PHASE 2a OPEN-LABEL, MULTICENTER TRIAL OF NAPTUMOMAB ESTAFENATOX (NAP) IN COMBINATION WITH DOCETAXEL FOLLOWING OBINUTUZUMAB PRETREATMENT IN SUBJECTS WITH CHECKPOINT INHIBITOR PRETREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

Investigational Treatment	Naptumomab estafenatox (NAP) and docetaxel with obinutuzumab pre-treatment
Clinical Trial Sponsor	NeoTX Therapeutics Ltd, 2 Pekeris Street Rehovot 7670202, Israel Phone: +972 (0)3 912 5853
Protocol Number	NT-NAP-102-1
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Study Phase	2a
Protocol Version	8.1
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DOCUMENT HISTORY

Document	Version Date	Summary of Main Changes and Rationale
Original protocol	*25-NOV-2020*	*Not applicable (N/A)*
Amendment 1 (version 2)	*28-JAN-2021*	1. Updated COVID-19 guidance (appendix 15.7) 2. Adding inclusion criterion to allow the inclusion of patients that already received COVID-19 vaccine, who completed all doses of the vaccine and at least 14 days have passed since the last dose before receiving obinutuzumab pre-treatment (inclusion criterion #12). 3. B cell level footnote was updated in the schedule of activities table, to clarify the timepoints for assessment. 4. Removal of post-NAP treatment ECG test on C1D1 and C4D1 and a change in the timepoint from C1D4 to C1D5, after the completion of docetaxel administration. 5. Allowing flexibility in the study drug NAP regimen, by allowing increase in dose on cycle 3 or 4 based on NAP plasma levels.
Amendment 2 (version 3)	*12-APR-2021*	1. Removal of the option to dose escalating to the 20 µg/kg/day on Cycles 3 or 4 2. Inclusion of NAP dose modifications in tabular format according to anticipated NAP toxicities and actions to be taken 3. Inclusion of guidelines for identification and management of cytokine release syndrome 4. Change of primary endpoint to ORR with a target of 30% 5. Specified patients receiving substrates of CYP enzymes for which small changes in concentration could lead to altered safety or efficacy should be

		monitored closely and have doses adjusted as indicated 6. Revised timing of ECG around the anticipated Tmax of NAP 7. Inclusion of additional PK sampling on D4 of each NAP cycle 8. Clarification that all assessments of Day 1, with the exception of PK sampling for NAP and cytokines, should be performed on the day of docetaxel treatment if NAP is discontinued due to an AE and treatment is continued with single agent docetaxel 9. Reduction in the frequency of B-cell tests 10. Correction of typographical discrepancies between the Schedule of Assessment (Section 6) and the Assessment (Section 7) sections 11. Update of the format of subject identification/ numbering
Amendment 3 (version 4)	*27-APR-21*	1. Inclusion of the option to evaluate lower dose and/ or additional schedules of NAP, if the target response rate is achieved at 15 ug/kg/day 2. Revision of section 5.2.4 Stability of Reconstituted and Diluted Naptumomab Estafenatox (NAP), to indicated that stability information on reconstituted and diluted NAP can be found in the IFU (Information For Use) and the Pharmacy Manual 3. A clarification has been added regarding docetaxel dose adjustments, section 5.1.1 4. Added clarifications under section 5.2.6 Dose Modifications for Naptumomab Estafenatox (NAP) 5. Table 2 - Schedule of Assessments, note #15, has been clarified with additional assessments that should not be performed when docetaxel is administered as a monotherapy 6. Removal of the statement in section 5.2.2 that every effort should be made to administer NAP over

		approximately 5 minutes of injection. NAP will be administered as slow bolus injection
Amendment 4 (version 5)	*17-JUN-21*	1. Daily dose of NAP amended to 10 µg/kg/day 2. The rationale for this change is updated in Section 1.6: Dose Selection Rationale and Risk 3. Section 5.2.6 Dose modifications was updated with the option to reduce the dose of NAP to 5 µg/kg/day where applicable
Amendment 5 (version 6)	*01-Feb-22*	1. Addition of abbreviations "EOD" and "GGT" 2. A clarification has been added in exclusion criterion #13 that all prior treatments should be completed 21 days prior to enrollment, which is D-13, obinutuzumab pre-treatment. 3. Exclusion criterion #14 was previously omitted from section 4.2 while it was present in the synopsis. This discrepancy has been corrected and the criterion is added back in this amendment. 4. Update of the rationale for daily dose of NAP at 10 µg/kg/day with updated data from an ongoing P1 study, in Section 1.6 5. Removal of the sentence that treatment must begin within 72 hours after the approval of the patient's eligibility form by the Medical Monitor, in section 4.3 and section 6. 6. New section (Premedication for docetaxel) has been added to clarify that if steroids are being initiated one day earlier of D5, it should be administered at least 1 hour after NAP administration on D4 of each cycle, (section 5.1.1) 7. Clarification on the time schedule for administration of pre-medications for NAP, in section 5.2.5 8. NAP dose delay section has been updated with the information that in case of any obinutuzumab related toxicities of grade ≥2 that exist on the first scheduled day of NAP administration (C1D1), Cycle 1 of NAP-

		docetaxel treatment may be delayed up to 7 days (section 5.2.7). 9. Evaluation of disease (EOD): enlarging the time-window allowed for imaging at screening to 3 weeks (instead of 2 weeks) prior to enrolment (D-13); and ongoing study imaging will be performed at the end of cycle 3 (63 days ± 7 days) instead of at the end of cycle 2, and every 9 weeks thereafter. A recommendation was also added to proceed 1-2 additional treatment cycle(s) of NAP/docetaxel beyond progression in patients who demonstrate objective progression but who are clinically stable, at the discretion of the Investigator, followed by a confirmatory imaging after 4-8 weeks. 10. Clarifications on the time to perform ECG, vital signs, PK and cytokines sampling (post NAP administration start time) in Schedule of Assessment (Section 6) and the Assessment (Section 7) sections. 11. Correction of a discrepancy in the schedule of the B-cell test between the Schedule of Assessment (Section 6) and the Assessment (Section 7) sections. 12. A new appendix has been added to provide guidance on the procedure and processing of samples, section 14.8: Example for B cells quantitation procedure. 13. A clarification on the types of tumor tissues which are not acceptable for biomarker test of 5T4 expression: bone samples, fine-needle aspiration, brushing, cell pellets and lavage, in sections 6 and 7. 14. Correction of typographical discrepancies between the Schedule of Assessment (Section 6) and the Assessment (Section 7) sections 15. Updated inclusion criterion #12 as well as appendix 14.7 for COVID related guidance with updated data from the CDC website. A clarification has also been added to provide guidance on documenting information on COVID-19 in “Medical History” and

		vaccinations in "Concomitant Medications", in section 7.1. 16. Addition of reference #23 in section 7.2.3 and section 14. 17. Addition of section 7.9.: "Unscheduled Visits". 18. Addition of section 10.6: "Protocol Deviations". 19. A clarification under section 8, that progression/worsening of underlying disease should not be considered as adverse event (AE or SAE). 20. A typographical error in the amount of WFI in the synopsis has been corrected. 21. A clarification on the pre-medications administered prior to obinutuzumab infusion and time of administration, in section 5.3.3. 22. Added note to the table of assessments to follow the pre-medication guidelines for each of the study treatments. 23. Provide detailed instructions on NAP administration in section 5.2.2.
Amendment 6, version 7.0 + 7.1 (correction of a discrepancy in ECG updated time points, section 7.2.4)	*17-Jul-22*	1. Updated dose reduction scheme has been implemented to adjust the reduction in percentage (by ~25%) rather than in fixed increments. NAP may be reduced by one dose level for G3 AEs, and by two dose levels for G4, life-threatening AEs (with the exception of hematologic toxicity and laboratory findings). A second dose reduction is allowed for G3 AEs. If the dose was reduced only once for a G3 AE (e.g., from 10 µg/kg/day to 5 µg/kg/day) and is tolerated well with no recurrences or further NAP related AEs at the reduced dose, then at the PI discretion, the dose may be increased by one dose level in the following cycle. 2. A clarification was added regarding a delay of a cycle due to docetaxel toxicity in section 5.1.2. If NAP and docetaxel are to be delayed due to toxicity of docetaxel, the whole cycle of NAP and docetaxel may be delayed up to 6 weeks. Further delays should be discussed with the Medical Monitor.

		3. Updated inclusion criterion #11: the collection of archival or fresh biopsies is mandatory to support the retrospective analysis of 5T4 level. 4. The efficacy evaluation has been changed from RECIST to iRECIST due to the immune mediated mechanism of action of NAP (section 14.1 and throughout the protocol). Supporting this change, is a case of pseudo-progression that followed by a response. 5. The schedule of disease assessment by imaging has been changed as follows: Ongoing study imaging will be performed at the end of cycle 2 (45 ± 7 days) and every 6 weeks (± 7 days) for the first 24 weeks and then every 9 weeks (± 7 days) thereafter. This schedule should be maintained even if cycles are delayed. Confirmatory scans will be performed after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter. 6. With the CDC guidance that recommends the administration of the vaccine to immunocompromised patients, it has been decided to remove the COVID-19 related inclusion criterion (previously #12) and a clarification has been added to refer to the CDC guidelines for recommendations on the timing of the vaccine under section "14.7.2 Recommendations for the study patients regarding COVID-19 Vaccines". 7. Survival follow up time has been changed to allow longer overall survival assessment from '6 months after the last subject has been enrolled' to '6 months following treatment completion of the last subject into the trial'. 8. Due to accumulating data with NAP in several clinical trials, it has been decided to ease the burden of safety labs and remove the following tests: a) CBC and Serum Chemistry were previously collected on screening, day -12, and then on day 1 and day 4 of each cycle. Day 15 is a safety follow up visit and remains unchanged. In this amendment the time-points have been changed to be collected at screening, day -12 and then day 1 of each cycle but day 4 will be collected only on cycles 1, 2 and 3. Both will also be collected at EOT as previously done and as clinically indicated.

		b) Urinalysis was previously collected on screening, day 1 of each cycle, day 15 and at EOT. This has been changed in this amendment to be collected at screening, C1D1, EOT and as clinically indicated. c) Coagulation panel was previously collected at screening, C1D4, C1D15, C4D1 and EOT visit. The tests during NAP treatments have been removed, however due to a known risk of Disseminated Intravascular Coagulation (DIC) related to obinutuzumab treatment, 2 new time-points have been added at D-12 and at C1D1 prior to NAP treatment (screening and EOT timepoints have not been changed). Changes are implemented on section 6: Study Procedures and section 7: Assessments. 9. ECG was previously assessed at screening, at 5min (+3min) post NAP initiation time on: C1D1, C1D4, C4D1, C4D4, and at EOT visit. All timepoints during the treatment have been removed and ECG will be performed at screening, EOT and as clinically indicated throughout the study. This revision is done under sections 6 & 7. **Rationale:** Data from two ongoing clinical studies conducted with NAP (13 patients in the current P2 study and 50 patients in an ongoing P1 study of NAP and durvalumab following pre-treatment of obinutuzumab), in addition to safety data from past clinical trials in over 300 patients treated with NAP, were reviewed for ECG assessments at various timepoints. Specific data from the current study were reviewed for ECGs at the time of the peak plasma levels of NAP, at the following timepoints: • 13 patients on C1D1 • 13 patients on C1D4 • 9 patients on C4D1 • 8 patients on C4D4 • 5 patients at End of Study visit No significant abnormalities and/ or shifts from baseline, including QTcF changes, were detected at any of those timepoints. In addition – neither AEs nor SAEs were identified to be related to any ECG abnormalities. Important to note, the challenge of multiple protocol procedures

		required in the short timeframe post NAP administration. The ECG as well as PK sample collection and vital signs – all are requested at the same timepoint, which is a significant challenge for those taking care of the patients. 10. Added clarifications (section 5.2.7) for dose delay of NAP between cycles, allowing 7 days delay for any reasons and the need to discuss with the Medical Monitor for any delays beyond the indicated window. A clarification was also added that the schedule of the imaging should be maintained even if cycles are delayed. 11. A clarification has been included under section 7.3 Efficacy Assessments, in cases that CT contrast agent is unavailable and for the general use of PET-CT in the study. 12. Correction of a typographical error for vital signs collection after the end of the obinutuzumab infusion. Corrected to 'every 30 minutes (± 5 min) for 1 hour after **the end** of the infusion' instead of '1 hour after **start** of the infusion'. This correction is done under sections 6 & 7. 13. A clarification has been added to section 7.2.5 Laboratory Determinations, that if the b-cell test was missed in any of the visits, it is important to collect it in the next scheduled visit.
Amendment 7, version 8.0	*12-Dec-22*	1. Collection of available results in patients' medical history of NGS results, TMB (tumor mutational burden) and PD-L1 to better understand if these biomarkers can be predictive of response. This addition is done under sections: "abbreviation", 1.1, 2.1.3, 2.2.3 and 3. Changes are also implemented in sections 6 and 7. 2. Section 1.6: Dose Selection Rationale and Risk was updated with ongoing P1b study data and the study number in NIH website. 3. Change in the regimen of NAP, starting cycle 7, to dose only on Day 1 instead of days 1-4. Starting Cycle 7, NAP may be increased to 15 µg/kg and will be administered on Day 1 followed by docetaxel on Day 2, in 21 days treatment cycles. Once docetaxel has been discontinued (either completed or stopped for toxicity), NAP as monotherapy will be given on a 28-day cycle, but not earlier than C7. In patients whose NAP dose was reduced due to toxicities during

		cycles 1-6, NAP dose will not be further increased in cycle 7. Rationale: After 6 cycles only a booster dose may be needed every cycle. Reducing days of NAP treatment will simplify the schedule and regimen of NAP. Dose increase to 15 μg/kg given only on day 1 is not expected to increase NAP toxicity profile, as NAP related toxicities predominantly occur on cycles 1-2 based on collected data with 15 μg/kg on days 1-4. Changes are implemented in sections 1.6, 3, 5.1, 5.2.2, 5.2.6, 6 and 7. 4. NAP premedication in section 5.2.5: IV fluids recommendations have been updated to avoid excess of IV fluid and paracetamol dose was adjusted to comply with standard paracetamol commercial doses (500-650mg). 5. A Clarification has been added in section 4.5 that patients may be re-screened if failed previous screening. 6. NAP administration time has been updated to allow to shorten the time if no IRRs ≥G2 occurred in a previous full cycle. A clarification that any IV fluids given simultaneously with NAP are prohibited has also been added. All changes implemented in section 5.2.2. 7. A clarification has been included under section 5.2.3 on NAP dose calculation based on subject's weight. 8. NAP dose modification table in section 5.2.6 has been updated for cases of G3 or G4 NAP related hematologic AEs, the next cycle dose will be reduced only if has not been resolved to G2. 9. Update of section 5.4, Prohibited concomitant medication, and section 7, Concomitant medications: Hematopoietic growth factors (e.g. G-CSF, erythropoietin) and approved COVID treatments (e.g. Paxlovid) are allowed during the study. 10. Biomarkers collection schedule update: Addition of samples timepoints for PK, ADAs, Nab and HAMA: collection on day 1 of every 2 cycles after cycle 6. Changes are done under sections 6 and 7.5. 11. Correction of typographical errors and other inconsistencies throughout the protocol. 12. A flexibility in the time of collection of safety lab tests on Day 1 of each cycle to allow a broader window: up to 72 hours prior to any study drug

		treatments instead of up to 15 minutes in CBC, serum chemistry, coagulation panel, pregnancy test, thyroid panel and symptom directed physical exam. Changes are done under sections 6 and 7.5. 13. Reducing number of CBC and chemistry tests. Day 4 – CBC and chemistry are to be taken on Day 4 of cycle 1 only, with a broader window of up to 24 hours, but after the NAP administration on day 3. Changes are done under sections 6 and 7.5. 14. Evaluation of disease (EOD): Adding brain MRI at screening with further follow up if positive. This change is implemented in sections 6 and 7.3. 15. Number of urinalysis tests was reduced and will be performed at the Screening visit only and then as indicated. Sections 6 and 7.2.5 were updated. 16. Serum chemistry lab test was removed from Day -12. Updated in sections 6 and 7.2.5. 17. Clarification in sections 6, 7.7 and 9.4, that EOT visit will be performed prior to start of any new anti-cancer treatment. 18. Time of observation post NAP treatment has been updated as follows and implemented in sections 5.2.2, 6 and 7.2.3: During cycle 1 (days 1-4) and cycle 2 Day 1 (C2D1), all subjects should be observed for 3 hours post injection of NAP at the site. If no G3 or higher infusion related reactions occurred, time of observation can be shortened to 1 hour on further treatment days. Subjects who experience any TEAEs during the observation period and/or any other medical condition requiring further monitoring at the discretion of the investigator, should be further observed as clinically appropriate. Subjects should be advised that in any case of severe and/or persistent fever, chills, or shortness of breath beyond 5-7 hours post NAP administration, they should seek a medical attention. **Rationale:** Data from two ongoing clinical studies conducted with NAP (approximately 80 patients) show that most of the infusion related reactions occurred during the first cycle (mostly days 1 and 2) and on the first day of the second cycle. Patients who did not experience any infusion related reactions during these treatment days were less prone to experience any significant AEs on further treatment days. All those toxicities were manageable with

		appropriate medical treatment, rapidly reversible and without long-term sequelae. Based on this experience, we can recommend on a shortened time of observation as described above. 19. The exploratory objective and endpoint for Nab analysis was removed as method is still under development. 20. Repeated thyroid function lab tests will continue after treatment discontinuation only in subjects with abnormal results at EOT. Subjects will be followed up until resolution or initiation of a new anti-cancer treatment. End of Study term was removed as it is no longer needed. Changes were implemented in Table 2 and section 7.2.5. 21. Day -12 treatment will be delayed if platelet count is below 75,000/μL, coagulation abnormalities and/or any signs and symptoms of bleeding or thrombosis are present. The second obinutuzumab dose can be delayed by Day -7. Any further delay in obinutuzumab dosing is to be discussed with the Medical Monitor. Implemented in section 5.3.4. 22. Inclusion criterion #11 has been changed to add an exception "if discussed with the Medical Monitor".
Amendment 7, version 8.1	*25-Dec-22*	1. Additional corrections of typographical errors and other inconsistencies throughout the protocol.

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ABREVIATIONS

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen-presenting cells
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CL	Creatinine clearance
CPI	Checkpoint Inhibitor
CR	Complete Response
CRF	Case report form
CRO	Contract research organization
CRS	Cytokine release syndrome
CSA	Clinical study agreement
CT	Computed tomography
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDP	Exposure during pregnancy
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOD	Evaluation of Disease
EOT	End of treatment

Abbreviation	Term
FDA	Food and Drug Administration (United States)
FT4	Free thyroxine
FU	Follow-up
G	Grade
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HAMA	Human Anti-Murine Antibodies
HBc	Hepatitis B core
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis C virus
IB	Investigator's brochure
ICH	International Conference on Harmonization
iCPD	Immune confirmed progression disease
ID	Identification
IHC	Immunohistochemistry
IFN-γ	Interferon gamma
INR	International normalized ratio
IO	Immuno-oncology
IP	Investigational product
iPR	Immune partial response
IRB	Institutional review board
iRECIST	Immune Response evaluation criteria in solid tumors
iSD	Immune stable disease
IUD	Intrauterine device
iUPD	Immune unconfirmed progression disease
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test
mAB	Monoclonal antibody
MHC	Major histocompatibility complex
MOA	Mechanism of action
MOH	Ministry of Health
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
Nab	Neutralizing Antibodies
NAP	Naptumomab estafenatox
NGS	Next Generation Sequencing
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate

Abbreviation	Term
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PD	Progressive Disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
p.o.	By mouth
PR	Partial response
PS	Performance Status
PT	Prothrombin time
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
R/R	Relapsed/Refractory
SAE	Serious adverse event
Sag	Superantigen
SAP	Statistical analysis plan
SCC	Squamous Cell Carcinoma
SD	Stable disease
SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Event
TMB	Tumor mutational burden
TNF- α	Tumor necrosis factor alpha
TRBV	T cell receptor beta variable
TSH	Thyroid-stimulating hormone
TTS	Tumor-targeted superantigen
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	White blood cell
WFI	Water for injection

SIGNATURES

Signature of Sponsor Representative

PHASE 2 OPEN-LABEL, MULTICENTER TRIAL OF NAPTUMOMAB ESTAFENATOX (NAP) IN COMBINATION WITH DOCETAXEL FOLLOWING OBINUTUZUMAB PRETREATMENT IN SUBJECTS WITH CHECKPOINT INHIBITOR PRETREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

I have read and approve the protocol and appendices. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Council on Harmonization (ICH) Guidelines for GCP and the ethical principles that have their origins in the Declaration of Helsinki, as well as all applicable privacy laws.

Signature : _____

Ilana Lorber, MD
Medical Director

Date : _____

Signature of Investigator

PHASE 2 OPEN-LABEL, MULTICENTER TRIAL OF NAPTUMOMAB ESTAFENATOX (NAP) IN COMBINATION WITH DOCETAXEL FOLLOWING OBINUTUZUMAB PRETREATMENT IN SUBJECTS WITH CHECKPOINT INHIBITOR PRETREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the Sponsor and Principal Investigator). Any changes in procedure will only be made, if necessary, to protect the safety, rights, or welfare of the subjects. I agree to treat all subjects entered in the study as per protocol and keep the appropriate records and documentation required. I will ensure that all staff participating in the study will be appropriately trained and informed about the study.

