TITLE: A Phase II Study of durvalumab (MEDI4736) in combination with a CSF-1R Inhibitor (SNDX-6352) Following Chemo or Radio-Embolization for Patients with Intrahepatic Cholangiocarcinoma

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Principal Investigator:	Lei Zheng, MD PhD 1650 Orleans St, Rm 351 Baltimore, MD 21287 [redacted]
Co-Principal Investigator:	Marina Baretti, MD 1650 Orleans St, CRB I 4M12 Baltimore, MD 21287 [redacted]
Regulatory Specialist:	Rose Parkinson, PhD [redacted]
Statistician:	Hao Wang, PhD [redacted]
Lead Research Nurse:	Sheila Linden, RN [redacted]
Program Manager:	Katrina Purtell [redacted]
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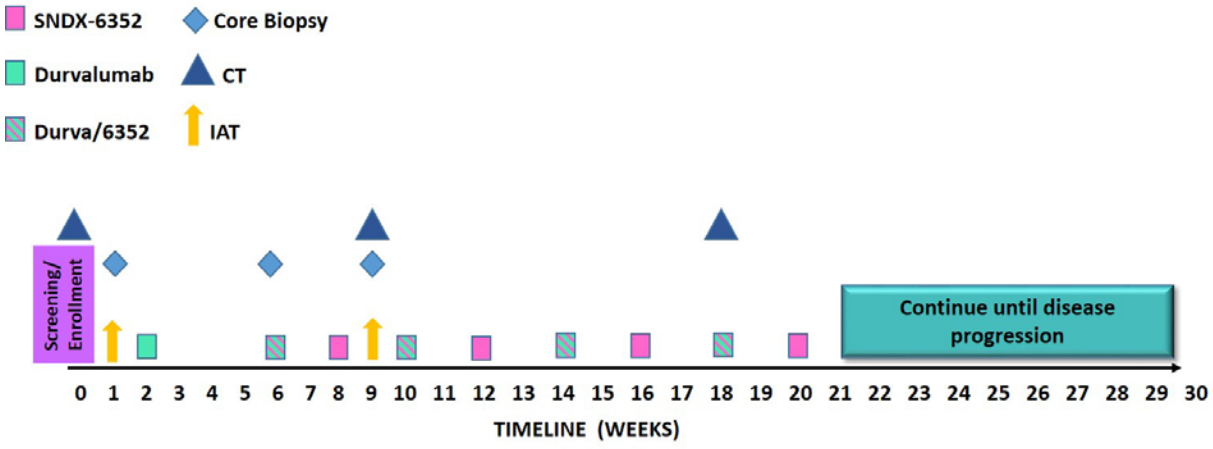
SCHEMA



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1. OBJECTIVES

1.1. Primary Objectives

1.1.1. To assess the objective response rate (ORR) in patients with intrahepatic cholangiocarcinoma receiving combination therapy with durvalumab and a CSF-1R inhibitor (SNDX-6352) after receiving intra-arterial therapy (IAT).

1.1.2. To determine the safety and feasibility of combination therapy with durvalumab and a CSF-1R inhibitor (SNDX-6352) in patients after receiving intra-arterial therapy (IAT).

1.2. Secondary Objectives

1.2.1. To determine the overall survival (OS) of patients with intrahepatic cholangiocarcinoma receiving combination therapy with durvalumab and a CSF-1R inhibitor (SNDX-6352) after receiving intra-arterial therapy (IAT).

1.2.2. To determine the progression-free survival (PFS) of patients with intrahepatic cholangiocarcinoma receiving combination therapy with durvalumab and a CSF-1R inhibitor (SNDX-6352) after receiving intra-arterial therapy (IAT).

1.2.3. To determine duration of response of patients with intrahepatic cholangiocarcinoma receiving combination therapy with durvalumab and a CSF-1R inhibitor (SNDX-6352) after receiving intra-arterial therapy (IAT).

1.3. Exploratory Objective

1.3.1. To assess correlative immunologic parameters in biopsy specimens, including PD-L1 expression.

1.3.2. To explore potential molecular determinants of response, progression, and disease stability using next generation sequencing and other sequencing techniques

1.4. Primary Endpoint

1.4.1. Efficacy Endpoint

- To assess object response using mRECIST criteria for patients receiving IAT followed by durvalumab/SNDX-6352

1.4.2. Safety Endpoints

- Grade 3 or higher toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 5.0)
- Incidence, nature and severity of all adverse events

1.5. Secondary Endpoints

1.5.1. Efficacy Endpoints

- Progression-free survival (PFS) of patients with intrahepatic cholangiocarcinoma receiving combination therapy with durvalumab and a CSF-1R inhibitor (SNDX-6352) after receiving intra-arterial therapy (IAT), defined as the time from the start of IAT until first documented evidence of disease recurrence or death.
- OS, defined as the time from the start of IAT until death from any cause.
- Duration of response among the patients who have objective response.

1.6. Exploratory study endpoints

1.6.1. Correlative Endpoints

- Granzyme B+ CD8 T cells. The change of Granzyme B+ CD8 T cells after single agent durvalumab vs after combination durvalumab/SNDX-6352 from the same patients, and the change compared to pretreatment biopsy of the same patient as the baseline.
- IHC, flow cytometry, quantitative PCR assays, microarray analysis, and next generation sequencing compared between pre- and post-treatment tumor specimens and research blood samples
- To assess correlation between immune parameters and clinical outcomes

1.7. Study Design

This is an open-label, single institution, single arm study of the combination of durvalumab and SNDX-6352 (axatilimab) in patients with intrahepatic cholangiocarcinoma undergoing intra-arterial therapy.

Up to 30 patients with unresectable intrahepatic cholangiocarcinoma will be selected to receive either trans-arterial chemo-embolization (cTACE) or radio-embolization (Y90) per defined criteria based on tumor size and location. A core biopsy will be performed at the beginning of this intra-arterial therapy (IAT) procedure. Immunotherapy will start one week following the first IAT procedure. During the first 28-day cycle of immunotherapy, durvalumab will be given on Day 1 as a single agent treatment. After cycle 1, a post-durvalumab single agent research biopsy will be performed. Beginning with the second cycle, durvalumab and SNDX-6352 combination therapy will be given on Day 1 (both drugs) and Day 15 (SNDX-6352 only) of each 28 day cycle. After cycle 2 (the first cycle during which patients will receive combination therapy), a post-durvalumab/SNDX-6352 research biopsy will be performed at the start of the second IAT procedure. After the second IAT procedure, additional cycles of durvalumab and SNDX-6352 combination therapy will be administered until disease progression.

Liver MRI will be performed before the first IAT (at screening) and before the second IAT (week 9). CT chest/abdomen/pelvis will be performed at screening, before the second IAT (week 9), prior to Cycle 5 immunotherapy (week 18), and approximately every 8 weeks thereafter to assess disease progression per mRECIST criteria. Patients may continue the immunotherapy if CT or MRI shows local progression until two IATs have been performed. After the second IAT, the patient will be taken off the study if local progression is confirmed at a subsequent scan or if any extrahepatic

disease progression has occurred. Objective response will be assessed as the best overall response during the study.

2. BACKGROUND

2.1. Disease Type

Cancer in the liver, both encompassing primary and metastatic liver carcinoma is one of the most prevalent malignancies. Biliary tract cancers (BTC) broadly includes tumors of the gallbladder, intrahepatic bile ducts (ICC), extrahepatic bile ducts, perihilar/distal bile ducts, and the ampulla of Vater have dismal 5 year survival rates ranging from 5-15%[1,2]. Of the nearly 10,000 diagnoses of BTC in the US annually, the majority present as advanced disease that is managed with intra-arterial therapy (IAT), including chemo- and radio-embolization as well as systemic chemotherapy[3]. ICC comprises 10-15% of worldwide primary liver malignancies and is the second most common primary liver malignancy after hepatocellular carcinoma (HCC) with varying worldwide incidence. In recent years, global incidence has been increasing[4]. SBRT is being increasingly utilized in management of BTC. Median overall survival after liver directed therapy is approximately 13.2 months[5]. Response rates in small studies with Y90 have been reported ranging from 12- 27%. The response rates from TACE have been challenging to compare since tumor necrosis is often reported as a response. However response rates have been reported ranging from 8.7-37%. Our group previously reported a retrospective analysis of 198 ICC patients who received IAT, including conventional transarterial chemoembolization (cTACE) (64.7%), drug-eluting beads (DEB) (5.6%), bland embolization (TAE) (6.6%), or yttrium-90 radio embolization (23.2%)[5]. The outcomes of this study will be compared to this historical control. In this historical control cohort, assessment of tumor response revealed complete or partial response in 25.5% patients, while 61.5% had stable disease; 13.0% had progressive disease. Furthermore, systemic therapy for advanced disease is not extremely effective. Standard first-line systemic chemotherapy (cisplatin and gemcitabine) provides median PFS and OS of 8.0 and 11.7 months, respectively[6]. Thus a better therapeutic strategy is necessary.

