STATISTICAL ANALYSIS PLAN

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

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SIGNATURE PAGE

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REVISIONS HISTORY LOG

Changes to the approved SAP should be logged in this table.

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision
2.0	04SEPT2020	LKing	Synopsis	Updated to make more succinct and less repetitive of protocol.
			Section 3	Updated objectives and endpoints per Protocol Amendment 5
			Section 4.1	Updated per Protocol Amendment 5 and to make more succinct. Removed study schematic figure. Added table to summarize cohorts.
			Section 5	Updated per Protocol Amendment 5 sample size estimates and informed consent documents.
			Section 6	Defined the retreatment population
			Section 7.1	Added convention to present tables by study part (Dose Escalation and Highest Dose), thereby creating table repeats for each study part.
			Section 7.5	Updated list of subgroups for analysis.
			Section 7.6	Added conventions to be used for missing dates.
			Section 8.4	Added pembrolizumab and ipilimumab as combination study drugs
			Throughout	Cosmetic editing. Additional analyses added per sponsor requests and per Protocol Amendment 5.
2.1	21Dec2020	Dtemplin	Throughout	Cosmetic editing Updated abbrevations table and list of tables

			Section 9.3	Added last treatment date to PFS censoring rule.
			Section 10.1	Added related to pem or ipi to overall AE summary
			Section 12	Removed association analysis.
2.2	23Feb2021	PHealy	Throughout	Cosmetic editing and formatting
			Section 10.1	Revised definition of treatment emergent adverse event to match protocol
2.3	22Aug2022 07OCT2022	PHealy LBender	Throughout	Editing and formatting based preparation for study closure.
2.4	29Nov2022	PHealy	Throughout	Editing in response to Intensity review.
3.0	12Dec2022	PHealy	Throughout	Editing in response to Intensity review. Particular focus regarding inability to utilize RECIST/iRECIST
3.1	22Feb2023	LKing/Intensity	Section 9.1	Added efficacy analysis with response evaluable population. Added new population – scan evaluable population.
			Section 9.2	Updated censoring rule for OS.
			Section 10.1	Clarified groups for maximum severity AE tables
			General	Reference to SAP appendix with programming clarifications

* Provide first initial and last name.
** Update the last revision dates on the cover page and the header.

SYNOPSIS

Sponsor: Intensity Therapeutics, Inc., Westport, CT	
Product: INT230-6	**Phase of development:** Phase 1/2
Protocol title: A Phase 1/2 Safety Study of Intratumorally Administered INT230-6 in Adult Subjects with Advanced Refractory Cancers	

Objectives:

Primary:

- The primary objective is to assess the safety and tolerability of multiple intratumoral (IT) 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 or the treatment when combined with immunotherapies and not the underlying disease.

Secondary:

- Assess the preliminary efficacy of INT230-6 alone and when combined with immunotherapies by measuring the disease control rate (CR+PR+SD) as assessed by iRECIST
- 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
- Characterize the overall safety profile of the 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 RECIST or iRECIST
- Characterize the pharmacodynamics (PD) profile of the INT230-6 formulation in subject blood and 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 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 alone or as a treatment combined with immunotherapies. A sentinel subject was enrolled at the lowest dose and followed for 4 weeks prior to escalating or adding additional subjects. Gradual intra-subject dose escalation was 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 was complete, and no MTD was obtained, then set a maximum total dose of 175 mL of INT230-6 was to be used for all dosings. In certain amendment INT230-6 treatment shall consisted of an induction phase for certain cohorts along with a maintenance regimen. INT230-6 was also tested in combination with checkpoint antibodies.

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). The first (A) is 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). The 2nd (B1) cohort is in deep tumors and starts with up to 5.0 mL and escalates the total dose and maximal dose per any one tumor. Cohort 3 (EA) will explore an every 2 week administration in superficial tumors. Cohort 4 (EC) follows the every 2 week schedule at a higher drug load (1:2 ratio) in both superficial and deep tumors and will escalate the total dose and maximal dose per any one tumor. Cohort 5 (EC2) follows the Q2 week schedule at an intermediate drug load (1:3 ratio) in both superficial and deep tumors and will escalate the total dose and maximal dose per any one tumor. The 6th cohort (DEC) doses combinations of pembrolizumab and escalating doses of INT230-6 and includes a safety lead-in cohort that doses INT230-6 only into superficial tumors.

Maximum Highest Dose of INT230-6

There are 3 cohorts that use up to a maximum total dose of INT230-6 of 175 mL for all 5 induction doses as well as a maintenance dose. The maintenance dose is a single dosing session of INT230-6 given every 9 weeks ± 10 days up to a maximum total dose amount of 175 mL. The maximum 175 mL dose cohorts were EC3, DEC2, and FEC, and each followed 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) dosed INT230-6 alone for any tumor type. The 8th cohort (DEC2) combined fixed dose of pembrolizumab with the same INT230-6 dosing regimen as EC3 as outlined in Protocol Supplement A. The 9th cohort (FEC) was a combination of a CTLA4 antibody, ipilimumab, with the same INT230-6 dosing regimen as EC3. A 10th cohort (G Cohort) was designed to be a combination of INT230-6 with another molecule. However, no other cohort after FEC was added. All cohorts and decisions to escalate the dose and introduce new subject populations were governed by the Study Steering Committee (SSC).

Expansion Cohorts

DEC2 and FEC are expansion cohorts of 10-16 subjects with various tumor types. These groups allowed for better point estimates of the safety and preliminary efficacy in a homogenous population of INT230-6 combined with immune checkpoint inhibitor drugs. Decisions on expansion cohorts for monotherapy (e.g., for EC3) were possible; however, no such cohort was added.

Number of subjects enrolled:

The sample size was estimated to be between 100 and 175 subjects during dose escalation and expansion. The final enrollment consisted of 110 subjects two of whom participated in more than one cohort.

Statistical methods:

Safety Analyses: All recorded adverse events were listed and tabulated by system organ class, preferred term, dose and cohort and coded according to version 25.1 of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of adverse events were tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results were listed and summarized by cohort. Any significant physical examination (PE) findings and results of clinical laboratory tests were to be listed. Electrocardiogram (ECG) listings were to be evaluated by the investigator and abnormalities, if present, were to be listed.

Adverse Events were summarized for all reported data and by study period: a) up to and including 28 days post last dose of initial treatment.

Efficacy Analyses: 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 criteria based on RECIST or iRECIST. DCR was tabulated overall and by subgroups of interest.

For DCR, exact binomial 95% confidence intervals will be computed using the Clopper-Pearson method. Median time to response and duration of response will be summarized for those subjects with responses, using the Kaplan-Meier method; overall survival (OS) will be similarly summarized. Individual tumor measurements, tumor burden, % changes in tumor burden, and progression free survival (PFS) will be listed.

Changes in overall survival will be presented graphically for all monotherapy subjects, for monotherapy subjects receiving an INT230-6 dose volume over the course of their treatment less than or ≥ 40% of their incoming reported total tumor burden, with pembrolizumab, with ipilimumab and in all sarcoma types (collectively) for monotherapy and combined with iplimumab.

Pharmacokinetic Analyses: The pharmacokinetic analyses described will be reported in a separate report. A brief summary of the results will be included in this CSR. 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 (C_{max}), 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 will be developed for this study to measure total platinum in human samples as a surrogate for cisplatin.

In addition, a separate pharmacokinetic report shall be prepared that showtime plots of plasma concentrations, C_{max} and AUC_{TAU} 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 $\log(C_{max})$ 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 C_{max} and AUC_{TAU}. Summary statistics for trough [minimum plasma drug concentration C_{min}] concentrations will be tabulated by dose and study cycle. Plots of C_{min} 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 the separate report.

Exploratory Biomarkers (Immune Function and others): The analyses regarding biomarkers to assess pharmacodynamic effects will be reported in separate report(s). A brief summary of the biomarker work shall be included in this CSR.

