Protocol Number: IT-01

Development Phase: Phase 1/2

Date: March 23, 2021

Version: Amendment 6.0

A Phase 1/2 Safety Study of Intratumorally Administered INT230-6 in Adult Subjects with Advanced Refractory Cancers

The Following changes are summarized

Document	Date of Issue	Summary of changes
Amendment 6	March 2021	This protocol amendment incorporates previous changes encompassed by administrative letters dated June 2020 and July 2020. This amendment focuses on simplifying the clinical trial: • Modified inclusion criteria: Subjects with metastatic disease who have failed one or more approved standard therapies, or have no alternate indicated therapy available. • New exclusion criteria: Subjects with tumors >15 cm (in longest diameter). Treatment plan for subjects with tumors that are 9 to15 cm must be discussed with and approved by the medical monitor. • Removed blood biomarkers and PK collection, processing and shipping. • Text has been added to introduce a simpler method to calculate the INT230-6 dose for tumor injections. • Added an additional clinical site- Houston Methodist. • Minor grammatical, editorial, and formatting changes for clarification purposes.
Amendment 5	April 2020	This amendment focuses on simplifying the dosing regimen of INT230-6 creating new monotherapy cohort EC3 and aligning this across all combination arms as seen in the DEC/DEC2 and FEC supplements: • INT230-6 dosing is simplified to allow up to a maximum 175ml total into as many lesions as feasible, and intrapatient dose escalation is removed. • INT230-6 dosing is divided into two periods, the Q 2wk for 5 doses as induction and then once every 9 weeks +/- 10 days for maintenance. Note retreatment has been removed. • The criteria for assessing response has been changed from RECIST 1.1 to iRECIST. • Other minor changes to improve the clarify and consistency of the protocol and supplements.
Amendment 4	June-2019	• This protocol amendment incorporates previous changes encompassed by administrative letters dated November 2017, January 2018, June 2018 and March 2019 plus additional recommendations by the Study Steering Committee in February 2019: • Allows for different combinations to be incorporated by supplements.

		• Incorporates new investigators (Administrative letter November 2017). • Incorporates cohort E-A (Administrative letter: January 2018) every two-week dosing with higher starting dose. • Incorporates Cohort EC (Administrative Letter: June 2018) every two-week dosing at higher dosing and 1:2 drug to tumor volume loading ratio. • Administrative letter March 2019. • New cohort EC2 superficial and deep tumors dosed every 14 days at a 1:3 drug to tumor volume loading ratio. • Change in schedule for PK moving day 7 post to 1 hour post next dose; no change in number of PK sample collections. • Removed Cohort Schema • Include Schedule of Events for "E" (every two-week dosing) cohorts. • Clarified Post dose follow up. • Clarified retreatment process criteria. • Include availability of a 30 mL drug product vial.
Amendment 3	14-August-2017	This protocol amendment was made per requests by and in agreement with the FDA as follows: • Two inclusion criteria were changed (former #2 and #10). • A new exclusion criterion was added regarding refusal. • Exclusion criterion #6 (PD-1 combo) was modified. • Baseline in section 13.1 was clarified to be cycle 1, day 0. • Table 9 footnote 4 typographical error was corrected. • Corrected typographical and spelling errors throughout the document.
Amendment 2	19 -July-2017	This protocol was updated per the rational below. • Modified section 6 Cohort A1 per rational, others for improved clarity. • Section 7.1, modified inclusion criteria #2 and #10. • Updated Sponsor's address and list of investigators, abbreviations. • Updated section 9.7 to note new PK collection information. • Revised the Schema.

		• Section 13.1 moved PT, PTT, INR to hematology from chemistry. • Provided more detail on exploratory endpoint RECIST modification section 13.2. • Updated PK section 13.3 for improved clarity. • Made minor wording and other changes to improve the consistency and clarity.
Amendment 1	12-Dec-2016	The protocol was updated based on feedback from the US FDA and Canada's Health Canada. • The starting dose was reduced to 5 mL from the proposed 7.5 mL. • The DLT criteria were modified and the DLT window was extended to 28 Days from 14 days, • Inclusion criteria were modified to require more stringent hemoglobin, platelet and coagulation parameters for subjects with deep tumors, • Additional safety background information was included in a number of sections, • Delayed tumor biopysing for at least the first 20 subjects i.e.,10 superficial, and 10 deep tumors until the SSC reviews study safety data, • Expanded the descriptions in section 6 and the schema diagram to better clarify and specify the criteria for initiation of all cohorts after A1. • Added new section 9.12 to describe conditions for the discontinuation of study drug due to adverse events. • Added new section 10.2 to describe the management of selected adverse events. • Made minor wording and other changes to improve the consistency and clarity of the protocol.
Original protocol	October 5, 2016	

RATIONALE for Amendment 1: The regulatory agencies sought to improve clarity on i) escalation within or initiation of new cohorts, ii) how adverse events would be managed (including drug or immune related AEs), iii) patient stopping procedures, iv) imaging of injection of tumors to improve necrosis monitoring of injected tumors, v) reducing bleeding risk as well as drug extravasation and vi) remove section inconsistencies.

RATIONALE for Amendment 2: In an effort to facilitate appropriate patient selection, recruitment and to support enrollment, the entry criteria have been modified. The additional changes made improve the clarity and consistency of the protocol with its corresponding manuals and other ancillary documents. Changes to section 6 cohort A1 were as a result of dosing the sentinel patient.

RATIONALE for Amendment 3. These changes were made per request by and in agreement with FDA.

RATIONALE for Amendment 4. Several adjustments from the steering committee were implemented via administrative letters. This amendment seeks to incorporate these changes plus include the most recent steering committee recommendations on new cohorts (combinations and higher dose cohort EC2). Additional minor changes were made to improve the clarity and consistency of the protocol.

RATIONALE for Amendment 5. Fifty-five patients have been treated and the safety has been reviewed for the monotherapy and combination with pembrolizumab arms. There has been only 1 event that qualified for a technical DLT, which was a grade 3 abdominal pain, which was reviewed by the SSC and felt not to be dose limiting. Side effects have been mainly low-grade pain at the injection site, and the pharmacokinetics support minimal exposure to the cytotoxic agents in the formulation. We have therefore decided to simplify the dosing, to a fixed maximal amount of 175mL. Retreatment has also provided benefit. As a result, Sponsor will add a periodic maintenance dose of INT230-6. To capture the potential treatment benefit, the response criteria was amended to focus on iRECIST. This criteria was first introduced to capture the unique response pattern seen with immunotherapy. This study has demonstrated increases in tumor volume at the first scan which sometimes are associated with decreased contrast uptake. We see an influx of immune cells on the 1 month tumor biopsy. Sponsor therefore chose to focus on the iRECIST principles for assessing response. Safety data was reviewed by the Study Steering Committee and supported initiation of the phase 2 portion of the protocol with the combination of pembrolizumab and INT230-6. Additional minor changes were made to improve the clarity and consistency of the protocol. In collaboration with the National Cancer Institute Sponsor conducted research in murine cancer models combining INT230-6 with CTLA-4 antibodies. Sponsor's published results show strong synergy of the combination with tumor growth inhibition and survival. Amendment 4 discussed an outline of the cohort with a CTLA-4 antibody (cohort FEC). This amendment defines the specifics of the dosing and the CTLA-4 antibody being used in cohort FEC (ipilimumab).

RATIONALE for Amendment 6. The primary goal for Amendment 6 is to simplify the INT230-6 dose calculation and ensure patients enrolled are likely to benefit from study drug. 70 patients have been treated in IT-01 as of December 31, 2020. After SSC determination of safety in subjects receiving the fixed dose regimen and adequate characterization of the pharmacokinetics, we have removed the PK sampling. In addition, blood biomarker sampling has been discontinued while we focus on the tumor associated biomarkers. A new exclusion criterion was added to exclude subjects that have a tumor(s) > 15 cm (in longest diameter). Further, treatment plan for subjects with tumors that are 9 to 15 cm should be discussed with and approved by the medical monitor.

INVESTIGATOR'S AGREEMENT

I have read the IT-01 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Responsible Physicians	Ian B. Walters, MD Syed Mahmood, MD	61 Wilton Road Westport, CT 06880 Office Phone Number: Dr. Walters: (O) 203-221-7378 Dr. Walters: (C) 510-406-1911 Dr. Mahmood (O) 203-293-4224 Dr. Mahmood (C) 646-541-0149 Office Fax Number: 203-557-3023 Email: iwalters@intensitytherapeutics.com smahmood@intensitytherapeutics.com
Drug Safety Physician	Syed Mahmood, MD	See above
SAE Contact	ProPharma	Fax: 919-844-6948 clinicalsafety@propharmagroup.com

2. SYNOPSIS

Name of Sponsor Company: Intensity Therapeutics, Inc., Westport, CT
Name of Trial Management Company: Catalyst Clinical Research, LLC, Wilmington, NC (Catalyst)
Name of Investigational Product: INT230-6
Name of Active Ingredient: INT230-6 is supplied in a frozen, single use 10mL or 30 mL amber vial. Each vial contains: Cisplatin (CIS) 0.5mg/mL Vinblastine Sulfate (VBL) 0.1mg/mL Sodium 2-hydroxybenzoylaminooctanoate (SHAO) 10mg/mL (as free acid)
Title of Study: A Phase 1/2 Safety Study of Intratumorally Administered INT230-6 in Adult Subjects with Advanced Refractory Cancers
Study center(s): University of Southern California (USC), Princess Margaret Hospital (PMH), Fox Chase Cancer Center (FCCC), Johns Hopkins University (JHU), University of Massachusetts Worcester (UMass), Columbia University (CU), Houston Methodist (HM)
Principal Investigator: Lillian Siu (PMH) **Investigators:** Anthony El-Khoueiry (USC), Anthony Olszanski (FCCC), Nilofer Azad (JHU), Giles Whalen (UMass), Matthew Ingham (CU), Luis Camacho (HM)
Studied period (years): First subject enrolled: May 25, 2017 Estimated date last subject completed: July 2024 **Phase of development:** 1/2
Objectives: **Primary:** • The primary objective is to assess the safety and tolerability of multiple intratumoral doses of INT230-6 in subjects with advanced or recurrent malignancies. This will be assessed by the rate of > grade 3 Adverse Events (AEs) attributed to INT230-6 and not the underlying disease **Secondary:** • Assess the preliminary efficacy of INT230-6 by measuring the disease control rate (CR+PR+PD) as assessed by iRECIST • Characterize the pharmacokinetic profile of multiple doses the three INT230-6 components (CIS, VBL, and SHAO) after single and then multiple IT tumor site injections

- To characterize the overall safety profile of INT230-6

Exploratory:

- Characterize tumor response in injected and non-injected sites
- Evaluate various tumor and anti-tumor immune response biomarkers that may correlate with tumor response
- Evaluate overall response by iRECIST
- Characterized the pharmacodynamics (PD) profile of the INT230-6 formulation in subject treated and untreated tumors
- To assess the progression free and overall survival in subjects receiving INT230-6

Methodology:

This is a clinical study of a new investigational treatment that uses a novel drug product called "INT230-6" to treat advanced cancers. INT230-6 is a fixed ratio, multi-agent formulated drug product designed specifically for intratumoral (IT) injection. This study will determine the safety of administering a fixed volume of INT230-6 per cm^3 of tumor into superficial, followed by multiple deep tumors. A sentinel subject will be enrolled at the lowest dose and followed for 4 weeks prior to escalating or adding additional subjects. Gradual intra-subject dose escalation will be done to increase the total amount of drug delivered to enable large tumors to be fully dosed at the proposed drug to tumor ratios. Once escalation dosing cohorts are complete, if no MTD is obtained, then set a fixed total dose of INT230-6 to be used for all dosings. Using fixed doses INT230-6 treatment shall consist of an induction phase for certain cohorts along with a maintenance regimen. INT230-6 will also be tested in combination with additional agents such as checkpoint antibodies in escalation or fixed dosing.

Dose escalation

There are 6 cohorts of subjects in the escalation portion of the protocol where INT230-6 dosing is increased over 5 doses. These escalation cohorts are (A, B1, EA, EC, EC2 and DEC). **Enrollment in these cohorts is closed.**

Cohort 1 (A) was a superficial tumor cohort starting at up to 5.0 mL of total dose with a low tumor load (1:4 ratio of drug to tumor).

Cohort 2 (B1) was a deep tumor cohort starting at up to 5.0 mL and escalates the total dose and maximal dose per any one tumor.

Cohort 3 (EA) explored administration in superficial tumors every 2 weeks.

Cohort 4 (EC) explored administration in both superficial and deep tumors every 2 weeks at a higher drug load (1:2 ratio) and will escalate the total dose and maximal dose per any one tumor.

Cohort 5 (EC2) explored administration in both superficial and tumors every 2 weeks at an intermediate drug load (1:3 ratio) and will escalate the total dose and maximal dose per any one tumor.

Cohort 6 (DEC) combined pembrolizumab and escalating doses of INT230-6 and includes a safety lead-in cohort that doses INT230-6 in superficial tumors.

Fixed Dose INT230-6

There are 4 cohorts that use a maximum total fixed dose of INT230-6 of 175 mL for all 5 induction doses and along with maintenance doses. The maintenance dose is an INT230-6 dose given every 9 weeks +/- 10 days up to a maximum total dose amount of 175 mL. The fixed dose cohorts are EC3, DEC2, FEC and potentially GEC and each follows the Q2 week INT230-6 dosing schedule at drug load to tumor volume ratio of 1:3 into both superficial and deep tumors for tumor types defined in the appropriate supplement.

Cohort 7 (EC3) explores administration of INT230-6 monotherapy for any tumor type.

Cohort 8 (DEC2) combines a fixed dose of pembrolizumab with the same INT230-6 dosing regimen of EC3 as outlined in Supplement A.

Cohort 9 (FEC) combines a fixed dose of ipilimumab with the same INT230-6 dosing regimen of EC3 as outlined in Supplement A.

Future Cohort 10 (G cohort) combines INT230-6 with other molecules.

Additional cohorts can be added depending on review of safety data by the Study Steering Committee. All cohorts and decisions to escalate the dose and introduce new subject populations will be governed by the Study Steering Committee (SSC).

Expansion cohorts

The SSC reviewed the safety and any available biologic and/or tumor measurement data, a decision to open expansion cohorts of 10-16 subjects with a single tumor type was made. These groups will allow for better point estimates of the safety and preliminary efficacy in a homogenous population.

Number of subjects (planned):

The sample size (estimated to be between 100 and 175 subjects) during dose escalation cannot be precisely determined but depends on the observed toxicity. In expansion cohorts, up to 16 subjects will be treated at fixed doses in a tumor type, to provide preliminary assessment of tumor response, in addition to safety assessment.

Diagnosis and main criteria for inclusion:

Key Inclusion Criteria

1. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
2. Men and Women $\geq$ 18 years of age on the day of signing consent.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2; **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for ECOG criteria)**.
4. Populations: INT230-6 will be injected into deep or superficial tumors for subjects with histologically or cytologically confirmed advanced or metastatic cancers; **(for pembrolizumab**

and ipilimumab combinations please see supplements DEC/DEC2 and FEC for Populations).

5. Includes subjects with loco-regional disease that have relapsed/recurred within 6 months of chemo-radiation and who have no standard of care.
6. Subjects with metastatic disease who have failed one or more approved standard therapies, or have no alternate approved therapy available. Failure of all approved therapies that have a modest or marginal impact on survival is not required as long as the treating physician believes that treatment on study is appropriate for the subject and documents that the subject elects to defer the approved therapies.

   Note: There is no limit on the number of prior therapies that a patient (subject) may have received prior to enrollment in any cohort.
7. Subjects must have measurable disease by iRECIST 1.1 criteria including one target tumor for injection by the local site investigator/radiology. Superficial tumors must have one tumor greater than or equal to 1.0 cm, deep tumors greater than or equal to 1.0 cm (as measured by caliper (for non-injected tumors only) or image guidance). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Subjects must have a minimum of one injectable lesion as determined by the investigator (for superficial tumors) or radiologist (deep tumors).
9. Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer: systemic or IT) must have been completed at least 4 weeks prior to dosing (with the exception of kinase inhibitors or other short half-life drugs, a 2 week washout is acceptable prior to treatment) and all adverse events have either returned to baseline or stabilized.

   Note: Subjects who have received prior platinum therapy are eligible irrespective of their response.
10. Prior systemic radiation therapy (either IV, intrahepatic or oral) completed at least 4 weeks prior to study drug administration; **(for ipilimumab combination please see supplement FEC exclusion criteria).**
11. Prior focal radiotherapy completed at least 2 weeks prior to study drug administration.
12. Prior major treatment-related surgery completed at least 4 weeks prior to study drug administration.
13. No prior primary or metastatic brain or meningeal tumors unless clinically and radiographically stable as well as off steroid therapy for at least 2 months.
14. Life expectancy ≥8 weeks; **(for ipilimumab combination please see supplement FEC inclusion criteria).**
15. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP)
    b. A WOCBP subject who may become pregnant or who are sexually active with a partner and who could become pregnant agrees to use an effective form of barrier contraception during the study and for at least 180 days in monotherapy; **(for pembrolizumab and**

ipilimumab combinations please see supplements DEC/DEC2 and FEC for pregnancy criteria). (Male subjects must agree to use contraception and refrain from sperm donation during the study for 180 days after administration of study drug.)

16. Have adequate organ function as defined by the below screening laboratory values that must meet the following criteria:
    a. WBC ≥2000/μL (≥2 x 10^9/L).
    b. Neutrophils ≥1000/μL (≥1 x 10^9/L); **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for neutrophil criteria)**.
    c. **For subjects with planned superficial only injections:** PT, PTT/aPTT, and INR ≤1.5 × ULN, Platelets ≥70x10^3/μL (≥ 70 x 10^9/L), Hemoglobin ≥8 g/dL
    d. Creatinine within the institution's laboratory upper limit of normal or calculated creatinine clearance >50 ml/min; **(for pembrolizumab combination please see supplements DEC/DEC2 for creatine criteria)**.
    e. ALT (SGOT)/AST (SGPT) ≤2.5 x ULN without, and ≤ 5 x ULN with hepatic metastases.
    f. Bilirubin ≤2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin <3.0 mg/dL (<52 μmol/L); **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for bilirubin criteria)**.
    g. **For subjects with planned deep tumor injections**: PT, PTT/aPPT, and INR within normal limits; Platelet count ≥100,000/μL; hemoglobin ≥ 9 g/dL.

    Note: ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal.

    [1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

17. Additional criteria for combination arms can be found in the appropriate supplements.

Key Exclusion Criteria

Subjects who exhibit any of the following conditions at Screening will not be eligible for admission into the study: **See DEC/DEC2, FEC, or potentially GEC supplements for additional criteria specific to those cohorts.**

1. History of severe hypersensitivity reactions to cisplatin or vinblastine or other products of the same class.
2. Other prior malignancy, except for adequately treated basal or squamous cell skin cancer or superficial bladder cancer, or any other cancer from which the subject has been disease-free for at least 2 years.
3. Subjects with tumors >15 cm (in longest diameter). Treatment plan for subjects with tumors that are 9 to15 cm must be discussed with and approved by the medical monitor.
4. Underlying medical condition that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.
5. Concurrent medical condition requiring the use of immunosuppressive medications, or systemic corticosteroids (topical steroids are permitted); systemic corticosteroids must be

discontinued at least 4 weeks prior to dosing. Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Non-absorbed intra-articular steroid injections will be permitted; or use of other investigational drugs (drugs not marketed for any indication) within 30 days prior to study drug administration. Use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

6. For deep tumor cohorts, subjects who require uninterrupted anticoagulants of any type, on daily aspirin therapy or NSAIAs.
7. Use of other investigational drugs (drugs not marketed for any indication) within 28 days prior to study drug administration.

Pregnancy Exclusion:

A WOCBP who has a positive urine pregnancy test (e.g., within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

NOTE: For specific inclusion/exclusion criteria relating to a potential combination, please refer to the combination specific supplement.

Investigational product, dosage and mode of administration:

INT230-6 administered intratumorally, a fixed combination of cisplatin, vinblastine and SHAO

Duration of treatment:

In A1 and B1 cohorts, subjects received injections monthly for up to 5 doses of INT230-6 (4 months). In E cohorts, injections are given every 2 weeks for up to 5 doses. Cohorts EC3, DEC2, FEC and potentially GEC will utilize the once every 2 weeks dosing for 5 doses followed by maintenance dosing once every 9 weeks +/- 10 days until CR, PD or 2 years, whichever is first. Given the short half-life of the components of INT230-6, safety follow up post the last dose of treatment is 28 days for monotherapy cohorts. Subjects are followed regularly until progression and/or start of subsequent anti-cancer therapy. Afterwards subjects will transition to a less frequent survival follow up. The total expected duration of the study is 5 years.

Reference therapy, dosage and mode of administration:

NA

Criteria for evaluation:

Efficacy:

Since this is a locally administered product, it allows for multiple efficacy analyses. The primary efficacy measure will be disease control rate (CR+PR+SD) as assessed by iRECIST. Since immune system activation is expected from preclinical studies, the trial will collect samples from the peripheral blood and from tumors to look at markers of activation. Furthermore, observing tumor shrinkage in non-injected bystander tumors would also indicate potential immune activation. In order to take the whole picture into account, the exploratory endpoints will look at overall tumor response, time to progression and overall survival.

