reconstituted ABRAXANE suspension in the intravenous bag prior to administration. Discard the reconstituted suspension if proteinaceous strands, particulate matter, or discoloration are observed.

2.8 Stability

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted ABRAXANE in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours.

Discard any unused portion.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension, for intravenous use: white to yellow, sterile lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-dose vial for reconstitution.

4 CONTRAINDICATIONS

ABRAXANE is contraindicated in patients with:

- Baseline neutrophil counts of < 1,500 cells/mm^3 *[see Warnings and Precautions (5.1)]*
- A history of severe hypersensitivity reactions to ABRAXANE *[see Warnings and Precautions (5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

Severe myelosuppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Monitor for severe neutropenia and thrombocytopenia by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer). Do not administer ABRAXANE to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm^3 *[see Contraindications (4)]*.

In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of ABRAXANE therapy, reduce the dose of ABRAXANE in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every-3-week cycles of ABRAXANE after ANC recovers to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In patients with NSCLC, resume treatment if recommended at permanently reduced doses for both weekly ABRAXANE and every-3-week carboplatin after ANC recovers to at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an ANC of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle *[see Dosage and Administration (2.6)]*.

In patients with adenocarcinoma of the pancreas, withhold ABRAXANE and gemcitabine if the ANC is less than 500 cells/mm^3 or platelets are less than 50,000 cells/mm^3 and delay initiation of the next cycle if the ANC is less than 1500 cells/mm^3 or platelet count is less than 100,000 cells/mm^3 on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended *[see Dosage and Administration (2.6)]*.

5.2 Severe Neuropathy

Sensory neuropathy is dose- and schedule-dependent *[see Adverse Reactions (6.1)]*. If ≥ Grade 3 sensory neuropathy develops, withhold ABRAXANE treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of ABRAXANE *[see Dosage and Administration (2.6)]*.

5.3 Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis.

If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt ABRAXANE and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels *[see Dosage and Administration (2.6)]*.

5.4 Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine.

Monitor patients for signs and symptoms of pneumonitis and interrupt ABRAXANE and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with ABRAXANE and gemcitabine.

5.5 Severe Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Do not rechallenge patients who experience a severe hypersensitivity reaction to ABRAXANE with this drug *[see Contraindications (4)]*.

Cross-hypersensitivity between ABRAXANE and other taxane products has been reported and may include severe reactions such as anaphylaxis. Closely monitor patients with a previous history of hypersensitivity to other taxanes during initiation of ABRAXANE therapy.

5.6 Use in Patients with Hepatic Impairment

The exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment. Closely monito patients with hepatic impairment for severe myelosuppression.

ABRAXANE is not recommended in patients who have total bilirubin >5 x ULN or AST >10 x ULN. In addition, ABRAXANE is not recommended in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤10 x ULN). Reduce the starting dose for patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.5), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

5.7 Albumin (Human)

ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

5.8 Embryo-Fetal Toxicity

Based on mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with ABRAXANE and for at least six months after the last dose of ABRAXANE *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥ 20%) with single-agent use of ABRAXANE in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea *[see Adverse Reactions (6.1)]*.

The most common adverse reactions (≥ 20%) of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue *[see Adverse Reactions (6.1)]*. The most common serious adverse reactions of ABRAXANE in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of ABRAXANE in combination with gemcitabine for pancreatic adenocarcinoma *[see Clinical Studies (14.3)]*, the most common (≥ 20%) selected (with a ≥ 5% higher incidence) adverse reactions of ABRAXANE are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration *[see Adverse Reactions (6.1)]*. The most common serious adverse reactions of ABRAXANE (with a ≥ 1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of ABRAXANE are peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of ABRAXANE are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in ABRAXANE dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%).

6.1 Clinical Trials Experience

Metastatic Breast Cancer

Table 6 shows the frequency of important adverse reactions in the randomized comparative trial for the patients who received either single-agent ABRAXANE or paclitaxel injection for the treatment of metastatic breast cancer.

Table 6: Adverse Reactions in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260 mg/m^2 over 30 min (n=229)	**Paclitaxel Injection 175 mg/m^2 over 3 h[a] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 10^9/L	80	82
< 0.5 x 10^9/L	9	22
Thrombocytopenia		
< 100 x 10^9/L	2	3
< 50 x 10^9/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
Hypersensitivity Reaction[b]		
All	4	12
Severe[c]	0	2
Cardiovascular		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[c]	3	4
Abnormal ECG		
All Patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[c]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[c]	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms[c]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[c]	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22
Severe Symptoms[c]	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms[c]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[c]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[c]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32

	Percent of Patients	
	ABRAXANE 260 mg/m^2 over 30 min (n=229)	**Paclitaxel Injection 175 mg/m^2 over 3 h[a] (n=225)**
Injection Site Reaction	<1	1

[a] Paclitaxel injection patients received premedication.
[b] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[c] Severe events are defined as at least Grade 3 toxicity.

Other Adverse Reactions

Hematologic Disorders
Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. Pancytopenia has been observed in clinical trials.

Infections
Infectious episodes were reported in 24% of the patients treated with ABRAXANE. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)
Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory
Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with ABRAXANE.

Neurologic
The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders
Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible.

Arthralgia/Myalgia
The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events
Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

Non-Small Cell Lung Cancer
Adverse reactions were assessed in 514 ABRAXANE/carboplatin-treated patients and 524 paclitaxel injection/carboplatin-treated patients receiving first-line systemic treatment for locally advanced (stage IIIB) or metastatic (IV) non-small cell lung cancer (NSCLC) in a multicenter, randomized, open-label trial. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion.

The differences in paclitaxel dose and schedule between the two arms limit direct comparison of dose- and schedule-dependent adverse reactions. Among patients evaluable for adverse reactions, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1. Patients in both treatment arms received a median of 6 cycles of treatment.

The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the ABRAXANE plus carboplatin treatment group).

Table 7 provides the frequency and severity of laboratory-detected abnormalities which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 toxicity between ABRAXANE plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 7: Selected Hematologic Laboratory-Detected Abnormalities with a Difference of ≥ 5% for grades (1-4) or ≥ 2% for Grade 3-4 Toxicity Between Treatment Groups

	ABRAXANE (100 mg/m^2 weekly) plus carboplatin		Paclitaxel Injection (200 mg/m^2 every 3 weeks) plus carboplatin	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia[1,2]	98	28	91	7
Neutropenia[1,3]	85	47	83	58
Thrombocytopenia[1,3]	68	18	55	9

[1] 508 patients assessed in ABRAXANE/carboplatin-treated group.
[2] 514 patients assessed in paclitaxel injection/carboplatin-treated group.
[3] 513 patients assessed in paclitaxel injection/carboplatin-treated group.

Table 8 provides the frequency and severity of adverse reactions, which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 between either treatment group for the 514 ABRAXANE plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 8: Selected Adverse Reactions with a Difference of ≥5% for All Grade Toxicity or ≥2% for Grade 3-4 Toxicity Between Treatment Groups

		ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=524)	
System Organ Class	Adverse Reaction	Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Nervous system disorders	Peripheral neuropathy[a]	48	3	64	12
General disorders and administration site conditions	Edema peripheral	10	0	4	<1
Respiratory thoracic and mediastinal disorders	Epistaxis	7	0	2	0
	Arthralgia	13	<1	25	2

System Organ Class	Adverse Reaction	ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=524)	
		Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Musculoskeletal and connective tissue disorders	Myalgia	10	<1	19	2

[a] Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.

Adenocarcinoma of the Pancreas

Adverse reactions were assessed in 421 patients who received ABRAXANE plus gemcitabine and 402 patients who received gemcitabine for the first-line systemic treatment of metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial. Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group. For the treated population, the median relative dose intensity for gemcitabine was 75% in the ABRAXANE/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of ABRAXANE was 81%.

Table 9 provides the frequency and severity of laboratory-detected abnormalities which occurred at a higher incidence for Grades 1-4 (≥ 5%) or for Grade 3-4 (≥ 2%) toxicity in ABRAXANE plus gemcitabine-treated patients.

Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4 Events) in the ABRAXANE/Gemcitabine Arm

	ABRAXANE (125 mg/m^2)/ Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in ABRAXANE/gemcitabine-treated group.
[b] 388 patients assessed in gemcitabine-treated group.
[c] 404 patients assessed in ABRAXANE/gemcitabine-treated group.
[d] Neutrophil growth factors were administered to 26% of patients in the ABRAXANE/gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of ≥ 5% for all grades or ≥ 2% for Grade 3 or higher in the ABRAXANE plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
	Alopecia	212 (50%)	6 (1%)	21 (5%)	0

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Skin and subcutaneous tissue disorders	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy[a]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections [b]	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Psychiatric disorders	Depression	51 (12%)	1 (<1%)	24 (6%)	0

[a] Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).
[b] Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococcal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia
Vascular disorders: hypertension
Cardiac disorders: tachycardia, congestive cardiac failure
Eye disorders: cystoid macular edema

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine only; no patients developed Grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the ABRAXANE arm was 140 days. Upon suspension of ABRAXANE dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of ABRAXANE-treated patients with Grade 3 peripheral neuropathy, 44% resumed ABRAXANE at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received ABRAXANE/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the ABRAXANE arm with pneumonitis died.

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of ABRAXANE or with paclitaxel injection and may be expected to occur with ABRAXANE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions
Severe and sometimes fatal hypersensitivity reactions. Cross-hypersensitivity between ABRAXANE and other taxanes has been reported.

Cardiovascular
Congestive heart failure, left ventricular dysfunction, and atrioventricular block. Most patients were previously exposed to cardiotoxic

drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
Pneumonitis, interstitial pneumonia, and pulmonary embolism
Radiation pneumonitis in patients receiving concurrent radiotherapy.
Lung fibrosis has been reported with paclitaxel injection.

Neurologic
Cranial nerve palsies and vocal cord paresis, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reduced visual acuity due to cystoid macular edema (CME). After cessation of treatment, CME may improve, and visual acuity may return to baseline. Abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage.

