University of Iowa Hospitals and Clinics
Holden Comprehensive Cancer Center

Immunotherapy combined with Yttrium-90 RadioEmbolization in the treatment of Colorectal Cancer with Liver Metastases [iRE-C – Clinical Trial]

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Summary of Changes

Section	Change
07 June 2022	
Title page	Updated date
3.2.16	Removed 3.2.16 exclusion regarding Hepatitis B, Hepatitis C and HIV requirement.
3.2.5	Revised exclusion criteria 3.2.5 to add "infections." Updated exclusion to read as: "Co-morbid systemic illnesses, infections, or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens."
4.1	Removed Hep B surface ag, Hep C ab, HIV 1/2, from Test Schedule.
18.0	Pathology Considerations/Tissue Biospecimens- updated location of specimens to University of Iowa Tissue Procurement Core
04 March 2022	
Title page	Updated PI Name and contact information.
03 April 2020	
Title page	Updated date; inserted IDE number
1.4.5 [FDA requested edit]	Removed "…last dose of…" so sentence reads, "….fixed dose durvalumab and the dose limiting toxicity (DLT) observation phase for 8 weeks post Y90-RE."
1.4.7 [FDA requested edit]	Edited sentence to read, "The dose limiting toxicity (DLT) observation phase is 8 weeks post Y90-RE."
3.1.7 [FDA requested edit]	Changed inclusion criterion from *"These include at least treatment with a fluoropyrimidine, oxaliplatin, and/or irinotecan-based therapy, an anti-VEGF therapy and, if RAS wild-type, an anti-EGFR therapy, unless deemed intolerant or not suitable by the treating oncologist."* to "*These include at least treatment with a fluoropyrimidine, oxaliplatin, and/or irinotecan-based therapy and an anti-EGFR therapy if RAS wild-type (unless deemed intolerant or not suitable by the treating oncologist), with or without an anti-VEGF therapy."*
3.1.7 [FDA requested edit]	Inserted inclusion criterion to specify a minimum gap of 4-weeks between Tc-99m-labelled mAA eligibility mapping and any anti-VEGF therapy; renumbered inclusion criteria accordingly.
3.2.14 [FDA requested edit]	Reduced steroid allowance to 10 mg prednisone equivalent
7.4.2	Removed "up to" to clarify the DLT window is 8 weeks post Y90-RE

Y90-RE /Durvalumab	Added, “Any event resulting in a delay of cycle 2 ≥ 14 calendar days,”
	Added, “Any Grade 3 irAE…”
	Added Grade 4 neutropenia lasting > 5 days
	Added any instance of grade 4 thrombocytopenia
	Added any instance of grade 3 thrombocytopenia with accompanying hemorrhage
7.4.2 [FDA requested edits]	Added grade 3 nausea / vomiting exception
	Added grade 3 nausea / vomiting / diarrhea exception
	Added grade 4 vomiting / diarrhea exception
	Added grade 3 hypertension exception
	Added grade 3 metabolic abnormalities exception
	Added grade 3, 4, 5 electrolyte abnormality exception
	Added grade 3, 4 elevation in amylase/lipase exception
	Added grade 3 rash exceptions
	Changed Grade 3 diarrhea or colitis dose modification to permanently discontinue
Table 8.21 [FDA requested edits]	Added grade 2 to hyperglycemia/T1DM
	Added grades 2 & 4 to hypothyroidism
	Added grade 2 to hyperthyroidism
	Added grade 1 to dose modification for infusion related reaction

03 April 2020 *(cont'd)*	
Table 8.21 [FDA requested edits]	Clarified, "…and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)…" to pneumonitis grade 2 dose modification
	Clarified, "…and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)…" to all other non-hematologic events grade 3 dose modification
	Clarified, "…and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)…" to pneumonitis grade 2 dose modification
17.5.3 [FDA requested edits]	Clarified mRECIST as evaluation criteria for ORR
	Clarified time point window
	Clarified response categories and evaluation criteria
17.5.3	Inserted text from Appendix A.9 regarding results reporting
Footer	Updated protocol date
04 March 2020	
Title page	Reformatted, updated to include IDE sponsor
Throughout	Clarified section numbers; formatting updated for consistency
1.2.3	Inserted 'Tc-99m' prior to MAA for clarification
1.2.3	Inserted further details regarding calculation of prescription activity as well as protective measures for lung and bowel.
1.4.2	Inserted information about the Tc99m MAA eligibility mapping for eligibility and screening.
3.2.1	Provided Cockcroft Gault formula
3.2.1	Included recommendations from FDA for total bilirubin and serum creatinine
3.2.2	Incorporated recommendations from FDA
4.0	Clarified footnote 18 for inclusion of the Tc99m labelled MAA mapping.
7.1.2	Inserted information from package insert on radiation dose.
10 (overall)	Heavy revision for compliance and consistency with FDA, IRB, and DSMC requirements.
10.2.2	Clarified that subjects will be followed for up to 2 years for radiation associated adverse effects; this determination will be made by an authorized user (NRC).
16 (new section)	Created section in investigational device; renumbered subsequent sections accordingly.
17.3	Updated to address concerns and queries from FDA
17.5.3	Defined evaluable patient

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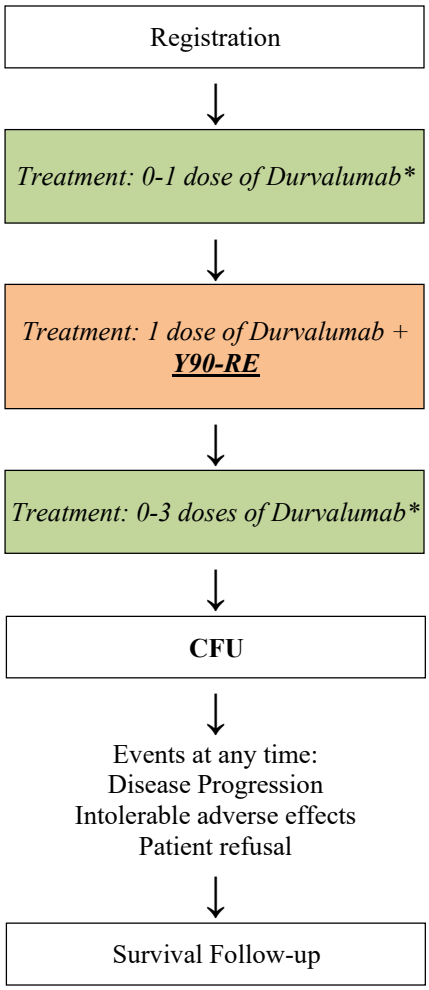
Schema

Prior to discussing protocol entry with the patient, call the Registration Office and discuss with clinical trial coordinator and/or Study PI for dose level and to ensure that a place on the protocol is open to the patient.



Cycle = 14 days; *number of durvalumab doses post Y90-RE are dependent on assigned cohort level

Generic name: durvalumab Brand name(s):IMFINZI® Abbreviation: MEDI4746 Availability: Investigational

1.0 Background

1.1 Colorectal cancer (CRC)

Colorectal cancer (CRC) accounts for approximately 135,000 new cancers diagnosed annually in the United States. Despite recent advances in treatment, it still remains the third most common cause of cancer mortality, causing 50,000 deaths per year. (Siegel, et al, 2016; Ryerson, et al, 2016) Patients who have isolated liver metastases that are amenable to surgical resection may be potentially cured. However, less than 25% of patients present with easily resectable disease. (Khatri, et al, 2005; Morris, et al, 2010) A number of interventional oncologic loco-regional modalities have emerged to treat patients who are not surgical candidates and provide disease control. One such promising modality is radioembolization (RE), which consists of delivering transvascular brachytherapy to the tumor via the hepatic artery. A phase III trial comparing RE with chemotherapy to chemotherapy alone demonstrated an improved time to liver progression by approximately eight months. (Hendlisz, et al, 2010) Overall survival benefit, however, is lacking based on more recent randomized controlled trials, and underlying patient- and tumor-related factors are being explored.

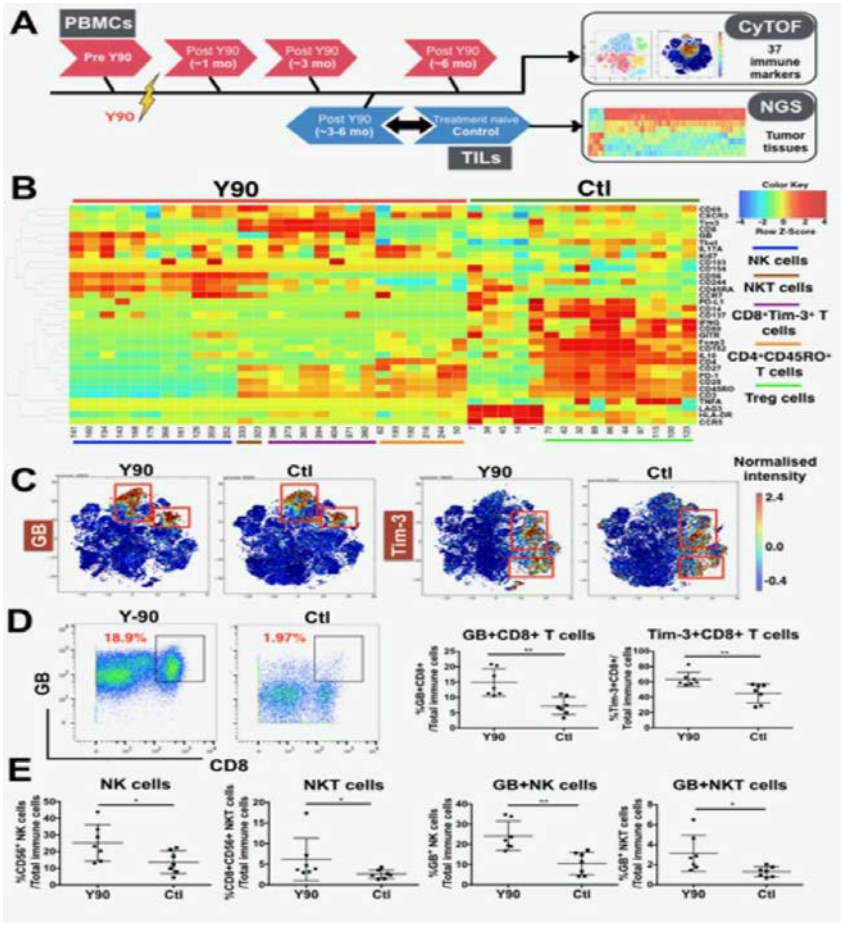
In recent years, immune checkpoint inhibitors (ICIs) have revolutionized the treatment of a number of cancers. They target the programmed cell death ligand-1 (PD-L1), Programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4) pathways. These immune escape mechanisms allow tumors to progress by evading the body's immune response. ICIs inhibit these pathways and activate lymphocytes to recognize tumor antigens, thereby enhancing tumor killing (Pardoll, et al, 2012). They have shown activity and efficacy in a number of malignancies including melanoma, lung cancer, renal cell cancer, bladder cancer, head and neck cancer, and Hodgkin lymphoma. (Topalian, et al, 2012; Brahmer, et al, 2012; Rosenberg, et al, 2016; Robert, et al, 2015; Ferris, et al, 2016; Gettinger, et al, 2016)

Immunotherapy alone in patients with metastatic colorectal cancer (mCRC) had been of limited value until recently. The factors identified behind immunotherapies working for some cancers while not others include tumor related factors (mutational burden) and host related factors (immune response). In colorectal cancers, these tumors can be classified as microsatellite instability-high (MSI-H) with a high mutational burden (Lynch-syndrome like) and microsatellite stable (MSS), with a low mutational burden. The results of a landmark immunotherapy trial published in 2015 for the first time showed great promise for immunotherapies in mCRC. Of note, while seven out nine patients who were MSI-H had an objective response, 0 out 18 patients who were MSS had a response to anti-PD-1 blockade. (Le, et al, 2015) Unfortunately, MSI-H tumors constitute a very small proportion (~5%) of mCRC. Therefore, novel approaches are needed to make immunotherapy a viable option for MSS tumors, which constitute more than 95% of the tumors. Furthermore, immunotherapy is only approved for this particular patient subset after failure of traditional chemotherapy and not first-line.

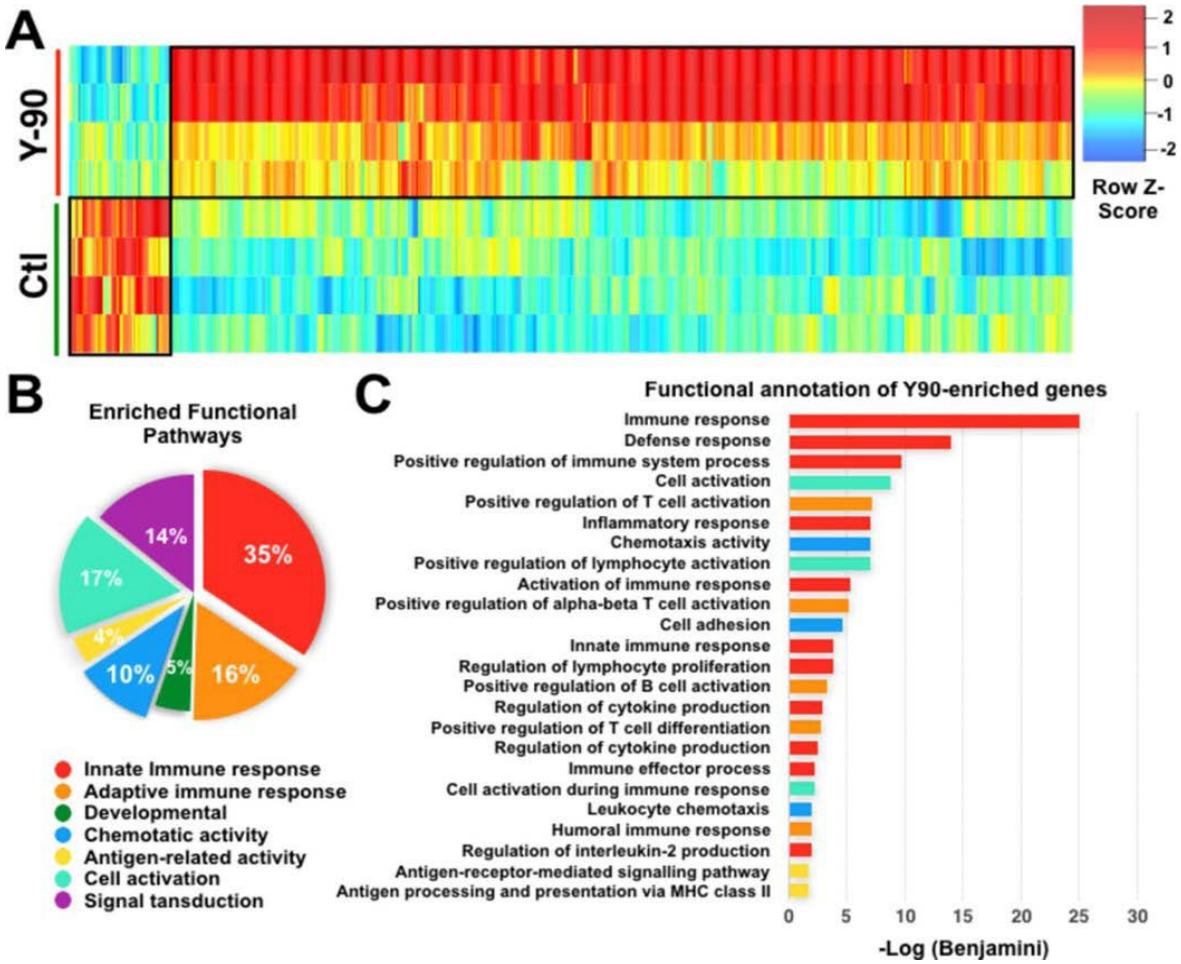
Increasing exposure of neo-antigens to the immune system could be one potential strategy to enhance the response of immunotherapy to patients with mCRC. Yttrium 90-radioembolization (Y90-RE) in combination with immunotherapy may result in immunotherapy working for patients with mCRC and/or increasing the efficacy of Y90-RE. Furthermore, the "abscopal effect" is a phenomenon in the treatment of cancer where localized treatment of a tumor causes an effect on the treated tumor, and tumors outside the localized treatment field. It has been reported in a number of different human cancers. This phenomenon has also been demonstrated in mouse tumor models and been shown to be mediated by immune mechanisms, and therefore, does not occur in immunodeficient mice. Tumor cells exposed to radiation can undergo an immunogenic death that exposes tumor antigens and triggers an anti-tumor immune response that results from an increase in maturation of antigen presenting cells. Additionally, radiation makes the tumor microenvironment conducive to effector T-cell recruitment and function. It induces chemokines involved in the recruitment of effector T cells, thereby making the tumor susceptible to T-cell attack. (Herrera, et al, 2017) Y90-RE in essence, provides not only local radiation therapy to the treated tumor but also a potential opportunity for immunotherapy to work for patients for whom immunotherapy was not an

option by increasing exposure to neo-antigens and altering the tumor microenvironment. Radiation in general has been combined with immunotherapy for a number of malignancies. Therefore, we hypothesize that combining immunotherapy agents with Y90-RE is feasible, safe and will improve outcomes in patients with mCRC with liver-predominant metastases.

Current Y90-RE relies on the transarterial administration of several million yttrium-90 (Y90) containing resin or glass microspheres ranging from 20-30 microns that provide intratumoral brachytherapy through the emission of beta particles. It provides a unique dosimetry advantage by relying on an inherent dose preferential related to tumor relative hyperarteriolization and the minor parenchymal penetration of emitted beta particles. (Hazel, et al, 2016; Ruers, et al, 2012; Kasi, et al, 2015) In contrast to external photon or proton radiotherapy, Y90-RE is not only treating in field disease, but also via in situ tumor ablation generating both antigen exposure and changes in the tumor microenvironment (TME) from an immune standpoint. (den Brok, et al, 2004) Both the antigen exposure and immune related changes in TME are aspects that can be harnessed to generate a more robust, effective and potentially durable immune response against the tumor. Some of the recent small translational studies are showing that the tumor microenvironment from an immune perspective does undergo changes post-RE (Chew, et al, 2018).



Panel A: from Valerie et al 2018: Immune profiles of tumour infiltrating leucocytes (TILs) isolated from Yttrium-90 (Y90)-radioembolization (RE)-treated and treatment-naïve tumours. Valerie Chew et al. Gut doi:10.1136/gutjnl-2017-315485



Panel B: from Valerie et al 2018: Next-generation sequencing (NGS) and pathway analysis of post-Yttrium-90 (Y90)-radioembolization (RE) and treatment-naïve (control (Ctl))

ICIs have shown remarkable durable efficacy in a number of cancers by harnessing the body's immune system to attack the tumor. Unfortunately, in mCRC this effect is limited to a small percentage of tumors that are MSI-H who have failed immunotherapy. By combining ICIs with radioembolization, we could potentially increase the number of patients who could attain durable benefit from immunotherapy and Y90-RE. The safety data as well as the translational data generated from this trial would also be of value for other tumor types since Y90-RE is utilized for treatment of other primary and secondary liver tumors as well.

1.2 Y-90 Radioembolization (Y90-RE)

Y-90 radioembolization (Y90-RE) is a combination of radiation therapy and in the case of glass microembolization to treat cancer of the liver. Radioembolization consists of the transarterial administration of yttrium-90 containing glass or resin microspheres as tumor brachytherapy for hepatic malignancy. Radioembolization safely achieves tumor biological equivalent doses that exceed both external beam radiotherapy by exploiting tumor hypervascularity as an inherent dose preferential and the limited parenchymal penetration of beta particles. (Kennedy, et al, 2014) These properties allow for ablative doses of radiation with minimal toxicity administered in as little as one or two outpatient sessions. (Riaz, et al, 2011; Gates, et al, 2014) It results in a minimally invasive treatment in which the primary mechanism is delivery of radiation with microembolization of the vascular bed. Glass Radioembolization employs microspheres with the radioactive isotope yttrium-90 incorporated within the glass microsphere. Normally the microspheres are made by tiny glass or resin beads. Those microspheres will be placed inside the blood

vessels that feed a tumor. The microspheres will be delivered by catheter through the skin after X-Ray imaging and a contrast material in order to visualize the blood vessel. TheraSphere®, an Y90-RE owned by BTG International Canada will be used in this clinical trial. As per the FDA approved USPI Technitium-99m (Tc-99m) labeled Macroaggregated Albumin (MAA) scintigraphy will precede microsphere administration to ensure proper delivery of radiotherapy and minimize collateral toxicity.