Safety:

Assessment of safety will be determined by ongoing review of clinical laboratory tests (blood and urine sampling for clinical laboratory parameters), pregnancy testing, Eastern Cooperative Oncology Group (ECOG) performance status, physical examination including vital sign measurements, any needed or completed electrocardiogram (ECG), and adverse events.

Pharmacokinetic:

Individual subject PK profiles will be tabulated following the intratumoral administration of INT230-6. Sponsor expects that the PK profiles of three analytes SHAO/CIS/VIN given intratumorally may have significant inter-subject variability. This variability is due to the expected release kinetics into the blood stream following intratumoral dosing of INT230-6 via a) absorption into the tumor's blood vasculature and b) from release from tumor microenvironment over time. Final analysis of the PK at the doses given indicates that only 5% of the active ingredients for a given dose are present in the blood. The concentration is very consistent and have a meaningful dose response. As a result, the SSC determined that PK sample collection is no longer necessary at these dose levels in Amendment 6.

Statistical methods:

Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, and dose and coded according to version 19.1 of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG listings will be evaluated by the investigator and abnormalities, if present, will be listed.

Adverse Events will be summarized for all reported data and by study period: a) up to and including 28 days post last dose of initial treatment, and b) from first dose of re-initiation of treatment, for subjects who re-initiate study therapy while in follow-up, up to 28 days post-dose of the last re-treatment dose for all monotherapy cohorts. Please see cohort supplements for combination follow up.

Efficacy Analyses: In order to perform preliminary evaluation of anti-tumor activity, injected tumor response (ITR), bystander tumor response (BTR) overall objective response (ORR), and disease control rate (DCR) will be tabulated by frequency distribution overall and by tumor type.

For DCR in each expansion cohort, an exact binomial 95% confidence interval will be determined by Clopper-Pearson method. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using Kaplan-Meier method; PFS will be similarly summarized. Individual tumor measurements, tumor burden and % changes in tumor burden will be listed. Changes in tumor burden will be presented graphically.

With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type, the 90% confidence interval for a disease control rate would be (3.4% to 36%) if 2 subjects (12.5%) had a response, (5.3% to 42%) if 3 (19%) subjects had a response, (9.0% to 48%) if 4 (25%) subjects had a response, and (13.2% to 54.8%) if 5 (31%) subjects had a response.

Pharmacokinetic Analyses:

A final PK analysis section will be included in the final clinical study report. The release kinetics of each analyte is not expected to be uniform across subjects. Sponsor shall assess the blood concentrations of the three analytes for each subject at the first cycle. Sponsor shall correlate the systemic measurement (Cmax, AUC) of the 3 analytes to measured markers of systemic toxicity (in particular renal and blood – the known toxicities of the two active agents; cisplatin & vinblastine). Human plasma will be analyzed for the concentration of vinblastine and SHAO using validated LC/MS/MS methods, and for cisplatin using a validated ICP-MS method. For pharmacokinetic profiling platinum drugs, total platinum levels in subject plasma or urine are routinely determined by spectroscopy methods as a surrogate. Thus an ICP-MS method will be developed for this study to measure total platinum in human samples as a surrogate for cisplatin.

In addition, scatter plots of Cmax and AUC(TAU) versus INT230-6 dose volume will be provided for the first dosing. Dose proportionality per subject normalized to tumor volume will be assessed, by estimating the slope of linear regression of SHAO/CIS/VIN log(Cmax) on log(dose) and of log(AUC(TAU)) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameter (slope of the linear regression) will be calculated for Cmax and AUC (TAU). Summary statistics for trough (Cmin) concentrations will be tabulated by dose and study cycle. Plots of Cmin vs. cycle will be assessed for Cohorts A1, B1 versus E Cohorts provided by dose. For D and F cohorts refer to the appropriate supplements. Pharmacokinetic concentrations from sparse samples will be listed and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report. The SSC will evaluate whether PK sample collection can be stopped after a certain number of patients have been treated in cohort DEC2 and cohort FEC.

Exploratory Biomarkers (Immune Function and others) Analyses: Summary statistics for immune function and other exploratory markers, such as but not limited to flow cytometry outcomes, cytokines, quantitative immunoglobulins, quantitative inflammatory infiltrates, T-cell repertoire and their changes (or percent changes) from baseline will be tabulated by cycle visit and dose to assess pharmacodynamic effects. In addition, the time course of biomarker outcomes will be investigated graphically, by summary plots (i.e., box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored. Possible associations of various biomarkers measures (baseline value or change from baseline) with clinical outcome (e.g., tumor response) may will be explored based on data availability, using response-evaluable subjects, to assess explore predictive markers in tumors. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g., tumor-based markers may be similarly presented, depending on data availability.

Administrative interim analyses on safety and efficacy or on PK, and selected biomarkers may be provided at several times prior to completion of the study in order to facilitate program decisions and to support study presentations or publications.

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List of Abbreviations and Definitions of Terms

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
APC	Antigen-presenting cells
ALT	Amino Alanine Transferase
AST	Aspartate Aminotransferase
AUC	Area under the curve
BOR	Best overall response
BP	Blood Pressure
BTR	Bystander tumor response
BUN	Blood Urea Nitrogen
cc or cm^3	Cubic centimeter
Cmax	Maximum blood concentration of an analyte
CIS	Cisplatin
CR	Complete response
CRF or eCRF	Case report form or electronic case report form
CT	Computed tomography
CTA	Clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cells
DCF	Data clarification form
DCR	Disease control rate
dL	Deciliter
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOT	End of Trial
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose - positron emission tomography
FIH	First in human
GCP	Good clinical practices

Abbreviation or Specialist Term	Explanation
GLP	Good laboratory practices
GMP	Good manufacturing practices
HIPPA	Health Information Portability and Accountability Act
HMGB1	High Mobility Box Group 1
HR	Heart Rate
ICF	Informed consent form
ICH	International Council on Harmonization
IFN	Interferon
IP	Intraperitoneal
IRB/IEC	Institutional review board/independent ethics committee
irAE	Immune related adverse event
iCPD	iRECIST confirmed progressive disease
iRECIST	immune Response Evaluation Criteria in Solid Tumors
iUPD	iRECIST unconfirmed progressive disease
IT	Intratumoral
ITR	Injected tumor response
IV	Intravenous
LDH	Lactic Acid Dehydrogenase
mAb	Monoclonal antibody
MeDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MSI-CRC	Microsatellite Instable Colorectal Cancer
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
ng	Nanogram
NSAIA	Non Steroidal Anti-inflammatory Agent
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1

Abbreviation or Specialist Term	Explanation
PFS	Progression free survival
PK	Pharmacokinetic
PMH	Princess Margaret Hospital
PR	Partial response
PVG	Pharmacovigilance
RB	Rose Bengal
REB	Review ethics board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous
SCID	Severely compromised Immune deficient
SD	Stable disease
SHAO	8-((2-hydroxybenzoyl)amino)octanoate (sodium salt form)
SLD	Sum of longest diameters
SNP	Single nucleotide polymorphism
SOP	Standard operating procedures
SSC	Study Steering Committee
TBD	To be determined
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
ULN	Upper Limit of Normal
UM	University of Miami
USC	University of Southern California
VBL	Vinblastine Sulfate or Vinblastine
WOCBP	Women of childbearing potential
WHODD	World Health Organization Drug Dictionary

3. INTRODUCTION AND RATIONALE

3.1. Background

This trial is a phase 1/2 safety study of intratumorally administered INT230-6 in adult subjects with Advanced Refractory Cancers. This trial is an adaptive open label exploration of INT230-6. The trial enrolls any advanced cancer subjects with an accessible tumor for injection who have failed or are not a candidate for approved therapies. The trial will be governed by a Study Steering Committee (SSC) who will review the data and help to adapt the protocol to minimize the number of subjects need for each stage. Since administration of the investigational material is direct to the tumor, biopsies of the tumor before and during treatment will enable assessment of immunologic effects in the tumor and help to understand possible pharmacodynamic effects.

In the phase 1 portion INT230-6 was given in escalating amounts to the subject by increasing the number of tumors injected, increasing the total volume per tumor injected and increasing the concentration by tumor. Many of these escalations were done with intra-subject increases. The drug components are well known, but this combination and mode of administration had not been delivered before, therefore the trial sought to begin with tumors that are superficially palpable to establish safety data before progressing to tumors which required imaging guidance. The central objective of the phase 1 portion of the study was to characterize the safety and tolerability of INT230-6 alone and in combination with other therapeutic agents. The SSC has reviewed the safety and preliminary efficacy data from subjects in the phase 1 portion of the study. The SSC recommended initiation of phase 2 expansion cohorts of subjects.

In the phase 2 expansion cohort portion of the study, the objective will be to characterize INT230-6's effect on the disease control rate as monotherapy and in combination with other drugs. Given the mechanism of action, Sponsor expects measurement of both the injected tumor responses as well as any bystander (untreated) tumor responses will be straightforward.

Cisplatin (as an IV product) is considered an irritant at concentrations <0.5 mg/mL. Vinblastine sulfate is considered a vesicant when dosed IV at 1 mg/mL. In Sponsor's local tolerance toxicology study both 2 and 5 mL of INT230-6 were injected directly in 3 different tissue types of healthy dogs (subcutaneously, intraperitoneal and intrahepatic) over 8 days. There were no gross or microscopic vessication observations due to INT230-6 in any tissues when given locally. The current status of the safety aspects of the drug product and this study, including clinical adverse events, can be found in the investigator's brochure. Please refer to the latest version of the investigator's brochure for safety information.

3.2. Systemic chemotherapy

Systemic chemotherapy has formed the mainstay of the treatment of solid tumors from 1980s and onward offering the ability to kill rapidly dividing cells. Many cytotoxic agents have components of their mechanism that involve immune activation (Galluzzi_2015 (1)). Yet when tumors are shrinking during the course of treatment, there is little evidence of a memory immune effect that is maintained. There are several hypotheses for this observation. While chemotherapy may be pro-inflammatory, there are many anti-inflammatory signals in the tumor microenvironment (checkpoints, regulatory cells, etc.). Recent approaches have combined chemotherapy with checkpoint inhibition to see if this aspect could yield a more robust immune effect (Rizvi_2016 (2)). Also, systemic administration of these agents results in impairment of bone marrow function. It is

also speculated that the kinetics of tumor cell death are slower than the kinetics of the innate immune system. In other words, the innate system clears tumor antigens faster than they can be processed by the adaptive immune system (Obeid_2007 (3)). However, given the number of tumors that remain sensitive to chemotherapy, this approach continues to be utilized and efforts to minimize impact on normal tissues are being studied.

3.3. Local administration of cytotoxic agents

In an effort to spare subjects from the side effects of systemically administered chemotherapy, researchers have delivered drugs directly to the tumor. In animal models (typically localized disease), this has shown some promise. However, in multiple clinical trials in advanced cancer patients, these approaches have failed to show superior outcomes compared to systemically administered drugs (Lammers_2006 (4)). This is likely due to the poor diffusive and dispersive ability of these prior intratumoral formulations. For the most part cytotoxic agents are hydrophilic and do not disperse throughout the tumor. Research by the Sponsor indicates that intratumoral delivery of aqueous solutions are ejected from the tumor. In addition, since many cancer cells could be circulating or residing in small amounts in other tissues, localized approaches often fail to treat the full extent of the disease. IV administration can disperse drug broadly via the bloodstream; however, given systemic effects, only low drug doses ultimately reach the tumor and even less is taken up by the cancer cells. Typically, cytotoxic drugs require active transport to enter cells, a process mediated by receptors. Receptor transport is slow and efflux pumps within cancer cells often remove the drugs. As a result of negative trials, registrational efforts for intratumoral delivery approaches of cytotoxic agents has been largely abandoned.

3.4. Immunotherapy

The concept of cancer immunotherapy has been around for many years, but its use is limited to a few settings (BCG in bladder and high dose IL-2 in melanoma). In the 2000's with the discovery of checkpoints and their role in suppressing anti-tumor immunity research on cancer treatments incorporating the immune system accelerated. CTLA4 antibodies demonstrated that by blocking cancer's negative signal, a proportion of metastatic melanoma patients could achieve a long-lasting response off of treatment. Response to these treatments seemed to require an inflamed tumor and/or a high mutational burden in order for effect use of checkpoint inhibitors (Snyder_2014 (5)). Further improvement on this concept was seen with the discovery of anti-PD-1 antibodies which seem to be more selective in activating the immune system and more capable of promoting an immune response than CTLA4 molecules. Anti-PD-1 therapy has seen promising activity in a variety of tumor types and has been approved for use in melanoma, lung, urothelial, hepatocellular, gastric, cervical, hematologic, microsatellite unstable, and renal cancers (Pembrolizumab_Package_Insert (6)). Yet many patients still do not respond to immunotherapy treatment. Some improvement in melanoma can be seen if both approaches are given simultaneously (anti-CTLA4 combined with anti-PD1).

3.5. Drug Product INT230-6

INT230-6 is multi-component, new drug product specially formulated for intratumoral administration. The technology used in the product facilitates dispersion of drugs throughout the

tumor and diffusion into cancer cells. INT230-6 is comprised of a cell permeation enhancer molecule with two, potent anti-cancer payloads (cisplatin and vinblastine) in fixed ratio. The enhancer is not covalently bound to the drugs. Typically, the permeability of cancer cell membranes is more fluid than healthy cells (Sok_2002 (7)). Thus, the presence of the enhancer allows for increased passive diffusion of the therapeutic agents into the cancer cells. Both cisplatin and vinblastine function inside the cell. Vinblastine acts by binding to tubulin leading to depolymerization of the microtubule and mitotic arrest. This interrupts the cell cycle and stops replication of the cell (Vinblastine_Package_Insert (8)). Cisplatin has a proposed mechanism of action that introduces a defect in the DNA, causing DNA damage and ultimately apoptosis (Dasari_2014 (9)). Once the two molecules diffuse into the cell, the permeation enhancer is diluted from the drugs, which remain in higher concentration within the cell. The combination of tubulin inhibition and cell apoptosis cause significant cell death throughout the injected tumor. Data generated by the Sponsor show increased influx of dendritic and T-cells into the tumor. The result is a robust CD8 response that clears the remaining live tumor cells. Results from studies (Walters_2015 (10)) also show a CD4/CD8 memory response is also induced that can protect treated animals against re-exposure to the same cancer cell line. This approach offers patients the potential for a targeted and generally nontoxic therapy – one that kills a large portion of the injected tumors - stimulates a systemic immune response to clear the tumor that eliminates distal tumor cells and prevents recurrences.

3.6. Rationale for IT-01 Study Design

3.6.1. Preclinical data with INT230-6 in cell lines

INT230-6 has been studied in vitro with multiple patient derived and cancer cell lines. In Caco-2 monolayer studies, INT230-6 has demonstrated the ability to diffuse drugs through the membrane without disruption of the cell surface architecture. The drugs also penetrate into the nucleus. A critical ratio of enhancer to drug ratio is required to achieve this transport. In addition, Sponsor studied the release of LDH by cells treated with INT230-6. Results showed that when the drugs enter the cell, the membrane integrity is intact and LDH is not released (Intensity_in_vitro_e237 (11)). INT230-6 thus has strong dose dependent, growth inhibition of tumor cells.

3.6.2. Preclinical data with INT230-6 in vivo models

Intratumoral drug dispersion of formulations in tumors with and without cell penetration enhancers was evaluated using BxPc3 pancreatic tumor xenographs. A butterfly needle was placed into the center of a tumor (>500 mm3). Various amounts of either INT230-6 (N=8) or aqueous cisplatin (drug) (N=6) preparation with 3 drops of India Ink (~150 µL/10mL in each preparation) were injected over 90 seconds using metered pump at drug dose to tumor volume ratios of approximately 1:11 or 1:5. The needle was left in the tumor for an additional 30 seconds following injection. After euthanasia, tumors were removed, dissected, then fixed and sliced for Haemotoxylin and Eosin (H&E) staining.

The intratumorally dosed cisplatin without the enhancer showed substantial leakage from the injected tumors into the interstitial space between the tumor and skin. The injected INT230-6 appeared to be fully absorbed into the tumor (**Figure 1**). INT230-6 plus ink dispersed throughout the tumor as seen in (**Figure 2**); however, drug without the penetration enhancer was poorly absorbed into the tumor and almost no ink is observed to be absorbed within the tumor. This

advantage in dispersion (using measured dispersion diameters) for the INT230-6 preparation was highly significant ($p<0.005$) when compared to the cisplatin/vehicle group.

Figure 1: Leakage from the intratumoral injection site of the preparations with and without the SHAO penetration enhancer.

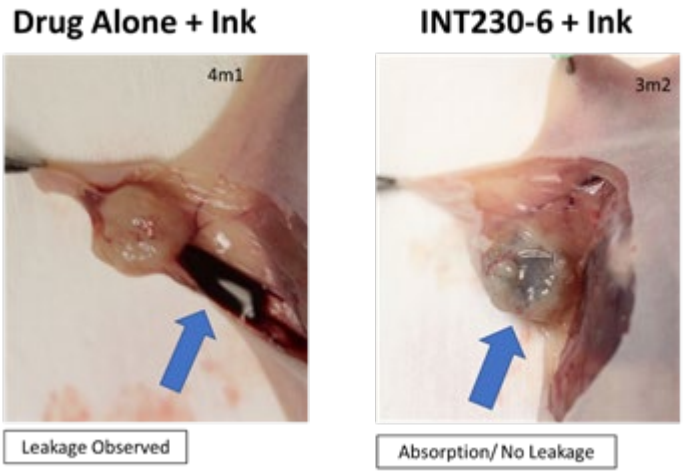
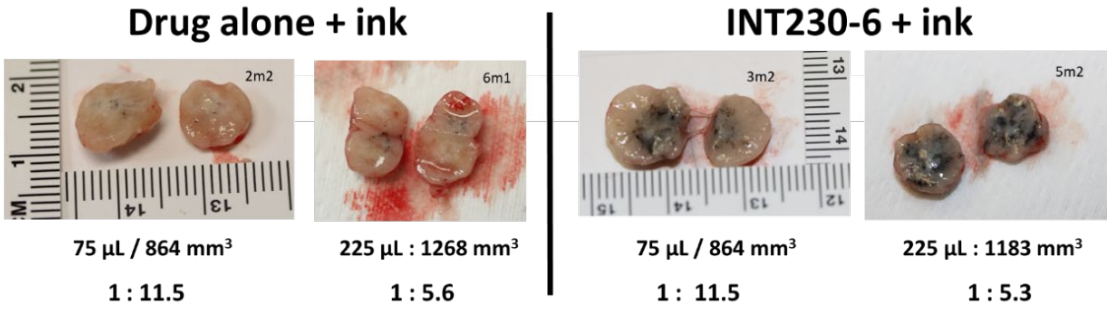


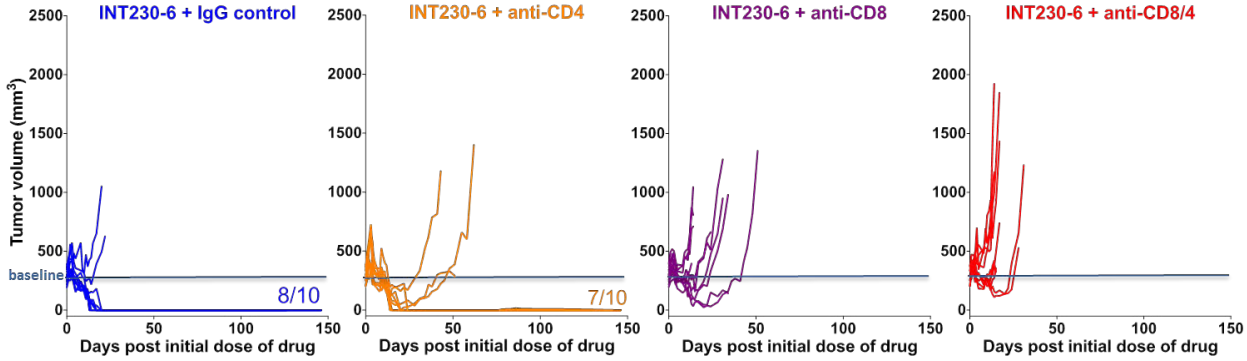
Figure 2: Comparison of dispersion following one-time, intratumoral injection of 75 or 225 µL for 90 seconds of drug only with ink compared to INT230-6/ink.