Possible associations between changes in biomarker measures of interest and pharmacokinetic exposure were explored. Possible associations of various biomarkers measures (baseline value or change from baseline) with clinical outcome (e.g., tumor response) may be explored based on data availability. Administrative interim analyses such as ad hoc presentations or date for safety meetings 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. No formal interim analyses were conducted for this study. Any reports for exploratory biomarkers will be added as addendums to the SAP.

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
SIGNATURE PAGE 2
REVISIONS HISTORY LOG 3
SYNOPSIS 5
TABLE OF CONTENTS 8
LIST OF TABLES 10
1. LIST OF ABBREVIATIONS 11
2. INTRODUCTION 13
3. STUDY OBJECTIVES AND ENDPOINTS 13
3.1. Research Hypothesis 13
3.2. Objectives and Endpoints 13
4. STUDY DESIGN 18
4.1. General Study Design and Plan 18
4.1.1. Dose Escalation 19
4.1.2. Highest Dose 20
4.1.3. Expansion Cohorts 21
4.1.4. Long Term Follow up 21
4.1.5. Survival Follow-up Period 21
4.2. Study Population 21
4.2.1. Selection of Study Population 21
4.2.2. Subject Replacement 22
4.3. Randomization and Blinding 22
4.4. Study Assessments 22
4.5. Protocol Deviations 22
5. SAMPLE SIZE DETERMINATION 22
6. ANALYSIS POPULATIONS 22
6.1. All Enrolled Population 22
6.2. All Treated Population 22
6.3. Pharmacokinetic Population 23
6.4. Response Evaluable Population 23
6.5. Scan Evaluable Population 23

6.6. Exploratory Biomarker (Immune Function and others) Population 23
6.7. Retreatment Population 23
7. GENERAL STATISTICAL CONSIDERATIONS 23
7.1. General Reporting Conventions 24
7.2. Interim Analyses 25
7.3. Multi-Center Studies 25
7.4. Multiple Comparisons / Multiplicity 26
7.5. Examination of Subgroups 26
7.6. Handling of Dropouts or Missing Data 26
7.7. Outlier Handling 27
7.8. Adjustments for Covariates 27
8. SUMMARY OF STUDY POPULATION DATA 27
8.1. Subject Disposition 27
8.2. Protocol Deviations 28
8.3. Demographics and Baseline Characteristics 28
8.4. Dosing and Extent of Exposure 28
8.5. Prior and Concomitant Medications 29
9. EFFICACY ANALYSES 29
9.1. Additional Efficacy Analysis 30
9.2. Progression-Free Survival and Overall Survival 30
10. SAFETY ANALYSES 31
10.1. Adverse Events 32
10.2. Clinical Laboratory Evaluations 34
10.3. Vital Signs 34
10.4. ECGs 34
10.5. Physical Examination 35
11. CLINICAL PHARMACOLOGY ANALYSES 35
12. OTHER ANALYSES 35
12.1. Pharmacokinetic Analysis 35
12.2. Exploratory Biomarkers of Immune Response 35
12.3. Pharmacodynamic Analyses 35
13. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL 35

14. REFERENCES 36
15. TABLES, FIGURES, LISTINGS 36
APPENDIX 1. 37
1. TOTAL TUMOR BURDEN (TTB) 37
2. % DOSED TTB 37
3. INJECTED TUMOR RESPONSE RATE (ITR) 37
4. BYSTANDER TUMOR RESPONSE RATE (BTR) 37
5. PROGRESSION DEFINITION 38
6. IMPUTATION OF END DATE OF LAST PRIOR ANTI-CANCER THERAPY 38
7. PEMBRO LISTINGS/RETREATED SUBJECTS 38
8. IMPUTATION OF END DATE OF LAST PRIOR ANTI-CANCER THERAPY 38
OTHER NOTES 39

LIST OF TABLES

Table 1: Abbreviations 11
Table 2: Objectives and Endpoints 13
Table 3: Dosing for Phase 1 Cohorts 18

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations

Abbreviation	Explanation
AE	Adverse event
AUC	Area under the concentration-time curve
$AUC_{\tau au}$	Area under the concentration-time curve over dosing interval tau
BMI	Body mass index
BTR	Bystander tumor response
Ce3	A contract research organization
CIS	Cisplatin
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
DBP	Diastolic blood pressure
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FIH	First in human
HR	Heart rate
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IT	Intratumoral
ITR	Injected tumor response
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective response rate
PD	Progressive disease
PD	Pharmacodynamics
PD1	Programmed death-1

Abbreviation	**Explanation**
PE	Physical examination
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SD	Standard deviation
SHAO	8-((2-hydroxybenzoyl)amino)octanoate (sodium salt form)
SOC	System organ class
SOD	Sum of diameters
SOP	Standard operating procedure
SSC	Study steering committee
TEAE	Treatment-emergent adverse event
TLF	Tables, listings and figures
TTB	Total Tumor Burden
TTR	Time to response
VBL	Vinblastine sulfate or vinblastine
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Intensity Therapeutics, Inc. Protocol IT-01, entitled "*A Phase 1/2 Safety Study of Intratumorally Administered INT230-6 in Adult Subjects with Advanced Refractory Cancers*". This is a Phase 1/2 trial to evaluate the safety, tolerability, and preliminary efficacy of INT230-6 in adult subjects with advanced refractory cancers. The research hypothesis of the study is that INT230-6, when administered intratumorally (IT) to one or more tumors at a sufficient loading to the subject's total tumor burden (TTB), will safely reduce tumor burden and promote an immune response against the cancer allowing subjects to have an increase in survival.

This SAP is intended to describe the planned analyses of the primary and secondary endpoints and other analyses mentioned in the protocol, as well as the presentation of study data to be included in the clinical study report (CSR) for Protocol IT-01. Additional analyses that were not mentioned in the protocol, but which are now planned, are also described. A discussion of the steps taken to prepare the data for analysis, such as study milestones, data partitioning and derived data, is provided. Examples of tables and figures that will be used to summarize the data are included in the companion document *IT-01 Tables, Listings and Figures Shells*.

This SAP has been developed according to Ce3 SOP 700: Developing and Maintaining a Statistical Analysis Plan, and accordingly, this plan and any deviations from this plan must be finalized, approved, and placed on file before the study database is locked.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Research Hypothesis

INT230-6 when administered intratumorally (IT) to one or more tumors at an optimal dose to tumor volume ratio (i.e., greater than 1 mL per 4 cc of tumor) while treating a sufficient amount of the visible disease will safely reduce tumor burden, stabilize disease, promote an immune response against the cancer, and extend overall survival.

3.2. Objectives and Endpoints

Objectives and endpoints are described in Table 2.