1.2.1 Variances in Radioembolization

Applications of radioembolization include whole liver, lobar, and segmental treatments encompassing surgical neoadjuvant, bridge to transplantation, definitive radiotherapy, and palliative intention. Greater than 50% complete pathologic response rates in hepatocellular carcinoma (HCC) and metastatic colorectal carcinoma (mCRC) previously treated with radioembolization in liver explants and hepatic resection specimens are evidence of its ablative potential. (Vouche, et al, 2014; Shah, et al, 2017; Lewandowski, et al, 2016) Randomized control trial data has shown palliative radioembolization to be well tolerated with concurrent systemic chemotherapy in mCRC. Differing safety and efficacy outcomes can be seen due to techniques, methodologies, institutional practices, selection of patients and products used.

1.2.2 Glass Radioembolization for Liver Predominant Colorectal Carcinoma

Although the largest prospective randomized trial utilizing radioembolization for the treatment of liver metastatic colorectal carcinoma were performed with resin spheres, our current trial will be utilizing glass microspheres. The two products vary in specific activity (60 Bq vs 2500 Bq), specific gravity, and administration technique. Although data from a prospective randomized study utilizing glass microspheres for colorectal hepatic metastases (EPOCH) is yet unavailable, multicenter retrospective data demonstrates both safety and tumor response in utilizing glass for this indication. Results from this analysis demonstrated that in 531 patients, the most common clinical adverse events were fatigue (55%), abdominal pain (34%) and nausea (19%). Grade 3 or 4 hyperbilirubinemia occurred in 13% of patients. Median overall survival from first Y90-RE treatment was 10.6 months (95% CI 8.8-12.4). Performance status, tumor burden ≤25%, no extra-hepatic metastases, albumin >3 g/dL and having received ≤2 chemotherapeutic agents independently predicted better improved outcomes (Hickey, et al, 2016). These are relatively consistent with the published literature for resin microspheres.

1.2.3 Radioembolization Dosimetry

The understanding of how to best deliver transvascular microsphere brachytherapy has slowly matured since its inception in the mid 1960's to the current iteration. Dosimetry began as an empiric administration approximately 20 years ago which resulted in high toxicity and low efficacy. The notion of tailoring the dose to an individual's anatomy led to the development of body surface area dosimetry or the BSA method. This has been the most widely studied method for delivering resin microspheres which have a lower specific gravity and activity when compared to glass microspheres. The advantages to the BSA method are mainly rooted in the conservative doses that rarely result in toxicity, but even less commonly achieve major responses. An alternative method and most used approach for glass microspheres, which are orders of magnitude greater in activity to resin spheres (2,500 vs 60 Bq/sphere), is the Medical Internal Radiation Dose or MIRD formula. This has a distinct advantage to BSA in that it factors true anatomic volumes in which a predetermined activity is administered which gives a generic dose.

Unfortunately, this method does not take into consideration the tumor favoring dose preferential of vascular conduit therapy amongst other flow altering factors and the true microsphere deposition is not accounted for. The 3D evaluation of Tc-99m MAA as a temporary particle simulant prior to radioembolization has prompted the compartmental approach in which the general sorting of Tc-99m MAA can be converted to a presumed dose after treatment. While this is an improvement, the technique has traditionally assumed single infusion points from the main hepatic arteries and may not match the heterogeneous distribution of liver metastases in patients. The angiosomal approach involves segmenting the liver based on individual supplying arteries and performing individual volumetric and compartmental assessments to determine the

strength of dose to each volume based on tumor content and risk of overall hepatic dysfunction based on hepatic substrate and volume of treatment. If the tumor to parenchyma ratio is high, then dose escalation is performed given the higher chance for efficacy with less collateral damage. The converse is also true. An additional subset involves the compartmentalization of doses achieved through preferential deposition of spheres related to tumor hypervascularity. This can be prospectively approximated through the analysis of Tc-99m MAA deposition, which has shown to be highly predictive of normal tissue deposition but less predictive of tumor deposition. This can be utilized to determine the risk of normal tissue complications and overall guide dosimetry, typically limited by the non-target organ dose. The majority of glass administrations will utilize a qualitative assessment of administered activity equating to a MIRD dose that can be both with ablative and non-ablative intent based on the tumor to parenchyma ratio within each treatment angiosome. The previously mentioned retrospective analysis of glass radioembolization utilized for colorectal carcinoma showed a median radiation dose delivered to the liver of 120.2 Gy (range, 35–391 Gy).

Non-ablative doses typically range from 40-80 Gy and ablative doses may exceed 120 Gy per lobe with segmental administrations measuring >190 Gy. To prospectively determine dosimetry as a fixed range for all patients may prove challenging as oncologic intent, performance, liver substrate, tumor stage, tumor vascularity and arterial physiology are all variable.

At our institutions and centers with more expertise in interventional oncology, the focus of our interventional oncology group is to maximize dose when possible but maintaining safety as a primary objective. Additionally, Y90-RE is done with as much parenchymal sparing as possible while delivering higher doses to the areas of maximum tumor involvement. The treatment in conjunction could potentially allow for not only durable local control but also systemic control by exposure of neoantigens. The more durable control stems from increased PD-L1 expression noted post radiation as a mechanism of evasion and resistance to therapy, which can be overcome by anti-PD1/PD-L1 agents.

Target dose administrations will fall within package insert recommendations of 80 Gy to 150 Gy per lobe of liver in order to prevent radioembolization-induced liver disease (REILD). Required activity at the time of administration may be calculated as

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Target Liver Mass (kg)}]}{50}$$

and the actual dose delivered to the liver is

$$\text{Dose (Gy)} = \frac{50[\text{Injected Activity (GBq)}][1 - \text{F}]}{\text{Affected Liver Mass (kg)}}$$

, where F is the lung shunting fraction measured during the Tc-99m labelled MAA eligibility study.

Safety is the primary goal of our clinical trial. For patients who are deemed candidates through multi-disciplinary decision, this factors all the recent updates and guidelines. Variation in doses would not be a concern since all the patients will be treated at one institution (University of Iowa). Important aspects factored in this patient selection includes but is not limited to absence of shunting to bowel along the GI tract. Protective measures against radiation pneumonitis require a lung shunting fraction (F) <15% or estimated lung doses <30 Gy for a single Y90-RE administration and a cumulative total of <50 Gy from multiple administrations.

1.2.4 Radioembolization and Immunomodulation

In addition to promotion of immunity, radiation may exhibit certain immuno- inhibitory effects. Radiation upregulates transforming growth factor β and galectin-1 which have been shown to indirectly suppress T cell activity. (Demaria, et al, 2015) Although radioembolization does not rely on the embolic effect of microspheres, high particle volume treatments may reduce local blood supply. (Pellerin, et al, 2013) Transient lymphopenia has been previously observed in patients undergoing radioembolization which is usually of no clinical consequence, but this effect may interfere with immune response. (Salem, et al, 2005). While radiation induces tumor vascular normalization, it can also exacerbate local hypoxia via endothelial damage and venoocclusive associated interstitial hypertension which theoretically abates local immune response (Park, et al, 2012; Fan, et al, 2014). Although preclinical models support hypofractionated external beam therapy to maximize effective anti-tumor immune response, the equivalent dosimetry of brachytherapy has not been specifically studied for this purpose (Dewan, et al, 2009). Ultimately, understanding the precise role and balance of both potential immunostimulatory and inhibitory effects of radioembolization will require considerable investigation. Some of the recent studies, however, (as shown in panel A and B earlier) do offer proof of principle in terms of value of potentially combining immune checkpoint inhibitors in conjunction with Y90-RE (Chew, et al, 2018) approaches.

1.2.5 Hepatic Benefit of Radioembolization

Of all radiotherapy modalities, radioembolization is unique in its ability to provide low normal tissue complication rates with whole organ treatment. This offers potentially more comprehensive immune exposure of heterogeneous tumor clones in both patients with metastatic disease and field defects while conceptually preventing local expansion untreated variants. (Greaves, et al, 2012; Li, et al, 2013; Zarour, et al, 2017) Radioembolization is also distinctive in its ability to achieve the highest reported doses of radiation (>2,000 Gy segmental MIRD uniform distribution, >11,000 Gy tumor uniform distribution) (Riaz, et al, 2011) with minimal toxicity in anatomic locations that would otherwise be unamenable to other ablation modalities including stereotactic body radiation therapy. (Scorsetti, et al, 2014) In further contradistinction to external source radiation, repeat segmental brachytherapy treatments of parallel structure organs such as the liver are unconstrained by cumulative non-target dose. Radioembolization is also not compromised by physiologic movement and does not require fiducial placement.

1.2.6 Controversies in Radioembolization for Colorectal Carcinoma

Although the predominant cause for morbidity and mortality in patients with metastatic colorectal carcinoma arises from involvement of critical organs, namely the liver and peritoneum, survival benefits by providing locoregional therapy have been challenging to establish. The CLOCC trial showed that for patients with favorable biology, there was a benefit to performing radiofrequency ablation vs chemotherapy alone in patients with hepatic colorectal metastases. (Ruers, et al, 2011) Translating this to radioembolization has not been successful. The final analysis of SIRFLOX demonstrated a progression free survival benefit in the liver vs chemotherapy alone, however only showed a survival benefit in patients with right-sided primary colon cancer. (Wasan, et al, 2017) Of note, this was not the primary outcome of this study.

Dosimetry in radioembolization presents a formidable challenge given both the nonuniformity of methods and the variability of administration inherent to vascular brachytherapy. Given that most patients who undergo either resection or locoregional therapy for hepatic metastases are at high risk for non-target disease progression, either due to limitations in staging or tumor biology assessment, there is a formidable challenge in delineating at which point cytoreduction conveys benefit to patients. In general, the concept ofresponse depth, or a low hepatic tumor state, appears to be a reasonable objective at face value, particularly if achieved while maintaining a high quality of life.

Unfortunately, factors that ultimately contribute to patient demise in colorectal cancer are a concatenation of deficits that are unique to tumor genotype, subject performance and physiologic reserve, and

permutations of iatrogenic intervention. In the actual trial, one critique was the lack of continuation of what would be considered standard of care therapy including use of anti-VEGF agents and/or anti-EGFR agents as well as Regorafenib and/or TAS-102. Systemic therapy was less likely to be continued and outcomes based on tumor based genetic testing were not presented. As to which patients can truly benefit from such an approach is still debatable and not established. There are patients with mCRC who may benefit from a personalized approach of utilizing Y90-RE in combination with immunotherapy as is being proposed on this clinical trial.

1.3 Durvalumab

Durvalumab, commercial name IMFINZI®, a PD-L1 inhibitor owned by AstraZeneca, received accelerated approval from FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma. It comes as 500mg/10mL or 120mg/2.4mL solution in a single-dose vial, and will be further diluted prior to intravenous infusion.

1.4 Clinical Trial

1.4.1 Clinical Data to Date

This clinical trial will be the first trial combining Y90-RE and durvalumab and therefore no previous clinical data of this combination is available.

A similar trial which employs the Y90-RE and PD-1 inhibitor nivolumab is currently in the stage of recruiting/ongoing on clinicaltrials.gov website, but not open yet to the best of our knowledge (NCT03307603). There are other trials employing other checkpoint inhibitors that are showing that they are in development as well (details not available).

1.4.2 Dose Rationale

For each subject, the starting dose of Y90-RE will be personalized based on the lobe and number of metastatic lesions. The actual dose will comply with the FDA-approved prescribing information (Appendix). Each subject will receive a fixed dose of 750mg of durvalumab with at least 2 weeks between doses depending on the dose level assigned to. This will coincide with the Tc99m labelled MAA eligibility mapping and treatment with Y90-RE and every 2 weeks visits with labs post Y90-RE, which is the preferred standard practice at most institutions. As noted in the study schema, there is margin for a few days before or after the planned 2-week cycle to accommodate scheduling issues. The timing and frequency of durvalumab varies on the dose level. Please discuss with the principal investigator and study clinical trial coordinator to know which dose level the patient is assigned to. From a safety perspective since we need to know about the shunting to other organs prior to the Y90-RE, the mapping can be done during the screening or even prior to considerations for this study if already performed within 12 months of intended Y90-RE, it would not need to be repeated unless as per interventional radiology.

Note: The dosing of Y90-RE, dose and administration will be as per FDA approved USPI. Goal is to deliver an ablative radiation dose to the targeted region and trigger a release of neo-antigens in order to augment immunotherapy; all the while minimalizing collateral damage by sparing normal liver parenchyma. As noted in the protocol, there are numerous dosing methods in place for Durvalumab.

1.4.3 Rationale for Combination of Y90-RE and Durvalumab

While surgery remains the conventional definitive treatment for metastatic liver cancer, many patients are unamenable at presentation and most will ultimately sustain disease recurrence. (Vigano, et al, 2013; Cucchetti, et al, 2009) The inherent limitations of traditional staging with serologic, imaging, and histologic assessment lack the sensitivity to detect microscopic disease in its entirety outside of the treatment field. Theoretically, extirpation of metastatic disease may remove tumor antigens that, if properly exploited, could potentially generate signal for comprehensive immune mediated disease control. For patients with surgically unmanageable disease, locoregional treatments that maximize antigenic exposure may produce

immunologic responses that could provide a powerful adjunct to therapy while maintaining quality of life with a minimally invasive, outpatient, procedure.

Sustained immune tumoricidal responses require complex environmental interactions of antigen recognition and presentation, T cell activation, T cell relevance in the setting of continuous tumor genetic variation, and circumvention of tumor suppression mechanisms. The locoregional modalities which have shown particular promise in preserving tumor antigen allowing for host activation include cryoablation, irreversible electroporation, ischemic therapies such as embolization, and vascular micro-brachytherapy achieved via transarterial radioembolization. A large body of literature has been already generated to support ionizing radiation as an immunologic adjuvant to many of these requirements. (Kang, et al, 2016)

Localized radiation therapy holds great promise as an immunologic antitumor adjuvant. Radioembolization has a wide range of exclusive properties that warrant exploration to determine how best to incorporate it within the radiotherapeutic inventory. Given an increasing knowledge base and experience with radioembolization, and the current enthusiasm for immunotherapy-based oncology, currently recruiting clinical trials will hopefully materialize the promise of their synergism.

The clinical benefit of using Y90-RE in combination with durvalumab is yet to be known since immunotherapy has not, to date, significantly benefited patients with mCRC. However, addition of Y90-RE may improve the antigen exposure to immunotherapy and further improve the outcome of the treatment.

Furthermore, both Y90-RE and durvalumab will be used at the dose recommended by the manufacturer in which the doses are well established. Given the absence of any significant untoward side effects, major safety issue is not expected and there is potential benefit. Concurrent translational and correlative data would significantly improve insights on how to help improve immunotherapy as an option for patients with mCRC.

1.4.5 Rationale for Durvalumab Dose Escalation

The trial, for each subject, will consist of a screening period, a treatment and observation phase. The treatment phase is approximately 2 months with Y90-RE in combination with fixed dose durvalumab and **the dose limiting toxicity (DLT) observation phase for 8 weeks post Y90-RE**. The rationale for the proposed dosing schema is keeping in mind the timing of toxicities that are typically seen post Y90-RE. Most patients have elevation of their liver enzymes the first 1-2 weeks. Therefore, with the dosing escalation, we did not include the added dose at week 2 for the first dose escalation (see dose level table – section 7.41 and Table 1 section 1.23 below). Patients get fixed dosing of immunotherapy, which is the case for all immunotherapy-based studies. Depending on the dose level, patients can get a maximum of 2 doses before and 3 doses post Y90-RE. As noted in Table 1 (section 1.23 below), while dose level 1 and dose level -1 have the same number of durvalumab administrations, they are different since dose level 1 get 2 doses pre-Y90-RE (‘priming doses of immunotherapy before Y90-RE) while dose level -1 only get 2 doses post-Y90-RE.

1.4.6 Study Design

This clinical trial will be conducted as a single-center, open-label, Phase I trial to evaluate the feasibility and safety of Y90-RE in combination with a fixed dose of durvalumab in subjects with liver-predominant, mCRC. It can be offered in the refractory setting and/or more so integrated into the current standard systemic chemotherapy ± biologics, by focusing on enhancing the effect of Y90-RE with immunotherapy. Therefore, there is the option for patients with significant liver-predominant disease burden that are considered candidates for Y90-RE to temporarily discontinue their current chemotherapy in order to participate within this trial. Subjects will be approached for screening at outpatient clinic visit appointments and interested qualified subjects will be consented and offered participation in this trial. Once consent has been obtained, for eligible subjects, baseline values will be established, and subjects will begin treatment and be followed-up for the next three months. The washout period to begin treatment (cycle 1 day 1) for

this clinical trial will be at least 2 weeks after prior chemotherapy or biologic. Screening can begin prior. The goal is to keep the duration on the clinical trial minimal.

The trial, for each subject, will consist of a screening period, a treatment and observation phase. The treatment phase is approximately 2 months post-Y90-RE in combination with fixed dose durvalumab. The DLT observation phase will be for 8 weeks post dose of Y90-RE.

The trial will be performed in **18 subjects** with mCRC with liver metastasis and the safety of immunotherapy (durvalumab) with Y90-RE will be investigated in an accelerated titration design. This would allow a maximum tolerated dose with the minimum number of subjects. At any point as noted below if there is a DLT, the study design defaults to a standard 3+3 design. Assuming a 10% loss of subjects after enrollment, the dose escalation design will require at least 9 evaluable subjects to establish the highest dose level as the maximum tolerated dose (MTD). If less than 18 subjects are administrated in the dose escalation, the rest of subjects will be administrated the MTD in the expansion cohort. **Sample size of maximum of 18 was based on an accelerated titration design and on the correlative studies including pre- and post-biopsies. The primary goal of this study is to establish safety and with a secondary goal of looking at biomarkers and other immune signals as noted.**

This study will utilize an accelerated titration design. The dose levels to which patients will be assigned in sequential cohorts are listed in the table 1.

Table 1. Dose escalation cohort of durvalumab*

	Immunotherapy (Durvalumab) Administrations						
	Pre-Y90 doses		Y90-Radio-embolization	Post-Y90 doses			Number of Administration of Durvalumab
Dose level	Week-2	Week0		Week2	Week4	Week6	
-2						X	1
-1					X	X	2
1 (start)**	X	X					2
2	X	X			X		3
3	X	X			X	X	4
4	X	X		X	X	X	5

** Please note: As noted above, the rationale for the proposed dosing schema is keeping in mind the timing of toxicities that are typically seen post Y90-RE. Most patients have elevation of their liver enzymes the first 1-2 weeks. Therefore, with the dosing escalation, we did not include the added dose at week 2 for the first dose escalation (dose level 2). Patients get fixed dosing of immunotherapy, which is the case for all immunotherapy-based studies. Depending on the dose level, patients can get a maximum of 2 doses before and 3 doses post Y90-RE (dose level 4).*

***While dose level 1 and dose level -1 have the same number of durvalumab administrations, they are different since dose level 1 get 2 doses pre-Y90-RE ('priming doses of immunotherapy before Y90-RE) while dose level -1 only get 2 doses post-Y90-RE.*

A single patient will be treated per dose level until the first DLT is recorded. Once the first DLT is recorded, two additional patients are treated at the same dose level and the trial reverts to a standard 3+3 design. At which time, decisions on when and how to dose escalate are described below.

