Abbreviated Title: M7824, M9241 and SBRT

NIH Protocol # 20C0074

Version Date: 11/10/2021

NCT Number: NCT04327986

Title: A Phase I/II Study of the Immune Checkpoint Inhibitor M7824 and the Immunocytokine M9241 in Combination with Stereotactic Body Radiation Therapy (SBRT) in Adults with Advanced Pancreas Cancer.

NCI Principal Investigator

Udo Rudloff, MD, PhD
Rare Tumor Initiative, POB, NCI
Building 10, Room 2B-38D
Bethesda, MD 20892
Phone: 240-760-6238
E-Mail: rudloffu@mail.nih.gov

Investigational Agents:

Drug Name:	M7824	M9241
IND Number:	146972	146972
Sponsor:	CCR	CCR
Manufacturer:	EMD Serono	EMD Serono
Supplier:	EMD Serono	EMD Serono

Commercial Device: Stereotactic Body Radiation Therapy

PRÉCIS

Background:

- At time of diagnosis, fewer than 10% of newly diagnosed pancreatic cancer patients present with resectable disease (patients who can undergo surgery) and patients able to undergo a margin-negative surgical resection (R0) are reported to have the most favorable outcome.
- Locally advanced, non-metastatic pancreas cancer (LAPC) is observed in up to 30% of all pancreas cancer patients at time of diagnosis (including both borderline resectable and non-resectable disease).
- The primary goal of neoadjuvant therapy in LAPC is, among tumor control and extension of survival, the conversion to resectable disease achieving a R0 resection.
- Radiation therapy (RT) is commonly used as neoadjuvant treatment for LAPC.
- However, currently used RT neoadjuvant treatment regimens result in only about 40%-60% of patients with borderline resectable pancreas cancer to undergo surgical resection, in initially unresectable LAPC patient conversion are even lower, with only 7% - 19% able to undergo resection.
- Combining immunotherapy and radiation therapy could synergistically improve anti-cancer activity.
- M7824 is a bifunctional fusion protein consisting of an anti-programmed death ligand 1 (PD-L1) antibody functioning as an immune checkpoint inhibitor and the extracellular domain of transforming growth factor beta (TGF-β) receptor type 2, a TGF-β trap.
- The M9241 immunocytokine is composed of 2 IL-12 heterodimers, each fused to one of the H-chains of the NHS76 antibody, which has affinity for both single- and double-stranded DNA. M9241 targets delivery of IL12, a proinflammatory cytokine that has been shown anti-tumor activity including objective responses in phase I clinical trials, to regions of tumor necrosis where DNA has become exposed, e.g. after radiation therapy.
- We hypothesize that released neo-epitopes upon increased DNA damage induced by radiation therapy together with the local proinflammatory action of M9241 will complement the anti-tumor activity of M7824 in locally advanced pancreas cancer.

Objectives:

- To determine the safety and tolerability and the recommended phase 2 dose (RP2D) of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with pancreas cancer.
- To determine a preliminary estimate of efficacy as best overall response (BOR) according to RECIST 1.1 of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with locally advanced pancreas cancer.

Eligibility:

- Histologically or cytologically proven pancreatic adenocarcinoma.
- Patient must be eligible to undergo stereotactic body radiation therapy (SBRT) (Cohorts 2-3).

- Patients must have measurable disease.
- Age ≥18 years

Design:

- This is an open label Phase I/II trial. During phase I the safety and tolerability of M7824 and M9241 will be evaluated and recommended Phase II dose (RP2D) of M7824 and M9241 in combination with SBRT will be estimated. During phase II efficacy of the M7824 and M9241 in combination with SBRT will be examined.
- Patients will receive treatment in cycles consisting of 28 days (with exception of additional administer of M7824 alone in Phase IA).
- Treatment will continue until unacceptable toxicity or disease progression.
- If during treatment patient become candidate for curative surgery, treatment will be stopped and can be restarted after surgery in case if surgical exploration does not result in the successful removal of the tumor.

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form

1 INTRODUCTION

1.1 STUDY OBJECTIVES:

1.1.1 Primary Objectives:

- To determine the safety and tolerability and the recommended phase 2 dose (RP2D) of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with pancreas cancer.
- To determine a preliminary estimate of efficacy as best overall response (BOR) according to RECIST 1.1 of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with locally advanced pancreas cancer.

1.1.2 Secondary Objectives:

- To assess overall survival (OS) in patients after completion of RT in combination with M9241 and M7824.
- To assess progression-free survival (PFS) for all participants.
- To assess progression-free survival (PFS) for participants who did not undergo surgical resection.
- To determine fraction of patients with LAPC who are able to undergo surgical resection after M7824 and M9241 in combination with SBRT treatment.
- For patients who underwent surgical resection after M7824 and M9241 in combination with SBRT treatment:
    - To determine time-to-recurrence of the disease
    - To determine complete pathological response rate(s)

1.1.3 Exploratory Objectives:

- To determine ADA profile of M7824 in combination with M9241.

- To determine the PK of M7824 in combination with M9241.
- To evaluate serum cytokines and tumor necrosis factor (TNF) levels pre-treatment and on-treatment.
- To correlate the tumoral immune infiltrate via IHC with clinical outcome.
- To evaluate impact of genomic profile of advanced pancreatic cancers on clinical response to M7824 and M9241 in combination with SBRT.
- To correlate circulating free tumor DNA (ctDNA) levels with clinical course of pancreatic cancer patients treated with M7824 and M9241 in combination with SBRT.
- To measure subjective Health-related Quality of Life (HRQoL) affecting disease-specific symptoms and treatment-related concerns pre-treatment and on-study and compare HRQoL scores with historical controls of other Quality of Life (QoL) interventions in advanced pancreas cancer patients.
- To evaluate the impact of M7824 in combination with M9241 on tumoral perfusion measured by perfusion-weight Dynamic Contrast-enhanced (DCE) Magnetic Resonance Imaging (DCE-MRI).

1.2 BACKGROUND AND RATIONALE

Rationale for this study is provided by available preclinical and clinical evidence of the individual mono-immunotherapy components:

- TGFβ blockade and PD-L1 inhibition, --- by M7824
- local increase in IL-12 function, --- by M9241, and
- enhanced anti-tumor immunogenicity, --- by radiation therapy (RT)

which synergize / cooperate treatment effect when combined:

- cooperation of PD-L1 checkpoint inhibition with RT
- cooperation of TGFβ blockade with RT
- IL-12 immunotherapy (M9241) in combination with RT
- IL-12 immunocytokine therapy (M9241) in combination with TGFβ- and PD-L1 inhibition (M7824).

1.2.1 Neoadjuvant therapy for locally advanced pancreas cancer (LAPC)

Pancreatic cancer is a life-threatening disease with a dismal outcome. In 2016, about 48,960 people (24,840 men and 24,120 women) were diagnosed with pancreatic cancer, and 40,560 people (20,710 men and 19,850 women) are estimated to have died of pancreatic cancer.[1] AACR estimates deaths due to pancreas cancer to rank 2nd among all cancer-related deaths in the U.S. by 2030.[2] At time of diagnosis, fewer than 10% of newly diagnosed pancreatic cancer patients present with resectable disease (patients who can undergo surgery; stage I - IIA) and patients able to undergo a margin-negative surgical resection (R0) are reported to have the most favorable outcome achieving 5-year survival rates of 25 – 30% (**Figure 1**).

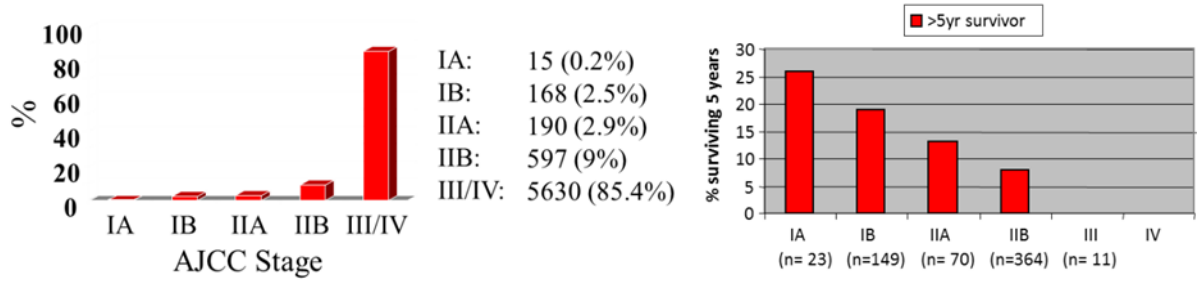


Figure 1: Percent patients at different AJCC stages at time of initial diagnosis of pancreas cancer. Left: per 7th edition of American Joint Commission of Cancer, AJCC more than 6,000 pancreas cancer patients presenting between 2000 and 2005 to Memorial Sloan-Kettering Cancer Center, NY, and their corresponding 5-year survival rates (right) from MSKCC Pancreatic Cancer Registry.

Approximately 50 to 60 % of patients at time of diagnosis have metastatic disease (stage IV).[3] The rest (one third) of all patients with pancreas cancer have disease that is locally advanced because of local interface or invasion of adjacent structures.[4-6] While ultimately a continuum of disease progression LAPC is subdivided into borderline resectable pancreas cancer characterized by a higher risk of a margin positive surgical resection due to one, or more, interface(s) of the tumor with a mesenteric structure and unresectable, locally invasive disease.[5, 7] There are no commonly agreed criteria of borderline resectable pancreas cancer, different organizations have published slight variations of primarily radiographic criteria which are listed in **Appendix A**.

The primary goal of neoadjuvant therapy in LAPC is, among tumor control and extension of survival, the conversion to resectable disease achieving a R0 resection.[4] Some series have reported for patients with initially borderline resectable pancreas cancer who after neoadjuvant therapy were able to undergo a margin-negative surgical resection of their tumor similar outcomes like for patients with initially resectable disease.[4, 6, 8, 9] However, even after multimodality therapy that includes surgical resection, 5-year overall survival only reached 25 – 30% with an ongoing risk of systemic and locoregional disease recurrence speaking to the systemic nature of the disease and making pancreas cancer, even in its early stages, a near incurable condition.[4, 7, 9]

Patients unable to undergo margin-negative resection have a poor outcome frequently similar to patients with stage IV disease and have poor quality of life indices due to challenging palliation of gastric outlet, biliary duct obstruction, or neuropathic pain due to local tumor progression.[4] Currently used neoadjuvant RT treatment regimens result in only about 40 – 60% of patients with borderline resectable pancreas cancer to undergo surgical resection and in unresectable LAPC patient conversion are even lower, with only 7% - 19% being able to undergo resection which is increased to 29% with the use of the most involved and toxic combination of triple FOLFIRINOX chemotherapy in combination with RT in highly selected patients.[5, 6, 10] **Figure 2** shows the flow diagram and outcome differences between all locally advanced pancreas cancer patients (intent-to-treat), outcome of patients who were able to undergo surgical resection, and patients who could not undergo surgery of one of the first sentinel series on the use of neoadjuvant therapy using gemcitabine-based chemoradiation therapy.[9]

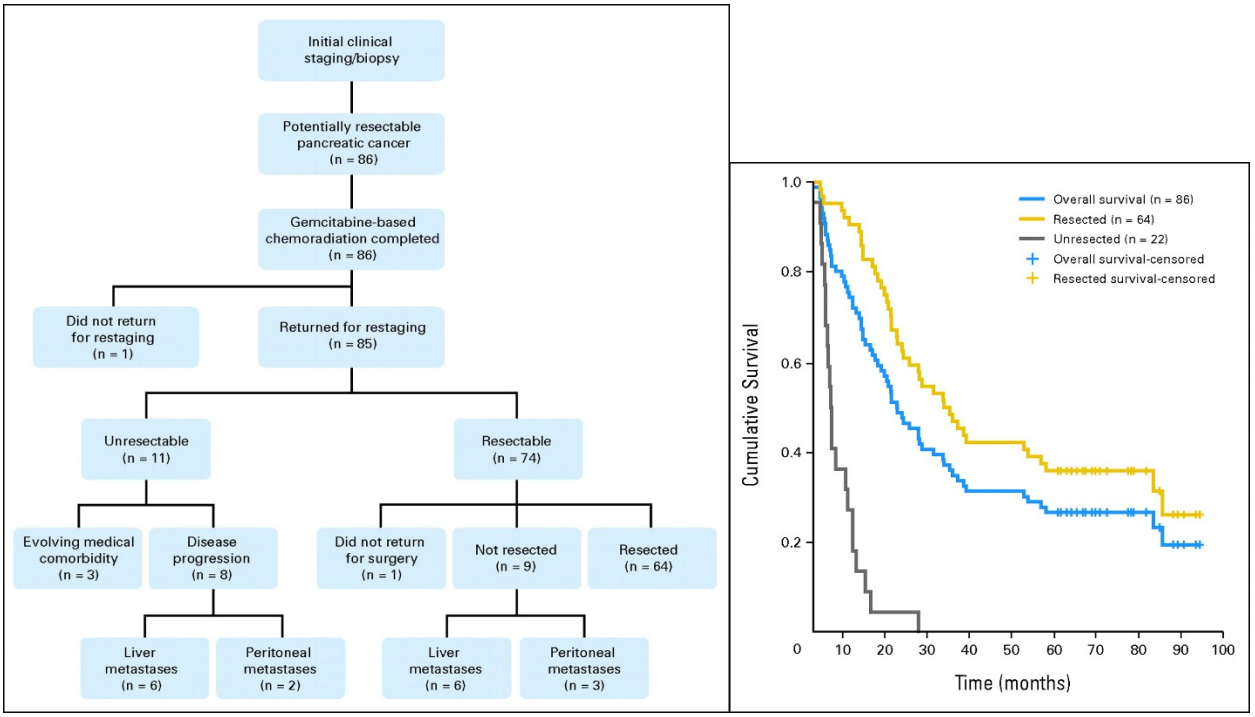


Figure 2: MDACC experience of preoperative gemcitabine-based chemoradiation (EBRT) for patients with potentially resectable (borderline) adenocarcinoma of the pancreatic head. Flowchart of all 86 patients on the left, survival curve for all 86 patients and survival curves for the patients who underwent pancreaticoduodenectomy (PD; n=64) versus those who did not undergo PD (n=22). The median overall survival for all patients (intent-to-treat) was 22.7 months, for the resected patients 34 months, and for patients not taken to surgery 7 months.[9]

Thus, the primary goal of neoadjuvant therapy in LAPC is, among tumor control and extension of survival, the conversion to resectable disease achieving a R0 resection. Neoadjuvant therapy provides the theoretical advantages over standard adjuvant therapy including

- treatment of distant micro metastasis
- assessment of tumor response to treatment, and
- better triaging and selection of patients for surgical resection (summarized in [11]).

2016 American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines on locally advanced pancreas cancer (LAPC) recommend 'Initial systemic therapy with combination regimens is recommended for most patients who meet the following criteria: Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, a favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy.[5] There is no clear evidence to support one regimen over another, and physicians may offer therapy on the basis of extrapolation from data derived from studies in the metastatic setting. For many patients, induction chemotherapy may be offered up front, followed by radiation therapy (CRT), on the basis of patient and physician preference.[5, 12]

If there is an insufficient response to initial induction chemotherapy, which is not uncommonly difficult to judge due to the inability of current radiologic criteria to confidently discriminate between tumor tissue, fibrous tissue without tumor, or fibrous tissue with tumor nests, or if there

is local tumor extension without the development of metastasis after induction chemotherapy, RT may be offered to patients who meet criteria with regard to their performance status, organ function, and preference.[4, 5] Overall, patients with locally advanced pancreas who receive neoadjuvant therapy receive in 98% of cases some form of systemic chemotherapy and in up to 94% RT although the rates for RT administration have recently dropped due to the introduction of oxaliplatin and gem/abraxane-containing chemotherapy regimens into the neoadjuvant setting.[4] RT, like in the proposed study, is generally given either as

- external beam radiation therapy (EBRT) delivering a total dose of 50 – 54 Gy in daily fractions of 1.7 – 3Gy over 4 to 8 weeks, or less frequently with less data available, as
- stereotactic radiation therapy (SBRT) using an abbreviated schedule delivering 5 – 6.6 Gy in 5 session.[5, 6, 12]) (please see Section **1.2.7**.)

RT is combined with a chemo sensitizing agent which is either oral capecitabine (oral 5-FU pro-drug; 830mg/m2 PO twice daily) or gemcitabine (300mg/m2 weekly; therapeutic dose 1,000mg/m2) with despite direct comparison in a radio-chemotherapy (RCT) no clear superiority in efficacy of one over the other.[13] For this study on the days of SBRT 830mg/m2 capecitabine twice daily by mouth is given.

Figure 3 provides a flow chart of summary of treatment algorithm of pancreas cancer aligned with ASCO 2016 Practice Guidelines. While the algorithm lists specific chemotherapy regimens in the management of LAPC patients who undergo neoadjuvant treatment, there is currently no consensus that one is superior to the other (FOLFIRINOX vs gemcitabine-based regimens including gem/abraxane) and ASCO Guidelines suggest an individual-based decision making.

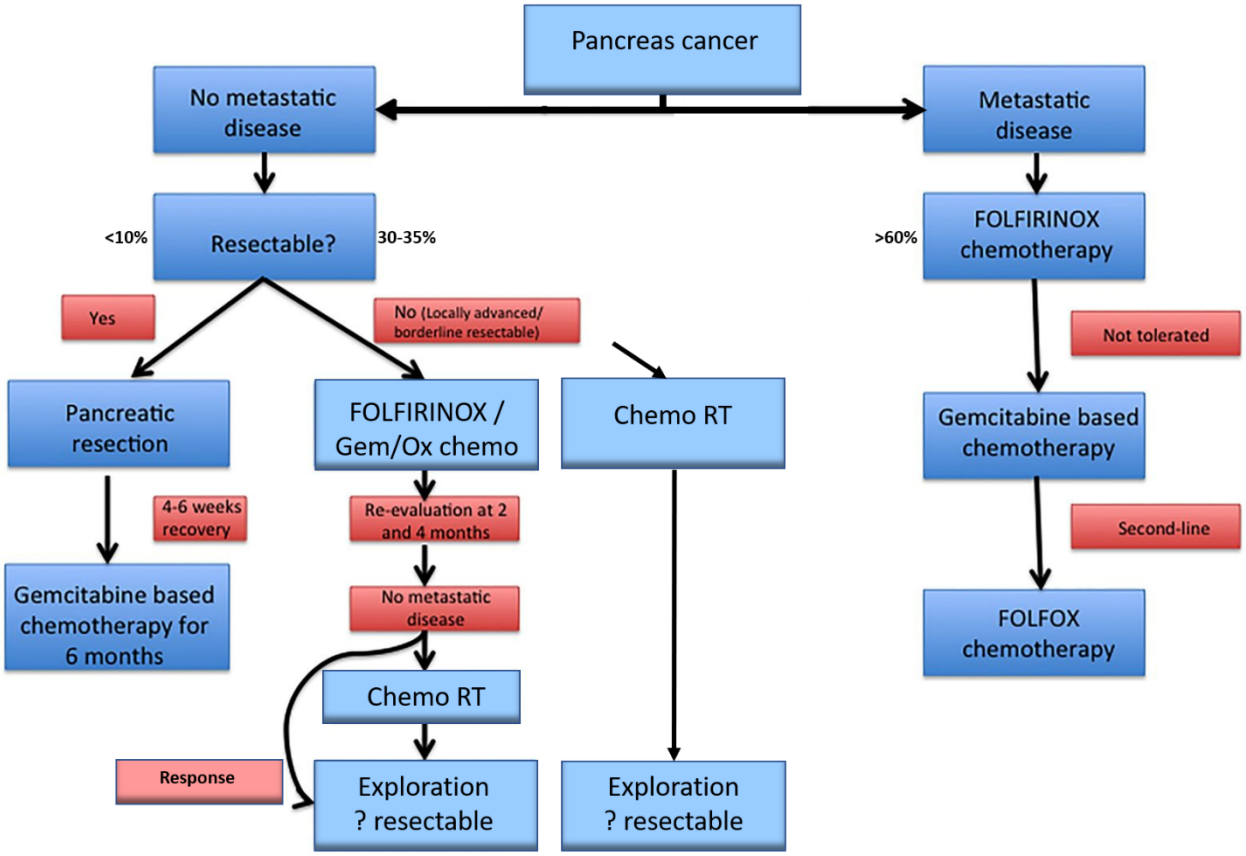


Figure 3: Overview of currently practiced treatment algorithm for patients diagnosed with pancreas cancer. Please note that there is currently no level I recommendation of type of 1st vs 2nd line chemotherapy in the metastatic setting, or chemotherapy regimens used in the neoadjuvant treatment of LAPC.

Overall, there is a medical need to improve current neoadjuvant treatment of LAPC, ideally with a combination of agents which improves both local response rates as well as long term control of undetected micro metastasis, the to-date most common cause of death in LAPC and pancreas cancer patients in general.