Table 2: Objectives and Endpoints

Cohort	Cohort Description	Number	Objective	Endpoint
A1 B1 EA EC EC2	Dose Escalation, Monotherapy	PRIMARY	Safety and tolerability of multiple intratumoral doses of INT230-6 in subjects with advanced or recurrent malignancies	Grade 3, 4, or 5 study drug-related adverse events

Cohort	Cohort Description	Number	Objective	Endpoint
		SECONDARY	1) Assess the preliminary efficacy of INT230-6 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	1) Disease Control Rate (CR+PR+SD) as defined by criteria based on RECIST 1.1 2) C_{max}, C_{min}, T_{max}, AUC_{TAU}, Accumulation index 3) Incidence and severity of treatment-emergent adverse events (TEAEs) Clinical laboratory results (hematology, chemistry, urinalysis) ECOG performance status Physical examination, including vital sign measurements ECG results
		EXPLORATORY	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 criteria based on RECIST or 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 (PFS) and overall survival (OS) in subjects receiving INT230-6 and cancer subtype of sarcoma.	1) Injected and Bystander tumor response rates to be conducted outside of this SAP. 2) Biomarker results 3) Response adjudicated as complete (CR), partial (PR), stable disease (SD), progressive disease (PD) or Not evaluable (NE); Best overall response and duration or response 4) PD profile results 5) PFS and OS as defined in Section 9.2 of this document
EC3	Highest set Dose, Monotherapy	PRIMARY SECONDARY EXPLORATORY	Objectives are the same as the above cohorts	

Cohort	Cohort Description	Number	Objective	Endpoint
DEC	Dose Escalation, Combination Therapy	PRIMARY	Assess the safety and tolerability of INT230-6 with pembrolizumab	Grade 3, 4, or 5 study drug-related adverse events attributed to the combination and not the underlying disease
		SECONDARY	1) Characterize the overall safety of INT230-6 combined with pembrolizumab 2) Assess the injected tumor response 3) 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.	1) Incidence and severity of treatment-emergent adverse events (TEAEs) Clinical laboratory results (hematology, chemistry, urinalysis) ECOG performance status Physical examination, including vital sign measurements ECG results 2) Injected Response Rates 3) C_{max}, C_{min}, T_{max}, AUC_{TAU}, Accumulation index
		EXPLORATORY	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) Characterize the pharmacodynamics (PD) profile of the INT230-6 plus pembrolizumab in subject blood and in treated and untreated tumors 4) Assess the overall survival in subjects receiving INT230-6 plus pembrolizumab meeting inclusion criteria.	1) Bystander Response Rates, Objective Response Rates, Best Overall Response, Duration of Response 2) Biomarker results 3) PD profile results 4) PFS and OS as defined in Section 9.2 of this document
DEC2	Highest INT230-6 Dose, Combination Therapy	PRIMARY	Preliminary efficacy of INT230-6 combined with pembrolizumab	Disease control rate (CR + PR + SD) of multiple intratumoral doses of INT230-6 combined with pembrolizumab and assessed with criteria based on RECIST or iRECIST
		SECONDARY	1) Characterize the overall safety of INT230-	1) Grade 3 or higher adverse events attributed to the

Cohort	Cohort Description	Number	Objective	Endpoint
			6 combined with pembrolizumab 2) Assess the injected tumor response 3) 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.	combination and not the underlying disease Incidence and severity of treatment-emergent adverse events (TEAEs) Clinical laboratory results (hematology, chemistry, urinalysis) ECOG performance status Physical examination, including vital sign measurements ECG results 2) Injected Tumor Response Rate
		EXPLORATORY	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 criteria based on RECIST or iRECIST 4) Characterize the pharmacodynamics (PD) profile of the INT230-6 plus pembrolizumab in subject blood and in treated and untreated tumors 5) To assess the progression free and overall survival in subjects receiving INT230-6 plus pembrolizumab meeting inclusion criteria.	1) Injected and Bystander Response Rates; Objective response rates; Best overall response; Duration of Response 2) Biomarker results 3) Response adjudicated as complete (CR), partial (PR), stable disease (SD), progressive disease (PD) or Not evaluable (NE); Best overall response and duration or response 4) PD profile results 5) PFS and OS as defined in Section 9.2 of this document
FEC	Highest Dose, Combination Therapy	PRIMARY	Assess preliminary efficacy of multiple intratumoral doses of INT230-6 combined with the standard dose and schedule of Ipilimumab (3 mg/kg Q3 wk for 4 doses)	Disease control rate (CR + PR + SD) based on RECIST or iRECIST

Cohort	Cohort Description	Number	Objective	Endpoint
		SECONDARY	1) Characterize the overall safety of the combination 2) Assess the preliminary efficacy of INT230-6 with Ipilimumab by measuring the injected and bystander tumor response 3) Characterize the pharmacokinetic profile of multiple doses of the three INT230-6 components cisplatin (CIS), vinblastine sulfate (VBL) and the cell penetration enhancer (SHAO) after single and then multiple IT tumor site injections	1) Grade 3 or higher adverse events attributed to the combination and not the underlying disease Incidence and severity of treatment-emergent adverse events (TEAEs) Clinical laboratory results (hematology, chemistry, urinalysis) ECOG performance status Physical examination, including vital sign measurements ECG results 2) Injected and Bystander Response Rates 3) C_{max}, C_{min}, T_{max}, AUC_{TAU}, Accumulation index
		EXPLORATORY	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 criteria based on RECIST or 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 (PFS) and overall survival (OS) in subjects receiving INT230-6. 6) Explore the activity of the combination of IN230-6 with Ipilimumab compared to INT230-6 alone in patients with the same tumor types such as sarcoma.	1) Injected and Bystander tumor response rates 2) Biomarker results 3) Response adjudicated as complete (CR), partial (PR), stable disease (SD), progressive disease (PD) or Not evaluable (NE); Best overall response and duration or response 4) PD profile results 5) PFS and OS as defined in Section 9.2 of this document 6) Subgroup analysis of efficacy endpoints

4. STUDY DESIGN

4.1. General Study Design and Plan

This is a first-in-human (FIH) Phase 1/2, open label, non-randomized study. Subjects will have refractory, advanced cancers and will have failed at least 1 therapy 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.

Table 3 provides details on the Phase 1 cohorts included in this study. More details on dosing and injection can be found in the Study Protocol.

Table 3: Dosing for Phase 1 Cohorts

Study Part	Cohort	Tumor Type	Tumor Ratio (Dose)	Dosing Schedule	Combination Drug	Other
Escalation	A1	Superficial	1:4	Once per 28 days	No	Retreatment option after completing 5 doses
	B1	Superficial + Deep	1:4	Once per 28 days	No	
	EA	Superficial	1:4	Every 2 weeks	No	
	EC	Superficial and/or Deep	1:2	Every 2 weeks	No	
	EC2	Superficial and/or Deep	1:3	Every 2 weeks	No	
	DEC	Superficial and/or Deep	1:3	Every 2 weeks	Anti-PD1	
Phase 2/ Dose	EC3	Superficial and/or Deep	1:3 (Maximum 175 mL)	Every 2 weeks for 5 doses (Induction treatment)	No	Maintenance treatment every 9 weeks after completing 5 doses
	DEC2	Superficial and/or Deep	1:3 (Maximum 175 mL)	Every 2 weeks for 5 doses (Induction treatment)	Anti-PD1	
	FEC	Superficial and/or Deep	1:3 (Maximum 175 mL)	Every 2 weeks for 5 doses (Induction treatment)	Anti-CTLA4	

For purposes of analysis Cohorts A, B1, EA, EC are to be combined as one group as are cohorts EC2 and EC3. The A/B1,EA/EC population is defined as low loading monotherapy treatment, where low loading refers to a lesser potential for proper treatment of a subject's total tumor burden due to dose volume restrictions on INT230-6 during escalation. Cohort EC2/EC3 is defined as high loading monotherapy treatment, where high loading refers to a greater potential for proper treatment of a subject's total tumor burden due to meaningfully higher dose volume amounts allowed for INT230-6.

4.1.1. Dose Escalation

The Phase 1 portion of the study included the administration of escalating doses of INT230-6 in a 3+3+3 design for Cohorts A1, B1, EA, EC, EC2, and a 6+6 design for Cohort DEC and FEC. The SSC, comprised of the majority of study investigators plus representatives from the Sponsor, reviewed safety data regularly on an ongoing basis on all subjects. Decisions to increase the number of subjects in a cohort, to increase the concentration injected into the tumors, and the decision to begin treating deep tumors required agreement from this committee. The SSC reviewed the data on the sentinel subjects and facilitate the decision to recruit more subjects. After each escalation cohort, the SCC reviewed safety to determine escalation into the next cohort.