Number of patients with DLT at a given dose level	Decision Rule
0 out of 3	Enter 3 patients at the next higher dose level
1 out of 3	Enter up to 3 additional patients at the same dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of these 3 patients experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≥2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

Up to 6 patients will be treated at each dose level. The MTD will be defined as the highest dose level for which at most 1 out of 6 patients experience a DLT. If DLT meets the stopping boundaries set by the above dose algorithm at dose level 1 (for example, more than 1 out of 3 or more than 1 out of 6 patients), the next cohort of 3 patients will be entered at the dose level of -1. If dose level -1 meets the stopping boundaries, the next cohort of 3 patients will be entered at dose level -2.

If an MTD is determined, an expansion cohort using the RP2D will be carried out in additional patients for a maximum of 18 patients. If an MTD is not determined, the expansion cohort will utilize the dosing scheme from cohort 4.

After the end of treatment visit (EoT) subjects (if applicable) are to resume the previously discontinued chemotherapy until all cycles have been administered or treatment is discontinued as per regular standard of care or secondary resection if deemed a candidate. The decision to resume the previously discontinued chemotherapy is to be done at investigators discretion. As the patients will commence a different treatment regime, no active follow-up will be done as part of this study other than progression free survival and overall survival.

The clinical trial will be conducted at one site, the Holden Comprehensive Cancer Center, University of Iowa.

1.4.7 Number of Subjects

This clinical trial will recruit 18 subjects. The estimated recruitment rate is at least one subject every 1-2 months, in which a minimum of 12-18 subjects will be enrolled over a period of 18-24 months. The number of subjects in the dose escalation will depend on the number of dose levels needed to determine the MTD or confirm the current dosing for durvalumab can be used in combination with Y90-RE. **The dose limiting toxicity (DLT) observation phase is 8 weeks post Y90-RE**.

In the expansion cohort, the remaining subjects (from the total 18 subjects) will be treated at the MTD dose of the combination of Y90-RE and durvalumab. Since all patients received immunotherapy and Y90-RE, they would be included in the evaluation of efficacy objectives and correlative components of the study.

1.4.8 Duration of Participation

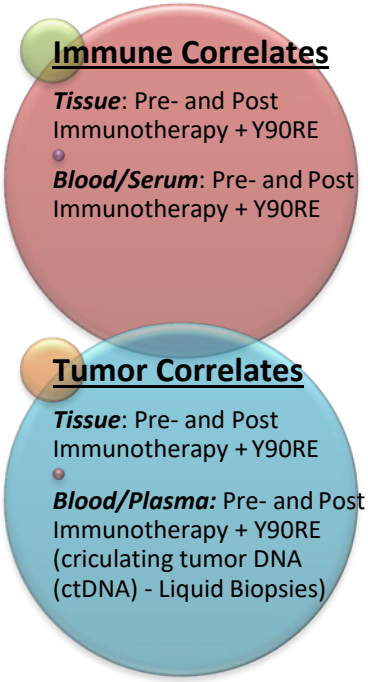
The total duration of the trial for each subject will be approximately three months (from the first subject first visit to first subject last observation). The entire trial from the first subject enrollment to the last subject visit (end of treatment visit) will last 24 months. For the purpose of data analysis, the trial will start with first subject signing informed consent and will end when the last subject performed the last clinical follow up visit, under the standard protocol. After the last clinical follow up visit, planned time needed for final report/publication following last subject last visit is six months.

1.3 Correlative Research

- Immune Correlates (Pre- and Post- immunotherapy and Y90-RE)
- Tumor Correlates (Pre- and Post- immunotherapy and Y90-RE)

The specifics and timing of sample collection are detailed in the schedule of testing/**companion laboratory manual** for this clinical trial. Both in-house research/clinical as well as commercially available platforms would be utilized to accomplish the goals listed.

Broadly speaking as noted, the main goal would be study 2 main correlates (pre- and post- Y90-RE and immunotherapy) from a) an immune perspective and b) tumor perspective. As noted in detail in the schedule of testing and companion laboratory manual, there are additional serial collections from a blood testing perspective to allow for assessment of blood-based immune markers as well as tumor based liquid biopsies (circulating tumor DNA testing – ctDNA testing).



1.3.1 Immune correlates:

Analysis of immune cells by flow cytometry: Analysis of immune cell populations via flow cytometry will allow for more quantitative and in-depth profiling of immune cells. In addition, these experiments will be done at the University of Iowa at the time of sample collection.

Immune cell analysis of peripheral blood and tumor tissue: Frequencies of innate (monocytes, macrophages, neutrophils, dendritic cells, NK cells) and adaptive (CD4+ T cells, CD8+ T cells, NKT cells, B cells) immune cells present in the peripheral blood or tumors of patients will be determined via flow cytometry. In addition, we will examine expression of inhibitory markers on T cells including, but not limited to, PD-1, CTLA-4, TIM3 and LAG3. For peripheral blood samples we will compare frequencies of immune cell populations at the several serial time points as denoted in the table. Tumor infiltrating cells in tumor tissue samples will be compared at two time points for the tissue as denoted in the schedule of testing/companion laboratory manual.

Serum cytokine and chemokine analysis: Use of a Multiplex assay will allow us to examine multiple cytokine and chemokine targets at multiple time points with use of minimal serum sample. These again would be done at the University of Iowa at the time of sample collection. Serum will be collected from peripheral blood of patients at 8 different time points as denoted in the table. A bead based multiplex assay will be used to quantitatively measure levels of 27 different cytokines and chemokines at various time points. This analysis will be done at the University of Iowa.

From a tumor microenvironment perspective, would evaluate for immune related changes including PD-L1 and PD-1 expression and tumor-infiltrating lymphocytes.

1.3.2 Tumor correlates:

We will have 2 timepoints of tumor evaluation in terms of tissue i.e. pre- and post-immunotherapy and Y90-RE. Additionally, a unique and strong aspect of this study is the use of **liquid biopsies** (ctDNA/circulating tumor DNA testing) at multiple serial timepoints.

- We will measure the variant allele fraction (%) and the spectrum of mutations through next generation sequencing based platforms.
- Tumor mutation burden would also be estimated and studied.
- On tissue whole exome sequencing would be performed pre- and post-immunotherapy and Y90-RE.
- Gain and/or loss of clones and sub-clones would be studied serially on liquid biopsies.

Details of the tissue and immune based collection including specimen and handling requirements outlined in details in schedule of testing/**companion laboratory manual** for this clinical trial.

Of note, if enough tissue is available and lesions are safe/amenable to biopsy, feasibility of developing patient derived organoids, xenografts and cell-lines at the time of pre- and post-treatment biopsies will be evaluated.

Additional Correlates:

- For patients where we have stool and swab samples available, we would run panel-based microbiome profile inhouse with Dr. Ashutosh Mangalam's lab. Initially the specimens would be biobanked.
- Where tissue is sufficient, would assess the feasibility of developing a cell line and/or organoid for drug testing. However, the tissue correlates outlined earlier take priority first.

2.0 Goals

2.1 Primary Goal

2.1.1 To assess the feasibility and safety of Y90-RE combined with immunotherapy durvalumab to treat liver-predominant mCRC.

2.2 Secondary Goals*

2.2.1 To report **treatment related adverse events** in patients treated with the combination treatment of Y90-RE and durvalumab as assessed by Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0

2.2.2 To determine the **Recommended Phase II dose (RP2D**) of durvalumab in combination with Y90-RE to treat liver-predominant mCRC.

2.2.3 To determine the efficacy of combination treatment of Y90-RE and durvalumab in patients with liver-predominant mCRC measured by overall response rate (**ORR**) (complete response (CR) + partial response (PR)) post-Y90-RE and immunotherapy.

2.2.4 To determine the efficacy of combination treatment of Y90-RE and durvalumab in patients with liver-predominant mCRC measured by the disease control rate (**DCR**) (CR+PR+stable disease (SD)) at 2 months post-Y90-RE treatment.

2.2.5 To determine the efficacy of the regimen in the treated liver metastases (liver-specific progression free survival (**Liver-PFS**) in the lesions in the Y90-RE field).

2.2.6 To determine the efficacy of the regimen in the patient as a whole (**PFS**); including both Y90-RE field and outside the Y90-RE field.

2.2.7 To determine the efficacy of combination treatment of Y90-RE and durvalumab in subject with liver-predominant mCRC as measured by overall survival (**OS**) at 1-year and 2-year.

2.2.8 To determine duration of response (**DOR**) in the Y90-RE field and outside of Y90-RE field

* *Given Y90-RE to the liver and use of immunotherapy, all response assessments by modified RECIST (mRECIST) as well as immune RECIST (iRECIST). In all instances, the landmark time is the initiation of immunotherapy.*

2.3 Correlative Research

2.3.1 To assess the changes in immune infiltration (TISSUE: tumor-infiltrating lymphocytes – **TILs (CD-3, CD-8)**, **PD-L1 and PD-1 expression,** pre- and post-Y90-RE and immunotherapy).

2.3.2 To analyze serial changes in **immune cells** (BLOOD) pre- and post-Y90-RE and immunotherapy

2.3.3 To determine changes in the expression profile and in levels of circulating tumor DNA (**ctDNA**) in blood pre- and post- treatment.

2.3.4 To evaluate **mutation burden** by whole-exome sequencing pre- and post-treatment (TISSUE)

2.3.5 To evaluate concomitant expression profile changes through **RNA-Seq** pre- and post-treatment (TISSUE)

2.3.6 To evaluate the **feasibility** of developing patient derived organoids, xenografts and/or cell-lines at the time of pre- and post-treatment biopsies

2.3.7 Correlation of outcomes based on **subtypes** of mCRC (sidedness, mutational/molecular subtypes)

2.3.8 To report on any *abscopal effects* seen in terms of responses outside the Y90-RE field.

3.0 Registration Patient Eligibility

Prior to discussing protocol entry with the patient, call the GI clinical trial coordinator or PI for dose level and to ensure that a place on the protocol is open to the patient.

3.1 Inclusion Criteria

3.1.1 Age ≥18 years

3.1.2 Histological or cytological confirmation of colorectal cancer with metastasis to the liver. Mismatch repair or microsatellite instability status of the tumor needs to be known. Tumors need to be mismatch repair proficient (for mismatch repair deficient tumors immunotherapy is already approved).

3.1.3 Patient must have at least 1 liver lesion measurable as defined in Section 11.0.

3.1.4 Must have liver metastases and be appropriate for treatment with Y90-RE therapy as determined by the treating medical oncologist and interventional radiologist/oncologist, and nuclear medicine physician(s).

NOTE: the goal of therapy is safety and parenchymal sparing. Typically, since the treatment is personalized, the goal is to have at least 30% liver parenchymal sparing post treatment.

3.1.5 Must have a metastatic focus amendable to biopsy. It is permissible to use same or alternative lesion for biopsy for assessment for tumor response and changes in microenvironment (mandatory pre- and post-Y90-RE biopsy).

3.1.6 **At least 2 but no more than 3 lines of therapy** allowed in metastatic setting. These include at least treatment with a fluoropyrimidine, oxaliplatin, and/or irinotecan-based

therapy and an anti-EGFR therapy if RAS wild-type (unless deemed intolerant or not suitable by the treating oncologist), with or without an anti-VEGF therapy.

NOTE: adjuvant and/or maintenance chemotherapy does not count as an additional line of therapy. (Patients with more than 3 lines of therapy are at risk for liver disease from prior systemic therapies and would not be reasonable candidates for Y90-RE).

3.1.7 At least a 4-week gap between anti-VEGF therapy and the IR Tc-99m labelled MAA eligibility mapping

3.1.8 ECOG Performance Status (PS) 0 or 1 (Appendix I).

3.1.9 Negative *serum* pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.

3.1.10 Females of childbearing potential (FOCBP), must use appropriate method(s) of contraception. FOCBP are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). Additionally, FOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with durvalumab plus 5 half-lives of durvalumab (13 weeks) plus 30 days (duration of ovulatory cycle) for a total of 17 weeks post-treatment completion (details in appendix).

3.1.11 Men who are sexually active with FOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with durvalumab plus 5 half-lives of durvalumab plus 90 days (duration of sperm turnover) for a total of 25 weeks post-treatment completion (details in appendix).

3.1.12 Provide written informed consent.

3.1.13 Ability to complete questionnaire(s) by themselves or with assistance.

3.1.14 Willingness to provide mandatory blood specimens for correlative research (see Section 14.0).

3.1.15 Willingness to provide mandatory tissue specimens for correlative research (see Section 17.0). ***NOTE:*** If tissue is deemed inaccessible, patient cannot participate in study.

3.1.16 Willingness to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.1.17 Must have a life expectancy of at least 6 months.

3.2 Exclusion Criteria

3.2.1 Any of the following laboratory abnormalities:

- Hemoglobin <9.0 g/dL
- Absolute neutrophil count (ANC) <1500/mm^3
- Platelet count <100,000/mm^3
- Total bilirubin >1.5 x ULN or > 2.0 mg/dL, whichever is lowest (exception for patients with Gilbert Syndrome, who cannot have a total bilirubin > 3.0 mg/dL)
- Alanine aminotransferase (ALT) and Aspartate transaminase (AST) >2.5 x ULN
- Serum creatinine > 1.5 x ULN or 2.0 mg/dL, whichever is lowest.

OR

- Calculated creatinine clearance <30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age}) (\text{weight in kg})}{(72) (\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age}) (\text{weight in kg}) (0.85)}{(72) (\text{serum creatinine in mg/dL})}$

**NOTE: These can be repeated if outside of range to determine eligibility. Growth factor support not allow. Transfusion support for low hemoglobin allowed up to 5 days prior to start of treatment.*

3.2.2 Patients with any of the following contraindications to TheraSphere treatment:

- Shunting to the bowel along the gastrointestinal tract
- Lung shunting of ≥ 15%
- Estimated dose to lungs ≥ 30 Gy in a single administration
- Cumulative estimated dose to lungs ≥ 50 Gy for multiple administrations
- Liver size ≤ 1.5L

3.2.3 Prior radiation therapy unless reviewed by the IDE sponsor and approved. This is on a case-by-case basis. Radiation plans should be provided for review.

3.2.4 Persons who are actively breastfeeding a child and unwilling to discontinue.

3.2.5 Co-morbid systemic illnesses, infections, or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.2.6 Untreated central nervous system (CNS) metastatic disease (including spinal cord and leptomeningeal disease). ***NOTE***: Patients with previously treated CNS metastases that are radiographically and neurologically stable for ≥ 6 weeks are permitted.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, autoimmune disease, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements. Please note: with respect to autoimmune disease, patients with history of *severe* autoimmune disease or *active* autoimmune disease within two years of study entry or have a medical condition that requires systemic immunosuppression are excluded from the study.

3.2.8 Received any other investigational agent incorporating chemotherapy and/or biologics within 14 days prior to first dose of durvalumab which would be considered as a treatment for the primary neoplasm. For patients on active treatment, last treatment and 1st dose of Durvalumab should be at least ≥ 14 days. ***EXCEPTION*:** Other forms of concurrent observational studies are permitted.

3.2.9 Other active malignancy ≤3 years prior to registration. ***EXCEPTIONS:*** Non-melanoma skin cancer, lentigo maligna- in-situ, or carcinoma-in-situ of the cervix. Also, prior malignancy already treated with curative intent and with no known active disease present would be considered eligible.

3.2.10 History of unstable cardiac disease defined as one of the following:

- Congestive heart failure > class II New York Heart Association (NYHA). (Appendix II)
- Unstable angina (angina symptoms at rest) or new onset angina (began ≤ 3 months prior to registration)
- Myocardial infarction ≤ 3 months
- Uncontrolled cardiac ventricular arrhythmias. ***EXCEPTION***: Subjects that are stable on anti-arrhythmic therapy are eligible.

3.2.11 Any concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment within 14 days of first dose of durvalumab. ***NOTE***: Subjects can be screened during washout period.

3.2.12 History of severe allergic reactions (i.e. Grade 4 allergy, anaphylactic reaction from which the subject did not recover ≤ 6 hours of initiation of supportive care)

3.2.13 Failure to recover from toxicities from prior anti-cancer therapy, defined as having not resolved to National Cancer Institute (NCI) CTCAE version 5.0 Grade ≤ 1. ***EXCEPTIONS:*** Alopecia and laboratory values listed per the exclusion criteria. Also subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any investigational products (i.e. hearing loss) will be permitted.

3.2.14 Use of steroids. ***EXCEPTIONS***: Systemic glucocorticoids will be permitted as long as it is ≤10 mg of prednisone equivalent. Topical steroids, such as bronchodilators and local steroid injections are also permitted if clinically required.

3.2.15 Patients with renal failure currently requiring dialysis of any kind.

3.2.16 Patients weighing <30kg will be excluded from enrollment

3.2.17 History of allogenic organ transplantation

4.0 Test Schedule

4.1 Test schedule for metastatic CRC

	Screening	**Active Monitoring Phase**						
Tests and procedures	*Reg*	*Cycle 1*	***Cycle 2 (2nd dose of Durva + Y90-RE)****	*Cycle 3*	*Cycle 4*	*Cycle 5*	*End of treatment visit*[12]	*Clinical Follow-up*[13] *(every 3 months)*
Window	21 days	±5 days	**±5 days**	±5 days	±5 days	±5 days	±5 days	
History and exam[3], Wt[5], BP, HR, ECOG PS	X							
Exam, Wt[5], BP, HR, ECOG PS		X	**X**	X	X	X	X	X
Adverse event assessment	X	X	**X**	X	X	X	X	X
Concomitant medication review	X	X	**X**	X	X	X	X	X
Height	X							
IR Consult	X							
Pregnancy test[1]	X		**X**		X		X	X
Hematology group CBC w/ 5-part differential	X	X	**X**	X	X	X	X	X
Chemistries[21]	X	X	**X**	X	X	X	X	X
Thyroid Function Test TSH, free T4, amylase, lipase, Vitamin D	X		**X**		X		X	X
Creatinine clearance	X	X	**X**	X	X	X	X	X
Coagulation PT, PTT, INR	X						X	
Cholesterol, triglycerides	X							
IR Tc-99m labelled MAA eligibility mapping		X[18]						
Tumor measurement[2]	X						X	X
ECG[6]	X		**X**		X		X	
Urinalysis[7]	X	X	**X**	X	X	X	X	X
Administer durvalumab[8,R]		X[16,17,18,19]	**X[9,16,17,18,19]**	X[19]	X[17,18,19]	X[17,18,19]		
Administer Y90-RE			**X**					
Patient Questionnaire Booklets[4] (Appendix *III*)		X	**X**	X	X	X	X	
Mandatory Research Specimens (see companion Lab Manual)[10,R]	X	X[14,15,16,17]	**X[14,15,16,17]**	X[17]	X[15,16,17]	X[15,16,17]	X	
Mandatory Research Tissue specimens (see companion Lab Manual)[11,R]	X (Pre-treatment)[18]						X (Post-treatment)[19, 20]	

Cycle = 14 days

1. For women of childbearing potential only. Serum pregnancy test. Must be done ≤7 days prior to registration.
2. A scan is required at baseline prior to the first dose of durvalumab. The scan does not need to be repeated as long as it is ≤ 28 days prior to registration. Preferably we would recommend a CT of the chest and pelvis; and an MRI of the abdomen for assessment of liver metastases. If an MRI cannot be performed, a CT chest, abdomen, and pelvis would be acceptable. Please use same imaging throughout the study.
3. History and exam include prior surgery, cancer-related and other treatment and known positivity for Hepatitis B surface antigen, Hepatitis C virus antibodies, and Human Immunodeficiency Virus antibodies 1 /-2.
4. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission
5. Body weight to be measured within 72 hours prior to durvalumab administration.
6. Single 12-lead ECG after 5 min rest in supine position.
7. Gross (dipstick) urine examination: Leukocytes, nitrite, pH, protein, glucose, ketone, urobilinogen, bilirubin, blood (hemoglobin and erythrocytes). If abnormalities are detected by dipstick, then a microscopic sediment test should also be performed. If a UTI is suspected, it can be treated.
8. Durvalumab administration over 60 minutes. Following infusion, subjects must be observed for 30 minutes post infusion for potential infusion related reactions. The number of doses administered is per dose level for each patient cohort.
9. The 2nd durvalumab dose can be done ≤ 5 days prior to Y90-RE or same day as long as it is before the Y90-RE.
10. Blood biomarkers will be collected in the morning of visit. Kits are required.
11. Tissue specimens must be collected the following timepoints: pre-treatment [screening/prior to cycle 1 of Durvalumab (fresh as well as archived if available)], and post-treatment. Kits are required (banking, clinical as well as real-time send out).
12. Visit will occur 8 weeks after Y90-RE.
13. Clinical follow-up visits will be performed at least every 3 months (or as per standard physician practice) for 2 years.
14. Cohort 1- Durvalumab given at cycle 1 and cycle 2 only
15. Cohort 2- Durvalumab given at cycle 1, 2, and 4
16. Dose escalation cohort- Durvalumab given cycle 1, 2, 4 and 5
17. Dose expansion cohort- Durvalumab given cycle 1, 2, 3, 4, and 5
18. As long as the lesion is amenable to a biopsy and is done, the biopsy can be done on the Tc-99m labelled MAA eligibility mapping day to save patient a visit. Has to be prior to anti-PD1 therapy though. From a safety perspective since we need to know about the shunting to other organs prior to the Y90-RE, the mapping can be done during the screening or even prior to considerations for this study if already performed within 12 months of intended Y90-RE, it would not need to be repeated unless as per interventional radiology. Biopsy still needs to be done as noted.
19. If there is complete response of the lesion in the field of Y90-RE, tissue biopsy of the field would still be done to assess for the immune changes and an alternative tumor lesion can be biopsied for testing of the tumor itself.
20. At the time of progression, patient would be approached for a tissue biopsy and research blood sampling similar to the end of treatment visit.
21. Creatinine, ALP, ALT, AST, total bili, direct bilirubin, AlkPhos, GGT, total protein, uric acid, BUN, Na, K, Ca, Cl, LDH, CPK, inorganic phosphate, CEA, CA-19-9, ESR, CRP

* 2 research blood drawn (pre-post Y90 RE on the day of procedure). Timing not important.