Study NT-NAP-102-1 is being conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements in the United States. Some of these requirements include:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations)

It is agreed that the conduct and results of this study will be kept confidential.

This trial will be conducted under an IND. It is agreed that the study will not be initiated without the approval of the Institutional Review Board (IRB).

Principal Investigator Name: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

PROTOCOL TITLE	PHASE 2a OPEN-LABEL, MULTICENTER, TRIAL OF NAP IN COMBINATION WITH DOCETAXEL FOLLOWING OBINUTUZUMAB PRETREATMENT IN SUBJECTS WITH CHECKPOINT INHIBITOR PRETREATED ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER
PROTOCOL NO.	NT-NAP-102-1
PHASE	2a
INVESTIGATIONAL TREATMENT	NAP
BACKGROUND AND RATIONALE	Prior to the era of checkpoint inhibitors (CPIs), docetaxel given as a single agent was found to prolong survival vs. best supportive care, despite a marginal effect on response rate, in patients with NSCLC previously treated with a platinum-based combination chemotherapy regimen (1). More recently, PD-1 and PD-L1 inhibitors were shown to further improve overall survival (OS) vs. docetaxel (2)(3)(4)(5). OS, including squamous and non-squamous NSCLC, was about 12 months for the CPIs vs. about 9 months for docetaxel, while there was no difference in progression -free survival (PFS). At 12 months, however, the estimated PFS rates were generally around 20% for the CPIs and 10% for docetaxel; the PFS rate at 6 months with docetaxel was approximately 30%. Overall, the response rates to CPIs varied between 14% and 20%, while the response rates to docetaxel varied between 9% and 13%. Docetaxel remains a standard of care for patients previously treated with CPIs. NAP is a recombinant protein with a Fab moiety targeting the 5T4 antigen fused with a genetically engineered superantigen moiety (6). The 5T4 antigen is an oncofetal glycoprotein that is upregulated in most NSCLC (6)(7)(8). It is also present on stem cells. The superantigen is responsible for initiating the inflammatory reaction that leads to tumor cell kill. In a first step, the bridging of T cell receptors and MHC class 2 molecules by the superantigen results in the activation and expansion of T-cells, primarily in peripheral lymph nodes, outside of the immunosuppressive tumor environment. In the case of NAP, the superantigen has been specifically designed to bind very selectively to the subset of T-cells expressing the TCRVβ 6.4 (TRBV 7-9) sequence on their T cell receptor, avoiding non-specific T cell over-stimulation. In a second step, the traffic of T-cells is redirected towards tumors expressing the 5T4 antigen bound to NAP,

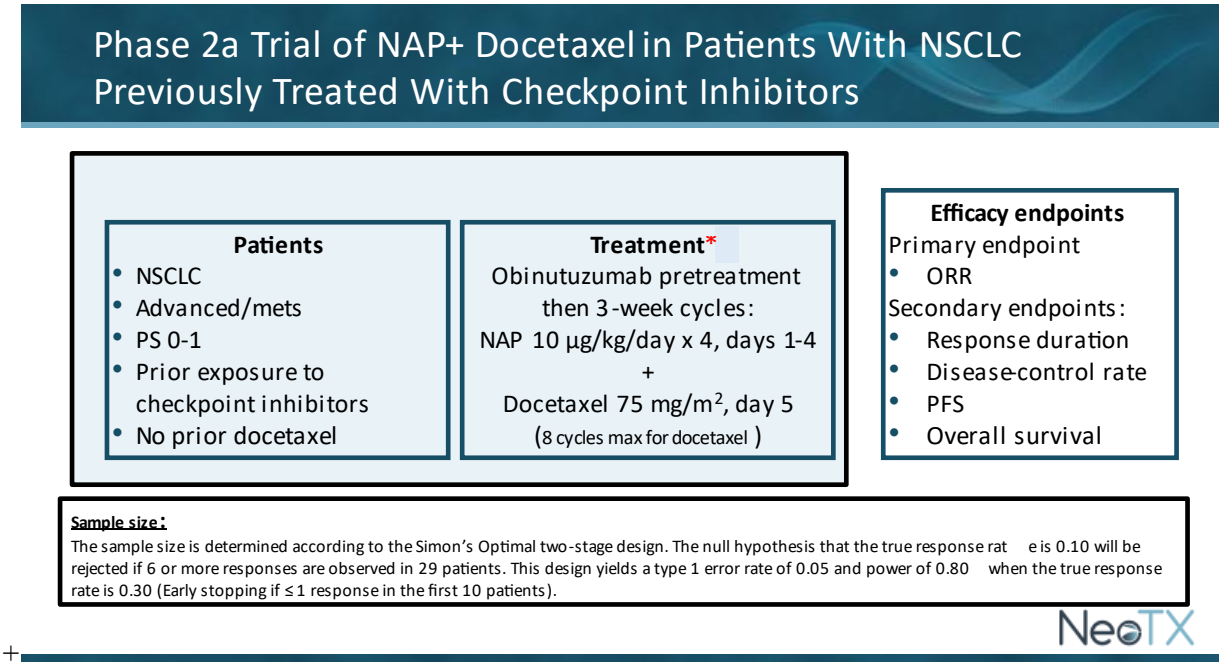
	resulting in tumor infiltration and, ultimately, tumor cell kill. This mechanism of action is unique. This is a native immune response with the tumor being recognized as a bacterial product. In preclinical in vivo models, a murine version of NAP was found to result in synergistic antitumor activity in combination with docetaxel and checkpoint inhibitors (9)(10)(11)(12). More than 300 patients have been treated with NAP, providing an extensive safety data base, but experience in NSCLC has been limited. In a small dose escalation trial of NAP and docetaxel in combination, one patient with an adenocarcinoma of the lung and liver metastases achieved a partial response for 10+ years. That patient had shown clear resistance to a prior docetaxel regimen (13). Antibodies binding to NAP (anti-SEA/E-120) may interfere with the exposure and activity of NAP. Low levels of anti-drug antibodies (ADAs) may be present at baseline, but these levels do increase after initial exposure to NAP, potentially resulting in significant reduction in NAP blood levels in subsequent treatment cycles. Obinutuzumab (14)(15), a new-generation, glycoengineered, humanized type 2 anti-CD20 monoclonal antibody currently approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma, depletes B cells and can eliminate the formation of ADAs, presumably without adversely impacting on T cell activation nor on dosing, activity or safety of NAP. In vitro studies have shown that T cells are activated and expand in similar frequencies when cultured with B cells, monocytes or both (16). In fact, CD14+ monocytes demonstrated a higher capacity to mediate the activation and expansion of TRBV7-9+ T cells as compared to B cells. These observations suggest that CD14+ monocytes alone can efficiently mediate NAP activation and expansion of TRBV7-9+ T cells in human blood. Hence, when given as a pretreatment, obinutuzumab, is expected to prevent the occurrence of ADAs and may result in more prolonged exposure to NAP, therefore potentially enhancing its antitumor activity. In this trial, obinutuzumab will be given once, over 2 days, on days -13 and -12 prior to the first cycle of treatment with the combination of NAP and docetaxel. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cell level.
OBJECTIVES	**Primary Objectives** • To describe the objective response rate (ORR) and duration of response (DOR) with the combination of NAP / docetaxel,

	following obinutuzumab pre-treatment in subjects with checkpoint inhibitors pre-treated NSCLC **Secondary Objectives** • To describe the safety profile of the combination of NAP / docetaxel, following obinutuzumab pretreatment in subjects with relapsed/refractory (R/R) NSCLC • To evaluate the overall survival (OS) defined as the time from day 1 of treatment until death due to any cause • To assess the possible impact of prior taxane exposure on the antitumor activity of the NAP/docetaxel combination • To describe the effect of obinutuzumab pretreatment on the development of anti-drug antibodies and human anti-mouse antibodies to NAP • To describe blood levels over time of NAP when administered after B-cell suppression **Exploratory Objectives** • To evaluate and characterize the pharmacodynamic effect of NAP /docetaxel on biomarkers in the circulation in subjects pre-treated with obinutuzumab • Clinical activity in relationship to biomarkers including 5T4, NGS results, TMB expression and PD-L1 level in the tumor.
STUDY DESIGN	This is an open-label, multicenter, phase 2a clinical trial of the combination of NAP /docetaxel following pretreatment with obinutuzumab in subjects with NSCLC who have progressive neoplastic disease despite having been treated with at most 2 prior systemic therapies, including a checkpoint inhibitor; approximately 35 subjects will be entered for efficacy analysis of 28 evaluable subjects. Subjects will receive obinutuzumab, 1,000 mg, administered by IV infusion on Days -13 and -12 of the first treatment cycle, in order to reduce the titer of anti-drug antibodies to NAP. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cell level. If an increase back to the normal level of B cell level is observed, additional biomarkers and PK level will be tested in the following visit. NAP will be administered in a dose of 10 μg/kg/day by IV bolus on Days 1 – 4 of treatment cycles 1-6, followed by docetaxel, 75 mg/m^2 on Day 5.

	Treatment cycles with the combination NAP/docetaxel will be 21 days in duration. Growth factors may be used at the discretion of the investigators. The combination of NAP and docetaxel will be given for a maximum of 8 cycles (unless, in the opinion of the investigator, the patient may derive benefit from continuing docetaxel). Starting Cycle 7, NAP at a higher dose of 15 μg/kg will be administered on Day 1 and docetaxel on Day 2, in 21 days treatment cycles. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. In patients whose NAP dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7. Dose increase to 15 μg/kg in advanced cycles is not expected to increase NAP toxicity profile, as NAP related toxicities predominantly occur on cycles 1-2, and this dose increase may overcome ADA formation with time. NAP as a single agent will be continued until disease progression, untoward toxicity or non-compliance for a maximum of up to 24 months from day 1 of therapy. Subjects will be screened to assess eligibility within 14 days prior to entry. Subjects must have received at least 1 and no more than 2 prior systemic regimens for the treatment of advanced/metastatic NSCLC. Patients are required to have progressed following treatment with both platinum-based chemotherapy and an anti-PD-L1 antibody administered either sequentially or concurrently. A prior PD-1/PD-L1 inhibitor is, however, not required if there was prior exposure to targeted therapies for driver mutation positive tumors (e.g. EGFR or ALK inhibitors). Entry into this trial is restricted to patients with incurable disease, including those who relapse within 6 months from chemoradiotherapy for Stage III disease. Subjects will have available archival or fresh tissue collected for the retrospective determination of tumoral 5T4 levels. Subjects will be assessed for the primary efficacy endpoint of objective response rate (ORR) according to the iRECIST criteria. Response duration is also a focus of interest in this study. In addition, disease control rate, combining the ORR with subjects demonstrating stable disease (SD), progression-free survival (PFS), PFS rate at 6 and 12 months and overall survival (OS) will also be determined. If available, NGS results, TMB expression and PD-L1 levels will be collected for the expression of exploratory tumor biomarkers. Ongoing study imaging will be performed at the end of cycle 2 (45 ± 7 days) and every 6 weeks for the first 24 weeks and then every 9 weeks (± 7 days) thereafter. Confirmatory scans for responses (PR or CR) will be performed after 6 weeks (± 7 days) during the first 24

	weeks and every 9 weeks thereafter. As NAP is known to induce an inflammatory reaction in the tumor, pseudo-progression may be observed and therefore, in patients who demonstrate objective progression but who are clinically stable, 1-2 additional treatment cycle(s) of NAP/docetaxel may be administered beyond progression at the discretion of the Investigator, followed by a confirmatory imaging as per the original schedule, every 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks (± 7 days) thereafter. The safety of the combination of NAP /docetaxel following pretreatment with obinutuzumab in a B-cell suppressed setting will be assessed in all treated subjects including adverse events, the results of ECGs, results of laboratory determinations, findings on physical exams, vital signs and reporting of the ECOG Performance Score. All treatment emergent AEs (TEAEs), drug-related AEs, SAEs and drug-related SAEs as well as hematology and chemistry lab results will be summarized using the worst grade per subject according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The pharmacokinetics of NAP will be based on plasma drug levels obtained at various timepoints after administration. The pharmacodynamics of the combination of NAP /docetaxel following pretreatment with obinutuzumab will be determined by measuring levels of cytokines (e.g., IL-2, IFNγ, IL-6 and TNFα) in serum. The immunogenicity of NAP will be assessed based on levels of anti-drug antibodies and human anti-murine antibodies (HAMA) collected at various times after administration of NAP. Neutralizing antibodies (Nab) will be also collected and kept for future analysis. The primary efficacy endpoint of this trial is ORR. A Simon 2-stage design will be used with the following assumptions: H0=10%. H1= 30%, α=0.05 and power=0.80. Accordingly, the target accrual is 29 subjects. Subjects who discontinue from treatment for any reason will continue to be followed for survival (even if the subject receives subsequent anti-neoplastic therapy). Subjects will be followed for survival until 6 months after the last subject has completed study treatment. Subjects who discontinue from treatment for reasons other than progression will continue to be followed for progression by CT/MRI scans every 6 weeks for the first 24 weeks, every 9 weeks thereafter; if such a subject receives subsequent anti-neoplastic

	therapy, further follow-up for progression will stop. A graphical description of the trial is depicted below (Fig. 1).



* Starting Cycle 7, NAP at a higher dose of 15 µg/kg will be administered on Day 1 and docetaxel on Day 2, in 21 days treatment cycles. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. In patients whose NAP dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7.

Figure 1. Study Schema

PLANNED NUMBER OF SUBJECTS	The trial will enroll approximately 35 subjects.
PLANNED NUMBER OF STUDY SITES	Approximately 10 study sites in the US will participate in the trial.
ENROLLMENT CRITERIA	Inclusion Criteria Subjects must meet ALL of the following criteria to be eligible for enrollment into the study: 1. Subjects must be at least 18 years of age 2. Subjects must have histologically and/or cytologically confirmed NSCLC 3. Subjects must have incurable (advanced or metastatic) disease at the time of enrolment (Patients who relapse within 6 months from chemoradiotherapy for stage III disease are considered incurable)

	4. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 5. Subjects must provide signed informed consent prior to any study specific procedures that are not part of standard medical care. 6. Subjects must have measurable neoplastic disease based on the iRECIST criteria 7. Subjects must have received at least 1 and no more than 2 prior systemic regimens for the treatment of advanced/metastatic NSCLC. Patients are required to have progressed following treatment with both platinum-based chemotherapy and an anti-PD-(L)1 antibody administered either sequentially or concurrently. A prior PD-1/PD-L1 inhibitor is, however, not required if there was prior exposure to targeted therapies for driver mutation positive tumors (e.g. EGFR or ALK inhibitors). 8. Subjects must have adequate hematologic and organ function: • WBC ≥3000/μL • Absolute neutrophil count ≥1500/μL • Platelets ≥100,000/μL • Hemoglobin ≥9.0 g/dL • Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance (CL) >40 mL/min, as determined by Cockcroft-Gault (using actual body weight) • AST ≤ 1.5 X ULN; ALT ≤ 1.5 X ULN; Alk phos ≤ 2.5 X ULN; bilirubin must be within normal limits • International Normalized Ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy and the INR, PT or PTT is within therapeutic range of intended use of anticoagulants 9. Subjects must be willing and able to comply with scheduled visits, procedures, drug administration plan, etc. as outlined in the protocol 10. Subjects should have an estimated life expectancy of at least 12 weeks

	11. Archival or fresh tumor tissue from a biopsy of a tumor lesion not previously irradiated must be provided for retrospective 5T4 analysis, unless discussed with the Medical Monitor. Exclusion Criteria 1. Subjects with active infection requiring treatment within 3 days of C1D1. 2. Subjects with other active neoplastic disease requiring concurrent anti-neoplastic treatment 3. Subjects with known, suspected or documented parenchymal brain metastases unless treated with surgery and/or radiation, with the subject neurologically stable and off pharmacologic doses of systemic glucocorticoids; subjects with leptomeningeal metastases are not eligible. Patients should have completed brain radiation for at least 14 days and be off steroids per exclusion criteria 7. 4. Active or previously documented autoimmune or inflammatory disorders such as, but not limited to rheumatoid arthritis, systemic lupus erythematosus, uveitis, ulcerative colitis, Crohn's syndrome, Wegener's syndrome, multiple sclerosis, myasthenia gravis, scleroderma and sarcoidosis. The following are exceptions to this criterion: • Vitiligo or psoriasis not requiring systemic treatment (within the last 2 years) • Subjects with endocrinopathies (e.g. following Hashimoto syndrome) stable on hormone replacement or do not require any therapy. 5. History of primary immunodeficiency 6. Subjects with a history or prior allogeneic organ transplant 7. The use of immunosuppressive agents within 28 days of enrolment (D-13; obinutuzumab pre-treatment) including, but not limited to, cyclosporine, mycophenolate, azathioprine, methotrexate, adalimumab, infliximab, vedolizumab, tofacitinib, dupilumab, rituximab, etc. Pharmacologic doses of glucocorticoids defined as glucocorticoid equivalents of >10 mg/day of prednisone (with the exception of systemic steroids given as a premedication before each of the study medications, or used prior to administration of radiographic contrast material in

	subjects with allergies) are not acceptable within 14 days prior to enrollment. Subjects are permitted to receive topical, intranasal, inhalational and intra-ocular glucocorticoids. 8. Subjects who have uncontrolled inter-current illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations and substance abuse that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to follow the dictates of the protocol. 9. Subjects who have received a live attenuated vaccine within 28 days prior to the first dose of obinutuzumab. 10. Subjects with hepatitis B (positive HBV surface antigen [HBsAg]), hepatitis C (hepatitis C antibody) or HIV (HIV antibody). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible; subjects positive for hepatitis C (HCV) antibody who have completed a course of antiviral therapy are eligible if polymerase chain reaction (PCR) is negative for HCV RNA. 11. Female subjects who are pregnant or breastfeeding. 12. Male or female subjects of reproductive potential who are not willing to employ effective birth control from Screening to 90 days after the last dose of study treatment. Highly effective methods of contraception are defined as one that results in a low failure rate (e.g., less than 1% per year) when used consistently and correctly. 13. Prior treatment with chemotherapy or other systemic antineoplastic therapy within 21 days; experimental therapy 21 days or 5 half-lives, whichever is shorter. All prior treatments should be completed 21 days prior to enrollment (D-13; obinutuzumab pre-treatment). 14. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

	15. Subjects who have undergone major surgery or trauma within 4 weeks of study entry (D-13; obinutuzumab pre-treatment). 16. Subjects with Grade 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Medical Monitor. Subjects with neuropathy grade >2 are not eligible. 17. Subjects who have been treated with one of the study drugs (NAP and/or docetaxel). 18. Subjects with NYHA Class III or IV CHF, myocardial infarction or acute coronary syndrome within 6 months prior to study enrollment, ongoing angina pectoris, severe peripheral vascular disease, CVA within 6 months of study enrollment or any other concomitant medical disorder that might interfere with the subject's participation in the trial or interpretation of the study data. 19. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms in women and ≥450 ms in men, calculated from 3 ECGs (within 15 minutes at 5 minutes apart). 20. Subjects on strong inducers or inhibitors of CYP3A4. 21. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients (including kanamycin). 22. Subjects with a history of progressive multifocal leukoencephalopathy (PML).
INVESTIGATIONAL PRODUCTS	Obinutuzumab will be supplied in a single-dose vial containing 1,000 mg in 40 mL of preservative free solution. The obinutuzumab solution must be stored at 2 – 8^0 C. NAP will be supplied as 1.25 mg of a lyophilized powder in a 10 mL single-use glass vial to be reconstituted with 1.2 mL of WFI supplied in a second vial, after which the concentration of NAP will be 1 mg/mL. The lyophilized NAP must be stored at 2 – 8^0 C. Docetaxel will be obtained commercially
TREATMENT REGIMEN AND DURATION	Treatment cycles will be 21 days in duration with NAP/docetaxel combination. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration.

	Obinutuzumab further diluted in normal saline is to be administered on Day -13 of the first cycle in a dose of 1,000 mg at a rate of 50 mg/hr, with the rate of infusion increased in 50 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. On Day -12 of the first cycle, obinutuzumab is to be administered in a second dose of 1,000 mg. If no infusion reaction occurred during the previous infusion when the rate of administration was 100 mg/hr or faster, administer the second infusion starting with a rate of 100 mg/hr with the rate of infusion increased in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cell level. NAP will be administered in a dose of 10 μg/kg daily X 4 on Days 1 – 4 of treatment cycles 1-6. NAP-docetaxel combination treatment will continue for a maximum of 8 cycles (unless, in the opinion of the investigator, the patient may derive benefit from continuing docetaxel). Starting Cycle 7, NAP at a higher dose of 15 μg/kg will be administered on Day 1 and docetaxel on Day 2, in 21 days treatment cycles. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. In patients whose NAP dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7. NAP as a single agent will be continued until disease progression, untoward toxicity or non-compliance for a maximum of up to 24 months from day 1 of therapy. The reconstituted solution will be further diluted with a supplied diluent to reach the required dose for administration. Fully diluted NAP will be administered as an IV bolus injection. Docetaxel will be administered in a dose of 75 mg/m^2 on day 5 of every 3 weeks cycle as an IV infusion over 1 hour for a maximum of 8 cycles (unless, in the opinion of the investigator, the patient may derive benefit from continuing docetaxel) or until progression, untoward adverse reactions or non-compliance, whichever comes first. During cycles 1-6 docetaxel will be given on Day 5, and on Day 2 if given in any further cycles. Premedication regimens before each of the study drugs will be detailed in the full protocol.
STATISTICAL CONSIDERATIONS	The primary endpoint is ORR. A subject is considered evaluable if there is at least one pre-treatment and one post-treatment tumor

AND SAMPLE SIZE DETERMINATION	assessment (according to the iRECIST criteria) in the absence of eligibility and compliance issues. iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans will be performed as per the original schedule, every 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks (± 7 days) thereafter. Sample size is derived from a Simon's Optimal two-stage design testing the null hypothesis H0: true ORR ≤ 0.10 versus the alternative H1: true ORR ≥ 0.30. With one-sided alpha = 0.05 and power = 0.80, 6 or more responses in a total of 29 subjects may be of further clinical interest. The trial may be stopped if there is a single responder or no responder in the first 10 patients.
STATISTICAL ANALYSES	Descriptive statistics will be used to describe the results of the trial. Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of subjects within a particular category
EFFICACY EVALUATION	Overall response rate (ORR) is the proportion of subjects who achieve a best response of iCR or iPR by iRECIST. ORR will be calculated in all evaluable patients, and in all treated subjects. Immunotherapy 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. iRECIST requires the confirmation of progression, which should be done after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter. The ORR with corresponding exact 95% confidence intervals, will be summarized. Disease control rate, duration of response, progression free survival (PFS) and overall survival (OS) will be analyzed as well. Time-to-event data will be estimated and summarized using the Kaplan-Meier method.
SAFETY EVALUATION	Safety will be evaluated in all treated subjects.