INT230-6 demonstrated reduction in tumor burden that was statistically superior to no treatment controls in immune competent BALB/C mouse models. Sponsor, in collaboration with the National Cancer Institute (NCI), investigated the impact on INT230-6 on promoting a T-cell response. Colon-26/CT26/4T1 studies all reveal strong anti-tumor activity of INT230-6. Key features include the ability to reduce tumor burden from baseline in the majority of animals, high rates of complete responses that are dependent on CD8 T-cell activity, an ability to shrink and in some cases clear distal untreated tumors, and the ability to induce long term immunity which is co-dependent on CD4 and CD8 T-cells. Biopsies of tumors over time indicate recruitment of dendritic cells and lymphocytes to the tumor within 10 days of treatment (Bloom_2015 (12)) Walters_2015 (10)). Presumably these are facilitating antigen presentation of tumor antigens expressed by intact tumor cells that are no longer replicating and are undergoing cell death. Sponsor suggests that antigen processing is occurring with evidence of cross priming. Mice, given colon cancer SC using Sponsor's technology achieved a complete response. Animals rechallenged with a 4T1 breast cancer inoculation in the absence of any new treatment became more resistant to this challenge than naïve animals with no drug therapy. There are publications in the literature of shared antigens

between different tumor types (Bright_2014 (13)). Further experiments indicate that responses in the injected tumors are partially due to enhanced cytotoxicity during the first week after treatment, but in part due to presence of CD8 T-cells. When CD8 T-cells are depleted prior to treatment animals see regression of their tumors initially then regrowth with no complete responders. These results compare to 80% complete responders if CD8 T-cells are present (see Figure 3).

Figure 3: Activity of INT230-6 in Colon26 model, results of different treatment groups with and without intact T-cells.



Depletion study results; depletion prior to treatment with INT230-6 - (Panel A) IgG control i.e., no depletion 8/10 complete responses, (Panel B) CD4 cell depletion 7/10 complete responses, (Panel C) CD8 cell depletion 0/10 complete responses, or (Panel D) dual CD4/CD8 cell depletion 0/10 complete responses.

Multiple preclinical studies support consecutive injections (up to 5 daily injections in a cycle) into the same nodule (approximately 300mm^3). In addition, studies support repeating the treatment cycle after a period of rest yields improved efficacy outcomes without an increase toxicity. In fact, there was some weight loss in the first cycle that resolved and nearly non-existent in subsequent cycles. A preclinical study showed that after 3 days of injection 75% of a tumor became necrotic while the animals continued to be injected without additional complications. The Sponsor believes that the totality of preclinical data demonstrating no observed or increased toxicity with significantly increased efficacy justifies in the protocol using tumor injection with multiple cycles of tumor reinjection.

3.6.3. Checkpoint blockade

Nature has created checkpoints on the immune system to regulate the activity of the immune cells. These pathways are crucial for self-tolerance to prevent the immune system from attacking healthy cells indiscriminately. Large pharmaceutical companies such as Merck, Roche, AstraZeneca, Pfizer and Bristol Myers Squibb (BMS) have developed new types of anti-cancer anti-body drugs with the ability to modify and block the checkpoints on the immune system. These large molecules are the current immunotherapy that have shown long term durable responses in patients.

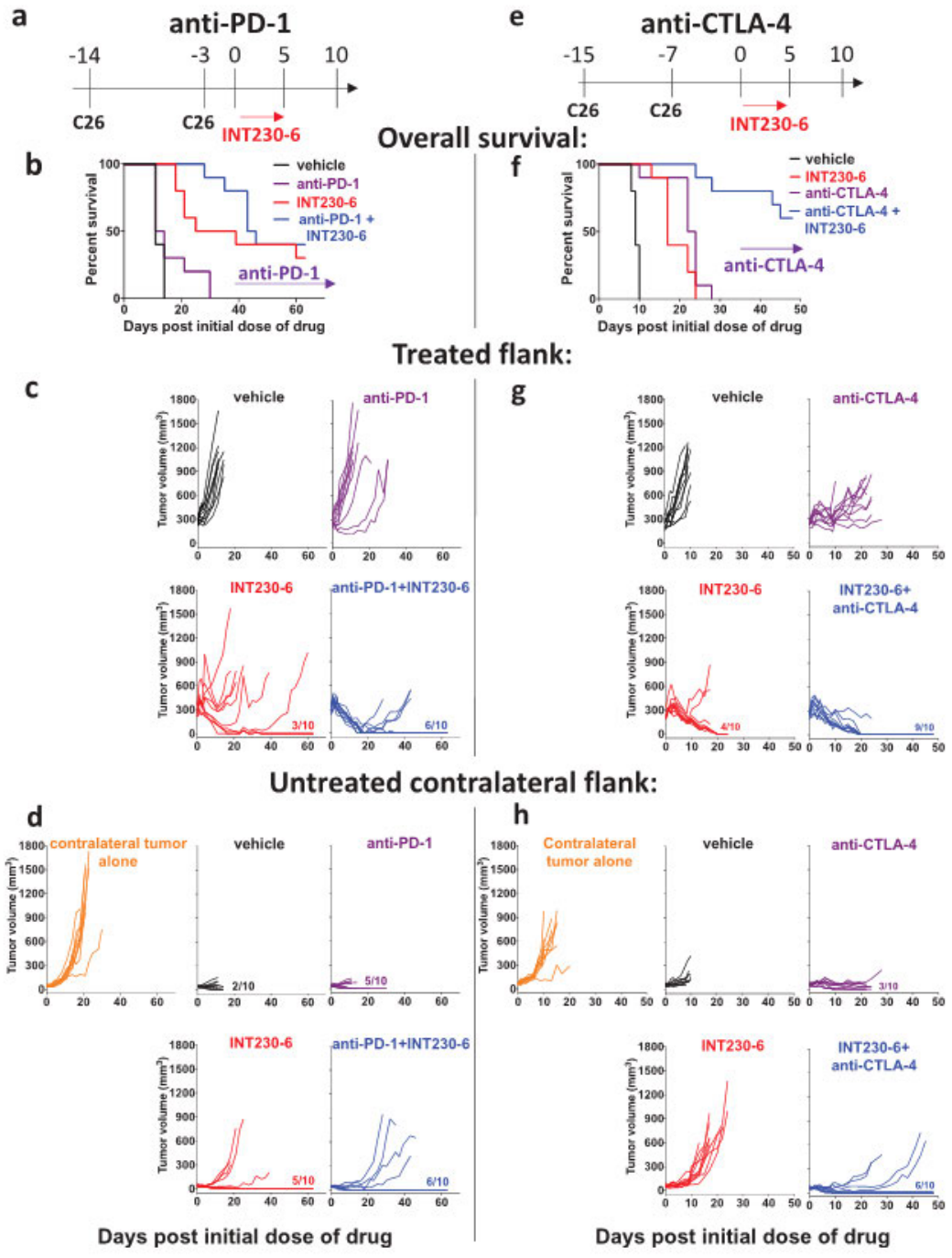
However, these checkpoint molecules have shown success in only some types of cancers – often those that are the most mutated. Sales of these drugs are currently in the billions of dollars. Approved

checkpoint inhibitors block CTLA4 and PD-1 and PD-L1; however, many more targets are in clinical development.

Our belief was that our products would be synergistic with checkpoint inhibitors. We along with our partners at the National Cancer Institute conducted experiments to demonstrate that our lead drug INT230-6 is synergistic with these new checkpoint blockage drugs. Results show strong benefit in regressing tumors with the combination of INT230-6 and checkpoint inhibitors and improving survival. The data from the combination of INT230-6 with both anti-PD-1 or CTLA-4 antibodies in a dual tumor (metastatic) cancer mouse cancer model. The data was generated by our partners at the National Cancer Institute and under our CRADA.

Figure 4: Tumor Growth Inhibition Curves Combining INT230-6 with Checkpoint Inhibitors

a) Illustration of INT230-6 and anti-PD-1 treatment regimen (top). (26 (1x10^6) were inoculated into the right flank (day - 14). Contralateral tumors were inoculated 11 days after primary tumors (day - 3). Primary tumors were treated with INT230-6 (50 µl / 400 mm^3 tumor, 5 sequential days) starting on day 0. Average primary tumor volume on Day 0 was 290mm^3 and average contralateral tumor volume was 42mm^3• Anti-PD-1 treatment (100µg) was given on day 0, 3, 7 and 10. b) Kaplan-Meier plot (below illustration) and individual responses of c) treated (ipsilateral) (middle) and d) contralateral flank (bottom) are shown of vehicle (black), anti-PD-1 (purple), INT230-6 (red) and anti-PD-1+ INT230-6 (blue) treatment as well as contralateral tumor only control (orange, n = 10 / group). Fractions (e.g., 3/10) indicate the number of mice that completely lost tumor that the indicated flank. Log-rank test was significantly different between vehicle and INT230-6 ($p < 0.0001$), vehicle and anti-PD-1 + INT230-6 ($p < 0.0001$), anti-PD-1 and INT230-6 ($p < 0.01$) and anti-PD-1 and anti-PD-1 + INT230-6 ($p < 0.0001$). Two-way ANOVA with Sidak's multiple comparison test of growth curves showed that untreated contralateral tumors only were significantly different ($p < 0.0001$) from all groups on secondary site. Furthermore, vehicle was significantly different ($p < 0.0001$) from INT230-6 and INT230-6+anti -PD-1 on day 8 and 11 on the primary site. Vehicle was significantly different ($p < 0.05$) from INT230-6+anti-PD-1 on day 11 on the secondary site. INT230-6 was significantly different anti-PD-1 or INT230-6+anti-PD-1 on day 16 ($p < 0.01$) and day 18 ($p < 0.001$) on the primary tumor site. INT230-6 was significantly different ($p < 0.01$) from INT230-6 + anti-PD-1 on day 18 on the contralateral site. Anti-PD-1 was significantly different ($p < 0.0001$) from INT230-6+ anti-PD-1 on day 8 and 11 at the primary site only. e) Illustration of INT230-6 and anti-CTLA-4 treatment regimen (top). C26 (l x10^6) tumor cells w ere inoculated into the right flank (day -15). Contralateral tumors were inoculated 7 days after primary tumors (day - 8). Primary tumors were treated with INT2306 (50 µl/400 mm^3) tumor, 5 sequential days) starting on day 0. Average primary tumor volume on day 0 was 250mm^3 and average contralateral tumor volume was 60 mm. Anti-CTLA-4 treatment (100 µg) was given on day 0, 3 and 6. f) Kaplan-Meier plot (below illustration) and individual responses of g) treated (ipsilateral) (middle) and h) contralateral flank (bottom) are shown of vehicle (black), anti -CTLA-4 (purple), INT230-6 (red) and anti-CTLA-4+ INT230-6 (blue) treatment as well as contralateral tumor only control (orange, n = 10/group). Fractions (e.g., 4/10) indicate the number of mice that completely lost tumor in the indicated flank. Log-rank test was significantly different between vehicle and all other groups ($p < 0.0001$), INT230- 6 and anti-CTLA-4+ INT230-6 ($p < 0.0001$) and anti-CTLA-4 and anti-CTLA-4+ INT230-6 ($p < 0.0001$). All experiments were performed twice. Two-way ANOVA with Sidak's multiple comparison test of growth curves showed that untreated contra-later tumors were significantly different ($p < 0.0001$) from all other groups on the contralateral site. Vehicle was significantly different ($p < 0.0001$) from INT230-6, antl-CTLA-4 and antl-CTLA-4+ INT230-6 on day 6 and 8 at the primary (ipsilateral) site. Vehicle was significantly different from antl-CTLA-4 (day 8: $p < 0.0001$) and antl-CTLA-4+ INT230-6 (day 6: $p < 0.001$, day 8: $p < 0.0001$) at the contralateral site. INT230-6 was significantly different from antl-CTlA-4 at the primary site (day 8: $p < 0.05$, day 10: 0.001) and secondary site (day 8: $p < 0.01$, day 9: $p < 0.001$, day 10: $p < 0.0$ 001). INT23o-6 was significantly different from antl-CTLA-4 + INT230-6 at the contralateral site only (day 6: $p < 0.05$, day 8- 10: $p < 0.0001$). Anti-CTLA-4 was significantly different from an tl-CTLA-4 + INT230-6 at the primary site (day 8: $p < 0.01$, day 9: $p < 0.05$, day 10: $p < 0.0001$) and at the secondary site (day 6: $p < 0.05$).


a
anti-PD-1
-14
-3
0
5
10
C26
C26
INT230-6
e
anti-CTLA-4
-15
-7
0
5
10
C26
C26
INT230-6
Overall survival:
b
Percent survival
vehicle
anti-PD-1
INT230-6
anti-PD-1 + INT230-6
anti-PD-1
Days post initial dose of drug
f
Percent survival
vehicle
INT230-6
anti-CTLA-4
anti-CTLA-4 + INT230-6
anti-CTLA-4
Days post initial dose of drug
Treated flank:
c
vehicle
anti-PD-1
INT230-6
anti-PD-1+INT230-6
Tumor volume (mm³)
3/10
6/10
g
vehicle
anti-CTLA-4
INT230-6
INT230-6+ anti-CTLA-4
Tumor volume (mm³)
4/10
9/10
Untreated contralateral flank:
d
contralateral tumor alone
vehicle
anti-PD-1
INT230-6
anti-PD-1+INT230-6
Tumor volume (mm³)
2/10
5/10
5/10
6/10
Days post initial dose of drug
h
Contralateral tumor alone
vehicle
anti-CTLA-4
INT230-6
INT230-6+ anti-CTLA-4
Tumor volume (mm³)
3/10
6/10
Days post initial dose of drug

3.7. Prior Experience with Similar Investigational agents

Companies have recently reported results from locally administered (IT) products. These companies report that local administration of their products is able to demonstrate distal responses through presumed immune activation. These IT approaches claim good safety of the procedure and translation from preclinical models to the clinical setting.

The firm Oncosec has developed a DNA plasmid which expresses IL-12 by in vivo electroporation (i.e., intratumoral needle placement with electric current). Immunosec performed a phase 1 study in melanoma which revealed that in 10 patients (53%) there was evidence of a systemic response resulting in either stable disease or objective regression of untreated bystander tumors. In addition, in three of these patients (15%), all of the distant tumors regressed completely in either the absence of any other systemic antitumor therapy (two patients) or after treatment with dacarbazine (one patient). In vivo electroporation was associated with minimal systemic toxicity. No hematologic abnormalities were observed. The most frequent adverse event related to treatment was transient pain during the electroporation procedure (13 patients had grade 1 and eleven had grade 2 pain) and bleeding around the treatment site (13 patients had grade 1 and 11 grade 2 hemorrhage). A dose-proportional increase in IL-12 protein expression compared with pretreatment was seen in all patients with no significant IL-12 spillage into circulation and a correlative increase in tumor levels of IFN-gamma. The experimental regimen was found to be safe and well tolerated, with minimal systemic toxicity and with transient pain associated with the administration (Daud_2016 (14)).

Provectus has developed an intralesional (IL) formulation of Rose Bengal (RB), an inert dye. In preclinical studies, utilizing an OVA-expressing B16 melanoma murine model, Provectus found that intratumoral RB treatment led to increased tumor- specific T-cells with memory characteristics. Intratumoral RB therapy also increased antigen-specific T-cell proliferation and enhanced tumor regression. In addition, IL RB facilitated dendritic cells (DCs) infiltrating lymph nodes draining from tumor. Incubation of melanoma cells with RB led to necrosis and the release of High Mobility Group Box 1 (HMGB1), which activated DCs. The blockade of HMGB1 significantly reduced the antigen-presenting ability of DCs. Subsequently they performed a pilot clinical study in melanoma patients. Intratumoral RB led to tumor regression in both RB-injected and un-injected tumors, associated with an increase in circulating T-cells. Increased tumor-specific response was found from those circulating T-cells of 5 out of 7 tested patients after IL RB treatment. HMGB1 levels in patient sera were also elevated (Liu_2016 (15)). Broadly, Provectus demonstrated response rates of approximately 50% in the injected melanoma tumors, and some bystander responses (33% CR+ PR) which correlated with injected tumor responses (Thompson_2015 (16)).

Based on a comparison of Sponsor's murine data, Sponsor expects INT230-6 will be more potent than either approach of Oncosec or Provectus. INT230-6 acts by inducing direct tumor cell death due to potent agents. In addition, INT230-6 attracts inflammatory cells to the tumor microenvironment. Sponsor's preclinical program, although not with a direct comparison to these other therapies, INT230-6 showed the ability to regress large

(>300m^3) tumors as well as more pronounced effects on bystander untreated tumors (Intensity_E238 (18)).

On October 27, 2015 the U.S. Food and Drug Administration (FDA) approved the first intratumorally dosed oncolytic virus therapy, talimogene laherparepvec (T-VEC, or Imlygic®). The agency approved T-VEC for the treatment of some patients with metastatic melanoma that cannot be surgically removed. The approval was based on the results of a multicenter phase III clinical trial of patients with metastatic melanoma lesions in the skin and lymph nodes. Substantially more patients in the trial treated with T-VEC had a decrease in the size of their skin and lymph node lesions that lasted at least 6 months compared with patients treated with granulocyte macrophage colony-stimulating factor.

The treatment appears to work by directly killing cancer cells and stimulating an immune response against tumors, the trial investigators believe. Findings from the trial were published (Andbaka_2015(17)). In the international phase III trial, called OPTiM, 436 patients with unresectable stage IIIB to IV melanoma were randomly assigned to receive either T-VEC or GM-CSF. T-VEC was injected directly into the tumors, and subsequent doses were administered 3 weeks after the first dose, then once every 2 weeks. GM-CSF was administered subcutaneously every day for 14 days, in 28-day cycles. The durable response rate, which was measured as an objective response to therapy that lasted for at least 6 months, was significantly higher in patients who received T-VEC (16.3 percent) than in those who received GM-CSF (2.1 percent). T-VEC also improved median overall survival, which was 23.2 months in the T-VEC arm and 18.9 months in the GM-CSF arm.

3.8. Nonclinical Program for INT230-6

Sponsor sought guidance from FDA for a proposed nonclinical program during a pre-IND meeting held in August 2014 to enable an IND submission. Sponsor recognized the possibility of local and systemic exposures if INT230-6 injections via absorption in tumor blood vessels or seepage from the tumor. Sponsor and FDA agreed on a nonclinical program consisting of 3 studies.

- a non-GLP dose range finding study in rats
- a non-GLP local tolerability study in dogs
- a GLP study in rats

The non-GLP rat study was to determine systemic toxicity using both intraperitoneal (IP) and intravenous (IV) administration of INT230-6. The objectives of the study were a) to evaluate the effects of various dose volumes and regimens of INT230-6 on local and systemic toxicity; b) to assess systemic exposure; and c) to compare IP vs IV dosing. The non-GLP study would serve to determine the conditions most appropriate for a GLP study to characterize systemic toxicity in rats and determine the human starting dose. The non-GLP rat study successfully characterized the range of toxicities of INT230-6 and confirmed (per the vinblastine label) that IP administration in rats does represent systemic

exposure comparable to IV administration. Thus, Sponsor conducted only IV administration for the pivotal (GLP-compliant) toxicology study of INT230-6 to enable higher dosages and exposures to be characterized for systemic toxicity evaluation. The rat was the most suitable species to evaluate systemic exposure because it is a sensitive model for all relevant endpoints except for emesis, which could have significantly disrupted the toxicology assessment if carried out in a larger species (e.g., dog).

The GLP compliant rat study confirmed that administration of INT230-6 did not result in any new or previously unreported systemic toxicity. Toxicities observed were consistent for either cisplatin or vinblastine. The GLP study was conducted using once-weekly dosing for 3 weeks at three dose volumes. This regimen exceeds the proposed clinical starting regimen of once monthly. A 6-week non-dosing observation period enabled evaluations of recoveries, and satellite animals characterized plasma exposures to all three analytes after the first and last doses.

Furthermore, the sponsor conducted a local tolerability toxicology study in dogs to assess local tolerance effects of human-scale dosages of INT230-6 in the event that a physician missed the targeted tumor and injected healthy tissue or that the drug (or components) partially seeped from a superficial or deep body tumor into the surrounding tissue. Plasma exposures were also assessed. There were 3 treatment groups in the study: 5 mL of vehicle/dose, 2 mL of INT230-6/dose and 5 mL of INT230-6/dose, with each animal dosed on Day 0 subcutaneous, Day 3 intraperitoneal and Day 8 intrahepatic (IH). Other than injection site reactions attributed to extravasation from the IP dosing site, there were no observed clinical, macroscopic or histopathological observations or effects on surrounding healthy tissue in any INT230-6 treated dog groups for SC, IP or IH dosing attributable to the formulation.

3.9. Starting Dose Selection Method and Dose Escalation

FDA agreed to a protocol that used 1/10 of the STD_{10} to set the starting dose. The STD_{10} in the rat pivotal study was approximately 7.5 mL/kg[1]. As a result, 1/10 of the rat STD_{10} is 0.75 mL/kg, which equates on a body surface area basis to a human dose of 7.3 mL/60 kg subject[2]. Therefore, Sponsor proposed that the maximum permissible starting dose for the first-in-human (FIH) trial be up to 5.0 mL per subject. The target dose per tumor of INT230-6 for the first cohort was 0.25 mL per cm^3 of the tumor's volume (i.e., 1:4 loading dose). This drug dose volume to tumor volume ratio has consistently shown to saturate large tumors in pharmacology testing and resulted in anti-tumor activity in multiple preclinical models. An injected or to-be-injected tumor's volume was determined using the ellipsoid calculation method ([redacted]) using the imaging technique available at the site (e.g., CT, ultrasound, or MRI). In Amendment 6, Sponsor is implementing a method to set INT230-6 dose for an individual tumor based on longest diameter.

[1] The actual value for 7.5 mL/kg IV was 12.9%.
[2] (0.75 ÷ 6.2 = 0.121 mL/kg, or 7.3 mL for a 60 kg person (60 x 0.121).