R Research funded (see Section 19.0)

4.2 Survival Follow-up

	Survival Follow-up				
	q. 3 months until PD	At PD	After PD q. 3 months	Death	New Primary
Survival Follow-up	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

5.0 Stratification Factors OR Grouping Factor

None.

6.0 Enrollment Procedures

6.1 Call the GI clinical research coordinator/PI for slot reservation.

6.2 Correlative research is mandatory in this trial and the subject will automatically be registered to this component (see Sections 3.19d, 3.19e 14.0, 17.31, 17.32, and 17.34*)*. Please contact PI if there are any questions or concerns or exceptions.

6.3 Documentation of IRB approval must be on file before an investigator may enroll any patients.

6.4 Prior to enrollment, verify the following:

- IRB approval
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.5 Treatment cannot begin prior to screening and must begin ≤ 21 days after screening.

6.6 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.8 Treatment on this protocol must commence at University of Iowa Holden Comprehensive Cancer Center institution under the supervision of a medical oncologist.

6.9 Case has been discussed or an interventional oncologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.10 Study drug is available on site.

6.11 Blood draw kit is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule

Use actual weight or estimated dry weight if fluid retention. Quality Control and Definitions of Deviations will be done according to the guidelines in Appendix IV

7.1.1 Treatment medication table

Agent	Dose Level	Route	ReRx
Durvalumab	750 mg	IV	q2w*

Cycle= 14 days

Note: All cycles will be based on durvalumab given once at least two weeks apart. The number of durvalumab doses are dependent on the cohort assigned during dose escalation.

*Refer to table 1 section 1.23 to see the number and timing of durvalumab immunotherapy administrations.

7.1.2 Treatment table for Y-90 Radioembolization (Y90-RE)

Agent	ReRx
TheraSpheres™	Per Table 1 section 7.4.1

Cycle= 14 days

Note: Y90-RE is administered 2 weeks post first durvalumab dose administration with cycle 2 of Durvalumab. The immunotherapy dose is prior to the Y90-RE. The immunotherapy does not have to be the same day as long as it is prior to Y90-RE.

Note: The Y90-RE dose and administration will be as per the FDA approved USPI for each patient. Goal is to deliver an ablative radiation dose to the targeted region and trigger a release of neo-antigens in order to augment immunotherapy; all the while minimalizing collateral damage by sparing normal liver parenchyma. Per package insert, recommended Y90-RE dose is 80 Gy to 150 Gy per lobe of liver; this is intended to prevent radioembolization-induced liver disease (REILD). Upper limit for dose administration is also determined by the lungs, which may receive an estimated dose of no more than 30 Gy from a single administration nor a cumulative total of 50 Gy from multiple administrations.

As noted in the protocol, there are numerous dosing methods in place for Durvalumab.

7.2 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 14 days during treatment and every 90 days during clinical follow-up (Active Monitoring Phase).

7.3 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

7.4 Phase I – determination of Maximum Tolerated Dose (MTD)

7.4.1 Dose Escalation

	Immunotherapy (Durvalumab) Administrations						Number of Durvalumab Administrations (total)
	Prior to Y90-RE		**Y-90 Radioembolization (Y90-RE)**	**Post Y90-RE**			
Dose level	Week -2	Week 0		Week2	Week 4	Week 6	
-2						X	1
-1					X	X	2
1 (start)	X	X					2
2	X	X			X		3
3	X	X			X	X	4
4	X	X		X	X	X	5

7.4.1.1 Treatment by a local medical doctor is not allowed. All patients to be treated at University of Iowa.

7.4.1.2 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.4.2 Definitions of Dose Limiting Toxicities (DLT)

A DLT will be defined as any Grade 3 or higher treatment-related toxicity that occurs during the DLT observation phase (8 weeks post Y90-RE), including:

- Any event resulting in a delay of cycle 2 by ≥ 14 calendar days
- Any Grade 4 immune related adverse event (irAE)
- Any Grade 3 immune related AE (irAE) that does not resolve to ≤ Grade 1 or to baseline with immunosuppressive therapy within 3 weeks
- Any Grade 3 colitis
- Any Grade 3 noninfectious pneumonitis irrespective of duration
- Grade 4 neutrophil count decreased lasting longer than 5 calendar days
- Grade 4 platelet count decreased
- Grade 3 platelet count decreased with hemorrhage
- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 7 days of the initiation of maximal supportive care
- Any other Grade 3 irAE (excluding colitis or pneumonitis), that does not downgrade to Grade 2 within 7 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN
- Total bilirubin > 5 × ULN
- AST or ALT > 5-8 × ULN with concurrent increase in total bilirubin > 2 × ULN without evidence of cholestasis or alternative explanations, e.g., viral hepatitis, disease progression in the liver, etc. (Hy's Law). Exception: If it is present at cycle 3 but resolves at cycle 4 it is not a DLT.
- Any ≥ grade 3 non-hematologic toxicity, except:
  - Grade 3 nausea or vomiting that lasts < 48 hours and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
  - Grade 3 nausea, vomiting, and diarrhea lasting < 72 hours in the absence of maximal medical therapy
  - Grade 4 vomiting and diarrhea lasting < 72 hours in the absence of maximal medical therapy
  - Grade 3 hypertension in the absence of maximal medical therapy
  - Grade 3 metabolic abnormalities (e.g. hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia) that recover to ≤ Grade 1 within 48 hours
  - ≥ Grade 3 electrolyte abnormality lasting < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention.
  - Grade 3 or 4 elevation in serum amylase and/or lipase that are not associated with clinical or radiographic evidence of pancreatitis.
  - Grade 3 rash < 5 calendar days
  - Grade 3 rash that resolves to ≤ Grade 1 within 3 weeks
  - Grade 3 fatigue lasting ≤ 7 days
  - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic

- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 7 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility

8.0 Dosage Modification Based on Adverse Events **(details tabulated in appendix VIII)**

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects.

8.1 Treatment schedule modifications in patients based on adverse events

Patients will be evaluated by the study team prior to each dose of durvalumab for an adverse event check. Determination will be made if the adverse event is treatment-related (possible, probable or definite), i.e. a toxicity (see Section 10; Adverse event monitoring and reporting). If any adverse event has occurred, then the treatment schedule will be modified as in Section 8.2.

8.2 Treatment schedule modifications for durvalumab

Adverse events (both non-serious and serious) associated with durvalumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Durvalumab must be withheld for drug-related toxicities and severe or life-threatening AEs per Table 8.21 below. See Section 9.0 for supportive care guidelines, including use of corticosteroids.

Table 8.21 Dose Modification Guidelines for Drug-Related Adverse Events for Durvalumab

CTCAE System/Organ/Class	Adverse Event	Grade	Action
Gastrointestinal disorders	Diarrhea or Colitis	2	Hold all protocol treatment until Grade 0-1. If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		3, 4	Permanently discontinue all protocol treatment
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased, and blood bilirubin increased	2	Hold all protocol treatment until Grade 0-1. If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		3-4	Permanently discontinue all protocol treatment
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	T1DM or 2-4	Hold all protocol treatment until clinically and metabolically stable.

Table 8.21 Dose Modification Guidelines for Drug-Related Adverse Events for Durvalumab

CTCAE System/Organ/Class	Adverse Event	Grade	Action
Endocrine disorders	Endocrine disorders-Other, specify: Hypophysitis	2-4	Hold all protocol treatment until Grade 0-1. If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
	Hypothyroidism	2-4	Therapy with durvalumab can be continued while thyroid replacement therapy is instituted
	Hyperthyroidism	2-3	Hold all protocol treatment until Grade 0-1. If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		4	Permanently discontinue all protocol treatment
General disorders and administration site conditions	Infusion related reaction	1, 2	Follow infusion related reaction treatment guidelines (Table 9.21). Hold all protocol treatment until Grade 0-1. If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		3, 4	Follow infusion related reaction treatment guidelines (Table 9.21). Permanently discontinue all protocol treatment
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	Hold all protocol treatment until Grade 0-1 and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent). If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		3-4	Permanently discontinue all protocol treatment
Renal and urinary disorders		2	Hold all protocol treatment until Grade 0-1 and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent). If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		3-4	Permanently discontinue all protocol treatment
All Other Non-hematologic Events		3	Hold all protocol treatment until Grade 0-1 and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent). If AE does not resolve to Grade 0-1 within 2 weeks, then permanently discontinue all protocol treatment
		4	Permanently discontinue all protocol treatment

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.21 Neutropenia

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), PEGylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

9.22 Anemia

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia but should be clearly noted as concurrent medications.

9.23 Thrombocytopenia

Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Immunotherapy-related toxicities

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

All toxicities will be graded according to NCI CTCAE, Version 5.

Patients should be monitored for signs and symptoms of immunotherapy-related toxicities, which include but are not limited to the following:

9.5.1 Pneumonitis

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

9.5.2 Diarrhea/colitis

Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.5.3 Type 1 Diabetes Mellitus

if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

For **T1DM** or **Grade 3-4** Hyperglycemia:

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

9.5.4 Hypophysitis

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

9.5.5 Hyperthyroidism or hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events: non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- **Grade 3-4** hyperthyroidism treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Grade 2 – 4** hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

9.5.6 Hepatic

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
- Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

9.5.7 Renal failure or nephritis

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

9.5.8 Rash

- **Grade 2**: Treat symptomatically with topical steroid cream, as well as antihistamines (i.e., loratadine, diphenhydramine, etc.). For patients that do not respond, consider starting steroids at 0.5 mg/kg prednisone or equivalent.
- **Grade 3:** As above for grade 2 and Start steroids at 1 mg/kg prednisone or equivalent.
- If any signs of Steven Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TENS), immediately hospitalize patient and treat with high dose IV steroids (1-gram methylprednisolone) and consult dermatology.

9.5.9 Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
Table 9.21 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of durvalumab.
Table 9.21 Infusion reaction treatment guidelines as per standard care are included in the appendix.

10.0 Adverse Event (AE) Monitoring and Reporting

This study is monitored by internal oversight specialists at the University of Iowa. The Data and Safety Monitoring Plan of the Holden Comprehensive Cancer Center provides standard operating procedures to monitor all investigator-initiated trials at UIHC by the Data and Safety Monitoring Committee (DSMC). A copy of the detailed data and safety monitoring plan for this study is on file with the Data and Safety Monitoring Committee of the Holden Comprehensive Cancer Center and the IRB of record; an abbreviated copy is provided (Appendix).

This study has been assigned as a risk level 4 as it utilizes an investigator sponsored IDE [P. McNeely, MD, sponsor].

10.1 Definitions

10.1.1 Adverse Event [durvalumab]

Any untoward medical occurrence or undesirable event experienced in a subject of a clinical investigation that associated with the use of a drug in humans, whether or not considered drug related. Note: this term is for study drug and not the study device

10.1.2 Suspected Adverse Reaction [durvalumab]

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. [21CFR§312.32(a)]

10.1.3 Unexpected adverse event or unexpected suspected adverse reaction [durvalumab]

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions

that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. [21CFR§312.32(a)]

10.1.4 Serious Adverse Event [durvalumab]

Per 21CFR§312.32, an adverse event is considered serious if, in the view of the investigator, the adverse event results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- An inpatient hospitalization or a prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or,
- An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

10.1.5 Serious Adverse Reaction [durvalumab]

A serious adverse event for which there is a reasonable possibility that the drug caused the serious adverse event.

10.1.5 Adverse effect [90Y TheraSpheres]

Any adverse medical occurrence that may or may not be related to the investigational device

10.1.6 Unanticipated Adverse Device Effect (UADE) [90Y TheraSpheres]

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [21CFR§812.3(s)]

10.1.7 Attribution to durvalumab or 90Y-TheraSpheres

When assessing whether an adverse event (AE) is related to durvalumab or an adverse effect is related to 90Y-TheraSpheres, the following attribution categories are utilized:

- Definite - The AE *is clearly related* to the agent(s)/procedure.
- Probable - The AE *is likely related* to the agent(s)/procedure.
- Possible - The AE *may be related* to the agent(s)/procedure.
- Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
- Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.2 Determination of Reporting Requirements

Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v5). The principal investigator will have final responsibility for determining the attribution of toxicity as it is related to durvalumab. The IDE sponsor will have final responsibility for determining the attribution of toxicity as it is related to 90Y-TheraSpheres.

The clinical research team is responsible for collecting and recording the research data. As these results are collected, all toxicities and adverse events will be identified and reported to the principal investigator (PI). The principal investigator (PI) will determine final relationship of the event to the investigational product (ascorbate):

- Grade 1 and 2 events do not require attributions assigned.
- Grade 3 and higher adverse events require attribution assigned to durvalumab and 90Y TheraSpheres.
- All serious adverse events, regardless of severity, require attribution assigned to durvalumab and 90Y TheraSpheres.
- All dose limiting toxicities, regardless of severity, require attribution assigned to durvalumab and 90Y TheraSpheres.

10.2.1 Exemption from reporting requirements

The following hospitalizations are exempted from reporting because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry

10.2.2 Reporting window

The adverse event collection window is from the first treatment (durvalumab or TheraSphere) through 30 days after the final administration (durvalumab or TheraSphere). Medical records and study records will be reviewed for up to 2 years post-embolization for radiation-induced adverse events. These will be assessed by the IDE-sponsor or delegate and captured in the electronic data capture system.

10.3 Institutional Review Board reporting requirements

10.3.1 Serious adverse drug reactions

In a subject enrolled by a UI investigator, any adverse events meeting criteria of both serious *and* attributed (possible, probable, or definite) occurring to the study agent must be reported within 10 business days to the University of Iowa Institutional Review Board. Both expected and unexpected SAE must be reported. Thus:

- Serious adverse events only
- Attributable to durvalumab (i.e., drug related)
- Report to the IRB *via* HawkIRB within 10 business days of event

10.3.2 Serious adverse device effects

In a subject enrolled by a UI investigator, any adverse device effect meeting criteria of both serious *and* associated (possible, probable, definite) to the use of the study device must be reported within 10 business days to the University of Iowa Institutional Review Board. Both anticipated and unanticipated device effects must be reported. Thus:

- Serious adverse device effects only
- Attributable to 90Y-Theraspheres (i.e., device related)
- Report to the IRB *via* HawkIRB within 10 business days of effect

10.4. FDA reporting requirements [90Y TheraSphere IDE, P. McNeely, sponsor]

10.4.1 Unanticipated adverse device effects

Adverse device effects meeting criteria of serious, unanticipated, *and* associated (possible, probable, or definite) to 90Y-Theraspheres must be reported by the sponsor or the sponsor's appointed designee to the FDA within 10 working days of the sponsor's initial receipt of information:

- Causing **serious** adverse effect on health or safety or any life-threatening problem or death.
- **Unanticipated** adverse effects only: the effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application)
- **Associated** with 90Y TheraSpheres with a causal relationship as described

To help the sponsor meet these reporting requirements, all unanticipated adverse device effects must be reported to the IDE sponsor **within 1 business day**. This coincides with SAE reporting requirements for the DSMC.

10.4.2 Unanticipated serious problems

The IDE sponsor will report any unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects within 10 working days of the sponsor's initial receipt of information. To help the sponsor meet these reporting requirements, all unanticipated problems must be reported to the IDE sponsor **within 1 business day**.

10.5. The Holden Comprehensive Cancer Center's Data and Safety Monitoring Committee [NCI]

Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator-initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional reporting requirements:

- A scanned copy of the completed eligibility checklist, with screening information and PI signature, will be attached in OnCore for ongoing review by DSMC staff.

- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.
- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

Monitoring will involve the following:

- review eligibility of patients accrued to the study,
- check for the presence of a signed informed consent,
- determine compliance with protocol's study plan,
- determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
- compare accuracy of data in the research record with the primary source documents,
- review investigational drug processing and documentation,
- assess cumulative AE/SAE reports for trends and compare to study stopping rules.

10.5.1 Routine Adverse Event Reporting Requirements

An adverse event (AE) is defined in the *CTEP, NCI Guidelines* [2005] as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure (attribution of unrelated, unlikely, possible, probably or definite)." Routine adverse events occurring in study subjects are captured in OnCore, the clinical trials management system, for review and assessment by the P.I. and IDE sponsor as well as the DSMC.

10.5.2 Routine Adverse Device Effect Reporting Requirements

An adverse effect is defined by FDA as "Any adverse medical occurrence that may or may not be related to the investigational device." All adverse effects occurring in study subjects will be captured in OnCore, the clinical trials management system, for review and assessment by the P.I. and IDE sponsor as well as the DSMC.

10.5.3 Serious Adverse Events

Any experience or condition meeting the definition of a serious adverse event (SAE; 21CFR312.32) occurring in a study subject from the first day of study treatment and typically continue through the 30-day follow-up period after treatment is discontinued will be captured. Investigators **must** report to the DSMC any SAE, regardless of attribution to study drug. SAEs must be reported *via* an OnCore SAE Report ≤ 1 business day of learning of the event.

10.5.4 Unanticipated Device Effects

Any experience or condition meeting the definition of an unanticipated adverse device effect (UADE) in a study subject (SAE; 21CFR812.3(s)), from the first day of study treatment and typically continue through the 30-day follow-up period after treatment is discontinued will be captured. Investigators **must** report to the DSMC any unanticipated adverse device effect *via* an OnCore SAE Report ≤ 1 business day of learning of the effect.

10.5.5 Dose limiting Toxicities

Any adverse event meeting the criterion of a dose limiting toxicity will be reported *via* an OnCore SAE Report ≤ 1 business day of learning of the event or from determining the event met DLT criteria.