	The safety assessments will include treatment-emergent adverse events (TEAEs), volunteered, observed, and elicited by general questioning in a non-suggestive manner. TEAEs will be graded according to NCI CTCAE version 5.0, grouped by MedDRA preferred term, and summarized by worst grade severity per subject. Serious AEs will be tabulated and summarized. Other AEs leading to discontinuation of study therapy or any other premature interruption will be tabulated and summarized. Clinical laboratory results will be collected pretreatment through 30 days after the last administration of any study treatment and prior to start of a new anti-cancer treatment. Clinically significant laboratory abnormalities, namely tests that result in treatment modification and/or require intervention, will be recorded as AEs. Where applicable, laboratory results will be classified according to the NCI CTCAE and will be summarized by worst grade per subject. Additional safety assessment will include physical examinations, vital signs, and ECG. No statistical tests will be performed for any of the safety assessments.
PHARMACOKINETIC EVALUATION	PK analysis will be performed on the PK population (i.e. enrolled subjects, with analyzable PK data and without relevant deviation interfering with the PK evaluations)
PHARMACODYNAMIC EVALUATION	The following parameters and the corresponding change from baseline will be measured and summarized by descriptive statistics and data listings for the NAP /docetaxel treatment: • Cytokine levels • B-cell levels • Anti-drug antibodies and human anti-murine antibodies (ADA and HAMA)

1 INTRODUCTION

1.1 Background and Rationale

Although the incidence of lung cancer has diminished over the last several years in many developed countries, most likely due to reductions in tobacco use, lung cancer remains one of the most frequently occurring malignancies. For 2020, it is estimated that there will be over 225,000 new cases of lung cancer and over 135,000 deaths from lung cancer in the US; lung cancer remains the leading cause of cancer deaths in the US (17). Lung cancer also remains the most frequently reported cancer, and the leading cause of cancer deaths, worldwide (18). The most common type of lung cancer, non-small cell lung cancer (NSCLC), represents about 80% of all lung malignancies.

For subjects with NSCLC whose tumors harbor known genetic mutations, agents targeted to these mutations have resulted in significant improvements in treatment. Third generation agents targeted to the epidermal growth factor receptor, such as osimertinib, result in objective response rates (ORR) of over 75% and produce progression-free survival (PFS) times of over 18 months (19). Unfortunately, most of these subjects ultimately relapse, as additional driver mutations evolve in their tumors.

The checkpoint inhibitor class of agents has probably had the most impact on outcomes in subjects with NSCLC, both in the 1st and 2nd line settings. Marked improvement in response rates, durations of response, progression-free survival times and overall survival times have been demonstrated by several checkpoint inhibitors when compared to standard platinum-based doublet therapy or to docetaxel. The degree of improvement in many of these outcomes, however, is often dependent on tumor proportional PD-L1 scores or the extent of tumor mutational burden and not all subjects derive benefit (20). Low tumor mutational burden (TMB) and low expression of PD-L1 have been associated with a high level of resistance to these inhibitors (24, 25). Lack of neoantigens on the tumor surface believed to attribute to anti PD-(L)1 resistance. Low TMB is a surrogate for the lack of neoantigens. NAP targeting causing tumor cells being covered by a superantigen, activates, expands, and redirects a subset of T-cells towards the tumor and generating tumor inflammation. This mechanism of action may presumably overcome tumor resistance to anti PD-(L)1 treatment also in the setting of low TMB.

Docetaxel as a single agent remains the standard of care for patients who have failed platinum-based regimens, targeted agents and checkpoint inhibitors. As a single agent versus best supportive care, docetaxel was found to prolong survival, despite a marginal effect on response rate (1). In more contemporaneous studies comparing checkpoint inhibitors to docetaxel in patients failing platinum-based regimens, OS, including squamous and non-squamous NSCLC, was about 12 months for the CPIs vs. about 9 months for docetaxel, while there was no difference in progression -free survival (PFS) (2)(3)(4)(5). At 12 months, however, the estimated PFS rates were generally around 20% for the CPIs and 10% for docetaxel; the PFS rate at 6 months with docetaxel was approximately 30%. Overall, the response rates to CPIs varied between 14% and 20%, while the response rates to docetaxel varied between 9% and 13%. Docetaxel remains a standard of care for patients previously treated with CPIs, but it is clear that there remains a need for additional novel therapies for the treatment of NSCLC.

1.2 Naptumomab estafenatox (NAP)

Naptumomab estafenatox (ABR-217620; NAP) was developed to activate and target subjects' T-cells to their own tumors, by fusing a superantigen (SAg) variant that activates T lymphocytes to the Fab moiety recognizing the tumor-associated oncofetal antigen 5T4, with the objective of eliciting a potent tumoricidal cytotoxic T cell response (6). The SAg moiety selectively engages the T cell receptor β variable (TRBV) 7-9. NAP has been engineered to have a low binding to human antibodies and to minimize killing of MHC class II positive cells.

The 5T4 antigen is a 72 kDa oncofetal trophoblast transmembrane glycoprotein that is broadly expressed on tumor cells of solid tumors but has very low expression on normal adult tissues (7). It is also expressed on cancer stem cells which are hypothesized to be responsible for chemotherapeutic resistance and recurrence of cancer. Significant upregulation of 5T4 has been reported in many types of carcinomas (6)(7)(8). Studies have shown a homogenous 5T4 expression, which in most cases is moderate to strong, in more than 95% of NSCLC tissue samples. The expression of 5T4 has been shown to influence adhesion, cytoskeletal organization, and motility, properties that might account for the 5T4 association with poorer clinical outcome in some cancers. The biology of 5T4 in normal and pathologic tissues is not well understood. No ligands or co-receptors have been identified for 5T4 to date and there is no evidence of circulating 5T4 antigens.

NAP 's superantigen moiety represents the culmination of a long development program in which genetically engineered versions of superantigen were tested in the clinic until epitopes were found that can engage the immune system effectively without creating safety concerns such as cytokine storms. In pre-clinical and clinical studies, NAP has demonstrated recognition enhancement: it induced T cell expansion, activation and infiltration into the tumor without undo safety concerns (7). This effect of NAP makes it an ideal drug for combination with different cancer therapies including chemotherapy, checkpoint inhibitors and CAR T cells.

1.3 Naptumomab estafenatox (NAP) Mechanism of Action

In the first phase of NAP treatment, T lymphocytes are activated and differentiate into effector cells (expansion phase, Fig. 2). In the second phase, the activated T cells localize and infiltrate to the tumor and mediate their anti-tumor actions (attack phase, Fig. 2).

The expansion phase is mediated by the SAg moiety. Superantigens act as potent mitogens for human T cells. Unlike conventional antigens, these SAgs bind to MHC class II on antigen-presenting cells (APC) outside of the conventional peptide-binding groove and stimulate T cells expressing specific TCR Vβ-chains, resulting in stimulation of a high proportion of T cells. SAgs activate both CD4 and CD8 T cells, and under certain circumstances CD4 T cells can also be cytotoxic to cells displaying the superantigen. Unlike the wild type superantigen, the SEA/E120 moiety of NAP was designed to bind to a specific subset of T cells expressing TCRVβ 7.9 (TRBV 7-9). NAP, via its SEA/E120 moiety, binds with intermediate/low affinity to the TCRVβ 7.9 and to MHC II, enabling the bridge between the T cell and APC. As a consequence, T cells are activated

and proliferate. Since only 2-5% of human T cells express TCR Vβ 7.9, this expansion phase is limited, ensuring a superior safety profile of the drug.

In the second phase of NAP treatment, by binding to the 5T4 antigen on the tumor cells, NAP molecules act as guiding beacons for the SAg-activated T cells, directing them to the tumor microenvironment. The activated T cells bind to the cancer cells through TCR-SAg interaction which enables their activation and the resulting tumor killing by direct lysis of the engaged 5T4-positive tumor cells and by indirect killing of the surrounding antigen-negative tumor cell variants by secretion of cytokines (paracrine effect) (6). NAP recognizes the 5T4 antigen with an affinity in the order of 1nM and induces T cell-mediated killing of tumor cells at concentrations around 10 pM.

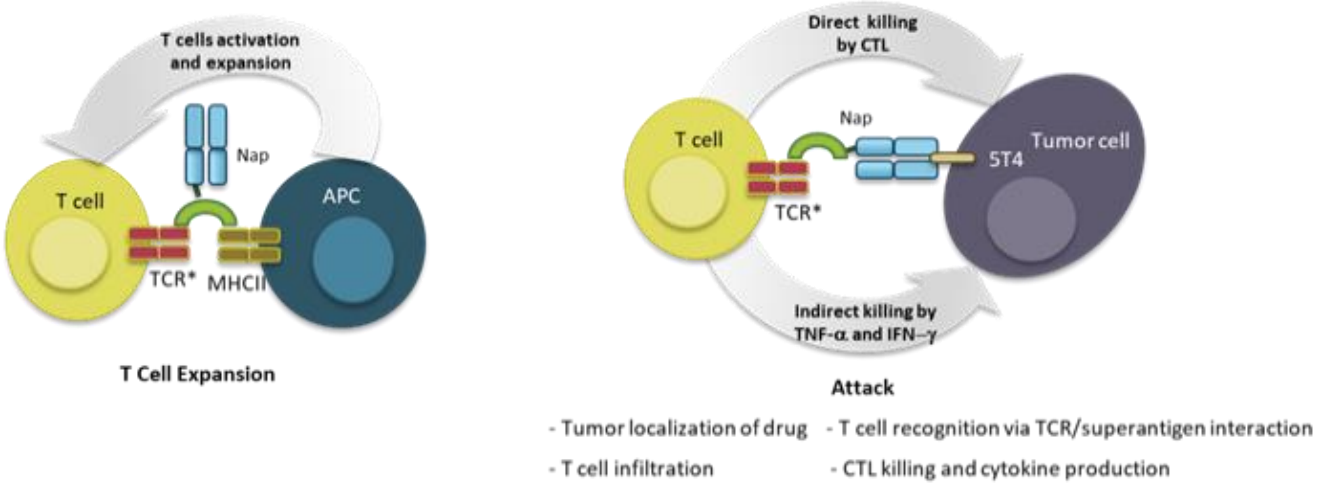
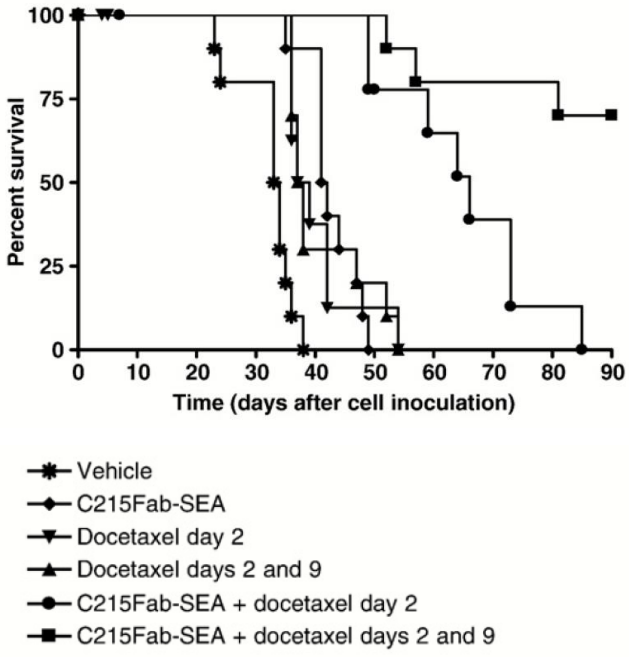


Figure 2. Mechanism of action of NAP

1.4 Pre-Clinical Antitumor Activity

In vitro and *in vivo* studies have shown synergistic anti-cancer effect of NAP or NAP 's surrogate murine molecule, C215Fab-SEA, in combination with checkpoint inhibitors (anti PD-(L)-1 and anti CTLA4) and cancer chemotherapeutic agents such as docetaxel (9)(10)(11)(12). Treatment of B16-C215 tumor bearing mice with the combination of C215Fab-SEA and docetaxel was found to be more effective in reducing the number of lung tumors as compared to mono therapies. Interestingly, it was shown that docetaxel at therapeutic doses did not interfere with superantigen induced T cell activation but rather appeared to enhance the response. Furthermore, C215Fab-SEA and docetaxel therapy synergistically prolonged long-term survival of the B16-C215 tumor bearing mice suggesting potential clinical benefit for the combined use (Fig. 3) (10).



Group	Median survival (days)	TTS	Doc2	Doc2,9	TTS+Doc2	TTS+Doc2,9
Vehicle	33	P<0.0001	P=0.001	P=0.0008	P<0.0001	P<0.0001
TTS	41.5		P=0.55	P=0.851	P<0.0001	P<0.0001
Doc2	38			P=0.982	P=0.0001	P<0.0001
Doc2,9	37.5					P<0.0001
TTS+Doc2	66					P=0.0035
TTS+Doc2,9	>90					

TTS = C215Fab-SEA, Doc = Docetaxel

Figure 3. Synergistic anti-tumor activity of tumor targeted super antigen in combination with docetaxel against the B16 murine melanoma

1.5 Clinical Studies

1.5.1 Phase 1 Monotherapy Trial

The safety and tolerability of NAP were assessed in a multicenter, multinational, open-label, phase 1, dose-escalation study (N=39), involving single-agent NAP administered as a bolus injection in subjects with non-small cell lung cancer (N=20), renal cell carcinoma (N=11) or pancreatic cancer (N=8) at doses ranging from 0.5-27.4 µg/kg/day x 5 consecutive days (13).

The pharmacokinetics of NAP showed a small volume of distribution (about 0.10 L/kg) and a low clearance (about 0.11 L/h/kg). The terminal half-life was determined to be about 1.1 h. Plasma concentrations seemed dose proportional. In most subjects, there was a low (0 - 100 pmol/mL) to intermediate (100 - 500 pmol/mL) increase in the levels of anti-SEA/E-120 antibodies prior to treatment cycle 2. There was a marked increase in the levels of blood cytokine levels 3 h after administration of NAP. Whereas the levels of IL-2 and IFN-γ were mainly increased during treatment cycle 1, the levels of IL-6 and IL-10 were also increased during treatment cycle 2. During treatment cycles 3 and 4, only effects on the levels of IFN-γ and IL-6 were detected. The TCR-Vβ profile from 15 subjects was determined at baseline and again on Day 12. A selective expansion of T cells expressing TCR-Vβ7.9 was observed on Day 12 compared to baseline.

The most frequent adverse reactions were nausea, vomiting, diarrhea, hypotension, chills, and fever. The frequency and severity of AEs increased with increasing doses of NAP, but the majority of AEs (92%) were grade 1 or grade 2 in severity. Transient liver enzyme elevations were also encountered. Dose-limiting toxicities (DLTs) occurred at doses above 20 µg/kg/day x 5 and included fever, hypotension, liver toxicity and acute vascular leak syndrome. These DLTs were reversible with no significant long-term consequences during the entire follow-up duration of 5-6 months.

Fourteen subjects (36%) had stable disease (SD) on day 56: seven NSCLC (25%) and seven RCC (64%) subjects. The recommended phase 2 dosage was set at 15 µg/kg/day for subjects with RCC and 22 µg/kg/day for subjects with NSCLC and pancreatic cancer.

1.5.2 Phase 1 Trial in Combination with Docetaxel in NSCLC

Increasing doses of NAP (10.3, 16.5, 22 µg/kg) and docetaxel were administered to 13 subjects with advanced NSCLC. NAP was administered on Days 1 – 4 and docetaxel on Day 5 of each treatment cycle. Two patients achieved a partial response, and 5 achieved stable disease. One of the partial responders had demonstrated previous resistance to docetaxel and remained in remission for 10+ years. That patient had received NAP at the highest dose of 22 µg/kg. The most frequently reported AEs were fever, hypotension, nausea, chills tachycardia, neutropenia and asthenia. The majority (87%) of these AEs were grade 1 or grade 2 in severity. One subject required a dose reduction in docetaxel from 75 mg/m^2 to 55 mg/m^2 due to neutropenia.

As with NAP monotherapy, there was a marked increase in the levels of blood cytokines 3 hours after administration. While IL-2 and IFNγ were primarily increased during Cycle 1, IL-6 and IL-10 levels also increased during Cycle 2. Repeat tumor biopsies on treatment were obtained from 2 subjects treated at the higher dose of NAP and demonstrated enhanced tumor-associated T-cell infiltration during NAP treatment; 1 of these subjects was the subject with the markedly prolonged

survival described above. Also, as with NAP monotherapy, the majority of subjects developed low to intermediate levels of anti-SEA/E-120 antibodies (13).

1.5.3 Phase 2/3

A randomized (1:1) phase 2/3 trial involving treatment of 513 subjects with renal cell carcinoma with NAP (15 µg/kg/day x 4 consecutive days on weeks 1, 9 and 17) and interferon alpha or interferon alpha alone did not meet its primary endpoint and failed to show a survival benefit for the tested combination (21). In a post-hoc exploratory subgroup analysis, subjects with less than the median concentrations of anti-NAP antibodies and IL-6, significantly benefitted from addition of NAP. In this subgroup, the median overall survival (OS)/progression-free survival (PFS) was 63.3/13.7 months versus 31.1/5.8 months for the subjects receiving IFN alone (p=0.02, hazard ratio 0.59/p=0.02, hazard ratio 0.62). Most of the adverse events resulting from treatment with NAP, related to increased levels of cytokines. Pyrexia (61%), vomiting (37%), nausea (35%), chills (27%), and back pain (19.5%) were the more common adverse events reported in the NAP treatment arm. Grade 3 hypotension occurred in 2% of subjects. The adverse events were transient, often mild and no Grade 4 or 5 toxicities were observed.

Antibodies binding to NAP (anti-SEA/E-120) may interfere with drug exposure and efficacy. At baseline, only low levels of anti-SEA/E-120 antibodies were detected. After the first treatment cycle, anti-SEA/E-120 concentrations were increased in the great majority of subjects, they increased by more than a 300-fold, in contrast to the phase 1 trials where only low to intermediate increases were detected for up to 4 treatment cycles. It was suggested that the combination of NAP with interferon alpha might actually have adversely affected the potential therapeutic effect of NAP. IFN-α is known to accelerate the formation of antidrug antibodies (ADA) (22), which might account for the high ADAs titers seen in the study, resulting in significant reduction in the NAP blood levels in cycles 2 and 3.

1.6 Dose Selection Rationale and Risk

In the previously conducted phase 1 trials, no DLTs were observed at doses up to 20 µg/kg in the initial phase 1 trials. The most frequent adverse reactions consisted of nausea, vomiting, diarrhea, hypotension, chills, fever and back pain. Transient liver enzyme elevations were also encountered. Dose-limiting toxicities (DLTs) occurred at doses above 20 µg/kg/day x 5 and included fever, hypotension, liver toxicity and acute vascular leak syndrome. These DLTs were reversible with no significant long-term consequences.

Antibodies binding to NAP (anti-SEA/E-120) may interfere with the exposure and activity of NAP. Low levels of anti-drug antibodies (ADAs) may be present at baseline but these levels are expected to increase after initial exposure to NAP, as has been seen in previous clinical trials, potentially resulting in significant reduction in NAP blood levels in subsequent treatment cycles. Obinutuzumab, a new-generation, glycoengineered, humanized type 2 anti-CD20 monoclonal antibody currently approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma, depletes B cells and can eliminate the formation of ADAs, presumably without adversely impacting on T cell activation nor on dosing, activity or safety of NAP. Hence, when

given as a pretreatment, obinutuzumab, is expected to prevent the occurrence of ADAs and may result in more prolonged exposure to NAP, therefore potentially enhancing its antitumor activity. In this trial, obinutuzumab will be given once, over 2 days, prior to the first cycle of treatment with the combination of NAP and docetaxel. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cells level.

