Study Protocol

Hepatic artery infusion pump (HAIP) therapy in combination with targeted delivery of IL-12 for patients with metastatic colorectal cancer or intrahepatic cholangiocarcinoma: a phase II trial protocol

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Background: Treatment of advanced liver tumors remains challenging. Although immune checkpoint inhibition has revolutionized treatment for many cancers, responses in colorectal liver metastases and biliary tract cancers remain suboptimal. Investigation into additional immunomodulatory therapies for these cancers is needed. Interleukin-12 (IL-12) is a pro-inflammatory cytokine with robust anti-tumor activity, but systemic adverse effects largely terminated therapeutic development of recombinant human IL-12 (rhIL-12). PDS01ADC is a novel human monoclonal antibody (NHS76) conjugated to two IL-12 heterodimers with established safety in phase I trials. The NHS76 antibody specifically targets histone/DNA complexes which are accessible only in regions of cell death and this antibody has been shown to accumulate locally in tumors.

Methods: Patients with unresectable metastatic colorectal cancer (mCRC) or unresectable intrahepatic cholangiocarcinoma (ICC) will receive synchronization of subcutaneous PDS01ADC with floxuridine delivered via a hepatic artery infusion pump (HAIP). The primary outcome measured in this study will be overall response rate as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary outcomes measured in this study will include hepatic and non-hepatic progression-free survival (PFS), overall survival, and safety of PDS01ADC combination therapy with HAIP.

Discussion: Poor clinical response of these liver tumors to immunotherapy is likely due to various factors, including poor immune infiltrate into the tumor and immunosuppression by the tumor microenvironment. By exploiting the tumor cell death induced by HAIP locoregional therapy in combination with systemic

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chemotherapy, PDS01ADC is poised to modulate the tumor immune microenvironment to improve outcomes for patients undergoing HAIP therapy.

Trial Registration: ClinicalTrials.gov (ID NCT05286814 version 2023-10-18); https://clinicaltrials.gov/study/NCT05286814?term=NCT05286814&rank=1

Keywords: Metastatic colorectal cancer (mCRC); intrahepatic cholangiocarcinoma (ICC); hepatic artery infusion pump (HAIP); interleukin-12 (IL-12); floxuridine

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Introduction

Immunotherapy, namely immune checkpoint inhibition, has revolutionized cancer treatment. However, many cancers appear to be completely resistant to currently approved treatments (e.g., microsatellite stable colorectal cancer liver metastases), while other cancers seem to benefit marginally (e.g., cholangiocarcinoma). With median survival for patients with unresectable colorectal liver metastasis and advanced biliary tract cancer of approximately 20 and 12 months, respectively (1,2), identification of improved therapeutic approaches is vital.

Interleukin-12 (IL-12) is a cytokine produced by antigen-presenting cells and neutrophils (3,4) that stimulates cytotoxic immune effectors including natural killer (NK) cells, natural killer T (NKT) cells, and $CD8^+$ T cells (5). Specifically, IL-12 acts directly on T cells via the IL-12 receptor, and induces differentiation of $CD4^+$ T cells toward a Th1 program, promoting production of interferon-gamma (IFN-γ) which supports cell-mediated immunity (6). IL-12 has also been demonstrated to support effector memory T cell development and oppose angiogenesis. In a B16 melanoma tumor model, IL-12 expressed within tumor nodules mediated recruitment of leukocytes inclusive of $CD8^+$ T cells into the tumor (7). The subsequent use of recombinant IL-12 (rIL-12) across multiple pre-clinical models replicated the anti-tumor properties of IL-12, including liver tumors (5). Despite great enthusiasm for the clinical utility of IL-12 in cancer treatment, recombinant human IL-12 (rhIL-12) was poorly tolerated (8,9). Importantly, the maximum tolerated dose (MTD) of IL-12 prevented the accumulation of biologically relevant concentrations of IL-12 within the tumor environment.