10.6 Principal Investigator Reporting Requirements

As per 21CFR812.50, the principal investigator shall prepare and submit the following complete, accurate, and timely reports to the IDE Sponsor of 90Y TheraSpheres (P. McNeely, MD):

- **Withdrawal of IRB approval**. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
- **Annual Progress Report**. An annual progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
- **Deviations from the investigational plan**. An investigator shall notify the sponsor and the reviewing IRB (see §56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with §812.35(a) also is required.
- **Informed consent.** If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- **Final report**. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
- **Other**. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

11.0 Treatment Evaluation/Measurement of Effect

Various measurement options exist that are being done in patients with liver cancer and liver metastases and immunotherapy that are of value to consider. These include:

- RECIST 1.1
- iRECIST
- mRECIST

11.1 Treatment evaluation using mRECIST as well as iRECIST Guidelines

The first scan prior to treatment initiation will be performed; the next scan will be then performed at the end of treatment visit. It will then continue every 8-12 weeks per physician discretion until disease progression is confirmed or withdrawn of consent. (See Section 4.0).

Disease progression for this protocol is defined as meeting the mRECIST as well as iRECIST criteria detailed in appendix VI.

11.2 Definitions of measurable and non-measurable disease

11.21 Target Lesion Response mRECIST

- **Complete Response -** Disappearance of any intratumoral arterial enhancement in all target lesions.
- **Partial Response -** At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
- **Progressive Disease –** An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.
- **Stable Disease –** Any cases that do not qualify for either partial response or progressive disease.

11.22 Nontarget Lesion Response

- **Complete Response -** Disappearance of intratumoral arterial enhancement in nontarget lesions.
- **Incomplete Response/Stable Disease -** Persistence of intratumoral arterial enhancement in 1 or more nontarget lesions.
- **Progressive Disease –** Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

Special recommendations for assessment of tumor response in nontarget lesions in patients with HCC and cirrhosis can be made regarding the following:

- **Portal vein thrombosis:** Malignant portal vein thrombosis should be considered a nonmeasurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of treatment.
- **Porta hepatis lymph node:** Lymph nodes detected at the porta hepatis can be considered as malignant if the lymph node short axis is at least 20 mm.
- **Pleural effusion and ascites:** Cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease.

11.23 Appearance of New Lesions

In the assessment of tumor progression, the following concepts have been adopted by mRECIST for HCC:

- A newly detected hepatic nodule will be classified as HCC, and therefore will be declared as evidence of progression, when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging (i.e., hypervascularization in the arterial phase with washout in the portal venous or late venous phase).
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans. The date of progression is defined as the time a new lesion was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

11.24 Overall Response Assessment

In mRECIST for HCC, identical to conventional RECIST v1.1, overall subject response is a result of the combined assessment of both intra- and extrahepatic target lesions, non-target lesions, and new lesions.

12.0 Descriptive Factors

Baseline characteristics pertaining to the patient as well as the tumor would be reported. With respect to the patient, this would include but not limited to age, sex, the performance status, lines of prior therapy and types of previous therapies received. We would also report on pharmacogenomics assessed on each patient. With respect to the tumor, we would obtain information including but not limited to mutational status (RAS/RAF), mismatch repair status (or microsatellite instability), tumor mutation burden (based on NGS assay), RNA-seq and PD-L1/PD-1 expression.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Reason Off Treatment (from the Off-Treatment Form)	***Go to CFU, SFU, or end folder rollout***
1 = Treatment (Intervention) Completed Per Protocol Criteria	CFU
2 = Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	CFU/SFU/No follow-up
3 = Adverse Events/Side Effects/Complications	CFU
4 = Disease Progression, Relapse During Active Treatment (Intervention)	SFU
5 = Alternative Therapy	SFU/No follow-up
6 = Patient Off-Treatment (Intervention) For Other Complicating Disease	SFU
7 = Death On Study	No follow-up
8 = Other	SFU/SFU/No follow-up
10 = Disease Progression Before Active Treatment (Intervention)	No follow-up
24 = Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention)	No follow-up

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the survival follow-up phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 4.0.

13.4 Observation

If the patient has achieved CR, PR, or SD, the patient will be observed at 3 months, every 3 months for 1 year, and then every 3 months for up to 5 years from time of registration.

13.5 Duration of therapy for CR

Patients who achieve a CR will receive a maximum total of cycles for assigned cohort. After completion of cycles, they should be observed (see 13.4 above) every 3 months for 2 years or until PD and then they will go to survival follow-up.

13.6 Duration of therapy for PR or SD

Patients who are in PR or SD will continue on therapy for a maximum total of cycles for assigned cohort. After completion of cycles, they should be observed (see 13.4 above) every 3 months for 2

years or until PD and then they will go to survival follow-up (see 13.5 above). Subsequent treatment is at the discretion of their attending physician

13.7 Non-CNS PD

Patients who develop non-CNS PD at any time should go to event monitoring. These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.8 Unevaluable patients

If a patient fails to complete the first cycle of treatment, prior to administration of Y-90, for reasons other than toxicity, the patient will be regarded as unevaluable and will be replaced.

13.9 Ineligible

A patient is deemed *ineligible* if after enrollment, it is determined that at the time of screening, the patient did not satisfy each and every eligibility criterion for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

If the patient never received treatment, on-study material must be submitted. Survival Follow-up will be required per Section 4.0 of the protocol.

13.10 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.11 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

OR

For intent to treat trials, use this wording (consult stats) A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the survival follow-up of the study, and survival follow-up will be required per Section 4.0 of the protocol.

14.0 Body Fluid Biospecimens

Please refer to the **companion laboratory companion** manual for details on collection/processing/kits.

15.0 Drug Information

IND Exempt. See prescribing information for full information.

15.1 Durvalumab (MEDI4736, IMFINZI™):

15.1.1 **Background:** Durvalumab is a human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells) and cluster of differentiation (CD)80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

15.1.2 **Formulation**: Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure

15.1.3 **Preparation and storage**: Withdraw desired volume from vial and dilute in either 0.9% sodium chloride or 5% Dextrose in Water to a final concentration of 1 to 15 mg/mL. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature. Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

15.1.4 **Administration:** Durvalumab is delivered through an IV administration set with a 0.2- or 0.22-micron filter. The standard infusion time is 1 hour. Do not co-administer other drugs through the same infusion line. Flush the IV line with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered.

15.1.5 **Pharmacokinetic information**:

- **Volume of Distribution:** The mean volume of distribution at steady state was 5.6 liters
- **Half-life elimination:** The mean terminal half-life at steady state was approximately 18 days.
- **Excretion:** Mean steady state clearance was 8.2 mL/hr.

15.16 **Potential Drug Interactions**: Durvalumab is an immunoglobulin; therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted.

15.17 **Known potential toxicities**:

- **Very common, > 10%:** Fatigue, cough, decreased appetite, dyspnea, nausea, constipation, diarrhea, pyrexia, back pain, anemia, vomiting, pruritus, arthralgia, headache, asthenia, peripheral edema, rash.
- **Common, 1% - 10%:** Abdominal pain, hypothyroidism, insomnia, urinary tract infection, myalgia, dizziness, AST and ALT increased, musculoskeletal pain, upper respiratory tract infection, pneumonia, weight decreased, pain in extremity, hyponatremia, productive cough, dehydration, hyperthyroidism, musculoskeletal chest pain, radiation pneumonitis, hypokalemia, GGT increased, blood alkaline phosphatase increased.
- **Rare, <1% (Limited to important or life-threatening):** Pulmonary embolism, respiratory failure, COPD, hemoptysis, atrial fibrillation, pericardial effusion.

15.18 **Procurement**: Durvalumab will be provided free of charge to study participants from AstraZeneca.

15.2 Nursing Guidelines

15.2.1 Anti PD-L1 side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.2.2 Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.2.3 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.

15.2.4 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.2.5 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.2.6 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are a concern given the mechanism of action of this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.2.7 Pancreatitis is possible with anti PD-L1 therapy based on mechanism of action. Instruct patients to report abdominal pain, nausea and vomiting to the study team.

15.2.8 Patients who are started on steroid therapy for any side effects of anti PD-L1 toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

16.0 Device Information

This medical device is utilized under an investigator-sponsored Investigational Device Exemption (IDE), P. McNeely, M.D. IDE Sponsor. The use and prescription of TheraSpheres is not under the HDE approval.

16.1 TheraSpheres [Yttrium-90 Glass Microspheres)

16.1.1. **Background**: TheraSpheres is indicated only for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters and is approved for this indication under Humanitarian Device Exemption H980006.

16.1.2. **Regulatory Status.** Use of this device is limited to the subjects meeting explicit protocol criteria under the investigational device exemption (IDE XXXXXX, McNeely sponsor-investigator).

16.1.3. **Labeling.** The investigational device and/or package will have a label stating it is for investigational use only and limited by Federal law to investigational use, as well as all other required contents per 21CFR§812.5(a)

16.1.4 **Records**. Shipment, disposition, and destruction of the device must be documented by research personnel authorized per the delegation log. Accountability and receipt records documenting the device life-cycle must be used per 21CFR§812.40.

16.1.5 **Prescription**. Individuals authorized to prescribe must be an authorized user (10CFR§35) and have been delegated the authority from the IDE sponsor.

16.1.6 **Administration**. TheraSpheres will be planned and administered per the approved package insert as well as following currently recommended guidelines: Sangro et al (2017), Lau et al (2012), Venkatanarsimha et al (2017), as well as the EANM procedure guideline for intra-arterial radioactive compounds (Giammarille et al 2011). Per package insert, targeted administrations will fall within recommended values of 80 Gy to 150 Gy per lobe of liver in order to preventing radioembolization induced liver disease (REILD). Required activity at the time of administration and actual dose delivered to the liver may be respectively calculated as

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Target Liver Mass (kg)}]}{50}$$

$$\text{Dose (Gy)} = \frac{50[\text{Injected Activity (GBq)}][1 - \text{F}]}{\text{Affected Liver Mass (kg)}}$$

, where F is the lung shunting fraction measured during the Tc-99m labelled MAA eligibility mapping. Additional eligibility criteria will include the absence of shunting to bowel along the GI tract as well as a lung shunting fraction (F) <15% or estimated lung doses <30 Gy for a single Y90-RE administration and a cumulative total of <50 Gy from multiple administrations. As noted earlier, from a safety perspective since we need to know about the shunting to other organs prior to the Y90-RE, the mapping can be done during the screening or even prior to considerations for this study if already performed within 12 months of intended Y90-RE, it would not need to be repeated unless as per interventional radiology.

16.1.7 **Drug interactions**. External beam radiation is known to interact with immunotherapy, often resulting in heightened immune responses. (Wang et al, 2018, PMID 29556198).

16.1.8 **Radiation observation window**. Due to the long-term side effects of radiation therapy, it is recommended subjects be followed for a minimum of 2 years post-radiation.

16.1.9 **Procurement**. Investigational device will be ordered by the IDE sponsor or delegate. Upon receipt, it will be labelled as per 21CFR§812.5(a) and secured. Subject will be billed for the research device as allowed under 42CFR§405 Subpart B upon approval by the appropriate CMS contractor.

17.0 Statistical Considerations and Methodology

17.1 Study Design

This is a single arm phase I study designed to determine the maximally tolerated dose (MTD) and toxicity profile of Yttrium-90 radioembolization combined with immunotherapy in the treatment of liver-predominant, metastatic colorectal cancer using the accelerated titration design.

Once the MTD is reached, if total accrual is less than 18, additional patients will be enrolled in an expansion cohort to reach full accrual of 18 patients.

17.2 MTD Definition and Determination

For this protocol, the patient must return to clinic for evaluation at least every **14** days +/- 5 days. Patients will be treated and observed for a minimum of **8** weeks post-Y90-RE before new patients are treated. Doses will not be escalated in any individual patient.

MTD Definition: The MTD will be defined as the highest dose level for which at most 1 out of 6 patients experience a dose-limiting toxicity (DLT). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% (1-(1-0.25)^6).

Refer to Section **7.42** for definition of dose-limiting toxicity (DLT).

MTD Determination:

This study will utilize an accelerated titration design. The dose levels to which patients will be assigned in sequential cohorts are listed in the table below.

	Immunotherapy (Durvalumab) Administrations						
	Pre-Y90 doses		Y90-Radio-embolization	Post-Y90 doses			Number of Administration of Durvalumab
Dose level	Week -2	Week 0		Week 2	Week 4	Week 6	
-2						X	1
-1					X	X	2
1 (start)	X	X					2
2	X	X			X		3
3	X	X			X	X	4
4	X	X		X	X	X	5

In the first phase, a single patient will be treated per dose level until the first DLT is recorded. Once the first DLT is recorded, two additional patients are treated at the same dose level and the trial reverts to a standard 3+3 design in the second phase. At which time, decisions on when and how to dose escalate are described below.

Number of patients with DLT at a given dose level	Decision Rule
0 out of 3	Enter 3 patients at the next higher dose level
1 out of 3	Enter up to 3 additional patients at the same dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of these 3 patients experience DLT, then dose

	escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≥2 out of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

Up to 6 patients will be treated at each dose level. If DLT meets the stopping boundaries set by the above dose algorithm at dose level 1 (for example, more than 1 out of 3 or more than 1 out of 6 patients), the next cohort of 3 patients will be entered at the dose level of -1. If dose level -1 meets the stopping boundaries, the next cohort of 3 patients will be entered at dose level -2.

17.3 Sample Size

This phase I study is expected to require 9 evaluable patients to establish the highest dose level as the MTD. We do not expect serious adverse events or DLTs based on experience of treating patients with Y90-RE. Experience with immunotherapy as well has been reassuring from a safety perspective. Anecdotally, we have had some patients who were on immunotherapy for HCC, which got FDA approved in October 2017 who got Y90-RE with no untoward side effects and good responses. Given the clinical experience and data that is available so far, we do not expect to reach the maximum accrual dictated by budget restrictions during the MTD determination portion of the study. Once the MTD is determined, additional patients will be accrued in an expansion cohort in order to reach full accrual of 18 patients between Phase I and the expansion cohort.

The primary objective of the expansion cohort is to evaluate whether Y90-RE in combination with durvalumab confers an immune response (mechanism of action) irrespective of dose level as estimated by the change in frequency of immune cells pre- and post-treatment. A sample size of 18 patients will allow the sample mean for the pairwise difference to be estimated with a 95% confidence interval half-width of 0.5 SD.

The overarching goal of the expansion cohort is to gain preliminary evidence as to whether Y90-RE in combination with durvalumab confers an immune response, the hypothesized mechanism of action. Immune response will be assessed by estimating the mean change in the frequencies of immune cells from pre-treatment to post-treatment. More specifically, each patient's immune cell frequencies at pre-treatment will be subtracted from the post-treatment value to obtain the pairwise difference for a patient. Immune cell analysis will include, but is not limited to, the frequencies of innate (monocytes, macrophages, neutrophils, dendritic cells, NK cells) and adaptive (CD4+ T cells, CD8+ T cells, NKT cells, B cells) immune cells. A change is immune cell frequencies after treatment is anticipated, but the expected average change for each type of immune cell is not known, thus the purpose of the expansion cohort. No formal hypotheses are being tested, rather the change in immune profile along with other data obtained (e.g. changes in circulating tumor DNA, tumor response to treatment, etc.) will be collectively evaluated and used to inform a subsequent Phase II trial. From previously done similar studies, a 25% change is taken to represent a biologically meaningful downregulation of some of the key negative players (e.g. Tregs) and upregulation of positive players (e.g. PD-L1) expression, which will be taken into consideration when evaluating the immune profile.

17.4 Accrual and Study Duration

Given previous data for the similar studies and our clinical volume, it is expected that the annual accrual rate will be **12** patients. With that being said, we expect full accrual to be reached within **18** months if not sooner.

17.5 Analysis Plans

All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as an impetus for further study in Phase II trials rather than a definitive finding in and of itself.

17.5.1 Adverse Events Profile

The number and severity of all adverse events (overall, by dose-level, and by tumor group) will be tabulated and summarized in this patient population. The Grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

17.5.2 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading.

Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Please note for the response/efficacy evaluation, it will be mRECIST as well as iRECIST that will be reported. A confirmatory scan can be done 4 weeks post completion of therapy if there are clinical concerns.

17.5.3 Overall Response Rate

Overall response rate is defined as the proportion of evaluable patients that have achieved a complete response or partial response using mRECIST evaluation criteria. ORR will be evaluated at 2 months post-Y90RE treatment (± 5 business days).

ORR will be analyzed descriptively as a point estimate with a 95% confidence interval.

Results will be reported consistent with RECIST v1.1 (Appendix A.9).

An “evaluable subject” for the purpose of evaluation of the combinatorial therapy is one who receives both Y90-radioembolization and at least 1 dose of durvalumab.

Subjects who do not receive Y90-RE or received only a single incomplete dose of immunotherapy (i.e., allergic reaction), are considered non-evaluable for assessment of efficacy. These subjects would be replaced for the proposed sample size of 18.

All subjects included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

Each subject will be assigned one of the following categories: 1) complete response (mRECIST), 2) partial response (mRECIST), 3) stable disease (mRECIST), 4) progressive disease (mRECIST), 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

Category 4 (protocol specific definition): includes clinical progression as determined by the principal investigator and confirmed by the independent data and safety monitoring committee (DSMC).

Category 5 (protocol specific definition): death from malignant disease as determined by the principal investigator and confirmed by the independent data and safety monitoring committee (DSMC).

Category 6 (protocol specific definition): death from toxicity as determined by the principal investigator and confirmed by the independent data and safety monitoring committee (DSMC).

Category 7 (protocol specific definition): includes death not meeting categories 5 or 6, or death defined as not otherwise specified.

Category 9 (protocol specific definition): includes subjects who did not receive radioembolization, or who did not receive at least 1 complete infusion of durvalumab, or who did not undergo follow-up imaging (other than for clinical progression, toxicity, or death), or subjects who are lost to follow-up.

17.5.4 Disease Control Rate

Disease control rate is defined as the proportion of evaluable patients that have achieved a complete response, partial response, or stable disease by a specified time point. DCR will be evaluated at 2 months post-Y90RE treatment. DCR will be analyzed descriptively as a point estimate with a 95% confidence interval.

17.5.5 Overall Survival

Overall survival is defined as the time from randomization to death of any cause. Patients that are still alive at the time of analysis will be censored at the date they were last known to be alive. OS will be analyzed descriptively as a point estimate for the median with a 95% confidence interval using the Kaplan-Meier method.

17.5.6 Laboratory Correlates

Baseline tumor markers including CEA and CA-19-9 will be assessed and then at subsequent study visits. Complete differential would be obtained to assess and report neutrophil to lymphocyte ratio. Markers of inflammation ESR, CRP and vitamin D levels to be assessed at baseline and the subsequent visits.

17.6 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of either regimen in subsets defined by gender, race, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings, the samples sizes are not increased in order to provide additional power for such subset analyses.

18.0 Pathology Considerations/Tissue Biospecimens

DNA and RNA extraction will be performed at University of Iowa. DNA and RNA sequencing will be performed at TEMPUS. The biopsies (both clinical and research) will be performed at University of Iowa. Detailed instructions in the companion laboratory manual.

Tissue Samples are held at the University of Iowa Tissue Procurement Core.

Contact:
Kristen Coleman, PhD
Tissue Procurement Core
380 MRC
501 Newton Road
Iowa City, Iowa 52242

19.0 Records and Data Collection Procedures

19.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

19.2 Survival Follow-up

See Section 4.

19.3 CRF completion

Data will be collected through HCCC's Clinical Trial Management System (OnCore). See Appendix V. A.

19.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, registration number, and protocol number. Patient's name must be removed.

19.5 Supporting documentation

This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. These documents should be submitted within 14 days of registration.

19.6 Labeling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, registration number, and protocol number. Patient's name must be removed.