In an ongoing dose escalation and cohort expansion phase 1 trial of a 3-weekly regimen, NAP is given daily for 4 consecutive days in combination with durvalumab given on day 2 (NCT03983954). NAP was tested at 5 dose levels of 2, 5, 10,15 and 20 µg/kg/day (N=19). Two of six patients treated at the highest dose level experienced a DLT on day 1, an excessive infusion reaction in the first patient and creatinine elevation in a second patient who already had an abnormal creatinine level at baseline. The MTD was established at 15 µg/kg/day. The trial then incorporated obinutuzumab pre-treatment at two dose levels of NAP, 10 µg/kg/day and 15 µg/kg/day, with unremarkable safety findings (N=7). Among these initial 26 patients, 4 achieved a RECIST response: 1 CR for 24+ months in pancreatic cancer, 1 CR in a patient with cervical cancer, 1 PR for 17+ months in hepatocarcinoma resistant to prior nivolumab and 1 PR for 13 months in PD-L1 low peritoneal mesothelioma. The trial went on with expansion cohorts treated with NAP 10-15 µg/kg/day in combination with durvalumab and obinutuzumab pretreatment. At the higher dose level of NAP, 3 out of 13 subjects experienced grade 3 infusion reactions related to NAP (fever, chills, dyspnea and hypotension), which led to treatment discontinuation. In the total of 11 patients who received NAP 10 µg/kg/day in combination with durvalumab and obinutuzumab pretreatment, two subjects experienced grade 3 IRRs (chills in one patient and worsening of grade 2 dyspnea that predated NAP treatment in the other). No patients had treatment discontinuation for safety at that dose level of NAP. All those toxicities were manageable with appropriate medical treatment, rapidly reversible and without long-term sequelae. Based on this experience, the dose of 10 µg/kg/day for NAP has been selected as the recommended dose for the current trial. Dose increase to 15 µg/kg in advanced cycles is not expected to increase NAP toxicity profile, as NAP related toxicities predominantly occur on cycles 1-2, and this dose increase may overcome ADA formation with time.

Additional information regarding NAP can be found in the current investigator's brochure.

1.7 Obinutuzumab

Obinutuzumab is a humanized anti-CD20 monoclonal antibody that recognizes a specific epitope of CD20 on B cells. Upon binding to CD20, obinutuzumab mediates B-cell lysis through 1) engagement of immune effector cells, 2) by directly activating intracellular death signaling pathways (direct cell death), and/or 3) activation of the complement cascade. It is currently indicated for the treatment of chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) and is marketed in the U.S. as GAZYVA® (Genentech) (14)(15). The drug induces direct cell death and antibody-dependent, cell-mediated cytotoxicity (ADCC)/antibody-dependent cell-mediated phagocytosis (ADCP), with less complement-dependent cytotoxicity as compared to rituximab overall providing for faster and superior direct B cell death as compared to rituximab. In the pivotal

clinical study BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with repeated 4-week cycles of obinutuzumab, were B-cell depleted (CD19+ B-cell counts < 0.07 x 109/L) at the end of treatment period and remained depleted during the first 6 months of follow up. Recovery of B-cells was observed within 12-18 months of follow up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease (15). In vitro studies have shown that T cells are activated and expand in similar frequencies when cultured with B cells, monocytes or both (16). In fact, CD14+ monocytes demonstrated a higher capacity to mediate the activation and expansion of TRBV7-9+ T cells as compared to B cells. These observations suggest that CD14+ monocytes alone can efficiently mediate NAP activation and expansion of TRBV7-9+ T cells in human blood. Given these observations, ADA prevention with obinutuzumab is expected to deplete B cells, without impacting the NAP mode of action. Hence, when given as a pretreatment, obinutuzumab, is expected to prevent the occurrence of ADAs and may result in more prolonged exposure to NAP, therefore potentially enhancing its antitumor activity. In this trial, obinutuzumab will be given once, over 2 days, prior to the first cycle of treatment with the combination of NAP and docetaxel. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cells level.

1.8 Study Rationale

Given the ongoing need for novel therapies in the treatment of NSCLC, the previously observed preliminary activity of the combination of NAP /docetaxel in NSCLC and the presumptive ability of obinutuzumab to suppress the development of ADAs, this study will test the combination of NAP /docetaxel following pretreatment with obinutuzumab in a population of subjects with NSCLC who have failed checkpoint inhibitor therapy, in an effort to demonstrate an improvement in ORR as well as other measures of anti-tumor efficacy.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

To assess the ORR and response duration of NAP and docetaxel, following obinutuzumab pretreatment, in subjects with NSCLC previously treated with a checkpoint inhibitor.

2.1.2 Secondary Objectives

- To describe the safety profile of the combination of NAP / docetaxel, following obinutuzumab pretreatment in subjects with R/R NSCLC
- To evaluate the overall survival (OS) defined as the time from day 1 of treatment until death due to any cause
- To assess the possible impact of prior taxane exposure on the antitumor activity of the NAP/docetaxel combination
- To describe the effect of obinutuzumab pretreatment on the development of anti-drug antibodies and human anti-mouse antibodies to NAP
- To describe blood levels over time of NAP when administered after B-cell suppression

2.1.3 Exploratory Objectives

- To evaluate and characterize the pharmacodynamic effect of NAP /docetaxel on biomarkers in the circulation in subjects pretreated with obinutuzumab
- Clinical activity in relationship to biomarkers including 5T4, NGS results, TMB expression and PD-L1 level in the tumor.

2.2 Study Endpoints

2.2.1 Primary Endpoints

- Objective response rate (ORR), per iRECIST, of the combination of NAP /docetaxel following obinutuzumab pre-treatment in subjects with NSCLC previously treated with a checkpoint inhibitor

2.2.2 Secondary Endpoints

- Disease control rate (DCR) and duration of response (DOR) of the combination of NAP /docetaxel following obinutuzumab pre-treatment in subjects with NSCLC previously treated with a checkpoint inhibitor
- Progression-free survival (PFS) as well as the 6-month and the 12-month PFS rates of NAP /docetaxel following obinutuzumab pre-treatment in subjects with NSCLC previously treated with a checkpoint inhibitor
- Overall survival (OS) of NAP /docetaxel following obinutuzumab pre-treatment in subjects with NSCLC previously treated with a checkpoint inhibitor
- Incidence and characteristics of adverse events associated with NAP /docetaxel pretreated with obinutuzumab. Safety will be measured by infusion reactions (e.g. fever, chills, hypotension, tachycardia etc.), changes from baseline vital signs, physical findings, electrocardiograms (ECG), blood and urine safety and thyroid function laboratory tests, graded as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
- The pharmacokinetic profile of NAP
- The development of anti-drug antibody levels and human anti-murine antibody (HAMA)

2.2.3 Exploratory Endpoints

- Cytokine production over time (e.g., IL-2, IFNγ, IL-6, TNFα) and B-cell levels in subjects pre-treated with obinutuzumab.
- Clinical activity in relationship to biomarkers including 5T4, NGS results, TMB expression and PD-L1 level in the tumor.

3 STUDY DESIGN

This is an open-label, multicenter Phase 2a clinical trial of the combination of NAP/docetaxel following pretreatment with obinutuzumab in subjects with NSCLC who have progressive neoplastic disease despite having been treated with at most 2 prior systemic therapies, including a checkpoint inhibitor; approximately 35 subjects will be entered.

Subjects will receive obinutuzumab, 1,000 mg, administered by IV infusion on Days -13 and -12 of the first treatment cycle in order to reduce the titer of anti-drug antibodies to NAP. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cell level. If an increase back to the normal level of B cell level is observed, additional biomarkers and PK level will be tested in the following visit. NAP will be administered in a daily dose of 10 μg/kg by IV bolus on Days 1 - 4 of treatment cycles 1-6, followed by docetaxel, 75 mg/m^2 on Day 5.

Treatment cycles will be 21 days in duration and growth factors may be used at the discretion of the investigator. The combination of NAP/docetaxel will be given for a maximum of 8 cycles (unless, in the opinion of the investigator, the patient may derive benefit from continuing docetaxel). Starting Cycle 7, NAP at a higher dose of 15 μg/kg will be administered on Day 1 and docetaxel on Day 2, in 21 days treatment cycles. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. In patients whose NAP dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7. Dose increase to 15 μg/kg in advanced cycles is not expected to increase NAP toxicity profile, as NAP related toxicities predominantly occur on cycles 1-2, and this dose increase may overcome ADA formation with time. NAP as a single agent will be continued until disease progression, untoward toxicity or non-compliance for a maximum of up to 24 months from day 1 of therapy.

Subjects will be screened to assess eligibility within 14 days prior to entry. Subjects must have received at least 1 and no more than 2 prior systemic regimens for the treatment of advanced/metastatic NSCLC. Patients are required to have progressed following treatment with both platinum-based chemotherapy and an anti-PD-(L)1 antibody administered either sequentially or concurrently. A prior PD-1/PD-L1 inhibitor is, however, not required if there was prior exposure to targeted therapies for driver mutation positive tumors (e.g. EGFR or ALK inhibitors). Entry into this trial is restricted to patients with incurable disease, including those who relapse within 6 months from chemoradiotherapy for Stage III disease. Subjects will have available archival or fresh tissue collected for the retrospective determination of tumoral 5T4 levels.

Subjects will be assessed for the primary efficacy endpoint of objective response rate (ORR). ORR will be assessed according to the iRECIST criteria. In addition, disease control rate, combining the ORR with subjects demonstrating stable disease (SD), progression-free survival (PFS), PFS rate at 6 and 12 months and overall survival (OS) will also be determined. If available, NGS results, TMB expression and PD-L1 levels will be collected for the expression of exploratory tumor biomarkers.

Ongoing study imaging will be performed at the end of cycle 2 (45 days ± 7 days) and every 6 weeks for the first 24 weeks and then every 9 weeks (± 7 days) thereafter. Confirmatory scans for responses (PR or CR) will be performed after 6 weeks (± 7 days) during the first 24 weeks and

every 9 weeks thereafter. As NAP is known to induce an inflammatory reaction in the tumor, pseudo-progression may be observed and therefore, in patients who demonstrate objective progression but who are clinically stable, 1-2 additional treatment cycle(s) of NAP/docetaxel may be administered beyond progression at the discretion of the Investigator, followed by a confirmatory imaging after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks (± 7 days) thereafter. This schedule should be maintained even if cycles are delayed.

The safety of the combination of NAP /docetaxel following pretreatment with obinutuzumab in a B-cell suppressed setting will be assessed in all treated subjects based on the reporting of adverse events, the results of ECGs, results of laboratory determinations, findings on physical exams, vital signs and reporting of the ECOG Performance Score. All treatment emergent AEs (TEAEs), drug-related AEs, SAEs and drug-related SAEs as well as hematology and chemistry lab results will be summarized using the worst grade per subject according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

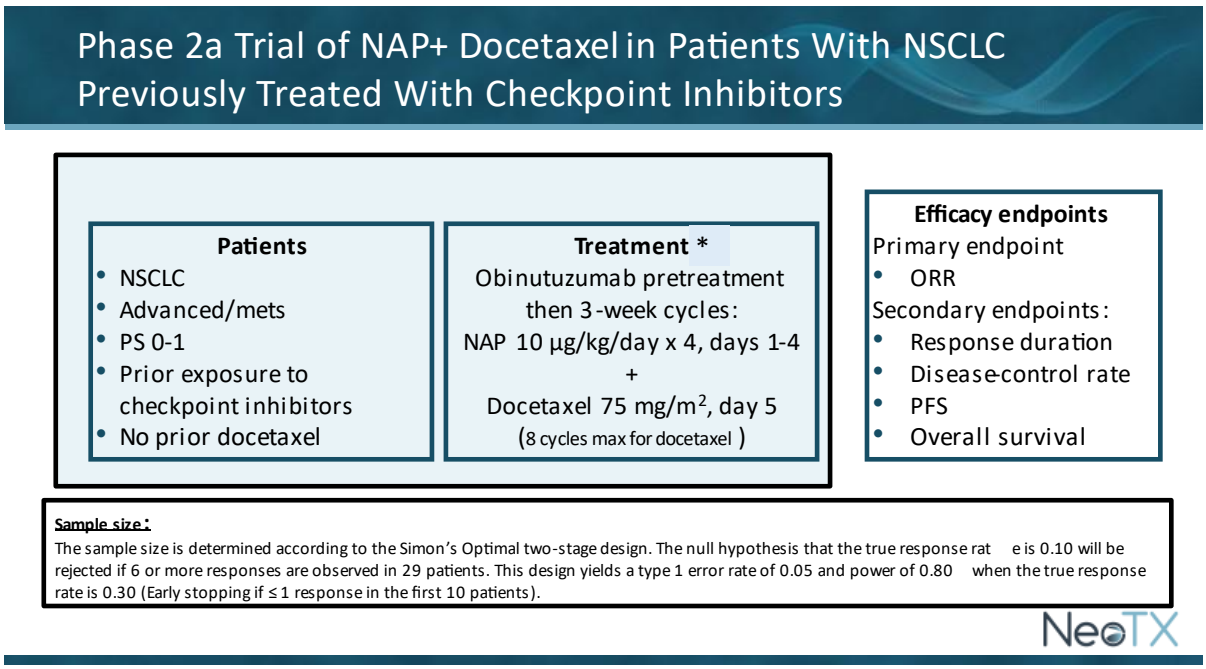
The pharmacokinetics of NAP will be based on plasma drug levels obtained at various timepoints after administration.

The pharmacodynamics of the combination of NAP/docetaxel following pretreatment with obinutuzumab will be determined by measuring levels of cytokines (e.g., IL-2, IFNγ, IL-6 and TNFα) in serum.

The immunogenicity of NAP will be assessed based on levels of anti-drug antibodies, human anti-murine antibodies (HAMA) collected at various times after administration of NAP. Neutralizing antibodies (Nab) will be also collected for future analysis.

The primary efficacy endpoint of this trial is the ORR. With 29 evaluable entries, 6 subjects or more with a complete or partial response would make this regimen worthy of further investigation. Subjects who discontinue from treatment for any reason will continue to be followed for survival (even if the subject receives subsequent anti-neoplastic therapy). Subjects will be followed for survival until 6 months after the last subject has completed study treatment. Subjects who discontinue from treatment for reasons other than progression will continue to be followed for progression by CT/MRI scans every 6 weeks (± 7 days) for the first 24 weeks, every 9 weeks (± 7 days) thereafter; if such a subject receives subsequent anti-neoplastic therapy, further follow-up for progression will stop.

A graphical description of the trial is depicted below:



* Starting Cycle 7, NAP at a higher dose of 15 µg/kg/day will be administered on Day 1 and docetaxel on Day 2, in 21 days treatment cycles. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. In patients whose NAP dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7.

4 STUDY POPULATION

A total of approximately 35 subjects will be enrolled from approximately 10 study sites in the U.S.

4.1 Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for enrollment into the study:

1. Subjects must be at least 18 years of age
2. Subjects must have histologically and/or cytologically confirmed NSCLC
3. Subjects must have incurable (advanced or metastatic) disease at the time of enrolment (Patients who relapse within 6 months from chemoradiotherapy for stage III disease are considered incurable)
4. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
5. Subjects must provide signed informed consent prior to any study specific procedures that are not part of standard medical care.
6. Subjects must have measurable neoplastic disease based on the iRECIST criteria
7. Subjects must have received at least 1 and no more than 2 prior systemic regimens for the treatment of advanced/metastatic NSCLC. Patients are required to have progressed following treatment with both platinum-based chemotherapy and an anti-PD-(L)1 antibody administered either sequentially or concurrently. A prior PD-1/PD-L1 inhibitor is, however, not required if there was prior exposure to targeted therapies for driver mutation positive tumors (e.g. EGFR or ALK inhibitors).
8. Subjects must have adequate hematologic and organ function:
   - WBC ≥3000/µL
   - Absolute neutrophil count ≥1500/µL
   - Platelets ≥100,000/µL
   - Hemoglobin ≥9.0 g/dL
   - Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance (CL) >40 mL/min, as determined by Cockcroft-Gault (using actual body weight)
   - AST ≤ 1.5 X ULN; ALT ≤ 1.5 X ULN; Alk phos ≤ 2.5 X ULN; bilirubin must be within normal limits
   - International Normalized Ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy and the INR, PT or PTT is within therapeutic range of intended use of anticoagulants

9. Subjects must be willing and able to comply with scheduled visits, procedures, drug administration plan, etc. as outlined in the protocol
10. Subjects should have an estimated life expectancy of at least 12 weeks
11. Archival or fresh tumor tissue from a biopsy of a tumor lesion not previously irradiated must be provided for 5T4 retrospective analysis, unless discussed with the Medical Monitor.

4.2 Exclusion Criteria

Subjects with ANY of the following characteristics/conditions will not be included in the study:

1. Subjects with active infection requiring treatment within 3 days of C1D1.
2. Subjects with other active neoplastic disease requiring concurrent anti-neoplastic treatment
3. Subjects with known, suspected or documented parenchymal brain metastases unless treated with surgery and/or radiation, with the subject neurologically stable and off pharmacologic doses of systemic glucocorticoids; subjects with leptomeningeal metastases are not eligible. Patients should have completed brain radiation for at least 14 days and be off steroids per exclusion criteria 7.
4. Active or previously documented autoimmune or inflammatory disorders such as, but not limited to rheumatoid arthritis, systemic lupus erythematosus, uveitis, ulcerative colitis, Crohn's syndrome, Wegener's syndrome, multiple sclerosis, myasthenia gravis, scleroderma and sarcoidosis. The following are exceptions to this criterion:
   - Vitiligo or psoriasis not requiring systemic treatment (within the last 2 years)
   - Subjects with endocrinopathies (e.g. following Hashimoto syndrome) stable on hormone replacement or do not require any therapy.
5. History of primary immunodeficiency
6. Subjects with a history or prior allogeneic organ transplant
7. The use of immunosuppressive agents within 28 days of enrollment (D-13; obinutuzumab pre-treatment) including, but not limited to, cyclosporine, mycophenolate, azathioprine, methotrexate, adalimumab, infliximab, vedolizumab, tofacitinib, dupilumab, rituximab, etc. Pharmacologic doses of glucocorticoids defined as glucocorticoid equivalents of >10 mg/day of prednisone (with the exception of systemic steroids given as a premedication before each of the study medications, or used prior to administration of radiographic contrast material in subjects with allergies) are not acceptable within 14 days prior to enrollment. Subjects are permitted to receive topical, intranasal, inhalational and intra-ocular glucocorticoids.
8. Subjects who have uncontrolled inter-current illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension,

unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations and substance abuse that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to follow the dictates of the protocol.

9. Subjects who have received a live attenuated vaccine within 28 days prior to the first dose of obinutuzumab.
10. Subjects with hepatitis B (positive HBV surface antigen [HBsAg]), hepatitis C (hepatitis C antibody) or HIV (HIV antibody). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible; subjects positive for hepatitis C (HCV) antibody who have completed a course of antiviral therapy are eligible if polymerase chain reaction (PCR) is negative for HCV RNA.
11. Female subjects who are pregnant or breastfeeding.
12. Male or female subjects of reproductive potential who are not willing to employ effective birth control from Screening to 90 days after the last dose of study treatment. Highly effective methods of contraception are defined as one that results in a low failure rate (e.g., less than 1% per year) when used consistently and correctly.
13. Prior treatment with chemotherapy or other systemic antineoplastic therapy within 21 days; experimental therapy 21 days or 5 half-lives, whichever is shorter. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria. All prior treatments should be completed 21 days prior to enrollment (D-13; obinutuzumab pre-treatment).
14. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
15. Subjects who have undergone major surgery or trauma within 4 weeks of study entry (D-13; obinutuzumab pre-treatment).
16. Subjects with Grade 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Medical Monitor. Subjects with neuropathy grade >2 are not eligible.
17. Subjects who have been treated with one of the study drugs (NAP and/or docetaxel).
18. Subjects with NYHA Class III or IV CHF, myocardial infarction or acute coronary syndrome within 6 months prior to study enrollment, ongoing angina pectoris, severe peripheral vascular disease, CVA within 6 months of study enrollment or any other concomitant medical disorder that might interfere with the subject's participation in the trial or interpretation of the study data.

19. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms in women and ≥450 ms in men, calculated from 3 ECGs (within 15 minutes at 5 minutes apart).
20. Subjects on strong inducers or inhibitors of CYP3A4.
21. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients (including kanamycin).
22. Subjects with a history of progressive multifocal leukoencephalopathy (PML).

4.3 Enrollment

Subjects will be centrally enrolled; enrollment among the investigational sites will be competitive and there is no limitation on enrollment from a particular site.

Following completion of the Screening phase of the study, each site will submit a signed *'Eligibility Request Form'* to The Sponsor or its designee. The form will be reviewed and a decision on enrollment made within 24 hours.

4.4 Subject Identification

Each subject who has signed the informed consent will be identified by a unique study ID number (combination of a 5-digit unique site identity number and 3-digit subject number). Numbers will be allocated to subjects in a sequential order in each site.

4.5 Screen Failures

Subjects who fail to meet the entry criteria during the Screening period are defined as screen failures. A patient who failed screening may be re-screened. All screen failures will be recorded in the screening logs along with the reason for screen failure. The screening log will be kept in the Investigators Site File.

4.6 Subject Discontinuation or Early Withdrawal and Replacement

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study that requests to be withdrawn, or if it is determined that continuing in the study would result in an undue risk to the subject.

Subjects with major protocol enrollment violations, where the risk of remaining in the study outweighs any benefit, and those who do not receive a minimum of 1 treatment cycle for reasons other than toxicity or progressive neoplastic disease will be replaced, after being approved by The Sponsor.