The total injected volume and the maximum per any one tumor was escalated in the phase 1 portion of the study. As noted above, the toxicology program showed that INT230-6 administered IV resulted in no new toxicities. Only events expected for either vinblastine or cisplatin were observed. Please refer to the IB for further information.

To date, doses of INT230-6 up to 172 mL have been well tolerated. Following the phase 1, the SSC made a recommendation to increase dose levels of INT230-6 to 175 mL maximum dose. This regimen was submitted to the health authorities prior to activation of the fixed dose cohorts in Amendment 5. Theoretically the total amount of cisplatin and vinblastine administered intratumorally using INT230-6 could be considerably safer than the approved or MTD of IV administered cisplatin/vinblastine. If the agents are reduced/degraded or bound up while in the tumor microenvironment or inside the cancer cells the lesser toxicities effects could be expected. (Vinblastine binds to a cell's tubulin and cisplatin to the cell DNA. Should these processes occur within the cancer cells of the tumors, then systemic exposure would be reduced and corresponding morbidity due to the drugs decreased). Cohort EC has delivered doses of vinblastine in some subjects that have exceeded the typical IV dose, without any drug related grade 3 or higher AE's in those subjects.

3.10. Nonclinical Pharmacokinetics

PK data from IV administration of INT230-6 in male and female rats for each main component in INT230-6 is reported in Table 3 below. Plasma was analyzed for the concentration of vinblastine and SHAO using validated LC/MS/MS methods, and for cisplatin using a validated ICP-MS method. For pharmacokinetic studies, total platinum levels in subject plasma and urine are routinely determined by spectroscopy methods as a surrogate for platinum drugs. An ICP-MS method (Frontage Laboratories BTM-1942-R2) was developed for this study to measure total platinum in rat study samples. This document thus reports the ICP-MS measured total platinum values (obtained from plasma samples using method BTM-1942-R2) as cisplatin. The results of these analyses were used for toxicokinetic analyses.

Table 3: Animal PK		**Study Day 0**	**Study Day 0**	**Study Day 14**	**Study Day 14**
	Variable	Male	Female	Male	Female
Cisplatin	AUC_{last} (ng*h/mL)	54,500	58,200	83,700	67,900
5 mL/kg of INT230-6 Bolus	C_0 (ng/mL)	4150	9010	14100	12600
	$T_{1/2}$ (h)	53†	50†	69†	63†
	Cl (mL/min/kg)	0.663	0.633	0.398	0.503
	V_{ss} (L/kg)	2.61	2.25	2.02	2.28

*Note that total platinum is measured after cisplatin administration. Cisplatin, decay monoexponentially with a half-life of **about 20 to 30 minutes** following bolus administrations of 50 or 100 mg/m2 doses. Monoexponential decay and plasma half-lives of **about 0.5 hour** are also seen following 2-hour or 7-hour infusions of 100 mg/m^2.

		Study Day 0	**Study Day 0**	**Study Day 14**	**Study Day 14**
	Variable	Male	Female	Male	Female
SHAO	AUC_{last} (ng*h/mL)	51,500	55,200	87,000	71,000
5 mL/kg of INT230-6 Bolus	C_0 (ng/mL)	155,000	171,000	252,000	213,000
	$T_{1/2}$ (h)	4.7†	3.3†	3.7	4.2
	Cl (mL/min/kg)	16.2†	15.1†	9.57	11.7
	V_{ss} (L/kg)	0.132†	0.205†	0.089	0.123

		Study Day 0	**Study Day 0**	**Study Day 14**	**Study Day 14**
	Variable	Male	Female	Male	Female
Vinblastine	AUC_{last} (ng*h/mL)	78.1	63.1	197	148
5 mL/kg of INT230-6 Bolus	C_0 (ng/mL)	43.6	36.2	70.0	46.5
	$T_{1/2}$ (h)	2.7†	2.6†	6.0	5.8
	Cl (mL/min/kg)	80.8†	102†	40.2	53.7
	V_{ss} (L/kg)	18.1†	21.8†	14.4	19.3

† = Value is considered to be an approximation

Dose-related toxicity is therefore most likely to occur during treatment or within 14 days following treatment, however the DLT window shall be extended to 28 days.

4. STUDY OBJECTIVES

4.1. Research Hypothesis

INT230-6 when administered intratumorally (IT) to one or more tumors will safely reduce tumor burden, control disease, and promote an immune response against the cancer.

4.2. Primary Objective

The primary objective is to assess the safety and tolerability of multiple IT doses of INT230-6 in subjects with advanced or recurrent malignancies. This will be assessed by the rate of grade 3 or higher adverse events attributed to INT230-6 and not the underlying disease.

4.3. Secondary Objectives

The secondary objectives are to: 1) Assess the preliminary efficacy of INT230-6 by measuring the disease control rate (CR+PR+SD) as assessed by iRECIST; 2) characterize the pharmacokinetic profile of multiple doses of the three INT230-6 components (CIS, VBL, and SHAO) after single and then multiple IT tumor site injections. 3) characterize the overall safety of the INT230-6.

4.4. Exploratory Objectives

The exploratory objectives are to: 1) Characterize tumor response in injected and non-injected sites; 2) Evaluate various tumor and anti-tumor immune response biomarkers that may correlate with tumor response; 3) Evaluate overall response by iRECIST; 4) Characterize the pharmacodynamics (PD) profile of the INT230-6 formulation in subject blood and treated and untreated tumors; 5) To assess the progression free and overall survival in subjects receiving INT230-6.

5. OVERVIEW OF STUDY DESIGN

5.1. Dose Escalation

This is a FIH Phase 1/2, open label, non-randomized study. Subjects will have refractory, advanced cancers and will have failed or not be a candidate for standard of care. Investigators will have the option to continue INT230-6 based upon safety, local tolerability, and tumor response. The phase 1 portion of the study was divided into up to escalating dose cohorts for administration of INT230-6 and for cohorts A1, B1, EA, EC follows a 3+3+3 design.

Certain cohorts employed a subject safety lead in e.g., Cohorts A, EA, DEC, FEC, etc. cohort to estimate the rate of DLTs. A rate of DLTs <33% is desirable. The DLT observation window is 28 days. If less than 2 out of the first 6 subjects would have experienced a DLT, then additional subjects with different tumor types could have been enrolled to better define the safety in the different tumor types. If 2 subjects would have experienced a DLT, then an additional 6 subjects could have been enrolled and followed for a 28 Day DLT window. If > 3 subjects would have experienced a DLT, the safety data would have been reviewed by the SSC and a lower dose of INT230-6 would have been explored. No DLTs were observed in the phase 1 portion of the study.

The first 6 cohorts used an intrapatient dose escalation in the amounts noted per tables 4, 5, 6, 7. Dose escalation occurred by an increase in the amount and number of tumors that can be injected in a single subject, or by opening new cohorts at higher total drug exposure.

5.1.1. A. SUPERFICIAL TUMORS at 1:4 ratio: Dosing once per 28 days, Cohort A1

Cohort A1 – Superficial tumors included cutaneous and subcutaneous tumors. Nodal tumors were included if they were visible and palpable. Examples of such cancers are melanoma, head and neck, breast, and lymphomas. A sentinel subject could have had up to 3 naïve, superficial tumors injected at Cycle1, Day 0, for a total of 5.0 mL of INT230-6. Depending on the extent of superficial disease, it may not have been possible to inject the maximum amount for a given subject. After the sentinel subject was on treatment for 28 days (i.e., up to 3 tumors injected on day 0 and 28 days follow up), if there were no DLTs, upon agreement from the SSC, more subjects could have been enrolled into Cohort A1, and received monthly injections as per the schedule on Days 0, 28, 56, 84 and 112 (n=2-9). Cohort A1 continued until at least 3 subjects could have had the opportunity to complete at least 56 days or 3 DLTs would have occurred. If 1 DLT was observed in the first 3 subjects, an additional 3 subjects at this dose level could have been added. If there was 1 more DLT in the first 6 subjects, 3 more would have been added. If a third dose-limiting toxicity was observed in any dose level, even if < 9 subjects are enrolled, enrollment in that dose level would have been discontinued and a lower dose level or intermediate dose level would have been explored. A rate of DLTs that exceeds 33% is unacceptable for this population. There were no DLTs in this cohort.

Efforts were made to avoid injecting INT230-6 into necrotic tissue. Redosing was permitted using ultrasound guidance to ensure proper needle placement. In any subject, if no DLTs were observed after 28 days of follow up, the subject could have received

injections into up to 5 superficial tumors (cycle 2). If no DLTs were observed after 28 days of follow-up, the subject could have received superficial injections into any superficial tumors monthly on days 56, 84 and 112 (total of 5 cycles).

For each injection day, there was a limit to the total volume of administration, a limit on the maximum number of tumors (cycles 1-2 but not cycles 3-5) that could have been injected, and a limit on the maximum volume that could be injected into the largest tumor. This information is highlighted in the following schedule (Table 4). Note that the injection volume on subsequent cycles could have declined as the tumor size changes over time.

Table 4: Cohort A1 0.25 mL/cm^3 tumor

	Cycle 1	Cycle 2	Cycle 3-5
maximum dose	5.0 mL	Up to 10 mL	Up to 15 mL
maximum number of tumors injected	up to 3	up to 5	No limit
maximum volume for largest tumor	Up to 5.0 mL	Up to 10 mL	Up to 15 mL

5.1.2. B. DEEP TUMORS AT 1:4 ratio: Dosing once per 28 days Cohort B1

Cohort B1 was initiated and followed the same schedule as Cohort A1, but also allowed injections in deep tumors with image guidance (Table 5). Deep tumors were defined as those that lie within the body such as in an organ and are not able to be felt by touch. Tumors in the pancreas, liver, colon, lung and stomach are examples of deep tumors. Note that a sentinel subject in this cohort could have received a single injection totaling up to 5.0 mL into a naïve, deep tumor (subjects; n=1); if no DLTs were observed, this subject could have received injections into up to 3 deep or superficial tumors 28 days later. Efforts were made to avoid injecting INT230-6 into necrotic tissue. Redosing was performed using CT or ultrasound guidance. If no DLTs were observed, the same subject could have received deep or superficial injections into any 5 tumors monthly on days 56, 84 and 112 (total 5 cycles).

After the sentinel subject was on treatment for 28 days (i.e., up to 1 injection and 28 days follow up) and upon agreement from the Study Steering Committee (SSC), more subjects could have received monthly injections as per the schedule on Days 0, 28, 56, 84 and 112 (n=2). Note that the injection volume on subsequent cycles could have declined as the tumor size changes over time.

Table 5: Cohort B1 0.25 mL/cm^3 tumor

Cohort B1 Superficial + Deep	Cycle 1	Cycle 2	Cycle 3-5
maximum dose	5.0 mL	Up to 15 mL	Up to 30 mL
maximum number of tumors injected	1	Up to 3	Up to 5
maximum volume for largest tumor	5.0 mL	Up to 10 mL	Up to 15 mL

Depending on the extent of disease, it might not have been possible to inject the maximum amount for a given subject. Cohort B1 continued until at least 3 subjects had the opportunity to complete at least three doses or if 3 DLTs had occurred. If 1 DLT was seen in the first 3 subjects, an additional 3 subjects at this dose level could have been added. If there was 1 more DLT in the first 6 subjects, 3 more could have been added. If ≥3 DLTs were seen in up to 9 subjects, the SSC would have paused accrual and reviewed the data. If a third DLT was observed in any dose level in any cohort, even if < 9 patients were enrolled, enrollment in that dose level would have been discontinued and a lower dose level or intermediate dose level in that Cohort would have been explored. A rate of DLTs that exceeds 33% is unacceptable for this population. There were no DLTs in this cohort.

5.1.3. C. SUPERFICIAL TUMORS AT 1:4 ratio: Every two-week dosing, Cohort EA

Cohort EA design is described in Table 6.

Table 6: Cohort EA injection every 2 weeks in superficial tumors

Cohort EA superficial	Cycle 1	Cycle 2	Cycle 3-5
maximum dose	Up to 20 mL	Up to 20 mL	Up to 30 mL
maximum number of tumors injected	Up to 3	Up to 5	No Limit
maximum volume for largest tumor	10 mL	Up to 10 mL	Up to 20 mL

Cohorts EA was initiated and continued until at least 3 subjects had the opportunity to complete at least three cycles or 3 DLTs would have occurred. If 1 DLT was seen in the first 3 subjects, an additional 3 subjects at this dose level would have been added. If there is 1 more DLT in the first 6 subjects, 3 more would have been added. If ≥3 DLTs were seen in up to 9 subjects, the SSC would have paused accrual and reviewed the data. If a third dose-limiting toxicity was observed in any dose level in any cohort, even if < 9 subjects are enrolled, enrollment in that dose level would have discontinued and a lower dose level or intermediate dose level in that Cohort would have been explored. A rate of DLTs that exceeds 33% is unacceptable for this population. There were no DLTs in this cohort.

5.1.4. D. SUPERFICAL and/or DEEP TUMORS every 2 weeks 1:2 ratio (Cohort EC) and 1:3 ratio (Cohort EC2)

Cohort EC was similar to Cohort EA but with a higher loading dose of INT230-6 (50% injection to tumor volume i.e., 0.50 mL/cm³ tumor) (Table 7a) and a higher total dose escalation. Cohort EC2 (Table 7b) had higher drug volumes at a lower drug loading (1:3) per tumor compared with EC.

Table 7a: Cohort EC Every 2 weeks in Superficial and Deep tumors					
Cohort EC Superficial and/or Deep Tumors	**Dose 1 (C1, D0 / Day 0)**	**Dose 2 (C1, D14 / Day 14)**	**Dose 3 (C2, D0 / Day 28)**	**Dose 4 (C2, Day 14 / Day 42)**	**Dose 5 (C3, D0 / Day 56)**
Total volume (mL)	30	60	120	120	120
Maximum volume for any one tumor (mL)	Up to 15	Up to 30	Up to 60	Up to 80	Up to 100
Maximum number of deep tumors allowed to be injected*	2	4	6	6	6
Maximum drug to tumor ratio**	1:2	1:2	1:2	1:2	1:2
Table 7b Cohort EC2					
Cohort EC2 Superficial and Deep Tumors	**Dose 1 (C1, D0 / Day 0)**	**Dose 2 (C1, D14 / Day 14)**	**Dose 3 (C2, D0 / Day 28)**	**Dose 4 (C2, Day 14 / Day 42)**	**Dose 5 (C3, D0 / Day 56)**
Total volume (mL)	100	130	160	190	220
Maximum volume for any one tumor (mL)	Up to 60	Up to 100	Up to 120	Up to 140	Up to 160
Maximum number of deep tumors allowed to be injected*	2	4	6	6	6
Maximum drug to tumor ratio**	1:3	1:3	1:3	1:3	1:3

*There was no limit to the number of superficial tumors allowed to be injected provided the total dose was not exceeded.
**Could have been lower than 1:2 (case of EC) or 1:3 (case of EC2) if the tumor size exceeded 2 to 3 times the maximal volume to be administered. (e.g., a 60 cc tumor on dose 1 received the max 15mL or 1:4, but on dose 2 could receive 30 mL or 1:3).

Cohort EC was initiated and continued until at least 3 subjects had the opportunity to complete at least three cycles or 3 DLTs had occurred. If 1 DLT was seen in the first 3 subjects, an additional 3 subjects at this dose level would have been added. If there was 1 more DLT in the first 6 subjects, 3 more would have been added. If ≥3 DLTs were seen in up to 9 subjects, the SSC would have paused accrual and reviewed the data. If a third dose-limiting toxicity was observed in any dose level in any cohort, even if < 9 subjects were enrolled, enrollment in that dose level would have discontinued and a lower dose level or intermediate dose level in that Cohort would have been explored. A rate of DLTs that exceeds 33% is unacceptable for this population. There were no DLTs in this cohort.

Cohort EC2 was initiated and continued until at least 6 subjects had the opportunity to complete at least three cycles or 4 DLTs had occurred. If 2 DLTs were seen in the first 6

subjects, an additional 6 subjects at this dose level would have been added. If ≥4 DLTs were seen in up to 12 subjects, the SSC would have paused accrual and reviewed the data. A rate of DLTs that exceeds 33% is unacceptable for this population. There were no DLTs in this cohort.

5.1.5. DEC Safety Cohort. COMBINATION WITH ANTI-PD-(L)1 agent(s):

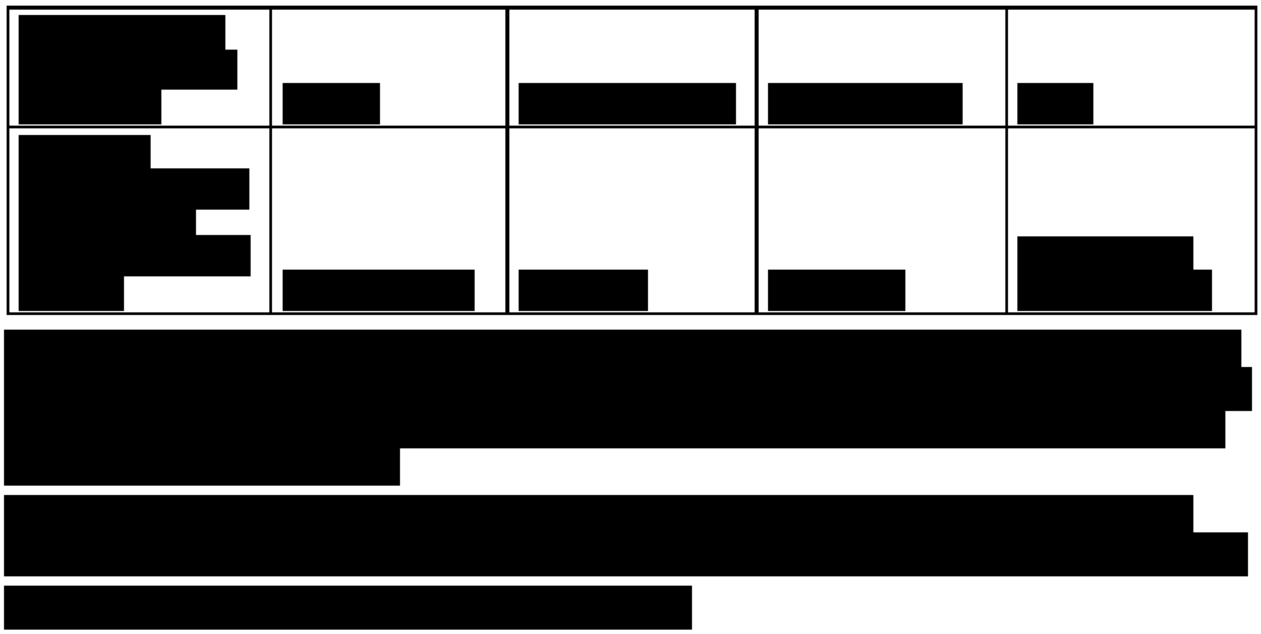
DEC was initiated and included a combination of INT230-6 plus an anti-PD-1 therapy. The SSC determined the subject population (tumor types) and the dose for this group of subjects. See Supplement A for details on the PD-1 agent.

5.2. Fixed Dose

Cohorts (EC3, DEC2, FEC and potentially GEC) shall use a maximum fixed dose of INT230-6 of 175 mL per dosing session with the number of tumors being dosed per session to be decided by the investigators.

Based on preliminary data from the IT-01 study, the ratio of length to width to height is very consistent across the first 200+ tumors that we have volumetric based dosing using the modified ellipsoid formula. We have used this data to simplify the dosing based on the longest diameter measurement alone. The dose of INT230-6 will be calculated using the algorithm in Table 8.

Table 8: INT230-6 Dosing calculations



5.2.1. E. SUPERFICAL and/or DEEP TUMORS (cohort EC3) Monotherapy of INT230-6

This cohort has simplified the dosing to inject up to the 175mL total dose of INT230-6 into a subject's tumors at each treatment (5 total for induction) session. There is 1 mL of INT230-6 dosed for each 3 cc of tumor volume (1:3) ratio with an induction dosing of 1 doses every 2 weeks for 5 doses with maximum fixed total dose of 175 mL with a maintenance dose of the same maximum of 175 mL given Q9 weeks +/- 10 days. Each tumor should receive up to its

maximum dose to achieve the 1:3 target ratio. The total dose is to be divided up and injected into as many tumors as feasible, with the aim to treat as many visible tumors as possible 1to 3 times during the course of the induction treatment. After the 5 doses, subjects continue to the maintenance phase where they can repeat injecting new lesions or previously injected lesions with up to 175mL once every 9 weeks. Treatment should continue until patient's tumors disappear (CR), confirmed progression (iCPD) or 2 years whichever is first.

5.2.2. DEC2 Cohorts. COMBINATION WITH ANTI-PD-1 agent(s): see Supplement A for details on each PD-1 agent.

DEC cohorts were initiated and are a combination of INT230-6 plus an anti-PD-1 therapy. The subject population (tumor types) and other details for this group of subjects is defined in Supplement A.

5.2.3. FEC Cohorts. COMBINATION WITH ANTI-CTLA4 agent(s): see Supplement B for protocol details for INT230-6 combinations with anti-CTLA-4 agent(s).