20.0 Budget

20.1 Costs charged to patient: routine clinical care

20.2 Tests to be research funded:

Research testing on blood and tissue specimens

20.3 Other budget concerns:

BTG International Canada, Inc. will provide University of Iowa with funding to support the costs of running this study.

AstraZeneca Pharmaceuticals will provide study drug durvalumab for use in this study

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Appendix I: ECOG Performance Status

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

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II: New York Heart Association Classification

Clinical Evaluation of Functional Capacity of Patients
with Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest *	Physical Ability To Work**
I	None	None	None	Full Time
II	Only Mild	Slight	Usually only slight or occasional	Usually Full Time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually Part Time
IV	May be present event at rest and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

Appendix III: EORTC QLQ-C30

PATIENT INFORMATION SHEET
Patient Completed Booklet
(Baseline)

You have been given a booklet to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed on the day you enroll in the study.

    i. Cycle 1-5 Pre-treatment
    ii. End of treatment visit. (8 weeks after Y90-RE treatment)

2. This booklet contains the following questionnaires:
    ☐ Quality of life (EORTC QLQ-C30)

3. Directions on how to complete each set of questions are written on the top of each set.

4. It is very important that you return the booklets to us, whether you finish the study or not.

5. You will be given the nurse's or study coordinator's name and telephone number. You can call anytime with any concerns or questions.

6. After completing this booklet, please return it to your nurse or physician.

Thank you for taking the time to help us.

EORTC QLQ - C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4

19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix IV: RECIST 1.1, iRECIST, mRECIST

IV.A. Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

A.1 Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.**
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter<20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- 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.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A.2 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mmor less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

A.3 Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

A.4 Response Criteria

Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response / Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

A.5 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

A.6 Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

A.7 Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.
- Duration of stable disease
- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

A.8 Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

A.9 Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

IV.B. Immunotherapy in cancer Response Evaluation Criteria in Solid Tumors (iRECIST) Quick Reference

Consensus-based guideline for assessing response to immunotherapy in cancer (iRECIST): Comparison with standard RECIST 1.1

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances (eg, in some trials with progression-based endpoints planned for marketing approval)	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST.

RECIST: Response Evaluation Criteria in Solid Tumours; iUPD: unconfirmed progression; iCPD: confirmed progression; iCR: complete response; iPR: partial response; iSD: stable disease.

IV.C. Modified Evaluation Criteria in Solid Tumors (mRECIST) Quick Reference

Modified RECIST for hepatocellular carcinoma

Response assessment	
Target lesions	
CR	Disappearance of all target lesions or disappearance of any intratumoral arterial enhancement in all target lesions.
PR	At least 30% decrease in the sum of the diameters of viable (enhancing) target lesions, taking as a reference the baseline sum of the diameters of target lesions.*
PD	Any increase of at least 20% in the sum of the diameters of viable target lesions, taking as a reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.*
SD	Any cases that do not qualify for either PR or PD.
Non-target lesions	
Malignant portal vein thrombosis	Should be considered a nonmeasurable lesion.
Lymph nodes	If detected at the porta hepatis, should be considered malignant if the short axis dimension is ≥2.0 cm.
Pleural effusions and ascites	Emergence of, or increase in, ascites is common during the course of treatment of a cirrhotic patient, and may reflect worsening of the underlying chronic liver disease and be unrelated to cancer progression. The same is true of pleural effusions. Cytopathologic confirmation of the neoplastic nature of any effusion that appears during treatment is required when the measurable tumor has met criteria for response or SD.
New lesions	A newly detected hepatic nodule is classified as hepatocellular carcinoma (and declared evidence of progression) when its longest diameter is at least 1 cm and the nodule has a typical vascular pattern on dynamic imaging (hypervascular in arterial phase with washout in the portal venous or late venous phase). Liver lesions >1 cm that do not show a typical vascular pattern can be diagnosed as hepatocellular carcinoma if there is at least 1 cm internal growth on subsequent scans.

RECIST: Response Evaluation Criteria In Solid Tumors; CR: complete response; PR: partial response; PD: progressive disease: SD: stable disease.
* Enhancement in the arterial phase reflects viable tumor tissue.

Adapted from: Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30:52.

Appendix V: Restrictions for blood donation and for those of childbearing age

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

Female patient of child-bearing potential

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

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

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period.

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

Women <50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are herein described. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Highly effective methods

Copper T intrauterine device
Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]
Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant®
Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing®
Injection: Medroxyprogesterone injection: e.g. Depo-Provera®
Combined Pill: Normal and low dose combined oral contraceptive pill
Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra®

Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

Blood donation

Patients should not donate blood while participating in this study of Durvalumab with Y90-RE for at least 90 days following the last infusion of durvalumab.

Appendix VI: TheraSpheres Prescribing Information

BTG

Package Insert

TheraSphere® Yttrium-90 Glass Microspheres

Humanitarian Device.

Authorized by Federal Law for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment. The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training and experience.

DESCRIPTION

TheraSphere® consists of insoluble glass microspheres where yttrium-90 is an integral constituent of the glass [1]. The mean sphere diameter ranges from 20 to 30 µm. Each milligram contains between 22,000 and 73,000 microspheres. TheraSphere® is supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vee-bottom vial secured within a clear acrylic vial shield. TheraSphere® is available in six dose sizes: 3 GBq (81 mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi) and 20 GBq (540 mCi). Custom dose sizes available: 0.5 GBq increments between 3 and 20 GBq.

A preassembled single use TheraSphere® Administration Set is provided for each dose. The TheraSphere® Administration Accessory Kit is supplied to new user sites. The kit includes re-usable accessories including an acrylic box base, top shield, removable side shield, bag hook and a RADOS RAD-60R radiation dosimeter (or equivalent).

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.1 hours (2.67 days). The average energy of the beta emissions from yttrium-90 is 0.9367 MeV.

Following embolization of the yttrium-90 glass microspheres in tumorous liver tissue, the beta radiation emitted provides a therapeutic effect [2-6]. The microspheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The microspheres, being unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumor and exert a local radiotherapeutic effect with some concurrent damage to surrounding normal liver tissue [7-14].

INDICATION

TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters. The device is also indicated for HCC patients with partial or branch portal vein thrombosis/occlusion, when clinical evaluation warrants the treatment.

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CONTRAINDICATIONS

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques (see Item 1 under **INDIVIDUALIZATION OF TREATMENT**);
- who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see Item 2 under **INDIVIDUALIZATION OF TREATMENT**);
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities or bleeding diathesis;
- who have severe liver dysfunction or pulmonary insufficiency; and
- who present with complete occlusion of the main portal vein (see Item 3 under **INDIVIDUALIZATION OF TREATMENT**).

PRECAUTIONS/WARNINGS

A retrospective study of 121 patients from 5 clinical trials has shown that the following 5 Pre-treatment High Risk Factors have been associated with at least 48% of all serious adverse events that were possibly related to use of the device and with 11 of the 12 deaths that were possibly related to use of the device:

- **infiltrative tumor type**
- **"Bulk disease" (tumor volume > 70% of the target liver volume, or tumor nodules too numerous to count)**
- **AST or ALT > 5 times ULN**
- **bilirubin > 2 mg/dL**
- **tumor volume > 50% combined with an albumin < 3 g/dL**

The physician should always take the above-noted Pre-treatment High Risk Factors into consideration for each patient when making decisions regarding the use of TheraSphere® for treatment.

- Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Adequate shielding and precautions for handling radioactive material must be maintained.
- As in the use of any radioactive material, care should be taken to ensure minimum radiation exposure to the patient extraneous to the therapeutic objective and to ensure minimum radiation exposure to workers and others in contact with the patient.
- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.
- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure.
- The TheraSphere® dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The TheraSphere® dose vial should always be stored in a shielded location away from personnel.

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ADVERSE REACTIONS

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Serious adverse events that occurred under clinical studies and that were definitely, probably or possibly related to TheraSphere®, or if the relationship was unknown, are summarized in Table 1 (based on published data to 2004). In addition to these serious adverse events, lymphocyte depression, which may be graded as moderate to severe but with no clinical sequellae, is expected to occur in some patients.

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract may cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs may cause edema and fibrosis that may not be reversible.

Extrahepatic shunting may be identified through the injection of Tc-99m MAA into the hepatic artery [19, 20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. In addition, placement of the delivery catheter in the hepatic branch distal to collateral vessels provides a safety margin with respect to inadvertent deposition of microspheres.

Some adverse events observed may be explained by the effect of attenuated radiation from the treated liver. Pleural effusion may be caused by attenuated radiation when the treated tumor is positioned proximal to the base of the lung. Similarly, treatment of tumors in the left lobe of the liver, in proximity to the gut, may explain some of the gastrointestinal events observed. Putative attenuated radiation effects to extrahepatic structures have generally been found to resolve over time.

The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with diseases that compromise the functioning of their normal liver tissue or patients with either diffuse tumors or a high tumor burden may be at greater risk of liver function impairment.

A number of patient baseline characteristics, indicative of either impaired normal liver function or tumor status, correlated with a higher incidence of liver-related serious adverse events in clinical trials.

A retrospective study of 121 patients from 5 clinical trials has shown that the following 5 Pre-treatment High Risk Factors have been associated with at least 48% of all serious adverse events that were possibly related to use of the device and with 11 of the 12 deaths that were possibly related to use of the device:

- infiltrative tumor type
- “Bulk disease” (tumor volume > 70% of the target liver volume, or tumor nodules too numerous to count)
- AST or ALT > 5 times ULN
- bilirubin > 2 mg/dL
- tumor volume > 50% combined with an albumin < 3 g/dL

The physician should always take the above-noted Pre-treatment High Risk Factors into consideration for each patient when making decisions regarding the use of TheraSphere® for treatment.

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Table 1

Treatment-Emergent Serious Adverse Events from 5 Clinical Studies (N=121) for Patients Undergoing TheraSphere® Treatment Therapy (2004)

Adverse Event	Severe N	(%)	Life Threatening N	(%)	Fatal N	(%)	Total N	(%)
Elevated bilirubin	16	(57.1)	10	(35.7)	2	(7.1)	28	(23.1)
Ascites	10	(100)	0		0		10	(8.3)
Abdominal pain	8	(100)	0		0		8	(6.6)
Elevated SGOT/SGPT	7	(100)	0		0		7	(5.8)
Gastric ulcer	4	(80)	0		1	(20)	5	(4.1)
Elevated Alkaline Phosphatase	4	(100)	0		0		4	(3.3)
Pain, not abdominal	4	(100)	0		0		4	(3.3)
Hepatic encephalopathy	2	(66.7)	1	(33.3)	0		3	(2.5)
Elevated LDH	3	(100)	0		0		3	(2.5)
Elevated prothrombin time	2	(66.7)	1	(33.3)	0		3	(2.5)
Liver failure	0		0		2	(100)	2	(1.7)
Cholecystitis	0		2	(100)	0		2	(1.7)
Nausea	2	(100)	0		0		2	(1.7)
Edema	0		2	(100)	0		2	(1.7)
Fatigue	2	(100)	0		0		2	(1.7)
Malaise	2	(100)	0		0		2	(1.7)
Death, not otherwise specified	0		0		2	(100)	2	(1.7)
Hepatic decompensation	1	(100)	0		0		1	(0.8)
Hepatitis	0		0		1	(100)	1	(0.8)
Radiation hepatitis	1	(100)	0		0		1	(0.8)
Duodenal ulcer	1	(100)	0		0		1	(0.8)
Hypertension	1	(100)	0		0		1	(0.8)
Hypotension	1	(100)	0		0		1	(0.8)
Pleural effusion	1	(100)	0		0		1	(0.8)
Aspiration pneumonia	0		1	(100)	0		1	(0.8)
Pneumonitis	0		0		1	(100)	1	(0.8)
Radiation pneumonitis	0		0		1	(100)	1	(0.8)
Fall	1	(100)	0		0		1	(0.8)
Gastrointestinal bleed	1	(100)	0		0		1	(0.8)
Hemorrhage, not otherwise specified	1	(100)	0		0		1	(0.8)
Decreased platelets	1	(100)	0		0		1	(0.8)
Allergic reaction	1	(100)	0		0		1	(0.8)
Bacterial sepsis	0		0		1	(100)	1	(0.8)
Hypoglycemia	1	(100)	0		0		1	(0.8)
Hepatorenal failure	0		0		1	(100)	1	(0.8)

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In 2014, adverse reactions experienced following treatment with TheraSphere® were analyzed from two data sets:

- a comprehensive systematic review of 24 observational studies published between January 2004 and December 2013 (across which 1,634 patients were treated with TheraSphere® for hepatocellular carcinoma). These data were used to compile Table 2, which shows all grade 3 or higher adverse reactions reported in the 24 observational studies [28,32,33,35,36-55].
- all adverse events spontaneously reported to the company between January 2004 and December 2013 (1.33% of treatments resulted in reported adverse reactions).

Frequencies of adverse reactions are defined as: very common (≥ 10%), common (≥ 1% to < 10%), uncommon (≥ 0.1% to < 1%), rare (≥ 0.01% to < 0.1%).

Table 2
Grade 3 or Higher Adverse Reactions Reported in Comprehensive Systematic Review (2014)

Outcome	Overall Descriptive Statistics			Within Study Descriptive Statistics	Implant Mode Used
	No. studies	No. patients	No. events (%)	Min to Max Observed Risk (%)	Number of Patients (#)
Gastrointestinal					
Abdominal pain	3	203	4 (1.9%)	0.0%-5.8%	Lobar (193) Segmental (10)
Ascites	6	411	25 (6.1%)	0.0%-13.8%	Lobar (293) Segmental (10) Undeclared (108)
Gastric Ulcer	3	281	1 (0.4%)	0.0%-0.8%	Lobar (281)
Nausea	2	343	5 (1.5%)	0.0%-9.6%	Lobar (52) Undeclared (291)
General					
Fatigue	3	203	4 (1.9%)	0.0-5.8%	Lobar (193) Segmental (10)
Hepatobiliary					
Cholecystitis	1	52	1 (1.9%)	1.9%	Lobar (52)
Hepatic Encephalopathy	1	108	3 (2.8%)	2.8%	Undeclared (108)
Respiratory, thoracic, and mediastinal					
Pleural effusion	2	216	1 (0.5%)	0.0%-0.9%	Lobar (108) Undeclared (108)

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Table 2 (continued)
Grade 3 or Higher Adverse Reactions Reported in Comprehensive Systematic Review (2014)

Outcome	Overall Descriptive Statistics			Within Study Descriptive Statistics	Implant Mode Used
	No. studies	No. patients	No. events (%)	Min to Max Observed Risk (%)	Number of Patients (#)
Laboratory					
Platelet Count Decreased	1	108	4 (3.7%)	3.7%	Lobar (108)
Decreased Albumin	3	411	57 (13.9%)	0.0%-33.3%	Lobar (113) Segmental (7) Undeclared (291)
Alkaline Phosphatase Increased	6	652	14 (2.1%)	0.0%-3.8%	Lobar (336) Segmental (25) Undeclared (291)
ALT Increased	5	521	21 (4.0%)	0.0%-8.3%	Lobar (113) Segmental (117) Undeclared (291)
AST Increased	4	413	59 (11.3%)	0.0%-18.9%	Lobar (5) Segmental (117) Undeclared (291)
Blood Bilirubin Increased	10	779	142 (18.2%)	2.0%-33.3%	Lobar (211) Segmental (169) Undeclared (399)
Creatinine Increased	1	108	0 (0.0%)	0.0%	Lobar (108)
Increased Prothrombin	1	108	3 (2.7%)	2.7%	Lobar (108)
Lymphopenia	2	120	79 (65.8%)	16.7%-71.3%	Lobar (113) Segmental (7)

Summary of all Adverse Reactions in Studies and Post-marketing Data (2014)

A comprehensive systematic review of published observational studies utilizing TheraSphere® showed very common adverse reactions (all grades) including flu-like symptoms such as fatigue (47.9%), abdominal pain (19.2%) and nausea (19.8%) as well as edema (33.3%) according to CTCAE 2.0 and 3.0. Approximately 10% or less of these very common adverse reactions were reported as CTCAE grade 3 or higher, including fatigue (1.9%), abdominal pain (1.9%) and nausea (1.5%), with no grade 3 or higher edemas reported (see Table 1). This reporting pattern is also reflected in post-marketing data; however percentage reporting rates are lower - fatigue (0.04%), abdominal pain (0.09%), nausea (0.07%), and edema (<0.01%).

Other common adverse reactions (occurring in 1% to <10% of the patients treated) found in the systematic review included ascites (9.2%), hepatic failure (6.9%), generalized pain (8%), hepatic encephalopathy (3.9%), cholecystitis (1.5%), and bacterial peritonitis (1.2%). These adverse events were also found in the post-marketing data but with reported rates of less than 1% for each. Cholecystitis reports in the post-marketing data in a few cases resulted from non-target radiation however cholecystitis requiring cholecystectomy is uncommon.

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Uncommon adverse reactions (≥ 0.1% to <1%) found in the systematic review were gastric ulcer (0.4%) and pleural effusion (0.9%). Eight ulcers (gastrointestinal ulcers (4), gastric ulcers (3), duodenal ulcers (1)) were reported in post marketing data with a frequency of 0.03%.

Laboratory changes found in the systematic review across all grades and classified as very common included increased AST (86.2%), lymphopenia (59.3%), increased ALT (56.2%), increased prothrombin time (53.5%), decreased albumin (55.3%), increased bilirubin (41.2%), increased alkaline phosphatase (29.7%), and decreased platelet count (25.0%). Increased creatinine (6.9%) was the only laboratory change classified as common. The majority of patients will experience a transient rise in alkaline phosphatase and ALT levels following treatment with TheraSphere®. Lymphopenia has not been reported to be associated with opportunistic infections or clinical sequalae.

The majority of adverse events reported from post market data are similar to those seen within the published literature. Reporting rates tend to be low (1.33% of patient doses resulted in reported adverse events with no individual adverse events reported >0.5%) and are not indication specific.

Adverse events not reflected in the published data are summarized below.

A number of adverse events in the post market setting were gastrointestinal disorders (84). The majority were non-serious, with the exception of the ulcers mentioned above, gastrointestinal hemorrhage (4), and gastritis (1). Death (12) from unconfirmed causes has also been reported after TheraSphere® treatment with a low frequency. It is difficult to determine if these events are related to treatment or to liver decompensation as a result of disease progression. Haemoptysis (1), pulmonary embolism (1), jaundice (5), liver abscess (3), bile duct obstruction (4), dyspnea (6), confused state (3), disorientation (3), and reports of patients requiring paracentesis (4) have also been reported through post market surveillance. Eleven cardiac disorders were reported over the ten year period; however the relationship to TheraSphere® treatment could not be confirmed. These included chest pain (3), myocardial infarction (1), and cardiac arrest (1), among others.

Biliary obstruction was reported in four patients over the ten year period. Biliary complications could occur as a result of radioembolization or may be related to disease progression. Also identified from post-marketing surveillance were radiation hepatitis (1) and radiation pneumonitis (2). Although the objective of the treatment is to administer TheraSphere® to the tumor while minimizing the effect on normal hepatic parenchyma, radiation hepatitis can be a complication if a larger proportion of normal parenchyma is irradiated than the patient can tolerate. Radiation pneumonitis is a very rare complication with the risk of its occurrence mitigated by conducting proper pre-treatment lung shunt studies to ensure the cumulative lung dose is limited to 50 Gy or lower.