1.2.2 Radiation and immunotherapy: a synergistic combination

Pancreatic cancer is highly chemotherapy and radiation therapy-resistant, making treatment options very limited. Contrary to immune-active tumors with an abundant infiltration of CD8+ T cells like melanoma, non-small cell lung carcinoma (NSCLC), or microsatellite high (MSI high) gastrointestinal (GI) tumors, pancreas cancer is an immune quiescent cancer which lacks infiltration of effector T cells and is resistant to single agent checkpoint inhibition treatment.[14-16] Whether the recent discovery of a molecular immunogenic subtype based on gene expression profiling conducted within the Cancer Genome Atlas (TCGA) effort changes this paradigm remains to be seen.[17]

During the process of tumorigenesis, tumor antigens, originating in large from somatic gene variants in the tumor (referred to as neoantigens), arise and are recognized by the host's immune system as foreign.[18] However, and in particular pancreatic tumors, cancers select effective immune evasive mechanism within the educated and reprogrammed tumor microenvironment to curb recognition of such tumor antigen recognition and T cell responses.[16, 19] Through myriad

immune suppressive stimuli, the T cell phenotype in the stroma mimics T cell exhaustion seen normally upon repeat and chronic antigen stimulation which include, but are not limited the upregulation of PD-L1 (B7-H1), indoleamine 2,3-dioxygenase (IDO), IL-10, lymphocyte activation gene 3 (LAG3), transforming growth factor-β (TGF-β), the education of CD4+ T regulatory cells from a naïve towards an effector/memory phenotype, or the attraction of a variety of cellular elements like MDSCs or M2 tumor-associated macrophages within the tumor microenvironment.[20]

1.2.3 Radiation therapy counters immune evasion

There are a variety of known molecular and immunologic mechanisms regarding how RT augments, both at the site of irradiation as well as at distant sites not included into the radiation field (abscopal effect), tumor responses which are not only under intense clinical evaluation but where early clinical efficacy signals of synergistic radiation and immunotherapy combinations have already emerged. In brief, mechanisms how RT induces, and augments anti-tumor responses include

- Radiation therapy mitigates evasion of antigen presentation of tumors: Expression of MHC-I molecules, critical for antigen recognition by cognate CD8+ T-cell receptors (TCR)s, is diminished in tumors as tumors can also lose the ability to process antigens intracellularly or can select for less antigenic clones. Radiation, on the other hand, augments MHC-I expression via HMGB-1/toll-like receptor 4 (TLR4) interaction[20-22]
- RT causes dying tumor cells to release high mobility group box 1 (HMGB-1), a well-described "danger signal" that binds and activates TLR4. Activation of TLR4 establishes a mechanistic link between an innate and adaptive immune response that may overcome the failure of the intrinsic immune system, or immunotherapy, to establish a link between the two[23]
- radiation-induced DNA damage or loss of ataxia-telangiectasia mutated (ATM, a protein involved in DNA repair) leads to the release of nuclear DNA in the cytoplasm (cytosolic DNA). After sensing cytosolic DNA, STING (stimulator of interferon genes) adaptor protein will bind to Tank-binding kinase 1 (TBK1), which will be followed by the activation of the transcription of IFN regulatory factor 3 (IFN3) to induce type I interferon (IFN) providing another connection between innate and adaptive immunity[24, 25]
- RT can also generate tumor-specific cytotoxic T cells. Cytotoxic T cells are more easily recruited to the irradiated tumor site due to the release of chemokines such as CXCL16; irradiated tumors also upregulate death receptors (e.g., FAS), promoting the cytotoxic effect of T cells at the tumor site[26]
- The destruction of tumor cells by RT releases usually intracellularly contained antigens which, upon release, gene generate T cell responses[20]

1.2.4 Current progress in immunotherapy for pancreas cancer

Considering the pleiotropy of anti-immunogenic cues in tumors, synergistic combinations of immunotherapy and RT are not limited to one immune pathway but can, and should, involve the targeting of a combination of immune suppressive cues to tip the anti-tumor responses towards tumor elimination [20]. Such a combinational approach, targeting several avenues of immune escape is also supported by clinical observations of immunotherapy in pancreas cancer to date:

while single-agent checkpoint blockade or single therapeutic vaccine therapy failed to elicit any anti-tumor activity, the triple combination of the GVAX vaccine, the anti-mesothelin vaccine CRS-207, a recombinant live-attenuated, double-deleted Listeria monocytogenes engineered vaccine secreting tumor antigens into the cytosol of antigen presenting cells, and mnetromonic cyclophosphamide chemotherapy (administered to reduce T regulatory cells), yielded improved overall survival compared to cyclophosphamide and GVAX [27]. Enhanced mesothelin-specific CD8 T-cell responses were associated with longer OS, regardless of treatment arm. In a follow-up randomized phase II study, the combination of cyclophosphamide, GVAX, and CRS-207 did not show a survival benefit over chemotherapy in patients with previously-treated metastatic pancreatic ductal adenocarcinoma (mPDA). These efforts are now extended, and complemented, by the addition of e.g. anti-PD-L1 checkpoint blockade to improve outcome of combination immunotherapy.[16]

Thus, based on the promise of combination immunotherapy and the pleiotropy of immunological anti-tumor effects of RT this study aims to exploit synergies of RT and immunotherapy using the dual checkpoint inhibitor M7824 targeting the immune checkpoints PD-1/PD-L1 and TGFβ and locally increased levels of IL-12 through the immunocytokine M9241 in combination with RT to improve outcome in locally advanced pancreas cancer. Examples of preclinical and clinical cooperativity/synergy for these individual immunotherapy combinations are as follows:

1.2.4.1 Cooperation of PD-L1 checkpoint inhibition and RT

The dual immune checkpoint inhibitor M7824 used in this trial has two components: one is the recombinant extracellular domain of the human TGFβ receptor, the other is a humanized monoclonal antibody fragment against PD-L1, which is identical to avelumab, the PD-L1 checkpoint inhibitor recently approved for advanced metastatic Merkel cell carcinoma and urothelial cancer and currently in a number of large phase III studies and in combination studies with radiation therapy [28].

Examples of cooperative/synergistic clinical efficacy of immune checkpoint blockade and RT include combining palliative RT with the anti-CTLA-4 checkpoint inhibitor ipilimumab in metastatic melanoma, the combination of the PD-1 inhibitor nivolumab or the CTLA-4 inhibitor ipilimumab with RT therapy for the treatment of brain metastasis in melanoma, or from early and ongoing clinical trials the combination of radiation and immune checkpoint therapy in (oligo)metastatic lung cancer patients treated with thoracic RT and immune checkpoint inhibitors or from the combination in patients with breast cancer [29-31]. Another strong signal for immune-editing of RT comes from the recently released PACIFIC study, a randomized, double-blind, phase 3 study comparing consolidation therapy with durvalumab versus placebo in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after the standard treatment for stage III NSCLC (platinum-based chemotherapy/RT). Patients were randomized to durvalumab (n = 473) or placebo (n = 236). The median PFS was 16.8 months (95% CI, 13.0-18.1) with durvalumab compared with 5.6 months (95% CI, 4.6-7.8) for placebo (HR, 0.52; 95% CI, 0.42-0.65; P <.001). The objective response rates were 28.4% versus 16%.0, respectively (P <.001).

Within this line, PD-L1 inhibition, as part of the dual checkpoint inhibitor M7824 in this clinical protocol, does synergize with radiation therapy in the syngeneic, immune competent pancreas KPC and Panc02 (data not shown from Panc02 mice) preclinical mouse models [32]. **Figure 4** shows that addition of anti-PD-L1 to high (12, 5 × 3, 20 Gy) but not low (6, 5 × 2 Gy) RT doses significantly improved tumor response in KPC allografts. Radio sensitization after PD-L1

blockade was associated with reduced CD11b+Gr1+ myeloid cell infiltration and enhanced CD45+CD8+ T-cell infiltration with concomitant upregulation of T-cell activation markers and increased CD8:Treg ratio. Depletion of CD8+ T cells abrogated radio sensitization by anti-PD-L1. Of note the triple combination of gemcitabine-based chemo irradiation, the addition of gemcitabine as a radiation sensitizer as suggested in the clinical trial, showed the largest anti-tumor impact in the KPC tumors (**Figure 5**).

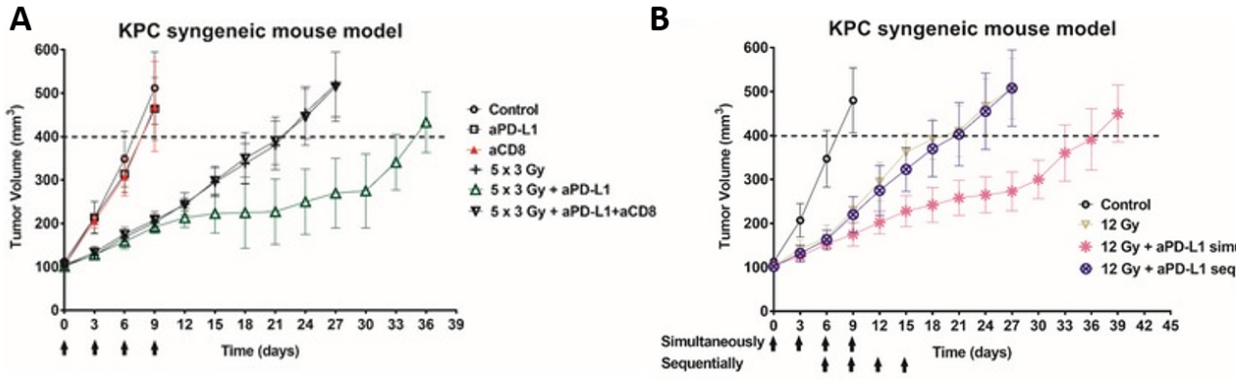


Figure 4: Synergistic effect of RT and PD-L1 inhibition in the syngeneic murine pancreas cancer KPC model. A. Fractionated RT synergizes with PD-L1 blockade to inhibit tumor growth. Synergistic effect is dependent on CD8 T cells. B. Simultaneous PD-L1 administration is superior to sequential administration (from [32])

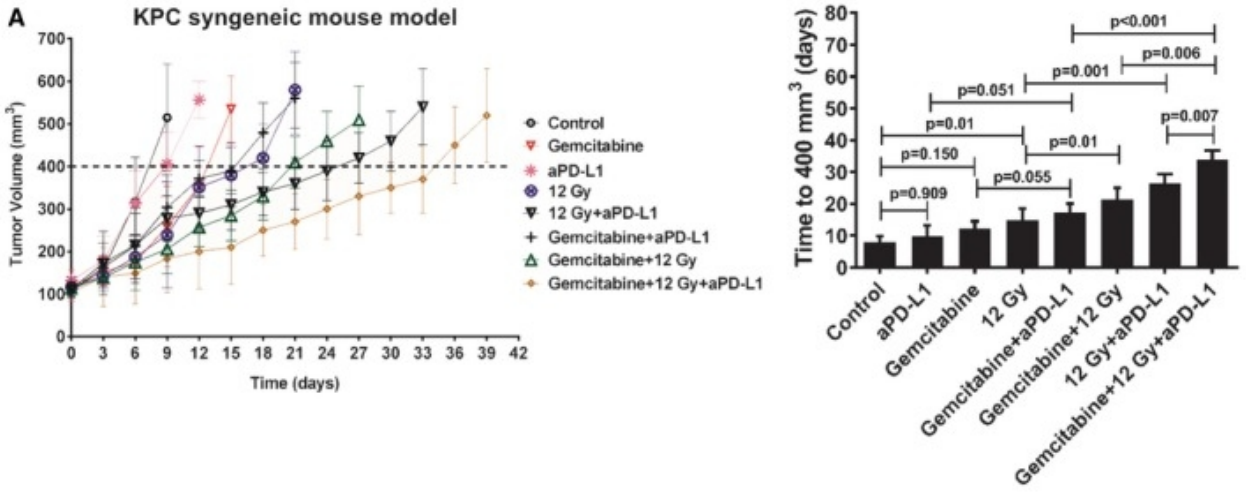


Figure 5: Triple combination of gemcitabine-based chemo irradiation with anti-PD-L1 shows superior efficacy compared to irradiation and PD-L1 blockade without chemo sensitization in KPC pancreas cancer allograft. Tumor growth of indicated regimens over time shown on left, time for tumors to reach 400m^2 on the right (from [32])

Thus, PD-L1 blockade enhances anti-tumor efficacy of RT in preclinical models of pancreas cancer. The cooperative effect is further improved through the addition of gemcitabine-based radio sensitization (CRT) as in the proposed trial.

1.2.4.2 Preclinical and clinical cooperation of TGFβ blockade in combination with RT

The TGF beta receptor small molecule inhibitor LY2157299 (galunisertib) is currently undergoing phase II clinical testing in combination with neoadjuvant chemoradiation in patients with rectal

adenocarcinoma (ExIST study - NCT02688712) and the mAb TGF beta inhibitor fresolimumab, an anti-transforming growth factor beta (TGFB) antibody, as part of the SABR-ATAC trial (Stereotactic Ablative Radiotherapy and anti-TGFB Antibody Combination - NCT02581787) in combination with RT for the treatment of NSCLC. TGF beta inhibitors are also combined with SBRT for glioblastoma.

These clinical trials are based on a plethora of preclinical data showing that TGFβ inhibition augments the effects of RT.

To show that above findings of

- cooperativity of PD-L1 inhibition and RT

- cooperativity of TGFβ inhibition and RT (the two components of M7824)

are indeed reproducible with the use of M7824, the dual PD-L1 and TGFβ inhibitor used in the proposed clinical trial, M7824 was tested in combination with RT in the syngeneic, immune competent MC38 cancer model:

Figure 6 shows the significant synergy between M7824 and RT, both at the local tumor site as well as at distant tumor sites (abscopal effect) leading (1) to significant tumor regression in the combination group in this model, and (2) significant induction of anti-tumor activity as shown by enhanced interferon gamma release of CD8+ T cell isolated from these tumors and co-cultured with cancer cells (EliSpot assay) [28]. M7824 and the first fraction of RT was given at the same time. Thus, both PD-L1 and TGFβ inhibition individually synergize with RT, with early clinical data in favor of immune checkpoint inhibition and radiation therapy emerging, and dual inhibition of PD-L1 and TGFβ signaling with M7824, as proposed in this study, in combination with RT causes tumor regression in preclinical syngeneic cancer models.

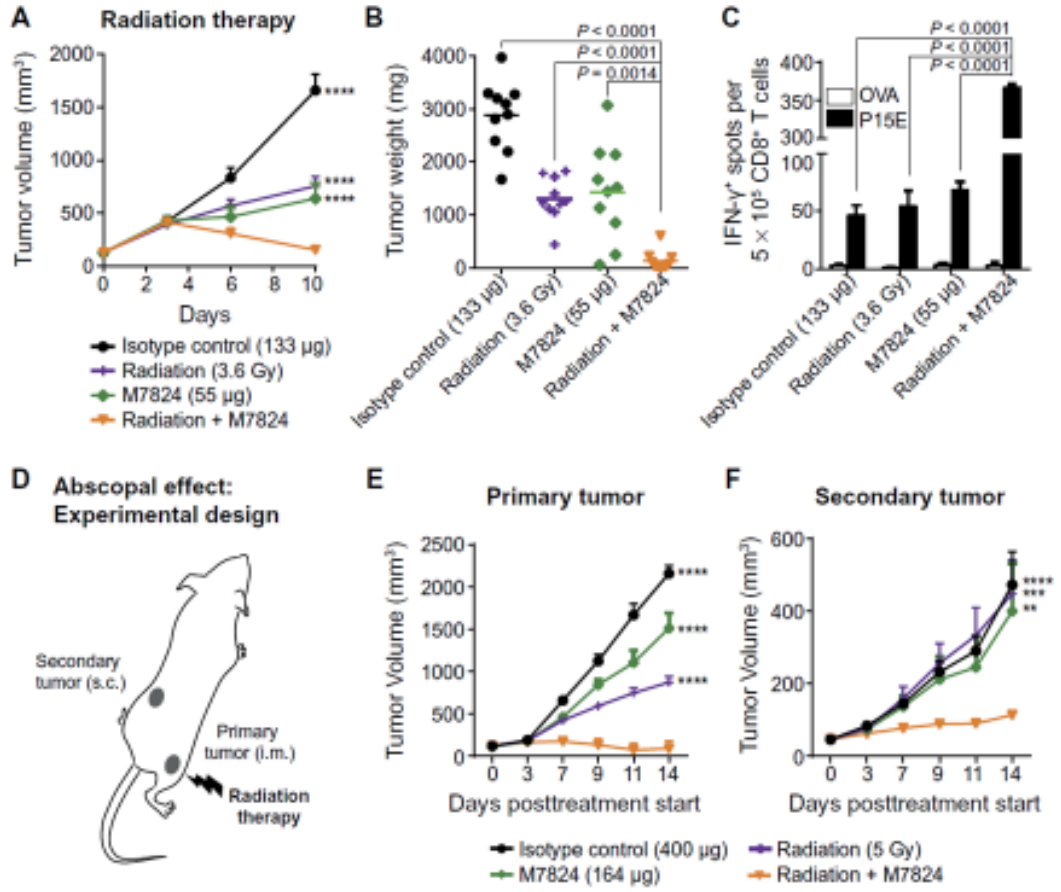


Figure 6: Low dose radiation combined with a single low dose of M7824 induced tumor regression that is associated with a strong T cell response in MC38 tumors. A. Tumor volume of MC38 mice treated with vehicle, low-dose irradiation, M7824, and the combination of RT and M7824. B. Tumor weights at 14 days. C. Intratumoral CD8+ T cell activity of four cohorts. D-F. Local irradiation in combination with M7824 induces anti-tumor responses at sites distant from irradiated tumors (from [28])

1.2.4.3 IL-12 immunotherapy in combination with RT

Interleukin-12 (IL-12) is a proinflammatory cytokine produced by activated phagocytes and dendritic cells (DCs) that plays a critical role in regulating the transition from innate to adaptive immunity. IL-12 acts directly on cytotoxic immune effector cells, namely natural killer (NK) cells, NKT cells, and CD8+ T cells, to stimulate their proliferation and increase their cytotoxic functions.[33] Furthermore, IL-12 drives differentiation of helper T cells down the Th1 pathway, thereby promoting the production of cytokines, most notably IFN-γ, that favor cell-mediated immunity.[34] There is also evidence that IL-12 acts directly on DCs to further stimulate IL-12 production and enhance antigen presentation.[35] By amplifying these positive immunostimulatory effects, therapeutic administration of exogenous IL-12 has the potential to promote effective anti-tumor immune responses.

Despite this therapeutic rationale, recombinant (r) IL-12 has yet to be approved for any indication, due to previously reported toxic side effects of systemic administration, which may have limited its ability to induce objective response rates, and delaying further clinical development.[36, 37] In a phase I study of rIL-12, dose levels tolerated during repeated administrations proved to be toxic in a subsequent phase II trial.

Nevertheless, IL-12 has shown some promising clinical activity in phase I trials, including stabilization of disease in renal cancer patients, with partial regression of a metastatic lesion.[38] This is a clear example of rIL-12's ability to create anti-tumor immune responses when applied at maximum tolerated dose (MTD) over an extended period of time.[39] Furthermore, higher objective response rates with rIL-12 have been reported in certain neoplastic diseases, including T-cell lymphoma (56%), non-Hodgkin's lymphoma (21%), and AIDS-related Kaposi's sarcoma (50-71%).[40-42]

The M9241 concept is one strategy to reduce the toxicity associated with systemic administration of recombinant human IL-12, by altering pharmacokinetics and selectively targeting delivery of IL-12 to tumors.[43] The NHS antibody component has been shown to selectively target human lung carcinomas as a radiolabeled monoclonal antibody. The M9241 immunocytokine is composed of two IL-12 heterodimers, each fused to one of the H-chains of the NHS76 antibody that has affinity for both single- and double-stranded DNA which are abundant in areas of tumor necrosis.[44] This antibody targets IL-12's delivery to regions of tumor necrosis where DNA has become exposed, like post-radiation therapy, thus increasing intratumoral exposure and reducing systemic exposure.[43] That pancreatic cancer is a solid organ malignancy with per se heterogenous and poor perfusion and high rate of necrosis is shown in **Figure 7**.

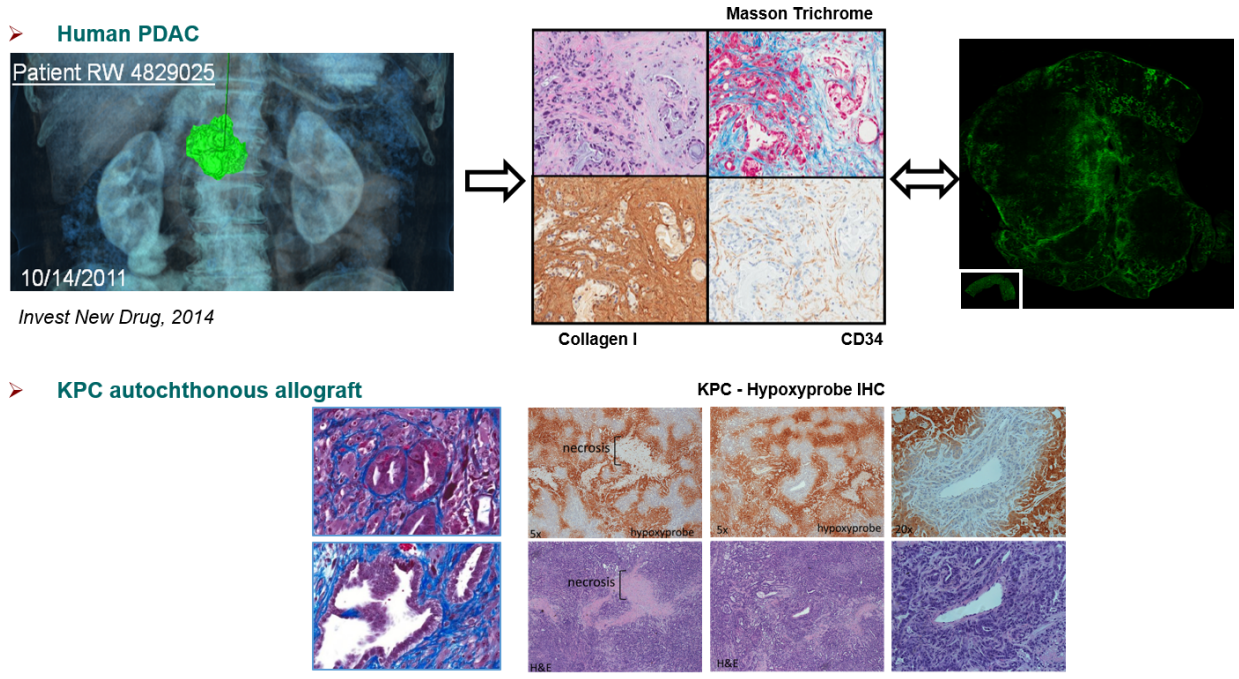


Figure 7: Example of dense human pancreatic cancer stroma. Masson trichrome, collagen I with poor vascularization (by anti-CD34 staining) (top) and large areas of poor perfusion (Dextran perfusion; upper right) with intratumoral necrosis (by hydroxy probe detection) in autochthonous murine pancreatic tumors (bottom).