Hepatic
Hepatic necrosis and hepatic encephalopathy leading to death in patients treated with paclitaxel injection.

Gastrointestinal (GI)
Intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis. In patients treated with paclitaxel injection, neutropenic enterocolitis (typhlitis) despite the coadministration of G-CSF, alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
Extravasation. Closely monitor the ABRAXANE infusion site for possible infiltration during drug administration *[see Dosage and Administration 2.1)]*.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported with paclitaxel injection. In some cases, the onset of the injection site reaction occurred during a prolonged infusion or was delayed up to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site has been reported.

Metabolic and Nutritional Disorders
Tumor lysis syndrome

Other Clinical Events
Skin reactions including generalized or maculopapular rash, erythema, and pruritus

Photosensitivity reactions, radiation recall phenomenon, scleroderma, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Conjunctivitis, cellulitis, and increased lacrimation have been reported with paclitaxel injection.

Accidental Exposure
Upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported.

Following topical exposure, tingling, burning, and redness have been reported.

7 DRUG INTERACTIONS

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data on ABRAXANE use in pregnant women to inform the drug-associated risk.

In animal reproduction studies, administration of paclitaxel formulated as albumin-bound particles to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicity at doses approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis (see Data). Advise females of reproductive potential of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data

In embryo-fetal development studies, intravenous administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryo-fetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight, and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles.

8.2 Lactation

Risk Summary

There are no data on the presence of paclitaxel in human milk, or its effect on the breastfed child or on milk production. In animal studies, paclitaxel and/or its metabolites were excreted into the milk of lactating rats (see Data). Because of the potential for serious adverse reactions in a breastfed child from ABRAXANE, advise lactating women not to breastfeed during treatment with ABRAXANE and for two weeks after the last dose.

Data

Animal Data

Following intravenous administration of radiolabeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations.

8.3 Females and Males of Reproductive Potential

Based on animal studies and mechanism of action, ABRAXANE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with ABRAXANE.

Contraception

Females

Advise females of reproductive potential to use effective contraception and avoid becoming pregnant during treatment with ABRAXANE and for at least six months after the last dose of ABRAXANE.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise males with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)].*

Infertility

Females and Males

Based on findings in animals, ABRAXANE may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pharmacokinetics, safety, and antitumor activity of ABRAXANE were assessed in an open-label, dose escalation, dose expansion study (NCT01962103) in 96 pediatric patients aged 1.4 to < 17 years with recurrent or refractory pediatric solid tumors. The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. No new safety signals were observed in pediatric patients across these studies.

Paclitaxel protein-bound exposures normalized by dose were higher in 96 pediatric patients (aged 1.4 to < 17 years) as compared to those in adults.

8.5 Geriatric Use

Of the 229 patients in the randomized study who received ABRAXANE for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. This study of ABRAXANE did not include a sufficient number of patients with metastatic breast cancer who were 65 years and older to determine whether they respond differently from younger patients.

A subsequent pooled analysis was conducted in 981 patients receiving ABRAXANE monotherapy for metastatic breast cancer, of which 15% were 65 years of age or older and 2% were 75 years of age or older. A higher incidence of epistaxis, diarrhea, dehydration, fatigue, and peripheral edema was found in patients 65 years of age or older.

Of the 514 patients in the randomized study who received ABRAXANE and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

Of the 431 patients in the randomized study who received ABRAXANE and gemcitabine for the first-line treatment of pancreatic adenocarcinoma, 41% were 65 years or older and 10% were 75 years or older. No overall differences in effectiveness were observed between patients who were 65 years of age or older and younger patients. Diarrhea, decreased appetite, dehydration, and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. Clinical studies of

ABRAXANE did not include sufficient number of patients with pancreatic cancer who were 75 years and older to determine whether they respond differently from younger patients.

8.6 Renal Impairment

No adjustment of the starting ABRAXANE dose is required for patients with mild to moderate renal impairment (estimated creatinine clearance 30 to <90 mL/min) *[see Clinical Pharmacology (12.3)]*. There are insufficient data to permit dosage recommendations in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 mL/min).

8.7 Hepatic Impairment

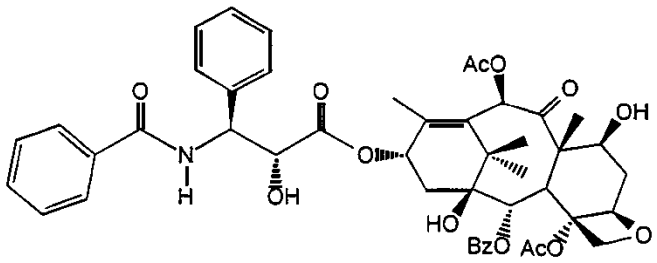
No adjustment of the starting ABRAXANE dose is required for patients with mild hepatic impairment (total bilirubin > ULN and $\leq$ 1.5 x ULN and aspartate aminotransferase [AST] $\leq$ 10 x ULN). Reduce ABRAXANE starting dose in patients with moderate to severe hepatic impairment *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*. ABRAXANE is not recommended for use in patients with total bilirubin > 5 x ULN or AST > 10 x ULN *[see Dosage and Administration (2.5), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*. ABRAXANE is not recommended for use in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment *[see Dosage and Administration (2.5)]*.

10 OVERDOSAGE

There is no known antidote for ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

11 DESCRIPTION

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. Paclitaxel is a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. The empirical formula is $C_{47}H_{51}NO_{14}$ and the molecular weight is 853.91. Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-dose vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel formulated as albumin-bound particles. ABRAXANE is free of solvents.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ABRAXANE is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

12.3 Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 (0.31 to 1.15 times the maximum approved recommended dosage) were determined in clinical studies. Dose levels of mg/m^2 refer to mg of paclitaxel in ABRAXANE. Following intravenous administration of ABRAXANE to patients with solid tumors, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

Following ABRAXANE infusion, paclitaxel exhibited linear drug exposure (AUC) across clinical doses ranging from 80 to 300 mg/m^2 (0.31 to 1.15 times the maximum approved recommended dosage). The pharmacokinetics of paclitaxel in ABRAXANE were independent of the duration of intravenous administration.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for ABRAXANE than for paclitaxel injection. There were no differences in terminal half-lives.

Distribution
Following ABRAXANE administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with ABRAXANE (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with ABRAXANE compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Elimination
At the clinical dose range of 80 to 300 mg/m^2 (0.31 to 1.15 times the maximum approved recommended dosage), the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m^2 and the mean terminal half-life ranges from 13 to 27 hours.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel in ABRAXANE was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3′-*p*-hydroxypaclitaxel and 6α, 3′-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4 *[see Drug Interactions (7)]*.

Excretion
After a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3′-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

Specific Populations
No clinically meaningful differences in the pharmacokinetics of paclitaxel in ABRAXANE were observed based on body weight (40 to 143 kg), body surface area (1.3 to 2.4 m^2), sex, race (Asian vs. White), age (24 to 85 years), type of solid tumors, mild to moderate renal impairment (creatinine clearance 30 to <90 mL/min), and mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN and AST ≤10 x ULN).

Patients with moderate (total bilirubin >1.5 to 3 x ULN and AST ≤10 x ULN) or severe (total bilirubin >3 to 5 x ULN) hepatic impairment had a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN) *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

The effect of severe renal impairment or end stage renal disease (creatinine clearance < 30 mL/min) on the pharmacokinetics of paclitaxel in ABRAXANE is unknown.

Drug Interaction Studies
Carboplatin: Administration of carboplatin immediately after the completion of the ABRAXANE infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUC_{inf} of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of ABRAXANE has not been studied.

Paclitaxel was clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel formulated as albumin-bound particles to male rats at 42 mg/m^2 on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a body surface area basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A dose of 42 mg/m^2 also reduced male reproductive organ weights, mating performance, and sperm production.

Testicular atrophy/degeneration was observed in single-dose toxicology studies in animals administered paclitaxel formulated as albumin-bound particles at doses lower than the recommended human dose; doses were 54 mg/m^2 in rodents and 175 mg/m^2 in dogs. Similar testicular degeneration was seen in monkeys administered three weekly doses of 108 mg/m^2 paclitaxel formulated as albumin bound particles.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats. Paclitaxel caused reduced fertility and reproductive indices, and increased embryo-fetal toxicity.

14 CLINICAL STUDIES

14.1 Metastatic Breast Cancer

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies

In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30-minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3-week intervals. Objective responses were observed in both studies.

Randomized Comparative Study

This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 11. There was no statistically significant difference in overall survival between the two study arms.

Table 11: Efficacy Results from Randomized Metastatic Breast Cancer Trial

		ABRAXANE 260 mg/m^2	**Paclitaxel Injection 175 mg/m^2**
Reconciled Target Lesion Response Rate (primary endpoint)[a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% – 26.73%]	25/227 (11.1%) [6.94% – 15.09%]
	p-value[b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% – 21.75%]	12/143 (8.4%) [3.85% – 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.

[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.

[c] Prior therapy included an anthracycline unless clinically contraindicated.

14.2 Non-Small Cell Lung Cancer

A multicenter, randomized, open-label study was conducted in 1052 chemotherapy naive patients with Stage IIIb/IV non-small cell lung cancer to compare ABRAXANE in combination with carboplatin to paclitaxel injection in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. ABRAXANE was administered as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel injection was administered as an intravenous infusion over 3 hours at a dose of 200 mg/m^2, following premedication. In both treatment arms carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 of each 21-day cycle after completion of ABRAXANE/paclitaxel infusion. Treatment was administered until disease progression or development of an unacceptable toxicity. The major efficacy outcome measure was overall response rate as determined by a central independent review committee using RECIST guidelines (Version 1.0).

In the intent-to-treat (all-randomized) population, the median age was 60 years, 75% were men, 81% were White, 49% had adenocarcinoma, 43% had squamous cell lung cancer, 76% were ECOG PS 1, and 73% were current or former smokers. Patients received a median of 6 cycles of treatment in both study arms.