2.2. Anti-PD-1/PD-L1 blockade (Durvalumab [IMFINZI])

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation is not a new concept[7]. Evidence demonstrates a relationship between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. Specifically, the presence of $CD8^+$ T-cells and the ratio of $CD8^+$ effector T-cells / $FoxP3^+$ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant MEL and RCC. TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma[8,9].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors[10-13]. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only

detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues[12]. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC),[14] pancreatic carcinoma,[15] hepatocellular carcinoma,[16] and ovarian carcinoma[17]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant melanoma[18]. Clear correlation between PD-L1 expression in many solid malignancies with minimal expression in normal tissue suggests PD-L1 may be an efficacious target for anti-cancer therapy.

2.3. CSF-1R Inhibition (SNDX-6352)

SNDX-6352 is a humanized IgG4 monoclonal antibody (mAb) with high affinity against colony stimulating factor-1 receptor (CSF-1R) and is being developed for the treatment of neoplastic diseases. CSF-1R is expressed on cells of the mononuclear phagocyte lineage including immunosuppressive macrophages that accumulate within the tumor microenvironment. These tumor-associated macrophages (TAMs) are believed to play a key role in inhibiting anti-tumor T-cell immune responses while promoting tumor progression. High levels of TAMs have been shown to correlate with poor prognosis for certain cancers and preclinical studies have demonstrated that inhibition of TAMs can enhance anti-tumor immune responses. By binding to CSF-1R and blocking activation by its two known ligands, colony stimulating factor-1 (CSF-1) and interleukin-34 (IL-34), SNDX-6352 can affect the migration, proliferation, differentiation, and survival of TAMs. By targeting this key cellular player in the pathogenesis of cancer, SNDX-6352 has the potential to slow disease progression and increase the clinical benefit of anti-tumor immunotherapeutic approaches.

2.4. Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure [IB] for Preclinical and Clinical Data

2.5. Rationale

Systemic therapy targeting the immune system has had unprecedented success in solid tumors previously regarded as non-immunogenic, for example lung cancer[19]. Activated T cells can be functionally inactivated in tumor tissue by engagement of the programmed cell death 1 (PD-1) receptor with its ligand (PD-L1)[20]. PD-L1/PD-1 functions as a checkpoint which regulates the effector phase of T cell responses[21]. The degree of somatic mutations or "mutational burden" in solid tumors has been associated with response to immunotherapeutic agents. In non-small lung cancer, this association results in improved objective response, durable clinical benefit and improved PFS with anti-PD-1 therapy[22]. In addition, PD-L1 expression had been found to be upregulated in this specific subcategory of BTC[23].

For hepatobiliary cancers, IAT, through DNA damaging chemoembolization and radioembolization, is anticipated to generate more somatic mutations in the liver cancer cells and potentially induce neoantigens. Colony-stimulating factor 1(CSF-1) and its receptor CSF-1R regulate the migration, differentiation, and survival of macrophages[24]. In solid tumors, tumor-associated macrophages (TAM) secrete growth factors which release immunosuppressive cytokines which promote tumor growth and are associated with poor prognosis[25]. CSF-1R

inhibition in combination with chemotherapy in preclinical models has been shown to result in increased CD8+ T cells, TAM-derived interleukin-10 (IL-10) production and a reduction in tumor burden[26]. CSF-1R inhibition alone rarely produces a potent anti-tumor response but there is emerging evidence that CSF/CSF-1R blockade can reprogram TAMs and render tumors more susceptible to PD-L1/PD-1 blockade[27].

In vitro binding studies showed that SNDX-6352 is able to bind recombinant and native, cell expressed human CSF-1R. Cross-reactivity to cynomolgus monkey CSF-1R was demonstrated by flow cytometric analysis of monocytes and in protein binding experiments using BIAcore technology. The affinity was shown to be similar to human CSF-1R. Functional in vitro assays based upon the release of monocyte chemoattractant protein-1 (MCP-1) following stimulation of primary monocytes showed that SNDX-6352 was equipotent in both human and cynomolgus monkeys.

Hepatobiliary cancers are abundantly infiltrated with macrophages and M2-tumor associated macrophages (TAM) is associated with the risk of developing metastasis[28,29]. SNDX-6352 is a human IgG4 monoclonal antibody designed to target the CSF-1R. By binding to CSF-1R and blocking activation by its two known ligands, colony stimulating factor-1 (CSF-1) and interleukin-34 (IL-34), SNDX-6352 can affect the migration, proliferation, differentiation, and survival of TAMs. A phase 1 dose escalation study of SNDX-6352 has been conducted in patients with unresectable, recurrent locally-advanced or metastatic solid tumors and the recommended Phase 2 dose (RP2D is 3 mg/kg every 2 weeks (Q2W).

2.6. Potential risks of durvalumab and SNDX-6352

2.6.1. Overall Risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues. Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects, can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

2.6.2. Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent

inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections. For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB. In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Appendix E). A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.6.3. SNDX-6352 monotherapy and in combination with durvalumab

A detailed summary of SNDX-6352 monotherapy AE data can be found in the current version of the SNDX-6352 Investigator Brochure Version 7, 20 Dec 2019.

2.7. Rationale for fixed dosing durvalumab

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (AUC_{ss},0-28, $Cmax_{ss}$, and $Cmin_{ss}$) using the population PK model. A fixed dose of 750 mg Q2Wwas selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady state Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W.

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

3. PATIENT SELECTION

3.1. Eligibility Criteria for enrollment into study

3.1.1. Have cytologically confirmed intrahepatic cholangiocarcinoma.

3.1.2. All disease must be localized to the liver (locally advanced).

3.1.3. Be a candidate for conventional transarterial chemoembolization or yttrium-90 radioembolization, the two most common modalities of IAT.

3.1.4. Have measurable disease by mRECIST. Measurable disease will be confirmed by radiological imaging (MRI, CT).

3.1.5. Age ≥18 years at time of study entry.

3.1.6. Body weight > 30 kg.

3.1.7. ECOG (World Health Organization) performance status 0-1 (**Appendix A**)

3.1.8. Life expectancy ≥12 weeks.

3.1.9. Adequate normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,500 cells/mm^3
- Hemoglobin ≥ 8 g/dL
- Platelets ≥ 100,000 cells/mm^3
- Serum creatinine < 1.5 x ULN
- AST and ALT < 2 x ULN
- Total bilirubin ≤ 1.5 x ULN**
- PT or INR ≤ 1.5 x ULN
- Albumin ≥ 2.8 g/dL
- Child Pugh Class A
- Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males: $\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$

Females: $\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$

**Subjects with Gilbert's Syndrome should have direct bilirubin within normal institutional limits.

3.1.10. Evidence of either post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients.

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 or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, hysterectomy, or tubal ligation).
- 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, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, hysterectomy, or tubal ligation).

If the urine test is positive or cannot be confirmed as negative, a negative serum pregnancy test will be required for the patient to be eligible. If patient has a positive serum pregnancy test, then an ultrasound must be done to rule out pregnancy in order to enroll on trial.

3.1.11. Men and women of child bearing potential must be willing to use an adequate method of contraception starting with Visit 1 through 120 days after the last dose of study therapy. Note: Complete abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.1.12. Capable of giving signed informed consent including compliance with the requirements and restrictions listed in the informed consent form.

3.1.13. Patient is willing and able to comply with the protocol for the duration of the study including treatment, scheduled visits and examinations, and follow up.

3.2. Exclusion Criteria

3.2.1. Candidate for surgical resection.

3.2.2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up of an interventional study.

3.2.3. Patients who have had major surgery 28 days prior to first dose of the study drug excluding minor procedures (dental work, skin biopsy, etc.), celiac plexus block, and biliary stent placement.

3.2.4. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization,

monoclonal antibodies) ≤ 14days prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca, MedImmune, Syndax, and the investigator.

3.2.5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, neuropathy and the laboratory values defined in the inclusion criteria

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or SNDX-6352 may be included only after consultation with the Study Physician.

3.2.6. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

3.2.7. History of allogenic organ transplantation.

3.2.8. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, checkpoint inhibitor-induced immune mediated reaction or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia.
- Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.
- Any chronic skin condition that does not require systemic therapy.
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
- Patients with celiac disease controlled by diet alone.