Thus, not only does this targeted strategy have the potential to reduce systemic toxicity, but it also has the potential to increase immune infiltration and activity locally within the tumor microenvironment, as well as systemically (abscopal effect), and is ideally suited to be combined with RT.[45, 46] With the other anti-tumor immunogenic effects of RT this in turn has the potential

to optimal prime otherwise non-immunogenic tumors like pancreas cancer to checkpoint inhibition and increase the spectrum of cancers which may respond to these agents. That administration of IL-12 limited by local intratumoral injection of an adenovirus (Ad) encoding interleukin-12 gene already can mediate improved anti-tumor immunogenicity has been shown by a previous phase I study of repeat intratumoral injections of Ad-IL-12 into primary liver, and secondary colon and pancreas cancer liver lesions.[47] In four of 10 assessible patients who received more than 4 injections a significant increase in tumor infiltration by effector immune cells including CD8+ T cells was note with some stable diseases and one objective tumor regression (in HCC).[47]

Figure 8 shows the significant synergy of M9241.

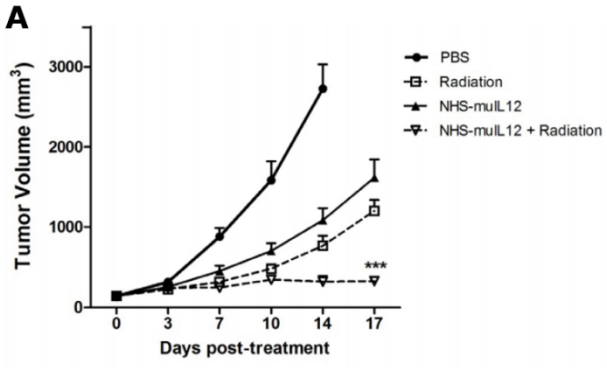


Figure 8: M9241 cooperatives with both radiation therapy. A. Effect of vehicle, M9241 monotherapy, low-dose radiation, and the combination of M9241 and RT in the Lewis lung cancer model. (from **[**44**]**)

Additionally, the two investigational agents M7824 and M9241 do cooperate in syngeneic murine models of cancer inducing tumor regressions and extension of survival (**Figure 9**). Immune profiling of both tumor and splenic immune subsets as well as T cell activity measures via EliSpot assays suggest cooperativity of two independent, non-overlapping immune strategies funneling into enhanced tumor antigen recognition and anti-tumor immunogenicity (data not shown).

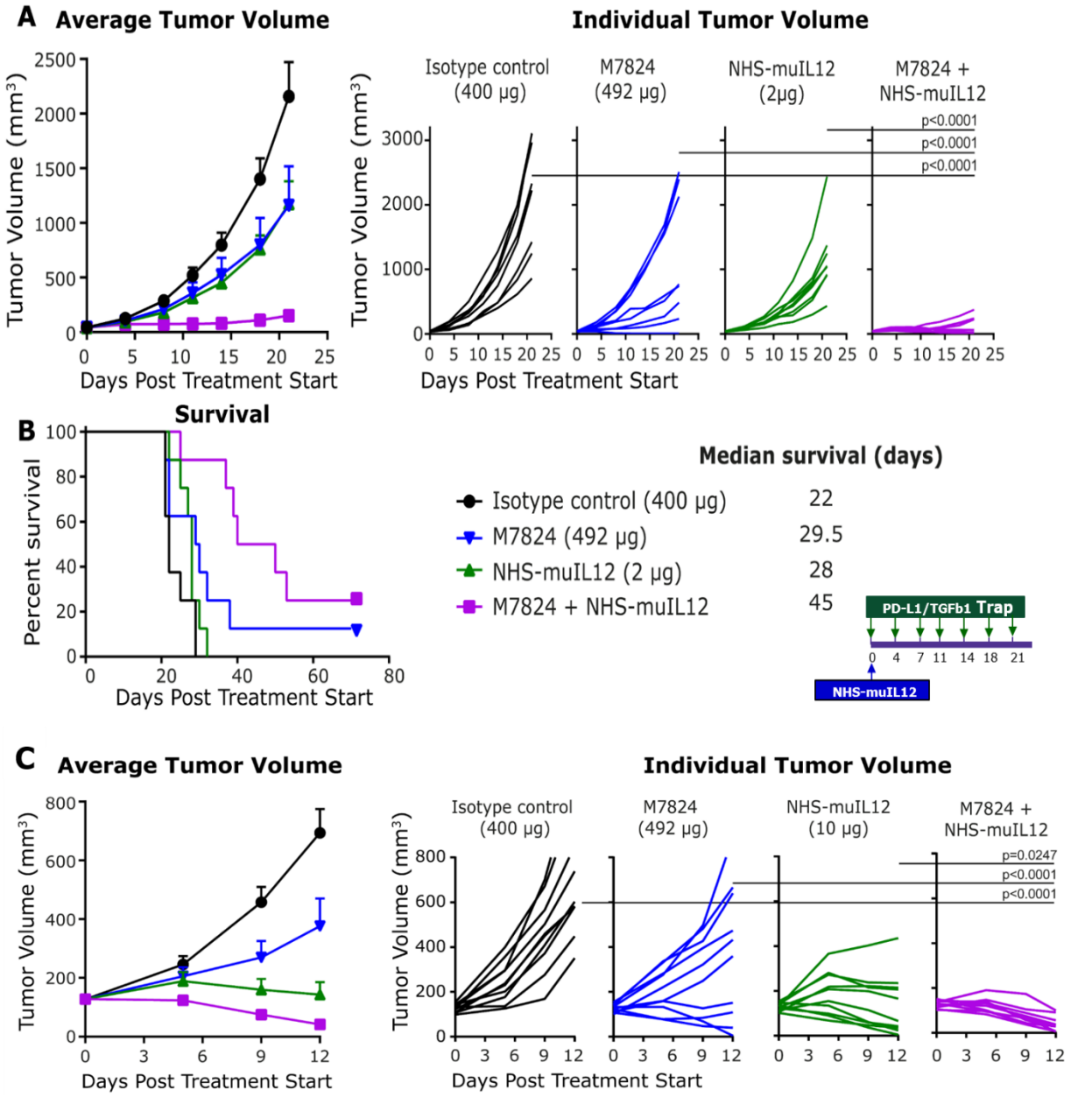


Figure 9: M7824 in combination with M9241 improves anti-tumor activity compared to M7824 and M9241 monotherapy. A. Anti-tumor activity, and B. Overall survival of mice with syngeneic MC38 tumors treated vehicle (black), M7824 alone (blue), M9241 (green), and the combination of M7824 and M9241 (purple). C. Anti-tumor activity of the same treatment regimens in the EMT-6 orthotopic breast cancer model in Balb/c mice.

In summary, the above data suggest that both of the investigational agents – the immunocytokine M9241 and the dual PD-L1 - TGFβ inhibitor M7824 – cooperate / exert synergistic activities with RT. Furthermore, the agents themselves, M7824 and M9241, independently cooperative in immune competent preclinical models of cancer. Thus, this trial derives its rationale of multiple synergies of combination immunotherapy and RT to improve outcome in LAPC.

1.2.5 M7824 (bintrafusp alfa; bifunctional fusion protein targeting PD-L1 and TGF-β)

To date, M7824 has been given to more than 600 patients at the 1,200 mg dose levels (please refer to Investigator Brochure, 04/2019). The important potential risks of M7824 include infusion-related reactions including hypersensitivity, immune related adverse event (irAE)s /autoimmune disorders, anemia, rash with hyperkeratosis/ keratoacanthomas/ squamous cell carcinoma (SCC) of the skin, possible embryo-fetal toxicity, and alterations in wound healing or repair of tissue damage [28]. All of these are considered important potential risks.

In line with early clinical experience of similar anti-TGFβ agents, the toxicity profile of M7824 is described as predominantly benign; in the recently released results of the phase I study NCT02517398 - 'Phase 1 Trial of M7824, a Bifunctional Fusion Protein Targeting PD-L1 and TGFβ, in Advanced Solid Tumors' with dose escalation cohorts of 1, 3, 10, and 20mg/kg (+ 1,200 mg flat starting dose in this study). M7824 given 2-weekly, the MTD was not reached: data suggested overall good tolerance. One out of 16 patients developed a keratoacanthoma which could be related to the TGFβ inhibition mechanism of M7824. There was no grade 4-5 adverse events (AEs). The only DLT observed was colitis. Overall, the MTD was not exceeded at doses up to 20 mg/kg. The overall safety profile of M7824 in Phase I was considered well tolerated, can be adequately managed, and was consistent across various tumor types.

Further updated information on these risks (e.g. presenting symptoms) can be found in the current version of the M7824 Investigator Brochure

Currently no clinical data exists for the combination of M9241 and M7824. Preclinical data has demonstrated potential synergy between PD-L1 blockade and muNHS-IL12 (M9241) which has led to the clinical evaluation of the combination of avelumab (anti-PD-L1) and M9241 in a phase Ib open-label, dose-finding trial in subjects with locally advanced, unresectable, or metastatic solid tumors (NCT02994953). At present, 16.8 mcg/kg Q4W via subcutaneous injection (dose level 8) is the current recommended phase II dose (RPD2) of M9241 without concerning safety signals in this trial.

1.2.5.1 Summary of Clinical Findings of M7824 including Adverse Events (AEs) in Pancreas Cancer Patients to date:

As of December 2017, at least N=36 patients with a diagnosis of advanced pancreas cancer have received at least one, or more, doses of 1,200 mg of M7824. Overall, the drug was well tolerated at the 1,200 mg dose level with a typical AE profile for an advanced cancer patient cohort. Of note, anemia was (6 out 36; 16.7%) was the most common grade 3 or greater toxicity. The only other grade 3 toxicities occurring in more than 10 percent of study subjects were fatigue (4 out of 36; 11.1%) and abdominal discomfort (4 out 36; 11.1%). There were 5 subjects with ≥grade 3 events listed as related to M7824. These include G4: lipase increased (1 event), and G3: anemia (2), colitis (1), diarrhea (1), ALT increase (1).

Preliminary clinical efficacy signal of the N=36 pancreatic cancer M7824 monotherapy cohort (provided by EMD Serono): while PD-1/PD-L1 monotherapy in unselected patients has not shown any activity preliminarily, clinical activity has been seen with objective responses and a prolonged disease stabilization rate of 16.7%. The cohort is being actively reviewed and remains dynamic.

At least 2 instances of nodular regenerative hyperplasia have been observed with the use of this agent.

1.2.6 M9241

M9241 was evaluated in a phase I study on safety, tolerability, pharmacokinetics, biological and clinical activity, as well as the effects on immune cell subsets and TCR clonality in patients with metastatic or locally advanced solid epithelial or mesenchymal tumors at the National Institute of Health (NIH) Clinical Center.[48]

A total of 59 patients were enrolled and treated with M9241. The single ascending dose cohort included a total of 22 patients who received one single dose administration of M9241 on day 1 and completed the study after 28 days of safety observation. In the multiple ascending dose escalation and expansion cohorts, a total of 37 patients were enrolled and treated every four weeks.

The primary objective of this trial was to determine the MTD as defined by the number of DLTs. None of the subjects treated with single or multiple doses up to and including 12.0 µg/kg experienced a DLT. At the 16.8 µg/kg dose level, one out of six subjects had a DLT (Grade 3 increase in ALT). At the 21.8 µg/kg dose level, two out of six subjects had a DLT (Grade 3 increase in AST and ALT; Grade 3 increase in lipase without clinical signs of a pancreatitis) and the MTD was determined to be 16.8 µg/kg administered subcutaneously every four weeks, per formal protocol criteria.

1.2.6.1 Treatment-related adverse events

The most frequently observed treatment-related adverse event was a decrease in lymphocyte count in 27 subjects (45.8%), followed by a decrease in WBCs in 24 subjects (40.7%), fever and an increase in AST, each in 21 subjects (35.6%), an increase in ALT in 20 subjects (33.9%), and anemia and flu-like symptoms, each in 18 subjects (30.5%) (**Table 1**).

Twelve of the overall 59 subjects (20.3%) experienced at least one ≥ Grade 3 treatment-related adverse event. These included events of a decrease in lymphocyte count in five subjects (8.5%), a decrease in neutrophil count in four subjects (6.8%), an increase in ALT in three subjects (5.1%), a decrease in WBCs in two subjects (3.4%), and hypokalemia, hyperhidrosis, an increase in alkaline phosphatase, an increase in AST, and an increase in lipase, each in one patient (1.7%). Of these subjects who had Grade ≥ 3 treatment-related AEs, all were transient and only one event (Grade 3 hyperhidrosis) was symptomatic. Only one Grade 4 event (asymptomatic decrease in lymphocyte count) was observed and no Grade 5 treatment-related AE was observed.

Table 1: Adverse Events of M9241

	Grade 1/2 **n (%)**	**Grade 3** **n (%)**	**Grade 4** **n (%)**
Decrease in lymphocyte count	21 (35.6%)	5 (8.5%)	1 (1.7%)
Decrease in neutrophil count	6 (10.2%)	4 (6.8%)	0
Thrombocytopenia	12 (20.3%)	0	0
Decrease in WBCs	22 (37.3%)	2 (3.4%)	0
Hyperglycemia	10 (16.9%)	0	0

	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypoalbuminemia	6 (10.2%)	0	0
Hypokalemia	0	1 (1.7%)	0
Hypophosphatemia	6 (10.2%)	0	0
Hyperhidrosis	0	1 (1.7%)	0
Anemia	18 (30.5%)	0	0
Fatigue	10 (16.9%)	0	0
Fever	21 (35.6%)	0	0
Flu-like symptoms	18 (30.5%)	0	0
Increase in ALT	17 (28.8%)	3 (5.1%)	0
Increase in alkaline phosphatase	12 (20.3%)	1 (1.7%)	0
Increase in AST	20 (33.9%)	1 (1.7%)	0
Increase in lipase	0	1 (1.7%)	0

Nine subjects (15.5%) experienced serious AEs, two of which (3.4%) were assessed as related to M9241 treatment. Generally, similar incidences of AEs and serious AEs were observed between the single dose and multiple dose groups despite different observation periods. In the latter, the rate of AEs ≥ Grade 3 and AEs related to M9241 was slightly higher. In the single dose group, no subject experienced an AE leading to permanent discontinuation of treatment and no subject had any serious AEs assessed as related to M9241 (**Table 1**).

Table 2 below summarizes Treatment Emergent Adverse Events of M9241 from phase I clinical testing.

TEAE categories	Single dose (*n* = 22) *n* (%)	Multiple doses (*n* = 37) *n* (%)	Overall (*n* = 59) *n* (%)
Any TEAE	21 (95.5%)	36 (97.3%)	57 (96.6%)
Any grade ≥3 TEAE	7 (31.8%)	15 (40.5%)	22 (37.3%)
Any TRAE	17 (77.3%)	31 (83.89%)	48 (81.4%)
Any grade ≥3 TRAE	2 (9.1%)	10 (27.0%)	12 (20.3%)[a]
Any TEAE leading to permanent discontinuation of study drug	0 (0.0%)	3 (8.1%)	3 (5.1%)
Any serious TEAE	3 (13.6%)	6 (16.2%)	9 (15.3%)
Any serious TRAE	0 (0.0%)	2 (5.4%)	2 (3.4%)

Table 2. Overview of known Treatment Emergent Adverse Events of M9241

Further updated information on these risks (e.g. presenting symptoms) can be found in the current version of the M9241 Investigator Brochure

1.2.6.2 Response to Therapy

No objective tumor responses were observed according to the modified RECIST criteria in the phase I study with M9241. Out of 30 subjects with measurable disease, 15 had stable disease and 15 had progressive disease as Best Overall Response (BOR). Five patients (prostate x2, colorectal, breast, chordoma) stayed on study treatment for ≥182 days. More specifically, two patients, one with prostate cancer and one with chordoma, had prolonged stable disease for 30+ months (ongoing) and 13 months, respectively.

1.2.6.3 Pharmacokinetics and Pharmacodynamics Data

PK data from the single dose and multiple dose cohorts show a dose dependent increase in $T_{1/2}$, C_{max}, and AUC for M9241. PD data from this trial demonstrates a time-dependent rise in plasma IFN-γ levels after administration and a subsequent rise of IL-10. These correspond to a rise in IL-12 similar to what is seen with the PK data, peaking around 36 hours, and then falling to near baseline levels around day 8. Looking only at the multiple dose patients, in most cases, despite a similar rise in the serum IL-12, a diminished rise in IFN-γ and IL-10 is observed after the second dose. The pharmacokinetic and pharmacodynamic parameters for M9241 dosed at the MTD of 16.8 µg/kg every four weeks are shown in **Appendix B**. A time-dependent rise in IFN-γ was noted after administration and a subsequent rise of IL-10. These corresponded to a rise in IL-12 similar to what was seen with the PK values, peaking around 36 hours, and then falling to near baseline levels around day 8. When patients were re-dosed at four weeks, in most cases, despite a similar rise in the serum IL-12, a diminished rise was noted in IFN-γ and IL-10 with the second dose. The frequencies of five refined immune cell subsets changed significantly one week post−cycle 1 vs. pre−M9241 (NHS-IL-12) treatment for 10 patients at dose level 8 (16.8 µg/kg) (**Appendix B**).

The frequencies of five refined immune cell subsets changed significantly one-week post−cycle 1 vs. pre−M9241 (NHS-IL-12) treatment for 10 patients at dose level 8 (16.8 µg/kg).

Overall, PD data from this trial (**Appendix B**) demonstrated a time-dependent rise in IFN-γ after administration and a subsequent rise of IL-10 about 36 to 48 hours after administration. Looking only at multiple dose patients, we observe, in most cases, despite a similar rise in the serum IL-12, a diminished rise in IFN-γ and IL-10 on the second dose. Overall, M9241 is well-tolerated with a benign safety profile which has, with the exception of lympho- and leukocytopenia, limited to no overlap with the toxicity profile known from RT.

1.2.7 Neoadjuvant RT for pancreas cancer – SBRT with Simultaneous Integrated Boost (SIB)

Both EBRT and stereotactic regimens are described in ASCO's 2016 Practice Guidelines on management of locally advanced, unresectable and potentially curable (borderline resectable) pancreas cancer as acceptable treatment modalities.[5, 6] The Eastern Cooperative Oncology Group trial as one of the few randomized studies provided hereby one of the strongest rationales for the inclusion of RT regimens into treatment algorithms of LAPC; the study compared gemcitabine chemotherapy with gemcitabine plus RT, and while it did not complete accrual and terminate early, it identified a signal for improved local control and survival for the combination group. [49]

Stereotactic body radiation therapy (SBRT) is a method of external beam radiotherapy which delivers higher doses compressed into fewer fractions. Due to its increased risk of toxicity to surrounding, not involved structures it is dependent robust target definition and respiratory motion

control.[50] These pre-requests are particularly important in SBRT of pancreatic head and body lesions which are surrounded by a complex GI and vascular structures.[51] Over the last decade there have been several series of SBRT treatment for LAPC emerged which attest to the safety of this approach overcoming the challenges of gross tumor volume delineation (GTV) and reduction of internal motion. **Table 3** provides an updated and extended review of studies on SBRT for the management of LAPC reflecting the recent increase in the use of SBRT for LAPC. Additional literature corroborating the safety and above outcomes of SBRT in LAPC include the large experience on 167 patients published by the Stanford group or a recent systematic review analyzing outcome with special focus on toxicity of 16 studies (572 pancreatic cancer patients) treated with SBRT.[52, 53] Overall, following neoadjuvant therapy, approximately up to one third of patients initially felt to be unresectable were converted to resectable status.[51, 54]

Table 3: Series of studies on the use of SBRT in LAPC.[55-65]

Study type	# of patients	Radiation dose	Chemotherapy	Median followup	Overall survival	Local control
Retrospective	77	25 Gy/1	Gemcitabine based (96%)	6 months	1 year: 21%	84%
Retrospective	88	25–33 Gy/5	Gemcitabine based (72%) FOLFIRINOX (15%)	14.5 months (LAPC) 10.5 months (BRPC)	1 year: 73% Median: 18.4 months	61%
Prospective	23	30 Gy/3	Gemcitabine	9 months	Median: 10.6 months	NR
Phase II	20	25 Gy/1	Gemcitabine based (100%)	NR	1 year: 50%	88–94%
Retrospective	47	24–36 Gy/3	Gemcitabine based (100%)	21 mos (survivors)	Median: 20 months	85%
Prospective	20	20–25 Gy/1 24–30 Gy/3	NR (68%)	14.5 months	Median 14.4 months	65%
Pilot	10	25 Gy/5	Concurrent gemcitabine (100%)	NR	Median 12.2 months	NR
Phase II	49	33 Gy/5	Gemcitabine based (100%)	13.9 months	Median: 13.9 months	78%
Retrospective	12	36 Gy/3 24 Gy/1	Gemcitabine based (92%)	NR	1 year: 92% Median: 47.2 months	NR. CR seen in 25%.
Prospective	157	30 Gy/5	Gemcitabine based (82%) FOLFIRINOX (14%)	14.0 months	Median: 18.1 months	78% in non-surgical patient
Retrospective	24	20–24 Gy/1	Gemcitabine based (79%)	12.5 months	1 year 80.4% Median 26.7 months	66%

Overall these studies consistently describe a median overall survival in LAPC of about 1 year, a grade 3 and higher toxicity rate of ~10-15%, primarily acute GI toxicity in the form of radiation enteritis with symptoms of nausea, vomiting, and abdominal pain, and less frequently bone marrow

depression with leukopenia and lymphopenia, as well as generalized symptoms of fatigue. There is an urgent medical need to improve these outcomes.

Since in the majority of patients, tumor motion exceeded the predicted range by 10% when using motion management planning strategies like four-dimensional computed tomography (4D CT), in order to improve accuracy and reduce damage to surrounding areas for regimens exceeding 5 Gy x 5 fractions the use of fiducial markers is recommended. Thus, the “current practice / standard of care" in leading medical centers is to use fiducials, along with respiratory motion management during treatment and doses in the order of 6.6 Gy x 5 to the tumor or greater.