Cohort FEC was initiated and is a combination of INT230-6 plus an anti-CTLA4 therapy. The subject population (tumor types) and other details for this group of subjects is defined in Supplement B.

5.2.4. GEC Cohorts. Cohorts containing the letter "G" dose INT230-6 with agents other than PD-(L)1 or CTLA-4 antibodies.

The subject population (tumor types) and other details for this potential group of subjects will be defined in a future Supplement C.

Study Steering Committee

The Study Steering Committee is comprised of the majority of study investigators plus representatives from the Sponsor. The SSC will review safety data regularly in an ongoing basis on all subjects. Decisions to increase the number of subjects in a cohort, to increase the loading concentration injected into the tumors, and the decision to begin treating deep tumors will require agreement from this committee. The SSC will review the data on any sentinel subjects and facilitate the decision to recruit more subjects.

Expansion Groups

The SSC has reviewed the safety and any available biologic and/or tumor measurement data from phase 1, and recommended opening expansion groups of 10-16 subjects with single tumor types. These groups allow for better point estimates of the safety and preliminary efficacy in a homogenous population of subjects. These groups try to optimize drug exposure (i.e., maximum injection volume and drug load) to facilitate the optimal tumor destruction potential.

5.3. Long Term Follow up

Subjects who completed therapy, including treatment with or without retreatment, treatment with maintenance, or discontinued treatment for any reason other than clinical or radiological progression will enter the Long Term Follow up period. Subjects will be evaluated every 8 weeks for one year (until Amendment 5), and every 9 weeks (Amendment 6). During this Long Term Follow up Period, if a subject progresses or receives an intervening anti-cancer therapy, the subject will then enter the Survival Follow up Period.

Subjects who discontinue treatment due to clinical or radiological progression or Withdraw Consent from study treatment(s) will not enter Long Term Follow up, but will enter survival follow up as outlined below.

5.4. Survival Follow-up Period

Following completion of the treatment and long-term follow-up, as applicable, all subjects will be followed for survival. After that initial assessment of all study subjects, any surviving subjects will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until study completion or termination by the Sponsor. With the exception of noting the first use of subsequent anti-cancer therapies, no other data (e.g., subsequent therapies, performance status etc.) beyond survival will be collected during these calls/visits.

5.5. Injection Procedure

For all injections, proper precautions to prevent bleeding will be followed per the institutional guidelines for anti-coagulants for this patient population. The risk of the procedure should be similar to a biopsy. Greater precautions should be taken when injecting deep tumors. Subjects cannot be on aspirin or NSAIAs. Anticoagulants must be held with proper washout period prior to injection and not re initiated until the physician is confident that there have been no bleeding complications from the procedure.

Cohort A1, EA:

Superficial Tumors

The minimum tumor size must be ≥ 1.0 cm in diameter on Day 0. An eligible superficial tumor is defined as one that has not been previously irradiated, and has had at least 4 weeks to heal after any surgery or open biopsy. Note superficial tumors that have been irradiated previously but have evidence of active tumor growth, can be considered.

Superficial tumor injection: A sentinel subject with accessible and eligible superficial tumors in the skin, subcutaneous tissues, and/or lymph nodes will receive up to 3 IT injections into different tumors that are considered the most **troublesome** (*defined as the largest that are without confounding factors to permit local toxicity assessment and*

which are causing the greatest morbidity (acknowledging that this is a subjective assessment). The largest tumor should be targeted first).

After IT injections, the sentinel subject was monitored for at least 6 hours post-injection with vital signs, physical exams including close examination of the injection site and surrounding tissues for any untoward reactions, safety labs, and adverse events (see Table 11 for 28 day dosing and Table 12 for 14 day dosing). If there were no safety concerns, the subject would have been discharged to return to the clinic on Day 1 for the same safety follow up as on Day 0. The subjects would have been admitted to the hospital for observation if deemed medically necessary. This subject would have returned for safety evaluations on Days 7 and 14. On Day 14 or day 28 (cohort dependent) the subject was evaluated for additional IT injections into superficial tumors. If the subject had no persistent adverse events greater than Grade 2 (NCI CTCAE v 4.03) that could reasonably be attributed to the IT injection or the components of INT230-6, the subject could have received repeat injections in up to 5 tumors on day 28, and on subsequent cycles any number tumors chosen by the investigator.

After this first subject completed at least 28 days of follow up without persistent ≥Grade 3 (NCI CTCAE v 4.03) adverse events that could reasonably be attributed to INT230-6, additional subjects were enrolled in this cohort.

Note: On subsequent cycles, previously injected or new tumors could have been treated. Data from animals suggest re-injecting the same tumors leads to better tumor control. Ultimately the decision to re-inject the same tumors was made by the treating physician. The total number of additional tumors that were readily injectable were considered. Ultrasound was used for needle placement to avoid injecting areas of necrosis.

Cohorts B1, EC, EC2, EC3, DEC, DEC2, FEC, GEC

All Tumor Types Including Deep Tumors

Subjects having previously identified deep tumors observed using ultrasound, CT scan, MRI or PET/CT technologies will be eligible for treatment of their deep tumors provided the inclusion and exclusion criteria are met. The procedure will be done with ultrasound- or CT scan-, directed IT injection into deep tumors of at least 1.0 cm in diameter. Most **troublesome tumors** are defined as the largest that are without confounding factors, such as an unclear window to approach the tumor, unclear path for the needle which avoids major structures, scarring, proximity to large vessels, large areas of necrosis, inability to ascertain a local toxicity assessment. Most troublesome tumors are causing the greatest morbidity (acknowledging that this is a subjective assessment). The technical feasibility will be assessed by an interventional radiologist during the screening process to determine if the subject can be treated with this approach and what the most suitable tumors are for injection. The largest tumor should be targeted first with the least amount of puncture wounds. Rex Medical deep tumor injection device (QuadraFuse) can be used to enable proper dispersion of the drug product throughout the different quadrants of

large tumors (device to be provided by the Sponsor). See PK and Biomarker Manual and Injection Manual for further information.

After IT injections, the sentinel subject in cohort B1 (any others are to be designated by the SSC) was monitored for at least 6 hours post-injection with vital signs, physical exams including close examination of the injection site and surrounding tissues for any untoward reactions, safety labs, and adverse events (see Table 12). If there were no safety concerns, the subject was discharged to return to the clinic on Day 1 for the same safety follow up as on Day 0. The subject would have been admitted to the hospital for observation if deemed medically necessary.

Subjects will return for safety evaluations on Days 7 and 14 for cohort B1 and weekly for all E cohorts. On Day 14 for all E cohorts, and Day 28 for cohort B1, subjects will be evaluated for additional IT injections. If the subjects have no persistent adverse events greater than Grade 2 (NCI CTCAE v 4.03) that can reasonably be attributed to the IT injection or the components of INT230-6, the subjects can receive repeat injections. Over the course of the induction phase, investigators should attempt, if safe, to dose as many tumors as possible at least 2 or 3 times at the proper dose as noted in Table 8.

It is not necessary to inject each tumor on each of the 5 induction dosing sessions. For subjects who received 3 injections at the proper dose (from Table 8) in a given tumor prior to completion of 5 dosing sessions decisions regarding further treatment should be discussed with the Medical Monitor.

Note: On subsequent cycles, previously injected or new tumors may be treated. Data from animals suggest re-injecting the same tumors leads to better tumor control. The treating physician will ultimately decide which tumors will be injected, taking into consideration the response of the injected tumor(s) and the number of additional tumors that can be readily injected. Ultrasound or CT guidance may be used for needle placement to avoid injecting areas of necrosis.

Methodology:

INT230-6 will be injected into the periphery of the accessible and deep body tumors through the smallest and shortest gauge needle as possible to reach the entire depth of the tumor. For deep body tumors, ultrasonography or CT guidance at physician's choice will be used to place the needle into the tumor. The needle will be moved throughout the tumor with a pullback technique (distal, middle and proximal) if possible and be removed after each injection or when all tumors have been injected (see Injection Manual for more details).

6. STUDY POPULATION

See supplements for further details on population specifics for DEC, DEC2, FEC cohorts or potentially GEC cohort.

6.1. Inclusion Criteria

1. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
2. Men and Women ≥ 18 years of age on the day of signing consent.
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for ECOG criteria)**.
4. Populations: INT230-6 will be injected into deep or superficial tumors for subjects with histologically or cytologically confirmed advanced or metastatic cancers; **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for Populations)**.
5. Includes subjects with loco-regional disease that have relapsed/recurred within 6 months of chemo-radiation and who have no standard of care.
6. Subjects with metastatic disease who have failed one or more approved standard therapies, or have no alternate approved therapy available. Failure of all approved therapies that have a modest or marginal impact on survival is not required as long as the treating physician believes that treatment on study is appropriate for the subject and documents that the subject elects to defer the approved therapies.

   Note: There is no limit on the number of prior therapies that a patient (subject) may have received prior to enrollment in any cohort.
7. Subjects must have measurable disease by iRECIST 1.1 criteria including one target tumor for injection by the local site investigator/radiology. Superficial tumors must have one tumor greater than or equal to 1.0 cm, deep tumors greater than or equal to 1.0 cm (as measured by caliper (for non-injected tumors only) or image guidance). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Subjects must have a minimum of one injectable lesion as determined by the investigator (for superficial tumors) or radiologist (deep tumors).
9. Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer: systemic or IT) must have been completed at least 4 weeks prior to dosing (with the exception of kinase inhibitors or other short half-life drugs, a 2 week washout is acceptable prior to treatment) and all adverse events have either returned to baseline or stabilized.

   Note: Subjects who have received prior platinum therapy are eligible irrespective of their response.

10. Prior systemic radiation therapy (either IV, intrahepatic or oral) completed at least 4 weeks prior to study drug administration; **(for ipilimumab combination please see supplement FEC exclusion criteria).**
11. Prior focal radiotherapy completed at least 2 weeks prior to study drug administration.
12. Prior major treatment-related surgery completed at least 4 weeks prior to study drug administration.
13. No prior primary or metastatic brain or meningeal tumors unless clinically and radiographically stable as well as off steroid therapy for at least 2 months.
14. Life expectancy ≥8 weeks; **(for ipilimumab combination please see supplement FEC inclusion criteria).**
15. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

    a. Not a woman of childbearing potential (WOCBP)
    b. A WOCBP subject who may become pregnant or who are sexually active with a partner and who could become pregnant agrees to use an effective form of barrier contraception during the study and for at least 180 days in monotherapy; **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for pregnancy criteria)**. (Male subjects must agree to use contraception and refrain from sperm donation during the study for 180 days after administration of study drug.)

16. Have adequate organ function as defined by the below screening laboratory values that must meet the following criteria:
    a. WBC ≥2000/μL (≥2 x 10^9/L).
    b. Neutrophils ≥1000/μL (≥1 x 10^9/L); **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for neutrophil criteria)**.
    c. **For subjects with planned superficial only injections:** PT, PTT/aPTT, and INR ≤1.5 × ULN, Platelets ≥70x10^3/μL (≥ 70 x 10^9/L), Hemoglobin ≥8 g/dL
    d. Creatinine within the institution's laboratory upper limit of normal or calculated creatinine clearance >50 ml/min; **(for pembrolizumab combination please see supplements DEC/DEC2 for creatine criteria)**.
    e. ALT (SGOT)/AST (SGPT) ≤2.5 x ULN without, and ≤ 5 x ULN with hepatic metastases.
    f. Bilirubin ≤2 x ULN (except subjects with Gilbert's syndrome, who must have total bilirubin <3.0 mg/dL (<52 μmol/L); **(for pembrolizumab and ipilimumab combinations please see supplements DEC/DEC2 and FEC for bilirubin criteria)**.
    g. **For subjects with planned deep tumor injections**: PT, PTT/aPPT, and INR within normal limits; Platelet count ≥100,000/μL; hemoglobin ≥ 9 g/dL.

    Note: ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal.

[1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

17. Additional criteria for combination arms can be found in the appropriate supplements.

6.2. Exclusion Criteria

Subjects who exhibit any of the following conditions at Screening will not be eligible for admission into the study: **See DEC/DEC2, FEC, or potentially GEC supplements for additional criteria specific to those cohorts.**

18. History of severe hypersensitivity reactions to cisplatin or vinblastine or other products of the same class.
19. Other prior malignancy, except for adequately treated basal or squamous cell skin cancer or superficial bladder cancer, or any other cancer from which the subject has been disease-free for at least 2 years.
20. Subjects with tumors >15 cm (in longest diameter). Treatment plan for subjects with tumors that are 9 to15 cm must be discussed with and approved by the medical monitor.
21. Underlying medical condition that, in the Principal Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.
22. Concurrent medical condition requiring the use of immunosuppressive medications, or systemic corticosteroids (topical steroids are permitted); systemic corticosteroids must be discontinued at least 4 weeks prior to dosing. Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Non-absorbed intra-articular steroid injections will be permitted; or use of other investigational drugs (drugs not marketed for any indication) within 30 days prior to study drug administration. Use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.
23. For deep tumor cohorts, subjects who require uninterrupted anticoagulants of any type, on daily aspirin therapy or NSAIAs.
24. Use of other investigational drugs (drugs not marketed for any indication) within 28 days prior to study drug administration.

Pregnancy Exclusion:

A WOCBP who has a positive urine pregnancy test (e.g., within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

NOTE: For specific inclusion/exclusion criteria relating to a potential combination, please refer to the combination specific supplement

7. ASSIGNMENT TO STUDY

The investigative site will contact Catalyst for treatment assignment once a subject is determined to be eligible for enrollment. Subjects who meet all eligibility requirements will be assigned to a treatment group as determined by Catalyst. Once assigned, numbers for screen failures, non-treated, non-evaluable, or discontinued subjects will not be re-used.

8. DOSAGE AND ADMINISTRATION

8.1. Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. In this protocol, investigational product(s) is: INT230-6, an anti-PD1 (pembrolizumab), CTLA-4 antibody (ipilimumab), or other drug.

8.2. Non-Investigational Product

Other medications used in the study as support or rescue medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products. In this protocol, non-investigational products are local anesthesia, anti-emetics (if prescribed by the investigator) and sedation.

8.3. Physical Description of Study Drug

INT230-6 is supplied in a frozen single use 10 mL or 30 mL amber vial. Each vial contains:

Name of Active Ingredients:

Cisplatin, (cis-diamminedichloroplatinum - CIS) 0.5mg/mL and

Vinblastine Sulfate (VBL) 0.1 mg/mL

Name of Important Excipients:

Sodium 2-hydroxybenzoylaminooctanoate (SHAO) 10 mg/mL (of free acid).

8.4. Packaging and Labeling

The study drug will be packaged and labeled according to current good manufacturing practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy and Drug Product Labeling Manual.

8.5. Ordering Study Drug

Clinical supplies may be requested by completing the Clinical Supplies Request Form and faxing it or e-mailing the form to the Sponsor with a copy to Catalyst.

8.6. Storage

Sterile INT230-6 has demonstrated that when stored frozen for 2 years at -20°C all three main ingredient substances comprising the drug product retain approximately ~100% of their T=0 concentrations upon thaw. Long term stability studies are in process. Confirmation of the drug product's stability for use beyond 24 months shall be provided prior to use for drug product batches older than 24 months.

INT230-6 vials must be stored at a temperature of approximately -20°C (-15°C to -25°C is acceptable) and should be protected from light. Recommended safety measures for preparation and handling of INT230-6 include laboratory coats and gloves. After INT230-6 has been removed from the freezer, the total storage time (at room temperature) is not to exceed 4 hours.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent.

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

8.7. Study Drug Preparation and Administration

INT230-6 is to be administered as an intratumoral injection. Each 10 mL or 30 mL vial of INT230-6 must be thawed to room temperature prior to use. (See Injection and Dosing Manual Section 2.1 for determining the number of vials to thaw for each subject session for each cohort). Heating of the INT230-6 vials is not permitted. Thaw by placing the vials needed for dosing on a bench at room temperature. After one hour gently shake the vials to assure that any particulates that may be visible go into solution. INT230-6 must be dosed within 1 to 4 hours following removal from the freezer assuring that the vial is at room temperature at time of preparation. Injection of tumors must be performed under ultrasound, endoscopic or CT guidance. The extent of necrosis in the tumor should be assessed prior to re-injecting the same tumor.

If dosing into superficial tumors, prepare a standard syringe and sufficiently sized 22 gauge (or finer e.g. 23, 24 gauge) needle of proper length for the size of the tumor. (See below for dosing deep tumors). Remove the foil overseal from the vial and place the needle into the rubber stopper. Draw the appropriate drug volume for the tumor to be dosed into the syringe at either the 0.25 mL per cm^3 of tumor or 0.5 mL per cm^3 of tumor

ratio (depending on the cohort to be dosed). Use a fractionating technique to assure that the dose of INT230-6 is administered to each quadrant of the tumor. If known, dose into the proliferating portion of the tumor rather than into any necrotic areas. Administer the entire dose throughout the tumor (**moving the needle throughout the tumor as outlined per the Injection Manual**) gently pushing the plunger. Prior to withdrawing the needle from the tumor, count to 30 to assure time for the INT230-6 formulation to thoroughly diffuse throughout the tumor. If tumor is superficial with potential for ulceration (e.g. melanoma), please cover with an occlusive dressing which can be removed in 48 hrs.

For dosing into deep tumors note Sponsor shall provide a special syringe (see PK and Biomarker Manual and Injection Manual for further intratumoral deep tumor dosing information). **Note:** it takes approximately 1 mL to prime the tubing for the injection device.

Care must be taken to maintain the sterility of the INT230-6 solution as the product does not contain any anti-microbial preservative or bacteriostatic agents. Do not reinsert the needle into the vial after the subject has been dosed. Use a fresh, clean drawing needle if more material from the vial is to be used.

Anti-PD1and anti CTLA4 therapy will be prepared as directed in the relevant Supplements

Training videos have been prepared by the Sponsor for:

25. Drug Preparation
26. Dosing Superficial Tumors
27. Deep Tumor Dosing

It is expected that research staff who are involved in any of the above activities (drug preparation, labelling or dosing) view the videos and that training is documented prior to involvement in such activities.

8.8. Drug Accountability

Sponsor will provide the study drug supply. All study drug(s) will be supplied to the Investigator by Sponsor or its designee. Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels (approximately -20°C). The Investigator or designated study person must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to Sponsor at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or vials destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

8.9. Dose Adjustments

Intrasubject dose reductions for the management of toxicities are not permitted unless discussed with and approved by the Sponsor Medical Monitor.

8.10. Incomplete Dosing

Depending on the technique used for injection, it is possible that a single tumor will not allow for the full volume of administration. Every effort should be made to deliver the total dose, across the permitted number of tumors. Depending on the overall tumor burden this may not be possible, in which case it should be recorded in the CRF. If the tumor shrinks after one or more injections, the total volume declines, less total drug can be given, this will be recorded in the CRF.

8.11. Dose Delay

Delay of up to 14 days are permitted for treating on the next cycle for safety reasons. If the delay is greater than 2 weeks, then the subject should come off study unless discussed with and approved by the medical monitor. These delays are not intended for administrative type/scheduling issues due to holidays, weather, etc. The visit windows in Table 10 should be used in such circumstances. If, in the case of such delay it is beyond the allowed visit window, approval via a Protocol Waiver Form from Sponsor Medical Monitor should be obtained prior to the visit occurring.

8.12. Permanent Discontinuation of Study Drug Due to Adverse Events

INT230-6 should be permanently discontinued for a subject due to the occurrence of any of the following AEs that have not resolved prior to the next treatment

- Any CTC Grade ≥3 immunologic related event that persists >1week despite treatment per institutional guidelines
- CTC Grade 4 neutropenia > 7 days or neutropenic fever
- Persistent ≥ CTC Grade 3 anemia despite growth factor support
- Platelets < 70,000 for superficial tumors, <100, 000 for deep tumors
- ≥ CTC Grade 3 elevation in liver enzymes
- ≥ CTC Grade 4 neuropathy
- Creatinine >1.5mg/dl
- Any anaphylactic type reactions
- ≥ Grade 3 nausea or vomiting that persists despite maximal supportive care

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the Investigator, presents a substantial clinical risk to the subject with continued treatment

8.13. Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure the destruction of drug is according to applicable regulations, guidelines and institutional procedures. Appropriate records of the disposal must be maintained at all times. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible Sponsor Study Monitor.

8.14. Return of Study Drug

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

9. TOXICITY AND MANAGEMENT

9.1. Dose Escalation

Cohorts A1, B1, EA, EC, EC2, DEC escalated doses. Cohorts EC3, DEC2, FEC start out with a fixed total dose for each treatment session. For doses within Cohorts EC3, DEC2, FEC, investigators may decide to treat certain tumors on one visit and then treat additional tumors on subsequent visits that may involve an increase of INT230-6 dose given. This section describes the management of the potential toxicities.