Due to the clinical limitations of rhIL-12, investigation shifted toward the targeted delivery of IL-12 to tumors, including the novel immunocytokine NHS-IL12 (PDS01ADC). NHS-IL12 is composed of two IL-12 heterodimers covalently linked to the NHS76 human immunoglobulin G1 (IgG1) antibody (10). NHS76 targets histones on DNA accessible via compromised membrane integrity in necrotic cells, facilitating preferential accumulation and persistence in tumor relative to normal tissues (11,12). Pre-clinical studies, including colorectal cancer cell line xenografts, have demonstrated superior tumor volume growth reduction by NHS76 antibody fused to murine IL-12 (NHS-muIL12) in comparison to recombinant murine IL-12 (rmuIL-12) (12,13). Depletion of $CD8^+$ T cells abrogated the anti-tumor effects of NHS-muIL12, and re-challenge of tumor-cleared mice following NHS-muIL12 administration demonstrated significantly delayed tumor outgrowth compared to naïve mice, suggesting expansion of tumor-specific cellular immune responses following NHS-muIL12 treatment (12).

In response to these promising pre-clinical data, two phase I trials were conducted in patients with locally advanced or metastatic solid tumors. These trials evaluated NHS-IL12 alone in a single- or multi-dose escalation study (14-16) or in combination with avelumab/anti-programmed death ligand 1 (anti-PDL1) (17). Following NHS-IL12 monotherapy, two of 30 patients with measurable disease demonstrated prolonged (>12 months) stable disease (15). Following a dose-escalation of NHS-IL12 in combination with avelumab, among 36 patients who received both drugs, two patients had a prolonged complete response and nine patients had stable disease (17). Notably, for patients receiving NHS-IL12 monotherapy, stratification by IFN-γ responsiveness demonstrated increased T cell receptor diversity and increased tumor infiltrating lymphocyte density among recipients with a high serum IFN-γ response to NHS-IL12, suggesting that NHS-IL12 alone may successfully facilitate increased T cell infiltration of solid

tumors in a subset of patients (15).

As NHS-IL12 accumulation in tumors is mediated via NHS76 antibody recognition of exposed histone/DNA complexes, a rational approach to increase tumor-targeting has been to combine the drug with systemic therapy. For example, in a murine colon cancer model, NHS-muIL12 demonstrated increased efficacy in combination with either entinostat or docetaxel compared to either drug alone (12,18). Additionally, sunitinib or gemcitabine also exhibited increased efficacy in combination with NHS-muIL12 compared to either drug alone in a Lewis lung carcinoma model (12). HAIP chemotherapy presents a unique combinational approach alongside NHS-IL12 for the treatment of liver tumors, such as metastatic colorectal cancer (mCRC) and intrahepatic cholangiocarcinoma (ICC). HAIP therapy exploits the hepatic artery derived blood supply of liver tumors (19), allowing direct infusion of floxuridine (FUDR) to the local tumor environment (20). Hepatic artery infusion of FUDR has been shown to promote tumor cell death (21) and has a 94–99% first pass-metabolism by the liver (22), facilitating high dose delivery of drug directly to the liver while limiting systemic side effects. Thus, the MTD of FUDR delivered directly to the liver by HAIP greatly exceeds that achievable by systemic administration by an estimated 400-fold.

We hypothesize that a high rate of tumor cell death in the liver resulting from FUDR will expose histone/DNA complexes, promoting increased accumulation of NHS-IL12 within these tumors. Subsequently, locally increased NHS-IL12 within the tumor will facilitate reprogramming of the tumor microenvironment, promoting immune control of disease in conjunction with chemotherapy-induced tumor cell death. Thus, combination of HAIP regional therapy with immune modulation by tumor-targeting NHS-IL12 has the potential for highly synergistic anti-tumor efficacy. Here, we expand on previous phase I trials to investigate the safety and efficacy of NHS-IL12 in combination with HAIP-administered FUDR and systemic chemotherapy in patients with mCRC and ICC. We present this article in accordance with the SPIRIT reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-71/rc).