Since borderline resectable patients are, in theory, potentially curable, if the tumor can be resected, the primary purpose of the radiation is to reduce the size of the tumor and to sterilize what would be the margins of resection, so that the resection can have the best odds of being part of a curative management plan. In the absence of surgery, a biologically equivalent dose (BED) of ~100 Gy should be delivered to achieve maximum ablative effect within the tumor. However, tumor control and reduction in tumor size (conversion from unresectable to resectable) is achieved with treatment strategies with a BED. **Table 4** of listing converting BED of different SBRT regimens shows that 5 Gy x 5 (25 Gy total) is likely to improve resect ability. This study will deliver 5 Gy x 5 (25 Gy total) via SBRT with simultaneous integrated boost after mandatory placement of fiducials (biliary metal stent acceptable as alternative). **Table 4** compares Equivalent Dose in 2 Gy fractions (EQD2), Biological Equivalent Dose (BED), and treatment delivery and radiobiological considerations for selected dose/fractionation schemes that can be used for treating advanced pancreatic cancers.

Table 4: Biologically equivalent doses of different SBRT regimens for the treatment of LAPC

EQD2

alpha/beta	8 Gy x 1	5 Gy x 5	3 Gy x 12	6.6 Gy x 5	25 Gy x 1
3	17	40	43.2	**63**	140
7	13	33	40	**50**	88
10 (tumor)	12	31	39	**46**	72

BED

alpha/beta	8 Gy x 1	5 Gy x 5	3 Gy x 12	6.6 Gy x 5	25 Gy x 1
3	29	67	72	**106**	233
7	17	42	51	**64**	114
10 (tumor)	14	37	47	**55**	87

Current Uses of Hypofractionated Dose, Fractionation in Stage III-IV Pancreas Cancer

Dose, fx	8 Gy x 1	5 Gy x 5	3 Gy x 12	6.6 Gy x 5	25 Gy x 1
Common Use	Metastatic, palliative	Metastatic, palliative	Preoperative LAPC, improve rate of negative margins	**Standard of Care for LAPC**	Locally advanced, not surgical candidate
Fiducials required?	no	no	no	**yes**	yes
Radiobiology (immune)	Predicted immune adjuvant	Possible immune adjuvant	Not predicted immune adjuvant	**Predicted/possible immune adjuvant**	Not predicted immune adjuvant
Radiobiology (tumor control)	Intermediate	Intermediate	Good for pre-op	**Good**	Excellent, but more duodenal ulcer risk

A biliary metal stent, or other radio-graphically identifiable marker, in or adjacent to the pancreatic mass could potentially serve the same function of the fiducials, and it is expected that 20-30% of our locally advanced pancreas patients have stents in place. Huhuet at al evaluated the correlation of tumor motion with implanted fiducial markers or with biliary stent, and confirmed that both fiducial markers and biliary stent motion correlated well with tumor motion, and that tracking of both would be clinically appropriate.[66]

Figure 10 shows an example of a LAPC patient treated with SBRT and SIB, where the primary tumor was treated with 5 fractions of 5 Gy (total 25 Gy) under National Cancer Institute (NCI) study 15-C-0027 ('Immune Checkpoint Inhibition (Tremelimumab and/or MEDI4736) in Combination With Radiation Therapy in Patients With Unresectable Pancreatic Cancer') by Dr. J. Jones at the Clinical Center. The adjacent diagram delineates an example of dose SIB dose levels that can be used to deliver different doses to different areas of tumor involvement or risk.

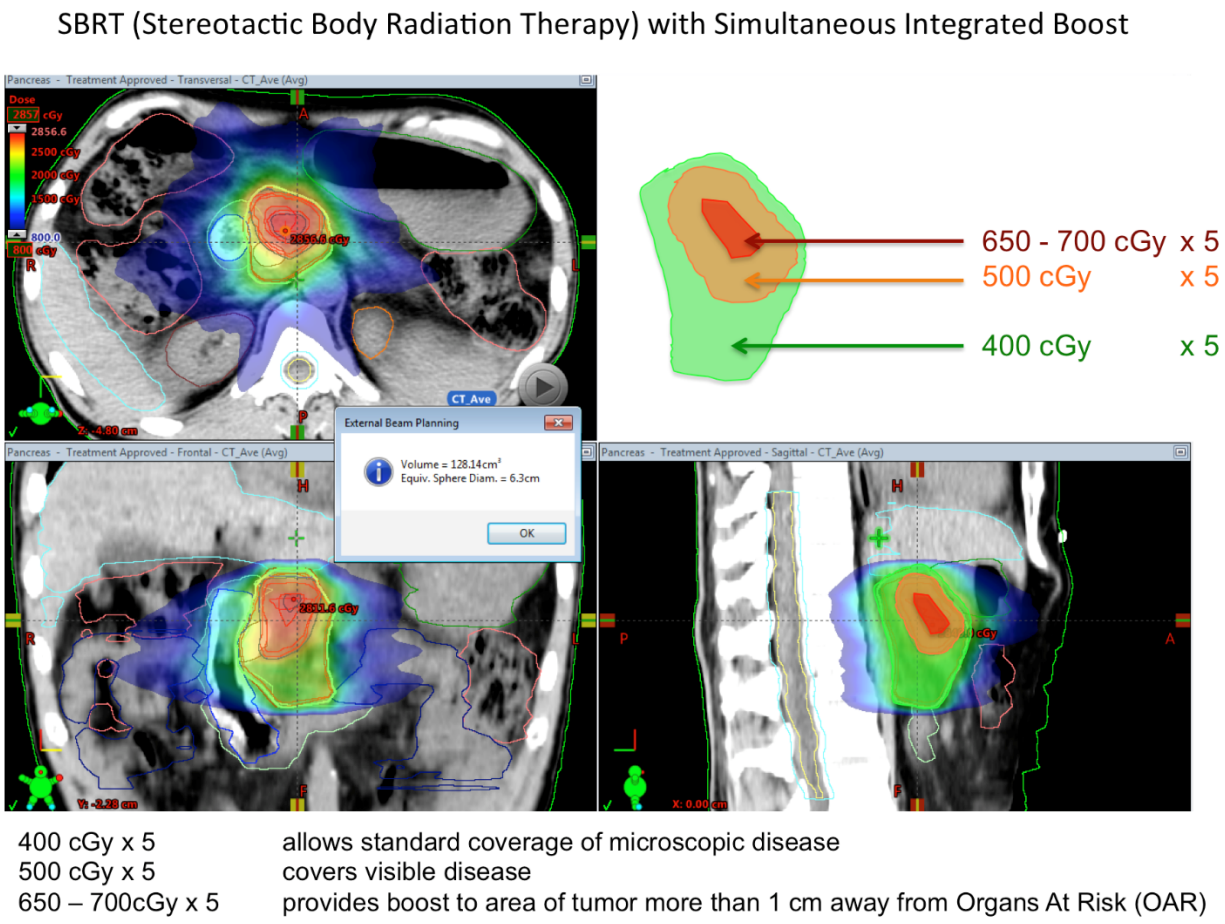


Figure 10: Isodose fields with drop-offs by SBRT with SIB

The safety of the above treatment scheme has also been reported by other institutions. A retrospective review from the Moffitt Cancer Center analyzed 73 patients with LAPC or borderline resectable pancreatic cancer who underwent chemotherapy followed by SBRT to a dose of 35 Gy to the area of vessel involvement and 25 Gy to the remaining tumor over 5 fractions.[67] Thirty one of 32 patients with borderline resectable cancer achieved an R0 resection. Median overall survival at 1 year for borderline resectable versus LAPC patients was 16.4 versus 15 months. Those patients with borderline resectable lesions who attained R0 resection had improved median overall survival as compared with nonsurgical patients, although 1-year local control in nonsurgical patients was 81%. There was no grade 3 or greater acute toxicities. Four patients were noted to have late grade 3 toxicities (3 with GI bleeding requiring embolization and 1 with anorexia resulting in feeding tube placement). It is important to note that toxicities due to RT cannot infrequently occur in a delayed fashion; for example, in of the largest retrospective reviews on SBRT in LAPC median time to grade 2 to 4 toxicities was 6.3 months. At 6 months, the actuarial rate of toxicity was 11%, and at 12 months, this rose to 29%.[68]

The optimum sequence of immune-oncology agents and RT has not been established. We have elected to start M7824 and M9241 2 weeks prior to SBRT because of maximal MHC expression and tumor antigen presentation that is changed by radiation happens within 48-72 hours after radiation. While cross-presented antigen, upregulated by cGAS/STING/dsDNA-related

mechanisms, and dsDNA released by the irradiated and dying but not-yet-disappeared cells can in many tumors persist for very long periods of time as they march towards eventual mitotic catastrophe, giving the immunomodulating agents upfront priming the microenvironment towards antigen recognition and CD8 T cell response appears to have the highest likelihood of exploiting all RT-induced changes which might not be synchronous for immunogenic synergy. Administering the M7824 and M9241 beginning 2 weeks prior to SBRT allows for the delivery of radiation shortly after M7824 and M9241 have been introduced, with M7824 and M9241 continuing during and after the radiation, so that the predicted peak period of antigenicity following radiation coincides with activity of the immunomodulatory agents.

1.2.8 Health-related quality of life

It is conceivable that clinical benefit of the tested combined M7824 and M9241 with RT approach is limited to improvement in QoL measures of treated patients. For example, some of the studies of SBRT listed in **Table 3** showed 'only' self-reported improvement in pain scores and QoL parameters but no change in traditional efficacy readouts response or survival when compared to historical controls. To evaluate the impact of M7824 and M9241 in combination with RT on patients' pain scores and treatment-related reported symptoms, scores of symptom subsets of the FACT-Hep (**Appendix C**) will be longitudinally completed before and during the treatment.

The 'Functional Assessment of Cancer Therapy' (FACT-G; version 4) with the hepatobiliary and pancreatic specific module (FACT-Hep)' is a 45-item self-report instrument developed specifically to measure HRQoL in patients with hepatobiliary cancer (i.e. liver, bile duct and pancreatic cancers; please see (**Appendix C**).[69] It consists of the FACT-G, which assesses symptoms and other HRQoL concerns across four dimensions (physical well-being [PWB; seven items], social/family well-being [SWB; seven items], emotional well-being [EWB; six items] and functional well-being [FWB; seven items]) together with an 18-item disease-specific hepatobiliary cancer subscale (HCS; on page 3 of the instrument) including back and stomach pain, gastrointestinal symptoms, anorexia, weight loss and jaundice in patients with hepatobiliary cancers. It was developed by a process of item generation based on input from patients with hepatobiliary cancers, item reduction based on clinician input, scale construction and reliability/validity testing. Respondents of FACT-based questionnaires rate each item using a five-point Likert-type scale ranging from 0 (not at all) to 4 (very much). The FACT-Hep questionnaire has been shown to be a reliable instrument that correlates with clinical indicators of disease progression and response to treatment and can aid interpretation of HRQL data. Multiple studies in advanced pancreas cancer have reported QoL data in the 2nd and 3rd line setting using the instrument, and measures obtained during this study will be compared to these historical controls.

1.2.9 Rationale for this clinical trial

The administration of M7824 and M9241 in combination with SBRT to subjects with locally advanced pancreatic cancer is justified by the following:

- The synergistic action of PD-L1 inhibition mediated by the dual PD-L1 TGFβ blocker M7824 and RT, including the emerging clinical data of improved outcome upon checkpoint blockade and RT.
- The synergistic action of M9241 and RT.
- The synergistic action of M7824 and M9241.

- Administered dose and schedule of the standard RT is not changed due to the addition of M7824 and/or M9241.
- M7824 and M9241 and RT have largely non-overlapping toxicity profiles which are manageable.

1.2.9.1 Rationale for M7824 and M9241 Dose Levels with special consideration of overlapping toxicities with SBRT

The safety run-in of M7824 and M9241 will be carried out in patients with stages III and IV or locally advanced pancreas cancer.

The toxicity profile of M7824 is predominantly benign, see section **1.2.5**.

M7824 and SBRT carry hematological toxicities (anemia for M7824), M9241 and SBRT harbor overlaps in hematological and non-hematological GI toxicities in the form of lymphopenia as well as LFT elevations (although they were for M9241 reported as clinically not significant). While these AEs for monotherapy with M7824 and M9241 appear to be manageable and not life-threatening (predominantly grade 1 and 2 for M9241) it is not known what the side effect profile is in combination with SBRT. Thus, there is a dedicated safety run-in cohort to determine safety and tolerability of M7824 and M9241 when combined with SBRT (Phase IB part of the study).

The first 6 patients will receive M7824 at a fixed dose of 1,200 mg on day -14 followed by M7824 +M9241 combination on cycle 1 day 1.

The rationale for the starting dose of 16.8µg/kg of M9241 via subcutaneous injection every 4 weeks, which was found to be the MTD of this agent, is based on the clinical safety data of this dose in the phase I study of 59 patients conducted at the Center for Cancer Research NIH.[48]

Due to the transient clinically mild nature of these AEs (see section **1.2.6.1**) M9241 is initially combined at its MTD of 16.8µg/kg every 4 weeks dose with M7824.

The safe dose of M7824 and M9241 will then be combined with SBRT. M7824 and M9241 will be started 2 weeks prior to start of a 5-day course of SBRT with a second dose of M7824 close to start of SBRT. Possible overlapping hematological (leukopenia) or non-hematological toxicity with SBRT (transient LFT elevations, GI symptoms) should be manageable with e.g. G-CSF support (neupogen; filgrastim) or modifications / adjustments in the RT schedule. Since M7824 available PK/PD profile suggests no risk of accumulation of the drug upon repeat dosing, the second dose of M7824 toxicity before start of SBRT should be predictable and not be cumulative. In the event of ≥grade 3 DLTs in the first 6 patients, dose de-escalation of M9241 will occur for following patients.

2 ELIGBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- Histologically or cytologically proven pancreatic adenocarcinoma (subjects with endocrine or acinar pancreatic carcinoma are not eligible).
- Patients must have stage III or IV pancreatic cancer (Cohort 1) or locally advanced pancreas cancer (LAPC), either borderline resectable pancreas cancer (**Appendix A**) or locally advanced, unresectable pancreas cancer (Cohorts 2 and 3).

- Patient must be eligible to undergo stereotactic body radiation therapy (SBRT) and have fiducial markers placed (any metal biliary stents are an acceptable alternative) (Cohorts 2-3).
- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of M7824 and M9241 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
- ECOG performance status of 0 to 1 (**Appendix D)**
- Must have measurable disease, per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.
- Adequate hematological function defined by:
  - white blood cell (WBC) count ≥ 3×10^9/L
  - with absolute neutrophil count (ANC) ≥ 1.0×10^9/L,
  - lymphocyte count ≥ 0.5×10^9/L,
  - platelet count ≥100×10^9/L, and
  - Hgb ≥9 g/ dL (in absence of blood transfusion)
- Adequate renal function defined by:

Creatinine OR Measured or calculated creatinine clearance (CrCl) (eGFR may also be used in place of CrCl) [A]	• < 1.75x institution upper limit of normal OR • ≥ 45 mL/min/1.73 m^2 for participant with creatinine levels ≥ 1.75 X institutional ULN
[A] Creatinine clearance (CrCl) or eGFR should be calculated per institutional standard.	

- Adequate hepatic function defined by:
  - a total bilirubin level ≤ 3 × ULN,
  - an AST level≤5×ULN,
  - ALT level ≤5 ×ULN
- Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression
- Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
- The effects of the study treatment on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) at the study entry, for the duration of study treatment and up to 120 days after the last dose of the drug for males and up to 60

days for females. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

- Patient must be able to understand and willing to sign a written informed consent document.

2.1.2 Exclusion Criteria

- Treatment with any investigational agent within 28 days before treatment initiation.
- Prior therapy with any antibody / drug targeting T cell coregulatory proteins (immune checkpoints) such as anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody.
- Anticancer treatment within designated period before treatment initiation including:
  - major surgical procedure (such as laparotomy) within 28 days
  - minor surgical procedure (such as biliary stenting) within 7 days
  - chemotherapy with published half-life known to be 72 hours within 7 days
  - chemotherapy with unpublished or half-life greater than 72 hours within 28 days
- Previous radiotherapy to the primary tumor (including palliative radiotherapy)
- Concurrent treatment with non-permitted drugs, including but not limited to immunotherapy or immunosuppressive drugs (see Section **4.2**).
- History of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless patient is in complete remission and for a minimum of 3 years.
- Rapidly progressive disease which, in the opinion of the Investigator, may predispose to inability to tolerate treatment or trial procedures.
- Receipt of any organ transplantation, including allogeneic stem-cell transplantation, except of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant)
- Significant acute or chronic infections including tuberculosis (history of exposure or history of positive tuberculosis test; plus, presence of clinical symptoms, physical or radiographic findings)
- Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent with the exceptions:
  - diabetes type I, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible;
  - subjects 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;
  - administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation.

- Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3 NCI-CTCAE v5.0), any history of anaphylaxis or history of uncontrolled asthma.
- Known alcohol or drug abuse.
- Clinically significant cardiovascular / cerebrovascular disease as follows: cerebral vascular accident / stroke (< 6 months prior to treatment initiation), myocardial infarction (< 6 months prior to treatment initiation), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia.
- Administration of live vaccines within 30 days prior to treatment initiation.
- HIV, HCV, HBV patients on antiviral drugs are excluded due to the absence of previous experience on combination of antiviral and this trial drugs and possible interaction.
- Subjects with a history of serious intercurrent chronic or acute illness, such as cardiac or pulmonary disease, hepatic disease, bleeding diathesis or recent (within 3 months) clinically significant bleeding events, or other illness considered by the Investigator as high risk for investigational drug treatment.
- Subjects unwilling to accept blood products as medically indicated.
- Female patients who are pregnant or breastfeeding. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with M7824 or M9241, breastfeeding should be discontinued.

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites, including clinicaltrials.gov and the CCR website, and on NIH social media platforms. Outside providers and colleagues may directly refer patients for screening into this study. The study will be also presented to PanCan.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for study #01-C-0129 on which screening activities will be performed. Assessments performed at outside

facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Within 28 days prior to treatment initiation unless otherwise noted below:

- Complete medical history and physical examination, including height, weight, vital signs, and ECOG performance status.
- EKG
- Laboratory Evaluation
    - Hematological profile: CBC with differential and platelet count;
    - Biochemical profile: Acute care panel (that includes sodium, potassium, BUN, creatinine), Hepatic panel (that includes AST, ALT, total bilirubin), Mineral panel (that includes calcium, phosphorus, albumin, and magnesium), and uric acid;
    - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy) (7 days prior to treatment initiation);
- CT of chest, abdomen and pelvis (or MRI of chest, abdomen and pelvis if clinically indicated);
- A brain CT / MRI scan if clinically indicated;
- Histologic or cytologic confirmation (at any time point prior to treatment initiation). If there is no available documentation, biopsy will be performed to confirm the diagnosis.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.3.1 Treatment assignment procedures (For registration purposes only):

Cohorts

Number	Name	Description
1	Phase IA	Subjects with stage IV or III pancreas cancer, enrolled to M9241 de-escalation dose levels in combination with M7824.
2	Phase IB	Subjects with locally advanced pancreas cancer (LAPC), enrolled to M9241 de-escalation dose levels in combination with M7824 and SBRT.
3	Phase II	Subjects with locally advanced pancreas cancer (LAPC), enrolled at the recommended for phase 2 combined dose (RP2D) of M7824 and M9241 after the RP2D is established in combination with SBRT.

Arms

Number	Name	Description
1	Arm 1A	De-escalating doses of M9241 in combination with M7824.
2	Arm 1B	De-escalating doses of M9241 in combination with M7824 and SBRT
3	Arm 2	RP2D of M7824 and M9241 in combination with SBRT

Arm assignment

Subjects in Cohort 1 will be directly assigned to Arm 1A.

Subjects in Cohort 2 will be directly assigned to Arm 1B.

Subjects in Cohort 3 will be directly assigned to Arm 2.

2.4 BASELINE EVALUATION

Tests done at screening do not need to be repeated on baseline if performed in designated time frame prior to start of protocol treatment.

Within 28 days prior to first dose:

- Complete medical history and physical examination, including weight, vital signs, ECOG performance status, and skin assessment
- CT of chest, abdomen and pelvis (or MRI of chest, abdomen and pelvis if clinically indicated)
- EKG
- CEA, CA19-9, CA-125
- T4, TSH
- Amylase/ lipase
- Research Quality of Life assessment (subject-reported outcomes / symptom severity assessments the 4th version of the 'Functional Assessment of Cancer Therapy with the hepatobiliary and pancreatic specific module (**Appendix C**). (For English speaking subjects only).
- Collection of archival tumor sample if available for research (collected within 6 months prior to treatment)
- Research blood for ADA sampling, cytokines, TNF and cfDNA
- Research perfusion MRI (Cohort 1A only)

Within 72 hours prior to start of protocol treatment:

- Concomitant Medications and baseline symptom collection;
- Hematological profile: CBC with differential and platelet count;

- Biochemical profile: Acute care panel (that includes sodium, potassium, BUN, creatinine), Hepatic panel (that includes AST, ALT, total bilirubin), Mineral panel (that includes calcium, phosphorus, albumin, and magnesium), and uric acid
- PT, INR, aPTT, fibrinogen
- Urinalysis
- Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy)

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open label Phase I/II trial which consists of safety run-in phases IA and IB and an expansion phase II.

During the safety run-in phase IA, the safety and recommended Phase IB dose of M7824 in combination with M9241 will be determined in Cohort 1 (**Schema 1**).

During safety run-in phase IB the safety and recommended Phase II dose (RP2D) of M7824 in combination with M9241 and SBRT will be determined in Cohort 2 (**Schema 2**).

During Phase II, when RP2D of M7824 and M9241 in combination with SBRT is estimated, we will proceed with enrollment to Cohort 3 to evaluate efficacy of the M7824 and M9241 in combination with standard SBRT.

Patients will receive treatment in cycles consisting of 28 (+/- 3) days (**Note:** in Phase IA there is additional one-time infusion of M7824 at Day -14).

Administration of M7824 will be every 2 weeks by IV infusion on Days 1 and 15 of every cycle, starting on Cycle 1. (Note: in Phase IA there will be additional infusion of M7824 at Day -14).

Administration of M9241 will be every 4 weeks by subcutaneous injection on Day 1 of every cycle, starting on Cycle 1.

SBRT on this trial will be delivered per standard of care (Phase IB and Phase II), starting on Day 17 (+5 days) of Cycle 1 and continue for 5 consecutive business days (except federal holidays).