4.6.1 Reasons for Treatment Discontinuation

Reasons for discontinuation from study treatment include the following:

- Progressive neoplastic disease (objective or clinical progression)
- An adverse event or intercurrent medical condition that precludes further administration of protocol therapy or continuation with the requirements of the trial
- A subject withdraws consent for continued treatment
- A female subject becomes pregnant
- A subject is unwilling or unable to continue the study or is lost-to-follow-up

- A subject is non-compliant to the point where the risk of continued participation in the trial outweighs potential benefits
- The Investigator decides that withdrawal from the study is in the best interest of the subject
- A subject requires a prohibited medication or treatment

Subjects who discontinue the trial for reasons other than progressive neoplastic disease should continue to be followed until progression by CT/MRI scans every 6 weeks (± 7 days) for the first 24 weeks, every 9 weeks (± 7 days) ***thereafter, or until the initiation of new anti-cancer treatment.***

4.6.2 Reasons for Study Discontinuation

Reasons for discontinuation from the trial may include the following:

- The development of progressive neoplastic disease
- The death of a subject
- A subject is lost to follow-up
- A subject withdraws consent for continued participation in the trial
- A request by a regulatory authority to discontinue the study
- Issues with the manufacturing or supply of protocol therapy that precludes continuation of the trial
- Conditions no longer make it reasonable for the Sponsor to continue the study

5 STUDY DRUGS

5.1 Docetaxel

Docetaxel will be administered IV over 1 hour on Day 5 of cycles 1-6 and starting cycle 7 on Day 2 of a 21- day treatment cycle in a dose of 75 mg/m^2 for a maximum of 8 cycles (unless, in the opinion of the investigator, the patient may derive benefit from continuing docetaxel).

Subjects should be pre-medicated according to institutional standards. Docetaxel should be stored according to directions in the Full Prescribing Information. For complete information regarding administration of docetaxel, refer to the appropriate Full Prescribing Information, SmPC or local product monograph.

5.1.1 Premedication for Docetaxel

Subjects should receive pre-medications prior to docetaxel administration as per the standard of care at each clinical site. If corticosteroids are administered in multiple days regimen, starting 1 day prior to docetaxel (on Day 4 of each cycle 1-6, and starting cycle 7 on Day 1) it should be administered at least 1 hour after NAP administration.

5.1.2 Docetaxel Dose Adjustments

Dose of docetaxel may remain the same throughout the study unless the patient's weight changes ≥10% from baseline.

If docetaxel cannot be administered on schedule because of NAP-induced adverse reactions, docetaxel is to be delayed by a maximum of one week and skipped in the absence of adequate recovery; the next NAP cycle is then delayed by a maximum of one week as well, as described in sections 5.2.6 and 5.2.7.

If NAP is discontinued, docetaxel may continue as monotherapy, as described in section 5.1. If on the day of scheduled treatment with docetaxel, the ANC is <1,500/μL and/or the platelet count is <100,000/μL, hold docetaxel and repeat the ANC and platelet counts weekly. Once toxicity due to myelosuppression has resolved re-treatment with docetaxel will be at a reduced dose as described below. If a second dose delay is required due to myelosuppression despite the dose reduction, discontinue docetaxel. Patients who develop ≥grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely. If NAP and docetaxel are to be delayed due to toxicity of docetaxel, the whole cycle of NAP and docetaxel may be delayed up to 6 weeks. Patients, for whom any treatment cycle is delayed, for any reason, beyond the indicated window, will be discussed with the medical monitor to determine whether they should be continued. The schedule of the imaging should be maintained, though, even if cycles are delayed.If docetaxel is discontinued due to toxicity, Day 5 (Cycles 1-6) or Day 2 (cycle 7 onwards) assessments should not be performed.

Docetaxel Dose Reduction

The dose of docetaxel must be reduced to 55 mg/m^2 in the event the subject experiences any of the following during a treatment cycle:

- Febrile neutropenia

- ANC <500/μL for > 1 week
- Platelet count <25,000/μL for > 1 week
- Grade 3 or higher, or cumulative cutaneous toxicities
- Any other Grade 3 or higher toxicity (except nausea, vomiting or diarrhea brought under control with appropriate medical therapy within 72 hours)
- The need for a dose delay as described above

5.2 Naptumomab Estafenatox (NAP; ABR-217620)

Naptumomab estafenatox (NAP; ABR-217620) is a recombinant fusion protein consisting of a chimeric staphylococcal enterotoxin A/E (SEA/SEE) superantigen with several additional substitutions that is linked to a Fab moiety recognizing a tumor-associated glycoprotein, 5T4.

5.2.1 Naptumomab Estafenatox (NAP) Packaging and Labeling

Naptumomab estafenatox (NAP) is provided in two separate packaging: One lyophilized drug product stored at 2-8 ºC and one dilution kit stored at RT. A dilution kit containing water for injection (WFI), Dilution Solution, empty sterile glass vial, syringes and complete instructions for the reconstitution and dilution is also supplied. NAP is provided as a lyophilized powder for injection. The container-closure system consists of 10 cc colorless glass, type I vials and bromobutyl stoppers. The vials are sealed with aluminum caps. Each vial contains 1.25 mg NAP and is intended to be reconstituted and diluted prior to use in two steps: Reconstitution with 1.2ml of the supplied water for injection (WFI) followed by further dilution with diluent (Dilution Solution). The Dilution Solution is a sterile, pyrogen-free, clear and colorless solution supplied in 10 cc glass bottles containing 10 mL of the diluent.

For any additional Study Drug related information, refer to the Pharmacy Manual.

The product may contain residual trace kanamycin from the manufacturing process, which could lead to allergic reactions in highly susceptible individuals.

5.2.2 Naptumomab Estafenatox (NAP) Preparation and Administration

A dilution kit is supplied for dilution of NAP. All handling of NAP should be performed using an aseptic technique. Sterile gloves should be used. For safety precautions, see Safety Data Sheet for NAP (provided separately).

NAP will be administered in a dose of 10 μg/kg/day on Days 1 – 4 of cycles 1-6. Starting Cycle 7, NAP will be administered on Day 1 only in a dose of 15 μg/kg (unless the dose was previously reduced due to toxicity). The reconstituted NAP will be diluted with the supplied diluent to reach the required dose for administration. Fully diluted NAP (5 mL) will be administered as an IV slow bolus injection (i.e., administered directly, not via a running IV line). On cycle 1, it could either be administered viacentral line (e.g. Port-a-Cath), slowly injected in approximately 3 minutes

followed by 10 mL slow (~2 min) saline flush or via a peripheral line (e.g. venflon), by a slow injection of approximately 5 minutes, followed by a flush per the site's standard practice.

If the subject did not experience any significant infusion related reactions on a full cycle (days 1-4), further NAP injections in the following cycles may be pushed in less than 5 min in total.

Any IV fluids given simultaneously with NAP are prohibited.

Administration of NAP should be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant), as allowed by local and institutional guidance.

During cycle 1 (days 1-4) and cycle 2 Day 1 (C2D1), all subjects should be observed for 3 hours post injection of NAP at the site. If no G3 or higher infusion related reactions occurred, time of observation can be shortened to 1 hour on further treatment days. Subjects who experience any TEAEs during the observation period and/or any other medical condition requiring further monitoring at the discretion of the investigator, should be further observed as clinically appropriate. Subjects should be advised that in any case of severe and/or persistent fever, chills, or shortness of breath beyond 5-7 hours post NAP administration, they should seek a medical attention.

5.2.3 Naptumomab Estafenatox (NAP) Dilution

Calculation for dilution will be performed by the relevant scheme in the instructions for dilution "Flow chart of Dilution Procedure" (found in the pharmacy manual), which must be accurately filled in and signed. All dilutions should be performed by strictly following the Instructions supplied with the dilution kit.

The calculation of the dose per subject weight should be done based on subject weight on the day of treatment. In sites restricted by pharmacy's procedures the dose can be calculated based on subject weight obtained within 14 days prior to that date. For the purpose of calculating study treatment dose, the subject's weight should NOT be rounded off to the closest kg value but rather recorded with 1 digit after the decimal point, for example, 70.5 kg, 60.4, 77.0 kg etc. However, after multiplying the weight by the relevant dose level (µg/kg), the final dose (in µg) should be rounded off, for example, 120.5 µg will be rounded to 121 µg and 150.4 µg will be rounded to 150 µg.

5.2.4 Stability of Reconstituted and Diluted Naptumomab Estafenatox (NAP)

For stability information on reconstituted and diluted NAP please refer to the IFU (Information For Use) and the Pharmacy Manual.

5.2.5 Premedication for Naptumomab Estafenatox (NAP)

The premedication should be initiated as prophylaxis prior to each NAP administration.

- Hydration:

  On Cycle 1:

- Day 1: 1L saline, IV, beginning 1-3 h before NAP dose.
- Day 2: 0.5 L saline, IV, beginning 1-3 h prior to NAP dose.
- Days 3-4: no hydration is needed unless the patient experienced G≥2 hypotension or G≥3 infusion related reactions on previous days, and then continue as on Day 2.

On Cycle 2:

- Day 1: 0.5 L saline, IV, beginning 1-3 h before NAP dose.
- Days 2-4: no hydration is needed unless the patient experienced G≥2 hypotension or G≥3 infusion related reactions on previous days, and then continue as on Day 1.

No hydration is needed on further cycles.

The saline hydration should be completed as close as possible to start of NAP administration.

Excess of IV fluids should be avoided in elderly patients who are prone to develop fluid overload (e.g., congestive heart failure, renal failure etc.). In such cases it is recommended to consult the medical monitor.

- 500-650 mg acetaminophen, oral, qid (x 4/day), unless specific contraindications exist (allergy or elevated hepatic transaminases), to be administered 30-60 minutes prior to NAP, as prophylaxis prior to each NAP injection, , and every 6 hours thereafter up to 24 h after last NAP dose of each cycle of NAP treatment. In case of fever > 38.5ºC the acetaminophen dose can be elevated to 1g to treat the AE.
- Systemic antihistamine, such as but not limited to promethazine IV, 30 to 60 minutes prior to NAP dosing,
- Anti-emetic agent such as ondansetron 8 mg or metoclopramide 10 mg, 30 to 60 minutes prior to NAP dosing.

5.2.6 Dose Modifications for Naptumomab Estafenatox (NAP)

The following dose modifications of NAP are required in case of the occurrence of any Grade ≥3 immune or non-immune AEs that are related to NAP. The dose of NAP will be reduced according to the table below; in general, NAP may be reduced by one dose level for G3 AEs, and by two dose levels for G4, life-threatening AEs (with the exception of hematologic toxicity and laboratory findings). A second dose reduction is permitted for G3 AEs at one level reduced dose, with 5 µg/kg/day being the lower dose allowed on this study. NAP treatment will be permanently discontinued if same grade 3 or higher adverse event recurs at 5 µg/kg/day reduced dose, (with the exception of hematologic toxicity and laboratory findings).

If, for any reason, the dose was reduced at once for a G3 toxicity, from 10 µg/kg/d to 5 µg/kg/day, and is tolerated well with no recurrences or further NAP related AEs at the reduced dose, then at the PI discretion, the dose may be increased by one dose level, to 7.5 µg/kg/day, in the following cycle.

Please note, NAP is administered in a dose of 10 µg/kg/day on Days 1 – 4 of cycles 1-6. Starting Cycle 7, NAP at a higher dose of 15 µg/kg is administered on Day 1. In patients whose NAP

dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7.

NAP may be administered in one of the following doses:

Dose Level	Dose of NAP
2*	15 µg/kg/day
1	10 µg/kg/day
-1	7.5 µg/kg/day
-2	5 µg/kg/day

* NAP at a higher dose of 15 µg/kg will be given starting cycle 7 only in patients whose NAP dose was not reduced due to toxicities during cycles 1-6. Otherwise, dose remain the same as in the previous cycle.

Adverse Event	Dose Modification	
	Within a Treatment Cycle	Between Cycles
General disorders and Infusion Related Reactions: (e.g. Fever, Chills, Tachycardia, Fatigue, Peripheral Edema, Hypotension) See also CRS treatment guidelines, Section 7.2.3	Events that do not resolve within 6 hours to grade 1 or baseline despite appropriate medical management, hold retreatment until resolution of the toxicity to grade 1 or baseline (see 5.2.7). The next NAP doses may be reduced by one dose level for G3 events and by two dose levels for G4 events, per investigator/Medical Monitor decision.	Events that do not resolve to at least grade 2 within 7 days, treat the next cycle (and all subsequent cycles) at one dose level below for G3 events and two levels below for G4 events.
Gastrointestinal disorders: (e.g. Nausea, Vomiting, Diarrhea)	Events that do not resolve within 6 hours to grade 1 or baseline despite appropriate medical management, hold retreatment until resolution of the toxicity to grade 1 or baseline (see 5.2.7). The next NAP doses may be reduced by one dose level for G3 events and by two dose levels for G4 events,	Events that do not resolve to at least grade 2 within 7 days, treat the next cycle (and all subsequent cycles) at one dose level below for G3 events and two levels below for G4 events.

	per investigator/Medical Monitor decision.	
Hematologic toxicity: Febrile neutropenia, Thrombocytopenia, Anemia	Skip remaining dose(s) of the cycle, for G3 or G4 events.	Events that do not resolve to at least grade 2 within 7 days, treat the next cycle at one dose level below.
Laboratory findings: (e.g. liver enzymes elevation)	Skip remaining dose(s) of the cycle, for G3 or G4 events.	Events that do not resolve to grade 2 within 7 days, treat the next cycle (and all subsequent cycles) at one dose level below.

5.2.7 Dose Delays for Naptumomab Estafenatox (NAP)/Docetaxel Combination

Dose Delay Prior to Cycle 1

In case of any obinutuzumab related toxicities of grade ≥2 that exist on the first scheduled day of NAP administration (C1D1), Cycle 1 of NAP- docetaxel treatment may be delayed up to 7 days. In the absence of resolution after this period, the patient will be discontinued from the study.

Dose Delays During a Treatment Cycle

Every effort should be made to administer NAP on Days 1 – 4 of treatment cycles 1-6 and on Day 1 of each subsequent cycle. Subjects who exhibit Grade 3 or higher toxicity during a treatment cycle will have treatment held until resolution of the toxicity to Grade 1 or baseline. The next NAP doses may be reduced by one dose level for G3 events and by two dose levels for G4 events, per investigator/Medical Monitor decision. If a treatment needs to be delayed or is missed during days 1-4, that treatment day will be skipped, and treatment will resume the following day. Missed treatments will not be made up. Subjects who do not receive at least two NAP doses within a given cycle at two consecutive cycles, due to AEs, will discontinue NAP and continue treatment with single agent docetaxel. If docetaxel cannot be administered once a treatment cycle has been initiated, docetaxel is to be delayed by a maximum of one week and skipped in the absence of adequate recovery; the next NAP cycle is then delayed by one week as well.

Dose Delay Between Treatment Cycles

If on Day 1 of the next scheduled treatment cycle, all toxicities from prior treatment cycles or intercurrent medical conditions have not reverted to Grade 1 or baseline, or if the ANC is <1,500/μL and/or the platelet count is <100,000/μL, treatment with NAP and docetaxel should be held and the subject followed weekly until resolution of any toxicity or intercurrent condition to Grade 1 or baseline and the ANC is >1,500/μL and the platelet count is >100,000/μL. If a delay is indicated for a cycle of NAP, the entire regimen of NAP + docetaxel is to be delayed. If, in the opinion of the investigator, toxicity due to NAP alone has not resolved by 6 weeks after the last NAP/docetaxel cycle, discontinue NAP and continue the subject on docetaxel alone. Once toxicity of docetaxel due to myelosuppression has resolved, re-treatment with docetaxel will be at a reduced dose as described for docetaxel monotherapy. If a second dose delay is required due to myelosuppression despite the dose reduction, discontinue docetaxel and continue NAP alone. Delays for any reasons, of up to 7 days in the visit schedule of a full cycle (not within a cycle), are allowed. Patients, for whom any treatment cycle is delayed, beyond the indicated window, will be discussed with the medical monitor to determine whether they should be continued. The schedule of the imaging should be maintained, though, even if cycles are delayed.

5.3 Obinutuzumab

Obinutuzumab is a humanized anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B cells. The molecular mass of the antibody is

approximately 150 kDa. Obinutuzumab will be administered on Days -13 and -12 of the first treatment cycle. Additional administrations of obinutuzumab may be considered during the study based on biomarkers collected and B cell level.

5.3.1 Obinutuzumab Packaging

Obinutuzumab is a sterile, clear, colorless to slightly brown, preservative-free liquid concentrate for intravenous use. Obinutuzumab is supplied at a concentration of 25 mg/mL in 1,000 mg single-dose 40 mL vials. The product is formulated preservative-free in 20 mM L-histidine/L-histidine hydrochloride, 240 mM trehalose, 0.02% poloxamer 188. The pH is 6.0. Obinutuzumab must be stored at 2°Cto 8°C (36°Fto 46°F). Protect from light. Do not freeze or shake obinutuzumab. Obinutuzumab prescription information can be found in the pharmacy manual.

5.3.2 Obinutuzumab Preparation

Withdraw 40 mL of obinutuzumab solution from the vial. Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag. Mix diluted solution by gentle inversion. Do not shake or freeze. Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix obinutuzumab with other drugs. No incompatibilities between obinutuzumab and polyvinylchloride (PVC) or non-PVC polyolefin bags and administration sets have been observed. The product can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.

5.3.3 Premedication for Obinutuzumab

Hypotension may occur during obinutuzumab intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration.

Subjects must receive intravenous corticosteroid (100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone) to be completed 1 hour prior to administration of obinutuzumab followed by oral analgesic/antipyretic 650 mg – 1,000 mg acetaminophen/paracetamol p.o. and an anti-histamine (e.g., diphenhydramine 50 mg p.o. or promethazine IV) at least 30 minutes prior to administration of obinutuzumab.

5.3.4 Obinutuzumab Administration

Obinutuzumab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur.

<u>Day (– 13) Administration</u>

Administer at 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Day (-12) Administration

CBC and coagulation lab tests are to be collected and results should be available prior to dosing. Day -12 treatment will be delayed if platelet count is below 75,000/μL, coagulation abnormalities and/or any signs and symptoms of bleeding or thrombosis are present. The second obinutuzumab dose can be delayed by Day -7. Any further delay in obinutuzumab dosing is to be discussed with the Medical Monitor.

If no infusion-related reaction or an infusion-related reaction of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

See pharmacy manual for more details regarding administration of obinutuzumab.

Infusion Related Reactions If a subject experience an infusion-related reaction (IRR), adjust the infusion as follows

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab. This will have no impact on the subsequent administration of NAP /docetaxel, which should occur as scheduled.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the IRR reaction occurred), and if subject does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue treatment if subjects experience a Grade 3 IRR at rechallenge.
- Grade 1–2 (mild to moderate): Reduce infusion rate or interrupt infusion and manage symptoms. Upon resolution of symptoms, continue or resume obinutuzumab infusion, and if subject does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.

5.3.5 Stability of Diluted Obinutuzumab

For microbiological stability, immediately use diluted obinutuzumab infusion solution. If not used immediately, store in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use.

5.4 Prohibited Concomitant Medication

The following medications and treatments are not permitted while a subject is on protocol therapy:

- Any investigational agent, regardless of the indication
- Any other anti-neoplastic agents, including cytotoxic agents, monoclonal antibodies, targeted agents (e.g., tyrosine kinase inhibitors), checkpoint inhibitors, etc.
- Systemic glucocorticoids equivalent to more than 10 mg/day of prednisone (with exceptions noted below). Topical, intranasal, inhalational and intra-ocular glucocorticoids are permitted. Intermittent, brief (less than 1 week) courses of pharmacologic doses of glucocorticoids are permitted for use as anti-emetics, premedications, severe AEs, in subjects with radiographic contrast allergies prior to radiographic procedures and for exacerbations of concomitant conditions such as asthma or COPD.
- Palliative radiation to a target lesion; prior to administering any palliative radiation, the medical monitor should be consulted.
- Other immunosuppressive agents, including (but not limited to), cyclosporine, mycophenolate, azathioprine, methotrexate, adalimumab, infliximab, vedolizumab, tofacitinib, dupilumab, rituximab, etc.
- Live vaccines during protocol treatment and until B-cell recovery occurs; vaccines derived from inactive viruses are permitted.
- Strong inhibitors or inducers of CYP3A4 (a list of these agents may be found in Appendix 14.5). In addition, because of the possibility of transient release of cytokines following dosing with NAP which can suppress other CYP450 enzymes, subjects receiving substrates of CYP enzymes for which small changes in concentration could lead to altered safety or efficacy should be monitored closely and have doses adjusted as necessary (Appendix 14.5)
- The use of herbal and unapproved homeopathic remedies is strongly discouraged, as these agents may have subtle but important pharmacologic effects (e.g., effects on the cytochrome P450 system)

Subjects who require any of the above treatments during the study will have protocol therapy discontinued and be scheduled for the End of Treatment (EOT) visit.

All other intercurrent illnesses will be treated at the discretion of the Investigator according to community standards of medical practice. Agents commonly used to treat the complications of malignancy, such as non-steroidal anti-inflammatory agents, opioid analgesics, anti-depressants, anxiolytics, anti-emetics, antibiotics, hematopoietic growth factors and bone agents (such as bisphosphonates and denosumab) are permitted, as are transfusions of blood products.

Hematopoietic growth factors (e.g. G-CSF, erythropoietin) and approved COVID treatments (e.g. Paxlovid) are allowed during the study.

5.5 Lifestyle Restrictions

The following restrictions apply while the subject is receiving protocol treatment and for the specified times before and after treatment:

5.5.1 Female subject of child-bearing potential

Female subjects of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Appendix 14.6). This should be used from the time of screening throughout the total duration of the drug treatment and until 90 days after the last dose of protocol treatment. Female subjects should refrain from breastfeeding throughout this period.