3.2.9. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

3.2.10. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

3.2.11. History of leptomeningeal carcinomatosis.

3.2.12. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with IV contrast of the brain prior to study entry.

3.2.13. History of active primary immunodeficiency.

3.2.14. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

3.2.15. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or SNDX-6352. The following are exceptions to this criterion:
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

3.2.16. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

3.2.17. Female patients who are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study drug.

3.2.18. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

3.2.19. Prior randomization or treatment in a previous durvalumab and/or SNDX-6352 clinical study regardless of treatment arm assignment.

3.2.20. Patients with prolonged heart rate-controlled QTc measurements (using Fredericia's formula), defined as $\geq$ 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval may be permitted with approval

of the medical monitor.

3.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

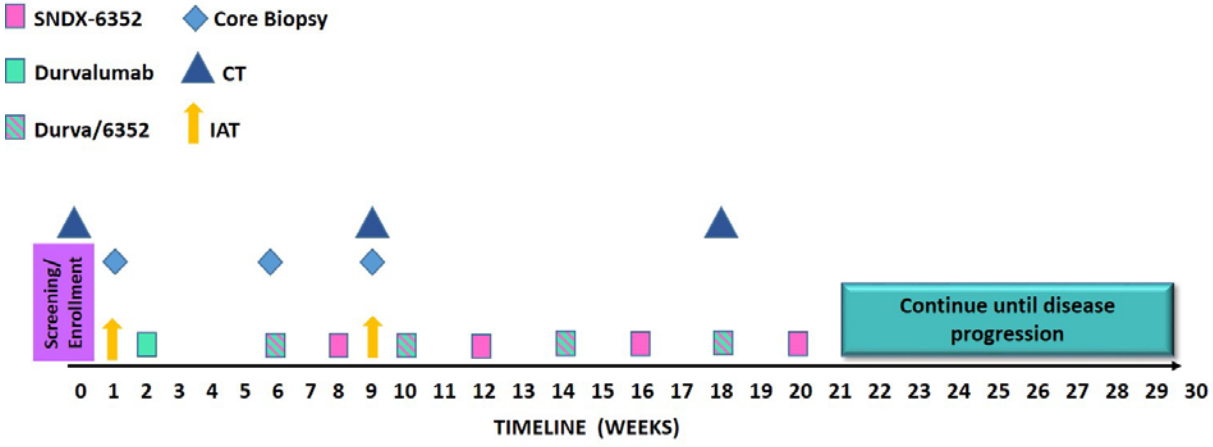
4. TREATMENT PLAN

4.1. Agent Administration

Treatment will be administered on an outpatient basis. Dosing delays are described in **Section 5.2**. Subjects will initially receive one 28-day cycle of single agent treatment with durvalumab on cycle 1 day 1 (week 2). In subsequent cycles, patients will receive durvalumab on day1 and SNDX-6352 on days 1 and day 15 of each 28-day cycle. Patients will continue 28-day cycles of the combination therapy until disease progression.

Patients will undergo intra-arterial therapy (IAT) with biopsy prior to start of cycle 1 immunotherapy (week 1) and after completion of cycle 2 (week 9). An additional biopsy will be performed prior to cycle 2 (week 6) treatment. An interventional radiologist in the study team will determine whether the patient is a candidate for chemo- vs. radio-embolization based on imaging criteria specified below. The determination on which type of IAT the patient should receive is not a randomization process, but is made according to the criteria below. Every subject will receive at least two IAT treatments, each approximately 8 weeks apart. Whether the patients should receive additional IAT treatments will be at the discretion of interventional radiologists. All IAT treatments an individual patient receives will be the same type (Y90 or cTACE).

Criteria for selecting method of Intra-Arterial Therapy (IAT)



Y90 (radio-embolization): MRI imaging with any of the following criteria:

- Multifocal disease with ≥ 6 lesions
- Bilobar location
- Size ≥ 6 cm

cTACE (Chemo-embolization): MRI imaging with any of the following criteria:

- Unifocal or multifocal disease < 6 lesions.
- Size < 6 cm

Table 1: Study Regimen (listed in order of administration)

Agent	*Premedications*	*Dose*	*Route*[1]	*Schedule*
Durvalumab	No prophylactic pre-medications unless indicated by previous experience in an individual subject	1500 mg	IV over 60 minutes	Day 1 of each 28-day cycle (Q4W)
SNDX-6352	No prophylactic pre-medications unless indicated by previous experience in an individual subject	3mg/kg	IV over 30 minutes	Day 1 and 15 of each 28-day cycle (Q2W) starting at cycle 2[2] Not given at cycle 1

[1] Infusion times are approximate (-5min/+10 min) and may need to be adjusted based on subject tolerability.

[2] **If treatment with SNDX-6352 and durvalumab produces recurrent (second occurrence), asymptomatic Grade 3 elevation in CK, without evidence of end organ damage, consider dosing SNDX-6352 every 4 weeks after consultation with sponsor.**

If retreatment with SNDX-6352 and durvalumab subsequently produces Grade 3 elevation in CK (third occurrence), permanently discontinue SNDX-6352 and consider starting durvalumab monotherapy after consultation with sponsor.

4.1.1. Durvalumab (IMFINZI)

Durvalumab will be administered as outlined in Table 1 above.

Subjects should be observed for a minimum of 30 minutes after administration of durvalumab, prior to the administration of SNDX-6352.

4.1.2. CSF1R inhibitor SNDX-6352

The dose amount required to prepare the SNDX-6352 infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing. If the patient experiences either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated. For weight change < 10%, the decision to recalculate the SNDX-6352 dose can be in accordance with institutional practice.

A mandatory 2-hour observation period after each SNDX-6352 infusion (for potential infusion-related reactions) is only required following the first 4 SNDX-6352 infusions. If no infusion reaction occurs in relation to the first 4 infusions, the post-infusion observation period may be discontinued at investigator's discretion. Patients who experience an infusion-related reaction at any point, must continue to undergo the mandatory observation after each infusion.

SNDX-6352 must be administered in a setting with immediate access to emergency medical equipment and medications to manage potentially life-threatening infusion reactions (e.g., anaphylaxis). Medications such as steroids (e.g., dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (e.g., IV antihistamines), bronchodilators, or equivalents, and oxygen should be immediately accessible.

4.2. General Concomitant Medication and Supportive Care Guidelines

4.2.1. Durvalumab

Durvalumab is a humanized monoclonal antibody. Subjects should be closely monitored for potential adverse reactions during antibody infusion and potential adverse events throughout the study.

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

4.2.1.1. Infusion Reactions

Durvalumab infusion are rare occurrences. Reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with durvalumab are shown below in **Table 2**.

Table 2: Guidance on Infusion and Hypersensitivity Reactions for durvalumab

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of durvalumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.2.2. SNDX-6352

It is recommended that patients receiving SNDX-6352 should be monitored for serum levels of CK; markers of liver function (e.g., levels of transaminases, LDH, bilirubin, coagulation disorders); muscle function; bone function; and signs indicative of inflammation (e.g., leukocyte alterations, C-reactive protein) and facial/periorbital swelling.

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

4.2.2.1. Infusion Reactions

As with other monoclonal antibodies, infusion-related reactions to SNDX-6352 may occur. Monitor patients during and following the infusion for signs and symptoms of infusion-related reactions from the start of the infusion until at least 1 hour after the end of the infusion, in an area containing resuscitation equipment and medications necessary for advanced life support and cardiopulmonary resuscitation. For Grade 1 or 2 infusion-related reactions, adjust SNDX-6352 dose per **Table 3**. Immediately and permanently discontinue SNDX-6352 for Grade 3 or 4 infusion- related reactions.

Table 3: Guidance on Infusion and Hypersensitivity Reactions for SNDX-6352

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	The infusion rate should be decreased by 50% for the duration of the infusion. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Additional pre-medication may be administered at the investigator's discretion.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	**The infusion must be stopped until resolution** to Grade ≤1; the infusion may then be resumed at 50% of the prior infusion rate. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Subject may be pre-medicated 1.5h (± 30 minutes) prior to infusion of SNDX-6352 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Additional pre-medication may be administered at the investigator's discretion.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.2.3. Immune-Related Adverse Events (irAEs) for durvalumab and SNDX-6352

Immune-related AEs (irAEs) are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Complete Algorithms for managing all irAEs are found in **Appendix E**.