Note: This protocol will proceed to phase IB only after Radiation Safety approval of SBRT procedure, currently pending because of new SBRT guidance for pancreatic cancer.

After SBRT completion, treatment with M7824 in combination with M9241 will continue until patient meets off treatment criteria (Section **3.11.1**).

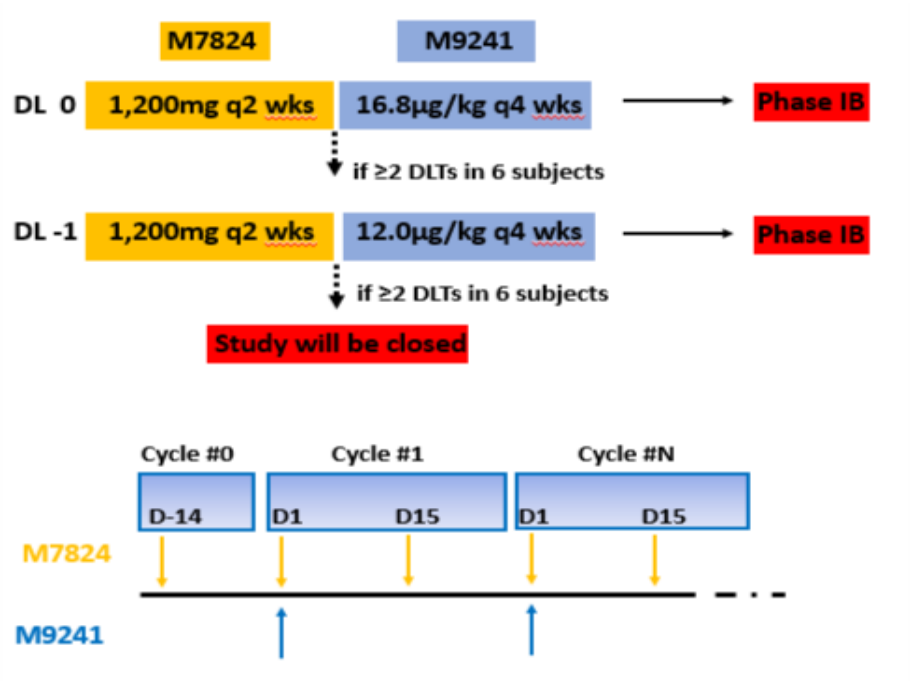
For patients who are benefiting from combination therapy, since we don't know which agent is driving the response (i.e. either of the drugs alone or the combination), in the event that one drug is causing toxicities and have to be discontinued, it is reasonable to continue the other drug to see if the patient might benefit from it. Since it might not be known which of the tow immuno-oncology agents (M7824 or M9241) contributes to a possible positive signal, omission of one may allow a better designation for the beneficial anti-tumor effect. Based on preclinical rationale outlined in Section **1.2.3**, there is a reasonable expectation that SBRT combined with either M9241 or M7824 may still be beneficial.

At Cycle 3 Day 15 (+/- 7 days) patient will undergo imaging and every 2 Cycles (+/-5 days) thereafter.

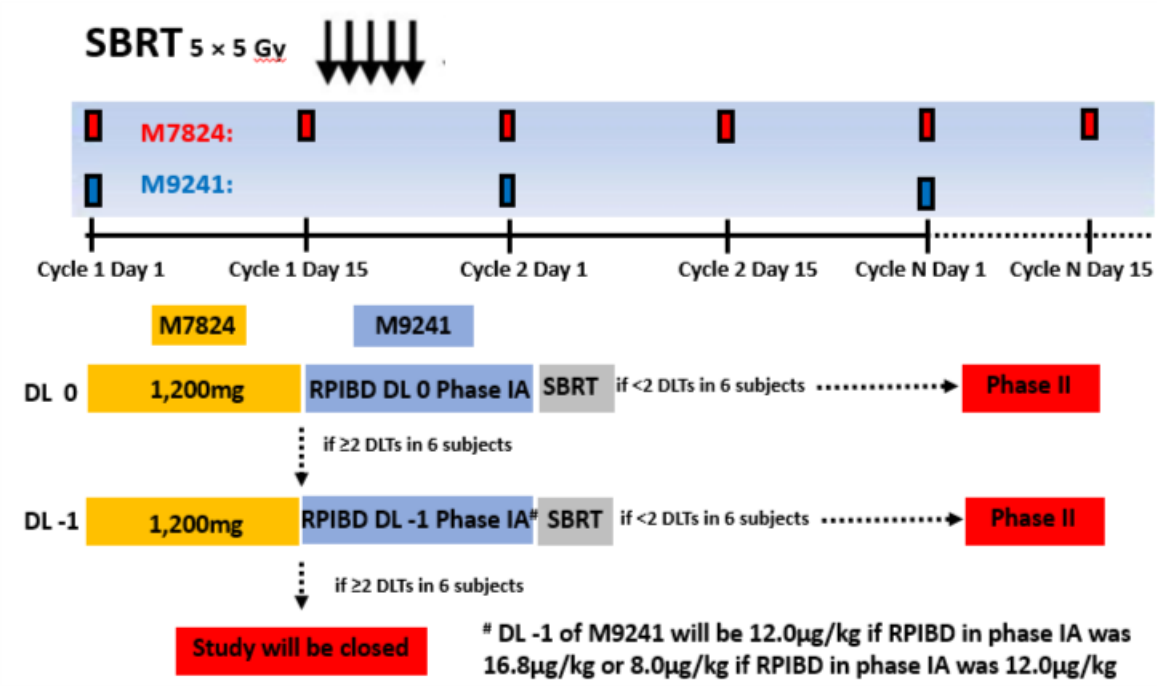
If during the treatment patient's tumors become resectable per standard of care, M7824 and/or M9241 will be stopped at least 5 days prior to the scheduled date of surgery. Surgery is not part of this protocol and will be done as standard of care procedure with enrollment of patient to another surgical protocol in NIH or at home institution.

If surgical exploration does not result in a successful removal of the tumor, patient will be able to return to treatment following recovery from surgery (See section **3.5.3**). If tumor removed successfully, patient will be taken off protocol treatment.

Schema 1: Phase IA.



Schema 2: Phase IB



3.1.1 Dose Limiting Toxicity

The DLT period for the phase IA is 6 weeks (Day -14 to Day 28 of Cycle 1), the DLT period for the phase IB is 4 weeks (from Day 1 Cycle 1 to Day 28 Cycle 1).

Any Grade ≥ 3 adverse event (AE), occurring during the DLT evaluation period, **except** for those listed below:

- Adverse event unrelated, or unlikely related to study agents AND probably or definitely related to other causes
- Grade 3 or 4 clinically asymptomatic neutropenia if not lasting > 1 cycle (14 days) (observed on laboratory value only)
- Clinically asymptomatic grade 3 thrombocytopenia if not lasting > 1 cycle (14 days) (observed on laboratory value only with no clinically discernable bleeding events)
- Grade 3 diarrhea or skin toxicity that resolves to Grade ≤ 1 in less than 7 days after medical management (e.g., immunosuppressant treatment) has been initiated
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to ≤ Grade 1 or Baseline grade.

- Any isolated and single Grade 3 liver function test abnormality in the form of transaminase, alkaline phosphatase, or bilirubin elevation with NO other associated laboratory (or other) abnormality that is not associated with symptoms or clinical manifestations of hepatitis or any immune-related event and which has resolved to Grade ≤ 1 within the subsequent cycle (14 days)
- Any isolated and single Grade 3 amylase or lipase abnormality with no other associated laboratory (or other) abnormality that is not associated with symptoms or clinical manifestations of pancreatitis and which has resolved to Grade ≤ 1 within the subsequent cycle (14 days)
- Any isolated and single Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor and has resolved to Grade 2 not requiring blood transfusions or erythroid growth factor therapy with the subsequent cycle (14 days).

Failure to resume SBRT after a hold of ≥1 week will be analyzed as a DLT within respective dose level group (Phase IB only)

3.1.2 Phase IA/IB:

Every subject of each dose level group of the phase 1 study will be observed for at least 7 days after first dose of M7824 or M7824 and M9241 before the subsequent subject can be treated.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced and not included in the evaluation.

The recommended phase 2 dose (RP2D) is the dose levels of M7824 and M9241 in combination with SBRT at which ≤1 of 6 individuals experienced a DLT during the first cycle (28 days) of combinational treatment with M7824, M9241 and SBRT.

In case of DLT, DLT will be documented and patient, per PI discretion, may continue study treatment if toxicity could be managed by interruption of the dose of study treatment or dose reductions (See Section **3.4**). Patient, once having DLT, will not be used for DLT evaluation on another dose level if treated on another dose level.

SBRT

Dose modifications dosage adjustment is based upon the degree of hematologic and non-hematologic toxicity experienced by the patient at the discretion of the treating radiation oncologist. Patients will be monitored with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, SBRT should be modified or suspended according to the standard guidelines on management of RT-associated toxicities and discretion of the treating radiation oncologist (See section **3.4.3**). These subjects will be part of the DLT evaluation of the respective M7824 and M9241 dose level they were accrued to.

Failure to resume SBRT after a hold of ≥1 week will be analyzed as a DLT within respective dose level group. In case of DLT, attributed to SBRT, patients will be taken off SBRT treatment and per PI discretion may continue M7824 and M9241 only.

3.1.2.1 Cohort 1, Phase IA, Arm 1A

6 to 12 patients will be enrolled into Arm 1A.

Dose de-escalation will proceed in dose levels of 6 patients.

6 subjects will be enrolled in Dose Level 0 (**Table 5**). Patients will be treated with M7824 starting on Day -14 plus M9241 starting on Day 1 of Cycle 1.

If < 2 patients experience a DLT during DLT period, DL 0 will be used as recommended Phase IB dose for Arm 1B.

If ≥ 2 patients experience a DLT during DLT period at DL 0, the DL 0 enrollment will be stopped.

The next 6 subjects will be enrolled into Dose Level -1. If < 2 patients experience DLT during DLT period, this dose DL -1 will be used as recommended Phase IB dose for Arm 1B.

If ≥ 2 patients experience a DLT at DL -1, the enrollment will be stopped and no further attempts at completing the safety run-in of M7824 in combination with M9241 will be conducted and Arm 1B and phase II expansion cohort of M7824 and M9241 in combination with SBRT will not be carried out.

Table 5: Dose Levels of M7824 and M9241 in Arm 1A

Dose level	M7824, mg, IV every 2 weeks	M9241, µg/kg, SQ, every 4 weeks
DL 0	1,200	16.8
DL -1	1,200	12.0

3.1.2.2 Cohort 2, Phase IB, Arm 1B

6 to 12 patients will be enrolled in Arm 1B. Enrollment will start after completion of Arm 1A.

Dose de-escalation will proceed in dose levels of 6 patients.

6 subjects will be enrolled in Dose Level 0 (**Table 6**) and treated with combination of M7824, M9241 and SBRT.

If < 2 patients experience DLT during DLT period, the Dose level 0 will be the RP2D and next patients will be enrolled into Cohort 3 the phase II portion of the study.

If ≥ 2 experience a DLT at DL 0, the Dose Level 0 enrollment will be stopped, and DL -1 will be tested in 6 patients. If <2 patients experience a DLT, dose level -1 will be used as RP2D for M7824 and M9241 in combination with SBRT in the Phase II.

If ≥ 2 patients experience a DLT at DL -1, the dose Level -1 enrollment will be stopped and no further attempts at completing the Arm 1B of M7824 and M9241 in combination with SBRT will be conducted and Arm 2B and phase II expansion cohort of M7824 and M9241 in combination with SBRT will not be carried out.

Table 6: Dose Levels of M7824 and M9241 in combination with SBRT in Arm 1B.

Dose level	M7824, mg, IV every 2 weeks	M9241, µg/kg, SQ, every 4 weeks	SBRT
DL 0	1,200	MTD of M9241 estimated during Phase IA (16.8 or 12)	5 x 5 Gy
DL -1	1,200	If MTD estimated during Phase IA is 16.8 then 12.0	5 x 5 Gy
		If MTD estimated during Phase IA is 12.0, then 8.0	

3.1.3 Phase II, Cohort 3, Arm 2

The efficacy part of the study will be conducted with the M7824 and M9241 dose level found to be safe in combination with SBRT during phase IB. Once a recommended phase 2 dose of M7824 and M9241 has been determined, up to 25 subjects will be evaluated at that dose level, inclusive of those patients treated at the RP2D during the safety run-in.

Enrollment will start when RP2D is estimated and 28 days of observation after first treatment of 6th subject at RP2D in Arm 1B have passed.

During first stage of Phase II 16 patients will be enrolled. If 0 to 1 of 16 patients respond (PR or CR as defined in Section **6.3**), then no further patients will be enrolled. If 2 or more of the first 16 evaluable patients enrolled have a response (PR or CR), then during second stage accrual will continue until a total of 25 evaluable patients have been enrolled.

3.2 STUDY STOPPING RULES

For safety reasons, the enrollment will be temporarily halted until an expedited safety report has been evaluated by the investigators, IND sponsor, and submitted to the FDA for either of the following events attributable to treatment regimen occurring within 28 days of receiving investigational agent (s):

- One occurrence of grade 5 toxicity, attributable to treatment regimen.
- Two occurrences of grade 4 toxicity, attributable to treatment regimen.

3.3 DRUG ADMINISTRATION

3.3.1 M7824

M7824 will be administered as a 1-hour (-10 minutes / +20 minutes) IV infusion on Days 1 and 15 of every cycle, starting Cycle 1. In Phase IA there is additional infusion 14 days before Day 1 of Cycle 1.

On the days of combined M7824 and M9241 treatment M7824 will be infused at least 30 minutes after M9241 injection.

M7824 will be administered as an intravenous (IV) infusion via a peripheral OR central vascular access device (VAD) if patient has VAD already installed. Confirm patient has a titanium port before accessing the Central VAD. A 0.2-micron polyethersulfone (PES) in-line filter is mandatory for administration.

Current experience revealed that infusion related reactions (IRRs) to M7824 seldom occur and are generally mild to moderate in severity. Therefore, administration of a premedication is generally not required.

If an Investigator deems it necessary to administer a premedication to a particular participant, an antihistamine (for example, 25-50 mg diphenhydramine) and acetaminophen 500-650 mg intravenously or equivalent oral dose is recommended approximately 30 to 60 minutes prior to each dose of M7824. If Grade ≥ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Steroids as premedication are not permitted.

Hypersensitivity reactions may require immediate intensive care. M7824 should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1: 1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council United Kingdom and can be found at https://www.resus.org.uk/pages/reaction.pdf

For prophylaxis of flu like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), e.g., ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

Patients must be observed for 2 hours after the first M7824 dose. If no reactions are observed, the patients need to be monitored for only 30 minutes after subsequent doses.

If an allergic reaction occurs, the subject must be treated according to the best available medical practice. Please see the guidelines for handling of infusion-related reaction in **Table 8**.

Investigators should also monitor subjects closely for potential irAEs, which may become manifest after several weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

Vital signs must be measured within 30 minutes before and 30 minutes following M7824 infusions.

3.3.2 M9241

M9241 will be administered as a subcutaneous injection on Day 1 of every cycle.

M9241 will be injected at least 30 minutes before M7824 infusion.

3.3.3 SBRT

Radiation therapy will be starting on Day 17 (+5 days) of Cycle 1 and continue for 5 consecutive business days (except federal holidays).

A summary of the SBRT schedule in combination with M7824 and M9241 is shown in **Schema 2**.

3.4 DOSE MODIFICATIONS:

In case of toxicity as defined below, definitely attributed to one of the study drugs and/or SBRT, patient may be taken off this drug and/or SBRT and per PI discretion may continue treatment with another drug only or drug combined with SBRT.

When, at the beginning of a treatment cycle, treatment delay related to M7824 is indicated, per PI discretion treatment with M9241 and or SBRT might not be delayed.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one drug, the dose of another drug does not require modification.

3.4.1 M7824

Treatment modifications for reactions caused by M7824 are addressed in **Table 7, Table 8, Table 9, Table 10, Table 11,** and **Table 12.**

Table 7: Treatment Modification Guidance for Symptoms of Infusion-Related Reactions including Immediate Hypersensitivity.

NCI-CTCAE Grade	Treatment Modification for M7824
Grade 1 – mild Mild transient reaction; in general, infusion interruption not indicated; intervention not indicated.	• Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • Hold infusion if deemed necessary by the investigator.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, nonsteroidal anti inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	• Stop the infusion of the study intervention. • Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • If symptoms resolve quickly, resume infusion at 50% of original rate with close monitoring of any worsening signs and symptoms, otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. • If not improving, consider administration of glucocorticoids and stop the infusion for that day. • If the participant has a second IRR Grade ≥ 2 on the slower infusion rate despite premedication, the infusion should be stopped, and the investigator may consider withdrawal of this participant from the study.

NCI-CTCAE Grade	Treatment Modification for M7824
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion of study intervention immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended • Administration of glucocorticoids may be required • For Grade 3 or 4 IRRs, permanent discontinuation of study intervention is mandated
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.	
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.	

Table 8: Management of immune-mediated adverse events

Immune-related AEs are specific to immunotherapies and vary by organ system. The following immune-related AEs are important identified risks for M7824: • Immune-related pneumonitis • Immune-related hepatitis • Immune-related colitis • Immune-related nephritis and renal dysfunction • Immune-related endocrinopathies • (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders) • Immune related rash • Other immune-related events (myositis, myocarditis, encephalitis) The following immune-related AEs are important potential risks for M7824:

- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome

Recommended guidance and management for specific irAEs are provided in the current National Comprehensive Cancer Network (NCCN) guideline available at http://www.nccn.org.

Requirements in addition to NCCN guidelines:

- Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura inflammatory arthritis, myositis and polymyalgia-like syndrome.
- For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and it does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifested by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade ≤ 1, restarting treatment may be considered.
- For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry. If symptoms appear and/or changes in the physical exam are noted, treat as Grade 2.
- For myositis: in case of management with rituximab, treatment should be discontinued.
- For Grade 3 or 4 endocrinopathies: withhold until clinically stable or permanently discontinue depending on severity.
- For hepatitis with no tumor involvement of the liver: withhold if total bilirubin increases to more than 1.5 and up to 3 times ULN, permanently discontinue if more than 3 times ULN
- Hepatitis with tumor involvement of the liver: permanently discontinue if total bilirubin increases to more than 3 times ULN.

Table 9: Management of M7824 mediated Skin Reactions

- Hyperkeratosis
- Keratoacanthoma
- Cutaneous squamous cell carcinoma (cSCC)
- Basal cell carcinoma
- Actinic keratosis

Management

• Discontinuation or termination not required in most cases. Continuation of treatment should be evaluated by the Investigator.
• Emollients may be used
• Develop diagnostic and treatment plan in collaboration with Investigator and dermatologist
• Treatment follow-up will depend on number and localization of lesions.
  o Single lesion: full excision may be recommended
  o Multiple lesion or location not suitable for full excision: Mohrs surgery, cryotherapy or other standard treatment options depending on pathology. Retinoids may be used per Investigator decision.
• Close clinical follow-up for re-evaluation, resolution and potential recurrence should be implemented
• In general, treatment of M7824 mediated skin lesions should be based on local guidelines/standard of care.

Additional consideration: Keratoacanthoma lesions may resolve spontaneously without surgical intervention within weeks after discontinuing bintrafusp alfa. Consult with Medical Monitor as needed for management of M7824 mediated skin lesions.

Table 10: Management of Treatment-Related Anemia

• All relevant hematological testing for treatment-related anemias should be done prior to a blood transfusion, if clinically feasible
Basic Anemia Evaluation

• CBC with emphasis on red cell indices
• If indicated and at clinical discretion, the following should be considered:
  o Iron studies
  o Serum Folate and Vit B12 values
  o Coagulation factors
  o Fecal occult blood
  o Urinalysis
  o Hormone panel: TSH, Erythropoietin
  o Peripheral blood smear

Further recommendation based on suspected etiology (in addition to basic anemia testing)

• Suspected Hemolysis
  o bilirubin, LDH, Coombs test, haptoglobin
• Suspected bleeding:
  o Consider imaging/interventional radiology consultation as indicated
  o Consider imaging and/or endoscopy as clinically indicated
• Suspected aplastic anemia:
  o Hematology consultation
  o Consider bone marrow aspiration/morphologic evaluation

Additional consideration: In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Table 11: Management of Bleeding Adverse Events

Bleeding Adverse Events	

• Bleeding adverse events are considered an important identified risk for M7824.
• In general, mild and moderate mucosal bleedings resolve without discontinuation of treatment.
• These events may include, but are not limited to the following:
  o Epistaxis
  o Hemoptysis
  o Gingival bleeding
  o Hematuria	

Non-tumor Bleeding	
Grading	Management
Grade 2	• If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued. • If not resolved to Grade ≤ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, consult Medical Monitor to assess if clinically reasonable to administer the following infusion.
Grade 3	• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.) • In case of alternative explanations, hold study treatment until the event recovers to Grade ≤ 1

Grade 4	• Treatment must be permanently discontinued if no alternative explanation is identified.
Tumor Bleeding	
Grade ≥ 2	• Study treatment must be held till the event recovers to Grade ≤ 1 • Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.

Table 12: Impaired Wound Healing

• Impaired wound healing is considered important potential risk for M7824 • Management should be discussed with Medical Monitor for participants requiring surgery on study. • It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation. • Post-operative wound healing should be closely monitored

3.4.2 M9241

Modifications of M9241 are explained in **Table 14**

After Dose level -1, no more dose reduction is allowed, and patient will be taken off M9241 treatment.