The following dose escalation rules applied:

- Cohorts A1, B1
  - A sentinel subject will be on treatment for 28 days
  - If there are no Dose-limiting toxicities (DLTs), upon agreement from SSC, more subjects can be enrolled
  - Cohort will continue until at least 3 subjects have completed at least 56 days (A1) or 3 doses (B1) or if 3 DLTs (A1, B1) have occurred
  - If 1 DLT is seen in the first 3 subjects, an additional 3 subjects at this dose level will be added
  - If there is one more DLT in the first 6 subjects, 3 more will be added
  - If $\geq$ 3 DLTs are seen in up to 9 subjects, the SCC will pause accrual and review the data
  - At the time a third DLT is observed in any dose level, even if < 9 subjects are enrolled, enrollment in that dose level will be discontinued and a lower dose level or intermediate dose level will be explored
  - A rate of DLTs that exceeds 33% is unacceptable for this population
- Cohorts EA, EC
  - No sentinel subject required
  - Cohort will continue until at least 3 subjects have completed at least 3 cycles or 3 DLTs have occurred

  - If 1 DLT is seen in the first 3 subjects, an additional 3 subjects at this dose level will be added
  - If there is one more DLT in the first 6 subjects, 3 more will be added
  - If ≥ 3 DLTs are seen in up to 9 subjects, the SCC will pause accrual and review the data
  - At the time a third DLT is observed in any dose level, even if < 9 subjects are enrolled, enrollment in that dose level will be discontinued and a lower dose level or intermediate dose level will be explored
  - A rate of DLT's that exceeds 33% is unacceptable for this population
- Cohort EC2
  - No sentinel subject required
  - Cohort will continue until at least 6 subjects have completed at least 3 cycles or 4 DLTs have occurred
  - If 2 DLTs are seen in the first 6 subjects, an additional 6 subjects at this dose level will be added. If ≥ 4 DLTs are seen in up to 12 subjects, the SSC will pause accrual and review the data
  - A rate of DLT's that exceeds 33% is unacceptable for this population

Cohort DEC will include a combination of INT230-6 plus an anti-PD-1 therapy. The SCC will determine the subject population (tumor type) and the dose for this group of subjects. See Supplement A of the Protocol for details on the PD-1 agent.

4.1.2. Highest Dose

Monotherapy Cohort EC3 and Combination Cohorts DEC2 and FEC shall use up to a maximum dose of INT230-6 of 175 mL with the number of tumors being dosed per session to be decided by the investigators. The dose being set by the subject's tumor burden. After completing 5 doses of INT230-6, a maintenance single treatment of INT230-6 by intratumoral injection of up to 175 mL should be given every 9 weeks ± 10 days into target tumors until either progressive disease, radiologic or biopsy confirmed complete response, or two years. Refer to the Study Protocol for details on combination drug dosing. Decisions to increase the number of subjects in a cohort, to change the INT230-6 dose into the tumors, and the decision as to which populations to include will require consensus from the SCC.

Up to a maximum of 44 subjects will be enrolled in Cohort DEC2. Review of DLTs will continue for Cohort DEC2 with the following conventions:

- If 2 subjects experienced a DLT, an additional 6 subjects will be entered and followed for a 28 day DLT window
- If > 3 subjects experience a DLT, the safety data will be reviewed by the SSC to determine if a lower dose or lower loading ratio per tumor of INT230-6 could be explored

- If the DLT rate is excessive during enrollment of the additional 44 subjects, the SSC reviewed the data and determine how the INT230-6 dose will be decreased, and the number of additional patients enrolled on the study at the lower dose

For Cohort FEC, up to 15 subjects could be recruited into each of the following cancer types: metastatic hepatocellular carcinoma (HCC), breast cancer (BC) and soft tissue sarcoma. The overall cohort will employ a 6 subject safety lead-in to evaluate safety and toxicities. The safety data will be reviewed by the SCC to determine whether expansion to the total of 45 subjects should be permitted. For the HCC subjects in Cohort FEC, the first accrued HCC subject shall be evaluated at Day 28. This sentinel HCC subject must receive two INT230-6 doses and 1 ipilimumab dose prior to accruing the remainder of the HCC portion of the cohort. If there are more than 2 DLTs in the HCC cohort, the SSC will evaluate de-escalation of ipilimumab.

4.1.3. Expansion Cohorts

DEC2 and FEC are expansion cohorts of 10-16 subjects with various single tumor types. These groups will allow for better point estimates of the safety and preliminary efficacy in a homogenous population of INT230-6 combined with immune checkpoint inhibitor drugs. Decisions on expansion cohorts for monotherapy (e.g., for EC3) may be made at a later time.

4.1.4. Long Term Follow up

Subjects who complete a full course of treatment including those who receive retreatment or who have discontinued treatment for any reason other than clinical or radiological progression will enter the Long Term Follow up period. During this time, subjects will be evaluated every 8 weeks for the first year and every 3 months thereafter. 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 are Lost to Follow up or Withdraw Consent will not enter Long Term Follow up, but will enter survival follow up as outlined below.

4.1.5. 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.

4.2. Study Population

4.2.1. Selection of Study Population

Male and female subjects at least 18 years old who meet the inclusion and exclusion criteria as outlined in Protocol Section 6 will be enrolled in the study.

4.2.2. Subject Replacement

Subjects withdrawn from the study prior to completion of the DLT-evaluable period for a reason other than a DLT will be replaced.

4.3. Randomization and Blinding

This is an open-label non-randomized study.

4.4. Study Assessments

Details of scheduled assessments are presented in the study Protocol, with clarifications in Administrative letters 7 and 8. Tumor imaging occurred 12 weeks ± 10 days after first dose and every 9 weeks ± 10 days thereafter.

4.5. Protocol Deviations

No deviations from the protocol are anticipated. Any protocol deviations recorded will be categorized as major or minor prior to data release for the final analysis of the primary endpoint. A summary table of the major protocol deviations will be generated for both dose escalation and expansion stages. A listing of major protocol deviations will be provided, sorted by center and phase.summarized and listed.

5. SAMPLE SIZE DETERMINATION

The sample size was estimated to be between 100 and 175 subjects during dose escalation and expansion. The final enrollment consisted of 110 subjects two of whom participated in more than one cohort. Expansion cohorts may treat subjects in a specific tumor type (e.g., sarcoma that would include chordoma) to provide additional safety information and preliminary assessment of tumor response within a disease indication.

With 16 subjects treated in an expansion cohort in a given 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.

6. ANALYSIS POPULATIONS

6.1. All Enrolled Population

All subjects who sign the informed consent form, meet all inclusion/exclusion criteria, and are assigned to a cohort will be included. Subject disposition will be tabulated using this data set.

6.2. 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.

6.3. Pharmacokinetic Population

All available concentration-time data from subjects who receive INT230-6 will be reported. All available derived Pharmacokinetic (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. Further information will be provided in the PK manual. PK sampling was eliminated in Protocol Amendment 6. Pharmacokinetic analysis will be presented separately as an addendum.

6.4. Response Evaluable Population

Response evaluable population (REP) is 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. This population will be used for primary efficacy analyses.

6.5. Scan Evaluable Population

The Scan Evaluable Population (SEP) will be defined as all subjects who receive at least one dose of INT230-6, have a baseline tumor assessment with measurable disease, and at least one on-treatment tumor evaluation via a scan at two months or later post first dose.

6.6. Exploratory Biomarker (Immune Function and others) Population

All subjects who receive at least one dose of INT230-6, have a pre-dose and at least one post-dose 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 was eliminated in Protocol Amendment 6. Biomarker analysis will be presented separately as an addendum.

6.7. Retreatment Population

For Cohorts A1, B1, EA, EC, EC2, and DEC, those subjects who have completed treatment and have not started on any subsequent anti-cancer therapy will be eligible for retreatment. Prior to Study Protocol Amendment 5, three subjects had initiatied retreatment. This population assignment will no longer be applicable moving forward with the study. Given the few numbers, these three subjects will be described in the Clinical Study Report (CSR) with regards to safety and efficacy in the form of a case series and will also be included in summaries regarding their initial and subsequent treatment as applicable. No aggregate tables will be developed solely for this population.