The toxicity management written in the protocol supersede the toxicity management for individual agents.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to durvalumab and SNDX-6352, respectively.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

4.2.4. Prohibited and Restricted Therapies

Patients may not use any of the following agents during the study:

- Any non-study anticancer or immunotherapy agent (investigational or non-investigational)

- Any other investigational agents
- Any other immunotherapy treatment, including, but not limited to: IL-2, interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments. (See **Section 5.2** for dosing delays for steroids). Further, if patients require high dose steroids, while on study, durvalumab can be re-administered if the steroids are tapered over a 12-week period. The use of physiologic doses of corticosteroids may be approved after consultation with the IND Sponsor. Premedication with steroids for CT contrast allergy will be allowed if patient is unable to undergo MRI.
- Filgrastim (Neupogen® or G-CSF) or sargramostim (Leukine® or GM-CSF)

Patients should not donate blood while participating in this study and for at least 90 days following the last infusion of durvalumab or SNDX-6352.

4.3. Definition of an Overdose for this Protocol

Overdose will be defined as a patient receiving (accidentally or intentionally):
- ≥5 times the indicated dose of durvalumab or
- 15% more than the recommended dose of SNDX-6352

No specific information is available on the treatment of overdose of durvalumab and SNDX-6352. In the event of overdose, durvalumab or SNDX-6352 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse experience is associated with (results from) the overdose of test drug or vaccine, the adverse experience is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse experience must be reported within 24 hours to the IND Sponsor, JHMI IRB (contact information can be found in **Section 6.6.1)**.

4.4. Contraception, Use in Pregnancy, Use in Nursing

4.4.1. Contraception

The investigational agents may have adverse effects on a fetus *in utero*. Furthermore, it is not known if the investigational agents have transient adverse effects on the composition of sperm.

Given the potential risk related to pharmacologically-mediated inhibition of the PD-1 pathway, no reproductive or developmental toxicity studies were conducted with durvalumab. SNDX-6352 has also not been studied in pregnant women and must not be given to patients who are pregnant. Furthermore, animal reproduction studies have not been conducted with SNDX-6352. Therefore, potential effects of SNDX-6352 use during pregnancy are not known and the potential for developmental toxicity cannot be excluded.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by agreeing to use (or have their partner use) acceptable contraception during heterosexual activity. Complete abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):
- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):
- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or

progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.4.2. Use in Pregnancy

The investigational agents may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a patient inadvertently becomes pregnant while on treatment with combination immunotherapy, the patient will immediately be removed from the study. The pregnancy and outcome of the pregnancy of a patient or patient's partner will be reported per **Section 6.6.1.**

4.4.3. Use in Nursing Women

It is unknown whether the investigational agents are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

4.5. Unacceptable Toxicities

Unacceptable toxicities are defined as any AE that is temporally related to study drug administration and is not due to the subject's underlying malignancy and for which there is no clear evidence for an alternative etiology and meets one of the following NCI CTCAE criteria:

Hematologic Toxicities

- Grade 4 anemia
- Grade 3 or 4 neutropenia lasting ≥ 14 days
- Grade ≥ 3 neutropenia with fever
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with clinically significant bleeding

Non-Hematologic Toxicities

- Treatment-related ≥ grade 4 AEs
- Grade 3 Pneumonitis
- Grade 3 Nephritis

- Grade 3 elevated LFTs that do not improve to ≤ grade 2 after holding study drugs for two weeks.
- Grade ≥ 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ grade 1 severity within 2 weeks of starting therapy, or requires systemic therapy
- Any other Grade ≥ 3 toxicity that do not improve to ≤ grade 2 under therapy within 2 weeks except for the following:
    - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 1 within 7 days, with or without appropriate supportive therapy
    - Grade ≥ 3 rash that resolves to Grade ≤ 2 within 7 days
    - Grade 3 fatigue that resolves to ≤ Grade 2 within 14 days
    - Grade ≥ 3 laboratory abnormalities that, in the judgment of the investigator, are not clinically significant
    - Asymptomatic amylase/lipase elevation

The unacceptable toxicity definition **excludes** the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Isolated asymptomatic Grade 3 AST that is accompanied by Grade ≤1 ALT and total bilirubin (TB), and no changes from baseline of ALT or TB.
- Asymptomatic Grade 3 CK for which diagnostic evaluation (per guidelines in Appendix E) shows no evidence of end organ damage and it reduces to Grade 2 within 14 days of holding SNDX-6352.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 lymphopenia
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Grade 3 fever lasting ≤ 24 hours with or without medical therapy and is not considered an SAE

Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.

In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as an unacceptable toxicity. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.

The proportion of unacceptable toxicities will be monitored throughout the study. See **Section 12.3** for study stopping requirements due to toxicity.

Unacceptable toxicities require patient discontinuation from study treatment (see **Section 4.6** for complete list of criteria requiring treatment discontinuation).

4.6. Criteria for Removal from Study Treatment

Patients will be removed from study treatment when any of the criteria listed below applies. The reason for study treatment removal and the date the patient was removed must be documented in the Case Report Form.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Patient is lost to follow-up.

A subject must be discontinued from treatment (but may continue to be monitored in the post-treatment follow-up portion of the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Development of local recurrence or distant metastatic disease. Patients may continue to receive treatment after local recurrence until progression is confirmed on subsequent scans.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) (see **Section 4.5**)
- Investigator's decision to withdraw the subject
- Life-threatening durvalumab or SNDX-6352-related AE(s) per **Appendix E**
- Inability to reduce corticosteroid dose for immune-related adverse reactions to ≤10 mg prednisone or equivalent per day up to 30 days duration
- Patient's weight falls to ≤ 30 kg
- If in the opinion of the Investigator, a change or temporal or permanent discontinuation of therapy would be in the best interest of the patient. The IND Sponsor should be included in this decision
- Noncompliance with trial treatment or procedure requirements
- Patient becomes pregnant

4.7. Off Study/Safety Follow-up Visit

After a patient is discontinued from treatment, a mandatory Off Study/Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication (or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first). Procedures and assessments performed at this visit and beyond should follow the respective guidelines described in **Section 9**. The patient will be monitored for adverse events up to the mandatory Off Study/Safety Follow-Up Visit or to resolution of toxicity to Grade 0-1, whichever occurs later. Serious Adverse Events (SAEs) that occur within 90 days of the last infusion of durvalumab or before initiation of a new antineoplastic treatment should also be followed and recorded.

4.8. Duration of Follow Up

Subjects who discontinue from treatment should continue to follow up with their primary oncologist and be contacted every six months (with a +/- 1 month window) to monitor OS and for potential disease progression. Radiology reports may be collected for patients who came off study for reasons other than cancer progression. Information of other cancer therapies after discontinuation from the study treatment will be collected.

Subjects who are discontinued from the study treatment due to an unacceptable drug-related AE will be monitored for safety until the resolution of the AE to ≤ grade 1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first.

All subjects will be followed for at least 30 days after their last dose of study drug for the development of AEs. SAEs that occur within 90 days of the last infusion of durvalumab or before initiation of a new antineoplastic treatment should also be followed and recorded.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1. Dose Modifications

Dose reduction or dose increase of durvalumab or SNDX-6352 will not be permitted.

5.2. Dosing Delays

When the dosing of durvalumab is delayed, the dosing SNDX-6352 must also be delayed, and vice versa. Dosing may be held for up to 1 week. In this case, subsequent cycles should continue given that the dosing is a minimum of 2 weeks apart and they have not experienced an AE(s) necessitating discontinuation. If delayed more than 1 week, the Principal Investigator must be contacted for further instructions on continued treatment.

Durvalumab and SNDX-6352 will be withheld for suspected drug-related toxicities and severe or life-threatening AEs as per **Appendix E**. Additional guidance for toxicity management can be found in **Appendix E.**

Dosing of study therapy will be delayed if the following laboratory criteria are not met:

Absolute neutrophil count	≥ 1,000 cells/mm^3
Hemoglobin	≥ 8 g/dL
Platelets	≥ 50,000 cells/mm^3
Serum creatinine	≤ 1.5 x ULN
CPK[1]	≤ 5 x ULN (or ≤ 2.5 x ULN with clinical or lab signs of end organ damage / increased urine or serum myoglobin)
AST and ALT[2]	≤ 3.0 x ULN
Total bilirubin	≤ 1.5 x ULN

In case toxicity does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of study drug, study therapy discontinuation should be considered after discussion with the

Principal Investigator and IND Sponsor. With IND Sponsor and Drug Sponsor agreement, patients still at Grade 2 may continue in the study only if asymptomatic and controlled.

Two dosing delays due to the same toxicity will be permitted. In the event of a third occurrence of the same toxicity which would require dosing delay, study therapy will be discontinued permanently.