Methods

Design

This is an open label, single center, non-randomized phase II study designed to determine the safety and efficacy of NHS-IL12 (PDS01ADC) in combination with HAIP and systemic chemotherapy in patients with the following histologies:

(I) Arm 1: unresectable mCRC confined to the liver (n=24);

(II) Arm 2: unresectable ICC (n=24).

Patients with unresectable mCRC confined to the liver who were previously treated with first line chemotherapy will be assigned to arm 1 and will receive PDS01ADC + HAIP FUDR in combination with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) or leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI). Patients with unresectable ICC who were previously treated with first line chemotherapy will be assigned to arm 2 and will receive PDS01ADC + HAIP FUDR in combination with gemcitabine and oxaliplatin (GemOx). All patients will be enrolled at the NIH Clinical Center in Bethesda, Maryland (NCT05286814). The size of the two treatment arms were determined according to a Simon optimal two-stage phase II trial design (23) to determine if PDS01ADC will be able to improve upon expected response rates of 50% and 35% as previously reported for standard HAIP therapy for mCRC and ICC, respectively (24,25).

Eligibility

Eligible patients must be 18 years or older, have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and have a histologically or cytologically confirmed diagnosis of either unresectable mCRC (Cohort 1) or unresectable ICC confined to the liver (Cohort 2). All subjects must have received first line chemotherapy. For Cohort 2, clinical or radiographic evidence of metastatic disease to regional (porta hepatis) lymph nodes will be allowed, provided it is amenable to resection. Additionally, subjects must have adequate organ and marrow function as defined below:

- Leukocytes: ≥3,000/mcL;
- Absolute neutrophil count: >1,500/mcL;
- Platelets: ≥90,000/mm^3;
- Hemoglobin: >9 g/dL;
- Total bilirubin: <1.5× institutional upper limit of normal;
- Creatinine: within normal institutional limits.

Exclusion

Exclusion criteria include patients who are receiving any other investigational agents or who have previously received

either rhIL-12 or FUDR. Also excluded are patients with active autoimmune diseases, that may deteriorate when receiving an immunostimulatory agent with the following exceptions:

- Diabetes type I, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible;
- Patients requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤10 mg of prednisone or equivalent per day;
- Patients requiring administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) are eligible.

For Cohort 1 (mCRC), patients with incontrovertible radiographic evidence of disease outside of the colon/rectum (primary) and liver given unlikelihood of benefit from liver-directed therapy (with the exception of some lung lesions which may not truly represent metastasis), those who have undergone extra-hepatic metastasectomy and have a documented disease-free interval less than or equal to 4 months, or those with microsatellite instability (MSI)-high disease who need to be treated with check-point inhibitors are excluded.

For Cohort 2 (ICC) patients with presence of distant metastatic disease (except lymph nodes as described above), those with diagnosis of sclerosing cholangitis, or those with clinical evidence of portal hypertension (ascites, gastroesophageal varices, or portal vein thrombosis) are excluded.

Intervention

Eligible patients will undergo surgical HAIP placement. Each cycle of treatment will be 28 days. All patients will have 14 days of treatment with FUDR and dexamethasone in heparin/saline delivered by HAIP on days 1–14 of every cycle. On days 15–28 of every cycle, heparin/saline will be delivered by HAIP. On day 15 of every cycle, patients will receive NHS-IL12 (PDS01ADC) by subcutaneous injection. Beginning from Cycle 2 subjects will receive systemic chemotherapy on day 1 and day 15 of every cycle delivered intravenously. Patients with mCRC will receive either FOLFOX or FOLFIRI. Patients with ICC will receive GemOx. Treatment will be continued until a patient meets off-treatment criteria as defined in the study protocol. If a patient were to experience a substantial response to NHS-IL12/HAIP combination therapy, a subsequent second surgical operation may be undertaken to remove all remaining tumor(s) and render the patient no evidence of disease (NED).