Patients in the ABRAXANE/carboplatin arm had a statistically significantly higher overall response rate compared to patients in the paclitaxel injection/carboplatin arm [(33% versus 25%) see Table 12]. There was no statistically significant difference in overall survival between the two study arms.

Table 12: Efficacy Results from Randomized Non-Small Cell Lung Cancer Trial (Intent-to-Treat Population)

	ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=521)	**Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=531)**
Overall Response Rate (ORR)		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI	28.6, 36.7	21.2, 28.5
P-value (Chi-Square test)	0.005	
Median DoR in months (95% CI)	6.9 (5.6, 8.0)	6.0 (5.6, 7.1)
Overall Response Rate by Histology		
Carcinoma/Adenocarcinoma	66/254 (26%)	71/264 (27%)
Squamous Cell Carcinoma	94/229 (41%)	54/221 (24%)
Large Cell Carcinoma	3/9 (33%)	2/13 (15%)
Other	7/29 (24%)	5/33 (15%)

CI = confidence interval; DoR= Duration of response.

14.3 Adenocarcinoma of the Pancreas

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing ABRAXANE plus gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14 day screening period prior to study randomization were ineligible.

A total of 861 patients were randomized (1:1) to the ABRAXANE/gemcitabine arm (N=431) or to the gemcitabine arm (N=430).

Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to ABRAXANE/gemcitabine received ABRAXANE 125 mg/m^2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^2 as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m^2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m^2 on Days 1, 8, and 15 of each subsequent 28-day cycle. Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST (version 1.0).

In the intent-to-treat (all randomized) population, the median age was 63 years (range 27-88 years) with 42% ≥ 65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

Results for overall survival, progression-free survival, and overall response rate are shown in Table 13.

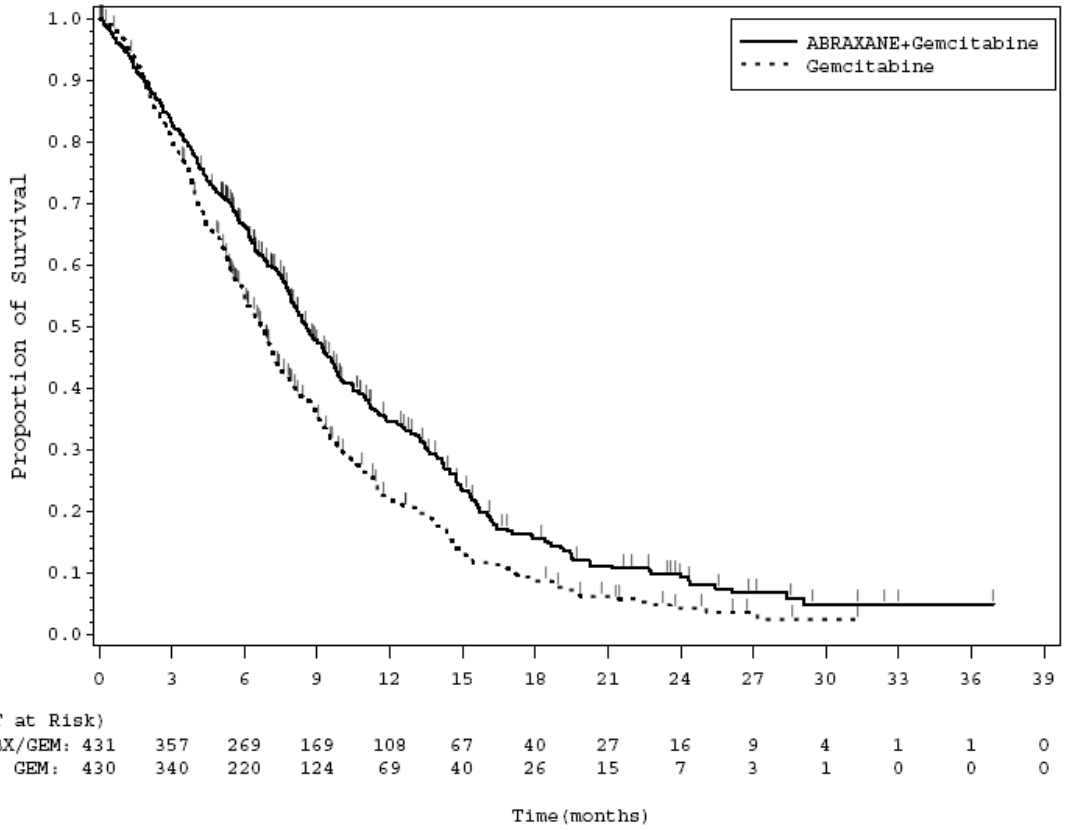
Table 13: Efficacy Results from Randomized Study in Patients with Adenocarcinoma of the Pancreas (ITT Population)

	ABRAXANE (125 mg/m^2) and gemcitabine (N = 431)	Gemcitabine (N = 430)
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (months)	**8.5**	**6.7**
95% CI	7.9, 9.5	6.0, 7.2
HR (95% CI) [a]	0.72 (0.62, 0.83)	
P-value[b]	<0.0001	
Progression-free Survival[c]		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival (months)	**5.5**	**3.7**
95% CI	4.5, 5.9	3.6, 4.0
HR (95% CI) [a]	0.69 (0.58, 0.82)	
P-value[b]	<0.0001	
Overall Response Rate[c]		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
95% CI	19.1, 27.2	5.0, 10.1
P-value [d]	<0.0001	

CI = confidence interval, HR = hazard ratio of ABRAXANE plus gemcitabine / gemcitabine, ITT = intent-to-treat population.
[a] Stratified Cox proportional hazard model.
[b] Stratified log-rank test stratified by geographic region (North America versus Others), Karnofsky performance score (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).
[c] Based on Independent Radiological Reviewer Assessment.
[d] Chi-square test.

In exploratory analyses conducted in clinically relevant subgroups with a sufficient number of subjects, the treatment effects on overall survival were similar to that observed in the overall study population.

Figure 1: Kaplan-Meier Curve of Overall Survival (Intent-to-Treat Population)



15 REFERENCES

1. OSHA Hazardous Drugs. OSHA http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is a white to yellow, sterile lyophilized powder supplied as:

NDC : 68817-134-50 100 mg of paclitaxel in a single-dose vial, individually packaged in a carton.

Store the vials in original cartons at 20ºC to 25ºC (68ºF to 77ºF). Retain in the original package to protect from bright light.

Abraxane is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the approved patient labeling (Patient Information).

Severe Myelosuppression

- Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their healthcare provider immediately for fever or evidence of infection *[see Warnings and Precautions (5.1), (5.3)].*

Severe Neuropathy

- Patients must be informed that sensory neuropathy occurs frequently with ABRAXANE and patients should advise their healthcare providers of numbness, tingling, pain, or weakness involving the extremities *[see Warnings and Precautions (5.2)].*

Pneumonitis

- Instruct patients to contact their healthcare provider immediately for sudden onset of dry persistent cough, or shortness of breath *[see Warnings and Precautions (5.4)]*.

Severe Hypersensitivity

- Instruct patients to contact their healthcare provider for signs of an allergic reaction, which could be severe and sometimes fatal *[see Warnings and Precautions (5.5)].*

Common Adverse Reactions

- Explain to patients that alopecia, fatigue/asthenia, and myalgia/arthralgia occur frequently with ABRAXANE.
- Instruct patients to contact their healthcare providers for persistent vomiting, diarrhea, or signs of dehydration *[see Adverse Reactions (6)]*.

Embryo-Fetal Toxicity

- ABRAXANE injection can cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Females of reproductive potential should use effective contraception during treatment with ABRAXANE and for at least six months after the last dose of ABRAXANE *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)].*
- Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment with ABRAXANE and for at least three months after the last dose of ABRAXANE *[see Use in Specific Populations (8.3)].*

Lactation

- Advise patients not to breastfeed while taking ABRAXANE and for two weeks after receiving the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

- Advise males and females of reproductive potential that ABRAXANE may impair fertility *[see Use in Specific Populations (8.3)].*

Manufactured for: Celgene Corporation
Summit, NJ 07901

ABRAXANE® is a registered trademark of Abraxis BioScience, LLC.
© 2005-2020 Abraxis BioScience, LLC.
All Rights Reserved.
Abraxis BioScience, LLC is a wholly owned subsidiary of Celgene Corporation.

U.S. Patent Numbers: www.celgene.com/therapies

ABRPI.012/PPI.012

Patient Information

ABRAXANE® (ah-BRAKS-ane)
(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

What is ABRAXANE?

ABRAXANE is a prescription medicine used to treat:

- advanced breast cancer in people who have already received certain other medicines for their cancer.
- advanced non-small cell lung cancer (NSCLC), in combination with carboplatin in people who cannot be treated with surgery or radiation.
- advanced pancreatic cancer, when used in combination with gemcitabine as the first medicine for advanced pancreatic cancer.

It is not known if ABRAXANE is safe or effective in children.

Do not receive ABRAXANE if:

- your white blood cell count is below 1,500 cells/ mm^3.
- you have had a severe allergic reaction to ABRAXANE.

Before you receive ABRAXANE, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- had a prior allergic reaction to a taxane.
- are pregnant or plan to become pregnant. ABRAXANE can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will check to see if you are pregnant before you start treatment with ABRAXANE.
  - You should not become pregnant during your treatment and for at least six months after the last dose of ABRAXANE.
  - You should use effective birth control (contraception) during your treatment and for at least six months after the last dose of ABRAXANE. Talk to your healthcare provider about birth control methods you can use during this time.

  Males with a female sexual partner who can become pregnant:
  - ABRAXANE can harm the unborn baby of your partner.
  - You should not father a child during your treatment and for at least three months after the last dose of ABRAXANE.
  - You should use effective birth control (contraception) during your treatment and for at least three months after the last dose of ABRAXANE.
- are breastfeeding or plan to breastfeed. Do not breastfeed during your treatment and for two weeks after the last dose of ABRAXANE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive ABRAXANE?