5.5.2 Male subjects with a female partner of childbearing potential

Non-sterilized male subjects who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and until 90 days after the last dose of protocol treatment. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.

Please note, females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.
- Women who are surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

5.5.3 Additional Restrictions: All Subjects

Subjects should not donate blood or blood components while participating in this study and for 90 days after receipt of the final dose of protocol therapy.

6 STUDY PROCEDURES

Subjects will be contacted and invited to participate in the screening process for this study. Upon arrival at the clinical site, subjects will be presented with the informed consent form (ICF) and all aspects of the study will be explained to them and their questions will be answered. Once subjects have provided their consent and signed ICF, they will begin the screening process and eligibility will be confirmed. Once permission for enrollment is given the subject will be enrolled via an interactive web-based system.

The study will be comprised of the following periods:

- A Screening period within 1-14 days. Assessments that take place at this visit are described in Section 7 and the Schedules of Assessments below. Pregnancy testing must be performed within 72 hours prior to first dose of obinutuzumab.
- A Treatment period: as long as the combination of NAP and docetaxel is administered, cycles are of 21-day treatment. When NAP is given as monotherapy and not earlier than cycle 7, cycles are of 28-day treatment. Treatment will continue until progression or fulfillment of any of the reasons for protocol therapy discontinuation as outlined in Section 4.6, for a maximum of up to 24 months from day 1 of therapy. If either NAP or docetaxel require discontinuation, the other drug will continue as monotherapy. NAP will be administered in a dose of 10 µg/kg/day on Days 1-4 of cycles 1-6, followed by docetaxel, 75 mg/m^2 on Day 5. Starting Cycle 7, NAP will be administered on Day 1 only in a dose of 15 µg/kg (unless the dose was previously reduced due to toxicity) and docetaxel on Day 2, in 21 days treatment cycles. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. In patients whose NAP dose was reduced due to toxicities during cycles 1-6, NAP dose will not be further increased in cycle 7 and stays the same as in the previous cycle. During these study visits, safety assessments, PK/PD and immunogenicity markers will be collected, and response assessments will be performed according to the schedule presented in Table 1. The assessments which will be performed are also described in Section 7.
- An End-of-Treatment (EOT) visit will take place 30 days (±3) following the last dose administration to assess for safety parameters and other evaluations and prior to start of a new anti-cancer treatment.

The following Schedules of Assessments describes all required study assessments and the timeframes in which these must be performed. All visits must occur within the pre-defined windows outlined in this protocol.

Guidance regarding how to manage subjects exposed to COVID-19 and recommendations for the vaccine, can be found in **Appendix 14.7.**

Table 1. **Schedule of Assessments: Cycle 1-6**

		Screening	Obinutuzumab		Treatment Cycle 1-6					
Procedure		Days -28-14	Day - 13	Day - 12	Day 1	Day 2	Day 3	Day 4	Day 5[22]	Day 15 only (± 2 d)
Sign consent[1]		X								
Review eligibility criteria		X								
Review medical history[20]		X								
Record demographic data		X								
Physical Exam	Complete physical exam	X			X					
	Symptom directed physical exam[21]		X		X				X	X
	Vital signs[2]	X	X[14]	X[14]	X[15]	X[15]	X[15]	X[15]	X	X
	Weight	X			X					
	Height	X								
	ECOG	X			X					
	ECG[3]	X								
Safety Labs	CBC[4]	X		X	X			X		X
	Serum chemistry[5]	X			X			X		X
	Coagulation panel[6]	X		X	X					
	Urinalysis[7]	X								
	Pregnancy test[8]	X			X					
	Thyroid panel[9]	X			X[9]					
	HIV, hepatitis serology[10]	X								
Extent of disease (EOD) assessment[11] CT/MRI		X			X every 6 weeks (± 7 days) from C1D1					
Tumor tissue[18]		X								

	Procedure	Screening	Obinutuzumab		Treatment Cycle 1-6					
		Days -28-14	Day - 13	Day - 12	Day 1	Day 2	Day 3	Day 4	Day 5[22]	Day 15 only (± 2 d)
PK sampling for NAP [12]					X			X		
Biomarkers	ADA and Nab [13]		X		X					X
	HAMA [13]		X		X					X
	Cytokines[16]				X					
	B Cell counts[17]		X		X					
Treatment	Obinutuzumab[19]		X	X						
	NAP[19]				X	X	X	X		
	Docetaxel[19]								X	
Concomitant medications		X	X	X	X	X	X	X	X	X
Adverse event reporting			X	X	X	X	X	X	X	X

Notes:

1. Obtain informed consent prior to performing any study-related procedures
2. Vital signs to include pulse, systolic and diastolic blood pressure, respiratory rate and temperature. Vital signs will be measured in supine position after at least five minutes of rest and prior to any treatment or premedication on treatment days.
3. ECGs to be performed in triplicate 5 minutes apart; QTc to be calculated via the Fridericia correction. Additional ECGs should be performed during the study if clinically indicated.
4. CBC to include WBC, differential, HGB, HCT, platelet count. Results should be available prior to any treatment and will be collected at screening, Day -12 prior to obinutuzumab treatment and up to 72 hours prior to study treatment on Day 1 of each cycle. **Cycle 1 only:** samples will be collected also on **Day 4,** a window is allowed up to 24 hours prior to Day 4, but after NAP administration on Day 3. No further samples will be collected on Day 4 of any subsequent cycles, unless it is clinically indicated. Sample will also be collected on cycle 1 day 15.
5. Serum chemistries to include sodium, potassium, chloride, bicarbonate, glucose, BUN/Urea, creatinine, AST, ALT, GGT, alkaline phosphatase, total bilirubin, LDH, calcium, magnesium, phosphorous, uric acid, total protein, albumin. Results should be available prior to any treatment and will be collected

at screening and up to 72 hours prior to study treatment on Day 1 of each cycle. Cycle 1 only: samples will be collected also on Day 4, a window is allowed up to 24 hours prior to Day 4, but after NAP administration on Day 3. No further samples will be collected on Day 4 of any subsequent cycles, unless it is clinically indicated. Sample will also be collected on cycle 1 day 15.

6. Coagulation panel to include INR and PTT. Results should be available prior to any treatment and will be collected at screening, Day -12 prior to obinutuzumab treatment, up to 72 hours prior to C1D1 and then as clinically indicted during the treatment cycles.
7. Urinalysis to include pH, specific gravity, dipstick determinations for protein, blood, glucose, ketones and will be collected at screening only and as clinically indicted during the treatment cycles.
8. Urine or serum pregnancy test will be performed at screening and up to 72 hours prior to Day 1 of each treatment cycle.
9. Thyroid panel to include, TSH, T3, free T4 and will be collected on screening, C3D1, C6D1. Thyroid panel will be collected up to 72 hours prior to any study treatment on treatment days..
10. Serologies to include HbsAg, HIV antibody, HCV antibody. Tests performed as part of routine clinical management are acceptable for use as the screening tests if performed up to 30 days prior to screening.
11. EOD assessment to include CT (Chest Abdomen Pelvis), MRI (brain), findings on physical exam and any other appropriate radiographic procedures to document sites of neoplastic disease. Scans (Chest Abdomen Pelvis and brain CT/MRI) performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and have been performed within three (3) weeks prior to D-13 obinutuzumab pretreatment. Ongoing study imaging will be performed at the end of cycle 2 (45 ± 7 days) and every 6 weeks for the first 24 weeks and every 9 weeks (± 7 days) thereafter. Confirmatory scans will be performed after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter. This schedule should be maintained even if cycles are delayed. Scheduled imaging of the brain is not required during the study unless there is involvement at baseline. Additional scans of any type may be done for clinical management and can be potentially used for RECIST evaluation upon consultation with the medical monitor.
12. PK samples for NAP will be drawn within 30 minutes prior to NAP administration start time, and then 5 minutes (+ 3 min) and 1 hour (± 15 min) after NAP administration start time.
13. Anti-drug antibodies (ADAs), HAMA and Neutralizing antibodies (Nab) to be obtained within 30 min prior to administration of NAP or obinutuzumab.
14. Vital signs to be obtained prior to premedication administration of obinutuzumab, then every 15 minutes (± 5 min) for the first hour of infusion, then every 30 minutes (± 5 min) for the remainder of the infusion and then every 30 minutes (± 5 min) for 1 hour after the end of the infusion.
15. Vital signs to be obtained prior to premedication administration of NAP and then 15, 30 (+ 5 min), 60 (+ 5 min), 180 minutes (+ 15 min) after NAP administration start time on cycle 1 (days 1-4) and cycle 2 day 1 (C2D1) only. On further treatment days vital signs will be collected before NAP premedication and then at 15, 30 (+ 5 min) and 60 (+ 5) minutes post-injection of NAP, unless the subject experienced any G3 or higher infusion related reactions previously, and therefore will continue monitoring up to 180 min (+15 min) post NAP administration.
16. Cytokine samples will be collected within 30 min before NAP administration start time, and then 1 h (±15 min) and 3 h (±15 min) after NAP administration start time.

17. B cell count will be collected on Day -13 and C1D1, prior to any study treatment on treatment days. Results are not required to be available prior to treatment. If the test was missed in any of the visits, it is important to collect it in the next scheduled visit. This sample should be analyzed at local laboratory according to Appendix 14.8.
18. Tumor tissue: Archival or fresh tumor tissue from a biopsy of a tumor lesion not previously irradiated must be provided and sent to central lab during screening for retrospective biomarker test of 5T4 expression. If there are multiple archival samples from different time points, the most recent sample should be submitted for analysis. Bone samples, fine-needle aspiration, brushing, cell pellets and lavage are not acceptable.
19. Follow pre-medication guidelines in section 5.3.3 for obinutuzumab, section 5.2.5 for NAP and section 5.1.1 for docetaxel.
20. Medical history review should also include the collection of NGS results, TMB expression and PD-L1 level, if available.
21. Symptom directed physical exam will be performed up to 72 hours prior to study drug administration. It will be performed on Day -13, Days 5 and 15 of Cycle 1, Day 1 and Day 5 of each subsequent treatment cycle and as clinically indicated.
22. If docetaxel is discontinued due to toxicity, Day 5 assessments should not be performed.

Table 2. **Schedule of Assessments: Subsequent Treatment Cycles for Cycle 7 Onward**

Procedure		Subsequent Treatment Cycles for Cycle 7 Onward					EOT	Long-term F/U
		Day 1	Day 2					
Physical Exam	Complete physical exam						X	
	Symptom directed physical exam[18]	X						
	Vital signs[1]	X[12]	X				X	
	Weight	X					X	
	ECOG	X					X	
	ECG[2]						X	
Safety Labs	CBC[3]	X					X	
	Serum chemistry[4]	X					X	
	Coagulation panel[5]						X	
	Urinalysis[6]						X	
	Pregnancy test[7]	X					X	
	Thyroid panel[8]	X					X	
Extent of disease (EOD) assessment[9] CT/MRI		X					X	X[13]
Follow-up for survival								X[14]
PK sampling for NAP [10]		X						
Biomarkers	ADA and Nab[11]	X					X	
	HAMA[11]	X					X	
	Cytokines[16]	X						

Procedure		Subsequent Treatment Cycles for Cycle 7 Onward					EOT	Long-term F/U
		Day 1	Day 2					
	B Cell counts[17]	X					X	
Rx	NAP[15]	X						
	Docetaxel[15]		X					
Concomitant medications		X	X				X	
Adverse event reporting		X	X				X	

Notes

1. Vital signs to include pulse, respiratory rate and systolic and diastolic blood pressure, respiratory rate and temperature. Vital signs will be measured in supine position after at least five minutes of rest and prior to any treatment or premedication on treatment days.
2. ECGs to be performed in triplicate 5 minutes apart; QTc to be calculated via the Fridericia correction. Additional triplicate ECGs should be performed during the study if clinically indicated and at EOT visit.
3. CBC to include WBC, differential, HGB, HCT, platelet count. Results should be available prior to any treatment and will be collected up to 72 hours prior to any study treatment on treatment days and at EOT visit.
4. Serum chemistries to include sodium, potassium, chloride, bicarbonate, glucose, BUN/Urea, creatinine, AST, ALT, GGT, alkaline phosphatase, total bilirubin, LDH, calcium, magnesium, phosphorous, potassium, uric acid, total protein, albumin. Results should be available prior to any treatment and to be collected up to 72 hours prior to any study treatment on treatment days and at EOT visit.
5. Coagulation panel to include INR and PTT. A coagulation panel should be obtained at EOT visit and as clinically indicted during the treatment cycles.
6. Urinalysis to include pH, specific gravity, dipstick determinations for protein, blood, glucose, ketones and will be collected at EOT visit and as clinically indicated.
7. Urine or serum pregnancy test to be obtained up to 72 hours prior to Day 1 of each treatment cycle and at EOT visit.
8. Thyroid panel to include, TSH, T3, free T4 and to be obtained on C9D1 and every third cycle for the duration of the study and at EOT. Thyroid panel will be collected up to 72 hours prior to any study treatment on treatment days. In the case of abnormal thyroid function at EOT visit, subject will be followed every 3 months up to resolution or starting a new anti-cancer treatment.

9. EOD assessment to include CT (Chest Abdomen Pelvis) and MRI (brain – if lesions present at baseline), findings on physical exam and any other appropriate radiographic procedures to document sites of neoplastic disease. Ongoing study imaging will be performed at the end of cycle 2 (45 days ± 7 days) and every 6 weeks for the first 24 weeks and then every 9 weeks (± 7 days) thereafter. Confirmatory scans will be performed after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter. This schedule should be maintained even if cycles are delayed. Scheduled imaging of the brain is not required during the study unless lesions are present at baseline. Additional scans of any type may be done for clinical management and can be potentially used for iRECIST evaluation upon consultation with the medical monitor.
10. PK samples for NAP will be drawn within 30 minutes prior to NAP administration start time, and then 5 minutes (+3 min) and 1 hour (± 15 min) after NAP administration start time. PK samples will be collected on Day 1 of every 2 cycles after cycle 6: cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20, cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32 and cycle 34. If B cell level is increased back to the normal range at any timepoint during the study, additional PK samples will be collected in the following visit.
11. Anti-drug antibodies (ADAs), HAMA and Neutralizing Antibodies (Nab) to be obtained within 30 minutes prior to administration of NAP and will be collected on Day 1 of every 2nd cycle after cycle 6: cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20, cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32 and cycle 34. Samples for ADAs, HAMA and Nab will be collected at EOT visit only if have not been collected on the previous visit. If B cell level is increased back to normal range at any timepoint during the study, additional samples for ADAs, HAMA and Nab will be collected in the following visit.
12. Vital signs to be obtained prior to administration of NAP premedication, and then 15, 30 (± 5 min) and 60 (± 5) minutes after NAP administration start time, unless the patient experienced any G3 or higher infusion related reactions in prior cycles which require further monitoring.
13. Subjects who discontinue treatment without progression will be followed for progression every 6 weeks (± 7 days) for the first 24 weeks and every 9 weeks thereafter.
14. All subjects will be followed for survival, by monthly (± 7 days) phone calls, for 6 months following treatment completion of the last subject into the trial
15. Follow pre-medication guidelines in section 5.2.5 for NAP and section 5.1.1 for docetaxel. Starting Cycle 7, NAP will be administered on Day 1 only in a dose of 15 µg/kg/day (unless the dose was previously reduced due to toxicity and then NAP dose will not be further increased) and docetaxel on Day 2, in 21 days treatment cycles. The combination of NAP and docetaxel will be given for a maximum of 8 cycles (unless, in the opinion of the investigator, the patient may derive benefit from continuing docetaxel), then NAP will be continued as a single agent (Day 2 assessments should not be performed) until disease progression, untoward toxicity or non-compliance for a maximum of up to 24 months from day 1 of therapy. Once NAP is given as monotherapy and not earlier than C7, cycles will be of 28 days of duration. If NAP is discontinued due to an AE and treatment is continued with single agent docetaxel, all assessments of Day 1, with the exception of PK sampling for NAP, cytokines, ADAs, HAMA, 12 Lead ECG and thyroid hormones, B-cells should be performed on the day of docetaxel treatment.
16. Cytokine samples will be collected within 30 min before NAP administration start time, and then 1 h (±15 min) and 3 h (±15 min) after NAP administration start time. Cytokine samples will be collected on Day 1 of every 2nd cycle after cycle 6: cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20,

cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32, and cycle 34. If B cell level is increased back to normal range at any timepoint during the study, additional cytokine samples will be collected in the following visit.

17. B cell count should be obtained on day 1 of each cycle starting from cycle 7 until B cell recovery to at least the lower limit of normal range or End of Treatment visit, whichever comes first. Results are not required to be available prior to treatment. This sample should be analyzed at **local laboratory** according to Appendix 14.8. If the test was missed, it is important to collect it in the next scheduled visit. In case of B cell recovery to at least the lower limit of normal range at any timepoint during the study, additional samples for PK, ADAs, HAMA and Nab will be collected in the following visit.
18. Symptom directed physical exam will be performed up to 72 hours prior to study drug administration.

7 ASSESSMENTS

All protocol-required assessments are briefly described below. A by-visit presentation of the different schedules of assessments is provided in Tables 1 and 2.

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that have been taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the time points indicated in the Schedules of Assessments. Whenever electrocardiograms (ECGs) and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG and then blood draws.

7.1 General Assessments

Demographics

The age, gender, race, and ethnic origin will be recorded at the Screening visit according to local regulations regarding the release of personal subject information.

Medical History

A medical history, conducted by interview or based on medical records, will be recorded at the Screening visit, and will include all pertinent prior medical conditions, documentation of histological or cytological proof of malignancy, NGS results, TMB expression and PD-L1 levels, and details of previous anti-cancer treatment or other medical procedures related to the subject's current disease, including a complete medications history of anticancer agents, prior surgery, prior radiation treatment and COVID-19 (both disease and vaccines).

Concomitant Medications

All prescription and over-the-counter or medications, vitamins, vaccinations and/or herbal supplements, including medications that are unrelated to cancer management, from 28 days prior to Screening throughout the entire study period, will be recorded. These include long-term as well as short-term or acute medications ongoing at the time of ICF signature or started at any time after ICF signature until 7 days after the last dose of study treatment is administered. Premedication prior to protocol therapy administration will also be recorded. Reason for use, start and end dates and dosage information (dose, unit, frequency) of all concomitant medications will be recorded.

Hematopoietic growth factors (e.g. G-CSF, erythropoietin) and approved COVID treatments (e.g. Paxlovid) are allowed during the study.

Non-permitted treatments are described in Section 5.4.

7.2 Safety Assessments

7.2.1 Physical Examination

A complete physical examination will be performed at Screening, on Day 1 of Cycle 1, as clinically indicated and at the End of Treatment (EOT) visit.

A symptom-directed physical exam, with focus on any areas of known neoplastic disease or on areas referable to any symptoms or AEs, will be performed on Day -13, Days 5 and 15 of Cycle 1, Day 1 and Day 5 of each subsequent treatment cycle and as clinically indicated. Symptom directed physical exam will be performed up to 72 hours prior to study drug administration.

The complete physical examination will cover a careful assessment of all body systems, including the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Particular attention should be placed on those areas involved by neoplastic disease.

7.2.2 ECOG Performance Score

The ECOG PS (Appendix 14.3) will be assessed at the Screening visit, then on day 1 of each cycle and at the EOT.

7.2.3 Vital Signs

Vital signs (temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure) will be measured as follows:

- ***Time points related to NAP administration start time*:**
  Vital signs will be obtained before NAP premedication administration, and at 15, 30 (+ 5 min), 60 (+5 min), and 180 minutes (+ 15 min) post-injection of NAP on cycle 1 (days 1-4) and cycle 2 day 1 (C2D1) only. On further treatment days vital signs will be collected before NAP premedication and then at 15, 30 (+ 5 min) and 60 (+ 5) minutes post-injection of NAP, unless the subject experienced any G3 or higher infusion related reactions previously, and therefore will continue monitoring up to 180 min (+15 min) post NAP administration. ***Time points related to Docetaxel administration start time*:**
  Vital signs will be obtained before Docetaxel treatment on day 5 of each cycle.
- ***Time points related to obinutuzumab administration start time:***
  Vital signs will be obtained before obinutuzumab premedication administration, then every 15 (+ 5 min) for the first hour of infusion, then every 30 minutes (± 5 min) for the remainder of the infusion and then every 30 minutes (± 5 min) for 1 hour after the end of the infusion.
- Vital signs will be also performed on day 15 of cycle 1, and at EOT visit.
- ***Weight*** will be measured at the start of each treatment cycle and at the EOT visit. The calculation of the dose per subject weight should be done on the basis of subject weight on the day of treatment. In sites restricted by pharmacy's procedures the dose can be calculated on the basis of subject weight obtained within 14 days prior to that date. For the purpose of calculating study treatment dose, the subject's weight should **NOT** be rounded off to the

closest kg value but rather recorded with 1 digit after the decimal point, for example, 70.5 kg, 60.4, 77.0 kg etc. However, after multiplying the weight by the relevant dose level (µg/kg), the final dose (in µg) should be rounded off, for example, 120.5 µg will be rounded to 121 µg and 150.4 µg will be rounded to 150 µg.

- ***Height*** will be measured at the screening visit

Vital signs will be measured in supine position after at least five minutes of rest. A special attention should be given to cytokine release syndrome (CRS). See instructions below.