Study endpoints

The primary endpoint for this study is to evaluate the overall response rate of NHS-IL12 (PDS01ADC) in combination with HAIP and systemic therapy in patients with unresectable mCRC or ICC. Patients will be evaluated for response at 8-week intervals with computed tomography (CT) and magnetic resonance imaging (MRI). Response and progression will be evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) (26). Secondary objectives include hepatic progression-free survival (PFS), extra-hepatic PFS, and overall survival. An additional secondary objective includes evaluation of safety of combination NHS-IL12 and HAIP therapy (*Figure 1*).

Scientific endpoints

The study will characterize each patient's immunologic response to NHS-IL12/HAIP combination therapy. Tumor biopsies will be obtained before treatment during HAIP placement and following the first cycle of HAIP therapy and NHS-IL12 administration. These tumor biopsies will be evaluated for immune cell infiltration including $CD8^+$ T cells, T cell receptor repertoire diversity, and expression of T cell exhaustion markers to characterize immunomodulation and immune surveillance of the tumor microenvironment. Additionally, perturbations of peripheral blood immune subsets, peripheral lymphocyte activation/exhaustion status, frequency of tumor antigen specific T cells within the peripheral blood, and serum cytokines will be measured to characterize systemic immunomodulation in response to treatment. To determine changes in both tumor and systemic inflammatory gene signatures, we will evaluate transcriptomics of both peripheral blood mononuclear cells (PBMCs) and tumor biopsies before and after treatment.

Registration details and study timeline

This phase II study is registered through clinicaltrials.gov (ID: NCT05286814) and sponsored by the National Cancer Institute (NCI). The study's start date was 10/24/2022 with an estimated completion date of 12/31/2028. This trial is