9.1.1. Dose-limiting Toxicity

A DLT is defined as a ≥ Grade 3 study drug-related adverse event (using NCI CTCAE Version 4.03) occurring during the first dose (DLT window extends up to 28 days after dosing), excluding:

- Grade 3 adverse event of tumor injection reaction (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) that resolves with supportive care measures within 48 hours
- Grade 3 or 4 nausea or vomiting that is adequately treated with supportive care and that resolve within one to two days
- Any bleeding that is self-limiting from or near the site of injection and resolves within 24 hours with non-invasive measures and without the need for transfusion
- Grade 3 or 4 electrolyte abnormalities that correct to below grade 3 with standard measures within 48 hours

A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the toxicity. Delayed DLTs are adverse events that meet the criteria of DLTs that occur after Cycle 1. If >1 member of a cohort should have a DLT for Doses 2 -5, then the SSC will determine how accrual shall proceed for that cohort.

Intrasubject dose escalation

Any events of ≥ Grade 3 that are considered study drug-related after cycle 1 for a subject will be reviewed by the SSC to assess if alterations in dosing levels and or frequency are needed for that subject. If more than one member of a cohort should have a ≥ Grade 3 event for cycles 2 to 5, then the SSC will determine how accrual should proceed for that cohort.

All adverse events that meet DLT criteria must be reported to the pharmacovigilance services vendor (ProPharma) within 24 hours of the study site being made aware of the event using the rapid notification procedures described in Section 13.3.2.

9.1.2. Stopping Rules for Dose-limiting Toxicity During Dose Escalation

Cohorts in the dose escalation portion will be expanded up to 9 subjects in the case of 1 or 2 DLTs. More than two DLTs in a dose escalation expanded cohort (N=9) will exceed

the MTD. At the time a third DLT is observed in any dose level in any cohort, even if < 9 subjects are enrolled, enrollment in that dose level will be discontinued and a lower dose level or intermediate dose level in that Cohort will be explored. Any delayed DLTs will be evaluated on a case-by-case basis. The SSC will provide additional oversight and will be reviewing safety on an ongoing basis and may make adjustments to this criterion based on the data.

Subjects who are tolerating a study drug dose level that is being reviewed due to DLTs that occurred in other subjects will not be automatically precluded from continued dosing during this safety review and will be allowed to continue dosing for as long as it is tolerated unless the safety review mandates dose reduction. After safety analysis by the Investigators and Sponsor (with FDA and IRB notification), a decision will be made whether to resume enrollment and continue dosing at the current dose or initiate a new cohort of subjects at a lower INT230-6 dose.

9.2. Possible Toxicities

Based on the safety experience in the first 70 patients, the most common treatment associated adverse event is injection site pain. Other constitutional adverse events (nausea, vomiting, decreased appetite and anorexia) have also been reported.

Additional theoretical toxicities that could be affected by INT230-6, which may or may not be increased with the combination of immune activating agents, such as hematologic, cardiovascular, hepatic, musculoskeletal, and other systems, and may include the following:

- Allergic reaction/hypersensitivity: Fever, chills, shakes, itching, rash, hyper- or hypotension, and difficulty breathing. It is likely that most injection-related adverse events will occur within the first 24 hours after the injection and may be treated by supportive treatment as indicated.
- Injection procedure: Pain during and after the injection, bleeding, infection, tumor ulceration and edema. The needle utilized for this is the same or smaller size than what is typically used for a biopsy. All attempts at using a single injection point for each tumor are suggested. Additionally, injection volumes of liquid into the tumor should provide some back pressure to help reduce the potential for bleeding. The Quadrafuse device has been used for injection of deep tumors and has a low rate of hemorrhage as a complication.
- Other potential adverse effects of INT230-6: Fatigue, anemia, leukopenia, hyponatremia, other laboratory abnormalities (including increases in gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), lipase, creatinine), nausea or vomiting, decreased appetite, weight loss, muscle aches, chills, dizziness, and urinary retention.
- Adverse effects associated with IV Cisplatin and Vinblastine are less likely given the dose used in this study: Renal damage, visual disturbances, hearing loss/tinitis, peripheral neuropathy, sensory loss/numbness, tingling, areflexia

and difficulty walking, xerostomia or xerosis, dehydration, dysgeusia, alopecia, thrombocytopenia, other blood abnormalities (low magnesium, calcium, potassium), bleeding, dark urine, chest pain or heart attack, sweating, depression, muscle cramps, pain including headaches.

- Extravasations: There are no reports of simultaneous extravasations of CIS and VBL so guidance on countermeasures does not exist. Also watch closely for any toxicities when given intradermally for skin tumors.

9.2.1. Management of select AEs

The following table describes potential AEs and the management suggestions for INT230-6. The investigator should use good medical judgement in determining the optimal care for his or her subjects.

Table 9: Dose Modification and Toxicity Management Guidelines for AEs Associated with INT230-6 using CTCAEv4.03

General instructions:

1. For situations where INT230-6 has been withheld, INT230-6 can be resumed after AE has been reduced to baseline or Grade 1
2. For severe and life-threatening AEs, INT230-6 should be permanently discontinued

AEs	Action taken to INT230-6	AE management	Monitor and follow-up
Allergic reaction or hypersensitivity	Hold drug if Grade $\geq$ 3	Follow the package insert for CIS and VBL, these AEs usually can be managed with by administration of epinephrine, corticosteroids, and antihistamines.	You may consider a rechallenge with INT230-6 if grade $\leq$2 and resolves with minimal treatment.
Typical cytotoxic effects including fatigue, nausea, vomiting, anorexia, decreased appetite	Hold drug if Grade $\geq$ 3	Supportive care as per institutional guidelines	Consider using anti-emetic premedication on next INT230-6 dose
Local reactions	Hold drug if Grade $\geq$ 3	apply heat packs, subcutaneous hyaluronidase	Consider prophylactic antihistamines and low dose corticosteroids on next INT230-6 dose
Injection pain	Hold drug if Grade $\geq$ 3	Pain control medications as prophylaxis and for treatment as per institutional standard	Consider prophylactic pain medication prior to subsequent injections. If Grade 3 or higher, do not increase INT230-6 dose

9.3. Stopping Rules for Clinical Deterioration

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression, or appearance of new

tumors or some enlarging tumors while certain target tumors are regressing ("mixed response"). It is thus reasonable to allow for these possibilities and continue to treat the subject until progression is confirmed and found to be advancing and continuing at the next imaging assessment. These considerations should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the Sponsor Medical Monitor and will be documented in the study records.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - Pathologic bone fracture in the region of cancer involvement
  - Cancer related to bone surgery
  - Spinal cord or nerve root compression
- Bladder outlet or urethral obstruction
- Development of new central nervous system (CNS) metastases
- Subjects that develop new CNS metastases in the setting of improving baseline disease may have focal radiation, resection, or other local curative procedures performed after consultation with the Medical Monitor.

If continued study therapy is deemed to offer the subject potential benefit, subjects may be allowed to restart study therapy after recovery from symptoms related to the procedure performed (i.e., local edema) and steroid dosing at < 10 mg prednisone/day or equivalent, after recovery to baseline or grade 1.

Subjects that have locally curative procedures while on study drug and subsequently develop new CNS metastases at a subsequent imaging assessment should discontinue study therapy and enter the follow-up period.

Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject even in the absence of any such documented clinical events.

10. COMPLIANCE

The Investigator or their designated study personnel will maintain a log of all study drugs received, dispensed, destroyed, and returned. Drug supplies will be inventoried and accounted for throughout the study.

The Investigator and the study personnel will ensure that each subject receives the calculated dose of the study drug based on tumor volume, as in section 5.2.

11. CONCOMITANT THERAPY

All medications taken within 14 days before the administration of study drug and all concomitant therapy administered during the study will be recorded on the relevant case report form (CRF), along with the reason for therapy use.

1. The use of local anesthesia and /or sedatives as well as anti-emetics to facilitate the injection procedure is permitted.
2. Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Non-absorbed intra-articular steroid injections will be permitted. Systemic corticosteroids required for the control of injection reactions must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration. The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted (other cases can be discussed with the medical monitor to allow higher doses for clear medical indications).
3. Use of new herbal remedies, other marketed anti-cancer chemo/immunotherapy drugs, or investigational drugs (drugs not marketed for any indication) is not permitted.
4. New chemotherapy or immunotherapy is not permitted.
5. Palliative/therapeutic therapies (e.g., focal radiotherapy for pain, thoracocentesis or paracentesis for comfort) may be administered after consultation with the Medical Monitor. Palliative radiation will not be delivered to injected tumor sites while on study.
6. Various growth factors are permitted as per ASCO guidelines after the 28 day DLT window.
7. The use of live vaccines while on study is prohibited. The use of any killed or attenuated vaccines for the prevention of influenza is permitted at any time without a study drug washout interval. The use of other killed or attenuated vaccines for the prevention of infectious diseases may be permitted on a case-by-case basis and must be discussed with the medical monitor prior to its use. A washout interval prior to and post vaccination may be required in these instances. Any vaccinations administered while on study must be documented in the subject's medical records and recorded in the CRF.

   All subjects should be maintained on the same concomitant medications throughout the study period, as medically feasible. Any new concomitant medications prescribed for the subject or changes to dosing/schedule of concomitant medications should be recorded on the appropriate CRF page. The addition of a new concomitant medication for which there is a concern that it may not be permitted should be first reviewed with the Sponsor Medical Monitor.

8. No concomitant medication information will be collected following subject discontinuation from the study except for concomitant medication use associated with study drug-related adverse events or adverse events that lead to discontinuation from study and start of next anti-cancer therapy. Additional information for combination arms can be found in the appropriate supplements.

11.1. Treatment of Isolated Tumors

Treatment of isolated/symptomatic tumors by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time beyond Cycle 2. All interventions should be discussed in advance with the Sponsor Medical Monitor. Palliative radiation will not be delivered to injected tumor sites while on study.

12. STUDY EVALUATIONS

12.1. Study Procedures by Visit

12.1.1. Overview

The study is divided into periods (Screening, Treatment, Long Term Follow-up and Survival Follow up) with associated evaluations and procedures that must be performed at specific time points. The Time and Events Schedules Table 10, Table 11 (every 28 day dosing) and Table 12 (every 14 day dosing cohorts) summarize the frequency and timing of efficacy, safety, and other study measurements.

As soon as the subject is considered for this study and before performing any study procedures, the subject will have the study explained to him/her and will be asked to give written informed consent and HIPAA authorization. Informed consent/HIPAA authorization must be obtained before any procedures that do not form a part of the subject's normal standard of care. Baseline imaging (within 28 days) and ECG as part of the subject's previous routine care (performed within 14 days) of first dose need not be repeated.

All subjects (withdrawn or completed) should have final evaluations and procedures performed.

12.1.2. Screening Period

Subjects will be evaluated for entry criteria during the Screening Period within 28 days before administration of study drug. The following procedures and evaluations will be completed for each subject before Day 0 and before inclusion in the study:

- Informed consent/HIPAA may be obtained $\leq$ 28 days before receiving study drug, and before any Screening procedures are performed;
- Review of Inclusion/Exclusion criteria;
- Medical history (to include collection of prior medications administered to the subject during the Screening Period, prior and concurrent medical conditions, and baseline signs and symptoms). Additional information on diagnosis confirmation and stage and tumor-specific therapy history will also be collected;
- Screening signs and symptoms: Note: Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF; Serious Adverse Events that occur after signing Informed Consent must be reported according to the safety reporting procedures and recorded in the eCRF;
- Vital sign measurements including temperature, O_2 Saturations, heart rate, and resting blood pressure;
- Height;

- Weight;
- Complete physical examination (including examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen [including liver and spleen], lymph nodes, and extremities). A brief neurological examination should also be performed to rule out potential brain involvement;
- ECOG performance status;
- Clinical laboratory tests:
- Hematology: Complete blood count (CBC) with differential (including absolute lymphocyte count) and direct platelet count (see Section 12.1.7) using ~5 mL of blood. Coagulation: PT, PTT/aPTT, INR[3];
- Chemistry (using ~5 mL of blood):

Alanine aminotransferase	Creatine phosphokinase	Phosphorus
Albumin	Creatinine	Potassium
Alkaline phosphatase	Gamma-glutamyl transpeptidase	Sodium
Aspartate aminotransferase	Glucose	Thyroid Stimulating Hormone,
Amylase	Lactate dehydrogenase	Total bilirubin
Bicarbonate	Lipase	Total protein
Calcium		Triglycerides
Chloride	Low density lipoprotein	Urea (or blood urea nitrogen)
Cholesterol (total)	Magnesium	Uric acid

- Electrolytes (including sodium, phosphorous, potassium, chloride, and bicarbonate);
- Urinalysis: Gross examination including specific gravity, protein, glucose, and blood. Urine microscopic analysis is mandatory with all other lab tests;
- Serum or urine pregnancy test (for all women of childbearing potential; pregnancy test must be negative to continue);
- 12-lead Electrocardiogram (ECG);
- Tumor imaging (CT/MRI or PET/CT of chest/abdomen/pelvis) and any other known sites of involvement (i.e. brain) within 28 days of first dose. The same imaging modality technique should be used throughout the protocol;

[3] INR should be measured only for those subjects taking warfarin, blood collection may require a separate draw

- Peripheral blood samples will be collected prior to initiation of study therapy. These samples will be analyzed for SNP. Prior to Amendment 6, blood samples were analyzed for flow cytometry parameters, cytokine panel, and quantitative immunoglobulins as outlined in Section 12.2.3;
- Prior concomitant medications;
- Interventional radiology assessment for deep tumors to assess feasibility and determine which tumors are best for injection.

Table 10: Screening Procedural Outline		
Procedure	Screening visit	Notes
Informed Consent	X	
Inclusion/Exclusion criteria	X	All criteria should be assessed at screening and confirmed prior to first dose
Medical History	X	Including malignancy diagnosis and summary of tumor specific therapy
Oncology and/or Interventional Radiology	X	Assess feasibility for intratumoral injection and determine which tumors are most appropriate for injection
Physical Examination	X	
Physical Measurements	X	Height and Weight; Body Surface Area
Brief Neurological Exam	X	
Vital Signs and O_2 sat	X	Including BP, HR, Temperature and O_2 saturation. Obtain at screening and **within** 4 hours of the first dose
ECG	X	Within 14 days prior to first dose
ECOG Performance Status	X	Within 14 days prior to first dose
Prior Medications	X	All prior medications to treat the neoplasm
Concomitant Medications	X	Within 14 days prior to first dose
Adverse Events Assessment	X	Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF. AEs meeting the definition of Serious must be reported according to the SAE reporting requirements.
Laboratory Tests	X	CBC w/differential, coagulation and chemistry panel (for full list of labs see Section 12.1.2) Urinanalysis with microscopic evaluation if dipstick is abnormal. Within 14 days prior to first dose. (INR only for subjects taking warfarin)
Pregnancy Test (WOCBP only)	X	Serum or urine
Screening/Baseline Tumor Assessment	X	CT, MRI or PET/CT of Head and Neck, Chest, Abdomen, and all other known sites of disease (i.e. Brain) within 28 days prior to first dose. At screening, all tumors ≥1 cm in diameter are to be reported with an estimate number of the number of tumors <1 cm recorded as well.
Enrollment	X	
Genetic Testing	X	See Table 14

12.1.3. Treatment Period

The Treatment Period of the study is divided into 28 day cycles with associated evaluations and procedures that must be performed at specific time points (see Table 11) every 28 day dosing and Table 12 every 14 day dosing). Subjects who meet selection criteria may start INT230-6 treatment within 28 days of screening. Subjects will receive injections of INT230-6 every 14 or 28 days based on their Cohort assignment. INT230-6 will also be dosed every 9 weeks +/- 10 days in the cohorts specifying maintenance dosing (EC3, DEC2, FEC and potentially GEC). Results of assessments must be reviewed before administering the next dose. The maximum duration of study therapy to be administered to an individual subject in this study is 2 years (up to maximum of 4 months of initial treatment plus maintenance therapies for certain cohorts as well as Follow up and Survival Follow up).

Every effort should be made to schedule visits within the protocol-specified windows. For injection delays (i.e., by 1 to 13 days) or missed doses, see Section 8.11 for administration details. A subject who is withdrawn from the study before the completion of the first cycle for a reason other than a DLT will be replaced.

12.1.3.1. Cycle 1

A cycle is defined as 28 days. Dose 1 (Cycle 1 Day 0) 1 will begin with the first IT injection of INT230-6 (Day 0) and will continue through to completion of evaluations by Day 28. For cohorts A1 and B1 subjects will be dosed every 28 days for a total of 5 cycles (Days 0, 28, 56, 84 and 112) with a response assessment every 2 months for the first year and then every 3 months until progression. In "E" Cohorts, subjects will be dosed every 14 days for a total of 3 cycles (Days 0, 14, 28, 42, and 56).

During Cycle 1 Day 0, the following evaluations will be performed as indicated in Table 11 for 28 day dosing and in Table 12 for 14 day dosing. Results will be recorded on the CRF:

- Physical Exam: A full physical Exam will be performed on Day 0. A Targeted physical examination (including measurement of vital signs as well as pulmonary, heart, abdomen, and skin assessments) will be conducted at all subsequent visits;
- Vital sign measurements to include temperature, pulse, O_2 saturation and resting blood pressure as defined in the Time and Events Schedule (Table 11 for every 28 day dosing and Table 12 for every 14 day dosing). Vital signs will be obtained before injection and then 15, 30, 60 post injection. In addition,180 and 360 minutes post injection vital signs are collected at C1D0.
- Weight;
- Assessment of signs and symptoms;
- Adverse Event Assessment;
- ECG;
- ECOG performance status;
- Serum sample for pharmacokinetics is eliminated in Amendment 6.Clinical laboratory tests (local laboratories; Hematology (using ~5 mL of blood), coagulation

and clinical chemistry laboratories (using ~5 mL of blood) **must be performed and reviewed before dosing**. Labs do not need to be repeated if obtained within 72 hours of starting treatment). This includes a CBC with differential and Chemistry as outlined in Section 12.1.2;

- Any new ≥ Grade 3 laboratory abnormality such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Sponsor Medical Monitor should be contacted;
- Urinalysis;
- Serum or urine pregnancy test to be performed locally (for all women of childbearing potential; pregnancy test must be negative before study drug administration to continue);
- CT/MRI Brain screening: CT/MRI Brain, only if clinically indicated by the development of new symptoms that suggest new CNS involvement;
- Tumor imaging (CT/MRI or PET/CT chest/abdomen/pelvis) **to be conducted only if imaging has not occurred within previous 29 days;**
- US/CT measurements of injected tumor;
- Response assessment and documentation;
- Cryopreserved peripheral blood mononuclear cells (PBMCs) and serum. **Collection eliminated in Amendment 6.**
- Tumor and blood samples that are available after completion of designated analyses may be used in the future for identification of potential predictive and/or pharmacodynamic markers. These assessments will provide exploratory insights into the immunomodulatory activity of INT230-6.;
- Concomitant medications;
- INT230-6 injections (after all other evaluations for the visit according to the Time and Events (Table 12) have been completed except for the post injection vital signs);
- Over 20 subjects have received INT230-6 more than 3 times into both superficial and deep tumors, with more than 10 subjects having had multiple deep tumor injections. The SSC reviewed the subject safety on February 8th, 2019 and authorized initiation of biopsies from both superficial and deep tumors; On Cycle 1 Day 0, an on-study biopsy of an injected tumor is mandatory prior to INT230-6 injection. If possible, a biopsy of one (1) bystander tumor selected and taken by the attending physician; however, if risk is too high to such bystander tumor, then the biopsy should not be taken. The SSC shall review periodically to determine whether subject biopsies can continue to be taken.

12.1.3.2. Cycles/Doses 2 - 5

INT230-6 injections (after all other evaluations for the visit according to the Time and Events Table have been completed except for the post-injection vital signs). During cycles 4 and 5 there

is no scheduled dosing of INT230-6 for patients being dosed every 14 days (E cohort, may apply to combination cohorts, see supplement for specific schedules).