CLINICAL STUDIES

1. 100 Gy HCC Study [22]

- *Objectives:* To define the activity of yttrium-90 microspheres given by hepatic artery infusion to a previously untreated patient with primary HCC; to evaluate the survival of patients treated with yttrium-90 microspheres; and to evaluate the toxicity of yttrium-90 microsphere therapy.
- *Study Design:* Patients with HCC were treated with a target dose of TheraSphere® of 100 Gy by injection through the hepatic artery. Patients underwent laboratory tests, history and physical examinations, and liver ultrasounds or computerized tomography (CT) scans for up to 2 years after treatment. Response duration was calculated from the date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the Southwest Oncology Group (SWOG; Operations Office, San Antonio, TX) grading system (last revised 12/94), i.e. grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and grade 5 = lethal/fatal. If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a

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51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

- *Patient Inclusion Criteria:* Presence of histologically confirmed unresectable HCC confined to the liver and at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status 0-3; estimated life expectancy greater than 12 weeks; absolute granulocyte count 2.0 x 10^8/L or greater; platelet count 100 x 10^9/L or greater; prothrombin time (PT) and activated partial thromboplastin time within normal limits; bilirubin less than 1.5 x upper normal limit; serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase less than 5 x upper normal limit; normal pulmonary function defined as no more than 30% greater or less than the expected normal.
- *Study Population and Treatment Administration:* Twenty-two patients were treated. Two patients were excluded from the evaluation of probable benefit due to an unconfirmed diagnosis of HCC. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion. Nine patients were classified as Okuda stage I and 11 patients as Okuda stage II. The median activity administered was 3.9 GBq (range, 2.0 GBq to 9.2 GBq). The median liver dose was 104 Gy (range, 46 Gy to 145 Gy).
- *Safety Results:* One patient suffered from a possible angiography contrast agent allergic reaction that was judged by investigator to be severe in nature. All 22 treated patients reported at least one treatment-emergent adverse event; however, the majority (85%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e. graded as severe, life threatening, or lethal/fatal) adverse events were liver related (45%) and gastrointestinal (19%). Liver toxicities were primarily elevated enzymes during the week after treatment. The gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Three patients died during the follow-up period. The deaths were attributed to hepatitis (death approximately 5 months after TheraSphere® treatment; judged as possibly related to TheraSphere®), gastric ulcer (death approximately 2 months after TheraSphere® treatment; judged as probably related to TheraSphere®), and radiation pneumonitis (death approximately 2 months after TheraSphere® treatment; judged as definitely related to TheraSphere® after the patient received an estimated dose of 56 Gy to the lungs as a result of pulmonary shunting).
- *Probable Benefit:* As of February 14, 1997, two patients remained alive resulting in a median survival of 378 days (95% CI, 209-719), with a minimum survival of 49 days and a maximum survival of 1,265 days. Based on a stratified Cox survival analysis model, activity ratio, Okuda stage, and liver dose appeared to influence survival by approximately the same magnitude of effect.

2. Pilot HCC [4] and Mixed Neoplasia Studies [3, 11]

- *Objectives:* The objectives of the Pilot HCC study were to define the activity of yttrium-90 microspheres administered by hepatic arterial infusion to patients with HCC and to evaluate the toxicity of yttrium-90 microsphere therapy.
- The objectives of the Mixed Neoplasia study were to evaluate the toxicity of yttrium-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of yttrium-90 glass microspheres administered by hepatic arterial infusion that would be suitable for Phase II-III studies in a similar patient population.
- *Study Design:* Patients in the Pilot HCC study received TheraSphere® in an amount that was determined to deliver a radiation absorbed dose of approximately 50 Gy to the tumor. The Mixed Neoplasia study was designed to treat patients with metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobilliary carcinoma. Patients received a single injection of TheraSphere® with an initial group of patients receiving a calculated radiation absorbed dose of 50 Gy to the liver; after determination of acceptable and reversible toxicity, a second group of patients received 75 Gy to the liver followed by a third group of patients who received 100 Gy to the liver.

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- For both studies, response duration was calculated from the date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the SWOG grading system (see above under 100 Gy HCC Study).
- *Study Population and Treatment Administration:* Thirteen patients, nine from the Pilot HCC study and four from the Mixed Neoplasia study, provide safety data. All 13 patients were treated once with TheraSphere®. The median activity administered was 2.6 GBq (range, 2.2 GBq to 6.6 GBq). The median liver dose was 74 Gy (range, 34 Gy to 105 Gy). Because of the dose escalation, seven patients received less than 80 Gy.
- *Safety Results:* All 13 treated patients reported at least one treatment-emergent adverse event; however, the majority (82%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (43%). Liver toxicities were primarily due to elevated enzymes during the week after treatment. Among the serious adverse events, two patients also experienced gastric ulcers. Two patients died during the follow-up period. The deaths were attributed to elevated bilirubin (elevated before TheraSphere® treatment that increased in severity 2 days after treatment and continued until the patient's death 2 weeks later; judged as possibly related to TheraSphere®), and pneumonitis, (death approximately 6 weeks after TheraSphere® treatment; judged as possibly related to TheraSphere®).
- *Probable Benefit:* Table 3 shows the median survival (months) following treatment with TheraSphere® at doses <80 Gy and ≥80 Gy in patients with adenocarcinoma and HCC.

Table 3
TheraSphere® Median Survival (Months)

	Dose <80 Gy	Dose ≥80 Gy
Adenocarcinoma	9.1 (n=22)	9.7 (n=50)
Hepatocellular carcinoma	3.6 (n=8)	11.1 (n=7)

3. Published Literature

Numerous studies have focused on the use of TheraSphere® for the treatment of unresectable HCC. There has been a high degree of consistency within the literature in terms of survival outcomes [26,35,42,45,47,49,51,53,55-58].

Longterm Survival of Patients (HCC) in Child Pugh A/B

Salem et al studied 291 patients and reported a median survival in Child Pugh A and Child-Pugh B of 17.2 and 7.7 months respectively.[55] Hilgard et al studied 108 patients and reported a median survival in Child-Pugh A and Child-Pugh B of 17.2 and 6.0 months respectively.[45]

Publication	No. of Patients	mOS of Child-Pugh A	mOS of Child-Pugh B
Salem et al[55]	291	17.2	7.7
Hilgard et al[45]	108	17.2	6.0

Longterm Survival of Patients (HCC) in With or Without PVT

Kulik et al studied 108 patients and reported a median survival in branch PVT patients of 10.1 months compared to 15.6 months in patients without PVT (p=0.0052)[35] whereas Tsai et al studied 22 patients with PVT and reported a median survival of 7.0 months.[57] Hilgard et al studied 33 patients with PVT and reported a median survival patients of 10.0 months compared to 16.4 months in 75 patients without PVT.[45] Salem et al studied 125 patients and reported a median survival in Child-Pugh A and Child-Pugh B with PVT of 10.4 and 5.6 months

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performed by injecting a tracer dose of Tc-99m MAA and observing with an Anger camera. The observed radiation from the lung field, divided by the total radiation observed by the camera is a measure of F. The product of F and A is then a measure of the activity that will be deposited into the lungs [23]. Based on clinical study experience [15, 16] with radioactive microspheres and TheraSphere® in HCC treatment, an upper limit of F x A of 610 MBq (16.5 mCi) is recommended. The estimated dose (Gy) to the lungs is equal to A (GBq) x F x 50, and assuming the total mass of both lungs to be 1 kg [24]; an upper limit of dose to the lungs from a single TheraSphere® treatment is 30 Gy.

3. Portal vein thrombosis (PVT) is observed in over 40% of HCC patients who are potential candidates for TheraSphere® treatment [34]. For patients presenting with PVT, the clinician should weigh the risk verses benefit of yttrium-90 microsphere treatment. In a retrospective analysis of 25 patients presenting with branch or partial portal vein thrombosis, there was no increase in hepatic failure, hepatic encephalopathy, worsening of pre-existing portal hypertension, or extension of pre-existing portal vein occlusion following treatment with TheraSphere® [35]. The most common adverse event observed after TheraSphere® treatment in HCC patients presenting with PVT was elevated bilirubin. In all cases, elevated bilirubin was not treatment related but was attributed to progression of liver disease or cirrhosis [36]. Patients who present with PVT and symptoms of severe portal hypertension are at risk of liver decompensation and the risk versus benefit should be weighed accordingly. Patients presenting with complete occlusion of the main portal vein should not be considered for treatment due to the higher risk of liver failure, and potential complications (e.g. intestinal infarct, necrosis, varical bleeding, ascites) associated with this condition.

INSTRUCTIONS FOR USE

Dosage and Administration

To correct for the physical decay of yttrium-90, the fractions that remain at selected time intervals from calibration are shown in Table 4.

Table 4
Yttrium-90 Physical Decay Table
Half-Life 64.1 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	26	0.755	56	0.546
-2	1.022	28	0.739	58	0.534
0*	1.000	30	0.723	60	0.523
2	0.979	32	0.707	62	0.511
4	0.958	34	0.692	64	0.501
6	0.937	36	0.678	66	0.490
8	0.917	38	0.663	68	0.479
10	0.898	40	0.649	70	0.469
12	0.878	42	0.635	72 (Day 3)	0.459
14	0.860	44	0.621	96 (Day 4)	0.354
16	0.841	46	0.608	120 (Day 5)	0.273
18	0.823	48 (Day 2)	0.595	144 (Day 6)	0.211
20	0.806	50	0.582	168 (Day 7)	0.163
22	0.788	52	0.570		
24 (Day 1)	0.771	54	0.558		

*Calibration Time

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respectively.[55] Mazzaferro et al studied 35 patients with PVT and reported a median survival in Child-Pugh A and Child-Pugh B of 16 and 6 months respectively.[51]

Publication	No. of Patients	mOS with PVT	mOS without PVT	mOS of Child-Pugh A with PVT	mOS of Child-Pugh B with PVT
Kulik et al[35]	108	10.1	15.6		
Tsai et al[57]	22	7.0			
Hilgard et al[45]	108	10.0	16.4		
Salem et al[55]	125			10.4	5.6
Mazzaferro et al[51]	35			16	6

Quality of Life in Patients (HCC)

Salem et al studied 56 patients and reported FACT-Hep QoL parameters (Social and Functional Well-being) increased significantly following radioembolization with TheraSphere.[58] Steel et al reported significantly greater quality of life at three months follow-up.[26]

Early Clinical Studies in Patients

Early clinical studies (100 Gy HCC Study[15], Pilot HCC[16], and Mixed Neoplasia Studies[16,11]) established the safety and probable benefit of TheraSphere® for unresectable HCC. Safety results from one study showed one patient suffered from a possible angiography contrast agent allergic reaction that was judged by investigator to be severe in nature. All 22 treated patients reported at least one treatment-emergent adverse event; however, the majority (85%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e. graded as severe, life threatening or lethal/fatal) adverse events were liver related (45%) and gastrointestinal (19%). The study reported a median survival of 378 days (95% CI, 209-719). Based on a stratified Cox survival analysis model, activity ratio, Okuda stage, and liver dose appeared to influence survival by approximately the same magnitude of effect. The Pilot HCC the Mixed Neoplasia Studies were intended to evaluate the toxicity of yttrium-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of yttrium-90 glass microspheres administered by hepatic arterial infusion that would be suitable for Phase II-III studies in a similar patient population. Safety results from these studies show that all 13 treated patients reported at least one treatment-emergent adverse event; however, the majority (82%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening or lethal/fatal) adverse events were liver related (43%).

INDIVIDUALIZATION OF TREATMENT

1. Gastroduodenal ulceration is a potential complication of misplaced deposition of radioactive microspheres. It is likely that inadvertent deposition of yttrium-90 microspheres in the terminal gastric vascular bed reflects the backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce gastrointestinal shunting, their effectiveness is uncertain. If such flow is present and cannot be corrected using established angiographic techniques, the patient is disqualified from treatment. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere® may be administered.

2. In some patients, part of the hepatic arterial blood supply bypasses the capillary bed and flows directly to the venous system. This may be associated with pathologic abnormalities of the liver. For such patients, a fraction F of microspheres injected into the hepatic artery will not be embolized in the liver but will flow to the heart and subsequently be deposited into the lungs. As the product of the bypass fraction, F, and the injected activity, A, increases the potential for delivering a damaging dose of radiation to the lungs increases. Consequently, it is essential that F be measured before use of this product. This procedure is

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Preliminary Patient Evaluation

Prior to the administration of TheraSphere®, the patient should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting [21]. Following the placement of the hepatic catheter, 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99m MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs and to confirm the absence of gastric and duodenal flow. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere® may be administered.

Calculation of Dose

The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{\text{[Desired Dose (Gy)] [Liver Mass (kg)]}}{50}$$

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

For the purpose of ordering TheraSphere®, use the Yttrium-90 Physical Decay Table (Table 4) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$Dose\ (Gy) = \frac{50\ [Injected\ Activity\ (GBq)]\ [1-F]}{Liver\ Mass\ (kg)},$$

where F is the fraction of injected radioactivity localizing in the lungs, as measured by Tc-99m MAA scintigraphy.

The upper limit of injected activity shunted to the lungs is F x A = 0.61 GBq.

TheraSphere iDOC™ (interactive Dose Ordering Calculator) is an online tool that assists with calculating and ordering dose vials for TheraSphere® treatment.

TheraSphere iDOC™ calculates standard or custom TheraSphere® dose vial size options, based upon user-specified information on the desired tissue absorbed dose (Gy), treatment date and time, lung shunt fraction and anticipated residual waste.

TheraSphere iDOC™ also facilitates electronic ordering of the chosen dose vial size by linking to and pre-populating the TheraSphere® Online Ordering form.

TheraSphere iDOC™ is located on the TheraSphere® website and can be accessed by entering www.therasphere.com into any browser.

When the TheraSphere® dose vial is received, the site will confirm it is the correct activity for the patient treatment by measuring in a dose calibrator.

Patient Catheterization

The following general guidelines are provided to facilitate the selection of the appropriate catheter for the administration of TheraSphere®:

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- A catheter with an internal diameter of ≥ 0.5 mm (0.020 inch) is required to deliver TheraSphere® to the liver. Excessive resistance to flow in the administration system due to a smaller catheter diameter may cause microspheres to be retained in the TheraSphere® Administration Set and in the catheter. This could result in a misadministration.
- Since the delivery of TheraSphere® is dependent on blood flow through the hepatic vasculature distal to the catheter tip, it is important that the catheter does not occlude the vessel in which it is placed to effect delivery of TheraSphere®.

TheraSphere® Administration Set and TheraSphere® Administration Accessory Kit

The TheraSphere® Administration Set (Diagram 1 & 2) consists of a sterile disposable tubing set and one empty sterile vial. The tubing set is made of pre-assembled, sterile components and is for single use only. The pre-assembled tubing set contains a needle plunger assembly and an integrated 20 cc syringe.

The one way valves incorporated in the Administration Set control the flow of liquid such that it will only flow in the appropriate direction. Pulling back on the syringe plunger will fill the syringe from the fluid source. Pushing the syringe plunger will move fluid toward the needle plunger assembly. Prior to the infusion, the Administration Set is manually pre-primed by pushing the sterile flushing solution through the set to purge air from the lines.

The TheraSphere® Administration Accessory Kit (Diagram 2) contains re-usable accessories including an acrylic box base, top shield, removable side shield, bag hook and a RADOS RAD-60R (or equivalent) radiation dosimeter. The TheraSphere® Administration Accessory Kit ensures optimal layout of the TheraSphere® Administration Set and TheraSphere® dose vial to facilitate monitoring of the infusion process and provides beta radiation shielding.

The Accessory Kit should be placed on a sturdy cart or table that is positioned beside the patient, close to the infusion catheter inlet luer fitting. The extension arm on the Accessory Kit facilitates alignment and positioning of the Administration Set / patient catheter connection.

Throughout the administration procedure, the TheraSphere® dose vial remains sealed within the clear acrylic vial shield in which it is supplied. The removable plug at the top of the acrylic vial shield provides access to the septum of the TheraSphere® dose vial. The needle plunger assembly (Diagram 3) is designed to snap into the top of the acrylic shield, and is not easily removed once snapped into place. This provides stability and alignment for the needles which are inserted through the septum when the tabs are pushed down on the plunger assembly.

A constant syringe pressure should be maintained for the duration of each flush, with a flow rate of equal to or greater than 20 cc per minute. One flush is 20 cc as indicated on the barrel of the syringe. Using a flow rate of less than 20 cc per minute (i.e. appropriate to the flow of the native vessel) may decrease the delivery efficiency of the administration system. Flushing should be continued until optimal delivery of TheraSphere® is achieved. A minimum of three flushes for a total of 60 cc is recommended. Infusion pressure should not exceed 30 psi on any flush. The pressure relief valve in the Administration Set has been included to prevent over pressurization.

The RADOS RAD-60R (or equivalent) electronic dosimeter is mounted in a holder on the Accessory Kit. Radiation monitoring of the Administration Set must be used to determine when optimal delivery has been achieved. The ratio of the dose rate reading taken on the electronic dosimeter before and after the infusion can provide a basis for estimation of the dose delivered to the patient.

In order to minimize the potential of a high radiation hand dose, use a hemostat, forceps or towels/gauze when handling parts of the Administration Set after infusion.

Percentage of dose delivered to the patient can be calculated based on ion-chamber radiation detector measurements of the dose prior to administration, compared to measurements of the waste after administration. Before administration the acrylic shield containing the dose is measured at a distance of 30 cm from the detector. After administration the 2L Nalgene waste container inside the beta shield is measured at a distance of

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30 cm from the detector at four rotational positions and these four measurements are averaged. The percentage of dose delivered to the patient can be calculated using the following equation:

$$Percentage\ of\ Dose\ Delivered\ (\%) = [\ 1 - \frac{Waste\ Measurement\ after\ Administration}{Dose\ Vial\ Measurement\ before\ Administration}\ ]\ x\ 100$$

where the *Dose Vial Measurement* is adjusted for the radioactive decay of Y-90 until the time that the *Waste Measurement* is made.

Instructions for TheraSphere® Infusion

The entire contents of the TheraSphere® dose vial are administered to the patient.

The administration instructions must be followed to optimize delivery of the calculated dose.

1. ***Items Required for TheraSphere® Administration***
   - Patient prescription for TheraSphere® (signed Written Directive)
   - Ionization survey meter
   - Geiger-Mueller (GM) contamination meter
   - Spill kit
   - A floor drape applied under the cart in the angiography suite.
   - A sterile drape placed on the cart.
   - Place the following sterile items on the draped cart:
     - Hemostat
     - Scissors
     - Sterile adhesive strips
     - Towels
     - Gauze
   - Place the following items on the cart:
     - Administration Set (in packaging)
       - Verify the expiry date.
     - TheraSphere® Administration Accessory Kit (acrylic box)
       - Remove the top shield
       - Fully extend the stainless steel arm

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4. ***Final Assembly***

- Close the white pinch clamp on the outlet tubing near label 'E'.
- Place the empty 20 mL vial in the holder on the acrylic box and push the relief valve tube into gripper clip 'A'.
- Insert the needle injector assembly into the acrylic dose vial shield. Press on the GREEN cap to lock it in place. You will hear or feel a click or snap.
- Place the inlet tubing through slot 'B' in the acrylic box. Place the outlet tubing through slot 'D' in the acrylic box. Loop the tubing around the side and place the fitting into the holder at 'C'.
- Clamp the priming line at label 'C' with the blue pinch clamp. For sets with no blue pinch clamp, clamp the priming line with hemostats (or equivalent).
- Push the YELLOW tabs on the needle injector assembly all the way down, locking the needles into the dose vial. You will hear or feel a click or snap at the bottom of travel.
- Ensure that the side shield is installed on the acrylic box. Place the top shield on the acrylic box with the sloped shield towards slot 'D'. Ensure that the tubing is not pinched or kinked.
- Move the cart close to the patient. Lower the bed to lowest position.
- Place a sterile towel under the extension arm holder 'E', and under holder 'C'.
- Place a sterile towel across the gap between the acrylic box and the patient.
- The Interventional Radiologist (IR) will flush the infusion catheter to ensure flow. Replace the infusion catheter if it is damaged or does not have satisfactory flow. Do not use a catheter extension or extra fittings. Replace the catheter if it is too short.
- Disconnect the outlet tubing labeled 'E' from the priming tubing at holder 'C'. Firmly connect the outlet tubing 'E' to the catheter.
- Place the catheter connection into the slotted holder 'E' at the end of the extended arm. Outlet tubing 'E' must be above the holder, with the infusion catheter hanging vertically below.
- The IR will verify the infusion catheter position.
- Release the white pinch clamp from the outlet tubing. Dents in tubing may be reduced by rolling outlet tubing with fingers.