Table 13: M9241 Dose Reduction Levels:

Dose Level (DL)	Agent Dose
0	16.8µg/kg (or 12.0µg/kg) every 4 weeks
-1	12.0µg/kg (or 8.0µg/kg) every 4 weeks

Table 14: M9241 Dose Modification Instructions

(CTCAEv5) Grade	Action
Non-hematological, Grade 1 or 2	Continue M9241 therapy at full dose prescribed. Apply maximum supportive care recommendations. If prolonged duration of Grade 2 adverse event (≥7 days) is affecting quality of life, decrease dose to DL -1, if symptoms persist and continue

(CTCAEv5) Grade	**Action**
	to affect quality of life for ≥7 more days, permanently discontinue M9241.
Non-hematological, Grade 3 or 4 (excluding cardiac, hepatobiliary events, interstitial pneumonitis or Grade 4 inflammatory response syndrome)	Apply maximum supportive care recommendations. Hold M9241 therapy until recovery to Grade ≤ 1 (up to 14 days). If non-hematological, symptomatic Grade 3 or 4 adverse events NOT resolved to Grade ≤1 within 14 days, discontinue M9241. If recurrence of adverse event after drug hold/ interruptions is observed, and maximum supportive care measures applied, hold drug once again until recovery to Grade ≤ 1 (up to 14 days) and restart drug at DL-1. If adverse event recurs, M9241 must be permanently discontinued.
Grade 3 or 4 interstitial pneumonitis or Grade 4 inflammatory response syndrome	M9241 must be permanently discontinued
Cardiac Adverse Events	
Cardiac (Severity corresponding to NYHA criteria)	M9241 therapy to be discontinued permanently in case of symptomatic NYHA class III and IV CHF. M9241 therapy to be held, continued, or resumed accordingly for patients with NYHA class I or II CHF.
Hepatobiliary Adverse Events	
Grade 2 AST/ALT	Hold M9241 for 2 weeks and restart drug at next scheduled dose at DL 0 (full dose) if events resolved to ≤ Grade 1. If adverse events NOT resolved to Grade ≤1 within 2 weeks, re-start M9241 at DL-1.
Grade 3 and 4 AST/ALT* and Grade ≥2 total bilirubin elevation	Hold M9241 for 2 weeks; restart drug at next scheduled dose at DL-1 if events resolved to ≤Grade 1. If adverse events NOT resolved to Grade ≤1 within 2 weeks, discontinue M9241 If Grade 3 AST/ALT or Grade 2 total bilirubin events recur after dose reduction to DL-1, then discontinue M9241.
Hematological, Grade 1 or 2	No modification required
Grade 3 or 4 thrombocytopenia associated with bleeding	M9241 must be permanently discontinued

(CTCAEv5) Grade	**Action**
event which does not result in hemodynamic instability but requires an elective platelet transfusion, or a life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit	
Grade 4 hematologic toxicity lasting ≥ 7 days despite of medical intervention (Note: Grade 4 neutropenia lasting >5 days)	M9241 must be permanently discontinued
Cytokine release syndrome	M9241 must be permanently discontinued
* retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists	

3.4.3 SBRT

Modifications of RT doses during SBRT due to local or systemic toxicities will be made at the discretion of the treating radiation oncologist. Early side effects happening during or shortly on or after treatment like fatigue, nausea, vomiting, abdominal cramps, diarrhea and skin changes tend to be short-term and treatable and will be managed with standard supportive care measures. In the rare event of pre-treatment leukopenia or thrombocytopenia, the following guide for dose adjustments of SBRT should be followed first:

Table 15: Recommended Dose Reductions for Myelosuppression

Absolute granulocyte count, x10^6/L		**Platelet count, x10^6/L**	**% of selected starting dose**
≥1,000	And	≥85,000	OK to treat
<1,000	Or	<85,000	Do not start RT

Hold SBRT for hematological toxicity until resolved to grade ≤ 1. If not resolved within 2 weeks, discontinue SBRT.

Dose Modifications for Non-Hematologic Adverse Reactions requiring permanent discontinuation of SBRT for any of the following:

- Severe grade 3 or higher hepatic toxicity
- ≥grade 3 GI bleeding or GI perforation

Hold SBRT (Grade 3 or 4) for other non-hematological toxicity until resolved to grade ≤ 1. If not resolved within 2 weeks, discontinue SBRT.

No dose modifications are recommended for alopecia, nausea, or vomiting.

3.4.3.1 Management of radiation-treatment related pain (radiation-induced pain flare)

The prophylactic use of dexamethasone or any other steroids is not allowed. Patient should be proactively managed with signs of radiation-induced pain flare which includes early hospital admission with adequate use of oral and intravenous combination analgesics as required. A pain scale should be established early and frequently repeated, patients should be assessed after baseline persistent pain has been stabilized with around-the-clock (ATC) analgesics on regular intervals. Short-acting opioid analgesics are the primary treatment, dose and/or dosing frequency of the ATC analgesic should be adjusted for patients with end-of-dose radiation-induced pain flare. Short-acting oral opioids can be considered when given preemptively in patients with predictable radiation-induced pain flare.

Hospital admission exceeding 1 week for management of radiation-induced pain flare should be considered grade 3 AE, hospital admissions to accommodate pain management for radiation-induced pain flare ≤7 days grade 2 AE.

3.5 ASSESSMENTS ON TREATMENT

3.5.1 Study assessments

Study assessments are presented in Study Calendar **3.8**.

3.5.2 End-of-Treatment Visit and Follow UP

See Study Calendar, Section **3.8**.

3.5.3 Treatment pauses for surgery

Surgery is not part of this protocol and will be done as standard of care procedure with enrollment of patient to another surgical protocol at the NIH Clinical Center or at home institution.

If during the treatment patient's tumors become resectable per standard of care, M7824 and/or M9241 will be stopped at least 5 days prior to the scheduled date of surgery.

If surgery performed outside NIH, we will ask patients to provide the outside surgical pathology report for determination of resection status (R0, R1, R2) and tumor sample from this surgery for research.

If surgical exploration does not result in a successful removal of the tumor as defined below:

- R0: closest tumor ≥1mm from surgical resection margin
- R1: tumor within <1mm of surgical resection margin

- R2: involvement of surgical resection margin with tumor (incomplete tumor clearance)
- "open and close"

treatment with M7824 and M9241 will resume 6-8 weeks after surgery when patient recovers. SBRT will not be repeated.

If surgical exploration results in a successful removal of the tumor, patient will be taken off study treatment.

Before post-surgery re-treatment with M7824 and M9241, Day 1 the following tests and examinations must be performed to evaluate safety of re-treatment and estimate baseline for tumor evaluations:

Within 28 days:

- CT/MRI of chest, abdomen and pelvis;
- Research Quality of Life assessment (subject-reported outcomes / symptom severity assessments the 4th version of the 'Functional Assessment of Cancer Therapy with the hepatobiliary and pancreatic specific module (**Appendix C**). (For English speaking subjects only)

Within 3 days:

- Physical examination, including weight, vital signs, EKG, and ECOG performance status;
- Adverse event and concomitant medications;
- Laboratory evaluation:
  - Hematological profile: CBC with differential and platelet count;
  - Biochemical profile: Acute care panel (that includes sodium, potassium, BUN, creatinine), Hepatic panel (that includes AST, ALT, total bilirubin), Mineral panel (that includes calcium, phosphorus, albumin, and magnesium), and uric acid;
  - CEA, CA19-9, CA-125
  - T4, TSH
  - Amylase/ lipase
  - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy)
  - Urinalysis.

Research blood will not be collected during post-surgery treatment

3.6 QUESTIONNAIRES

The rationale for questionnaires is discussed in Section **1.2.8** and timing is specified in Study Calendar **3.8.** The average time to complete these instruments is 20 minutes. For English speaking subjects only.

3.7 RESEARCH IMAGING

K_{trans} and K_{ep} perfusion measure of tumoral lesions measured on DCE-MRI with contrast will be measured at baseline, before treatment on day 1 of cycles 1 (+/-5 days) and 3 (+/-5 days). The scheme ensures perfusion measurements

- At baseline in the absence of M7824 and M9241

- After M7824 administration only (examining the effect of M7824 as a stromal modulator only; the anti-TGFβ component of the dual checkpoint inhibitor M7824 has been shown to act as a stromal modulator increasing perfusion in preclinical models as well as in few patients enrolled on 18-C-0061; M7824 in combination with gemcitabine in advanced pancreas cancer)

- After combined M7824 and M9241 (two doses) administration; this timepoint examines if the addition of M9241 alters the stroma and perfusion.

Patients in Cohort 1A only.

3.8 STUDY CALENDAR

Procedure	Screening	Baseline[1]	Day -14[1]	Cycles (28+/- 3 days)[1]		EOT visit[13, 16]	28 Days FU[14, 16]	Long Term FU[15, 16]
				Day 1	Day 15			
M7824 [2]			X	X	X			
M9241 [3]				X				
SBRT [4]					X (C1 only)			
Medical History	X							
Confirmation of Pathology	X							
Height	X							
Physical exam, weight, vital signs, ECOG [5, 17]	X	X		X	X	X	X	
Skin assessment		X		X[18]			X	
EKG [17]	X	X		X[6]	X[6]		X	
CBC with differential and platelets [17]	X	X	X	X	X	X	X	
Biochemical profile [7, 17]	X	X	X	X	X	X	X	

Procedure	**Screening**	**Baseline[1]**	**Day -14[1]**	**Cycles (28+/- 3 days)[1]**		**EOT visit[13, 16]**	**28 Days FU[14, 16]**	**Long Term FU[15, 16]**
				Day 1	**Day 15**			
Pregnancy testing (urine or serum) [17]	X	X		X				
A brain CT / MRI scan if clinically indicated	X							
Tumor evaluation [8, 17]	X	X		X (odd cycles, except C3)	X (C3 only)			X
CEA, CA19-9, CA-125[17]		X		X		X	X	
T4 and TSH[17]		X		X		X	X	
Amylase / lipase [17]		X		X		X	X	
Urinalysis[17]		X		X		X	X	
PT, INR, aPTT, fibrinogen		X		X			X	
Concomitant Medications[17]		X		X		X	X	
Baseline symptom collection		X						

Procedure	**Screening**	**Baseline[1]**	**Day -14[1]**	**Cycles (28+/- 3 days)[1]**		**EOT visit[13, 16]**	**28 Days FU[14, 16]**	**Long Term FU[15, 16]**
				Day 1	**Day 15**			
Collection of archival tumor sample if available for research		X						
FACT-Hep [9, 17]		X		X				
Adverse events [17]			X	X	X	X	X	X
Research MRI [10]		X		X				
Research blood for PK [11]			X	X	X			
Research blood for ADA sampling		X		X[12]				
Research blood for Cytokines and TNF		X		X				
Research blood for circulating free tumor DNA (cfDNA) assay		X		X		X		
Phone call or e-mail								X

[1] Baseline and Day -14 (Arm 1A) or C1D1 (Arm 2A and Arm 3) evaluations do not need to be repeated if performed at screening or baseline in designated time frame. All evaluations will be done within 72 hours before treatment initiation on treatment days. If treatment does not start within 28 days after enrollment, screening evaluations will be repeated.

[2] M7824 will be administered as an IV on Days 1 and 15 of every cycle. **Note:** Additional infusion on Day -14 in Arm 1A.

[3] M9241 will be administered as a subcutaneous injection on Day 1 of every cycle.

[4] SBRT Radiation therapy on Day 17 (+5 days) of Cycle 1 and continue for 5 consecutive business days (except federal holidays). It will be administered as short course (SBRT) of 5 fractions according to schedule assigned by radiation oncologist.

[5] Eye signs and symptoms and assessment of skin should be included into physical exam. If clinically indicated, ophthalmology and dermatology consults should be ordered.

[6] Cycle 1 only, before study treatment.

[7] Biochemical profile: Acute care panel (that includes sodium, potassium, BUN, creatinine), Hepatic panel (that includes AST, ALT, total bilirubin), Mineral panel (that includes calcium, phosphorus, albumin, magnesium), uric acid

[8] CT of chest, abdomen and pelvis (or MRI of chest, abdomen and pelvis if clinically indicated). Cycle 3 day 15 (+/- 5 days) and every 2 Cycles (+/-5 days) thereafter. If patient is taken off treatment for reason other than disease progression, imaging evaluations will continue during follow up period every 12 weeks (± 2 weeks) until progression. In addition, if PD, a confirmatory scan should be obtained 4 weeks (+ 1 week) following initial documentation of PD.

[9] Research Quality of Life assessment (subject-reported outcomes / symptom severity assessments the 4th version of the 'Functional Assessment of Cancer Therapy with the hepatobiliary and pancreatic specific module (**Appendix C**). (For English speaking subjects only. At baseline, cycles 2, 4 and every 12 weeks after that.

[10] At baseline, before treatment on day 1 of cycles 1 and 3 (+/-5 days). Cohort 1A only.

[11] See Section **5.1.3**

[12] Before dosing on Cycle 2 day 1

[13] All subjects should undergo an End-of-Treatment visit after discontinuation of M7824 and M9241 for any reason. This visit should be performed on the day of or within 7 days after the decision to discontinue trial treatment but before any new antineoplastic therapy is started (if possible), whichever occurs earlier. Research samples may be collected as logistically feasible. If it is known to the Investigator at the time of the End of-Treatment visit that the subject will start new treatment within 28 days of last treatment or they will be unable to return within 28 days of last treatment, assessments associated with the 28-Day Safety Follow-up visit may be conducted at the End-of-Treatment visit.

[14] A Safety Follow-up visit is scheduled 4 weeks (28 ± 5 days) after the last administration of M7824 or M9241 but before any new therapy is started, if possible, whichever occurs earlier. All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." In addition, all trial drug-related SAEs occurring after 28 Day Safety Follow up visit and ongoing at the Safety Follow-up visit have to be followed up in the same manner

[15] Subjects with PD will be followed every 12 weeks (± 2 weeks) by phone or e-mail for survival and further tumor therapy for 1 year after the last dose of study drug. After 1-year subjects will be followed for survival every 6 month. Subjects without progressive disease at 28-Day Safety Follow-up visit will be invited to Clinical Center to perform CT scans (or MRI scans if clinically indicated) every 12 weeks (± 2 weeks) until PD. Outside scans are acceptable.

[16] If subjects are not willing to come to NIH after treatment discontinuation for FU visits, they will be followed by phone call or e-mail.

[17] Must be done before re-treatment after surgery.

[18] Every 6 weeks

3.9 COST AND COMPENSATION

3.9.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.9.2 Compensation

None.

3.10 REIMBURSEMENT

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.11 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, efforts must be made to have all subjects complete a safety visit approximately 28 days following the last dose of study therapy.

3.11.1 Criteria for Removal from Protocol Therapy

- Patient request to be withdrawn from therapy
- Progressive disease as defined in section **6.3**. Subjects should continue treatment beyond the initial determination of PD, through their next tumor assessment, which in this case should be in 4 weeks if:
    - There are no new Grade 2 or greater symptoms or significant worsening of existing symptoms.
    - There is no increase in ECOG.
    - There are no new metastatic lesions
    - In the opinion of the Investigator, the subject does not require new anticancer therapy.
- Excessive toxicity (see section **3.4**)
- Necessity to administer a non-permitted concomitant drug (see section **4.2**)
- Surgical exploration results in a successful removal of the tumor
- PI discretion
- Positive pregnancy test
- The drug manufacturer can no longer provide the study agents

3.11.2 Off -Study Criteria

- Death

- Patient request to be withdrawn from study
- Lost to follow up
- PI discretion
- PI decision to end the study

3.11.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visits and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS / MEASURES

4.1 PERMITTED MEDICINES

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

4.2 PROHIBITED MEDICINES

The following treatments must not be administered during the trial:

- Immunotherapy including interferon, immunosuppressive drugs (for example, systemic corticosteroids except for short term treatment of allergic reactions, endocrine replacement therapy at low dose prednisone [≤ 10 mg daily] or equivalent, or for the treatment of irAEs or other appropriate short-term steroid use), or other experimental pharmaceutical products. Short term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (that is, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Prophylactic use of corticosteroids for infusion related reactions is prohibited.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines).

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment.

5 BIOSPECIMEN COLLECTION

5.1. CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

Studies will address the effect on TGFβ concentrations and other soluble factors in serum and/or plasma upon response to the study drugs, the impact of the somatic genotype on response to M7824 and M9241, and changes in the immune phenotype to predict efficacy of the administered combination immunotherapy. We also will evaluate intratumoral alterations of the immune milieu / stroma of pre- versus post-treatment archival tissues (pre-treatment biopsy and surgical specimen) as well as follow copies of circulating free tumor DNA levels during treatment.

5.1.1 Blood Collection

Blood samples will be originally sent to Blood Processing Core (BPC) for barcoding, initial processing and storage. From this facility coded linked samples will be sent to the designated places for analysis in batch shipments or upon request. Patients will undergo blood and tissue sampling for research purposes on the time points outlined in the Study Calendar **3.8**

5.1.2 Tumor and Tissue Collection

Archival tumor samples (collected within 6 months prior to treatment) might be collected at baseline and from the surgical specimen when patients undergo resection.

Test/assay	**Volume (approx.)**	**Type of tube***	**Collection point**	**Location of specimen analysis (and original processing)**
PK M7824	Blood, 4 mL	SST	See section **5.1.3**	EMD Serono (BPC)
ADA by ELISA	Blood, 4 mL	SST	See Study calendar **3.8**	EMD Serono (BPC)
Cytokines by ELISA	Blood, 8 mL	SST	See Study calendar **3.8**	EMD Serono (BPC)
TNF by ELISA	Blood, 2x3 mL	Light blue citrate	See Study calendar **3.8**	EMD Serono (BPC)
Immune marker panel evaluation by IHC	Archival tumor sample and		Baseline and at surgery	Laboratory of Pathology, NCI

Test/assay	**Volume (approx.)**	**Type of tube***	**Collection point**	**Location of specimen analysis (and original processing)**
	surgery sample			
161 DNA-target panel (Oncomine v3 Comprehensive Assay v3)	Archival tumor sample or surgery sample		Baseline or at surgery	Dr. M. Raffeld, Laboratory of Pathology NCI
Circulating free tumor DNA (ctDNA)	Blood, 6 mL	EDTA (purple top) tubes	See Study calendar **3.8**	Dr. M. Raffeld, Laboratory of Pathology NCI (BPC)

* Tubes/media may be adjusted at the time of collection based upon materials available and/or to ensure the best viable samples are collected for planned routine and/or research analysis at the time of procedure.

5.1.3 Pharmacokinetic analysis

Only during Phase IA.

PK samples should be taken:

Day -14

M7824 PK: predose, 1h post infusion of M7824 (+/- 15 minutes),

Cycle 1:

M7824 PK: predose, 1h post infusion of M7824 (+/- 15 minutes),

M7824 day 15 predose.

The investigation will be done by EMD Serono under CRADA with this company.

5.1.4 ADA

Anti-Drug Antibody development is an accepted mechanism of loss of efficacy administered human monoclonal antibodies. Measuring titers will ensure that any lack of efficacy of M7824 and/or M9241 is not due to ADA development.

Blood will be collected to analyze ADA according to Study Calendar **3.8**. Samples positive for ADAs will be re-analyzed to determine the titer. The investigation will be done by EMD Serono using ELISA under CRADA with this company.

5.1.5 Serum cytokines and serum TNF levels

One of the least elaborate ways to confirm that the administered M7824 is active and is engaging its target, is to measure suppression of TGFβ levels (via 'trapping') and induced changes in the cytokine profile systemically. Following TGFβ and cytokine levels longitudinally across treatment course will allow detection of lack of M7824 activity and can trigger additional investigations (ADA development) into lack of efficacy. Initial circulating TGF-β and cytokine levels (including γ-interferon and TNF) will also be tested for correlation with response to M7824 and M9241 or M7824 and M9241 in combination with SBRT therapy overall.

Blood will be collected to analyze soluble factors including cytokines and TNF concentrations according to Study Calendar **3.8**. The investigation will be done by EMD Serono using ELISA under CRADA with this company.

5.1.6 Changes in systemic and intratumoral immunogenicity of M7824 and /or M9241 in combination with SBRT (Immune marker panel evaluation by IHC)

Preclinical studies show that TGFβ and PD-L1 inhibition and local delivery of rIL-12 cooperate immunologically with RT to induce anti-tumor responses reducing immune evasive cues and enhancing T cell-mediated anti-tumor responses. Immune profiling of pre- and on-treatment specimens including surgical specimens aim to (1) investigate via staining of multiple markers using immunohistochemistry immunogenic cooperativity of M7824 and/or M9241 in combination with RT, and (2) identify an immunologic footprint, either at baseline measure or treatment-induced change, associated with response to the combination approach. This information will also inform on the design of future combination immunotherapy studies. This will be done in the Laboratory of Pathology, NCI.

5.2 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.2.1 Description of the scope of genetic/genomic analysis

5.2.1.1 Somatic genomic profile of pancreatic cancers derived from specimens

There is clinical evidence that mutation load drives outcome of immunotherapy in pancreas cancer, and emerging evidence that certain neo-epitopes derived from somatic mutations are more immunogenic than others. For example, it has been postulated that mutations in chromatin-remodeling genes, present in up to 17% of pancreas cancer specimens, or variants affecting the TGFβ receptor - SMAD axis, are positively associated with outcome to immunotherapy in cancer. Thus, early correlations between genotype and clinical outcome of patients aim to (1) improve future selection of patients for the dual TGFβ 'trap' PD-L1 blockade and M9241 immunocytokine therapy in combination with RT approach as well as (2) improve understanding of the mechanism of action of these agents in pancreas cancer which would aid design of future combination therapies.

We will use baseline archival samples as available for somatic tumor variant sequencing which will be performed by the CLIA-approved 50-cancer gene panel of the Molecular Pathology section (Dr. M. Raffeld lab).

5.2.2 Circulating free tumor DNA measures:

Measures of copies of genomic tumor DNA released into the circulation has been shown to be an accurate measure of tumor burden in patients with solid organ cancers and to have value to follow response to anti-cancer treatment both for the early identification of responders as well as patients

to recur after remission. Including longitudinal measurements from baseline and on-treatment of circulating free tumor DNA into explorative objectives examines the value of identifying responders early and the development of this test as a predictive biomarker for the tested M7824 M9241 combination treatments with SBRT.

We plan to characterize cfDNA from blood before and during treatment. All samples will be subjected to targeted sequencing. This will allow us to characterize somatic point mutations, and copy-number changes and will be performed in Dr. M. Raffeld' s laboratory.

5.2.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory.

5.2.4 Genetic counseling

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense). This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside the National Institutes for Health (NIH) without appropriate approvals and/or agreements, if required.