7. GENERAL STATISTICAL CONSIDERATIONS

All analyses described below will be carried out using SAS® Version 9.4 or higher. Continuous variables (e.g., age) are summarized using descriptive statistics. Categorical variables (e.g., race) are summarized using counts and percentages. Percentages are calculated using the total number of subjects in each cohort.

7.1. General Reporting Conventions

In this document, when describing tables to be generated, cohort groups will be referenced as being presented 'by treatment'. The following data conventions are applied to all data presentations and summaries.

Treatments

- Cohorts A, B1, EA, EC are to be combined for analysis and defined as low loading monotherapy treatment, where low loading refers to a lesser potential for proper treatment of a subject's total tumor burden due to dose volume restrictions on INT230-6 during escalation.
- Cohorts EC2 and EC3 are to be combined for analysis purposes and defined as high loading monotherapy treatment, where high loading refers to a greater potential for proper treatment of a subject's total tumor burden due to meaningfully higher dose volume amounts allowed for INT230-6.
- Cohorts DEC and DEC2 are to be combined to define INT230-6 with pembrolizumab treatment
- Cohort FEC is defined as the combination of INT230-6 with ipilimumab treatment.
  - Data will be described and summarized separately for low and high dose monotherapy cohort groups (A1/B1/EA/EC vs. EC2/EC3) and combination cohorts by treatment (DEC/DEC2 and FEC).
  - For assessments performed at defined time points, the data will be summarized and reported for each time point.
  - Summary tables for continuous variables will contain the following statistics: N (number of subjects in the population); n (number of subjects with data); mean; standard deviation (SD); median; minimum; and maximum; 25^{th} and 75^{th} percentiles when applicable. Selected statistics may also include a 2-sided 95% normal approximation confidence intervals (CIs) on the mean.
  - Summary tables for categorical variables will include: N (number of subjects in the denominator); n (number of subjects in the numerator); and percent and will be presented in the format XX (XX.X%), where the percentage is in parentheses. Selected statistics also may include 2-sided 95% CIs for the percent based on the exact Clopper-Pearson methodology for binomial proportions.
  - Unless noted to the contrary, the denominator used for the calculation of percentages will be the number of subjects in the specified analysis population who are in the cohort being summarized.
  - Date variables are formatted as yyyy-MM-dd for presentation. Time is formatted in military time as HH:MM for presentation.
  - The baseline value for a given parameter is the last non-missing value prior to the first dose. A value is considered to be post-baseline if it is obtained after the first study drug administration.

- Change from baseline is calculated as (post-baseline result – baseline result). Percent change from baseline is calculated as (change from baseline/baseline results * 100). If either the baseline or post-baseline result is missing, the change from baseline and/or percent change from baseline is set to missing as well.
- Data from study centers will be pooled for all analyses
- Study Day is defined as calendar date – date of first treatment + 1 if the calendar date is on or after the date of first treatment, and calendar date – date of first treatment if the calendar date is before the date of first treatment
- Measurements from unscheduled visits will be included in listings, but not summary tables
- Missing data conventions for individual endpoints are described in detail below for the endpoints
- Listings will be provided of all data collected in the electronic Case Report Form (eCRF)
- Wherever possible, data will be decimal aligned
- For continuous variables, use the following conventions for significant digits: mean (xx.x), median (xx.x), standard deviation (xx.xx), minimum (xx.x) and maximum (xx.x). If data results are less than 1, format decimal points to one more place than the measured value for all summary variables except format to two more places for standard deviations
- Version 25.1 of MedDRA will be used for this study.
- WHODRUG Enhanced Sep-2022 B3 will be used for this study.

The accompanying table, listing, figures (TLF) document to this SAP provides the expected layout and titles of the tables, figures, and listings. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. Please refer to the SAP appendix for additional programming notes.

7.2. Interim Analyses

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. No formal interim analyses are planned for this study.

7.3. Multi-Center Studies

This is a multi-center study. Given the small sample size of the study, no site effect will be considered in any statistical analysis.

7.4. Multiple Comparisons / Multiplicity

No adjustments for multiple tests or multiple comparisons will be utilized.

7.5. Examination of Subgroups

Analysis endpoints of safety and efficacy variables may be further explored with the following subgroups:

- Tumor ratio (1:4, 1:3, 1:2 or dose set by longest diameter formulas)
- Dose schedule (every 2 weeks versus every 4 weeks)
- Superficial tumor injection subjects versus deep tumor injection subjects
- Tumor type (Sarcoma)
- Status of prior treatment with platinum-based antineoplastics or vinca alkaloid therapies
- Subjects with less than 2 tumors injected compared to those with ≥ 2 tumors
- Tumor burden: subjects receiving ≥ 40% of tumor burden injected versus those receiving < 40% ; tumor burden is calculated based on EDC documentation of target, bystander, non-target, and new tumors. Subjects receiving ≥ 40% of baseline total tumor burden injected overall (during the course of therapy) and at first dose will be explored. For overall, the sum of all injection volumes will be used in the calculation.

The subgroups to be analyzed for each endpoint are described in Section 8, Section 9, and Section 10.

7.6. Handling of Dropouts or Missing Data

Where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators (e.g., using the response evaluable population). For survival analysis, dropouts without confirming events will be treated as censored.

All missing and partial start dates will be queried for a value. If a complete start date cannot be obtained, the following imputation rules apply in order to calculate duration of adverse event, concomitant medication use, or prior cancer history endpoints:

- Missing month and day
  - If the year of the incomplete start date is the same as the year of the date of study drug administration, then the missing month and day of the start date will be imputed to be the month and day of the start of study drug administration.
  - If the year of the incomplete start date is before the year of the date of study drug administration, December 31 will be assigned to the missing fields.
  - If the year of the incomplete start date is after the year of the date of study drug administration, January 1 will be assigned to the missing fields.

- Missing month only
  - If only the month is missing, the day will also be treated as missing, and both month and day will be replaced according to the above procedure.
- Missing day only
  - If the month and year of the incomplete start date are the same as the month and year of the date of study drug administration, the start date of study drug will be assigned to the missing field (i.e., AEs will be assumed treatment-emergent, and medications will be assumed concomitant).
  - If the month and year of the incomplete start date are before the month and year of the date of study drug administration, the last day of the month will be assigned to the missing field.
  - If the month and year of the incomplete start date are after the month and year of the date of study drug administration, the first day of the month will be assigned to the missing field.

If the stop date is complete and the imputed start date, when imputed as instructed above, is after the stop date, the start date will be imputed to equal the stop date.

7.7. Outlier Handling

Potential data entry errors manifested as outliers will be handled in the data management process through edit checks.

7.8. Adjustments for Covariates

There is no plan to adjust for any covariates.

8. SUMMARY OF STUDY POPULATION DATA

Tables related to the study population will be in Section 14.1 and listings in Section 16.2 of the TLF Shell Document and the CSR.

8.1. Subject Disposition

The total number of subjects enrolled and the total number of subjects in each analysis population will be provided by study part. Among subjects who received any study drug, frequency and percentage of subjects who completed treatment, prematurely discontinued and reasons for premature discontinuation, and reason for end of study will be tabulated.

Separate listings will be provided for subject disposition, inclusion/exclusion eligibility, and analysis population assignment. The disposition listing will include informed consent date, first treatment, last treatment, treatment duration (days), reason for premature discontinuation from study drug treatment, date of study discontinuation, reason for study discontinuation, date of subsequent anti-cancer therapy, and, if applicable, date of death.

8.2. Protocol Deviations

The number of protocol deviations per subject (mean, SD, median, minimum, and maximum), the number and percentage of subjects who presented at least one protocol deviation in each category, and the number and percentage of subjects who discontinued due to protocol violation will be summarized for each study part and overall.