- Physical Exam: A Targeted physical examination will be conducted at all visits;
- Vital sign measurements to include temperature, pulse, O_2 saturation and resting blood pressure. On the day of each injection, vital signs will be obtained before injection and then 15, 30 and 60 minutes post injection;
- Weight;
- ECOG performance status;
- Any new ≥ Grade 3 laboratory abnormality such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Sponsor Medical Monitor should be contacted.;
- Hematology with differential;
  - Coagulation
- Clinical chemistry; as outlined in Section 12.1.2.
- First tumor imaging (CT/MRI chest/abdomen/pelvis) should be done at 12 weeks +/- 10 days from the date of the first baseline scan (Cycle 1, D0) with repeat scans every 9 weeks +/- 10 days thereafter until end of study or confirmed progression whichever occurs first;
- Urinalysis;
- Serum or urine pregnancy test to be performed locally (for all women of childbearing potential; pregnancy test must be negative before study drug administration to continue);
- Response assessment and documentation;
- On Cycle 2 Day 0 only, an on-study biopsy of an injected tumor is mandatory and if possible a biopsy of one (1) bystander tumor selected and taken prior to dosing by the attending physician; however if the risk is too high to take a biopsy from a bystander tumor, then a biopsy should not be taken. The SSC shall review safety periodically to determine whether additional subject biopsies can continue to be taken;
- Tumor samples that are available after completion of designated analyses may be used in the future for identification of potential predictive and/or pharmacodynamic markers. These assessments will provide exploratory insights into the immunomodulatory activity INT230-6;
- Concomitant medications and AE assessment;

Table 11: Schedule of events every 28 day dosing

Procedure	Cycle1 (+/- 1 Day)				Cycle 2-5 (+/- 1 Day)			Maintenance
	Day 0 dosing	Day 1	Day 7	Day 14	Day 0 dosing	Day 7	Day 14	INT230-6 dosing every 9 weeks +/- 10 days
					repeat every 28 days for each cycle			
Safety Assessments								
Physical Examination	X							
Targeted Physical Examination[2]		X	X	X	X	X	X	X
Weight[3]	X				X			X
Vital Signs[4]	X	X	X	X	X	X	X	X
Assessment of Signs and Symptoms	X	X	X	X	X	X	X	X
Adverse Events Assessment	X	X	X	X	X	X	X	X
Laboratory Tests[5]	X	X	X		X	X		X
Pregnancy test[6]	X				X			X
ECOG Performance status[7]	X	X	X	X	X	X	X	X
US/CT of injected tumor[8]	X				X			X
Tumor imaging (CT/MRI chest/abdomen/pelvis)[9, 10, 11]	X[11]				X[9, 10]			
Additional blood or radiographic measures clinically indicated[12]	X				X			X
Clinical Drug Supplies	X				X			
Dispense Study Treatment	X				X			
Vital Status								
On study biopsy[13]	X				X			
PBMS and Serum Sample				X	X			

Table 11: Schedule of events every 28 day dosing

	Cycle1 (+/- 1 Day)				Cycle 2-5 (+/- 1 Day)			Maintenance
Procedure	**Day 0 dosing**	**Day 1**	**Day 7**	**Day 14**	**Day 0 dosing**	**Day 7**	**Day 14**	**INT230-6 dosing every 9 weeks +/- 10 days**
					repeat every 28 days for each cycle			
Serum sample for pharmacokinetics	**X**	**X**	**X**		**X**	**X**		
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Footnotes are shown after Table 13

Table 12: Schedule of events every 14 day dosing (monotherapy E cohorts)

	Cycle1 (+/- 1 Day)					Cycle 2 (+/- 1 Day)				Cycle 3 (+/- 1 Day)			Maintenance
Procedure	**Day 0 dosing**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 0 dosing**	**Day 7**	**Day 14**	**Day 21**	**Day 0**	**Day 7**	**Day 14**	**Every 9 weeks +/- 10 days**
	Safety Assessments												
Physical Examination	X												
Targeted Physical Examination[2]		X	X	X	X	X	X	X	X	X	X	X	X
Weight[3]	X					X				X			X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Signs and Symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[6]	X			X		X		X		X			X
ECOG Performance status[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
US/CT of injected tumor[8]	X			X		X		X		X			X
Tumor imaging (CT/MRI chest/abdomen/pelvis)[9, 10, 11]	X[11]												X[9, 10]
Additional blood or radiographic measures clinically indicated[12]	X					X				X			X
Clinical Drug Supplies	X			X		X		X		X			X
Dispense Study Treatment	X			X		X		X		X			X

Table 12: Schedule of events every 14 day dosing (monotherapy E cohorts)

	Cycle1 (+/- 1 Day)					Cycle 2 (+/- 1 Day)				Cycle 3 (+/- 1 Day)			Maintenance
Procedure	**Day 0 dosing**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 0 dosing**	**Day 7**	**Day 14**	**Day 21**	**Day 0**	**Day 7**	**Day 14**	**Every 9 weeks +/- 10 days**
Vital Status													**X**
On study biopsy[13]	**X**					**X**							
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Anti-Cancer medications													**X**
ECG[14] if medically indicated	**X**												

Footnotes are shown after Table 13

Table 13: Schedule Follow up Period				
	End of Treatment[1],	Long Term Follow Up (every 9 weeks from last cycle)	End of Follow Up (Subject has PD and moves to Survival FU)	Survival Follow Up
Targeted PE[2]	X	X	X	
Weight[3]				
Vital signs[4]	X	X	X	
Assessment of SXS	X	X		
Adverse Events	X	X		
Laboratory Tests[5]	X			
Pregnancy test[6]	X			
ECOG[7]	X			
Tumor imaging[9 10]		X	X	
Additional blood or radiologic assessment[11], as applicable[12]	X	X		
Vital status				X
Con meds	X	X	X	
Report any subsequent anti-cancer therapy			X	X

1 EOT visit to be completed when a subject withdraws from treatment and is not going to proceed to additional cycles of treatment.
2 Physical examination to be conducted and any new or worsening signs and symptoms are to be recorded.
3 Height/weight to be taken at baseline must be collected at these times as well, and then only repeat weights at the start of each cycle.
4 O_2 saturation and resting blood pressure. On the day of each injection, vital signs will be obtained before injection and then 15, 30 and 60 minutes post injection. In addition, for cycle 1, vital signs will be collected at 180 and 360 minutes, including O_2 saturation, and resting blood pressure.
5 CBC with Differential, Chemistry and Urinalysis as outlined in Section 12.1.2. Grade 3 laboratory abnormality should be assessed for potential risk to continued dosing. In the event of uncertainty, the Sponsor medical monitor should be contacted.≥ Grade 3 laboratory abnormality should be assessed for potential risk to continued dosing.
6 Serum or urine pregnancy testing must be performed for woman of childbearing potential and found to be negative before dosing.
7 ECOG performance status to be assessed before each injection.
8 Measurements used to guide placement of the needle for injection.
9 The same technique (CT/MRI or PET/CT) used at screening should be used throughout the study.
10 Investigators will assess tumor response using CT/MRI or PET/CT measurements. Assessments should occur 12 weeks +/- 10 days from the first dose (Cycle 1, D0) and then every 9 weeks +/- 10 days for every image thereafter.
11 Tumor imaging only needs to be collected if it has not occurred within the last 29 days.
12 Serum based disease markers if appropriate will be collected at the same timepoints as tumor imaging. Other imaging to be collected as clinically indicated (i.e., brain scans, etc.).
13 Subjects must consent to fresh repeat biopsies of tumors taken prior to dosing on days 0 and 28 (day 0 in cycle 2) during the course of the study at injection sites are mandatory unless cleared by the Sponsor medical monitor. Additionally, 1 biopsy of an untreated bystander tumor that is readily accessible without the need for general anesthesia should be taken by the attending physician if possible; however, if risk too high such bystander biopsy should not be taken. **The post-dose biopsy sample must be taken from the same lesion(s) that were collected at pre-dose (C1D0). If there is an issue that precludes the ability to biopsy the same pre-dose lesion at the later timepoint (C2D0), please inform the Medical Monitor and attempt to biopsy from the pre-dose lesions during a subsequent visit.**
14 Baseline ECG to be done and repeated only if medically indicated throughout the study.

12.1.4. Follow-up Period

Follow-up visits will be conducted after completion of the Treatment Period (induction and maintenance for those cohorts with maintenance treatment) or as indicated in Section 5.4. Patients who receive all 5 treatment doses or discontinue treatment for any reason except Disease Progression, or Withdrawal of consent should enter Long Term Follow up Period. These patients are to be evaluated every 9 weeks including scans until disease progression or they receive an intervening anti-cancer medication. After documented disease progression or receipt of an intervening anti-cancer medication, patients will enter Survival Follow up. During this time, patients will be contacted every 3 months for patient status (phone call or clinic visit). For subjects who discontinue treatment due to progression, follow-up should be completed approximately every 3 months as noted below (survival follow up). Completion of subsequent follow-up visits will depend on the status of the subject at the end of treatment. All subjects will be followed from the last visit until progression, initiation of a new therapy, or the duration of the study (4 years), whichever occurs first.

Following completion of the treatment and follow-up periods, all subjects will be followed for survival after completion of treatment phases and through the follow up period of the protocol. Subjects will have their survival status assessed approximately every 3 months by either a telephone, in-person contact, or chart review until study completion or termination by the Sponsor. No other data (e.g., subsequent therapies, performance status etc.) beyond survival will be collected during these calls/visits.

12.1.5. Study Participation

Each subject will have their study participation documented, including the number of cycles completed, the duration of the Follow-up Period, and if discontinuing from the study, the reason for discontinuation. At the end of each cycle, the subject continuation status for each subject will be documented on the CRF.

If for any reason, either study treatment or observations were discontinued, the reason will be recorded. The primary reasons for discontinuation will be documented:

- Adverse event(s)
- Protocol violation
- Disease progression (clinical or radiological)
- Subject withdrew consent
- Subject is lost to follow-up
- Death
- Other

Subjects who discontinue from the study should be followed until resolution and/or stabilization of any adverse event. All subjects who discontinue from the study should complete Follow-up Visits to be monitored for 28 days following the last dose of INT230-6 for the occurrence of study drug-related adverse events or other clinically significant adverse event. Subjects who are unable to complete the follow-up visits should be contacted at least once within 28 days following the last dose INT230-6.

12.1.6. Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Sponsor
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration
- for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Inability to comply with protocol
- Discretion of the investigator
- Disease progression or clinical deterioration as defined in Section 9.3
- Dosing delays greater than the maximum allowed dosing delays as defined in Section 8.11. All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 12.1.4. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

12.1.7. Safety Evaluations

The following evaluations will be performed during the study to measure the safety and tolerability of INT230-6: clinical laboratory tests (blood and urine sampling for clinical laboratory parameters see below), pregnancy testing, ECOG performance status, physical examinations including vital sign measurements, ECG, and the incidence and severity of treatment-emergent adverse events.

Hematology

Hematology analyses will consist of the following tests:

Hemoglobin	Mean cell volume
Hematocrit	Mean cell hemoglobin
Red blood cell count	Mean cell hemoglobin concentration
Platelet count	White blood cell count (total and differential)
	Coagulation; PT, PTT/aPTT, INR

Clinical Chemistry

Clinical chemistry analyses will consist of the following tests:

Alanine aminotransferase	Creatine phosphokinase	Phosphorus
Albumin	Creatinine	Potassium
Alkaline phosphatase	Gamma-glutamyl transpeptidase	Sodium
Aspartate aminotransferase	Glucose	Thyroid Stimulating Hormone
Amylase	Lactate dehydrogenase	Total bilirubin
Bicarbonate	Lipase	Total protein
Calcium		Triglycerides
Chloride	Low density lipoprotein	Urea (or blood urea nitrogen)
Cholesterol (total)	Magnesium	Uric acid

Urinalysis

Urinalysis with microscopic analysis will be performed by the clinical laboratory. Analytes will include: pH, glucose, ketones, blood, and protein. If abnormalities are noted on any of the dipstick results, microscopic analysis will be performed.

12.2. Efficacy Evaluations

Measured qualitatively (present only at screening), absent, progression, stable, and unevaluable.

12.2.1. Primary Efficacy Parameter

The primary efficacy parameter is disease control rate (CR + PR + SD), as assessed using iRECIST (Appendix 1 Section 18.1). Per iRECIST criteria, up to 5 target tumors are identified at baseline and followed., In this study, a target tumor is a single injected tumor identified at baseline or post baseline, and up to 10 target tumors will be followed. Please refer to the Statistical Analysis Plan for tumor definitions. Subject to PI discretion, cohorts EC3, DEC2, FEC and potentially GEC may have any number of tumors injected during a given session. Record as many tumor measurements in the CRF as possible.

Evaluation of individual injected tumors will take place at every visit, with overall response (Complete, Partial, Stable, Progressive, Not Evaluable) adjudicated for each. ITR calculation could include original target tumors, bystander tumors that become injected, and new measurable lesions that are injected.

12.2.2. Additional Efficacy parameters

An additional efficacy parameter is the injected tumor response (ITR) and bystander tumor response (BTR) rate, defined as either the number of injected or non-injected bystander tumors with confirmed CR or PR, divided by the total number of injected or bystander tumors identified at baseline. Tumor response status will be assessed using iRECIST response categories for tumors that have not been injected (as detailed in Section 18.1). Up to 9 bystander tumors will be identified at baseline and followed. Evaluation of individual bystander tumors will take place at every visit, with overall response (Complete, Partial, Stable, Progressive,

Not evaluable) adjudicated for each. BTR calculation will only include bystander tumors that are not injected at that visit.

An exploratory analysis will combine all efficacy measures (injected and bystander) to calculate an overall response rate (ORR) using iRECIST criteria, with the modification to allow more than 5 target tumors in the calculation of sum of diameters. The ORR will be based on the number of subjects with confirmed CR or PR, divided by the total number of subjects with measurable disease at baseline.

12.2.3. Exploratory Biomarkers of Immune Response

Additional sample collections efficacy may be performed to measure the impact of INT230-6 upon the potency of the immune response and evaluate biomarkers that may ultimately be associated with beneficial clinical responses (refer to PK and Biomarker Manual for additional information on biopsies).

Samples (including serum and PBMCs) for evaluation of cytokines, lymphocyte phenotype (by flow cytometry), quantitative immunoglobulins, disease-related biomarkers (or antibody responses to selected antigens), cellular immune responses to tumor antigens, and a panel of recall non-tumor antigens may be assessed.

Available slides and tissue samples from tumor biopsies collected before enrollment in this study may also be examined for tumor markers and inflammatory infiltrates.

Readily accessible tissue from the research-related biopsies will be collected at baseline and then on study (refer to PK and Biomarker Manual for additional information). Tissue samples from these tumor biopsies, as well as from any other clinically indicated and consented biopsies conducted during the study will be collected, to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

Additional sample collections and analyses may be performed at selected study sites with a site-specific amendment. All samples collected for these exploratory analyses will be stored and may be used for subsequent research relevant to tumor immune response.

Blood biomarkers collections have been eliminated in Amendment 6.

The following table is a summary of the samples to be collected.

Table 14: Tumor Biopsy and Genetic Sample collection

Blood biomarkers collections have been eliminated in Amendment 6.

Collection timing	Tumor Biopsy	Whole Blood Gene Expression	Whole Blood SNP
Screening		X	X
Cycle 1, Day 0 (prior to treatment)	X[1]		
Cycle 2, Day 0 (prior to treatment)	X[1]		

[1]Following the completion of 20 subjects through at least 3 treatment cycles each with a minimum of 10 subjects having had deep tumors injections and review by the SSC of the safety, a biopsy may to be taken immediately prior to injection of INT230-6 (refer to PK and Biomarker Manual for additional information). Safety of biopsying to be reviewed after 5 subjects by SSC. As of this amendment, safety has been demonstrated, and all subjects will have tumor biopsies.

12.3. Pharmacokinetic Evaluations

12.3.1. Sample Collection Volumes and Timepoints

PK sampling has been discontinued in Amendment 6. The SSC has eliminated dose escalation in Amendment 5. Most recent PK data shows that only 5% of the active ingredients for a given dose are present in the blood and the concentrations show a meaningful dose response. As a result, the SSC determined that PK sample collection is no longer necessary in Amendment 6. A final PK analysis section will be included in the final clinical study report.

13. ADVERSE EVENT REPORTING

Clinical adverse events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded on the Medical History/Current Medical Conditions CRF.

13.1. Definitions

An adverse event is any undesirable sign, symptom, clinically significant laboratory abnormality, or medical condition occurring after starting study treatment, even if the event is not considered to be study drug-related. Each adverse event is to be reported on an Adverse Event CRF page. Adverse events are graded using the Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Information about all adverse events, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected, and recorded on the Adverse Event CRF page and followed as appropriate. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before the injection of study drug are only considered adverse events if they worsen after receiving any study drug. Clinical events occurring before the administration of study drug but after signing the ICF and providing HIPAA authorization are to be recorded on the Medical History/Current Medical Conditions CRF page. All laboratory values are to be reviewed by the Investigator and abnormal values will be graded according to CTCAE Version 4.03 and reported in the study report.

A laboratory abnormality is considered an adverse event if it results in:

- discontinuation from study drug,
- necessitates therapeutic medical intervention,
- if the Investigator assesses the abnormality as an adverse event, or
- any laboratory test that is clinically significant or meets the definition of a SAE

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value). These adverse events will be recorded on the Adverse Events CRF page and will include all signs, symptoms, or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE Grade 1 through 5 or severity if CTCAE is not available
4. Relationship to the study drug - related or not related
5. Relationship to the dosing procedure – related or not related
6. Action(s) taken with study drug
7. Whether event was serious
8. Whether event is ongoing (i.e., not resolved).

Relationship to Study Drug

The relationship of each adverse event to study drug will be defined as "not related" or "related". The Investigator is responsible for determining the study drug relationship for each adverse event that occurs during the study. Assessments are to be recorded on the appropriate CRF page.

Not related

The temporal relationship of the clinical event to study drug administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Related

The temporal relationship of the clinical event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Action(s) Taken

The actions taken with study drug in response to an adverse event are described. One or more of these are to be selected:

- No action taken
- Study drug permanently discontinued due to this adverse event
- Study drug temporarily interrupted
- Study drug dosage adjusted

13.1.1. Safety Reporting for Adverse Events

All adverse events or other clinically relevant adverse events occurring up to 28 days after administration of the last dose of study drug will be collected for subjects continuing in the study.

For subjects who discontinue from the study within 28 days after the administration of the last dose of study drug:

- Study drug-related adverse event information will be collected and should be followed to resolution/stabilization
- Adverse events that lead to the discontinuation should be followed to resolution/stabilization
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit
- Only study drug-related serious or other clinically significant adverse events will be collected for all subjects > 28 days after the administration of the last dose of study drug.

A *nonserious adverse event* is an AE not classified as serious.

The collection of nonserious AE information should begin at initiation of study drug (day 0) and should conclude 28 days after last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 13.2). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

13.2. Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

1. is fatal or life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
2. requires or prolongs hospitalization;
3. is significantly or permanently disabling or incapacitating;
4. constitutes a congenital anomaly or a birth defect; or
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. (Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent (e.g. any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is a SAE.

Although pregnancy, overdose (greater than 50% more than the intended dose) and cancer are not always serious by regulatory definition, these events must be reported to the Sponsor within 24 hours (See Section 13.5 for reporting pregnancies).

NOTE: Progressive disease is not considered a SAE.

The following hospitalizations are not considered SAEs in Sponsor clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Hospitalizations occurring under the following circumstances are not considered serious adverse events: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, outpatient basis that does not result in admission (unless fulfilling the criteria above); hospitalization as part of the normal treatment or monitoring of the studied indication; or hospitalization to facilitate the work up of a Grade 1 adverse event, including overnight hospitalization following study drug administration for nonmedical reasons.

13.3. Rapid Notification of Serious Adverse Events

13.3.1. Reporting Responsibility

Any serious adverse event occurring in a subject after he/she has provided informed consent and HIPAA authorization, and while receiving study treatment; or during the 28 days following study drug administration; or within 28 days of the last visit for screen failures must be reported.

The timeframe for reporting after discontinuation of study drug may be extended if there is a strong suspicion that the study drug has not yet been eliminated or the pharmacodynamic effects of the study drug persist beyond 28 days. All serious adverse events must also be reported for the timeframe in which the study drug interferes with the standard medical treatment given to a subject.

The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. A SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that a SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Each serious adverse event must be reported by the Investigator to Propharma (SAE Reporting FAX 919-844-6948), or designee, within 24 hours of learning of its occurrence, even if it is not felt be related to study drug. Serious adverse events occurring after 28 days from the last dose of INT230-6 must be reported if deemed related to study drug. The report must include the adverse event term, subject identifier, attribution, description, concomitant medication used to treat the adverse event, and any other relevant information. Follow-up information about a previously reported serious adverse event must also be reported to Sponsor within 24 hours of receiving the information. Sponsor, or its designee, may contact the Investigator to obtain further information about a reported serious adverse event. If warranted, an Investigator Alert may be issued to inform all Investigators involved in any study with the same study drug that a serious adverse event has been reported.

13.3.2. Reporting Procedures

The Investigator must complete the Serious Adverse Event Report Form in English, assess the causal relationship to study drug, and send the completed form to the **SAE Reporting FAX Number** (919-844-

6948) within 24 hours, to Sponsor or its designee. The study monitor will review the Serious Adverse Event Report Form and the supporting source documents during monitoring visits.

Follow-up information should be sent to the same SAE Reporting Fax Number that received the original Serious Adverse Event Form, within 24 hours of the time the information is known. Either a new Serious Adverse Event Report Form is faxed (indicating that the information is a follow-up), or the original form may be re-faxed (with the new information highlighted and a new date provided). The follow-up report should describe whether the serious adverse event has resolved or is continuing, if and how it was treated, and whether the subject continued or permanently discontinued study participation. The form(s) and FAX confirmation sheet(s) must be retained in the investigational site study file.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee/Review Ethics Board (IRB/IEC/REB) of the serious adverse event and providing them with all relevant initial and follow-up information about the event. Sponsor or designee will communicate serious adverse events to the study sites as required by regulatory authorities.

SAEs must be recorded on the Sponsor SAE Report Form; pregnancies on a Sponsor Pregnancy Surveillance Form. These original Sponsor Forms are to remain on site. SAEs, whether related or not related to study drug, and pregnancies must be reported to Sponsor within 24 hours via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

SAE Email Address: clinicalsafety@propharmagroup.com

SAE Facsimile Number: 919-844-6948

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the Sponsor using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

13.4. Overdose

An overdose is defined as the accidental or intentional injection of any excessive dose of INT230-6 (for this study it is defined as $\geq$50% of the intended dose).