1. SPECIAL NOTE FOR ELEVATED CK: If retreatment with SNDX-6352 and durvalumab produces recurrent (second occurrence) asymptomatic Grade 3 elevation in CK, without evidence of end organ damage, consider dosing SNDX-6352 every 4 weeks after consultation with sponsor. If retreatment with SNDX-6352 and durvalumab produces recurrent (third occurrence) Grade 3 elevation in CK, permanently discontinue SNDX-6352 and consider starting durvalumab monotherapy after consultation with sponsor.

2. SPECIAL NOTE FOR ELEVATED AST: Patients who develop isolated Grade 2 AST elevation (i.e. without concurrent ALT or bilirubinemia to suggest a liver source of transaminase) may continue dosing with combined immunotherapy of durvalumab and SNDX-6352 since this elevation is thought to be due to pharmacodynamics effect rather than direct muscle toxicity. However, if there is grade 2 AST elevation with concurrent ALT or bilirubin elevation, then adjust treatment was written in Appendix E for grade 2 AST, ALT, bilirubin abnormality.

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

The PI has the primary responsibility for continuous internal monitoring for safety, protocol compliance, and identification, grading, coding, and required reporting of all anticipated and unanticipated adverse events and protocol problems. Although this responsibility is usually shared among the PI, research nurse, and data manager, the PI is ultimately responsible for grading and attribution of all events.

6.1. Definitions

6.1.1. Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory

findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator, requires the participant to have a study drug discontinued or interrupted, or requires the participant to receive corrective therapy.

6.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) > 24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

Events **not** considered to be serious adverse events are hospitalizations for the:

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

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.1.3. Events of Clinical Interest (ECI)

Events of clinical interest for this trial include:

- An overdose of study drug, as defined in **Section 4.3**, that is not associated with clinical symptoms or abnormal laboratory results.
- Hy's Law: AST or ALT ≥3X ULN and total bilirubin ≥2X ULN and, at the same time, an alkaline phosphatase < 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

If the Investigator has any questions in regards to an event being an ECI, the Investigator should promptly contact the Study Physician.

6.1.4. Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the Investigator. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases

- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.
- Infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix E). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator

Reporting forms are found in Appendices B and C.

6.2. Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

6.3. Grading

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's CTCAE (Version 5.0) and graded as shown below:

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

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

6.4. Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

6.5. Handling of Expedited Safety Reports

In accordance with local regulations, the IND Sponsor will notify investigators of all SAEs that are unexpected (i.e. not previously described in the Investigator Brochure), and definitely, probably, or possibly related to durvalumab or SNDX-6352. This notification will be in the form of an expedited safety report (ESR) that is to be faxed to the investigators and the study coordinators. Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and where required by local regulations, the investigator will submit the ESR to the appropriate IRB. The investigator and IRB will determine if the informed consent

requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.

6.6. Reporting

6.6.1. General

All adverse events will be collected from the first dose of the investigational agent through 30 days after the last dose of study drug, unless related to the investigational agents. Subjects who have an ongoing adverse event related to the investigational agents may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator. All adverse events (both expected and unexpected) will be captured on the appropriate study-specific Case Report Forms (CRFs).

All Serious Adverse Events (SAEs) will be collected and reported from the first dose of investigational agent through 90 days after the last dose of study drug or until a new anti-cancer treatment is initiated, whichever occurs first. All SAEs, regardless of relatedness to study drug, must be reported to the IND Sponsor, AstraZeneca, and Syndax within 24 hours of recognition using the form found in **Appendix C**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

ECIs will be collected and reported from the first dose of study drug through 30 days after the last dose of study drug or within 7 days prior to initiation of a new anti-cancer treatment, whichever comes first. ECIs must be reported within 24 hours to the IND Sponsor, AstraZeneca, and Syndax using the Adverse Event of Clinical Interest Case Report Form found in **Appendix B**. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports, ECI reports, and any other relevant safety information are to be sent to:

IND Sponsor (Lei Zheng): [redacted]
AstraZeneca: [redacted]
Syndax: [redacted]

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up

As soon as relevant information is available, a follow-up SAE report will be submitted to the IND Sponsor, AstraZeneca, and Syndax.

Any serious and unexpected adverse events that require expedited FDA reporting in accordance with 21 CFR 312.32, will concurrently be reported to AstraZeneca and Syndax.

A copy of the MedWatch report must be emailed to AstraZeneca and Syndax at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca and Syndax at the same time.

A ***cover page*** should accompany the ***MedWatch*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca/Syndax ISS reference number (ESR-16-11978)

Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

6.6.1.1 Deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported to AstraZeneca and Syndax as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca and Syndax as a SAE within **24 hours** as described above. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor, AstraZeneca/MedImmune, and Syndax Drug Safety.

6.6.1.2 Overdose

An overdose is defined in Section 4.3 of this protocol. Any overdose of a study drug is required to be reported within 24 hours of knowledge of the event to the IND sponsor, AstraZeneca/ MedImmune, and Syndax Patient Safety.

If an overdose of study drug is taken without any associated clinical symptoms or abnormal laboratory results, the overdose will be reported as a non-serious Event of

Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

If an AE is associated with (results from) an overdose of study drug, the overdose will be reported as a serious adverse experience, even if no other criteria for serious are met. Any AE resulting from an overdose must also be recorded in the AE log. Overdose does not automatically make the associated AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE.

There is currently no specific treatment in the event of an overdose of durvalumab or SDNX-6352. The investigator will use clinical judgment to treat any overdose.

6.6.1.3 Hepatic function abnormality

Hepatic function abnormality that fulfills the criteria of a potential Hy's Law case (see criteria in Section 6.1.3) , with or without associated clinical manifestations, is required to be reported as an ECI ("hepatic function abnormal") ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca and Syndax Patient Safety authorities using the contact information described above, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.

If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune and Syndax.

6.6.1.4 Pregnancy

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself or pregnancy of the patient's partner is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. 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 patient was discontinued from the study. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca and Syndax representatives

within **24 hours** of when he or she becomes aware of it. The designated AstraZeneca and Syndax representatives will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca and Syndax Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

Where a report of pregnancy in a patient's partner is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

6.6.2. Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC)

All serious adverse events will be reported to the IRB per institutional guidelines. Follow-up information will be submitted to the IRB as soon as relevant information is available.

6.6.3. Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the IND Sponsor.

6.6.3.1. Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed ( ) to the FDA within 7 calendar days of first learning of the event.

15 Calendar-Day Written Report:

The IND Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports. Follow-up information will be submitted to the FDA as soon as relevant information is available.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event.

6.6.3.2. IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

7. PHARMACEUTICAL INFORMATION

7.1. Durvalumab (IMFINZI)

7.1.1. Agent Accountability

The IND Sponsor or the Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.1.2. Mode of Action

Durvalumab is a highly selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Durvalumab is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region.

[redacted]

7.1.8. Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received, the amount administered to patients, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