All major and minor protocol deviations will be listed.

8.3. Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographics and baseline characteristics for the Safety Population.

Subject demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized by study part.

Medical and surgical history/physical findings will be coded using MedDRA Version 25.1 and summarized by system organ class (SOC)/ preferred term (PT) and study part. Cancer history at screening will be summarized by diagnosis and stage for each study part. Previous anti-cancer therapy, prior cancer surgery, and prior radiation therapy will be summarized by study part and tumor type. Previous anti-cancer therapy will be further categorized as the number and percentage of subjects having any platinum-based antineoplastics, vinca alkaloid therapies, anti-PD-1 agents, or other prior anti-cancer therapies. These summaries will include summary statistics of prior regimens per subject, best overall response, number experiencing peripheral neuropathy (platinum-based antineoplastics only), and number resistant to the therapy (platinum-based antineoplastics and vinca alkaloids only).

Duration on last prior therapy will be calculated as the earliest of Progression Date on prior therapy, Last Date on prior Treatment, or Date of IT-01 Screening less the earliest Treatment Initiation Date of Most Recent Prior Cancer Therapy, converted to months by dividing by 30.4375. A separate tornado plot will present duration on last prior therapy vs. duration on INT230-6 for Cohorts A/B1/EA/EC, EC2/EC3, DEC/DEC2 and FEC.

Listings will be provided for individual subject demographics and baseline medical and surgical history/physical findings, as well as cancer history at screening, previous anti-cancer therapy, prior cancer surgery and prior radiation.

8.4. Dosing and Extent of Exposure

The dose of INT230-6 administered to subjects will be summarized by total dose injected (mL), maximum dose injected into any one tumor (mL), number of tumors injected for each cohort and percent of total tumor burden injected. Drug leakage will also be listed. Subjects receiving study drug per protocol, subjects receiving partial or incomplete drug dose, and reasons for interruption will be summarized. Individual study drug administration records and deviations in administration will be listed, as well as the largest dose into any one tumor.

Pembrolizumab and ipilimumab administration will be summarized in a table and listing and will include total dose administered, dosing delays, reason for dosing delays, number and reasons of subjects permanently discontinuing drug, and number and reasons of infusion interruptions.

8.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD) Version Dec 2016. Prior and concomitant medications will be summarized by preferred term. A listing of prior and concomitant medications by subject will be provided. Non-drug treatments and procedures will be listed.

9. EFFICACY ANALYSES

Due to the method of action of the INT230-6 therapy observed over the course of the study, proper assessment utilizing RECIST or iRECIST was not possible. A response across all lesions using sum of diameters to assess efficacy over time using response criteria was not utilized. Thus, efficacy analyses will largely focus on the response of individual tumors (injected and bystander) as opposed to an overall tumor response, and any overall response will utilize the modified response criteria defined below.

Efficacy analyses will be conducted on the All Treated Population (ATP) , the Response Evalauble Population (REP), and the Scan Evaluable Population (SEP). RECIST 1.1 assessments were not collected. Rather injected tumor response and non-injected tumor response utilizing some of the RECIST criteria were evaluated. Sponsor utilized RECIST principles with the injected and non-injected tumor measurements obtained. Efficacy will be determined based on a modified version of RECIST 1.1 criteria. Specifically, complete response (CR) and partial response (PR) will be defined for injected tumors followed per RECIST 1.1 utilizing target lesions. Progressive disease will be determined by clinical or radiological deterioration leading to the subject being taken off-treatment at the discretion of the investigator. Stable disease (SD) is defined as any adequate assessment not considered CR, PR, or progression. The appearance of a new lesion will not necessarily be considered progression and if possible will be assessed. Any post-baseline visit where a target lesion present at baseline was not assessed will result in a Not Evaluable (NE) assessment for that lesion. Data will be presented by treatment and, when indicated, by subgroups.

The primary efficacy parameter is the disease control rate (DCR), defined as the number of subjects obtaining a best overall response of either CR, PR, or SD as described above divided by the total number of subjects in the analysis population. The DCR will be presented with accompanying 95% exact binomial confidence intervals for each study part for the ATP population, REP, SEP, and by subgroup.

At baseline, lesions are classified as measurable or nonmeasurable per either RECIST 1.1 guidelines, depending on the cohort. Baseline measurable lesions are further classified as target (injected) or bystander (non-injected), while non-measurable lesions are classified as non-target (non-target lesions are not eligible for injection). A sum of diameters (SOD) (longest for extranodal lesions and shortest for lymph nodes) will be calculated for all target lesions. Tumor volume (for target tumors with three dimensions) will also be calculated using the modified

ellipsoid method or by longest diameter if specified in an particular protocol amendment. Bystander lesions will be recategorized as target lesions once injected, but target lesions will always remain target lesions.

9.1. Additional Efficacy Analysis

Additional efficacy parameters include the duration of response (DOR), the injected tumor response (ITR), the bystander tumor response (BTR), progression free survival (PFS), and overall survival (OS). These endpoints will be summarized by treatment (see section 7 for definition of each treatment) and subgroup. Other than 1 listing reporting bystander tumors' diameter that declined over time that declined (noted below), the bystander tumor response rate (BTR) analysis will be conducted separately from the SAP from collected radiographic data.

DOR is defined as the time from first tumor assessment of CR, PR, or SD to the time of progressive disease or death due to any cause. For responders with no death or progression, DOR will be censored on the last non-PD tumor assessment or follow-up call.

The median DOR as obtained from Kaplan-Meier methods will be presented by treatment and subgroup and will include the median, 25^{th} percentile, 75^{th} percentile, and a 2-sided point-wise 95% confidence interval.

ITR will be based on the target tumors at the baseline visit; tumors that become target during the study will also be included in the ITR calculation at the time they are treated. The ITR is defined as the ratio of CR + PR in injected tumors / total number of injected tumors. Thus, bystander or non-target lesions dosed at later dates are not included in calculations for ITR.

The ITR will be calculated based on the maximum likelihood estimator and summarized in tables. The estimate of ITR will be accompanied by 2-sided 95% exact binomial confidence intervals as determined by the Clopper-Pearson method and assessed at each study-specified timepoint where an assessment is performed.

The BTR will follow the same definition as the ITR for bystander tumors. Note that bystander tumors that are injected on study will be included in the ITR calculation.

Individual tumor assessments for target and bystander, non-target, and new lesions will be listed, with location, method of assessment, longest diameter, shortest diameter, depth, volume, and percent change from baseline included for each target and bystander tumor, as well as Total Tumor Burden at Baseline, Cumulative Dose, Percent TTB dosed, and dose category ($< 40\%$ versus $\geq 40\%$) per subject. Another listing will be produced for the Abscopal effect of bystander tumors, defined as any bystander tumor with any decrease in tumor size at any point during the study, but before being injected with study drug.

9.2. Progression-Free Survival and Overall Survival

Progression free survival (PFS) and Overall Survival (OS) will be evaluated for the All Treated Population, the REP, and the SEP. PFS will be defined as the time (in months) from first dose of INT230-6 to either observation of clinical deterioration, removal from study, or occurrence of death due to any cause within 126 days (approximately 2 time intervals for tumor assessments) of the last tumor assessment. Progression date will be defined as the end of treatment date as captured per eCRF guidelines when the reason for end of treatment is either 'Radiographic

deterioration' or 'Clinical deterioration.' In subjects without a progression date or with a death date more than 126 days after the last tumor assessment, the PFS time will be censored on the date of last tumor assessment or last treatment date if the subject has no post-baseline tumor assessments. PFS analyses will consider tumor assessments after treatment discontinuation.

OS will be defined as the time (in months) from first dose of INT230-6 to death. Subjects for whom death is not reported will be censored at the date of end of study.