All samples will be barcoded, with data entered and stored in the secure databases. These databases create a unique barcode ID for every sample and sample box, which cannot be traced back to patients without database access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^0C according to stability requirements.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in database. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

5.3.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

BPC contact information

Please e-mail at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.3.1 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and Labmatrix ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the administration of the first study intervention through 28 days after the last study agent (s) is administered. Beyond 28 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE only if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.1.1 PK Data

The exact time of each blood draw for PK analysis will be recorded.

6.1.2 Tumor data

The tumor disease information that will be documented and verified at the Screening visit for each subject includes:

- Detailed history of the tumor, including histopathological diagnosis, grading and staging in accordance with the Union Internationale Contre le Cancer Tumor Node Metastasis Classification **at diagnosis** (UICC TNM).
  - The T and M category (T1-3 vs T4 and M0 or M1) of the tumor at the time of study entry, based on screening assessments
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy).
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy.

6.1.3 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Nondrug interventions should also be recorded in the eCRF.

The following outcome criteria will be captured if surgery performed while patient is on study:

- Number of patients explored
- Number of patients to undergo resection
- Number of R0, R1, and R2 resection

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, his will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

The PI will share coded linked human data generated in this research for future research:

- in an NIH-funded or approved public repository clinicaltrials.gov and dbGaP
- in BTRIS
- in publication and/or public presentations

- with approved outside collaborators under appropriate agreements
- at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response at Cycle 3 day 15 (+/- 5 days) and every 2 Cycles (+/-5 days) thereafter. In addition, if PD, a confirmatory scan should be obtained 4 weeks (+ 1 week) following initial documentation of PD.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [[70, 71]] and Modified Immune-related response criteria (**6.4**). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Disease Parameters

For the purpose of this study, the primary pancreatic tumor should be the target lesions with no other disease present. However, for the purpose of defining criteria for progression of disease, all RECIST criteria are reviewed here:

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥20 mm;
- By CT scan:
  - Scan slice thickness 5 mm or under as ≥10 mm
  - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 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 4 weeks before the beginning of the 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.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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 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.

6.3.3 Response Criteria

All the scans performed at Baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

Brain CT / MRI scan should only be performed, if clinically indicated by development of new specific symptoms or on the discretion of the Principal Investigator. For each subject, the Investigator will designate the measure of primary tumor status to follow for determining response: CT or MRI images of primary tumor mass. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Study Calendar **3.8**.

The foreseen treatment duration is until disease progression verified by a scan subsequent to the initial documentation of PD, unacceptable toxicity, or any criterion for withdrawal from the trial occurs (see Section **3.11.1**). **Before stopping the treatment, progressive disease should be confirmed by imaging 4 weeks after progression has been diagnosed according to RECIST 1.1.** If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 4 weeks later should be considered before performing the 28-Day Safety Follow-up visit. Treatment may be continued despite progression according to RECIST 1.1 at any time if:

- There are no new symptoms or worsening of existing symptoms.
- There is no new lesion outside the pancreas
- There is no decrease in ECOG PS.
- The Investigator does not consider it necessary to administer a salvage therapy.

The treatment should be stopped immediately, if the subject does not tolerate M7824 and M9241 in combination with CRT anymore or if therapeutic failure occurs, which requires urgent treatment with an additional drug or results in clinically significant progression / deterioration.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation).

- To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions according to RECIST 1.1.

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR should be confirmed according to RECIST 1.1 (**Error! Reference source not found.**). **In the case of a PR or CR, a confirmatory CT or MRI scan should be done no sooner than 4 weeks**.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

Table 16. Response Criteria for Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Subjects who have experienced SD, PR, or CR should continue treatment through the end of 24 months, although additional treatment is possible. If the Investigator believes that a subject may benefit from treatment beyond 24 months, it may be permissible.

6.3.4 Responses

6.3.4.1 Best overall response (BOR)

The duration of best overall response is measured from the time measurement criteria are met for CR, PR or SD (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

6.3.4.2 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. Stable Disease (SD) when sum of all target lesions does not qualify for CR/PR/PD for Target Lesion Response and Persistence of non-target lesions on Non-Target Lesion Response.

6.4 IMMUNE-RELATED RESPONSE CRITERIA (IRRECIST)

Modified immune-related response criteria (irRECIST) will also be employed in this study. This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. For this trial, the concepts of the irRECIST are combined with RECIST 1.1. Please refer to **Appendix E** for further details.

6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

We are also using additional grading criteria for radiation related adverse events (section **3.4.3.1**)

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP Office Of Compliance and Training / IRB Reporting

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here

7.3 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose de-escalation will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization:
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs) are serious or nonserious AEs that are of clinical interest and should be closely followed.

AESIs include following:

- Infusion-related reactions including immediate hypersensitivity.
- Immune-related adverse events.
- M7824 mediated skin reactions.
- Anemia.
- Bleeding AEs

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the Sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets a protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death due to disease progression is part of the study objectives (PFS and OS), and captured as an endpoints in this study, death due to disease progression will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

Hospitalization that is deemed to be due to disease progression, and not attributable to the intervention will not be reported as an SAE. The event, and the assessment that it was caused by disease progression will be documented in the medical records. The causality assessment of hospitalization will be re-evaluated any time when new information is received. If the causality assessment changes from disease progression to related to the study intervention, SAE report will be sent to the Sponsor in an expedited manner according to section **8.3**. If there is any uncertainty whether the intervention is a contributing factor to the event, the event should be reported as AE or SAE as appropriate.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions.

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours after the Investigator becomes aware of it.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 120 days after the last dose of study drug.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 120 days after the last dose should, if possible, be followed up and documented.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse

reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance with 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL NON-ADHERENCE REPORTING

Protocol non-adherence is defined as any noncompliance with the clinical trial protocol, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol non-adherence identified by the Staff or the site Monitor on the OSRO Site Protocol Non-Adherence Log. The protocol-specific, cumulative non-adherence log should be maintained in the site essential documents file and submitted to OSRO via OSROMonitoring@mail.NIH.gov on the **first business day of each month over the duration of the study**. In addition, any non-adherence to the protocol should be documented in the participant's source records and reported to the local IRB per their guidelines. OSRO required protocol non-adherence reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights of the participants are protected, that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Monitoring based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. The intensity and frequency of monitoring will be based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. OSRO Monitoring visits and related activities will be conducted throughout the life cycle of each protocol, with the first activity being before study start to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will take place at the study site(s). Monitoring visit reports will describe visit activities, observations, findings of protocol non-adherence and associated action items or follow-up required for resolution of findings. Monitoring reports will be distributed to the study PI, NCI CCR QA, coordinating center (if applicable) and the OSRO regulatory file.

If protocol non-adherence is identified by the Monitor (i.e., any noncompliance with the clinical trial protocol, GCP, or protocol-specific procedural requirements on the part of the participant, the

Investigator, or the site Staff) the Monitor will note the observation, review with site Staff and if unresolved, request that the Staff document the non-adherence on the protocol-specific OSRO Site Protocol Non-Adherence Log (see Section **8.8**).

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary endpoints:

- To determine the safety and tolerability and the recommended phase 2 dose (RP2D) of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with pancreas cancer:
  - number, severity, and duration of treatment-related AEs for the combination treatment of M7824 and M9241 administered in combination with a 5-day course of SBRT according to CTCAE v5.0
  - rate of completion of neoadjuvant SBRT courses when given with M7824 and M9241.
- To determine a preliminary estimate of efficacy as best overall response (BOR) according to RECIST 1.1 of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with locally advanced pancreas cancer will be measured by
  - Best Overall Response (BOR) according to RECIST 1.1

10.1.2 Secondary endpoints

- Overall survival in patients after completion of SBRT in combination with M9241 and M7824.
- Progression-free survival of all patients and PFS of patients who did not undergo surgical resection (expressed as median PFS).
- Fraction of patients with LAPC who can undergo surgical resection after M7824 and M9241 in combination with SBRT treatment.
- Time-to-recurrence in patients who underwent surgical resection will be measured as time from surgical resection to disease recurrence (expressed in months).
- Rate of complete pathologic response will be measured as fraction of patients who had a complete pathologic response of all patients who underwent surgery.

10.2 SAMPLE SIZE DETERMINATION

Phase I:

The investigational agents M7824 and M9241 will be first tested in combination for safety and tolerability prior to assessing both in combination with SBRT. The safety phase IA run-in of M7824 and M9241 will accrue either pancreatic cancer patients with locally advanced surgically unresectable disease or patients with stage IV disease.

Dose Level 0 of 1,200 mg for M7824 every 2 weeks will be tested in combination with 16.8µg/kg of M9241 every four weeks will be first given to 6 patients as a safety run-in. If there are 0-1

DLTs, the study will proceed to the phase IB of M7824 and M9241 in combination with SBRT starting with DL0.

If there are ≥2 DLTs at DL0, 6 patients will be enrolled at DL -1 (1,200 mg M7824 q2 weeks and 12μg/kg every 4 weeks). If 6 patients at the DL-1 have 0-1 DLTs, DL-1 will be combined with SBRT and the study will move to phase IB. If 2 or more DLTs are seen at the DL-1, there will be no further attempts of combining M7824 with M9241 and neither the M7824 and M9241 in combination with SBRT phase IB or the phase II part will be carried out. The first safety run-in of M7824 in combination with M9241 might have a minimum of 6 and a maximum of 12 patients.

The safe dose of M7824 and M9241 will then be given in combination with a 5-day course of SBRT. Estimated during phase IA DL of M7824 and M9241 will be given to 6 patients. If there are 0-1 DLTs in the first 6 subjects, the dose of M7824 and M9241 will be used as the recommended phase 2 dose and the study will proceed to the phase II part. If there are ≥2 DLTs in the initial combination with SBRT, there will be a dose reduction of M9241 (if recommended dose was 16.8 μg/kg, M9241 will be reduced to 12 μg/kg, if the safe dose of M9241 when combined with M7824 in the phase IA part was 12.0 μg/kg, the dose will be reduced to 8.0μg/kg). If there are 0-1 DLTs in the first 6 subjects, this dose of M7824 and M9241 will be used as the recommended phase 2 dose and the study will proceed to the phase II part. If there are ≥2 DLTs in 6 patients treated with the reduced M7824 levels in combination with SBRT, no further attempts will be made to combine M7824 and M9241 with SBRT and the study will not proceed to the phase II part. The second safety run-in of M7824 and M9241 in combination with SBRT might have a minimum of 6 and a maximum of 12 patients.

Following determination of safe doses of M7824 and M9241 when combined with SBRT the study may proceed to the phase II part. Thus, a minimum of 12 and a maximum of 24 evaluable patients will be enrolled in the phase I cohorts.

Phase II:

The study will be conducted using a Simon two-stage phase 2 minimax design. The objective of the trial will be to determine whether this novel combination of M7824 and M9241 in combination with SBRT can be associated with a response rate (PR + CR; RECIST) that can rule out 10% (p0=0.10) in favor of an improved response rate of 30% (p1=0.30). Using alpha=0.10 (probability of accepting a poor agent) and beta=0.10 (probability of rejecting a good agent), initially 16 evaluable patients will be enrolled into the phase II study, including up to 6 patients from the completed safety cohort Phase IB of M7824 and M9241 in combination with SBRT if they are completely eligible for the phase II portion of the trial. If 0 to 1 of 16 patients respond, then no further patients will be enrolled. If 2 or more of the first 16 evaluable patients enrolled have a response (PR or CR), then accrual will continue until a total of 25 evaluable patients have been enrolled. If 2 to 4 of the 25 has a clinical response, then this will be considered inadequate for further investigation of this regimen. If 5 or more of 25 (20%) respond, then this will warrant further investigation in a subsequent trial. Under the null hypothesis (10% response rate), the probability of early termination is 51.5%.

Thus, with up to 24 participants in the phase I cohort and up to 25 evaluable participants in phase II, the trial may require up to 49 participants to be treated. This number may be reduced by up to 6 patients if there are <2 DLTs in the second safety run-in of M7824 and M9241 in combination with SBRT and those patients are included in phase II. To allow for a small number of inevaluable

patients, the accrual ceiling will be set at 52 participants. With an anticipated accrual rate of 10 patients per year, it is expected that the trial may complete accrual within 5 years.

10.3 POPULATIONS FOR ANALYSIS

Evaluable for overall response: all patients who receive at least one dose of M7824 and M9241 in combination with SBRT at the dose level determined to be safe in the safety run-in Phase IB of M7824 and M9241 in combination with SBRT will be included in the statistical analyses performed.

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with M7824 and M9241 in combination with SBRT.

Evaluable for MTD: Subjects enrolled to the safety run-in portion of the study are evaluable. However, subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced and not included in the evaluation.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Patients who are in the safety evaluation will have the number of patients with a DLT determined. Patients who are in the efficacy evaluation and patients from the safety run-in administered the M7824 and M9241 in combination with SBRT dose used in the phase II part of the study will have the fraction of clinical responses determined.

10.4.2 Analysis of the primary endpoints

For the patients in the dose de-escalation portion, the safety and tolerability and the recommended phase 2 dose (RP2D) of M7824 and M9241 in combination with SBRT as neoadjuvant / perioperative treatment in subjects with pancreas cancer will be evaluated by reporting the number, severity, and duration of treatment-related AEs for the combination treatment of M7824 and M9241 administered in combination with a 5-day course of SBRT according to CTCAE v5.0 . The rate of completion of neoadjuvant SBRT courses when given with M7824 and M9241 will be reported as well using descriptive statistics.

Patients who are in the efficacy evaluation will have the fraction objective responses measured by RECIST1.1 determined by dividing the number of patients with an objective response by the number of evaluable patients who are treated at the MTD and reported along with two sided 80% and 95% confidence intervals.

10.4.3 Analysis of the secondary endpoints

The secondary endpoints will be analyzed as follows:

- Overall survival in patients after completion of SBRT in combination with M9241 and M7824 and Progression-Free Survival (PFS) of all patients and PFS of patients who did not undergo surgical resection (expressed as median PFS). Overall survival and PFS will be determined in all patients treated at the MTD of M7824 and M9241 in combination with SBRT, as well as patients who did not undergo surgery, using Kaplan-Meier curves.
- Fraction of patients with LAPC who are able to undergo surgical resection after M7824 and M9241 in combination with SBRT treatment. This will be reported along with a 95% confidence interval on the fraction.

- Time-to-recurrence in patients who underwent surgical resection will be measured as time from surgical resection to disease recurrence (expressed in months). Time-to-recurrence in patients will be calculated via Kaplan-Meier curves. Any comparisons with published results will be interpreted as being exploratory.
- Rate of complete pathologic response will be measured as fraction of patients who had a complete pathologic response of all patients who underwent surgery. This will be reported along with a 95% confidence interval.

10.4.4 Safety analyses

Patients in the phase I portion of the trial will be assessed for toxicity by reporting the grades of toxicity and the type of toxicity observed for all patients. Patients will be enrolled and evaluated in the phase I cohorts of the trial as described in the phase I sample size determination section. Patients will continue to be enrolled onto the phase II cohort if the cumulative fraction of patients with greater or equal grade 3 DLT is less than 1/3.

10.4.5 Baseline descriptive statistics

Limited demographic and clinical characteristics of all patients will be reported, for both the phase I and the phase II cohorts.

10.4.6 Planned interim analyses:

Toxicity will be assessed within each group of 6 patients accrued in the phase I cohorts M7824 in combination with M9241, and M7824 and M9241 in combination with SBRT. The fraction of patients who respond in the phase IB part who received M7824 and M9241 in combination with SBRT will be included into the efficacy assessment of the phase II cohort, as indicated in the phase II sample size determination section.

10.4.7 Exploratory analyses

The following are the exploratory objectives, along with the method of analysis of each:

- To determine M7824 PKs. This will be done using descriptive measures only.
- To determine ADA profile of M7824 in combination with M9241. This will be done using descriptive measures only.
- To evaluate serum cytokines and tumor necrosis factor (TNF) levels pre-treatment and on-treatment. These measures will be evaluated using descriptive statistics. Comparisons between pre-treatment and on-treatment levels may be done using a paired test such as a Wilcoxon signed rank test.
- To correlate the tumoral immune infiltrate via IHC with clinical outcome, the levels will be compared between responders and non-responders using an exact Wilcoxon rank sum test.
- To evaluate impact of genomic profile of advanced pancreatic cancers on clinical response to M7824 and M9241 in combination with SBRT. The prevalence of common somatic mutations identified within the 50-cancer gene panel (Molecular Pathology; Dr. M. Raffeld; for example, KRAS, TP53, SMAD/TGBR2, CDKN2A) obtained from each patient will be compared between responders and non-responders. This will be done using

either a Fisher's exact test, Cochran-Armitage trend test, or exact Wilcoxon rank sum test depending on the distributions of values.

- To correlate circulating free tumor DNA (ctDNA) levels with clinical course of pancreatic cancer patients treated with M7824 and M9241 in combination with SBRT. The levels will be compared between responders and non-responders using an exact Wilcoxon rank sum test.
- To measure subjective Health-related Quality of Life (HRQoL) affecting disease-specific symptoms and treatment-related concerns pre-treatment and on-study and compare HRQoL scores with historical controls of other QoL interventions in advanced pancreas cancer patients. Health-related Quality of Life (HRQoL) scores measuring patient-reported disease-specific symptoms and treatment-related concerns will be compared between responders and non-responders using an exact Wilcoxon rank sum test. The results will also be compared informally with historical controls of other QoL interventions in advanced pancreas cancer patients, using descriptive methods.
- To evaluate the impact of M7824 in combination with M9241 on tumoral perfusion measured by perfusion-weight Dynamic Contrast-enhanced (DCE) Magnetic Resonance Imaging (DCE-MRI). This will be done using descriptive statistics.

11 COLLABORATIVE AGREEMENT

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA (02666) is in place with EMD Serono for the supply of M7824 and M9241.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

No individual who meets the criteria for eligibility will be excluded from participation based on their race, ethnicity, gender, or socioeconomic status. Particular attention will be made to acquire a broad and diversified population.

12.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have pancreatic cancer, and because of unknown toxicities in pediatric patients.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **12.4.2**), all subjects will be offered the opportunity to direct their wishes for research and care to a surrogate, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify a LAR, as needed.

Please see section **12.5.1** for consent procedure.

12.4 RISK/BENEFIT ASSESSMENT FOR ALL PARTICIPANTS

12.4.1 Known Potential Risks

The primary risk to patients participating in this research study is from the toxicity of M7824 and M9241, or from both drugs in combination with SBRT. M7824 and M9241 are investigational agents designed to enhance antitumor efficacy of standard treatment, standard CRT in this protocol. The protocol provides for detailed and careful monitoring of all patients to assess for toxicity.

12.4.1.1 Risk of Rapid Progression

Three large studies of bintrafusp alfa were recently stopped when the drug manufacturer reviewed data that suggested that the studies would not be likely to prove the study treatment better than standard treatments. This data also suggested that there may be a portion of patients that have either no benefit from bintrafusp alfa, or that bintrafusp alfa will make the tumor grow faster. This has been described with other immunotherapy approaches also with studies suggesting this happens in about 15% of cases.

12.4.1.2 Risks of Blood Collection

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.4.1.3 Risks of EKG

Risks include some minor skin irritation from the electrodes

12.4.1.4 Risks of exposure to ionizing radiation

Subjects in Cohort 1 in this study may be exposed to radiation from up to 7 CT scans per year for disease assessment (approximately 7.7 rem per year). This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 0.8 out of 100 (0.8%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

During a year in this research study subjects in Cohort 2 and 3 will be exposed to 25 Gy (5 Gy X 5 days) of radiation from stereotactic body radiation therapy or SBRT. These subjects will also receive a much smaller amount of radiation from up to 7 CT scans for disease assessment. The amount of radiation from these scans adds minimal additional risk to the higher radiation doses received in the course of treatment. This radiation is currently under review by the NIH Radiation Safety Committee.

12.4.1.5 Risks of CT Scans

In addition to the radiation risks discussed above, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling

12.4.1.6 Questionnaires risk

Questionnaires may contain questions that are sensitive in nature. The patients are asked to only answer questions they are comfortable with.

12.4.1.7 Risks of urine collection

There are no risks of urine collection.

12.4.1.8 Risks of MRIs (DCE-MRI)

This study involves MRIs performed for research purposes. The main risk is allergic reaction to IV administered contrast agent. This risk is in the range of 1 to 1.5 %. There is also risk of claustrophobia during MRI and feeling uncomfortable because of loudness of the scanner.

12.4.1.9 Risk of losing data

This includes the risk that data obtained during this study can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document

12.4.1.10 Other Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

12.4.1.11 Non-Physical Risks of Genetic Research

Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

12.4.2 Known Potential Benefits

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival.

12.4.3 Assessment of Potential Risks and Benefits

For patients with locally advanced pancreas cancer, median overall survival is in the range of 9 months. It is possible that treatment on this protocol may reduce tumor burden, improve resection rates, increase survival, or lessen symptoms caused by the cancer.

Potential adverse reactions attributable to the administration of the study drugs utilized in this trial are discussed in sections **1.2.5.1, 1.2.6.1, 1.2.7**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity

A number of clinically appropriate strategies to minimize risks to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the potential benefit of the study therapy in subjects with pancreas cancer outweigh the risks associated with study treatment.

12.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) (e.g., legally authorized representative [LAR] for reconsent purposes if participant is an adult unable to consent) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant).

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the subject will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found here.

12.5.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.5**.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be

provided by the suspending or terminating party to study participants, associate investigators, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical site and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

14.1 M7824 (146972)

14.1.1 Acquisition and Accountability

Investigational M7824 is manufactured and supplied for the trial by EMD Serono Research and Development Institute. Drug will be delivered directly to the NIH Pharmacy. Individual IV bags will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. IV bags will be delivered from NIH Pharmacy to patient unit where drug will be infused to the patient.

14.1.2 Administration.

Please, see section **3.3.1**

14.1.3 Formulation and Preparation

M7824 is provided as a sterile liquid formulation and packaged at a 10 mg/mL concentration in USP/ Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL). The vials are closed with rubber stoppers in serum format complying with USP and Ph Eur with an aluminum crimp seal closure. Each single-use vial contains 600mg of M7824, formulated as 10mg/mL of active, 6% (w/v) Trehalose, 40 mM NaCl, 5 mM Methionine, 0.05% (w/v) Tween 20, 10 mM LHistidine at pH 5.5.

The liquid formulation is diluted directly with 0.9% sodium chloride solution for injection. The estimated volumes of delivery are anticipated to be no more than 250mL. The verified concentration range in the infusion solution is 0.16 mg/mL to 9.6 mg/mL

14.1.4 Storage and Stability:

Store intact vials, both lyophilized and liquid formulations, in the refrigerator (2°C – 8°C). Do NOT freeze the vials. The vials must be stored in the original packaging and protected from light until use.

Store reconstituted lyophilized vials and diluted infusion solutions at room temperature.

Reconstituted lyophilized vials, if not used immediately, are stable at room temperature for up to 24 hours.

When diluted with 0.9% Sodium Chloride Injection, USP to a concentration of 0.16 mg/mL to 9.6 mg/mL, chemical and physical in-use stability has been demonstrated for 72 hours when stored at room temperature.

14.1.1 Toxicity

Please refer to section **1.2.5** for details.

14.2 M9241 (146972)

14.2.1 Acquisition and Accountability

Investigational M9241 is manufactured and supplied for the trial by EMD Serono Research and Development Institute. Drug will be delivered directly to the NIH Pharmacy. Individual syringes will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. Syringes will be delivered from NIH Pharmacy to patient unit where drug will be infused to the patient.

14.2.1 Administration.

Please, see section **3.3.2**

14.2.2 Formulation and Preparation

M9241 is supplied as 1.5 mg/mL in 2 mL clear type 1 glass vials. Each vial contains 1 mL of the sterile M9241 solution.

14.2.3 Storage and Stability:

Store the intact vials in the refrigerator (2ºC – 8ºC), in the original packaging.

Stored the syringes prepared for SC injection at controlled room temperature (15ºC – 25ºC).

M9241 may be administered undiluted or doses may be diluted with 0.9% Sodium Chloride Injection, USP to a concentration =/> 0.05 mg/mL (50 mcg/mL).

Although chemical stability has been demonstrated for 24 hours at 25°C for syringes prepared as above, the manufacturer recommends immediate use and pharmacy will assign a 4-hour expiration to prepared syringes.

14.2.1 Toxicity

Please refer to section **1.2.6.1** for details.

14.3 STEREOTACTIC BODY RADIATION THERAPY

The radiation device is an FDA cleared commercial device located in the NIH Clinical Center. The device will be used/investigated in accordance with labeling and therefore will be IDE exempt under 812.2 (c) – category 1.

14.3.1 Toxicity

Please refer to Section **3.4.3** for details.

15 REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2016.* CA Cancer J Clin, 2016. **66**(1): p. 7-30.
2. Rahib, L., et al., *Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States.* Cancer Res, 2014. **74**(11): p. 2913-21.
3. Ma, J. and A. Jemal, *The rise and fall of cancer mortality in the USA: why does pancreatic cancer not follow the trend?* Future Oncol, 2013. **9**(7): p. 917-9.
4. Heinemann, V., M. Haas, and S. Boeck, *Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer.* Ann Oncol, 2013. **24**(10): p. 2484-92.
5. Khorana, A.A., et al., *Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2016. **34**(21): p. 2541-56.
6. Balaban, E.P., et al., *Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2016. **34**(22): p. 2654-68.
7. Kang, M.J., et al., *Clinical significance of defining borderline resectable pancreatic cancer.* Pancreatology, 2017.
8. Denbo, J.W. and J.B. Fleming, *Definition and Management of Borderline Resectable Pancreatic Cancer.* Surg Clin North Am, 2016. **96**(6): p. 1337-1350.
9. Evans, D.B., et al., *Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head.* J Clin Oncol, 2008. **26**(21): p. 3496-502.
10. Sadot, E., et al., *FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma.* Ann Surg Oncol, 2015. **22**(11): p. 3512-21.
11. Li, D. and E.M. O'Reilly, *Adjuvant and Neoadjuvant Therapy for Pancreatic Cancer.* Surg Oncol Clin N Am, 2016. **25**(2): p. 311-26.
12. Goodman, K.A., *Stereotactic Body Radiation Therapy for Pancreatic Cancer.* Cancer J, 2016. **22**(4): p. 290-5.
13. Mukherjee, S., et al., *Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial.* Lancet Oncol, 2013. **14**(4): p. 317-26.
14. Brahmer, J.R., et al., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.* N Engl J Med, 2012. **366**(26): p. 2455-65.
15. Shen, T., et al., *Prognostic value of programmed cell death protein 1 expression on CD8+ T lymphocytes in pancreatic cancer.* Sci Rep, 2017. **7**(1): p. 7848.
16. Foley, K., et al., *Current progress in immunotherapy for pancreatic cancer.* Cancer Lett, 2016. **381**(1): p. 244-51.
17. Bailey, P., et al., *Genomic analyses identify molecular subtypes of pancreatic cancer.* Nature, 2016. **531**(7592): p. 47-52.

18. Tran, E., P.F. Robbins, and S.A. Rosenberg, *'Final common pathway' of human cancer immunotherapy: targeting random somatic mutations.* Nat Immunol, 2017. **18**(3): p. 255-262.

19. Schnurr, M., et al., *Strategies to relieve immunosuppression in pancreatic cancer.* Immunotherapy, 2015. **7**(4): p. 363-76.

20. Kalbasi, A., et al., *Radiation and immunotherapy: a synergistic combination.* J Clin Invest, 2013. **123**(7): p. 2756-63.

21. Reits, E.A., et al., *Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy.* J Exp Med, 2006. **203**(5): p. 1259-71.

22. Zeng, J., et al., *Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas.* Int J Radiat Oncol Biol Phys, 2013. **86**(2): p. 343-9.

23. Apetoh, L., et al., *Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy.* Nat Med, 2007. **13**(9): p. 1050-9.

24. Lam, A.R., et al., *RAE1 ligands for the NKG2D receptor are regulated by STING-dependent DNA sensor pathways in lymphoma.* Cancer Res, 2014. **74**(8): p. 2193-2203.

25. Deng, L., et al., *STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors.* Immunity, 2014. **41**(5): p. 843-52.

26. Matsumura, S., et al., *Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells.* J Immunol, 2008. **181**(5): p. 3099-107.

27. Le, D.T., et al., *Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer.* J Clin Oncol, 2015. **33**(12): p. 1325-33.

28. Lan, Y., et al., *Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-beta.* Sci Transl Med, 2018. **10**(424).

29. An, Y., et al., *Stereotactic radiosurgery of early melanoma brain metastases after initiation of anti-CTLA-4 treatment is associated with improved intracranial control.* Radiother Oncol, 2017. **125**(1): p. 80-88.

30. Ahmed, K.A., et al., *Tolerability and Safety of Thoracic Radiation and Immune Checkpoint Inhibitors Among Patients with Lung Cancer.* Int J Radiat Oncol Biol Phys, 2017. **98**(1): p. 224.

31. Hu, Z.I., A.Y. Ho, and H.L. McArthur, *Combined Radiation Therapy and Immune Checkpoint Blockade Therapy for Breast Cancer.* Int J Radiat Oncol Biol Phys, 2017. **99**(1): p. 153-164.

32. Azad, A., et al., *PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy.* EMBO Mol Med, 2017. **9**(2): p. 167-180.

33. Aste-Amezaga, M., et al., *Cooperation of natural killer cell stimulatory factor/interleukin-12 with other stimuli in the induction of cytokines and cytotoxic cell-associated molecules in human T and NK cells.* Cell Immunol, 1994. **156**(2): p. 480-92.

34. van Herpen, C.M., et al., *Intratumoral rhIL-12 administration in head and neck squamous cell carcinoma patients induces B cell activation.* Int J Cancer, 2008. **123**(10): p. 2354-61.

35. Grohmann, U., et al., *IL-12 acts directly on DC to promote nuclear localization of NF-kappaB and primes DC for IL-12 production.* Immunity, 1998. **9**(3): p. 315-23.

36. Del Vecchio, M., et al., *Interleukin-12: biological properties and clinical application.* Clin Cancer Res, 2007. **13**(16): p. 4677-85.

37. Lacy, M.Q., et al., *Phase II study of interleukin-12 for treatment of plateau phase multiple myeloma (E1A96): a trial of the Eastern Cooperative Oncology Group.* Leuk Res, 2009. **33**(11): p. 1485-9.

38. Gollob, J.A., et al., *Phase I trial of twice-weekly intravenous interleukin 12 in patients with metastatic renal cell cancer or malignant melanoma: ability to maintain IFN-gamma induction is associated with clinical response.* Clin Cancer Res, 2000. **6**(5): p. 1678-92.

39. Mortarini, R., et al., *Peripheral burst of tumor-specific cytotoxic T lymphocytes and infiltration of metastatic lesions by memory CD8+ T cells in melanoma patients receiving interleukin 12.* Cancer Res, 2000. **60**(13): p. 3559-68.

40. Rook, A.H., et al., *Interleukin-12 therapy of cutaneous T-cell lymphoma induces lesion regression and cytotoxic T-cell responses.* Blood, 1999. **94**(3): p. 902-8.

41. Younes, A., et al., *Phase II clinical trial of interleukin-12 in patients with relapsed and refractory non-Hodgkin's lymphoma and Hodgkin's disease.* Clin Cancer Res, 2004. **10**(16): p. 5432-8.

42. Little, R.F., et al., *Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma.* Blood, 2006. **107**(12): p. 4650-7.

43. Paoloni, M., et al., *Defining the Pharmacodynamic Profile and Therapeutic Index of NHS-IL12 Immunocytokine in Dogs with Malignant Melanoma.* PLoS One, 2015. **10**(6): p. e0129954.

44. Fallon, J., et al., *The immunocytokine NHS-IL12 as a potential cancer therapeutic.* Oncotarget, 2014. **5**(7): p. 1869-84.

45. Eckert, F., et al., *Enhanced binding of necrosis-targeting immunocytokine NHS-IL12 after local tumour irradiation in murine xenograft models.* Cancer Immunol Immunother, 2016. **65**(8): p. 1003-13.

46. Eckert, F., et al., *Tumor-targeted IL-12 combined with local irradiation leads to systemic tumor control via abscopal effects in vivo.* Oncoimmunology, 2017. **6**(6): p. e1323161.

47. Sangro, B., et al., *Phase I trial of intratumoral injection of an adenovirus encoding interleukin-12 for advanced digestive tumors.* J Clin Oncol, 2004. **22**(8): p. 1389-97.

48. Strauss, J., et al., *First-in-Human Phase I Trial of a Tumor-Targeted Cytokine (NHS-IL12) in Subjects with Metastatic Solid Tumors.* Clin Cancer Res, 2019. **25**(1): p. 99-109.

49. Loehrer, P.J., Sr., et al., *Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial.* J Clin Oncol, 2011. **29**(31): p. 4105-12.

50. Guckenberger, M., et al., *Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer.* Strahlenther Onkol, 2014. **190**(1): p. 26-33.

51. Myrehaug, S., et al., *Stereotactic body radiotherapy for pancreatic cancer: recent progress and future directions.* Expert Rev Anticancer Ther, 2016. **16**(5): p. 523-30.

52. Pollom, E.L., et al., *Single- versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: outcomes and toxicity.* Int J Radiat Oncol Biol Phys, 2014. **90**(4): p. 918-25.

53. Brunner, T.B., et al., *SBRT in pancreatic cancer: what is the therapeutic window?* Radiother Oncol, 2015. **114**(1): p. 109-16.

54. Gillen, S., et al., *Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages.* PLoS Med, 2010. **7**(4): p. e1000267.

55. Chang, D.T., et al., *Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas.* Cancer, 2009. **115**(3): p. 665-72.

56. Moningi, S., et al., *The Role of Stereotactic Body Radiation Therapy for Pancreatic Cancer: A Single-Institution Experience.* Ann Surg Oncol, 2015. **22**(7): p. 2352-8.

57. Polistina, F., et al., *Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration.* Ann Surg Oncol, 2010. **17**(8): p. 2092-101.

58. Schellenberg, D., et al., *Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer.* Int J Radiat Oncol Biol Phys, 2011. **81**(1): p. 181-8.

59. Mahadevan, A., et al., *Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer.* Int J Radiat Oncol Biol Phys, 2011. **81**(4): p. e615-22.

60. Goyal, K., et al., *Stereotactic body radiation therapy for nonresectable tumors of the pancreas.* J Surg Res, 2012. **174**(2): p. 319-25.

61. Gurka, M.K., et al., *Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety.* Radiat Oncol, 2013. **8**: p. 44.

62. Herman, J.M., et al., *Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma.* Cancer, 2015. **121**(7): p. 1128-37.

63. Rajagopalan, M.S., et al., *Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer.* Radiat Oncol, 2013. **8**: p. 254.

64. Mellon, E.A., et al., *Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma.* Acta Oncol, 2015. **54**(7): p. 979-85.

65. Rwigema, J.C., et al., *Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins.* J Gastrointest Cancer, 2012. **43**(1): p. 70-6.

66. Huguet, F., et al., *Modeling pancreatic tumor motion using 4-dimensional computed tomography and surrogate markers.* Int J Radiat Oncol Biol Phys, 2015. **91**(3): p. 579-87.

67. Chuong, M.D., et al., *Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated.* Int J Radiat Oncol Biol Phys, 2013. **86**(3): p. 516-22.

68. Murphy, J.D., et al., *A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer.* Int J Radiat Oncol Biol Phys, 2010. **78**(5): p. 1420-6.

69. Webster, K., D. Cella, and K. Yost, *The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation.* Health Qual Life Outcomes, 2003. **1**: p. 79.

70. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

71. Wolchok, J.D., et al., *Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.* Clin Cancer Res, 2009. **15**(23): p. 7412-20.

16 APENDICES

16.1 APPENDIX A: DIAGNOSTIC CRITERIA OF BORDERLINE RESECTABLE PANCREAS CANCER

Criteria	Year	SMV/PV
MDACC	2006	• Short-segment occlusion[a]
AHPBA/SSO/SSAT	2009	• Tumor abutment • Encasement, but without encasement of the nearby arteries • Short segment venous occlusion resulting from either tumor thrombus or encasement[a]
Intergroup (Alliance)	2013	• Interface between tumor and vessel ≥180° • Occlusion[a]
ISGPS	2014	• Distortion or narrowing • Occlusion[a]
NCCN 2017	2017	• Contact >180° • Contact ≤180° with contour irregularity of the vein or thrombosis of the vein[a]

SMV – superior mesenteric, PV- portal vein.
a With suitable vessel proximal and distal.

Artery criteria.

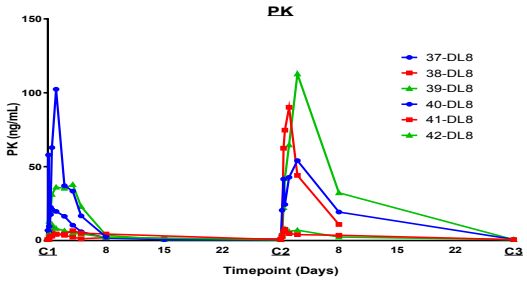
Criteria	Year	GDA	HA	CA	SMA
MDACC	2006		• Short-segment encasement/abutment of CHA		• Abutment ≤180°
AHPBA/SSO/SSAT	2009	• Encasement up to the HA	• Short segment encasement or direct abutment	• No extension	• Abutment ≤180°
Intergroup (Alliance)	2013		• Reconstructable, short-segment interface between tumor and vessel of any degree	• Interface between tumor and vessel < 180°	• Interface between tumor and vessel < 180°
ISGPS	2014	• Encasement up to the HA	• Short segment encasement or direct abutment	• No extension	• Abutment ≤180°
NCCN	2017		Head/uncinate process; • Contact with CHA without extension to HA bifurcation • Contact with variant arterial anatomy (ex: accessory/replaced RHA, replaced CHA, the origin of replaced or accessory artery)	Head/uncinate process; • No extension Body/tail: • Contact with the CA of ≤180° • Contact with the CA of >180° without involvement of the aorta and with intact and uninvolved GDA	• Contact ≤180°

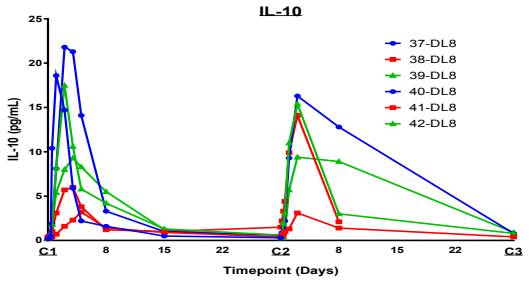
GDA, gastroduodenal artery; HA, hepatic artery; CA, celiac axis; SMA, superior mesenteric artery; CHA, common hepatic artery; RHA, right hepatic artery

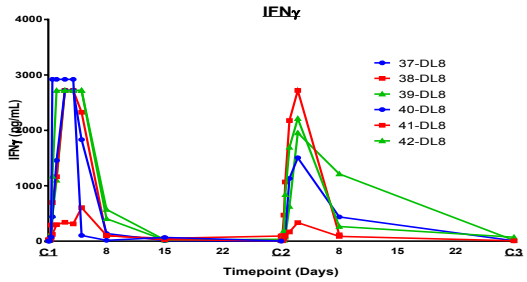
16.2 APPENDIX B: M9241 MULTIPLE DOSE PK PROFILE IN HUMANS AND M9241-INDUCED ALTERATIONS IN PLASMA CYTOKINE PROFILES AND PERIPHERAL BLOOD IMMUNE CELL PHENOTYPE.

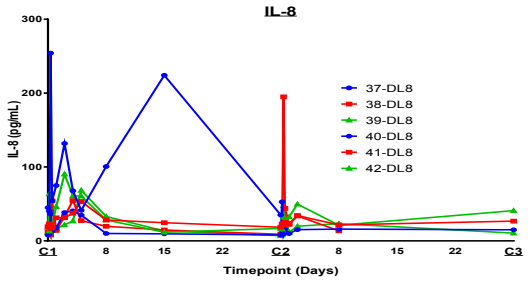
M9241 and plasma cytokine levels are shown from human subjects who received ≥2 doses of 16.8µg/kg M9241 by subcutaneous injection. Values for immune cell subsets are the frequency of the subset out of all PBMC shown as median (IQR). Graphs depicting three of these subsets. Changes of the immune chekcpoints TIM3 and PD-1 on NK between two administrations are shown.

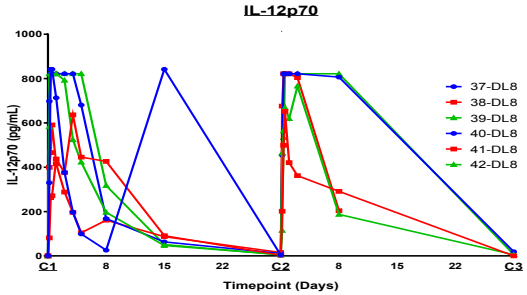
DL8: 16.8 mcg/kg

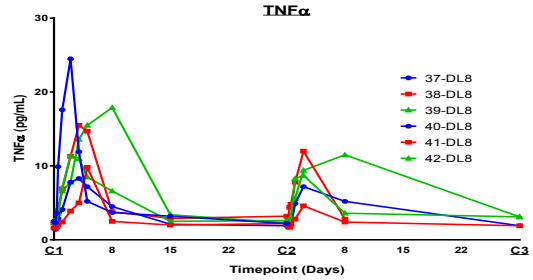




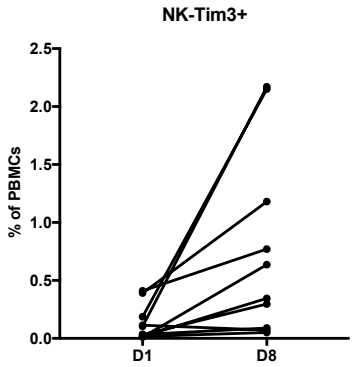


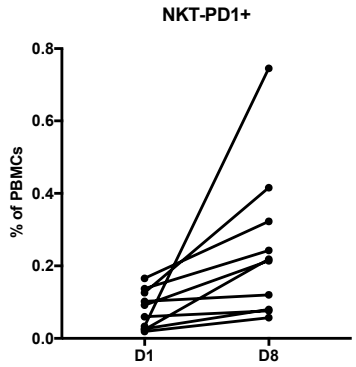


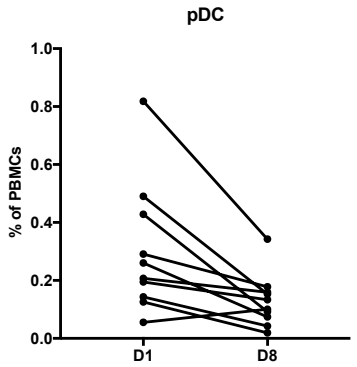




Immune cell subset	Day 1 (Pre treatment)	Day 8 (Post 1 cycle)	Direction of the change	P-value	Adjusted P-value
CD4-EMRA-PD-L1+	0.06 (0.04-0.09)	0.03 (0.01-0.05)	Down	0.002	0.038
NK-Tim3+	0.07 (0.02-0.24)	0.49 (0.08-1.42)	Up	0.0059	0.047
NK-Mature Tim3+	0.07 (0.03-0.21)	0.93 (0.25-1.53)	Up	0.002	0.018
NKT-PD1+	0.08 (0.03-0.13)	0.22 (0.08-0.35)	Up	0.002	0.008
pDC	0.2 (0.1-0.4)	0.1 (0.1-0.2)	Down	0.0039	0.02







16.3 APPENDIX C: FACT-HEP VERSION 4

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

16.4 APPENDIX D:PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

16.5 APPENDIX E:MODIFIED IMMUNE-RELATED RESPONSE CRITERIA (IRRECIST)

This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR:	Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.
Overall irPR:	Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%.
Overall irSD:	Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).
Overall irPD:	Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions (Tumor Burden)[1]	**Non-Index Lesions**	**New, Non-Measurable Lesions**	
Decrease 100%	Absent	Absent	irCR[2]
Decrease 100%	Stable	Any	irPR[2]
Decrease 100%	Unequivocal progression	Any	irPR[2]
Decrease ≥ 30%	Absent / Stable	Any	irPR[2]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[2]
Decrease < 30% to increase < 20%	Absent / Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Increase ≥ 20%	Any	Any	irPD

[1] Decreases assessed relative to baseline
[2] Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).