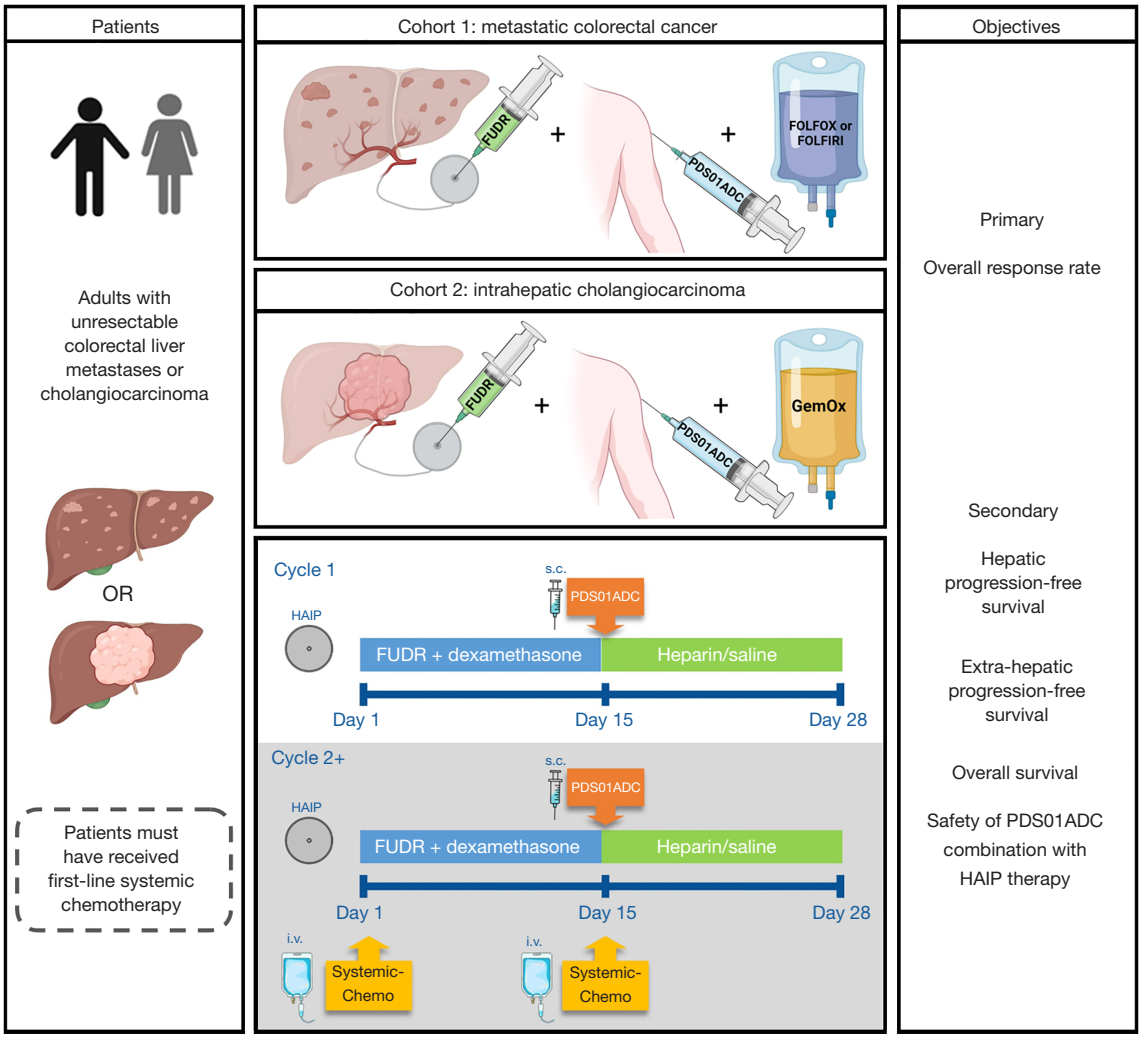

Figure 1 Summary of trial study population, treatment dosing schedule, and objectives to be measured in the study. Created with BioRender.com. FUDR, floxuridine; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan; GemOx, gemcitabine and oxaliplatin; HAIP, hepatic artery infusion pump; s.c., subcutaneous; i.v., intravenous.

actively recruiting participants. An estimated 48 participants will be enrolled in this study.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study (NCT05286814) was approved by the National Cancer Institute IRB (protocol 000307). Informed consent has been obtained from all individual participants who have enrolled in the study to date and will be obtained from all future individual participants as they enroll in the study.

Discussion

Despite advances in standard of care therapies, mCRC represents the second-leading cause of all cancer deaths worldwide and mortality rates for patients with ICC have not substantially improved (27,28). Following first line chemotherapy, select patients with mCRC and ICC benefit from hepatic locoregional chemotherapy via HAIP (29). Here, we will evaluate NHS-IL12 in combination with HAIP chemotherapy for the treatment of ICC and mCRC and evaluate immunologic mechanisms associated with patient outcomes. Pre-clinical studies widely support

the synergy of NHS-IL12 with various cytotoxic agents including both radiation and chemotherapy (12,18,30). FUDR has been demonstrated to cause cell death in murine tumor cell lines, making it amenable to combination therapy with NHS-IL12 (31). This concept is particularly important for tumors that have not responded to previously investigated immune therapies, including checkpoint inhibition. For the immune system to effectively contribute to tumor control, tumors must be amenable to immune infiltration and surveillance by immune effectors, which intratumoral IL-12 can mediate (7,15). For tumors such as mCRC and ICC with poor response to immune checkpoint blockade, NHS-IL12 presents a rational next step in the investigation of immunotherapies for these tumors.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-71/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-71/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-71/coif). J.S. reports receiving funding from a National Cancer Institute Cooperative Research and Development Agreement (CRADA) with PDS Biotechnology regarding NHS-IL12. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study (NCT05286814) was approved by the National Cancer Institute IRB (protocol 000307). Informed consent has been obtained from all individual participants who have enrolled in the study to date and will be obtained from all future individual participants as they enroll in the study.

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