Any overdose must be recorded in the trial medication section of the CRF. In the event of overdose of INT230-6, subjects should receive appropriate advice and supportive medical care by the investigator or his/her designee and be followed-up accordingly. For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or non-serious) – must be reported to the Sponsor in an expedited manner.

13.5. Pregnancy

Pregnancy testing must be performed in all women of childbearing potential throughout the study as specified in the Time and Event Schedule table, and the results of all pregnancy tests (positive or negative)

are to be recorded on the CRF. All women of childbearing potential must have a negative pregnancy test before each INT230-6 injection. If the pregnancy test is positive, the subject must not receive INT230-6 and must not continue in the study. The subject will be followed to determine the outcome of the pregnancy.

Females of non-childbearing potential are defined as females with functioning ovaries with a documented history of tubal ligation or hysterectomy or females who are post-menopausal, as defined by 12 months of spontaneous amenorrhea with an appropriate clinical profile, e.g., age appropriate, > 45 years, in the absence of hormone replacement therapy. In questionable cases, a blood sample for follicle stimulating hormone and estradiol will be obtained to confirm childbearing potential.

In addition, all women of childbearing potential should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the study Treatment Period part of the study or during the 60-day period following their last dose of study drug.

Male subjects should contact the Investigator immediately if they suspect they may have fathered a child during the study Treatment Period part of the study or during the 180-day period following their last dose of study drug. When possible, partner's pregnancies should be followed (to term) to determine the outcome.

13.5.1. Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued for the female study participant in an appropriate manner. Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g. x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Pregnancies should be reported to Propharma but will not be considered as SAEs. They will be tracked to determine the final outcome of the fetus. Propharma Pregnancy Questionnaire and Outcome forms will be used for this function. If the pregnancy ends in an unfavorable manner (i.e., miscarriage, birth defect, etc.), the investigator is responsible for determining if the outcome met SAE criteria.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Infants should be followed for a minimum of 8 weeks.

13.6. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

14. STATISTICAL METHODS

14.1. Sample Size Determination

The sample size (estimated to be between 100 and 175 subjects) during dose escalation and expansion cannot be precisely determined but depends on the observed toxicity.

There are 6 cohorts of subjects in the escalation portion of the protocol where INT230-6 dosing is increased over 5 doses. These escalation cohorts are (A1, B1, EA, EC, EC2 and DEC).

There are potentially 4 fixed dose cohorts (EC3, DEC2, FEC and G) that use a maximum total fixed dose of INT230-6 of 175 mL for all 5 induction doses as well as a maintenance dose. In EC3, DEC2 and FEC expansion cohorts, 10-16 subjects will be treated at fixed INT230-6 doses in a tumor type, to provide additional safety information and preliminary assessment of tumor response within a disease indication. G cohort will be a combination of fixed dose INT230-6 with other molecules. With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type the 90% confidence interval for an objective response rate would be (5.3% to 42%) if 3 (19%) subjects had a response, (9.0% to 48%) if 4 (25%) subjects had a response and (13.2% to 54.8%) if 5 (31%) subjects had a response.

14.2. Study populations

14.2.1. All Enrolled Population

All subjects who sign informed consent form will be included. Subject disposition will be tabulated using this data set.

14.2.2. All Treated Population

All subjects who receive at least 1 dose or any partial dose of INT230-6. This population will be used for safety analyses, and primary efficacy analyses.

14.2.3. Pharmacokinetic Data Set

All available concentration-time data from subjects who receive INT230-6 will be reported. All available derived PK parameter values will be included in the PK data set and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis. PK sampling has been eliminated in Amendment 6.

14.2.4. Response Evaluable Data Set

Response evaluable subjects will be defined as all subjects who receive at least one dose of INT230-6, have a baseline tumor assessment with measurable disease, and one of the following: 1) at least one on-treatment tumor evaluation, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation.

14.2.5. Exploratory Biomarker (Immune Function and others) Data Set

All subjects who receive at least one dose of INT230-6 and have at least one measurement for a specific marker will be included in the data set for that marker. All treated subjects with at least one baseline measurement will be included in predictive analyses; treated subjects with baseline measurement and at least one on treatment measurement will be included in pharmacodynamic assessments. Blood biomarker sampling has been eliminated in Amendment 6.

14.2.6. Retreatment Population

For cohorts A1, B1, EA, EC, EC2, DEC, those subjects who have completed treatment and have not started any subsequent anti-cancer therapy were eligible for retreatment. Subjects who qualified for re-initiation of treatment were evaluated for safety and efficacy based on availability of data.

14.3. Statistical Considerations

Please refer to the Statistical Analysis Plan (SAP).

14.3.1. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical conditions will be summarized by dose level using descriptive statistics.

14.3.2. Extent of Exposure

The dose of INT230-6 taken by subjects will be summarized by total dose and number of tumors injected. Additional parameters will be summarized, such a reason for study drug interruption and number of tumors with drug exuded. A by-subject listing of treatment exposure will be generated.

Combination study drugs for cohorts 7 and higher will also be summarized. Details will be provided in the statistical analysis plan.

14.3.3. Tumor Response.

The primary efficacy endpoint of disease control rate (DCR), defined as the sum of complete, partial and stable disease responses divided by the total number of subjects in the efficacy population, will be determined per iRECIST criteria for fixed dose and expansion cohorts. DCR will be tabulated by overall and by tumor type. Exploratory analysis will be conducted by cohort, Phase 1 cohorts (monotherapy and PD-1), Phase 2 cohorts (monotherapy, PD-1 and CTLA-4), Phase 1 and 2 cohorts (monotherapy and PD-1), tumor types, study visit, number of INT230-6 doses, number of cycles of INT230-6 (i.e., retreatment), and number of prior lines of therapy. Since iRECIST methods were not implemented at the time of dose escalation, DCR for these cohorts will be analyzed per RECIST v1.1.

For DCR, exact binomial 95% confidence intervals will be determined by Clopper-Pearson method. Median time to response and duration of response will be summarized for those subjects with confirmed responses, using Kaplan-Meier method; Progression free survival (PFS) will be similarly summarized. Individual tumor measurements, tumor burden and % changes in tumor burden will be listed. Changes in tumor burden will be presented graphically.

14.3.4. Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). Concomitant medications will be summarized. Tabulation will be made with respect to the proportion of subjects taking at least 1 concomitant medication for each preferred term during the study. A listing of concomitant medications by subject will be provided.

14.3.5. Safety

The primary objective is to assess the safety and tolerability of multiple intratumoral doses of INT230-6 in subjects with advanced or recurrent malignancies. This will be assessed by the rate of $\geq$ grade 3 AEs

attributed to study drugs (INT230-6 and others per the appropriate protocol supplement), and study procedure, and not the underlying disease.

Safety Analyses:

All recorded adverse events will be listed and tabulated by system organ class, preferred term, and coded according to version 19.1 of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized. Any significant physical examination (PE) findings and results of clinical laboratory tests will be listed. Electrocardiogram (ECG) listings will be evaluated by the investigator and abnormalities, if present, will be listed.

Adverse Events will be summarized for all reported data and by study period: a) up to and including 28 days post last dose of initial treatment, and b) from first dose of re-initiation of treatment, for subjects who re-initiate study therapy while in follow-up, up to 28 days post-dose of the last re-treatment dose. In order to better estimate MTD or toxicity frequency of some events of interest, logistic regression or constrained Bayesian estimation may be used to model frequency by INT230-6 dose level for each population arm or across population arms when combination of different population arms is deemed appropriate.

The following safety parameters will be evaluated:

Adverse Events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 28 days of discontinuation of dosing. The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. A SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that a SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) to categorize a system organ class and a preferred term for each adverse event. The number of subjects who experienced at least 1 adverse event, study drug related adverse event, severe (Grade 3 or above) adverse event, serious adverse event, and the number of subjects withdrawn due to adverse events will be summarized. For each system organ class and preferred term, summaries will be made with respect to the number and proportion of subjects having at least 1 occurrence of an adverse event during the study, using the worst grade reported within a subject. The incidence of adverse events will be presented overall, by system organ class and preferred term, intensity (based on NCI CTCAE Version 4.03), and additional grouping by severity and relationship to study drug. Individual listings of adverse events will be provided.

DLTs and study drug-related Grade >2 adverse events will be listed individually.

Physical Examination

Abnormal PE findings with onset prior to first dose of study drug will be recorded as medical history. Any abnormal or clinically significant findings on or after dosing will be recorded as an adverse event. Clinical significance will be determined by the Principal Investigator at each site.

Individual medical/surgical history will be listed by subject. Individual abnormal or clinically significant PE findings after dosing will be recorded as an adverse event and listed separately with AEs.

Vital Signs

Vital sign measurements and change from baseline will be summarized. Vital signs include weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI, derived), heart rate, oxygen saturation, and temperature. Individual vital sign measurements will be listed.

ECGs

ECG data will be read and interpreted locally. Summary statistics of ECG overall interpretation will be displayed. Per subject ECG test results at will be listed.

Abnormal clinically significant ECG findings on or after informed consent will be recorded as an adverse event and displayed with AEs.

Clinical Laboratory Tests

Clinical laboratory values will be summarized in SI units. Severity grades will be programmatically calculated using standard American Medical Association's (AMA) laboratory normal ranges [AMA Manual of Style, AMA 2009] and the quantitative NCI CTCAE 4.03 criteria (when available for a specific laboratory abnormality). Laboratory values considered to be normal by CTCAE criteria, meaning they do not qualify as Grade 1-4, will be assigned a severity grade of 0.

Summary statistics of numerical laboratory test results and changes of test results from baseline will be reported for hematology, coagulation, serum chemistry, and urinalysis at each scheduled time point. For values with categorical results, the frequency and percentage of each result category will be tabulated at each scheduled time point. Shift tables will also be included reporting change from baseline category (low, normal, high) to post-dose category (low, normal, high). Abnormal laboratory values that lead to a change in subject management or that are considered to be of clinical significance will be reported as an adverse event (serious adverse event if relevant) and summarized by SOC/PT and according to severity in the appropriate AE tables. Clinical significance will be determined by the Principal Investigator at each site.

Pregnancy test results will be displayed in a listing.

ECOG Performance Status

ECOG performance status will be summarized using descriptive statistics. ECOG performance status per subject during the trial will also be listed.

14.4. Efficacy

14.4.1. Pharmacokinetic Parameters

The release kinetics of each analyte is not expected to be uniform across subjects. Sponsor shall assess the blood concentrations of the three analytes for each subject at the first cycle. Sponsor shall correlate the systemic measurement [maximum plasma drug concentration (Cmax), area under the curve (AUC)] of the 3 analytes to measured markers of systemic toxicity [in particular renal and blood – the known toxicities of the two active agents; cisplatin (CIS) & vinblastine (VBL]. Human plasma will be analyzed for the concentration of VBL and 8-((2-hydroxybenzoyl)amino)octanoate (sodium salt form) (SHAO) using validated LC/MS/MS methods, and for cisplatin using a validated ICP-MS method. For pharmacokinetic profiling platinum drugs, total platinum levels in subject plasma or urine are routinely determined by spectroscopy methods as a surrogate. Thus, an ICP-MS method is developed for this study to measure total platinum in human samples as a surrogate for cisplatin.

In addition, scatter plots of Cmax and AUCTAU versus INT230-6 dose volume will be provided for the first cycle. Dose proportionality per subject normalized to tumor volume will be assessed, by estimating the slope of linear regression of SHAO/CIS/VIN log(Cmax) on log(dose) and of log(AUCTAU) on log(dose) based on a power model. Point estimates and 90% confidence intervals for the dose proportionality parameter (slope of the linear regression) will be calculated for Cmax and AUCTAU. Summary statistics for trough [minimum plasma drug concentration Cmin)] concentrations will be tabulated by dose and study cycle. Plots of Cmin vs. cycle will be assessed for cohorts by combining A1, B1 versus E Cohorts and grouping subjects by similar dose volumes of INT230-6. Pharmacokinetic concentrations from sparse samples will be listed, and may be used in combination with other studies for exposure-response or population pharmacokinetic modeling, which will be part of a separate report.

Administrative interim analyses of pharmacokinetic may be provided at various times during the study in order to support program decisions or publications. PK sampling has been eliminated in Amendment 6.

14.4.2. Exploratory Biomarkers (Immune Function and others)

The pharmacodynamic effects based on the immunomodulatory activity of INT230-6 on selected immune cell populations (for example, T-cell repertoire and their changes (or percent changes) on flow cytometry) and soluble factors in blood (cytokines), exploratory immune function markers including flow cytometry markers, humoral and cellular immune responses to tumor antigens (quantitative immunoglobulins, quantitative inflammatory infiltrates, when available) and a panel of recall non-tumor antigens will be assessed by summary statistics for outcomes from these markers and their changes (or percent changes) from baseline tabulated. In addition, the time course of biomarker outcomes will be conveyed graphically, by summary plots (i.e., box plots) or individual subject plots over time. Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure will be explored. Possible associations of various biomarkers measures (baseline value or change from baseline) with clinical outcome (e.g., tumor response) may will be explored based on data availability, using response-evaluable subjects, to assess predictive markers in tumors. Methods such as, but not limited to, logistic regression may be used to explore such associations. Measures from markers based on optional samples, e.g., tumor-based markers may be similarly presented, depending on data availability.

Potential associations of various biomarker measures (baseline value or change from baseline) with clinical outcome (e.g., tumor response or disease control) will be explored e.g., for expression levels of PD-L1 protein measured by immunohistochemistry techniques in tumor sections at baseline may be explored based on data availability, using response-evaluable subjects, to explore assess potential predictive effects of these

markers. Methods such as, but not limited to, logistic regression may be used to further assess such associations.

Measures from markers based on optional samples, e.g., tumor-based markers may be similarly presented, depending on data availability.

Administrative interim analyses of biomarker data may be provided at various times during the study (e.g., for the initial and the additional study cohorts) in order to support program decisions or publication. Blood biomarker assessments have been eliminated in Amendment 6.

15. ETHICAL ASPECTS

15.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with Sponsor and site SOPs. These are designed to ensure adherence to Good Clinical Practice (GCP), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP 1996 and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and Title 21, Part 312 (21CFR312).

The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee/Review Ethics Board (IRB/IEC/REB) approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment).

All potential serious breaches must be reported to Sponsor immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

15.2. Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. In CRFs and other study documents submitted to Sponsor or its designee, subjects will be identified by their initials, subject number, date of birth, and gender.

Personal medical information may be reviewed and/or copied for research, quality assurance, and/or data analysis. This review may be conducted by the study monitor, properly authorized persons on behalf of Sponsor, an independent auditor, IRBs/IECs or regulatory authorities. Personal medical information will always be treated as confidential.

15.3. Institutional Review Board/Independent Ethics Committee/Review Ethics Board

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC/REB. A signed and dated statement that the protocol, and ICF, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects have been approved by the IRB/IEC must be given to Sponsor before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to Sponsor or its designee. Any amendments to the protocol which need formal approval, as required by local law or procedure, will be approved by this committee. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes).

The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g. expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

15.4. Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Investigator, or designee, will explain to each subject (or legally authorized representative) the nature of the research study, its purpose, the procedures involved, the expected duration of subject participation, alternative treatment, potential risks and benefits involved, and any discomfort which may occur during the subject's participation in the study. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No subject can enter the study and no study-related procedures can be done before his/her informed consent has been obtained.

The ICF must be submitted by the Investigator with the protocol for IRB/IEC approval. Sponsor supplies a proposed ICF template that complies with regulatory requirements, includes all elements required by ICH, GCP and applicable regulatory requirements, and is considered appropriate for the study. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. Any changes to the proposed ICF suggested by the Investigator must be agreed to by Sponsor or its designee before submission to the IRB/IEC, and a copy of the approved version must be provided to the Sponsor study monitor after IRB/IEC approval.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.

6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The consent form must also include a statement that Sponsor and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (e.g., stroke subjects, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

16. ADMINISTRATIVE REQUIREMENTS

16.1. Protocol Amendments

Any change or modification to this protocol requires a written protocol amendment that must be approved by Sponsor before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/IEC of all centers and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC must be given to the Sponsor study monitor, or their designee. Examples of amendments requiring such approval are:

1. Increase in drug dosage or duration of exposure of subjects, or any significant increase in the number of subjects under study;
2. Significant change in the study design (e.g., addition or deletion of a control group);
3. Increase in the number of procedures to which subjects are exposed; or
4. Addition or deletion of a test procedure intended to improve safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by Sponsor in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary and is implemented by him/her for safety reasons, Sponsor should be notified and the IRB/IEC for the center should be informed within 1 working day. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Sponsor
- Regulatory Authority(ies), if required by local regulations
- Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Sponsor.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s). Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval; however, the IRB/IEC for each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include, but are not limited to:

1. Changes in the staff used to monitor studies (e.g. Sponsor staff versus a contract research organization); and

2. Minor changes (within regulatory guidelines) in the packaging or labeling of study drug.

16.2. Monitoring Procedures

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol, CRFs, and other study documents with the Investigators and their staff. During the study, the Sponsor Study Monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and also to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the study monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Sponsor monitoring standards require full verification for the presence of informed consent, HIPAA authorization, adherence to the inclusion/exclusion criteria, documentation of serious adverse events, and recording of efficacy and safety variables. Additional checks of the consistency of source data with the CRFs are performed according to the study-specific monitoring plan.

Representatives of Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Sponsor audit reports will be kept confidential.

The investigator must notify Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor.

16.3. Investigational Site Training

Sponsor and its contracted study management company, Catalyst, will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, deep tumor dosing procedures and enrollment of WOCBP.

16.4. Recording of Data and Retention of Documents

All information required by the protocol should be provided; any omissions or corrections should be explained. All CRFs should be completed and available for collection within a timely manner, preferably no more than 10 days after the subject's visit (except for the last visit of the last subject, which should be completed in a timely manner, preferably within 5 working days), so that the study monitor may check the entries for completeness, accuracy and legibility, ensure the CRF is signed by the Investigator and transmit the data to Sponsor or its designee.

The CRF will be completed by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

The Investigator must maintain source documents for each subject in the study. All information on CRFs will be traceable to these source documents, which are generally maintained in the subject's file. The source documents will contain all demographic and medical information, including laboratory data, ECGs, etc., and also a copy of the signed informed consent/HIPAA authorization, which should indicate the study number and title of the study.

Essential documents, as listed below, will be retained by the Investigator for the maximum period required to comply with national and international regulations, or institutional procedures, or for the period specified by the sponsor, whichever is longer. Sponsor will notify the Investigator(s)/institution(s) when study-related records are no longer required to be retained. The Investigator agrees to adhere to the document retention procedures by signing the protocol. The investigator must contact Sponsor prior to destroying any records associated with the study.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to Sponsor.

Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. CRF copies;
5. Subjects' ICF/HIPAA authorization; and
6. Any other pertinent study documents.

16.4.1. Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g. lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable

- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

16.4.2. Case report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub-investigator electronically through the Sponsor's electronic data capture tool.

Each individual electronically signing electronic CRFs must meet Sponsor training requirements and must only access the Sponsor electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

16.5. Auditing Procedure

In addition to the routine monitoring procedures, Sponsor, or its designees, may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. Sponsor, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform Sponsor immediately that this request has been made.

16.6. Publication of Results

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Sponsor. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Sponsor statisticians, and not by the Investigators themselves. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Sponsor.

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

Sponsor must receive copies of any intended communication in advance of submission (at least 30 working days for a journal submission and 15 days for an abstract or oral presentation). Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently disclosed, and provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers, as well as Sponsor personnel.

16.7. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by Sponsor or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by Sponsor (protocols, Investigators' Brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from Sponsor, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

16.8. Discontinuation of Study

Sponsor reserves the right to discontinue study for any reason at any time.

16.9. Data Management

16.9.1. Data Collection

Investigators must enter the information required by the protocol into the Electronic Data Capture (EDC) system. The electronic CRF (eCRF) will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

16.9.2. Database Management and Quality Control

Data items from the CRFs will be entered into the study database using data entry with verifications. Subsequently, the information entered into the database will be systematically checked by Data Management staff following Sponsor, or its designee, data management procedures. Obvious errors will be corrected by Sponsor personnel, or its designee. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the study site for resolution. After receipt in Data Management, the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be conducted as agreed upon by relevant team members.

Data will be entered into the EDC system by the authorized study site personnel. Electronic queries will be used to communicate eligible discrepant data with the study sites.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the Sponsor study team.

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18. APPENDICES

18.1. Appendix 1: iRECIST

18.1.1. iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

18.1.2. Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in Table 15 , the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

18.1.3. New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions

identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 15: Time-point (TP) iResponse Time Point Response (TPR)

Target Lesions	Non-Target Lesions*	New Lesions*	No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change O R decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non- iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

Table 16: iRECIST Best Overall Response (BOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

18.1.4. Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

18.1.5. Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions (including target, bystander, and non-target) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

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

Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case.[4] For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

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

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

19. SUPPLEMENTAL COMBINATION COHORTS

19.1. SUPPLEMENT A : COMBINATION OF PEMBROLIZUMAB WITH INT230-6 ARM DEC AND DEC2 SPECIFIC INSTRUCTIONS

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25. SUPPLEMENT B : COMBINATION OF IPILIMUMAB WITH INT230-6

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