Evaluation of cytokine release syndrome (CRS):
The toxicities related to CRS (23) should be carefully monitored during the entire treatment period and specifically on days of NAP dosing. See Appendix 14.4 for grading of CRS.
All subjects will receive NAP infusion at a health care facility, followed by on-site monitoring at the health care facility for at least 4 h post dosing on the first cycle and 3 hours on each subsequent cycle to monitor for signs and symptoms of CRS.
In addition, subjects and their family members/caregivers should be educated on potential CRS symptoms such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop anytime during the study.

Guidelines for the treatment of CRS*:

Grade 1	Monitor fluid status; maintain an open intravenous catheter Empiric treatment for febrile neutropenia Supportive care with antipyretics, analgesics, antiemetics, etc.
Grade 2	Administer bolus of intravenous fluids; consider ICU monitoring If hypotension persists following 2 fluid challenges, administer tocilizumab If hypotension persists following tocilizumab, begin vasopressor agents; consider adding dexamethasone Supplemental oxygen as needed Supportive care Echocardiogram to monitor cardiac function
Grade 3	Admit to ICU Administer bolus of intravenous fluids If hypotension persists following 2 fluid challenges, administer tocilizumab If hypotension persists following tocilizumab, begin vasopressor agents; consider adding dexamethasone; add high-dose dexamethasone for persistent hypotension Supplemental oxygen as needed (including high-flow oxygen, CPAP) Supportive care Echocardiogram to monitor cardiac function
Grade 4	Intravenous fluids, tocilizumab, pressors and corticosteroids as for Grade 3 Mechanical ventilation
* Adopted from: Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Therapeutics Clinical Risk Management 15:323-335, 2019.	

7.2.4 ECG

A 12-lead ECG will be taken for each participant at Screening, and at the EOT visit. Additional ECG could be done during the study if clinically indicated. At minimum, the following ECG parameters will be recorded: heart rate (HR), and PR, QT and QRS and QTcF intervals. In addition, a determination of whether the ECG was normal, abnormal but not clinically significant, or abnormal AND clinically significant will be recorded in the eCRF.

7.2.5 Laboratory Determinations

All safety lab evaluations will be performed by a local lab. All laboratory results will be reviewed by the Investigator and will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal AND clinically significant. In the latter case, the laboratory findings should be recorded as adverse events.

Complete blood count

Blood will be collected for complete blood counts (CBC) at the Screening visit, on Day -12, on Days 1, 4 and 15 of Cycle 1 and then on Day 1 only of every cycle thereafter involving combination or NAP/docetaxel monotherapy treatment, if applicable (when NAP/docetaxel is discontinued due to toxicity or intercurrent medical conditions). A CBC will also be obtained on the 30-day EOT visit. A time window for collection of CBC is available of up to 72 hours prior to study treatment on Day 1 of each cycle and up to 24 hours prior to Cycle 1 Day 4, but after NAP administration on Cycle 1 Day 3. Laboratory results must be known and within acceptable range prior to dosing. The CBC assessment will include a determination of hemoglobin, hematocrit, platelet count, white blood cells (WBC), and differential (to include percentage of each white blood cell).

B cell counts

B cell counts samples will be collected on Day -13, C1D1, and day 1 of each further cycle starting cycle 7 until B-cell recovery to at least the lower limit of normal range or End of Treatment visit, whichever comes first. If the test was missed in any of the visits, it is important to collect it in the next scheduled visit (results should be captured in the EDC under an unscheduled visit). If B cell level increased back to normal level at any timepoint during the study, additional samples for PK, ADAs, HAMA and Nab will be collected in the following visit. Results are not required to be available prior to treatment. This sample should be analyzed at **local laboratory** according to Appendix 14.8.

Serum chemistry

Blood will be collected for serum chemistry assessments at the Screening visit, on Days 1, 4 and 15 of Cycle 1, and then on Day 1 of every cycle thereafter. A serum chemistry sample will also be obtained on the 30-day EOT. A time window for collection of CBC is available of up to 72 hours prior to study treatment on Day 1 of each cycle and up to 24 hours prior to Cycle 1 Day 4, but after

NAP administration on Cycle 1 Day 3. Laboratory results must be known and within acceptable range prior to dosing.

Serum chemistries will include assessment of sodium, potassium, chloride, bicarbonate, glucose, BUN/Urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, Lactate dehydrogenase (LDH), calcium, magnesium, phosphorous, total protein, albumin, and uric acid.

Coagulation Panel

A coagulation panel, consisting of an international normalized ratio (INR) and activated partial thromboplastin time (aPTT) will be performed at Screening Day -12 prior to obinutuzumab treatment, up to 72 hours prior to C1D1,then as clinically indicated during treatment period and at the EOT visit.

Urinalysis

Urinalyses will be performed by dipstick at Screening and EOT visit ., then as clinically indicated. Urinalysis will include pH, specific gravity, dipstick determinations for blood, nitrites, glucose, ketones, protein and bilirubin or urobilinogen. A microscopic examination of the urine will be performed if clinically indicated.

Pregnancy Test – Urine or/ and Blood

For female subjects of childbearing potential, a urine pregnancy test will be performed at Screening, then up to 72 hours prior to any treatment on Day 1 of each treatment cycle and at the EOT. If urine pregnancy results cannot be confirmed as negative, a serum β-HCG pregnancy test, performed by the local laboratory, is required. A negative pregnancy result is required before the subject may receive any protocol therapy. In the case of a positive confirmed pregnancy, the subject will be withdrawn from the study and will not proceed to receive the investigational product.

Urine: A urine pregnancy test will be performed in women of child-bearing potential (WOCBP) only, up to 7 days prior to dosing of obinutuzumab on Day (-13).

Blood: A serum pregnancy test will be performed if a confirmation pregnancy test is necessary.

Thyroid Panel

A thyroid panel, to include a free T4, T3 and TSH will be performed during Screening, day 1 of cycles 3, 6, and every 3rd cycle as long as subject is on study treatment and at EOT. Thyroid panel will be collected up to 72 hours prior to any study treatment on treatment days. In the case of abnormal thyroid function at EOT visit, subject will be followed every 3 months up to resolution or starting a new anti-cancer treatment.

Viral Serologies

Viral serologies to include HBsAg, HCV antibody and HCV antibody to be performed at Screening. Tests performed as part of routine clinical management are acceptable for use as the screening tests if performed up to 30 days prior to screening.

7.3 Efficacy Assessments

The preferred method for tumor imaging is CT with contrast covering chest, abdomen and pelvis and mandatory brain MRI at screening (additional brain MRI will be performed during the study only if indicated). CT scan of the brain will also be acceptable if MRI is not available. MRI should only be used for subjects with a contraindication to receive contrast agents. In cases where CT contrast-agents are unavailable, a non-contrast CT should be used for chest and pelvis and MRI with contrast is recommended for abdomen (for better assessment of a specific region by the Radiologist e.g. for liver lesions).

Other specialized imaging or other techniques may also be appropriate for individual case. 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), and only if a baseline PET-CT is available. An initial tumor imaging will be performed within the Screening period (brain and CAP). Scans performed as part of routine clinical management will be acceptable for use as the screening scan if they are of diagnostic quality and have been performed within three (3) weeks prior to D-13 obinutuzumab pretreatment. Ongoing study imaging will be performed at the end of cycle 2 (45 days ± 7 days) and every 6 weeks for the first 24 weeks and then every 9 weeks (± 7 days) thereafter. This schedule should be maintained even if cycles are delayed. Confirmatory scans will be performed after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter. Any imaging performed for subjects without confirmed progression at early termination, diagnostic imaging/response assessments should continue every 6 (±1) weeks for the first 24 weeks and then every 9 weeks (± 7 days) thereafter, until confirmed progression of disease or initiation of alternate therapies. If a subject has a response or stable disease, they can be permitted to continue until progression.

As NAP is known to induce an inflammatory reaction in the tumor, pseudo-progression may be observed and therefore, in patients who demonstrate objective progression but who are clinically stable, 1-2 additional treatment cycle(s) of NAP/docetaxel may be administered beyond progression at the discretion of the Investigator, followed by a confirmatory imaging after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter.

The same imaging modality should be used in each subject throughout the trial. Imaging will continue at the defined interval until disease progression, pregnancy, the start of a new treatment or completion of study participation. Scans will be evaluated by a local radiologist using iRECIST (Appendix 14.1).

7.4 Pharmacokinetic Assessments

Plasma samples for PK analysis will be collected on Day 1 and Day 4 of cycles 1-6, and then on D1 of every 2 cycles after cycle 6 , within 30 min prior to NAP administration start time and then 5 minutes (+3 min) and 1 hour (±15 min) after NAP administration start time.

Details of sample collection and handling will be provided separately in a lab manual.

Table 3. PK Draws Timepoints

Cycle/Day	**Timepoint related to NAP administration start time**
D1 and D4 of cycles 1-6	-30 minutes + 5 minutes (+3 min) + 60 minutes (± 15 min)
D1 of every 2nd cycle after cycle 6 (cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20, cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32 and cycle 34)	-30 minutes + 5 minutes (+3 min) + 60 minutes (± 15 min)

7.5 Pharmacodynamic Assessments

Serum samples for cytokine levels analysis (such as IL-6, IL-10, IL-2, IFN-γ and TNF-α) will be collected within 30 min before NAP administration start time and then 1 h (±15 min) and 3 h (±15 min) after NAP administration start time on day 1 of cycles 1-6, and Day 1 of every 2 cycles after cycle 6: cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20, cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32 and cycle 34.

Serum samples for determining the levels of human anti-murine antibodies (HAMA) will be collected within 30 minutes prior to the administration of obinutuzumab or NAP on Day -13 and on day 1 of cycles 1-6, cycle 1 Day 15, and Day 1 of every 2 cycles after cycle 6: cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20, cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32and cycle 34.

Serum samples for determining the levels of anti-drug antibodies (ADAs) and neutralizing antibodies (Nab) will be collected within 30 minutes prior to the administration of obinutuzumab or NAP on Day -13 and on day 1 of cycles 1-6, cycle 1 Day 15 and Day 1 of every 2 cycles after cycle 6: cycle 8, cycle 10, cycle 12, cycle 14, cycle 16, cycle 18, cycle 20, cycle 22, cycle 24, cycle 26, cycle 28, cycle 30, cycle 32and cycle 34. Nab samples will be collected and kept for future analyses.

Samples for ADAs, HAMA and Nab will be collected at EOT visit only if have not been collected on the previous visit.

Details of sample collection and handling will be provided separately in a lab manual.

7.6 Tumor Biopsy

Tumor archival or fresh tissue from a biopsy of a tumor lesion not previously irradiated must be provided and sent to central lab during screening for retrospective biomarker test of 5T4 expression. If there are multiple archival samples from different time points, the most recent sample should be submitted for analysis.
The following samples of biopsy are not allowed for 5T4 analysis:

- Bone samples.
- Fine-needle aspiration, brushing, cell pellets and lavage.

Details of sample collection and handling will be provided separately in a lab manual.

7.7 End of Treatment/Early Termination Visit

Specific assessments and procedures to be performed for the End of Treatment/Early Termination visit are listed in Table 2. The End of Treatment visit will occur 30 days (±3) from the last dose of protocol therapy and prior to start of a new anti-cancer treatment.

7.8 Long Term Follow-Up

All subjects will be followed for survival, by monthly phone calls, for up to 6 months (± 7 days) following treatment completion of the last subject in the trial.

Subjects without confirmed progression at early termination, diagnostic imaging/response assessments should continue every 6 (±1) weeks in the first 24 weeks and every 9 weeks thereafter, until confirmed progression of disease or initiation of alternate therapies. Thyroid panel will also continue for subjects on study every 3 months for 6 months after study drug discontinuation.

7.9 Unscheduled Visits

Unscheduled visits are those visits that will occur between regularly scheduled visits and will be performed in order to assess a previously noted adverse event, abnormal/significant laboratory values, and/or clinical findings. In such cases, the patient will be contacted to arrange an unscheduled visit to assess the abnormalities. Only focused assessments are foreseen for these visits.

8 ADVERSE EVENTS REPORTING AND MEDICAL MANAGEMENT

As described in Section 8.13, any AEs attributed to study drug dosing, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

8.1 Adverse Events

Safety assessments will include recording TEAEs reported spontaneously by the subject or observed by the Investigator. Treatment-emergent AEs will be recorded at each visit on the appropriate eCRF. Any AEs occurring between (and including) Screening and D-13 visit will be recorded on the Medical History eCRF, as long as treatment has not been initiated. If an AE is recorded in Medical History and has worsened, it will be considered a TEAE.

All observed or volunteered AEs, regardless of study treatment and suspected causal relationship to protocol therapy will be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE, which must be assessed by the Investigator. Follow up by the Investigator should continue until the event or its sequelae resolve, return to a baseline state or stabilize.

As part of ongoing safety reviews conducted by the Sponsor, any nonserious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject administered a product or medical device after the subject signs the ICF for a clinical study; the event need not necessarily have a causal relationship with the treatment or usage. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether related to the investigational medicinal product. TEAEs are defined as events that emerge during treatment having been absent pre-treatment or worsen relative to the pre-treatment state.

All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF, as described in section 8.1.

Examples of AEs include but are not limited to:

- All suspected adverse medication reactions including:
  - Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
  - Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they were associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a subject with jaundice) are to be described separately unless the underlying pathophysiological cause is known
  - Clinically significant symptoms and signs
- All reactions from medication overdose, abuse, withdrawal, hypersensitivity, or toxicity.
- Seemingly unrelated illnesses, including the worsening of a pre-existing illness
- Injury or accidents **Note**: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs. The outcome of the accident should be recorded under Comments.
- Progression/worsening of underlying disease (progression of the malignancy under evaluation should not be considered as AE).

Pre-existing Conditions

A pre-existing condition (i.e. a disorder other than cancer present before the AE reporting period started and noted on the pre-treatment medical history form) is not to be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period. Planned or elective surgical procedures for pre-existing conditions that have not worsened are not TEAEs. However, any complication that occurs during a planned or elective surgery is a TEAE (Note: If the event meets the criteria for a SAE, such as an extended hospitalization, it will be considered an SAE). Conditions leading to unplanned surgical procedures may also be TEAEs.

New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of protocol therapy and have been identified after the subject's inclusion in this study.

Concomitant Procedures

Diagnostic and therapeutic procedures, such as surgery, are not to be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that began during the AE reporting period is to be reported as the AE and the resulting appendectomy noted as treatment for the AE.

Events of Special Interest (AOSI)

Given the expected immunostimulatory effects of the study treatment, special attention should be paid to immune-related adverse events. Immune-related AEs (irAEs) will be graded based on CTCAE.

In case the AOSI is classified as an SAE, an SAE report will be completed, signed and sent via email to the Sponsor or Sponsor's designee.

8.3 Unexpected Adverse Event

An adverse event is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended; or if a marketed product, not described as above in the full prescribing information, package insert or summary of product characteristics for an approved product.

8.4 Severity Assessment

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., 'severe' headache). This is not the same as a "serious" AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 5.0 (the NCI CTCAE files can be accessed online at the following URL:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

If there is not a specific NCI CTCAE grading scale for an AE, the severity will be characterized as mild, moderate, severe, life-threatening or fatal according to the following definitions:

- Grade 1 (mild) events are usually transient in nature and do not interfere with the subject's daily activities.
- Grade 2 (moderate) events introduce as low level of inconvenience or concern to the subject and may interfere with daily activities.
- Grade 3 (severe) events interrupt the subject's usual daily activities.
- Grade 4 (life-threatening)

• Grade 5 (fatal)

8.5 Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

In addition, if the Investigator determines that an AE is associated with a study procedure, the Investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the AE reporting requirements, if applicable.

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as defined below.

Causality: the relationship of each AE to study treatment will be defined as unrelated or related to study treatment using the following definitions:

- Unrelated: There is little or no possibility that the study treatment caused the reported AE; and other factor(s) including concurrent illnesses, progression and expression of the disease state, concurrent medications, or a reaction to concurrent medications appear to explain the AE.

- Related: There exists at least a reasonable possibility that the study treatment caused or contributed to the AE; an inability to identify an alternate etiology for an AE should not, by itself, justify a related attribution.

8.6 Serious Adverse Events

Treatment-emergent SAEs will be recorded at each visit throughout the study on the appropriate eCRF. Any SAEs occurring between (and including) Screening and Baseline visits will be recorded in the Medical History eCRF, as long as treatment has not been initiated.

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect

- Is an important medical event that doesn't fulfill any of the above criteria

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other SAE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse or a new malignancy.

Progression/worsening of underlying disease (progression of the malignancy under evaluation should not be considered as serious adverse event).

8.7 Hospitalization

Hospitalization is defined as any admission or stay in a hospital or equivalent healthcare facility lasting more than 24 hours or any prolongation of an existing admission. An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Admission to a rehabilitation facility
- Admission to a hospice facility
- Respite care (e.g., caregiver relief)
- Admission to a skilled nursing facility
- Admission to a nursing home
- Out-subject/same-day/ambulatory procedures
- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for workup of persistent pretreatment laboratory abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject

8.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected by the Sponsor and that is judged by the Investigator or Sponsor to be related to the study treatment administered. All SUSARs will be collected and reported to the regulatory authorities and relevant ethics committees in accordance with local pharmacovigilance requirements.

8.9 Serious Adverse Event Reporting Requirements

If an SAE occurs, The Sponsor and/or its pharmacovigilance designee(s) are to be notified within 24 hours of Investigator awareness of the event by sending a written, completed, and signed SAE report form to the following group mailbox or Fax:

Email: clinicalsafety@propharmagroup.com

Fax: (866) 681-1063

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., subject discharge summary or autopsy reports), should be transmitted or emailed to The Sponsor or its pharmacovigilance designee(s) at the Fax or email address above.

The Sponsor must report all fatal or life-threatening SAEs to regulatory authorities in an expedited manner within 7 calendar days of being made aware of the event; serious adverse event reporting to regulatory authorities and all participating investigators will be conducted by NeoTX in accordance with 21 Code of Federal Regulations (CFR) 312.32 and international regulations, as appropriate.

8.10 Reporting Period

For all AEs, the active reporting period to The Sponsor or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 calendar days after the last administration of the study treatment or initiation of alternate anticancer therapy. AEs that occur during the Screening period prior to first administration of any protocol therapy will be recorded as part of the medical history.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should elicit the reporting of adverse events from subjects in a non-prejudicial manner. Adverse events may also be recorded when they are volunteered by the subject, or through physical examination, laboratory tests, or other clinical assessments.

8.11 Action Taken Regarding the Study Drugs

The action taken towards the study drugs must be described as follows:

- Permanently discontinued
- Stopped temporarily/Dose delayed
- Dose modified
- No action taken
- Unknown/Not applicable

Indicate exactly for which study drug (or combination) the action was taken

8.12 Outcome

The outcome of each AE must be determined as follows:

Outcome	Clarification
Recovered/Resolved	Subject has fully recovered with no residual effects
Recovered Resolved with sequelae	Subject has recovered with residual effects
Not yet recovered/Not Resolved	Subject status improved but has not yet been recovered
Ongoing/Not Recovered/Not Resolved	Subject has not recovered and has no improvement
Fatal	Resulted in death of the subject
Unknown	e.g. lost to follow

8.13 Recording of Adverse Events

All AEs and SAEs occurring during the clinical investigation as defined above must be documented in the subject's medical records as well as in the eCRF. Whenever possible, diagnoses

should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the (S)AE to the study drugs in the source documents and in the eCRF. All measures required for (S)AE management must be recorded in the source documents and reported according to Sponsor's instructions.

All AEs occurring at any time during the study (including the follow-up period) will be followed by the Investigator until satisfactory resolution, return to a baseline state, stabilization or until final database lock. If necessary, in order to obtain additional information to ensure safety to the subject, additional tests may be taken at the discretion of the Investigator. Certain long-term AEs related to therapy cannot be followed until resolution within the setting of this study. In these cases, follow-up will be the responsibility of the treating physician.

All TEAEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection and reporting of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection and reporting of SAE information.

8.14 Pregnancy

8.14.1 Maternal Exposure

Female subjects should refrain from becoming pregnant during the study and for 90 days after the last dose of protocol therapy. If a subject becomes pregnant during the course of the study, protocol therapy must be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the Investigator must submit this information to The Sponsor on a Pregnancy Reporting From, regardless of whether an SAE has occurred as a consequence of this exposure.

The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify The Sponsor of the outcome. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs are as follows:

- Spontaneous abortion includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

In the case of paternal exposure, the Investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.14.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of NAP and/or durvalumab therapy.

Pregnancy of a male subject's partner is not considered to be an AE. Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Once consent is obtained, the Investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner and document in the source documents that the subject was given this form.

The outcome of any pregnancy in the female partner of a male subject (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose will be followed up and documented.

8.15 Withdrawal Due to Adverse Events

For a subject experiencing a recurrence of the same AE(s) at the same grade or greater, or a subject experiencing a recurrence of the same SAE, a consultation between the Sponsor and Investigator should be conducted to determine whether the subject should continue on therapy. A determination will then be made as to whether the subject should have NAP discontinued, docetaxel discontinued, or both agents discontinued based on the nature of the adverse event.

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE eCRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined above.

For subjects without confirmed progression at early termination, diagnostic imaging/response assessments should continue every 6 (±1), in the first 24 weeks and every 9 weeks thereafter, until confirmed progression of disease or initiation of alternate therapies. If a subject has a response or stable disease, they can be permitted to continue until progression.