- Your healthcare provider will prescribe ABRAXANE in an amount that is right for you.
- Your healthcare provider may give you certain medicines to help prevent allergic reactions if you have had an allergic reaction to ABRAXANE in the past.
- ABRAXANE will be given to you by intravenous (IV) infusion into your vein.
- Your healthcare provider should do blood tests regularly during treatment with ABRAXANE.
- Your healthcare provider may stop your treatment, delay your treatment, or change your dose of ABRAXANE if you have certain side effects.

What are the possible side effects of ABRAXANE?

ABRAXANE may cause serious side effects, including:

- **severe decreased blood cell counts.** ABRAXANE can cause a severe decrease in neutrophils, a type of white blood cell which helps fight infections, and blood cells called platelets which help to clot blood. Your healthcare provider will check your blood cell count during your treatment with ABRAXANE.

- **severe nerve problems (neuropathy).** Tell your healthcare provider if you have numbness, tingling, pain, or weakness in your hands or feet.
- **severe infection (sepsis)**. If you receive ABRAXANE in combination with gemcitabine, infections can be severe and lead to death. Tell your healthcare provider right away if you have a fever (temperature greater than 100.4° F) or develop signs of infection.
- **lung or breathing problems**. If you receive ABRAXANE in combination with gemcitabine, lung or breathing problems may be severe and can lead to death. Tell your healthcare provider right away if you suddenly get a dry cough that will not go away or shortness of breath.
- **severe allergic reactions.** Severe allergic reactions are medical emergencies that can happen in people who receive ABRAXANE and can lead to death. You may have an increased risk of having an allergic reaction to ABRAXANE if you are allergic to other taxane medicines. Your healthcare provider will monitor you closely for allergic reactions during your infusion of ABRAXANE. Tell your healthcare provider right away if you get any of these signs of a serious allergic reaction: trouble breathing, sudden swelling of your face, lips, tongue, throat, or trouble swallowing, hives (raised bumps), rash, or redness all over your body.

The most common side effects of ABRAXANE in people with breast cancer include:

- hair loss
- numbness, tingling, pain, or weakness in the hands or feet
- tiredness
- changes in your liver function tests
- nausea
- diarrhea
- infections
- decreased white blood cell count
- abnormal heartbeat
- joint and muscle pain
- low red blood cell count (anemia). Red blood cells carry oxygen to your body tissues. Tell your healthcare provider if you feel weak, tired, or short of breath.

The most common side effects of ABRAXANE in people with non-small cell lung cancer include:

- low red blood cell count (anemia)
- decreased platelet cell count
- numbness, tingling, pain, or weakness in the hands or feet
- tiredness
- decreased white blood cell count
- hair loss
- nausea

The most common side effects of ABRAXANE in people with pancreatic cancer include:

- decreased white blood cell count
- numbness, tingling, pain, or weakness in the hands or feet
- hair loss
- diarrhea
- vomiting
- rash
- tiredness
- nausea
- swelling in the hands or feet
- fever
- decreased appetite
- signs of dehydration including thirst, dry mouth, dark yellow urine, decreased urine, headache, or muscle cramps

Tell your healthcare provider if you have vomiting, diarrhea, or signs of dehydration that does not go away.

ABRAXANE may cause fertility problems in males and females, which may affect your ability to have a child. Talk to your healthcare provider if this is a concern for you. These are not all of the possible side effects of ABRAXANE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ABRAXANE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about ABRAXANE that is written for health professionals.

What are the ingredients in ABRAXANE?

Active ingredient: paclitaxel (bound to human albumin).

Other ingredient: human albumin (containing sodium caprylate and sodium acetyltryptophanate).

Manufactured for: Celgene Corporation Summit, NJ 07901
ABRAXANE® is a registered trademark of Abraxis BioScience, LLC.
© 2005-2020 Abraxis BioScience, LLC.
All Rights Reserved.
Abraxis BioScience, LLC is a wholly owned subsidiary of Celgene Corporation.
U.S. Patent Numbers: www.celgene.com/therapies
ABRPPI.012
For more information, call 1-888-423-5436.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 8/2020

Appendix 10: Package Insert for GEMZAR® (Gemcitabine)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gemzar safely and effectively. See full prescribing information for Gemzar.

GEMZAR (gemcitabine for injection) Powder, Lyophilized, For Solution For Intravenous Use

Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Dosage and Administration:
Dose Modifications for Non-Hematologic Adverse Reactions (2.5) 05/2014

Warnings and Precautions:
Capillary Leak Syndrome (5.8) 05/2013
Posterior Reversible Encephalopathy Syndrome (5.9) 05/2014

INDICATIONS AND USAGE

Gemzar® is a nucleoside metabolic inhibitor indicated:
- in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy (1.1)
- in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated (1.2)
- in combination with cisplatin for the treatment of non-small cell lung cancer (1.3)
- as a single agent for the treatment of pancreatic cancer (1.4)

DOSAGE AND ADMINISTRATION

Gemzar is for intravenous use only.
- Ovarian Cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle (2.1)
- Breast Cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle (2.2)
- Non-Small Cell Lung Cancer: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle (2.3)
- Pancreatic Cancer: 1000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle (2.4)

DOSAGE FORMS AND STRENGTHS

- 200 mg/single-use vial (3)
- 1 g/single-use vial (3)

CONTRAINDICATIONS

Patients with a known hypersensitivity to gemcitabine (4)

WARNINGS AND PRECAUTIONS

- Schedule-dependent toxicity: Increased toxicity with infusion time greater than 60 minutes or dosing more frequently than once weekly. (5.1)
- Myelosuppression: Monitor for myelosuppression prior to each cycle and reduce or withhold dose for severe myelosuppression. (5.2, 5.7)
- Pulmonary Toxicity and Respiratory Failure: Discontinue Gemzar immediately for unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity. (5.3)
- Hemolytic-Uremic Syndrome (HUS): Monitor renal function prior to initiation and during therapy. Discontinue Gemzar for HUS or severe renal impairment. (5.4)
- Hepatic Toxicity: Monitor hepatic function prior to initiation and during therapy. Discontinue Gemzar for severe hepatic toxicity. (5.5)
- Embryofetal Toxicity: Can cause fetal harm. Advise women of potential risk to the fetus. (5.6, 8.1)
- Exacerbation of Radiation Therapy Toxicity: May cause severe and life-threatening toxicity when administered during or within 7 days of radiation therapy. (5.7)
- Capillary Leak Syndrome: Discontinue Gemzar. (5.8)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue Gemzar. (5.9)

ADVERSE REACTIONS

The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Ovarian Cancer
- 1.2 Breast Cancer
- 1.3 Non-Small Cell Lung Cancer
- 1.4 Pancreatic Cancer

2 DOSAGE AND ADMINISTRATION
- 2.1 Ovarian Cancer
- 2.2 Breast Cancer
- 2.3 Non-Small Cell Lung Cancer
- 2.4 Pancreatic Cancer
- 2.5 Dose Modifications for Non-Hematologic Adverse Reactions
- 2.6 Preparation and Administration Precautions
- 2.7 Preparation for Intravenous Infusion Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Schedule-dependent Toxicity
- 5.2 Myelosuppression
- 5.3 Pulmonary Toxicity and Respiratory Failure
- 5.4 Hemolytic Uremic Syndrome
- 5.5 Hepatic Toxicity
- 5.6 Embryofetal Toxicity
- 5.7 Exacerbation of Radiation Therapy Toxicity
- 5.8 Capillary Leak Syndrome
- 5.9 Posterior Reversible Encephalopathy Syndrome

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Gender

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Ovarian Cancer
- 14.2 Breast Cancer
- 14.3 Non-Small Cell Lung Cancer (NSCLC)
- 14.4 Pancreatic Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

Gemzar in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

1.2 Breast Cancer

Gemzar in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

1.3 Non-Small Cell Lung Cancer

Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

1.4 Pancreatic Cancer

Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

2 DOSAGE AND ADMINISTRATION

2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dose of Gemzar is 1000 mg/m^2 as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after Gemzar administration on Day 1 of each 21-day cycle. Refer to carboplatin prescribing information for additional information.

Dose Modifications

Recommended Gemzar dose modifications for myelosuppression are described Table 1 and Table 2 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 1: Dosage Reduction Guidelines for Gemzar for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
Day 1	≥1500	and	≥100,000	100%
	<1500	or	<100,000	Delay Treatment Cycle
Day 8	≥1500	and	≥100,000	100
	1000-1499	or	75,000-99,999	50
	<1000	or	<75,000	Hold

Table 2: Gemzar Dose Modification for Myelosuppression in Previous Cycle In Ovarian Cancer

Occurrence	Myelosuppression During Treatment Cycle	Dose Modification
Initial Occurrence	Absolute granulocyte count less than 500 x 10^6/L for more than 5 days Absolute granulocyte count less than 100 x 10^6/L for more than 3 days Febrile neutropenia Platelets less than 25,000x10^6/L Cycle delay of more than one week due to toxicity	Permanently reduce Gemzar to 800 mg/m^2 on Days 1 and 8
Subsequent Occurrence	If any of the above toxicities occur after the initial dose reduction	Permanently reduce Gemzar dose to 800 mg/m^2 on Day 1 only

2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dose of Gemzar is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3 hour intravenous infusion before Gemzar administration.

Dose Modifications

Recommended dose modifications for Gemzar for myelosuppression are described in Table 3 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 3: Recommended Dose Reductions for Gemzar for Myelosuppression on Day of Treatment in Breast Cancer

Treatment Day	Absolute granulocyte count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	% of full dose
Day 1	≥1500	and	≥100,000	100%
	less than 1500	or	less than 100,000	Hold
Day 8	≥1200	and	>75,000	100%
	1000-1199	or	50,000-75,000	75%
	700-999	and	≥50,000	50%
	<700	or	<50,000	Hold

2.3 Non-Small Cell Lung Cancer

Recommended Dose and Schedule

Every 4-week schedule

The recommended dose of Gemzar is 1000 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar.

Every 3-week schedule

The recommended dose of Gemzar is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar.

Dose Modifications

Recommended dose modifications for Gemzar myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for Gemzar recommendations for non-hematologic adverse reactions.