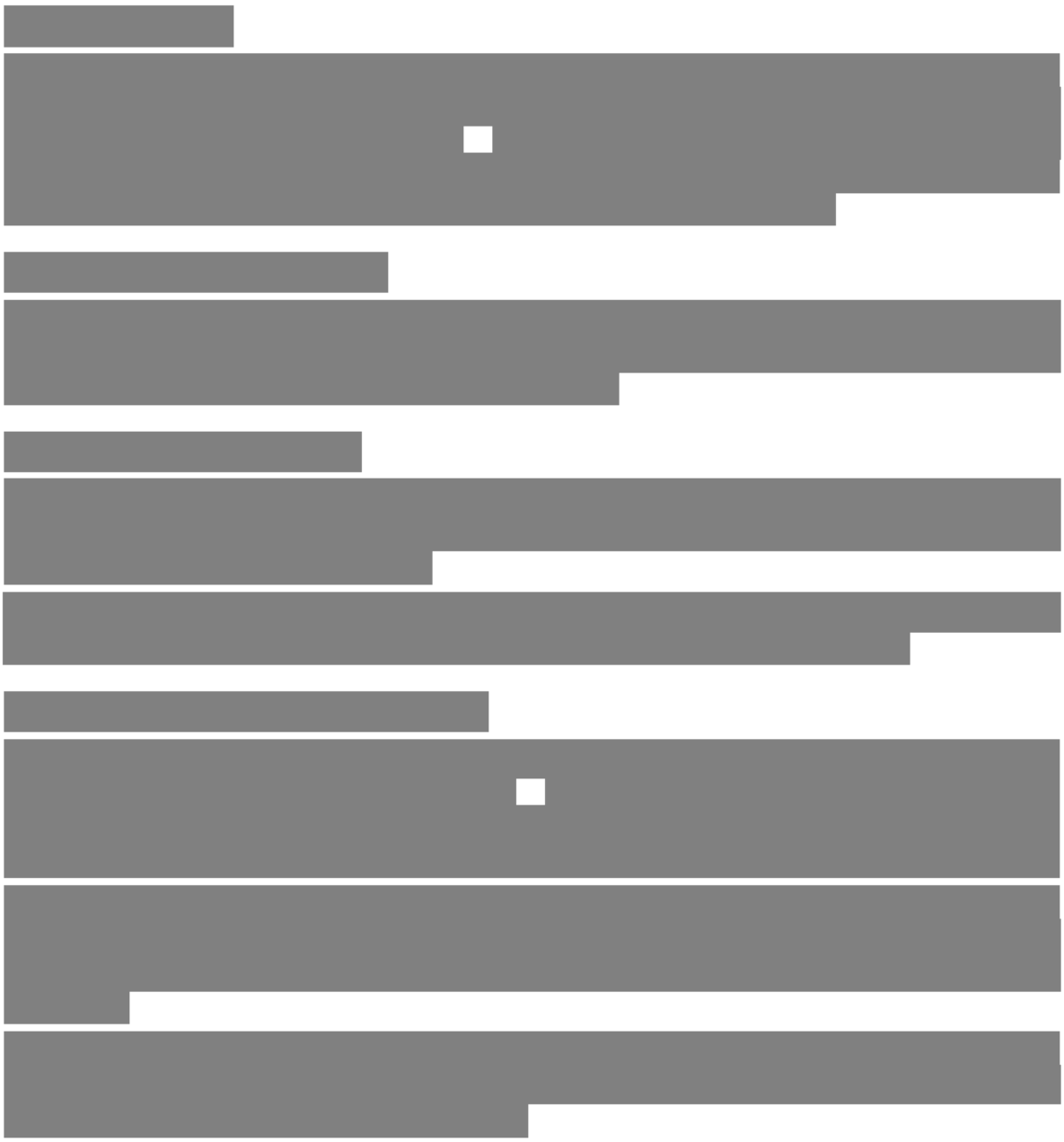
7.2. SNDX-6352

7.2.1. Agent Accountability

The IND Sponsor or the Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.2.2. Mode of Action

SNDX-6352 is a humanized IgG4 monoclonal antibody designed to target the colony stimulating factor-1 receptor (CSF-1R) to block the interaction between the CSF-1R and its ligand colony stimulating factor 1 (CSF1).



7.2.8. Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to subjects, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8. CORRELATIVE/SPECIAL STUDIES

8.1. Tumor and Immune Biology Correlative Studies

We will conduct correlative studies in further understanding the role of anti-PD-1 and anti-CSF1R antibody treatments in modulating tumor biology and immune biology, which will include, but not limited to the following objectives. One important goal of the clinical trial is to assess the effects of anti-PD-L1 antibody in combination with SNDX-6352 on the PD-L1/PD-1 and PD-L1/PD-1 associated pathways, M1 vs. M2 tumor-associated macrophages (CD68/iNOS vs. CD68/CD163), Th1 vs. Th2 vs. Th17, and Teff vs. Treg, and granzyme B+ CD8 T cells.

8.1.1. Multiplex Immunohistochemistry

Multiplex IHC of immune parameters including PD-L1 and PD-1 and a comprehensive analysis of tumor microenvironment will be performed on FFPE slides of pre-treatment and post- treatment core biopsy specimens using a previously established protocol[30]. We will examine the densities and distribution of effector T cell (Teff) markers including CD8 and Granzyme B, expression of immune suppressive signals including PD-1, PD-L1, and IDO1, immune activation signals including CD137(4-1BB) on T cells, and macrophage markers as described below, and the expression of T helper cell differentiation markers including Tbet (for Th1), GATA3 (for Th2), RORγT (for Th17), and Foxp3 (for Treg). Quantification of IHC on immune markers will be conducted as described previously[30] and will be supervised by our pathologist (Dr. Elizabeth Thompson).

8.1.2. Monocyte/Myeloid cell Response to CSF-1R inhibition

The response to CSF-1R inhibition can be measured using serum CSF-1 levels using ELISA and observing whether changes in their levels correlate with clinical response to CSF-1R inhibition. In addition, levels of CD14 (dim) CD16 (+) monocyte subsets in peripheral mononuclear cells can be measured using flow cytometry and also correlated with clinical response. Intratumoral response to CSF-1R inhibition will be measured by IHC of monocytes/macrophages (M1 vs. M2, DC, etc.) as described previously[30] on the FFPE slides of pre- and post-treatment biopsy specimens.

8.1.3. T cell Response to CSF-1R inhibition

Explorative Peripheral and Tumor-infiltrating T cell Repertoire Analysis: As part of explorative studies, we will also use next-generation sequencing to examine the T cell receptor (TCR) repertoire expressed by TIL prior to versus post durvalumab/CSF1Ri treatment and to compare with peripheral blood lymphocytes (PBL). We will determine if T cells in PBL undergo clonal expansion following the treatment, whether treatment-expanded T cell clones traffic to the TME.

Through our Next-Generation Sequencing CORE, whole exome sequencing (WES) will be performed on paired patient tumor and normal DNA isolated from FFPE tumor tissue and cryopreserved PBL respectively to identify tumor-specific non-synonymous mutations. RNA sequencing will be performed in parallel to confirm expression of mutant genes identified by WES. Expressed nonsynonymous mutations will be screened for candidate neoepitopes

using NetMHC HLA-binding predictions and a NetMHC cutoff binding score of 500. Predictions will be made for each tumor-matched HLA class I and class II molecule. We will determine whether the total number of expressed mutations, and/or the total number of predicted neoepitopes for each patient's tumor correlates with improved overall or disease-free survival.

Tumor antigen-specific T cells that traffic into the tumor are the most relevant T cells to study when evaluating antitumor immune responses. We will use a more comprehensive approach and examine the TCR repertoire in PBL and TIL using a next-generation sequencing approach established by Adaptive Biotechnologies. Using Adaptive's approach, we will specifically sequence the complementarity-determining region 3 (CDR3) of the TCR beta chain variable segment (TCR Vbeta). Sequencing will be performed on genomic DNA isolated from cryopreserved PBL and FFPE tumor tissue specimens. We will compare TCR repertoires in pre vs. post durvalumab/CSF1Ri treatment PBL and in pre- vs. post-treatment biopsy specimens from the same patients to identify TCR's expressed by T cells that expand following treatment. We will also compare TCR repertoires in PBL vs TIL from the same patients to identify any T cell clones that are induced or expanded in PBL by CSF-1R/PD-L1 blockade and also enriched in TIL. We will use these data to determine if T cells in PBL and TIL undergo clonal expansion following CSF-1R/PD-L1 blockade treatment, and if so, whether the treatment-expanded T cell clones traffic to the TME.

8.1.4. Plasma collection for ctDNA analysis

Plasma will be collected and stored for circulating tumor DNA (ctDNA) measurement and comparison.

8.2. Diagnostic Tissue Samples

Tissue, fluid, or blood may be collected from standard of care procedures used to treat or diagnoses immune related toxicities.

9. STUDY SCHEDULE

Procedure	Screen	IAT 1	Cycle 1 D1	Cycle 1 D15	Cycle 2 D1	Cycle 2 D15	Cycle 2 D22	Cycle 3 D1	Cycle 3 D15	Cycle 4 D1	Cycle 4 D15	Repeat through end of treatment Cycle 5 D1	Repeat through end of treatment Cycle 5 D15	EOT Visit[14]	Safety Follow-Up	Survival Follow-Up[15]
		Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 9	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	30 days from last dose	90 days from last dose	Q6 months
Visit Window[1]	-28 to 0	-	+7	+3	+7	+3	+7	+7	+3	+7	+3	+7	+3	+14	+14	(±1 month)
IAT[2]		X					X									
Durvalumab			X		X			X		X		X				
SNDX-6352					X	X		X	X	X	X	X	X			
Demographics, Med Hx	X															
Physical Exam[3]	X		X		X			X		X		X		X		
Vital signs, height[4]	X	X	X		X	X	X	X	X	X	X	X	X	X		
Weight	X		X		X			X		X		X		X		
Performance Status[3]	X		X		X			X		X		X		X		
Hematology profile[5,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry profile [6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
EKG[6]	X															
INR and PT[6]	X															
TSH[6,8]	X				X			X		X		X		X		
Pregnancy[9]	X				X			X		X		X		X		
HIV, HBC, HCV[10]	X															
Review Adverse events[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con meds[3]	X		X		X			X		X		X		X		
CT or MRI[11]	X						X					X		X		
Tumor measurements	X						X					X		X		
Biopsy[12, 16]		X			X		X									
Research Blood [6, 13, 16] - PBMC (up to 100cc) - plasma (up to 20cc) - serum (up to 5cc)	X						X					X				
Survival/ progression																X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