9 STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP).

9.1 Analysis Populations

Safety Population: includes all subjects who received at least one day of any study treatment (including pre-treatment, obinutuzumab).

Evaluable subject population: subjects completing at least one treatment cycle and having had an evaluable pre-treatment and one post-treatment tumor assessment (according to the iRECIST criteria) in the absence of eligibility and compliance issues.

9.2 Sample Size Determination

The primary endpoint is ORR. A subject is considered evaluable if there is at least one pre-treatment and one post-treatment tumor assessment (according to the iRECIST criteria) in the absence of eligibility and compliance issues.

Sample size is derived testing the null hypothesis H0: true ORR ≤ 0.10 versus the alternative H1: true ORR ≥ 0.30. With one-sided alpha = 0.05 and power = 0.80, 6 or more responses in a total of 29 subjects may be of further clinical interest. The trial may be stopped if there is a single responder or no responder in the first 10 evaluable subjects.

Patients who are found to be clearly ineligible on medical review or left the study before completion of one cycle for reasons other than disease progression or study drug toxicity, will be replaced.

9.3 Efficacy Analyses

All efficacy analyses will be performed on the evaluable subject population.

Descriptive statistics will be used to describe the results of the trial. Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, minimum and maximum. Categorical/discrete variables will be summarized using frequency tables showing the number and percentage of subjects within a particular category.

Response to treatment will be assessed using iRECIST criteria into the following categories: (iCR, iPR, iSD) complete response (iCR), partial response (iPR), stable disease (iSD), unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). Any subject with no evaluable response assessment at a scheduled time-point will be assigned a response of not evaluable (NE) at that time-point. Best overall response is the highest overall response achieved by the subject on study. Subjects with no evaluable response assessment on study will be scored as not evaluable (NE). Objective response rate (ORR) is defined as the proportion of subjects who achieve either an iCR or an iPR. Immunotherapy 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. iRECIST requires the confirmation of progression, which should be done after 6 weeks (± 7 days) during the first 24 weeks and every 9 weeks thereafter.

The ORR, with corresponding 95% confidence intervals, will be computed.

Disease control rate is the proportion of subjects demonstrating CR, PR, or SD. The analysis of disease control rate will be similar to ORR.

Duration of response (DOR), in subjects with CR or PR, is the time from the first observation of aCR or PR to the first documented PD. Duration of response of subjects with no PD will be censored at the date of last evaluable response assessment.

Distributions of DOR will be estimated using the Kaplan-Meier method. The median DOR will be estimated as well.

Progression-free survival (PFS) is the time from first day of study drug treatment (obinutuzumab) to the first time of documented PD or death for any cause. PFS of living subjects with no PD will be censored at the date last evaluable response assessment.

Distributions of PFS times will be estimated using the Kaplan-Meier product-limit method. The median PFS times with 2-sided 95% confidence intervals, as well of PFS rates at 6 and 12 months, will be estimated.

Overall survival (OS) is the time from first day of study drug treatment (obinutuzumab) to death for any cause. OS of living subjects will be censored at the date last known to be alive and will be assessed up to 6 months following treatment completion of the last subject in the trial. Analysis of OS will be similar to that of PFS.

9.4 Safety Analyses

Safety analyses will be performed on the safety population.

Adverse events (AEs) will be graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded using Medical Dictionary for Regulatory Activities (MedDRA).

Treatment emergent adverse events (TEAEs) are those AEs that occur or worsen on or after first study treatment up through 30 days post last study treatment, and/or any treatment-related adverse event, regardless of the onset date. TEAEs are summarized by the MedDRA System Organ Class, Preferred Term, and worst CTCAE grade per subject, by treatment group.

Serious adverse events (SAEs) are those events that result in death, are life-threatening, require or prolong inpatient hospitalization, result in persistent or significant disability/incapacity, or cause congenital anomaly/birth defect.

SAEs and AEs leading to dose reduction, dosing delay, discontinuation of study therapy or any other premature interruption will be tabulated and summarized by treatment group.

The incidence of CRS will be analyzed separately by the nature, onset, frequency and severity of CRS, dose modifications caused by CRS and tolerance of the modified dose or recurrence of CRS with dose reduction or drug withdrawal. Narratives will be prepared for subjects with fatal and/or severe CRS and will include the dose, the time to onset, duration, information about dose modification and any evidence of recurrence of CRS with dose reduction or drug withdrawal.

Clinical laboratory results will be collected pretreatment through 30 days after the last administration of any study treatment and prior to start of a new anti-cancer treatment. Clinically significant laboratory abnormalities, namely tests that result in treatment modification and/or require intervention, will be recorded as AEs. Where applicable, laboratory results will be classified according to the NCI CTCAE and will be summarized by worst grade per subject.

9.5 Pharmacokinetic Analysis

A detailed description of pharmacokinetic parameters to be analyzed will be part of a separate PK analysis plan.

PK analysis will be performed on the PK population (i.e. enrolled subjects, with analyzable PK data and without relevant deviation interfering with the PK evaluations).

9.6 Pharmacodynamic Analyses

The following parameters and the corresponding change from baseline will be measured and summarized by descriptive statistics and data listings for the NAP /docetaxel treatment:

- Cytokine levels
- B-cell levels
- Anti-drug antibodies and human anti-murine antibodies (ADA and HAMA)

10 ETHICS

10.1 Institutional Review Board/Ethics Committee

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC must be retained in the Investigator file. Copies of IRB/EC approvals should be forwarded to The Sponsor or its designee.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is when the change is necessary to eliminate an apparent immediate hazard to the subjects. In that event, the Investigator must notify the IRB/EC and The Sponsor in writing immediately after the implementation.

Before the start of the study, the Investigator (or Sponsor where required) will provide the IRB/EC with current and complete copies of the following documents:

- final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any updates or any other written materials to be provided to the subjects)
- Sponsor-approved subject recruiting materials
- Investigator Brochure (or equivalent information) and addenda
- additional available safety information as required
- information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator’s current curriculum vitae or other documentation evidencing qualifications (unless not required, as documented by the IRB/EC)
- information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- any other documents that the IRB/EC may require to fulfill its obligation

This study will be undertaken only after the IRB/EC has given full written approval of the final protocol and amendments (if any), the ICF(s) and updates (if any), applicable recruiting materials, and any other written information to be provided to the subjects, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the Investigator (or Sponsor where required) will send the following documents and updates to the IRB/EC for its review and approval, where appropriate:

- protocol amendments

- revision(s) to the ICF and any other written materials to be provided to the subjects
- new or revised subject recruiting materials approved by the Sponsor
- revisions to compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's Brochure addenda or new edition(s)
- summaries of the status of the study at intervals stipulated in guidelines of the IRB/EC (at least annually)
- reports of AEs that are serious, unlisted, and associated with study drugs
- new information that may adversely affect the safety of the subjects or the conduct of the study
- deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- notification if a new Investigator is responsible for the study
- Development Safety Update Report, Short-Term Study Specific Safety Summary and Line Listings, where applicable
- any other requirements of the IRB/EC

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IRB/EC for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the study subjects. If a deviation from or a change to the protocol was implemented to eliminate an immediate hazard to study subjects, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IRB/EC as soon as possible.

The Investigator (or Sponsor where required) will notify the IRB/EC about the study completion.

10.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996 and revisions), U.S. laws and regulations regarding conduct of clinical trials: National Health Regulations - Clinical Trials in Humans, 1980 (including all amendments until 1999)and the Declaration of Helsinki (World Medical Association).

The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB, or the regulatory authority(ies).

10.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law. The use of Subject initials should be avoided.

When study data are compiled for transfer to The Sponsor and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by the Sponsor or its designee. in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, the Sponsor and/or its designee will maintain confidentiality and protection of subjects' personal data to the extent possible and within applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB before use, and available for inspection.

Potential subjects will be fully informed of the nature of the study and of the risks and requirements of the study before any study-related assessment will be carried out. During the study, subjects will be given any new information that may affect their decision to continue participation. They will be informed that their participation in the study is voluntary and that they may withdraw from the study at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects or their legal representatives who are fully able to understand the risks, benefits, and potential AEs of the study, and who provide their consent voluntarily will be enrolled in the study.

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and the reviewing IRB.

Subjects will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and the Sponsor and/or its designee without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The language about the study used in the oral and written information, including the ICF, should be non-technical and practical and should be understandable to the subject (or the subject's legally acceptable representative). The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should

be appropriately recorded by means of the subject's personally dated signature. After having obtained consent, a copy of the ICF must be given to the subject.

The collection and processing of personal data from subjects enrolled in the study will be limited to those data that are necessary to investigate the safety, quality, and utility of the study drug used in the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data need to agree to keep the identity of the study subjects confidential.

The informed consent obtained from the subjects includes explicit consent for the processing of personal data and for the Investigator to allow direct access to subjects' original medical records for study-related monitoring, audit, IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

10.4 Subject Recruitment

Advertisements approved by IRBs and Investigator databases may be used as recruitment procedures.

The Sponsor will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are submitted to IRB for approval before use.

10.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, The Sponsor must be informed immediately.

In addition, the Investigator will inform The Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

10.6 Protocol Deviations

A protocol deviation is any change, divergence or departure from the IRB-approved protocol by the study staff (intentional or unintentional). All deviations are to be documented at the site and reported to the IRB according to the IRB's guidelines.

In the event of an emergency, the Investigator shall implement any medical procedures deemed appropriate for subject safety. All such procedures must have written documentation and be promptly reported to the Sponsor.

10.7 Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without a formal written amendment. All protocol amendments must be issued by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IRB approval nor when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazard to the subjects, in which case an amendment must be promptly submitted to the IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IRB must be provided to the Sponsor or his designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB only needs to be notified.

10.8 Subject Identification, Enrollment, and Screening Logs

The Investigator agrees to complete a subject identification log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness.

The subject identification log will be treated as confidential and will be filed by the Investigator in the study file. To ensure subject confidentiality, no copies will be made. All reports and communications related to the study will identify subjects by assigned study number only.

The Investigator must also complete a subject screening and enrollment log which reports on all subjects who were seen to determine eligibility for inclusion in the study.

10.9 Publication Policy

All data are the property of the Sponsor. Any formal presentation or publication of data from this study will be considered for joint publication by both the Sponsor and the Investigator(s). Prior to any such publication or presentation, the Sponsor reserves the right to review and comment on any articles, manuscripts, abstracts, posters, or other modes of presentation at least 30 days prior to submission. The Sponsor strongly discourages the publication of incomplete trial data.

Authorship of any publications will be based on the criteria of the International Committee of Medical Journal Editors (www.icmje.org).

11 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or its designee will conduct periodic monitoring visits during study conduct to ensure that the protocol and study requirements as well as Good Clinical Practices (GCPs) are being followed. The monitor will review source documents to confirm that the data recorded on eCRF are accurate. The Investigator and institution will allow the Sponsor monitor/auditors or its designee and appropriate regulatory authorities direct access to source documents.

During study conduct and/or after study completion, the study site may be subject to review by the IRB/EC and to quality assurance audits performed by the Sponsor or designee and to inspection by relevant regulatory authorities.

The Investigator or designee will notify the Sponsor, and/or its designee, immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with the Sponsor and/or its designee to prepare the study site for the inspection and will allow the Sponsor and/or its designee, whenever feasible, to be present during the inspection. The Investigator will promptly provide copies of the inspection findings to the Sponsor and/or its designee. Before submitting a response to the regulatory authorities, the Investigator will provide the Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

12 DATA HANDLING AND RECORD RETENTION

12.1 Electronic Case Report Forms

An eCRF should be completed for each included subject. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered into the eCRFs as well as any other data collection forms (source documents) and ensuring that these are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRF must be (electronically) signed by the Investigator to attest that the data contained on the eCRF are accurate. Any corrections to entries made in the eCRF or source documents must be dated, initialed, and explained (if necessary) and must be auditable.

12.2 Records Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRF, study source documentation and hospital records), all originally signed informed consent forms, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the Investigator according to the ICH guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or an independent third party arranged by the Sponsor. Study records must be kept for 15 years after completion or discontinuation of the study or for as required by applicable local regulations.

The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met. Requirements to prolong the retention time of records will be subject to an agreement with the clinical center.

13 REFERENCES

1. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in subjects with non-small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095 – 103, 2000

2. Borghaei H, Paz-Ares L, Horn L, et al: Nivolumab versus docetaxel in advanced nonsquamous non-small cell lung cancer. N Engl J Med 373:1627 – 1639, 2015

3. Rittmeyer A, Barlesi F, Waterkamp D, et al: atezolizumab versus docetaxel in subjects with previously treated non-small cell lung cancer (OAK): a phase 3, open-label, multicenter, randomised controlled trial. Lancet 373:255 – 265, 2017

4. Herbst RS, Baas P, Kim D-W, et al: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (JEYNOTE-010): a randomised controlled trial. Lancet 387:1540-1550, 2016

5. Barlesi F, Vansteenkiste J, Spigel D, et al: Avelumab versus docetaxel in subjects with platinum-treated advanced non-small cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncology 19:1468-1479, 2018

6. Hedlund G, Forsberg G, Nederman T et al: Tumor Targeted Superantigens, in Schmidt SR (ed): Fusion Protein Technologies for Biopharmaceuticals: Applications and Challenges First Edition. Hoboken, NJ, John Wiley and Sons, 2013, pp 365-381

7. Stern PL, Harrop R: 5T4 oncofoetal antigen: an attractive target for immune intervention in cancer. Cancer Immunol Immunother 66:415–426, 2017

8. Harper J, Lloyd C, Dimasi N et al: Preclinical evaluation of MEDI0641, a pyrrolobenzodiazepine-conjugated antibody–drug conjugate targeting 5T4. Mol Cancer Ther 16:1576-1587, 2017

9. Azulay M, Lifshits S, Fridman A, et al: NAP induces T cell recognition, turning anti-PD-1 unresponsive “cold” tumors into “hot” responsive tumors. Presented at the American Association of Cancer Research, Chicago, IL, April 14-18, 2018.

10. Sundstedt A, Celander M, Wallen Ohman M, et al: Immunotherapy with tumor-targeted superantigens (TTS) in combination with docetaxel results in synergistic anti-tumor effects. International Immunopharm 9: 1063-1070, 2009

11. Azulay M, Lifshits S, Shany E, et al. Selective T cell Redirection Proteins (STR) Enhance the Anti-Tumor Activity of Checkpoint Inhibitors (CPIs) and can Lead to Long-Lasting Immunity Against the Tumor. Presented at the SITC Annual Meeting November 2019.

12. Sundstedt A, Celander M, Eriksson H, et al. Monotherapeutically nonactive CTLA-4 blockade results in greatly enhanced antitumor effects when combined with tumor-targeted superantigens in a B16 melanoma model. J Immunother. 2012; 35 (4): 344-53.

13. Borghaei H, Alpaugh K, Hedlund G, et al: Phase I dose escalation, pharmacokinetics and pharmacodynamics study of naptumomab estafenatox alone in subjects with advanced cancer and with docetaxel in subjects with advanced non-small-cell lung cancer. J Clin Oncol 27:4116-4123, 2009

14. Tobinai K, Klein C, Oya N and Fingerle-Rowson G. A Review of Obinutuzumab (GA101), a Novel Type II Anti-CD20 Monoclonal Antibody, for the Treatment of Patients with B-Cell Malignancies. Adv Ther 34:324-356, 2017

15. Gazyva (obinutuzumab) prescribing information https://www.accessdata.fda.gov/spl/data/a4db57aa-aaf4-4714-97d5-b2daa6c67a73/a4db57aa-aaf4-4714-97d5-b2daa6c67a73.xml

16. NeoTX Data on File, in vitro experiment # 00082.

17. American Cancer Society, Cancer Facts and Figures 2020, https://www.cancer.org/research/cancer-facts-statistics.html.

18. Globocan 2018, https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf.

19. TAGRISSO® (osimertinib) Full Prescribing Information, https://www.azpicentral.com/tagrisso/tagrisso.pdf#page=1

20. Proto C, Ferrara R, Signorelli D, et al: Choosing wisely first line immunotherapy in non-small cell lung cancer (NSCLC): what to add and what to leave out. Can Treat Rev 75:39 – 51, 2019

21. Hawkins RE, Gore M, Shparyk Y, et al: A randomized phase II/III study of NAP + IFN alpha versus IFN alpha in renal cell carcinoma: Final analysis with baseline biomarker subgroup and trend analysis. Clin Cancer Res 22:3172-3182, 2016

22. Hervas-Stubbs S, Perez-Gracia JL, Rouzaut A, et al. Direct effects of type I interferons on cells of the immune system. Clin Cancer Res 2011;17:2619-2627. doi: 10.1158/1078-0432.CCR-10-1114. Epub 2011 Mar 3.

23. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638. Doi:10.1016/j.bbmt. 2018.12.758. Epub 2018 Dec 25.

24. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020; 21: 13531365

25. Galsky MD, Saci A, Szabo PM, et al. Nivolumab in patients with advanced platinum-resistant urothelial carcinoma: efficacy, safety, and biomarker analyses with extended follow-up from CheckMate 275. Clin Cancer Res 2020; 26: 5120-5128

14 APPENDICES

14.1 iRECIST Guidelines for Disease Evaluation

A detailed description of the iRECIST criteria may be found at the following:
Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18 (3): e143-e152.

14.2 CTCAE v5

The Common Terminology Criteria for Adverse Events (CTCAE) v5 may be found at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

14.3 Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Reference

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6):649-655.

14.4 Infusion Related Reactions and Cytokine Release Syndrome Grading (CTCAE v5)

Condition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-Related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention needed	Fatal

ASTCT Consensus Grading of CRS (23)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring vasopressors with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or[2]		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula[3], facemask, nonrebreather mask or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation

[1] Fever is defined as a temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and or hypoxia.

[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

14.5 Inhibitors and Inducers of CYP3A4

Strong Inhibitors	**Inducers**
Clarithromycin	Barbiturates
Indinavir	Brigatinib
Itraconazole	Carbamazepine
Ketoconazole	Efavirenz
Nefazodone	Enzalutamide
Nelfinavir	Modafinil
Saquinavir	Nevirapine
Ritonavir	Oxcarbazepine
Idelalisib	Phenobarbital
Ribociclib	Phenytoin
Telithromycin	Pioglitazone
	Rifabutin
	Rifampin
	St. John’s Wort
	Troglitazone

Source: Flockhart Table, https://drug-interactions.medicine.iu.edu/MainTable.aspx

CYP450 Sensitive Substrates

	Sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine
CYP2B6	bupropion[(a)]
CYP2C8	repaglinide[(b)]
CYP2C9	celecoxib[(c)]
CYP2C19	S-mephenytoin, omeprazole
CYP2D6	atomoxetine, desipramine, dextromethorphan , eliglustat[(e)], nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[(f)], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[(g)], midazolam, naloxegol, nisoldipine, saquinavir[(f)], simvastatin[(g)], sirolimus, tacrolimus, tipranavir[(f)], triazolam, vardenafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[(f)], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

14.6 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

14.7 COVID-19 Related Guidance

14.7.1 Guidance for Subjects on Study with COVID-19

Subjects who test positive for COVID-19, study treatment can be delayed for up to 2 weeks and may be resumed at the discretion of the investigator. This should be listed as COVID-19, in the adverse event listings.
Quarantined subjects due to possible exposure to COVID-19, should follow local policy for study visits and treatments. Every effort should be made to comply with the study protocol schedule.
Prior COVID disease details should be captured in the Medical History form. Vaccination information should be captured in Concomitant Medications form with standard terminology. Therefore, the patient should be asked by the treating physician if they just received or are planning to receive the Covid vaccine.

14.7.2 Recommendations for the study patients regarding COVID-19 Vaccines

These recommendations are based on Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States. The recommendations are as follows:

Considerations for timing of COVID-19 vaccination in relation to immunosuppressive therapies:

For timing of COVID-19 vaccination for immunocompromised patients, please refer to the CDC guidelines.

Reference: Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States; https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

14.8 Example for B cells quantitation Procedure

Collection:
Collect 5 ml blood in Cyto-Chex BCT tube. Samples will be stained and analyzed the same day received (most preferred) but can be performed up to 7 days from sample collection.

Reagents	Manufacturer	Catalog No.	Volume to use
CD45-Krome Orange	Beckman Coulter	BC-B36294	5µL
CD19-RPE	Beckman Coulter	BC-A07769	5µL
VersaLyse	Beckman Coulter	BC-A09777	1 mL

Staining samples:
Set up the following tubes for each sample.
Tube 1: CD45-KO + CD19-RPE

Staining Procedure:

- Adequately mix the sample before starting. Mix gently by inverting tube at least 8-10 times until all cells are thoroughly suspended
- Add 5 µL CD45, and 5 µL CD19 into a 15mL tube
- Pipet 100 µL of blood
- Incubate tube at RT in the dark for 30 minutes
- Add 1 mL Versalyse
- Vortex
- Incubate tube at RT for 10 minutes
- Centrifuge for 5 minutes 400g
- Decant supernatant
- Add 3 mL PBS and centrifuge for 5 minutes 400g
- Decant supernatant
- Add 600 µL PBS and vortex for 2-3 seconds
- Move the cells suspension into a proper 12X75 tube
- Samples are now ready for analysis on FACS Navius
- The FACS Navius is calibrated by the flow check protocol of the instrument
- The analysis will give the percentage of B cells out of Lympho absolute number
- In order to get the lympho absolute number perform a CBC count from the EDTA tube

Results values:

The results of the B-cells should be presented in percentages and absolute numbers. Please include in the report the result units (% and cells/microL) and the normal range.