PFS and OS will be summarized in a listing. The median time to OS as obtained from Kaplan-Meier methods will be tabulated by subgroup and will include the median, 25th percentile, 75th percentile, and a 2-sided point-wise 95% confidence interval. Hazard ratios may be determined between certain curves for the Kaplan Meier figures noted below.

A Kaplan Meier figure of OS for the All Treated, REP, and SEP populations will be presented for each of the following:

- a curve all treated monotherapy patients, a curve for subjects that received a dose to total tumor burden < 40% of tumor burden, a curve for those subjects that had a dose to total tumor burden ≥ 40%,
- a curve for escalation cohort combining A1, B1, EA, EC, and a curve for escalation cohort combining EC2 and EC3,
- a curve for sarcoma patients in the monotherapy cohort and a curve for monotherapy sarcoma patients having ≥ 40% of their total tumor burden treated,
- a curve for the pembrolizumab DEC/DEC2 combined cohort for subjects,
- a curve for all ipilimumab FEC cohort subjects,
- a curve for the ipilimumab FEC sarcoma subjects, a curve for all monotherapy sarcoma patients and a curve for monotherapy sarcoma subjects having ≥ 40% of their total tumor burden treated will be included.

10. SAFETY ANALYSES

The primary safety objective is to assess the safety of INT230-6 in subjects with advanced or recurrent malignancies as determined by the rate of ≥ Grade 3 AE's attributed to INT230-6 and not the underlying disease. Safety and tolerability of INT230-6 will be assessed for the All Treated Population. Adverse events will be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.03. Dose limiting toxicities (DLT) for this study are defined as a ≥ Grade 3 study drug-related adverse events occurring during the first dose (DLT window extends up to 28 days after dosing), with exceptions noted in Section 9.1.1 of the study Protocol.

Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs. Additional safety parameters to be measured/assessed include PE findings, vital sign measurements, hematology, coagulation, serum chemistries, urinalysis, ECOG performance status, and ECG.

Tables related to the safety analyses are located in Section 14.3 and listings in Section 16.2.

10.1. Adverse Events

Adverse event summaries will be based on treatment-emergent adverse events (TEAEs), and will be presented by study part. TEAEs are defined as any non-serious AE or unrelated serious AE (SAE) that occurs during or after administration of the first dose of treatment through 28 days after the last dose, any non-serious AE or unrelated SAE that occurs during or after retreatment up to 28 days post-dose of the last re-treatment, any related SAE occurring after first dose of treatment without respect to date of last dose, or any event that is present at baseline but worsens in intensity. Adverse events will be summarized by treatment. Events worsening in severity will be considered new AEs. AEs recorded in the eCRF that began prior to treatment will be recorded and displayed as part of the medical history.

All adverse events will be coded using Version 25.1 of MedDRA. Summaries of TEAEs will present data by System Organ Class (SOC) and preferred term (PT) in order of decreasing frequency of total SOC count, followed by decreasing frequency of total PT count. The following conventions will be followed in summarizing multiple occurrences of an adverse event for a certain assessment period when summarizing data from individual subjects:

- Each subject will be counted only once within SOC or PT
- The highest known severity within a body system or a PT will be assigned to the event
- The strongest relationship within a body system or a PT will be assigned to the event.

The denominator used for calculation of percentages will be the number of subjects in the All Treated population per cohort.

An overall summary of treatment emergent adverse events (TEAEs) will include:

- number and percentage of subjects with one or more TEAEs
- number and percentage of subjects with one or more INT230-6 monotherapy TEAEs
- number and percentage of subjects with one or more TEAEs for DEC and DEC2 cohorts (not by individual drug agent)
- number and percentage of subjects with one or more TEAEs for FEC cohort (not by individual drug agent)
- number and percentage of subjects with one or more procedure-related TEAEs for INT230-6 monotherapy treatments (all monotherapy cohorts combined)
- number and percentage of subjects with one or more related TEAEs for DEC and DEC2 cohorts (not by individual drug agent)
- number and percentage of subjects with one or more related TEAEs for FEC cohort (not by individual drug agent)
- number and percentage of subjects with one or more severe (Grade 3 or above) TEAEs

- number and percentage of subjects with one or more severe (Grade 3 or above) INT230-6 monotherapy treatment-related TEAEs (all monotherapy cohorts combined)
- number and percentage of subjects with one or more severe (Grade 3 or above) related TEAEs for DEC and DEC2 cohorts (not by individual drug agent)
- number and percentage of subjects with one or more severe (Grade 3 or above) related TEAEs for FEC cohort (not by individual drug agent)
- number and percentage of subjects with one or more serious adverse events (SAEs)
- number and percentage of subjects with one or more INT230-6 monotherapy-related SAEs (all monotherapy cohorts combined)
- number and percentage of subjects with one or more related SAEs for DEC and DEC2 cohorts
- number and percentage of subjects with one or more related SAEs (for FEC cohort)
- number of deaths (if any)
- number and percentage of subjects with one or more TEAEs resulting in discontinuation from the study

The frequency and percentage of TEAEs by SOC and PT for each treatment will be tabulated. The frequency and percentage of TEAEs by SOC/PT by maximum severity (Grade 1 - 5) will be presented by treatment. The frequency and percentage of Related TEAEs and of All TEAS (related or unrelated) by PT and by maximum severity will be presented for the following cohorts:

- Overall Monotherapy
- Monotherapy Cohorts A1/B1/EA/EC
- Monotherapy Cohorts EC2/EC3
- Combination Pembrolizumab Cohorts DEC/DEC2
- Combination Ipilimumab Cohort FEC
- Monotherapy Sarcoma Subjects
- Combination Ipilimumab Cohort FEC Sarcoma Subjects
- Note:Sarcoma includes chordoma.

The number and percentage of TEAEs by SOC/PT considered related to study drug will be summarized. Number and percentage of subjects experiencing Grade 3 or higher TEAEs by SOC/PT will be summarized. Number and percentage of subjects experiencing Serious TEAEs by SOC/PT will be summarized. The frequency and percentage of TEAEs that lead to study discontinuation will be presented. If a subject moves from monotherapy to combination therapy treatment, the summary adverse events will be calculated based on the treatment at the time of the event.

A listing of all AEs data sorted by subject, including the verbatim term, MedDRA SOC and preferred term, duration of AE (calculated as Stop Date – Start Date + 1), Outcome, Severity, Relationship to Study Drug, Relationship to Dosing Procedure, Action Taken, Subject Discontinued Y/N, DLT Y/N, and SAE criteria, if relevant, will be provided. Additionally, individual AE records of SAEs, any deaths occurring during the study, AEs that led to discontinuation, Grade ≥ 3 AEs, and DLTs will be listed separately.

10.2. Clinical Laboratory Evaluations

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. For laboratory tests without any CTCAE criteria, toxicity grades will be recorded as 99.

Summary statistics of numerical laboratory test results and changes of test results from baseline will be reported by treatmentfor 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 by treatment. Shift tables will also be included reporting change from baseline category (low, normal, high) to post-dose category (low, normal, high) for cohorts and overall. 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.

Individual test result records, including repeat assessments, and comments for hematology, coagulation, serum chemistry, and urinalysis will be displayed in listings. Laboratory values outside normal limits will be identified with flags for high, low, and normal limits in the listings. Pregnancy test results will be displayed in a listing.

10.3. Vital Signs

Vital sign measurements and change from baseline will be summarized by cohort, tumor type and study visit using descriptive statistics. 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.

10.4. ECGs

Summary statistics of ECG overall interpretation will be displayed by treatmentand study visit. Per subject ECG test results will be listed.

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

10.5. 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.

11. CLINICAL PHARMACOLOGY ANALYSES

Not Applicable.

12. OTHER ANALYSES

12.1. Pharmacokinetic Analysis

PK analysis is detailed in the PK manual. Pharmacokinetic are out of the scope of this analysis plan and will be summarized separately.

12.2. Exploratory Biomarkers of Immune Response

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.

Measures from markers based on optional samples, e.g., tumor-based markers may be similarly presented, depending on data availability. Additional information can be found in the Biomarker Manual.

Biomarker analyses are out of the scope of this analysis plan and will be summarized separately.

12.3. Pharmacodynamic Analyses

Pharmacodynamic analyses are out of the scope of this analysis plan and will be summarized separately.

13. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

None.

14. REFERENCES

None.

15. TABLES, FIGURES, LISTINGS

Tables, listings and figures will be generated according to the companion document which details the layout of the output. Minor style deviation from specification defined in the shell document in the final production is permissible.

APPENDIX 1.

The following information provides additional programming instructions to define important variables that are not available in the main SAP text.

1. TOTAL TUMOR BURDEN (TTB)

Step 1: If all 3 dimensions are reported, volume = (longest*shortest*depth*0.63)

Step 2: If not all 3 dimensions are reported and longest diameter is reported, volume calculation is based on the longest diameter measurement.

1. If .< longest < 1.5 cm, volume = 1 cm^3
2. If 1.5 ≤ longest ≤ 4 cm, volume = $longest^3/2$
3. If 4 < longest < 9 cm, volume = $longest^3/3$
4. If longest ≥ 9 cm, volume = $longest^3/4$
5. If shortest is only measurement reported, Diameter = shortest and follow step 2 tasks 1 to 4 for volume calculations

Step 3: Sum all calculated volume values across target and bystander tumors.

2. % DOSED TTB

Step 1. Calculate TTB of all of a patient's bystander and target tumors reported in the database using the TTB formulas above.

Step 2. Calculate patient's cumulative dose of INT230-6

Step 3. Calculate % Dosed TTB as (cumulative dose / Patient TTB) * 100.

3. INJECTED TUMOR RESPONSE RATE (ITR)

At a given visit, assess whether each injected tumor has achieved a PR or CR per RECIST 1.1. Count the total number of target (injected) tumors that achieve a PR or CR and divide by the total number of target tumors at that visit. This is the ITR. A PR is defined as a change ≥ 30% in tumor volume, a CR is defined as having no visible tumor.

Note: for re-baselining retreated subjects that switch to a new cohort, the last assessment prior to the first retreatment is used as the baseline reference for determining PR.

4. BYSTANDER TUMOR RESPONSE RATE (BTR)

Follow the method for ITR, instead using bystander tumors. Note that if a bystander tumor is injected on study, this tumor can no longer by considered bystander after the date of injection and will be included in the ITR calculation from that injection date visit onward. This can cause the denominator to be dynamic over visits.

5. PROGRESSION DEFINITION

Progression is defined as a patient who radiographically or clinically deteriorated as captured on any number of forms designating the patient is ending treatment or death. This includes the end of treatment form, end of maintenance form, follow-up form, and survival form. Note that typical RECIST 1.1 indications of progression such as an increase in sum of longest diameters of 20% or the presence of a new lesion are not considered progression for the purposes of PFS.

6. IMPUTATION OF END DATE OF LAST PRIOR ANTI-CANCER THERAPY

- If end date is completely missing, use IT-01 screening date
- If year is present and end month is missing, use the min of (IT-01 screening date, last date of year)
- If month is present and day is missing, use the min of (IT-01 screening date, last date of month)

7. PEMBRO LISTINGS/RETREATED SUBJECTS

Baseline listings (demographics, disposition, prior therapy, etc): the 2 retreated subjects should appear in the monotherapy listings only (we are already doing this – no change)

- Study drug administration: the 2 subjects monotherapy administration of INT230-6 should appear in the monotherapy table/listing. The INT230-6 administration that occurred during combination therapy should appear in the pembro table/listings.
- Safety: events should appear in the cohort in which they occurred (we're already doing this)
- Other event-based outputs related to safety (labs, ECG, vital signs): similar to adverse events, these assessments should appear in the cohort in which they occurred for the 2 retreated subjects.

8. IMPUTATION OF END DATE OF LAST PRIOR ANTI-CANCER THERAPY

- If end date is completely missing, use IT-01 screening date
- If year is present and end month is missing, use the min of (IT-01 screening date, last date of year)
- If month is present and day is missing, use the min of (IT-01 screening date, last date of month)

OTHER NOTES

- Footnote: “Subjects 004-002 and 002-009 were initially treated on monotherapy and were later retreated on combination therapy with pembrolizumab. Applicable events are presented in the display according to these patients corresponding regimen.”
- Regarding 001-005’s follow-up status and time to event outcomes like DOR, I confirmed there are no other indications this patient came off treatment/study, so I think we’ll leave as is. It would be useful to include this in the delivery email in case the sponsor wonders what’s going on with this one patient who is likely an outlier.

ITR/BTR re-baselining

Consider the below table for a hypothetical patient that had a baseline bystander tumor treated during the first treatment course and then later retreated.

USUBJID	VISIT	Cohort	TRLNKID	Treated	Tumor Class	Baseline Flag	BTR calculation	ITR calculation	Comments
1001	Screening	EC	BY-11	N	Bystander		N	N	Pre-baseline but not most recent assessment. Not used at all.
1001	Screening	EC	BY-11	N	Bystander	Y	Y	N	Baseline for BTR calculation
1001	C2D0	EC	BY-11	N	Bystander		Y	N	Tumor not yet treated so included in BTR calculation
1001	C4D0	EC	BY-11	N	Bystander	Y	Y	Y	Tumor not yet treated so included in BTR calculation AND also baseline for ITR calculation
1001	Repeat Assessment 1	EC	BY-11	Y	Target		N	Y	First treated visit. Tumor is now target and previous assessment is baseline for reference
1001	Repeat Assessment 2	EC	BY-11	Y	Target	Y	N	Y	Considered for ITR on first treatment AND is baseline reference for Retreatment
1001	C2D0 Retreatment	DEC	BY-11	Y	Target		N	Y	Included for Retreatment ITR calculation
1001	C4D0 Retreatment	DEC	BY-11	Y	Target		N	Y	Included for Retreatment ITR calculation
1001	C6D0 Maintenance	DEC	BY-11	Y	Target		N	Y	Included for Retreatment ITR calculation

Important notes:
-First Screening assessment is not included at all because there is a later screening assessment that can be used as baseline.
-Subject is considered for BTR through C4D0.
-Upon being treated as Repeat Assessment 1, subject is now considered for ITR. The last bystander measurement is used as baseline for ITR calculation on the first treatment course.
-Patient is retreated in the 3rd to last row (C2D0 retreatment). ITR calculation is restarted for new cohort, using the last record from the EC cohort as baseline.

Dosed TTB

Consider the following hypothetical patient's baseline tumor burden for calculation of Dosed TTB.

USUBJID	Tumor Class	TRLNKID	Longest Diameter	Shortest Diameter	Depth	(LD*SD*Depth*0.63)
1001	Target	T-1	4	3	3	22.68
1001	Target	T-2	2	1	1.5	1.89
1001	Bystander	BY-11	2	1	1	1.26
1001	Bystander	BY-12	1.5	1.2	1	1.134

To find TTB, we would simply add the tumors' individual LD*SD*D*0.63 calculations together: 22.68+1.89+1.26+1.134 = 26.964

To calculate % dosed TTB , we add up the total dose received by the patient and divide it by the patient's TTB. For example, if this patient received a total of 20 ml in T-1 and 1 ml in T-2 of INT230-6, the % dosed TTB would be (20mL + 2 mL) / (26.964 cc) * 100 = ~81.5%

Note that this example TTB calculation had all 3 measurements available (LD, SD, Depth) and so just uses Step 1 from the formula for TTB. Had less measurements been available, we would proceed to Step 2, calculate TTB as indicated, and sum them together in the same way.