1. Longer delays to be approved by the IND Sponsor. Delays are listed in days unless otherwise specified.
2. All subjects will receive at least two IAT treatments (cTACE or Y90). Patients may receive additional IAT treatments at the discretion of interventional radiologists. All IAT treatments will be the same type.
3. Focused physical examinations will be conducted. Physical exams, performance status, con med, and AE assessments can be made up to 3 days prior to infusion.
4. Height and pulse oximetry will be obtained at screen only. Blood pressure, pulse, and temperature will be measured at each indicated visit and at the following times on infusion days:
    - Durvalumab: Prior to infusion (any time prior), 30 minutes into infusion (± 5min), at the end of infusion (± 5min)
    - SNDX-6352: Start of infusion (0 min ± 5min), at the end of infusion (± 5min), and at 1 and 2 hours post-infusion (± 5min). The 2-hour post-SNDX-6352 vitals may be discontinued after the first 4 infusions provided no infusion reactions have occurred
5. CBC with differential including absolute eosinophil count, absolute neutrophils, absolute lymphocytes, and platelets.
6. Labs and research bloods may be collected within a window of up to 4 days prior to dosing. Unexpected Grade 3 or greater laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets toxicity criteria.
7. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, CK, LDH, CRP, amylase, lipase.
8. FT3 and FT4 to be checked reflexively if TSH is abnormal.
9. For WOCBP only. Serum or urine pregnancy tests must be repeated with each subsequent therapy (collected within a window of up to 3 days prior to dosing).
10. HIV-1/2 Ab, HBV surface antigen (HBsAg), anti-HBV core antibody (anti-HBc), and anti-HCV antibody
11. Radiologic evaluations (CT chest, abdomen, and pelvis with contrast) and tumor measurements will be performed. MRI will be done for those with contrast allergies. Interval scans may be done up to 7 days prior to the infusion/visit. Following the second scan (prior to second IAT), scans will be repeated approximately every 8 weeks (-1/+2 weeks) or every other cycle
12. Research biopsies will be performed during IAT procedure on Week 1, up to 1 week prior to Cycle 2 treatment, and during the IAT procedure on Week 9. Up to 6 core biopsies will be collected at each time point.
13. Research blood collected at baseline (screen), Week 9, and Week 18 only (not repeated at subsequent cycles). Detailed instructions for blood collection, processing, and storage are provided in the Laboratory Manual.
14. EOT Clinical assessments do not need to be repeated if they were done within last 7 days. EOT Scans do not need to be repeated if done within the past 6 weeks.
15. Subjects who discontinue treatment will be followed (by phone, email, or visit) every 6 months (± 1 month) after completion of EOT visit to monitor overall survival. Information on other cancer therapies and disease status will also be collected. In addition, SAEs that occur within 90 days (+14 day reporting window) of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.
16. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff.

10. MEASUREMENT OF EFFECT

10.1. Definitions

Evaluable for toxicity. Subjects are evaluable for toxicity if they receive at least one dose of durvalumab or SNDX-6352.

Evaluable for objective response. All patients who have received at least one dose of immunotherapy and have at least one post-baseline tumor assessment or discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered evaluable for response. Response criteria will be classified by modified RECIST (mRECIST) criteria **(Appendix D)**

10.2. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment. Subjects will be evaluated for anti-tumor effect by follow-up imaging (CT Chest/Abd/Pelvis, PET-CT imaging, MRI Chest/Abd/pelvis) as outlined above. All subsequent scans (post-treatment) will be compared to the same pretreatment CT, PET/CT, or MRI that was used prior to initiating of study treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the immune-related RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event guidelines and instructions for AE reporting can be found in **Section 6 (Adverse Events: List and Reporting Requirements)**.

11.1. Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator.

11.2. Safety Meetings

Scheduled meetings will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. Meetings will include the protocol principal investigator, study coordinator(s), research nurses(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3. Monitoring

This study is under the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (SKCCC). Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally by the Principal Investigator. The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

Dr. Lei Zheng will be holding the IND for this study. He will comply with all regulated reporting requirements to the FDA.

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size

This single arm phase 2 study aims to evaluate safety and efficacy of the combination of IAT durvalumab, and CSF-1R inhibitor (SNDX-6352) in 30 patients with unresectable intrahepatic cholangiocarcinoma. The primary endpoint is objective response (CR or PR) per mRECIST criteria. We plan to enroll up to 30 patients which results in 26 patients evaluable for objective response. The trial is design to demonstrate an improvement of ORR to 50% (alternative hypothesis) from a historical baseline of 25% or lower (null hypothesis).

Our group previously reported a retrospective analysis of 198 ICC patients who received IAT, including conventional transarterial chemoembolization (cTACE) (64.7%), drug-eluting beads

(DEB) (5.6%), bland embolization (TAE) (6.6%), or yttrium-90 radio embolization (23.2%)[5]. In this historical control cohort, assessment of tumor response revealed complete or partial response in 25.5% patients, while 61.5% had stable disease; 13.0% had progressive disease. Median overall survival was 13.2 months and did not differ on the basis of the type of IAT. Another study showed similar results while demonstrated that objective response rate following the initial session of IAT is 11%. In general, the patients would be observed without any therapy following IAT. Systemic therapy may be given following IAT, but would not result in any objective response. Objective response rate of approximately 20% is seen in other malignancies treated with single agent anti_PD-1. Therefore, we wish to test if the ORR of IAT followed by durvalumab and SNDX-6352 is higher than 25%. The minimum required level of efficacy that would warrant further study with the proposed regimen is a 50% ORR. The sample size is calculated to detect an improved ORR from 25% to 50%. A Simon's two stage minimax design is planned. A total of 11 patients will be entered in the first stage. If <=2 subjects show objective response (CR or PR), the treatment will be terminated and we will conclude the regimen is ineffective. If >=3 subjects respond, then additional 15 patients will be enrolled. If a total of 9 or fewer subjects respond in stage one and two combined, we consider the regimen ineffective. If a total of 10 or more respond, we conclude the regimen is promising and warrant further study. The maximum sample size will be 26 evaluable patients. The design has 90% power to detect an absolute 25% increase of ORR with one-sided type I error 0.09 (target type I error rate 0.1). The chance of early stopping is 0.46 when the ORR is 25%.

12.2. Primary Analysis

Objective response is defined as complete response (CR) or partial response (PR) per mRECIST. The ORR will be estimated as the proportion of patients who have CR or PR during the treatment, along with the 95% exact confidence intervals. Patients who receive at least one dose of durvalumab or SNDX-6352 and have at least one post-baseline tumor assessment or discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments are evaluable for ORR.

For safety evaluation, we will use count, and proportion with a 95% exact confidence interval to summarize toxicity per patient (total number of treated patients as the denominator), and per treatment cycles (total number of cycles as the denominator). Safety analysis population are patients who receive at least one dose of durvalumab or SNDX-6352.

Secondary endpoints include PFS, OS and duration of response. PFS is defined as the time from the date of first IAT until the date of disease progression (by mRECIST criteria) or death (by any cause in the absence of progression), whichever occurs earlier. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of last recorded tumor assessment. OS is defined as the time from the date of first IAT until death, and censored at the date of last known alive for those who do not die. The Kaplan-Meier survival curve of PFS and OS will be constructed and the corresponding 95% pointwise confidence intervals (CI) will be derived based on standard deviation of the log transformed survival function. e. The median PFS and OS together with its 95% CI will also be reported. Among the patients who have CR or PR, duration of response (DOR) is the time interval from initial response to the documented tumor progression. Median DOR will be estimated using Kaplan-Meier method, and swimmers plot will be used to demonstrate DOR.