2.4 Pancreatic Cancer

Recommended Dose and Schedule

The recommended dose of Gemzar is 1000 mg/m^2 over 30 minutes intravenously. The recommended treatment schedule

- Weeks 1-8: weekly dosing for the first 7 weeks followed by one week rest.
- After week 8: weekly dosing on Days 1, 8, and 15 of 28-day cycles.

Dose Modifications

Recommended dose modifications for Gemzar for myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 4.

Table 4: Recommended Dose Reductions for Gemzar for Myelosuppression in Pancreatic Cancer and Non-Small Cell Lung Cancer

Absolute granulocyte count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	% of full dose
≥1000	And	≥100,000	100
500-999	Or	50,000-99,999	75
<500	Or	<50,000	Hold

2.5 Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue Gemzar for any of the following

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-Uremic Syndrome
- Capillary Leak Syndrome
- Posterior reversible encephalopathy syndrome

Withhold Gemzar or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

2.6 Preparation and Administration Precautions

Exercise caution and wear gloves when preparing Gemzar solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemzar contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption. For further guidance on handling Gemzar go to "OSHA Hazardous Drugs" (refer to antineoplastic weblinks including OSHA Technical Manual) at OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

2.7 Preparation for Intravenous Infusion Administration

Reconstitute the vials with 0.9% Sodium Chloride Injection without preservatives.

Add 5 mL to the 200-mg vial or 25 mL to the 1-g vial. These dilutions each yield a Gemzar concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of Gemzar. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. Inspect visually prior to administration and discard for particulate matter or discoloration. Gemzar solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Do not refrigerate as crystallization can occur.

No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

3 DOSAGE FORMS AND STRENGTHS

Gemzar (gemcitabine for injection USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine.

4 CONTRAINDICATIONS

Gemzar is contraindicated in patients with a known hypersensitivity to gemcitabine.

5 WARNINGS AND PRECAUTIONS

5.1 Schedule-dependent Toxicity

In clinical trials evaluating the maximum tolerated dose of Gemzar, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of Gemzar is influenced by the length of the infusion *[see Clinical Pharmacology (12.3)]*.

5.2 Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemzar as a single agent and the risks are increased when Gemzar is combined with other cytotoxic drugs. In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving Gemzar in combination with another drug.

5.3 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of Gemzar. Discontinue Gemzar in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity *[see Adverse Reactions (6.1 and 6.2)]*.

5.4 Hemolytic Uremic Syndrome

Hemolytic Uremic Syndrome to include fatalities from renal failure or the requirement for dialysis can occur in patients treated with Gemzar. In clinical trials, HUS was reported in 6 of 2429 patients (0.25%). Most fatal cases of renal failure were due to HUS *[see Adverse Reactions (6.1 and 6.2)]*. Assess renal function prior to initiation of Gemzar and periodically during treatment. Consider the diagnosis of HUS in patients who develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN) *[see Dosage and Administration (2.5) and Use In Specific Populations (8.6)]*. Permanently discontinue Gemzar in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy. Renal failure may not be reversible even with discontinuation of therapy.

5.5 Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs *[see Adverse Reactions (6.1 and 6.2)]*. Administration of Gemzar in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency *[see Use in Specific Populations (8.7)]*. Assess hepatic function prior to initiation of Gemzar and periodically during treatment. Discontinue Gemzar in patients that develop severe liver injury.

5.6 Embryofetal Toxicity

Gemzar can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a woman becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to a fetus. *[see Use In Specific Populations (8.1)]*

5.7 Exacerbation of Radiation Therapy Toxicity

Gemzar is not indicated for use in combination with radiation therapy.

Concurrent (given together or ≤7 days apart) — Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which Gemzar was administered at a dose of 1000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given >7 days apart) — Excessive toxicity has not been observed when Gemzar is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive Gemzar after prior radiation.

5.8 Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving Gemzar as a single agent or in combination with other chemotherapeutic agents. Discontinue Gemzar if CLS develops during therapy.

5.9 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemzar as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI) and discontinue Gemzar if PRES develops during therapy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label

- Schedule-Dependent Toxicity *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.2)]*
- Pulmonary Toxicity and Respiratory Failure *[see Warnings and Precautions (5.3)]*
- Hemolytic Uremic Syndrome *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*
- Embryo-fetal Toxicity *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1), and Nonclinical Toxicology (13.1)]*
- Exacerbation of Radiation Toxicity *[see Warnings and Precautions (5.7)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.8)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Single-Agent Use:

The data described below reflect exposure to Gemzar as a single agent administered at doses between 800 mg/m^2 to 1250 mg/m^2 over 30 minutes intravenously, once weekly, in 979 patients with a variety of malignancies. The most common (≥20%) adverse reactions of single-agent Gemzar are nausea/vomiting, anemia, increased ALT, increased AST, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema. The most common (≥5%) Grade 3 or 4 adverse reactions were neutropenia, nausea/vomiting; increased ALT, increase alkaline phosphatase, anemia, increased AST, and thrombocytopenia. Approximately 10% of the 979 patients discontinued Gemzar due to adverse reactions. Adverse reactions resulting in discontinuation of Gemzar in 2% of 979 patients were cardiovascular adverse events (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension) and adverse reactions resulting in discontinuation of Gemzar in less than 1% of the 979 patients were anemia, thrombocytopenia, hepatic dysfunction, renal dysfunction, nausea/vomiting, fever, rash, dyspnea, hemorrhage, infection, stomatitis, somnolence, flu-like syndrome, and edema.

Table 5 presents the incidence of adverse reactions reported in 979 patients with various malignancies receiving single-agent Gemzar across 5 clinical trials. Table 5 includes all clinical adverse reactions, reported in at least 10% of patients. A listing of clinically significant adverse reactions is provided following the table.

Table 5: Selected Per-Patient Incidence of Adverse Events in Patients Receiving Single-Agent Gemzar[a]

	All Patients[b]		
	All Grades	Grade 3	Grade 4
Laboratory[c]			
Hematologic			
Anemia	68	7	1
Neutropenia	63	19	6
Thrombocytopenia	24	4	1
Hepatic			
Increased ALT	68	8	2
Increased AST	67	6	2
Increased Alkaline Phosphatase	55	7	2
Hyperbilirubinemia	13	2	<1
Renal			
Proteinuria	45	<1	0
Hematuria	35	<1	0
Increased BUN	16	0	0
Increased Creatinine	8	<1	0
Non-laboratory[d]			
Nausea and Vomiting	69	13	1
Fever	41	2	0

Rash	30	<1	0
Dyspnea	23	3	<1
Diarrhea	19	1	0
Hemorrhage	17	<1	<1
Infection	16	1	<1
Alopecia	15	<1	0
Stomatitis	11	<1	0
Somnolence	11	<1	<1
Paresthesias	10	<1	0

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=699-974; all patients with laboratory or non-laboratory data.
[c] Regardless of causality.
[d] For approximately 60% of patients, non-laboratory adverse events were graded only if assessed to be possibly drug-related.

- Transfusion requirements — Red blood cell transfusions (19%); platelet transfusions (<1%)
- Fever — Fever occurred in the absence of clinical infection and frequently in combination with other flu-like symptoms.
- Pulmonary — Dyspnea unrelated to underlying disease and sometimes accompanied by bronchospasm.
- Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%); <1% of patients. discontinued Gemzar due to edema.
- Flu-like Symptoms — Characterized by fever, asthenia, anorexia, headache, cough, chills, myalgia, asthenia insomnia, rhinitis, sweating, and/or malaise (19%); <1% of patients discontinued Gemzar due to flu-like symptoms
- Infection — Sepsis (<1%)
- Extravasation — Injection-site reactions (4%)
- Allergic — Bronchospasm (<2%); anaphylactoid reactions *[see Contraindications (4)]*.

Non-Small Cell Lung Cancer:

Table 6 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemzar-treated patients and at a higher incidence in the Gemzar plus cisplatin arm, reported in a randomized trial of Gemzar plus cisplatin (n=262) administered in 28-day cycles as compared to cisplatin alone (n=260) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) *[see Clinical Studies (14.3)]*.

Patients randomized to Gemzar plus cisplatin received a median of 4 cycles of treatment and those randomized to cisplatin received a median of 2 cycles of treatment. In this trial, the requirement for dose adjustments (>90% versus 16%), discontinuation of treatment for adverse reactions (15% versus 8%), and the proportion of patients hospitalized (36% versus 23%) were all higher for patients receiving Gemzar plus cisplatin arm compared to those receiving cisplatin alone. The incidence of febrile neutropenia (9/262 versus 2/260), sepsis (4% versus 1%), Grade 3 cardiac dysrhythmias (3% versus <1%) were all higher in the Gemzar plus cisplatin arm compared to the cisplatin alone arm. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm.

Table 6: Per-Patient Incidence of Selected Adverse Reactions from Randomized Trial of Gemzar plus Cisplatin versus Single-Agent Cisplatin in Patients with NSCLC Occurring at Higher Incidence in Gemzar-Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)][a]

	Gemzar plus Cisplatin[b]			Cisplatin[c]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[d]						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusion[e]	39			13		
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions[e]	21			<1		
Lymphopenia	75	25	18	51	12	5
Hepatic						
Increased Transaminases	22	2	1	10	1	0
Increased Alkaline Phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Elevated creatinine	38	4	<1	31	2	<1
Other Laboratory						

Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[f]						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

[a] National Cancer Institute Common Toxicity Criteria (CTC) for severity grading.

[b] N=217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data Gemzar at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[c] N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[d] Regardless of causality.

[e] Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

[f] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 7 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemzar-treated patients and at a higher incidence in the Gemzar plus cisplatin arm, reported in a randomized trial of Gemzar plus cisplatin (n=69) administered in 21-day cycles as compared to etoposide plus cisplatin alone (n=66) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) *[see Clinical Studies (14.3)]*. A listing of clinically significant adverse reactions is provided following the table.

Patients in the Gemzar cisplatin (GC) arm received a median of 5 cycles and those in the etoposide/cisplatin (EC) arm received a median of 4 cycles. The majority of patients receiving more than one cycle of treatment required dose adjustments; 81% in the (GC) arm and 68% in the (EC) arm. The incidence of hospitalizations for treatment-related adverse events was 22% (GC) and 27% in the (EC) arm. The proportion of discontinuation of treatment for treatment-related adverse reactions was higher for patients in the (GC) arm (14% versus 8%). The proportion of patients hospitalized for febrile neutropenia was lower in the (GC) arm (7% versus 12%). There was one death attributed to treatment, a patient with febrile neutropenia and renal failure, which occurred in the Gemzar/cisplatin arm.

Table 7: Per-Patient Incidence of Selected Adverse Reactions in Randomized Trial of Gemzar plus Cisplatin versus Etoposide plus Cisplatin in Patients with NSCLC[a]

	Gemzar plus Cisplatin[b]			**Etoposide plus Cisplatin[c]**		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[d]						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions[e]	29	-	-	21	-	-
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions[e]	3	-	-	8	-	-
Hepatic						
Increased ALT	6	0	0	12	0	0
Increased AST	3	0	0	11	0	0
Increased Alkaline	16	0	0	11	0	0
Phosphatase						
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0

Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-laboratory[f,g]						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0

[a] Grade based on criteria from the World Health Organization (WHO).

[b] N=67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 on Day 1 every 21 days.

[c] N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 and intravenous etoposide at 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[d] Regardless of causality.

[e] WHO grading scale not applicable to proportion of patients with transfusions

[f] Non-laboratory events were graded only if assessed to be possibly drug-related.

[g] Pain data were not collected.

- Flu-like syndrome: 3% in the Gemzar/cisplatin arm versus none in the etoposide/cisplatin arm.
- Edema: 12% in the Gemzar/cisplatin arm versus 2% in the etoposide/cisplatin arm.

Breast Cancer

Table 8 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemzar-treated patients and at a higher incidence in the Gemzar plus paclitaxel arm, reported in a randomized trial of Gemzar plus paclitaxel (n=262) compared to paclitaxel alone (n=259) for the first-line treatment of metastatic breast cancer (MBC) in women who received anthracycline-containing chemotherapy in the adjuvant/neo-adjuvant setting or for whom anthracyclines were contraindicated. *[see Clinical Studies (14.2)]*.

The requirement for dose reduction of paclitaxel were higher for patients in the Gemzar/paclitaxel arm (5% versus 2%). The number of paclitaxel doses omitted (<1%), the proportion of patients discontinuing treatment for treatment-related adverse reactions (7% versus 5%), and the number of treatment-related deaths (1 patient in each arm) were similar between the two arms.

Table 8: Per-Patient Incidence of Selected Adverse Reactions from Comparative Trial of Gemzar plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer[a] Occurring at Higher Incidence in Gemzar-Treated Patients

[Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemzar plus Paclitaxel (N=262)			**Paclitaxel (N=259)**		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Hepatobiliary						
Increased ALT	18	5	<1	6	<1	0
Increased AST	16	2	0	5	<1	0
Non-laboratory[c]						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Vomiting	29	2	0	15	2	0
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0

Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Rash/desquamation	11	<1	<1	5	0	0

[a] Severity grade based on National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0

[b] Regardless of causality.

[c] Non-laboratory events were graded only if assessed to be possibly drug-related.

The following clinically relevant, Grade 3 or 4 adverse reactions occurred with a higher incidence in the Gemzar plus paclitaxel arm compared with the paclitaxel arm: febrile neutropenia (5.0% versus 1.2%) and dyspnea (1.9% versus 0).

Ovarian Cancer

Table 9 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine-treated patients and at a higher incidence in the Gemzar plus carboplatin arm, reported in a randomized trial of Gemzar plus carboplatin (n=175) compared to carboplatin alone (n=174) for the second-line treatment of ovarian cancer in women with disease that had relapsed more than 6 months following first-line platinum-based chemotherapy. *[see Clinical Studies (14.1)]*. Additional clinically significant adverse reactions, occurring in less than 10% of patients, are provided following Table 9.

The proportion of patients with dose adjustments for carboplatin (1.8% versus 3.8%), doses of carboplatin omitted (0.2% versus 0), and discontinuing treatment for treatment-related adverse reactions (10.9% versus 9.8%), were similar between arms. Dose adjustment for Gemzar occurred in 10.4% of patients and Gemzar dose was omitted in 13.7% of patients in the Gemzar /carboplatin arm.

Table 9: Per-Patient Incidence of Adverse Reactions in Randomized Trial of Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer Occurring at Higher Incidence in Gemzar-Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemzar plus Carboplatin (N=175)			**Carboplatin (N=174)**		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusions[c]	38			15		
Platelet Transfusions[c]	9			3		
Non-laboratory[b]						
Nausea	69	6	0	61	3	0
Alopecia	49	0	0	17	0	0
Vomiting	46	6	0	36	2	<1
Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Diarrhea	25	3	0	14	<1	0
Stomatitis/pharyngitis	22	<1	0	13	0	0

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0.

[b] Regardless of causality.

[c] Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood transfusions included both packed red blood cells and whole blood.

Hematopoietic growth factors were administered more frequently in the Gemzar-containing arm: granulocyte growth factors (23.6% and 10.1%) and erythropoietic agents (7.3% and 3.9%).

The following clinically relevant, Grade 3 and 4 adverse reactions occurred more frequently in the Gemzar plus carboplatin arm: dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1 %), motor neuropathy (1.1% versus 0.6%), and rash/desquamation (0.6% versus 0).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Gemzar. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular — Congestive heart failure, myocardial infarction, Arrhythmias, supraventricular arrhythmias.

Vascular Disorders — Peripheral vasculitis, gangrene, and capillary leak syndrome *[see Warnings and Precautions (5.9)]*

Skin — Cellulitis, severe skin reactions, including desquamation and bullous skin eruptions

Hepatic — Hepatic failure, hepatic veno-occlusive disease

Pulmonary — Interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS)

Nervous System — Posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.9)]*

7 DRUG INTERACTIONS

No drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. *[see Warnings and Precautions (5.6)]*

Risk Summary

Gemzar can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, Gemzar is expected to result in adverse reproductive effects. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to a fetus.

Animal Data

Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (approximately 0.005 times the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 0.002 times the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. *[see Warnings and Precautions (5.6)]*

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemzar, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Gemzar have not been established in pediatric patients. The safety and pharmacokinetics of gemcitabine were evaluated in a trial in pediatric patients with refractory leukemia. The maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one-week rest period. The safety and activity of Gemzar were evaluated in a trial of pediatric patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) at a dose of 10 mg/m^2/min administered over 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation. No meaningful clinical activity was observed in this trial.

8.5 Geriatric Use

In clinical studies of GEMZAR, enrolling 979 patients with various cancers who received GEMZAR as a single agent, no overall differences in safety were observed between patients aged 65 and older and younger patients, with the exception of a higher rate of Grade 3-4 thrombocytopenia in older patients as compared to younger patients. In a randomized trial in women with ovarian cancer, 175 women received GEMZAR plus carboplatin, of which 29% were age 65 years or older. Similar effectiveness was observed between older and younger women. There was significantly higher Grade 3/4 neutropenia in women 65 years of age or older.

GEMZAR clearance is affected by age, however there are no recommended dose adjustments based on patients' age *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No clinical studies have been conducted with gemcitabine in patients with decreased renal function.

8.7 Hepatic Impairment

No clinical studies have been conducted with gemcitabine in patients with decreased hepatic function.

8.8 Gender

Gemzar clearance is affected by gender *[see Clinical Pharmacology (12.3)]*. In single-agent studies of Gemzar, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

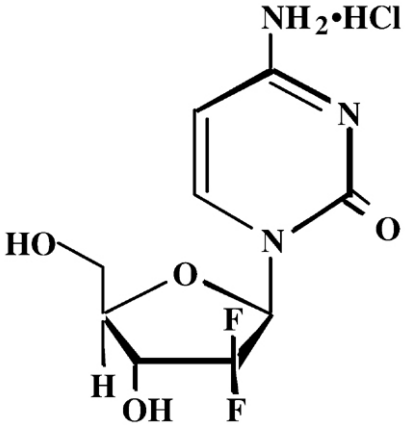
10 OVERDOSAGE

Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a dose-escalation study.

11 DESCRIPTION

Gemzar (gemcitabine for injection, USP) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66.

Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemzar is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

12.3 Pharmacokinetics

Absorption and Distribution

The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied from 500 to 3600 mg/m^2.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Elimination

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 10 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 10: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57

65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving <70 minute infusion.

Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

Drug Interactions

When Gemzar (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. Analysis of data from metastatic breast cancer patients shows that, on average, Gemzar has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine. Data from NSCLC patients demonstrate that Gemzar and carboplatin given in combination does not alter the pharmacokinetics of gemcitabine or carboplatin compared to administration of either single agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of Gemzar have not been conducted. Gemcitabine was mutagenic in an *in vitro* mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine IP doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day administered intravenously (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day administered intravenously (about 1/1300 the human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

The safety and efficacy of Gemzar was studied in a randomized trial of 356 women with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either Gemzar 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after Gemzar infusion on Day 1 of each cycle (n=178) or to carboplatin AUC 5 administered on Day 1 of each 21-day cycle (n=178). The primary efficacy outcome measure was progression free survival (PFS).

Patient characteristics are shown in Table 11. The addition of Gemzar to carboplatin resulted in statistically significant improvements in PFS and overall response rate as shown in Table 12 and Figure 1. Approximately 75% of patients in each arm received additional chemotherapy for disease progression; 13 of 120 patients in the carboplatin alone arm received Gemzar for treatment of disease progression. There was no significant difference in overall survival between the treatment arms.

Table 11: Randomized Trial of Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer - Baseline Demographics and Clinical Characteristics

	Gemzar/Carboplatin	Carboplatin
Number of randomized patients	178	178
Median age, years Range	59 36 to 78	58 21 to 81
Baseline ECOG performance status 0-1[a]	94%	95%
Disease Status Evaluable Bidimensionally measurable	 8% 92%	 3% 96%
Platinum-free interval[b] 6-12 months >12 months	 40% 59%	 40% 60%
First-line therapy Platinum-taxane combination Platinum-non-taxane combination Platinum monotherapy	 70% 29% 1%	 71% 28% 1%

[a] 5 patients on Gemzar plus carboplatin arm and 4 patients on carboplatin arm with no baseline Eastern Cooperative Oncology Group (ECOG) performance status.

[b] 2 on Gemzar plus carboplatin arm and 1 on carboplatin arm had platinum-free interval <6 months.

Table 12: Randomized Trial of Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer - Efficacy Outcomes

	Gemzar/Carboplatin (N=178)	Carboplatin (N=178)
Progression-free Survival		

Median (95% CI[a]) months	8.6 (8.0, 9.7)	5.8 (5.2, 7.1)
Hazard Ratio (95% CI)	0.72 (0.57, 0.90)	
p-value[b]	p=0.0038	
Overall Survival		
Median (95% CI) months	18.0 (16.2, 20.3)	17.3 (15.2, 19.3)
Hazard Ratio (95% CI)	0.98 (0.78, 1.24)	
p-value[b]	p=0.8977	
Investigator Reviewed Overall Response Rate	47.2%	30.9%
p-value[e]	p=0.0016	
CR[d]	14.6%	6.2%
PR plus PRNM[e]	32.6%	24.7%
Independently Reviewed Overall Response Rate[f]	46.3%	35.6%
p-value[e]	p=0.11	
CR[d]	9.1%	4.0%
PR plus PRNM[e]	37.2%	31.7%

[a] CI=confidence interval
[b] Complete response
[c] Partial response plus partial response, non-measurable disease
[d] log Rank, unadjusted
[e] chi Square
[f] Independently reviewed cohort - Gemzar/carboplatin (n=121), carboplatin (n=101); independent reviewers unable to measure disease detected by sonography or physical exam

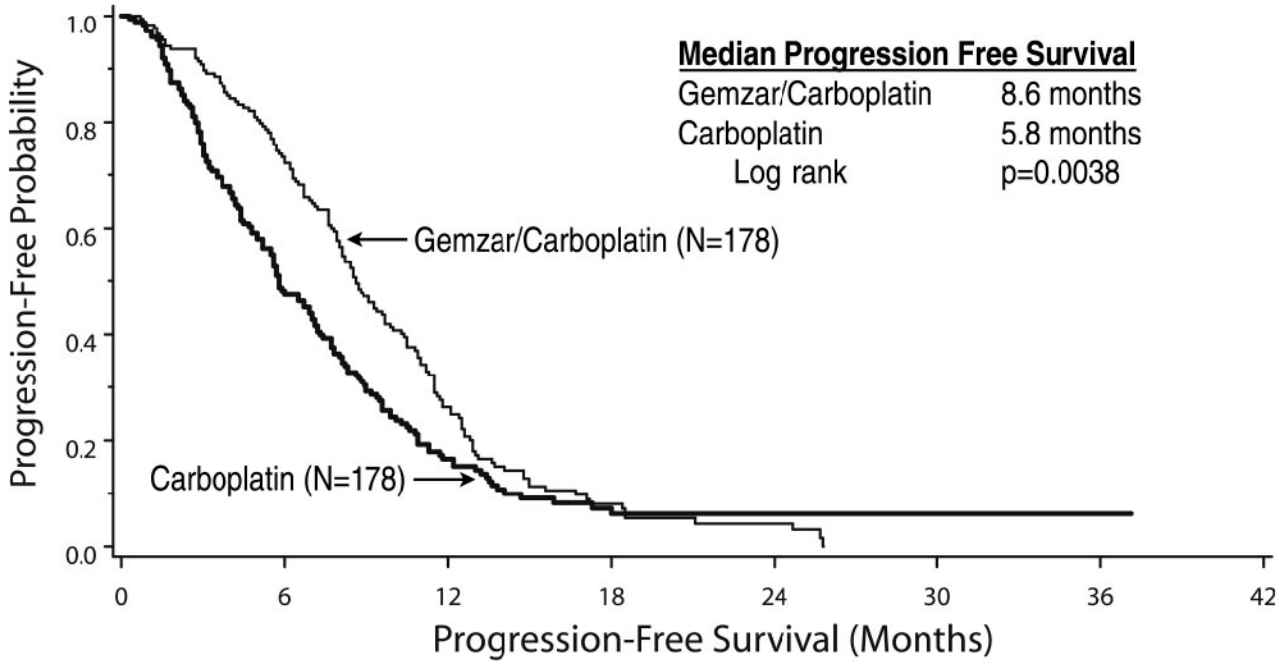


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemzar plus Carboplatin versus Carboplatin in Ovarian Cancer (N=356)

14.2 Breast Cancer

The safety and efficacy of Gemzar were evaluated in a multi-national, randomized, open-label trial conducted in women receiving initial treatment for metastatic breast cancer in women who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Patients were randomized to receive Gemzar 1250 mg/m^2 on Days 1 and 8 of a 21-day cycle and paclitaxel 175 mg/m^2 administered prior to Gemzar on Day 1 of each cycle (n=267) or to receive paclitaxel 175 mg/m^2 was administered on Day 1 of each 21-day cycle (n=262). The primary efficacy outcome measure was time to documented disease progression.

A total of 529 patients were enrolled; 267 were randomized to Gemzar and paclitaxel and 262 to paclitaxel alone. Demographic and baseline characteristics were similar between treatment arms (see Table 13). Efficacy results are presented in Table

13 and Figure 2. The addition of Gemzar to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to paclitaxel alone. There was no significant difference in overall survival.

Table 13: Randomized Trial of Gemzar plus Paclitaxel versus Paclitaxel in Breast Cancer

	Gemzar/Paclitaxel	Paclitaxel
Number of patients	267	262
Demographic/Entry Characteristics		
Median age (years)	53	52
Range	26 to 83	26 to 75
Metastatic disease	97%	97%
Baseline KPS[a] ≥90	70%	74%
Number of tumor sites		
1-2	57%	59%
≥3	43%	41%
Visceral disease	73%	73%
Prior anthracycline	97%	96%
Efficacy Outcomes		
Time to Documented Disease Progression[b]		
Median in months (95% CI)	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)
Hazard Ratio (95% CI)	0.650 (0.524, 0.805)	
p-value	p<0.0001	
Overall Survival[c]		
Median Survival in months (95% CI)	18.6 (16.5, 20.7)	15.8 (14.1, 17.3)
Hazard Ratio (95% CI)	0.86 (0.71, 1.04)	
p-value	Not Significant	
Overall Response Rate (95% CI)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)
p-value	p<0.0001	

[a] Karnofsky Performance Status.

[b] These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

[c] Based on the ITT population

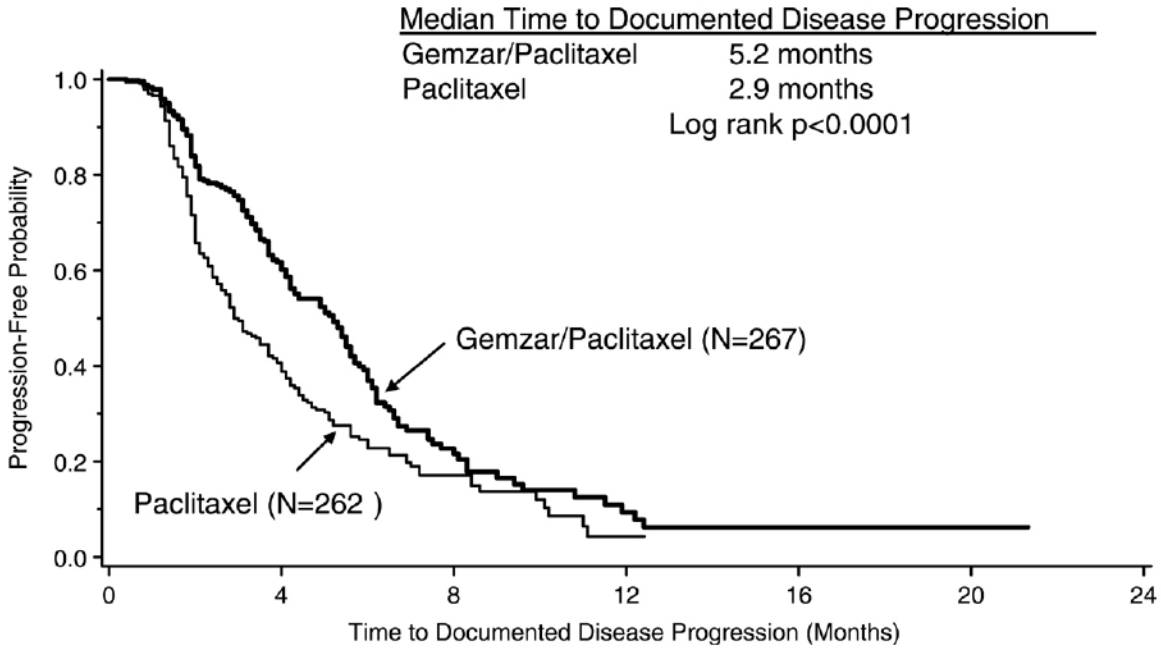


Figure 2: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemzar plus Paclitaxel versus Paclitaxel Breast Cancer Study (N=529)

14.3 Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of Gemzar was evaluated in two randomized, multicenter trials.

28-Day Schedule

A multinational, randomized trial compared Gemzar plus cisplatin to cisplatin alone in the treatment of patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Patients were randomized to receive Gemzar 1000 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle or to receive cisplatin 100 mg/m^2 on Day 1 of each 28-day cycle. The primary efficacy outcome measure was overall survival. A total of 522 patients were enrolled at clinical centers in Europe, the US, and Canada. Patient demographics and baseline characteristics (shown in Table 13) were similar between arms with the exception of histologic subtype of NSCLC, with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm having adenocarcinoma. Efficacy results are presented in Table 13 and Figure 3 for overall survival.

21-Day Schedule

A randomized (1:1), multicenter trial was conducted in 135 patients with Stage IIIB or IV NSCLC. Patients were randomized to receive Gemzar 1250 mg/m^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to receive etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 and cisplatin 100 mg/m^2 on Day 1 of a 21 -day cycle.

There was no significant difference in survival between the two treatment arms (Log rank p=0.18, two-sided). The median survival was 8.7 months for the Gemzar plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Log rank p=0.015, two-sided). The objective response rate for the Gemzar plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

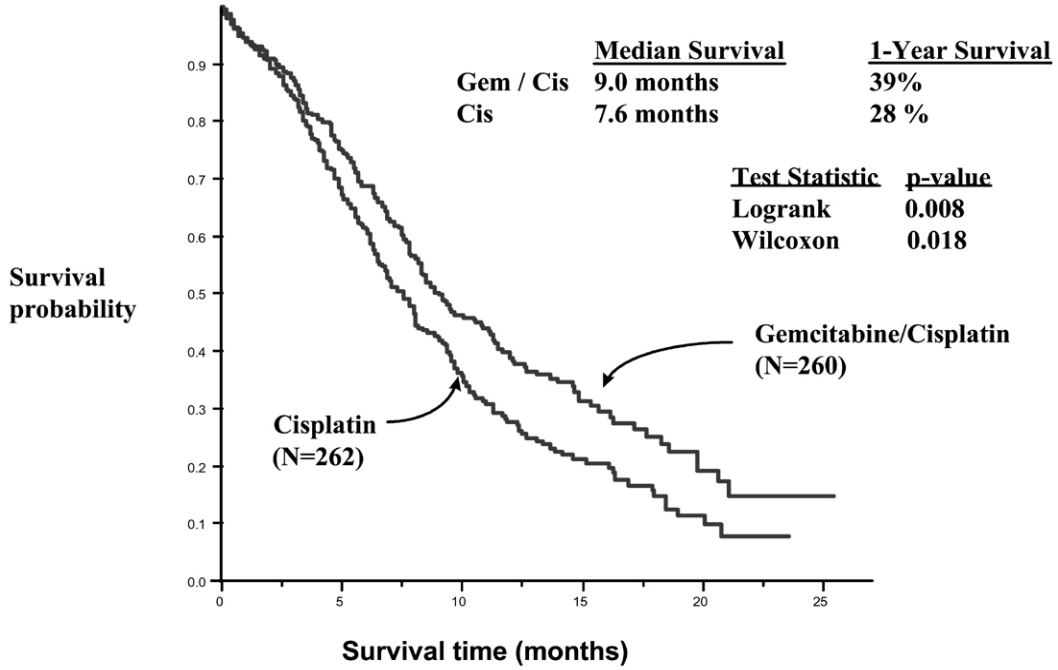


Figure 3: Kaplan-Meier Survival Curve in Gemzar plus Cisplatin versus Cisplatin in Patients with NSCLC Study (N=522)

Table 14: Randomized Trials of Gemzar plus Cisplatin in Patients with NSCLC

Trial	28-day Schedule[a]		21-day Schedule[b]	
Treatment Arm	Gemzar plus Cisplatin	Cisplatin	Gemzar plus Cisplatin	Etoposide plus Cisplatin
Number of patients	260	262	69	66
Demographic/Entry Characteristics				
Male	70%	71%	93%	92%
Median age, years	62	63	58	60
Range	36 to 88	35 to 79	33 to 76	35 to 75
Stage IIIA	7%	7%	N/A[c]	N/A[c]
Stage IIIB	26%	23%	48%	52%
Stage IV	67%	70%	52%	49%
Baseline KPS[d] 70 to 80	41%	44%	45%	52%

Baseline KPS[d] 90 to 100	57%	55%	55%	49%
Efficacy Outcomes				
Survival				
Median in months	9.0	7.6	8.7	7.0
(95% CI[e]) months	8.2, 11.0	6.6, 8.8	7.8, 10.1	6.0, 9.7
p-value[f]	p=0.008		p=0.18	
Time to Disease Progression				
Median in months	5.2	3.7	5.0	4.1
(95% CI[e]) months	4.2, 5.7	3.0, 4.3	4.2, 6.4	2.4, 4.5
p-value[f]	p=0.009		p=0.015	
Tumor Response	26%	10%	33%	14%
p-value[f]	p<0.0001		p=0.01	

[a] 28-day schedule — Gemzar plus cisplatin: Gemzar 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days.

[b] 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and intravenous etoposide 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[c] N/A Not applicable.

[d] Karnofsky Performance Status.

[e] CI=confidence intervals

[f] p-value two-sided Fisher's Exact test for difference in binomial proportions; log rank test for time-to-event analyses.

14.4 Pancreatic Cancer

The safety and efficacy of Gemzar was evaluated in two trials, a randomized, single-blind, two-arm, active-controlled trial conducted in patients with locally advanced or metastatic pancreatic cancer who had received no prior chemotherapy and in a single-arm, open-label, multicenter trial conducted in patients with locally advanced or metastatic pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The first trial randomized patients to receive Gemzar 1000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly dosing for 3 consecutive weeks every 28-days in subsequent cycles (n=63) or to 5-fluorouracil (5-FU) 600 mg/m^2 intravenously over 30 minutes once weekly (n=63). In the second trial, all patients received Gemzar 1000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly dosing for 3 consecutive weeks every 28-days in subsequent cycles.

The primary efficacy outcome measure in both trials was "clinical benefit response". A patient was considered to have had a clinical benefit response if either occurred:

- The patient achieved a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Karnofsky Performance Status) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occurring during the first 12 weeks of therapy.

OR

- The patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation.

The randomized trial enrolled 126 patients across 17 sites in the US and Canada. The demographic and entry characteristics were similar between the arms (Table 15). The efficacy outcome results are shown in Table 15 and for overall survival in Figure 4. Patients treated with Gemzar had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to those randomized to receive 5-FU. No confirmed objective tumor responses were observed in either treatment arm.

Table 15: Randomized Trial of Gemzar versus 5-Fluorouracil in Pancreatic Cancer

	Gemzar	5-FU
Number of patients	63	63
Demographic/Entry Characteristics		
Male	54%	54%
Median age	62 years	61 years
Range	37 to 79	36 to 77
Stage IV disease	71%	76%
Baseline KPS[a] ≤70	70%	68%
Efficacy Outcomes		
Clinical benefit response	22.2%	4.8%
p-value[b]	p=0.004	

Survival		
Median	5.7 months	4.2 months
(95% CI)	(4.7, 6.9)	(3.1, 5.1)
p-value[b]	p=0.0009	
Time to Disease Progression		
Median	2.1 months	0.9 months
(95% CI)	(1.9, 3.4)	(0.9, 1.1)
p-value[b]	p=0.0013	

[a] Karnofsky Performance Status.

[b] p-value for clinical benefit response calculated using the two-sided test for difference in binomial proportions. All other p-values are calculated using log rank test.

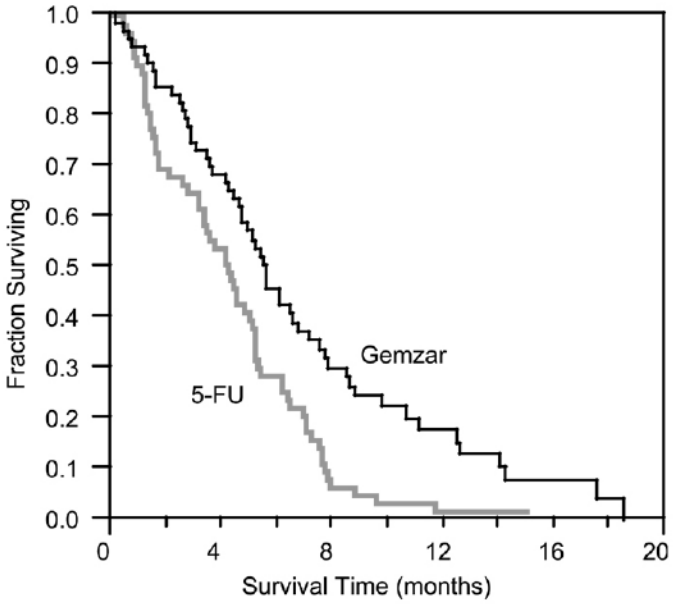


Figure 4: Kaplan-Meier Survival Curve

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemzar (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing:
200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial – NDC 0002-7501-01 (No. 7501)
1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial – NDC 0002-7502-01 (No. 7502)

16.2 Storage and Handling

Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F) [See USP Controlled Room Temperature] *[see Dosage and Administration (2.5 and 2.6)]*.

17 PATIENT COUNSELING INFORMATION

- Advise patients of the risks of low blood cell counts and the potential need for blood transfusions and increased susceptibility to infections. Instruct patients to immediately contact their healthcare provided for development of signs or symptoms of infection, fever, prolonged or unexpected bleeding, bruising, or shortness of breath *[see Warnings and Precautions (5.2)]*
- Advise patients of the risks of pulmonary toxicity including respiratory failure and death. Instruct patients to immediately contact their healthcare provider for development of shortness of breath, wheezing, or cough *[see Warnings and Precautions (5.3)]*
- Advise patients of the risks of hemolytic-uremic syndrome and associated renal failure. Instruct patients to immediately contact their healthcare provider for changes in the color or volume of urine output or for increased bruising or bleeding *[see Warnings and Precautions (5.4)]*
- Advise patients of the risks of hepatic toxicity including liver failure and death. Instruct patients to immediately contact their healthcare provider for signs of jaundice or for pain/tenderness in the right upper abdominal quadrant *[see Warnings and Precautions (5.5)]*

Marketed by: Lilly USA, LLC
Indianapolis, IN 46285, USA
Copyright © 1996, 2014, Eli Lilly and Company. All rights reserved.

A3.0NL 8181 AMP