5. ***TheraSphere® Administration***

ATTENTION: Beta radiation fields can be very high during microsphere transfer. Stand behind beta shielding or maintain distance.

- Record the starting time of the administration.
- Infuse TheraSphere® Y-90 glass microspheres using steady pressure on the syringe plunger. Infuse continuously until the syringe is empty (≥ 20 cc per minute).

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- Install the bag hook
- Electronic dosimeter (RADOS RAD 60R or equivalent)
  - Turn the dosimeter on and set to mR/h
  - Clip the dosimeter to its bracket on the acrylic box
- Saline bag (in packaging) or bottle (minimum 100 mL)
- Alcohol swabs
- 2L Nalgene waste container with beta shield
- TheraSphere® dose vial, in lead pot

2. Administration Set Priming

- Open the Administration Set packaging and remove the Administration Set and 20 mL empty vial.
- Insert the white non-vented spike into the saline bag (or bottle). Hang the saline bag on the bag hook.
- Insert the white vented spike into the empty 20mL vial.
- Remove the RED RUBBER cap shield cap from the needle injector assembly. Place the needle injector assembly on a sterile surface.
- Slowly fill and discharge the syringe to remove air from the Administration Set tubing and syringe. Continue priming vigorously with full pressure until there are no bubbles in the lines and there are continuous streams of saline flowing out of both needle holes in the needle injector assembly.
- Fill the syringe when priming is complete.

3. Dose Vial Preparation

- Lift the TheraSphere® dose vial in its lead pot and tilt the lead pot back and forth to 90 degrees to wet any microspheres on the vial septum. Tap the bottom of the lead pot firmly on a hard surface. Place the lead pot into the pot holder in the acrylic box base.
- Remove the lead pot lid and place it upside down on a non-sterile surface.
- Use a hemostat to remove the purple seal from the top of the dose vial acrylic shield. Discard the seal in the Nalgene waste container.
- Use a sterile adhesive strip to remove the dose vial acrylic shield plug. Discard the plug and sterile adhesive strip in the Nalgene waste container.
- Use an alcohol swab and a hemostat to swab the dose vial septum. Discard the swab in the Nalgene waste container.
- Record the dosimeter initial reading for the dose vial (mR/h).
- Measure and record the initial radiation field for the patient, using an ionization survey meter.

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NOTE: If the infusion pressure is over 30 psi, excess fluid will drip into the vented 20 mL vial. If this occurs, reduce the pressure being applied on the syringe until no flow is seen going into the vented vial. If the syringe flow is <20 cc per minute (i.e. appropriate to the flow of the native vessel) this may decrease the delivery efficiency of the administration system and result in higher residual in waste.

- Observe the outlet line and catheter for proper operation. If a problem is observed, inform the team and take corrective action.
- Re-fill the syringe for subsequent flushes by pulling back on the syringe plunger. A minimum of 3 flushes (60 cc total) are recommended. Continue flushes until the desired dosimeter reading is achieved.
- Record the number of flushes completed.
- Record the time that administration was completed.
- Record the final dosimeter reading.
- Measure and record the final radiation field for the patient using an ionization survey meter.

6. Disassembly

- Cut the inlet tubing at the indicated position.
- Remove the acrylic box top shield and side shield.
- The IR will remove the infusion catheter from the patient and lift the catheter connection out of the extended holder 'E'. Do not disconnect the catheter from the outlet tubing. Use care to control the tip of the infusion catheter and guide catheter as these may be contaminated with microspheres. Use gauze, a small towel, or hemostat to handle the catheters for radiation protection. Any item that has come in contact with microspheres is considered contaminated.
- Place all contaminated waste into the Nalgene waste container (in its beta shield), including the following:
  - Infusion catheter and guide catheter with attached tubing and towels/gauze
  - dose vial with attached needle injector assembly
    - lift the lead pot and dump out the dose vial.
  - contaminated items such as gauze, towels and gloves
- Cap the Nalgene waste container and place the acrylic lid on the beta shield. Remove for measurements to determine percent delivery and for disposal.
- Use a GM contamination meter to check IR's hands for contamination.
- Survey all staff leaving the room with the GM contamination meter.

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7. Cleanup and Waste Disposal

- Use a GM contamination meter to check for contamination on the cart, lead pot, equipment, and the areas under the catheter connection and cart.

  NOTE: Radiation from fluoroscopy, the patient, and the waste container will affect the ability to detect and measure contamination.

- Decontaminate and/or dispose of items as appropriate.

- As required, clean the TheraSphere® acrylic box with water, mild soap and a clean soft cloth. Alcohol wipes may be used (minimize alcohol contact with glued joints – alcohol degrades the glue over an extended time). Chlorine (bleach) disinfectants are also acceptable. Always use a clean soft cloth. **Do not use** industrial cleaner wipes, ammonia or abrasives to clean the acrylic parts.

- Replace the top and side shields on the acrylic box. Retract the extension arm and remove the bag hook. Turn off the dosimeter. Store the kit.

Troubleshooting

Problem	Action
1. Difficulty priming the Administration Set.	Verify that the tubing in the Administration Set is not pinched or kinked. Verify that the pinch clamp is not closed. The first priming flush should be performed very slowly to prevent small bubbles from forming in tubing and fittings. Subsequent priming flushes should be vigorous with full pressure. If saline leakage is observed, ensure connections are tight. If the issue cannot be identified and corrected, replace the Administration Set with a new one. Notify the manufacturer of the problem.
2. Leakage that may contain microspheres.	**Attention:** Any leakage from the dose vial, injector assembly, tubing 'D' through 'E', or the catheter connection at 'E' is likely to contain microspheres. Assess the extent of the leak. Ensure that the needle injector is properly inserted into the dose vial. If warranted, abort the infusion, disassemble the Administration Set and commence decontamination procedures. During decontamination, investigate the cause of the leak.
3. Leakage of saline during infusion.	Leakage observed from the syringe, the saline bag/bottle, or tubing lines 'A', 'B' and 'C' will only contain saline. If saline leakage is observed during TheraSphere® Administration, maintain steady pressure on the syringe. **Do not stop the flush.** At the end of the flush, address the saline leakage. Ensure that priming tube 'C' is clamped. Ensure connection to the syringe is tight. Adjust the saline bag or bottle connection.

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Problem	Action
4. Blood begins to flow back to the TheraSphere® dose vial, when the catheter is connected and the syringe is not being pushed.	This indicates that one of the fittings or the TheraSphere® dose vial septum is compromised. The procedure should be aborted if the issue cannot be identified and corrected. If issue has been identified and corrected, continue with administrations and observe the system for possible leaks (see Problem 2).
5. Excessive fluid flow resistance is experienced during infusion or Difficulty achieving the desired dosimeter reading.	Verify that the white pinch clamp is open. Verify that the tubing between the syringe and dose vial are not pinched or kinked. Verify that the tubing between the dose vial and catheter are not pinched or kinked. Verify that the yellow tabs are pushed all the way down. Apply sufficient pressure on the syringe to cause fluid to flow into the pressure relief vial. Apply and release pressure on the syringe several times rapidly. This may clear a collection of microspheres at the tip of the outlet needle. Close the white pinch clamp before performing any actions with the catheter. Verify that there is no blood coagulation or damage in the catheter. **Attention:** There may be microspheres in the outlet line and catheter. Use standard radiation safety methods to assess the components before handling. Use remote handling tools as appropriate.

RADIATION DOSIMETRY

The yttrium-90 in TheraSphere® is a constituent of an insoluble matrix thereby limiting irradiation to the immediate vicinity of the microspheres. The average range of the radiation in tissue is 2.5 mm. One GBq (27 mCi) of yttrium-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of yttrium-90 is 3.85 days: thus, the radiation dose delivered by yttrium-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

HOW SUPPLIED

TheraSphere® is available in six dose sizes: 3 GBq (81 mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi) and 20 GBq (540 mCi). Custom dose sizes available: 0.5 GBq increments between 3 and 20 GBq. The dose is supplied in 0.6 mL of sterile, pyrogen-free water in a 1.0 mL vee-bottom vial sealed within a clear acrylic vial shield.

Preassembled single use TheraSphere® Administration Sets are provided. Each new user site is provided with a TheraSphere® Administration Accessory Kit containing re-usable components. The kit includes an acrylic box, a RADOS RAD-60R (or equivalent) radiation dosimeter and a beta shield for the waste jar.

HANDLING AND STORAGE

Each TheraSphere® dose vial contains one of six available dose sizes of yttrium-90, a high-energy beta emitter. Even with low-density materials such as the acrylic vial shield, the attenuation of beta particles gives rise to Bremsstrahlung radiation that requires lead shielding. Users should avoid exposure by leaving the vial in the acrylic product container, and by leaving the acrylic container in the lead shield unless required for measurement.

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Handle the dose in the acrylic shield with remote handling tools if removed from the lead pot. Finger-ring dosimeters should be worn in the orientation most likely to record the highest exposure to the fingers.

The TheraSphere® dose vial should not be removed from its acrylic vial shield. It should be stored in the lead pot and acrylic shield in which it is packaged. The TheraSphere® dose vial, TheraSphere® Administration Set, and TheraSphere® Administration Accessory Kit should be stored at room temperature. The requirements of the applicable regulatory agency for safe handling and storage of radioactive materials should be consulted and must be followed.

DISTRIBUTION

TheraSphere® is manufactured and distributed for Biocompatibles:

Biocompatibles UK Ltd, a BTG International group company
Chapman House
Farnham Business Park
Weydon Lane
Farnham
Surrey GU9 8QL
UK
www.therasphere.com

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Explanation of Symbols on TheraSphere® Product Labels

Manufacturer.

Date of manufacture.

Caution, consult package insert for warnings and precautions.

Consult package insert.

Do not re-use.

Sterilized using irradiation.

Sterilized using ethylene oxide.

Quantity of items in package.

Batch code or lot number.

Use-by date.

Symbol Relevant to TheraSphere® Product

Does not contain latex.

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Diagram 2

TheraSphere® Administration Accessory Kit
(shown assembled with TheraSphere® Administration Set)

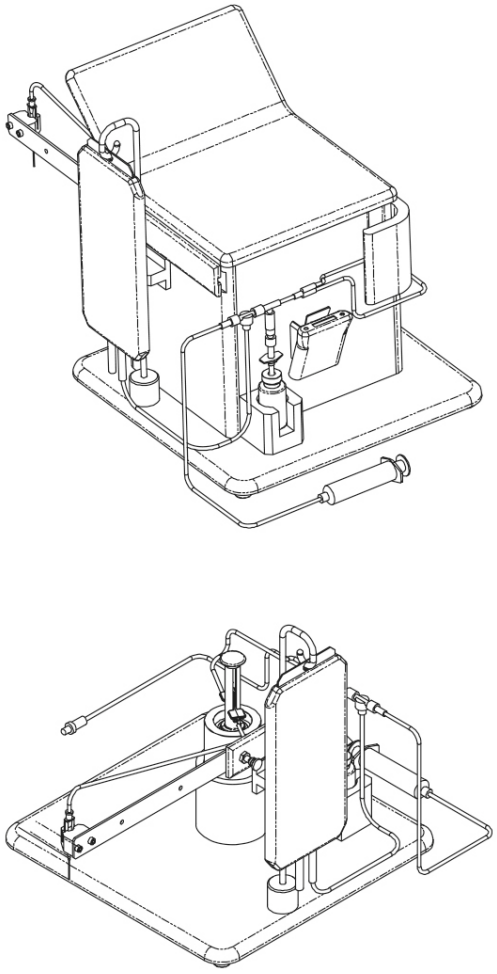

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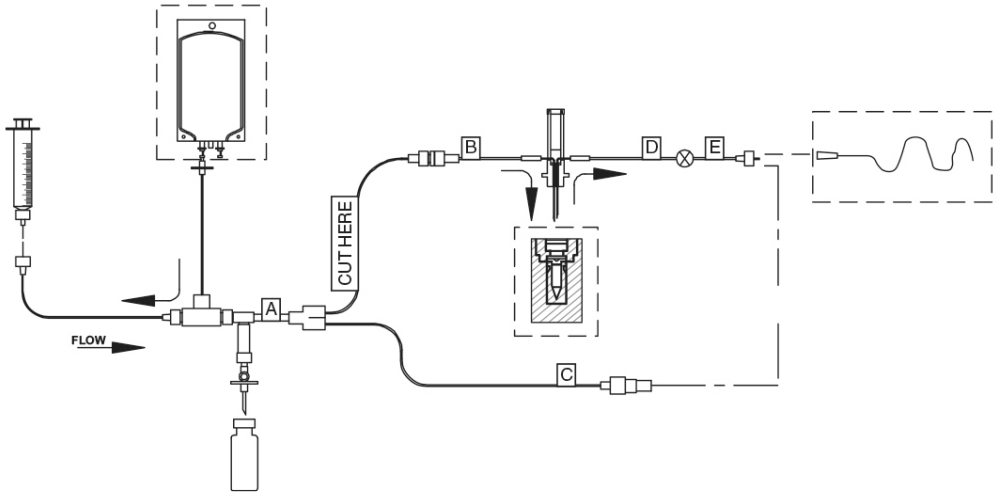
Diagram 1

TheraSphere® Administration Set



Items in dashed boxes are not supplied with the Administration Set

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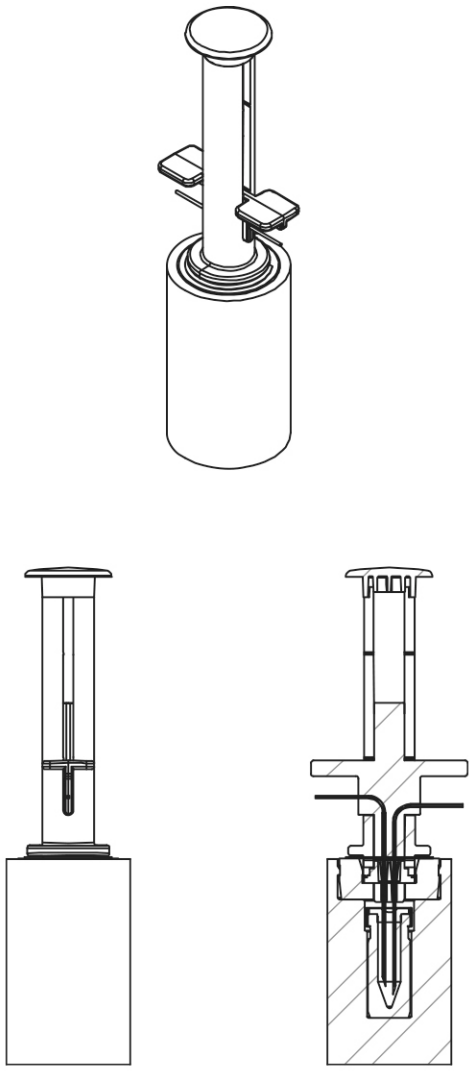
Diagram 3
Illustration of the Plunger Assembly Inserted into the Dose Vial in the Acrylic Shield



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(pages 29 through 32 of the USPI are blank and are not added here)

Appendix VII: Dosing Modification and Toxicity Management Guidelines

Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (below), **permanently discontinue study drug/study regimen for the following conditions:** – Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen – Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1:** No dose modification **Grade 2:** – Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: • The event stabilizes and is controlled. • The patient is clinically stable as per Investigator or treating physician's clinical judgement. • Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3:** – Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4**: – Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus and also liver function tests as noted earlier in the protocol).	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

Specific Immune-Mediated Reactions

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)		
Any	General Guidance	– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
Grade 1 (asymptomatic, clinical, radiographic, or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	– Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.
Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	– Hold study drug/study regimen dose until resolution to Grade ≤1. – If toxicity worsens, then treat as Grade 3 or Grade 4. – If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	– Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
Grade 3 or 4 Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation]	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
		– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea / Colitis		
Any Grade	General Guidance	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 Diarrhea: stool frequency of <4 over baseline per day Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated	No dose modifications.	– Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity worsens, then treat as Grade 3 or Grade 4. – If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	– Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
Grade 3 or 4 Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; limiting self-care ADL Grade 4 diarrhea: life threatening consequences) Grade 3 colitis: severe abdominal pain, fever; ileus; peritoneal signs Grade 4 colitis: life-threatening consequences, urgent intervention indicated	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis		
Any elevation in AST, ALT or TBIL (i..e, > ULN)	General Guidance	– Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
Grade 1 AST, ALT, or TBIL AST or ALT > ULN x 3 ULN and/or TBIL > ULN – 1.5 x ULN	– No dose modifications. – If it worsens, then treat as described for elevations in the row below.	Continue LFT monitoring per protocol.
Grade 2 AST, ALT, or TBIL AST or ALT >3.0 – 5 ×ULN and/or TBIL >1.5 – 3× ULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN. – If toxicity worsens, then treat as described for elevations in the row below. – If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN, or baseline, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Disyycuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
AST or ALT >5.0×ULN and/or	For elevations in transaminases ≤8 × ULN or elevations in TBIL ≤5 × ULN:	– Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
TBIL >3.0×ULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN, or baseline – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN, or baseline within 14 days and after completion of steroid taper. – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN or baseline within 14 days. For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis (i.e., elevated alkaline phosphatase) and in the absence of any alternative cause.[b] Note that this does not apply to the week 2 (cycle 3) post Y90-RE when this is usually seen and subsides in the upcoming weeks (cycle 4). Also for those with Gilbert's syndrome, would need to rely on AST/ALT rather than total bilirubin.	immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Nephritis or renal dysfunction (elevated serum creatinine)		
Any Grade	**General Guidance**	– Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
Grade 1 (serum creatinine > ULN to 1.5 × ULN)	No dose modifications.	Monitor serum creatinine weekly and any accompanying symptoms. – If creatinine returns to baseline, resume its regular monitoring per study protocol. – If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	– Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity worsens, then treat as Grade 3 or 4. – If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	– Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN	Permanently discontinue study drug/study regimen.	– Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)		
Any Grade (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	General Guidance	– Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
Grade 1	No dose modifications.	– Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
Grade 2	– For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity worsens, then treat as Grade 3. – If toxicity improves to Grade ≤1 or baseline, then resume	– Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
		consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids sooner. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
Grade 3 or 4	**For Grade 3:** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4 (or life-threatening):** – Permanently discontinue study drug/study regimen.	– Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased included in this section		
Any Grade (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	– Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
Grade 1 including those with asymptomatic TSH elevation	No dose modifications.	– Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
		cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2 Including those with symptomatic endorcinopathy	– For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short term- corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3 or 4	– For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. – Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)		
Any Grade (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	General Guidance	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
Grade 1	No dose modifications.	– See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
Grade 2	– For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. – For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. – If toxicity worsens, then treat as Grade 3 or 4. – Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	– Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
Grade 3 or 4	**For Grade 3:** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** – Permanently discontinue study drug/study regimen. –	– Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)		
Any Grade	General Guidance	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
		severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	– Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	– Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). **MYASTHENIA GRAVIS:** – Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. – If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. **GUILLAIN-BARRE:** – It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
		– Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3:** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. **MYASTHENIA GRAVIS:** – Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. – If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. **GUILLAIN-BARRE:** – It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. – Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis		
Any Grade	General Guidance Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	– The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study	– Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. – Consider using steroids if clinical suspicion is high.

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
*Treat myocarditis with mild symptoms as Grade 2.	drug/study regimen is held, resume after complete resolution to Grade 0.	
Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	– If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. – If Grade 3-4, permanently discontinue study drug/study regimen.	– Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")		
Any Grade	General Guidance	– Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.

Severity (CTCAE v 5.0)	Dose Modifications	Toxicity Management
		– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	No dose modifications.	– Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	– Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** – Permanently discontinue study drug/study regimen.	– Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Appendix VII Continued: Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Appendix VIII Continued: Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.