12.3. Safety monitoring plan

Toxicity will be monitored continuously through the course of treatment. Occurrence of grade 3 or higher immune-related hepatotoxicity attributable to study drugs at any time will be considered as a primary endpoint for purposes of this stopping rule. If the risk of these adverse events appears to be higher than 15%, we will temporarily halt the study pending safety investigation and dose modification. Specifically, we apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of risk being larger than 15% is 0.7 or higher. The monitoring rule uses beta (0.5, 2.5) as prior distribution. This means that our prior guess at the proportion of severe immune-related hepatotoxicity is 17%, and 90% probability that the rate of this AE is below 45%. Starting from the 3rd patient, the decision rule for toxicity stopping is as follows:

Stop if number of patients experiencing grade 3 or higher hepatotoxicity ≥:	2	3	4	5	6
In number of patients between:	3 - 8	9 - 13	14 - 19	20 - 25	26

Operating characteristics based on 10,000 simulations:

Risk of severe hepatotoxicity	.05	.10	.15	.20	.25	0.3
% of Time Study Stops	6.6%	26.1%	51.6%	72.1%	87.1%	95.1%
Expected Sample Size	24.8	21.5	17.3	13.6	10.4	8.2

Additionally, if unacceptable toxicities (as defined in **Section 4.5**) occur in >30% of subjects, then enrollment will be suspended until further review and consideration by the IND Sponsor and IRB.

12.4. Analysis of Immune Measurements

The list of immune markers is shown in Section 8. Continuous variables will be summarized with means or medians and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. Summaries for both pre and each time of post administration of immunotherapy will be computed. Plots (e.g. scatterplots, boxplots, and spider plots) will be used to show the changes in immune markers over time. The change of markers after treatment will be compared using paired t-tests (or Wilcoxon signed-rank tests if appropriate) for continuous variables and McNemar's tests for dichotomous variables. The associations between immune parameters and clinical outcomes (OS and PFS) will be evaluated using univariate and multivariate Cox regression models.

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Adverse Event of Clinical Interest (ECI) Reporting Form

Adverse Event of Clinical Interest (ECI) Reporting Form

Please notify within 24 hours:
IND Sponsor [redacted]
AstraZeneca ([redacted]
Syndax: [redacted]

Protocol Title:	A Phase II Study of durvalumab in combination with a CSF-1R Inhibitor Following Chemo or Radio-Embolization for Patients with Intrahepatic Cholangiocarcinoma		
Protocol #:	**Principal Investigator:**	**Signature of PI:**	**Date:**

Report Type:
☐**Initial** ☐**Follow-up** ☐**Final Follow-up** ☐**Addendum to:**

Section A: Subject Information

Subject ID:	**Age (years):**	**Gender:** ☐Male ☐Female

Section B: Event and Study Drug Information

Type of Intra-arterial Therapy (IAT) Received: ☐Y90 ☐cTACE		**Durvalumab**	**SNDX-6352**
	Total Dose:	1500 mg	
	Date of First Dose:		
	Date of Last Dose Prior to Event:		
	# of Total Doses:		
Dates of IAT:	**Action Taken w/ study drug**	☐ None ☐ Interrupted ☐Discontinued ☐Delayed	☐ None ☐ Interrupted ☐Discontinued ☐Delayed
	Event Abated after use stopped/ reduced?	☐Yes ☐No ☐N/A	☐Yes ☐No ☐N/A
	Event Reappeared After Reintroduction?	☐Yes ☐No ☐N/A	☐Yes ☐No ☐N/A

Event diagnosis or symptoms:	**Event Grade:**

Event Onset Date:	**Event End Date:**	**Date Event Discovered:**

Relationship to:	**Durvalumab**	**SNDX-6352**	**Y90/cTACE**	**Underlying Disease**
Unrelated	☐	☐	☐	☐
Related	☐	☐	☐	☐

Section C: Brief Description of the Event

Section D: Relevant Tests/Laboratory Data

Section E: Relevant Medical History

Section F: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section G: Comments

Additional Documents Attached (labs, scans, notes, etc.): ☐ Please specify, including dates

APPENDIX C: SAE Reporting Form

Serious Adverse Event Reporting Form

Please notify within 24 hours:
IND Sponsor [redacted])
AstraZeneca ([redacted])
Syndax: [redacted]

Protocol Title:	A Phase II Study of durvalumab in combination with a CSF-1R Inhibitor Following Chemo or Radio-Embolization for Patients with Intrahepatic Cholangiocarcinoma		
Protocol #:	**Principal Investigator:**	**Signature of PI:**	**Date:**

Report Type: ☐Initial ☐Follow-up ☐Final Follow-up ☐Death ☐Addendum to:	**Serious Criteria / Outcome (check all that apply):** ☐Death ☐Life-threatening ☐ Hospitalization or Elongation of Existing Hospitalization ☐ Persistent or Significant Disability ☐ Congenital / Birth Defect ☐ Other Important Medical Event ☐ New Cancer ☐ AE associated with Overdose	**Hospital Admission Date:**	**SAE ID:**
		Hospital Discharge Date:	**Date Event Discovered:**

Section A: Subject Information

Subject ID:	**Age (years):**	**Gender:** ☐Male ☐Female

Section B: Event and Study Drug Information

Event diagnosis or symptoms:	**Event Grade:**	**Cause of Death (if applicable):**	**Event Outcome:** ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Death ☐ Unknown

Event Onset Date:	**Event End Date:**	**Date of Death (if applicable):**

Section C: Study Drug Information

Investigational Product: Durvalumab (1500 mg IV), SNDX-6352 (3mg/kg IV)
Indication: intrahepatic cholangiocarcinoma

Type of Intra-arterial Therapy (IAT) Received: ☐Y90 ☐cTACE		**Durvalumab**	**SNDX-6352**
	Total Dose (mg):	1500 mg	
	Date of First Dose:		
	Date of Last Dose Prior to Event:		
	# of Total Doses:		

Dates of IAT:	Action Taken w/ study drug	☐None ☐Interrupted ☐Discontinued ☐Delayed	☐None ☐Interrupted ☐Discontinued ☐Delayed
	Event Abated after use stopped/ reduced?	☐Yes ☐No ☐N/A	☐Yes ☐No ☐N/A
	Event Reappeared After Reintroduction?	☐Yes ☐No ☐N/A	☐Yes ☐No ☐N/A

Relationship to:	Durvalumab	SNDX-6352	Y90/cTACE	Underlying Disease
Unrelated	☐	☐	☐	☐
Related	☐	☐	☐	☐

Section C: Brief Description of the Event

Section D: Relevant Tests/Laboratory Data

Section E: Relevant Medical History

Section F: Concomitant Drug (Not related to SAE)

Name of the Drug	Start Date	Stop Date	Route	Dose	Frequency

Section G: Comments

Additional Documents Attached (labs, scans, notes, etc.): ☐ Please specify, including dates

APPENDIX D: Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Criteria

Definitions

Target Lesions should meet ALL the following criteria:

- The lesion can be classified as a RECIST measurable lesion (i.e. can be accurately measured in at least 1 dimension as 1 cm or more)
- The lesion is suitable for repeat measurement
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI

Non-Target Lesions are those that meet ANY of the following criteria:

- Fails to meet one of more target lesion criteria above
- An infiltrative-type mass with ill-defined borders that therefore does not appear suitable for accurate and repeat measurements
- A lesion previously treated with locoregional or systemic treatments if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention

Assessment of target lesion response

- **Complete response (CR):** Disappearance of any intratumoral arterial enhancement in all target lesions.
- **Partial response (PR):** At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
- **Stable disease (SD):** Failure to meet the criteria for either partial response or progressive disease.
- **Progressive disease (PD):** An increase in at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

Assessment of non-target lesion response

- **Complete response (CR):** Disappearance of any intratumoral arterial enhancement in all non-target lesions.
- **Incomplete response/Stable Disease (IR/SD):** Persistence of intratumoral arterial enhancement in one or more non-target lesions.
- **Progressive disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Specific recommendations in mRECIST

- Measurement of the viable tumor should be performed on CT or MRI obtained in the arterial phase, when the contrast between viable vascularized tumor tissue and non-enhancing necrotic tissue is the highest
- The longest diameter of the viable tumor is not necessarily located in the same plane in which the baseline diameter was measured: a thorough careful evaluation of the scans is required
- The measurement of the viable tumor diameter should not include any major intervening areas of necrosis
- Pleural effusion or ascites: Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.
- Porta hepatis lymph node: Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.
- Portal vein thrombosis: Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target group.
- New lesion: A newly detected intrahepatic lesion can be classified as intrahepatic cholangiocarcinoma—and therefore will be declared as evidence of progression—when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of intrahepatic cholangiocarcinoma on dynamic imaging, that is, peripheral rim-like enhancement or hyperenhancement in the arterial phase with progressive or stable enhancement in the portal venous or late venous phase.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as intrahepatic cholangiocarcinoma by evidence of at least 1 cm interval growth in subsequent scans.
- An individual radiologic event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only at subsequent radiologic testing

Overall Response Assessment by mRECIST

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD