Cedars Sinai

CANCER

RESEARCH PROTOCOL

Leveraging Immunotherapy For Tumor downstaging to Milan Criteria in patients with Hepatocellular Carcinoma

Protocol Number: IIT2025-03-YANG-LIFT-HCC

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Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BCLC	Barcelona Clinic Liver Cancer stage
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
EKG	Electrocardigram
EOS	End Of Study
EOT	End of Treatment
FACS	Fluorescence-activated cell sorting
FU	Follow Up
GEE	Generalized Estimating Equations
H&P	History & Physical Exam
HCC	Hepatocellular Carcinoma
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protections Program
ICI	Immune Checkpoint Inhibitor
imAE	Immune-mediated Adverse Event
INR	International Normalized Ratio
IV (or iv)	Intravenously
LMM	Linear Mixed-effects Model
LRT	Locoregional Treatment
LT	Liver Transplantation
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
QMC	Quality Management Core
RETREAT	Risk Estimation of Tumor Recurrence After Transplant score
RFA	Radiofrequency Ablation
RFS	Recurrence-Free Survival
SAE	Serious Adverse Event
scRNAseq	Single-cell RNA sequencing
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SOC	Standard of Care
SPGT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACE	Transarterial Chemoembolization
TARE or Y90	Transarterial Radioembolization
TTP	Time to Progression
UCSF	University of California, San Francisco (transplant criteria)
WBC	White Blood Cells

STUDY SCHEMA

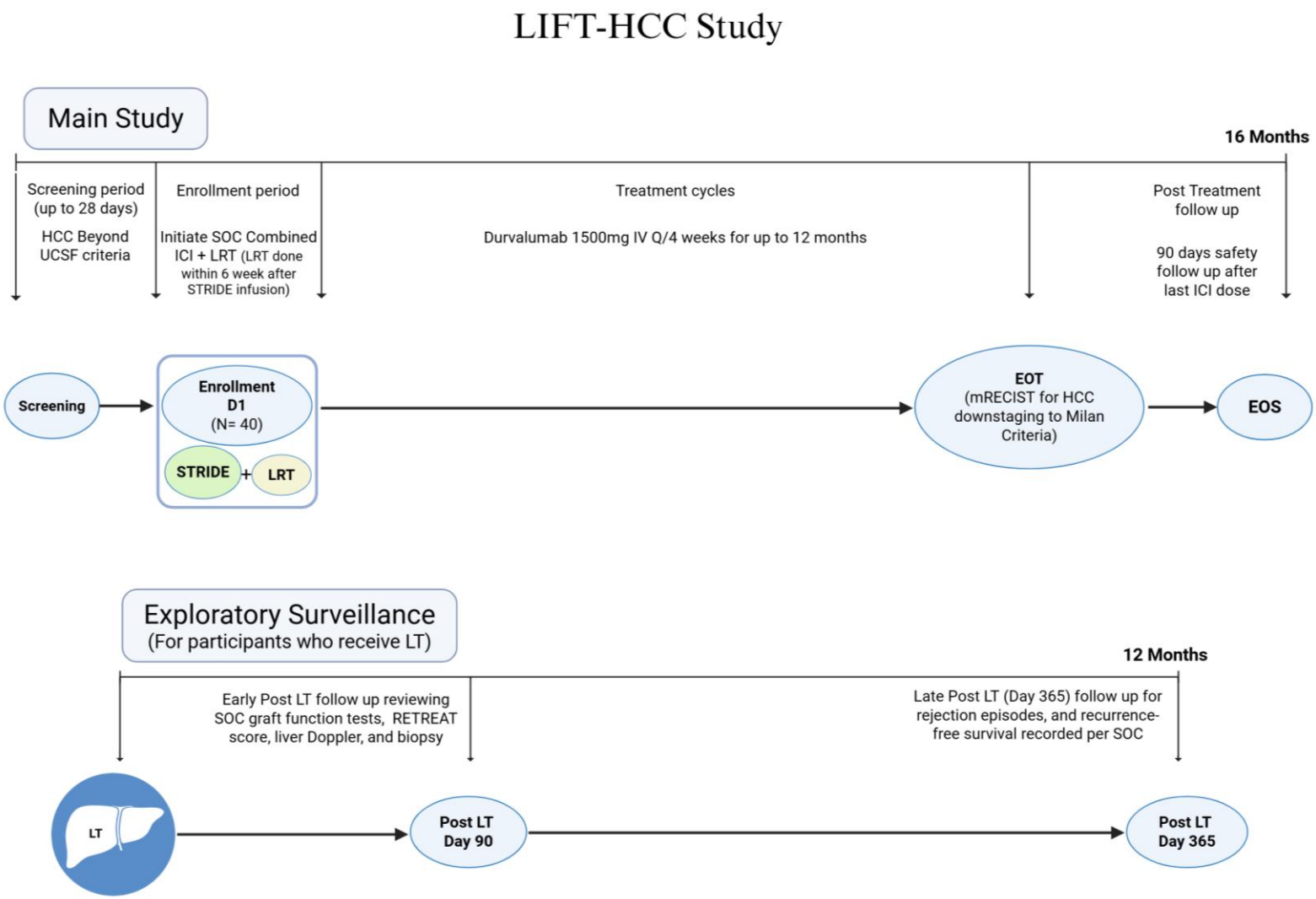

Figure 1. Study schematic diagram of the study design

Abbreviations and Notes: Immune checkpoint inhibitor, EOS: End of study (Day 90 after last research-related ICI dose), EOT: End of Treatment (marks the patient's last ICI dose given under study authority. If the treating physician later continues durvalumab or another ICI as standard of care, that therapy is documented as concomitant medication and does not reopen or extend the study calendar for that participant. LRT: (TACE, TARE-Y90, or RFA) Locoregional therapy, TACE: Transarterial Chemoembolization, Y90: (also referred as TARE) Transarterial Radioembolization, RFA: Radiofrequency Ablation, LT: Liver transplantation, mRECIST: Modified Response Evaluation Criteria In Solid Tumors, RETREAT score: se section 11.6, SOC:

Standard of care, Start STRIDE regimen: Tremelimumab 300mg IV once + Durvalumab 1500mg IV on C1D1, followed by Durvalumab 1500mg IV once every 4 weeks, UCSF: University of California, San Francisco.

STUDY SUMMARY

Study Title	Leveraging Immunotherapy For Tumor downstaging to Milan Criteria in patients with Hepatocellular Carcinoma (LIFT-HCC)
Short Title	LIFT-HCC
Protocol Number	IIT2025-03-Yang-LIFT-HCC
Study Phase	II
Study Design and Methods	Phase II, single-cohort, open-label, clinical trial designed to assess the success of combining Immune Checkpoint Inhibitor (ICI) and Locoregional Therapy (LRT) in intermediate to advanced stage HCC for tumor downstaging to Milan Criteria.
Study Duration	Approximately 4 years (36 months accrual + 12 months treatment/downstaging window + 3 months safety follow-up and data lock)
Study Site	Cedars-Sinai Medical Center and other Cedars-Sinai participating locations
Primary Objective	Assess the success rate of combining ICIs and LRT (as neoadjuvant treatment) in tumor downstaging to Milan Criteria within 12 months of baseline STRIDE dose in patients with HCC exceeding the UCSF criteria.
Number of Subjects	41
Study Population	Age ≥ 18 Patients with HCC beyond UCSF criteria, ECOG performance status ≤ 2, and Child-Pugh A or B7.
Study Intervention	STRIDE Regimen (Tremelimumab 300 mg AND Durvalumab 1500 mg) combined with LRT (TACE, TARE, or RFA)
Statistical Methodology	Simon two-stage design

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

In 2022, liver cancer was diagnosed in more than 860,000 individuals, making it the sixth most common type of cancer, and caused nearly 760,000 deaths, ranking third in cancer-related mortality (7.8% of all cancer deaths). Hepatocellular carcinoma (HCC), the most common type of liver cancer, accounts for 75-85% of these cases [1, 2] Liver transplantation (LT) is the standard treatment for patients at risk of liver-related death, including those with HCC, providing a curative option that enhances overall survival (OS) and recurrence-free survival (RFS) [3]. It offers the potential to eliminate both HCC tumors and the underlying diseased liver. However, it is generally reserved for patients with early-stage HCC. The increased likelihood of recurrence in patients with more advanced disease, combined with the limited availability of donor organs, makes LT primarily suitable for those in the early stages. For patients with HCC exceeding the Milan criteria, locoregional treatments (LRTs) can help reduce tumor size, enabling them to qualify for LT, with successful downstaging rates reported between 30-70% depending on the initial tumor burden [4-6]. Among those with a larger tumor burden at initial presentation, successful downstaging rate decreases to less than 30%, highlighting the unmet need for a robust, successful downstaging strategy.

Immune checkpoint inhibitors (ICIs) have demonstrated significant efficacy both as an adjuvant treatment for surgically treated HCC and as a first-line therapy for advanced-stage cases. Due to their success in advanced HCC, there is growing interest in exploring their use in earlier stages of the disease. TACE, TARE, and ablation are key types of LRTs used for early and intermediate-stage HCC, serving as essential treatments for downstaging or reducing the risk of waitlist dropout in patients awaiting live LT. Recent studies of using ICI in HCC treatment have sparked interest in utilizing immunotherapy as a pre-transplant downstaging strategy. The growing body of evidence supports the use of ICIs in reducing tumor burden and increasing eligibility for LT, offering hope for curative treatment in patients with advanced HCC.

However, integrating ICIs into the tumor downstaging and LT pathway demand thoughtful safety planning. While these agents boost anti-tumor immunity, they can also heighten the chance of allograft rejection, so clinical teams must balance efficacy with graft protection [7]. Early reports from case series to small cohort studies suggest rejection rates may not differ markedly from non-ICI recipients[8], yet the lack of large-scale, controlled studies limits definitive conclusions.

Practical safety strategies are emerging. Extending the washout interval between the final ICI dose and transplantation appears to lower rejection risk, offering a workable buffer[9]. Ongoing questions include how factors such as patient age, total ICI exposure, and concurrent therapies interact with this washout period. Well-designed prospective trials are still needed, but these evolving precautions provide a foundation for safer ICI use for tumor downstaging and potential curative transplantation.

1.2 Study Agent(s) Background and Associated Known Toxicities

Several ICI combination therapies have been tested in clinical trials, such as atezolizumab plus bevacizumab in the IMbrave150 trial [10], and durvalumab with tremelimumab (STRIDE regimen) in the HIMALAYA trial, see details below [11]. Both have shown promising results in treating advanced HCC. Additionally, camrelizumab combined with rivoceranib which was evaluated in in CARES- trial [12] is currently under FDA review, while atezolizumab-bevacizumab and durvalumab-tremelimumab combinations have been approved for advanced-stage HCC treatment. In addition to retrospective cohort studies reporting the safety and effectiveness of combining ICIs and LRTs [13], two Phase 3 randomized controlled trials have evaluated the combination of ICIs, LRTs, and tyrosine kinase inhibitors (TKIs) for intermediate-stage HCC. The EMERALD-1 trial [14] assessed TACE combined with durvalumab ± bevacizumab for unresectable HCC patients eligible for embolization. Similarly, the LEAP-012 trial [15] explored the combination of lenvatinib, pembrolizumab, and TACE for intermediate-stage HCC. Both trials have shown promising results with HR of 0.77 (95% CI:0.61–0.98; P = 0.032), grade 3–4 treatment-related adverse events occurred in 45 % of patients receiving durvalumab + bevacizumab, most commonly hypertension and anemia for EMERALD-1 trial. HR of 0.66 (95% CI:0.51–0.84; P < 0.01) for LEAP-012 trial in progression-free survival, with Grade 3–4 treatment-related adverse events were reported in 71 % of patients in the combination arm vs 31 % with TACE alone; hypertension, proteinuria and elevated liver enzymes were the most frequent events. Taken together, these data demonstrate that ICI-based combinations can down-stage intermediate-stage HCC with manageable toxicity, as grade 3–4 AE rates in the 45–70 % range are considered acceptable for contemporary HCC treatments. Further supporting the potential of these combination therapies in treating intermediate-stage HCC and successful downstaging.

Phase III HIMALAYA trial

The STRIDE regimen—comprising a single priming dose of tremelimumab (300 mg) combined with durvalumab (1,500 mg every 4 weeks)—was evaluated in the Phase III HIMALAYA trial as a first-line treatment for patients with unresectable hepatocellular carcinoma (HCC)[16]. Trial outcomes shown below:

Table 1.1: Summary of Phase III HIMALAYA Trial Outcomes

Efficacy Outcomes	
Overall Survival (OS)	Median OS with STRIDE was 16.4 months, compared to 13.8 months with sorafenib. Hazard Ratio (HR) for death was 0.78 (95% CI: 0.66–0.92; p = 0.0035), indicating a statistically significant improvement. At 4 years, 25.2% of patients treated with STRIDE were alive, versus 15.1% in the sorafenib group.
Objective Response Rate (ORR)	STRIDE achieved an ORR of 20.1%, compared to 5.1% with sorafenib.

Duration of Response	Median duration of response was 22.3 months for STRIDE, versus 18.4 months for sorafenib.
Progression-Free Survival (PFS)	Median PFS was similar between the two groups: 3.8 months for STRIDE and 4.0 months for sorafenib.
Safety and Toxicity	
Adverse Events (AEs)	Grade 3 or 4 AEs occurred in 50.5% of patients receiving STRIDE, compared to 52.4% with sorafenib. Treatment discontinuation due to AEs was less frequent with STRIDE (13.7%) than with sorafenib (16.8%).
Immune-Mediated Adverse Events (imAEs):	imAEs requiring high-dose corticosteroids occurred in 20.1% of patients on STRIDE. Only 5.7% discontinued treatment due to imAEs. Common imAEs included hypothyroidism, hepatic events, diarrhea/colitis, and rash.
Correlation with Outcomes	Patients experiencing imAEs had a median OS of 23.2 months, compared to 14.1 months in those without imAEs, suggesting a potential association between immune activation and improved survival.

These findings support the STRIDE regimen as an effective and tolerable first-line treatment option for patients with unresectable HCC, offering improved survival outcomes with a manageable safety profile.

1.3 Study Rationale

ICI therapy has demonstrated high efficacy in treating locally advanced HCC; however, their value in earlier stage disease to downstage tumors to Milan criteria remains untested in prospective trials. The present Phase II study therefore focuses on determining the proportion of patients who achieve successful radiologic downstaging to Milan criteria within 12 months of initiating the combined therapy and evaluate the regimen's safety and effectiveness in this earlier stage population, tracking immune-related adverse events, and treatment tolerability during the 12-month and the 3-month post treatment windows.

Data on LT listing, wait-list progression, and post-transplant graft outcomes will be collected, but these endpoints will be exploratory status; they will not gate primary study completion.

By anchoring the trial on a near-term, clinically actionable milestone (downstaging within one year) and rigorous safety monitoring, the study will generate the first prospective evidence for using ICI-based combination therapy to expand curative options in intermediate-stage HCC. Exploratory transplant-related outcomes and planned biospecimen analyses will supply additional insights for future precision-medicine strategies but will not extend the primary timeline or influence stopping decisions.

The study will incorporate standard-of-care (SOC) safety monitoring parameters and direct investigator oversight throughout the treatment and post-treatment follow up. Furthermore, the longitudinal collection of biospecimens will support translational research aimed at identifying novel biomarkers predictive of treatment response and long-term outcomes. This integrative approach will not only enhance clinical understanding but also advance the development of precision strategies in managing HCC patients eligible for transplantation.

1.4 Correlative Measures

We will conduct paired liver tumor biopsy during the lead-in phase of the clinical trial, and blood and stool will be collected at baseline and every 6-8 weeks after starting STRIDE treatment to understand predictors of response to ICI. We will aim to characterize the microenvironment to determine responders vs. non-responders for downstaging; recurrence risk stratification after ICI successful downstaging and liver transplantation.

We will test checkpoint molecules (Tim3, CTLA4, PD1, PDL1), IFNg, IL27 in circulation/serum, in tumor/liver, CD8 cytotoxic cells (cell numbers, markers of exhaustion, markers of cytotoxicity (Granzymes, Perforin), IFNg, markers of activation Innate cytotoxic cells (NK, ILC1; cell numbers, markers of exhaustion, markers of cytotoxicity (Granzymes, Perforin), neutrophils (long-lived= tumor promoting neutrophils), tumor associated macrophages/DC (pro-inflammatory (former M1) vs anti-inflammatory (former M2); cDC1 vs cDC2 B cells (Bregs (IL10+)-poor prognosis; B cells -good prognosis), Tregs (numbers, suppressor functions, conversion to effect cells (by scRNAseq trajectory analyses), microbiota analysis (if we go this way). Proposed correlative studies will involve 1) scRNA seq of biopsies vs. PBMC; 2) spatial analyses (biopsies); 3) multi-color FACS; 4) cytokine multiplex; and 5) microbiota 16s seq -> metabolomics.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To assess the success rate of combining ICIs and LRT (as neoadjuvant treatment) in tumor downstaging to Milan Criteria within 12 months of baseline STRIDE treatment in patients with HCC exceeding the University of California San Francisco (UCSF) criteria.

2.2 Primary Endpoint

- Proportion of evaluable patients whose tumor burden meets Milan criteria on contrast CT/MRI within 12 months of baseline STRIDE treatment, confirmed by using mRECIST assessment.

2.3 Secondary Objectives

- To assess the safety and tolerability of combining ICIs and LRT during the 12-month downstaging window.
- To determine the ORR per mRECIST at months 3, 6 and 12.
- To determine PFS within the 12-month period.

2.4 Secondary Endpoints

- Incidence, severity and relatedness of adverse events, graded by NCI CTCAE v5.0.
- ORR which includes the complete response (CR) and partial response (PR) rate assessed using mRECIST criteria at months 3, 6 and 12.
- PFS assessed by measurement of time from first dose to radiologic progression or death, censored at 12 months.

2.5 Exploratory Objectives

- Describe rates of LT listing, receipt of LT, and post-LT outcomes (graft survival, rejection, RETREAT score, recurrence-free survival), correlate washout interval between last ICI dose and LT with graft rejection and recurrence.
- Explore associations between novel biomarkers (tumor immune microenvironment, circulating immune cells, cytokines, microbiome) and clinical outcomes (downstaging success, PFS, post-LT outcomes.

2.6 Exploratory Endpoints

- LT listing rate and proportion undergoing LT within study follow-up, allograft rejection rate and time to rejection, RETREAT score distribution and post-LT recurrence-free survival.
- Correlative biomarker changes (immune profiling, microbiome shifts) versus clinical outcomes.

3.0 STUDY DESIGN

This is a Phase II prospective, single-cohort, open label clinical trial designed to evaluate the efficacy and safety of combining ICI and LRT in intermediate to advanced stage HCC (tumor burden beyond the UCSF) for tumor downstaging to Milan Criteria.

The study will enroll 41 evaluable adult participants (≥18 years old) with histologically, cytologically, or radiologically confirmed HCC and a life expectancy of at least 12 months. All participants must be beyond UCSF criteria for LT at the time of study entry.

The study is structured into three sequential periods:

- **Screening Period**: Patients will undergo eligibility assessments including imaging, laboratory testing, and medical history evaluation.
- **Treatment Period:** Eligible patients will receive combination therapy beginning with the administration of immune checkpoint inhibition using the STRIDE regimen (durvalumab plus tremelimumab) in conjunction with clinician-selected LRT (e.g., TARE, TACE or ablation). Administration of Durvalumab therapy will continue every 4 weeks until either successful downstaging to within Milan criteria or a maximum of 12 treatment cycles, whichever occurs first.

- **Post-Treatment Follow-up Period**: All patients will be followed for 3 months after completion of treatment period for post treatment safety monitoring. For participants who receive LT after the study, exploratory Post-LT Surveillance follow up for up to 365 days Post LT.

Throughout the study, standard-of-care (SOC) safety monitoring parameters and direct investigator oversight will be implemented to minimize treatment-related adverse events. See study schema (Figure 1) and Time and Events (Section 6.7) for reference.

3.1 Rationale for Study Design

The design of this trial reflects an urgent clinical need to explore effective downstaging strategies in patients with intermediate to advanced HCC who are beyond current transplant eligibility criteria. ICIs have demonstrated robust efficacy in advanced-stage HCC, and recent RCT studies suggest that their combination with LRTs may yield synergistic effects in tumor control. However, no prospective studies to date have systematically evaluated this combination specifically for the purpose of downstaging to Milan criteria.

Patients whose HCC exceeds Milan/UCSF transplant criteria yet remains confined to the liver currently lack effective treatment options. LRT alone rarely yields durable control, and existing systemic regimens have not been prospectively tested as neoadjuvant downstaging strategies. Preclinical and clinical signals indicate that ICI can potentiate LRT-induced tumor antigen release, creating a synergistic “in situ vaccine” effect [17]. Yet no prospective trial has quantified how often this combination can downstage tumors to Milan criteria within a clinically actionable timeframe.

Eligible local therapies include TACE, ablation, or resection. Radiotherapy were not included because they are not part of the standard downstaging practice at our institution and are not routinely offered in our transplant program [18].

To address this gap, we chose a Phase II, open-label design with an interim efficacy/futility stopping rule (Simon optimal two-stage). The trial’s primary endpoint provides a clear, near-term measure of therapeutic success and aligns with real-world transplant-listing practices. Focusing follow-up on the first year (active treatment period) also limits calendar time and directly answers the question most relevant to multidisciplinary tumor boards: Can this regimen create new surgical or transplant options, and is it tolerable while doing so?

Published series suggest that downstaging success rates with SOC LRT alone are approximately 25–40% [19]. While it is not possible to fully disentangle the contributions of local therapy versus ICI, exploratory analyses will collect detailed response and outcome data to aid interpretation.

Although all patients will be monitored for listing, transplantation, and post-LT outcomes, these events are exploratory, ensuring they do not delay primary analysis. Given variability in transplant wait times and post treatment safety measures, data completeness may be limited; these analyses will therefore be exploratory and hypothesis-generating. This will allow the study to first, quantify efficacy and safety of the regimen in intermediate advanced -stage HCC without waiting years for graft outcomes, second, generate

the first prospective benchmark for down-staging success, progression-free survival, and immune-related toxicity in this setting. And third, provide correlative biospecimens to interrogate immune and microbiome predictors of response.

3.2 Rationale for Study Population

The total number of subjects involved in the study will be 41. Of those, we estimate that approximately 30% will be cisgender women. The estimated racial/ethnic breakdown of the study may approximately be that 10% may be Black or African American, 20% may be Asian, and 5% may be Native Hawaiian-Pacific Islander. Approximately 40% of the subjects may be Hispanic. While this provides only an estimated breakdown of the study population, efforts should be made to ensure equitable recruitment of individuals who meet the above eligibility requirements.

4.0 PATIENT ELIGIBILITY

Patients must meet all the following inclusion criteria to be enrolled in the study:

4.1 Inclusion Criteria

1- Age ≥ 18 at the time of signing the Informed Consent Form.

2- Beyond UCSF criteria HCC with diagnosis confirmed histologically/cytologically, radiologically, or clinically per AASLD criteria, with life expectancy of at least 12 months.

3- Histologically confirmed HCC via liver biopsy obtained within 3 months prior to initiation of study treatment as part of SOC. If no historical biopsy is available, a biopsy must be performed at screening for confirmation. Screening liver biopsy may be conducted as part of research activities if not performed per SOC practice.

4- ECOG performance status ≤ 2 within 7 days prior to initiation of study treatment.
Child-Pugh A or B7 (5 to 7 points) at screening and within 7 days prior to study treatment. D1 ECOG/CTP may not repeat if screening ECOG/CTP collected within 7 days prior to D1.

5- HCC with Measurable disease by mRECIST (see Appendix 11.2) (at least one ≥10mm target lesion) that is not suitable for resection per standard clinical practice and beyond UCSF criteria (see section 11.5) confirmed with most recent imaging obtained within 3 months prior to screening.

6- For subjects of childbearing potential (SOCBP), negative serum or urine pregnancy test and agreement to use adequate contraception or abstinence from the time of screening until 3 months following the last dose of Durvalumab.

7- Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

4.2 Exclusion Criteria

1- Known fibrolamellar HCC, sarcomatoid HCC, other rare HCC variant, or mixed cholangiocarcinoma and HCC.
2- Extrahepatic spread with organ involvement other than liver.
3- Portal vein tumor thrombus (VP3-4) or any viable hepatic vein tumor thrombus at screening.
4- History of immune therapy exposure (and-PD-1, and PDL-1, and anti-CTLA-4) treatment.
5- Is pregnant or breastfeeding or expecting to conceive or impregnate someone during the study period.
6- Active or history of autoimmune diseases, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis.
7- Patient lacks interest or inadequate psychosocial support for organ transplantation.
8- Patients who have a known concurrent malignancy that is progressing or requires active treatment, who have not completely recovered from prior treatment, or who have a significant malignancy history that, in the opinion of the investigator, should preclude participation.
9- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
10- Active tuberculosis (TB), as documented by a positive purified protein derivative (PPD) skin test or TB blood test and confirmed by a positive chest X-ray within 3 months prior to initiation of study treatment.
11- Active co-infection with HBV and HCV. Participants with a history of HCV infection but who are negative for HCV RNA by PCR will be considered non-infected with HCV.
12- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact participant safety.
13- Treatment with investigational therapy within 28 days prior to initiation of study treatment.
14- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment.
15- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

- Participants who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible.
- Participants who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

16- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment, within 5 months after the final dose of ICI.

17- Radiotherapy within 28 days, or abdominal/pelvic radiotherapy within 60 days, prior to initiation of study treatment.

18- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions, or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; anticipation of need for major surgical procedure during the course of the study; or non-recovery from side effects of any such procedure.

19- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of the study drugs, may affect the interpretation of the results, or may render the participant at high risk from treatment complications

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Table 5.1: Study Drug Dosage and Administration

Drug	Dose	Route	Frequency	Duration
Tremelimumab	300 mg	I.V.	Once	N/A
Durvalumab	1500 mg	I.V.	Once every 4 weeks	Up to12 treatment cycles

Study treatment (Tremelimumab and Durvalumab) will be administered under standard of care (SOC) clinical practice guidelines within the institution, and dosing will align with FDA-approved regimens for the STRIDE protocol.. Tremelimumab and Durvalumab are commercially available and will be obtained locally. Study agents will be provided under institutional SOC access. All treatments will occur under direct supervision of qualified investigators during the up to 12 months study treatment duration. However, if clinically indicated per SOC practice, Durvalumab administration may be extended after month 12 strictly under treating physician management, research related assessments at this point will be limited to follow up on medical record review and survival status check. If a patient continues ICI beyond 12 months under SOC, further AEs/irAEs are not research assessments but may be captured

retrospectively by medical record review as part of exploratory objectives (e.g., incidence and severity comparisons between those who stop at 12 vs. those who continue SOC).
Locoregional treatment (LRT), including Transarterial Chemoembolization (TACE), Transarterial Radioembolization (TARE/Y90), or Radiofrequency Ablation (RFA), will be administered within 6 weeks of initiating immunotherapy, per SOC and multidisciplinary clinical evaluation. Treatment planning and sequencing will be individualized per tumor burden and patient-specific factors.

5.2 Rationale for Dose and Treatment Schedule

The selected dose and schedule for Tremelimumab and Durvalumab are based on the STRIDE regimen validated in the HIMALAYA trial for advanced HCC. This combination has shown a favorable safety profile and anti-tumor activity. Monthly Durvalumab dosing post-initial Tremelimumab bolus provides sustained checkpoint inhibition. Integration of LRT within the first 6 weeks complements immunologic priming, aiming to increase likelihood of tumor necrosis and immune cell infiltration to enhance downstaging.
This schedule allows flexibility for clinical judgment in tailoring LRT modality, accommodating variable tumor responses while maintaining immune pressure throughout the downstaging period.

5.3 Toxicities and Dosing Delays/Dose Modifications

STRIDE administration may be delayed at the investigator's discretion for any reason. Dose modifications per SOC guidelines are permitted. Refer to Section 5.5 for dose holding or discontinuation criteria. Refer to the respective package insert for detailed toxicity information.

5.4 Evaluable for toxicity

Any patient who receives at least one dose of study treatment is evaluable for toxicity and will be included in the safety analysis.

5.5 Dosing and Toxicity Safety Plan

This study includes enhanced vigilance for ICI and LRT-associated toxicities and complications through the 12-month down-staging window, and (exploratorily) for participants who later undergo LT. The safety plan includes:

- **Adverse Event Monitoring:** Special focus will be placed on identifying and grading immune-related adverse events (irAEs) commonly associated with ICI therapy, including but not limited to colitis, hepatitis, pneumonitis, endocrinopathies, and dermatologic reactions. LRT-specific complications (bleeding, post embolization syndrome, biliary injury) will be monitored with targeted labs/imaging. AEs and SAEs will be documented and reported per institutional and regulatory guidelines (see section 7).

- **On Treatment Additional Safety Monitoring:**

Table 5.2: On-Treatment Additional Safety Monitoring Plan

Time point	(Toxicity-triggered) Safety assessments
Baseline	H&P; ECOG; CBC, CMP, INR, albumin, bilirubin; TFT; cortisol ± ACTH; viral hepatitis serologies; pregnancy test (if applicable); contrast CT/MRI.
Day 1 of each ICI cycle (q 4 w)	Interval H&P; vitals; CBC, CMP, bilirubin, creatinine; TFT (q 8 w); random glucose.
Weeks 2 & 3 of Cycle 1	Focused visit or tele-check; CBC, CMP to catch early irAEs.
Within 7 days pre-LRT	CBC, CMP, coagulation panel; crossmatch if indicated.
Post-LRT (24 h- 7 days after LRT)	Clinical exam; labs for hemoglobin, AST/ALT, bilirubin; Doppler US if concern for vascular injury.
every 8 weeks through Month 12	Imaging safety/efficacy (Triphasic CT or MRI)
Day 1 and each On treatment study visits	Concomitant meds/ AEs, review for corticosteroid bursts, antibiotics, immunosuppressants, Any Grade ≥ 2 irAE triggers repeat labs every 48–72 h until improving to ≤ Grade 1.

On Treatment additional safety assessments are conditional and conducted as unscheduled visit, assessment may be triggered at the investigator's discretion after certain conditions like suspected treatment-related toxicity or dosing delay, time points of those conditional assessments may overlap and incorporated within the main study schedule of events, overlapping assessments do not need to be repeated.

Even though all grade 3–5 AEs will be captured, the Bayesian toxicity monitor applies only to the composite severe irAE endpoint defined above (see section 9.4). The composite of (severe-irAE) include any treatment-related grade 4–5 AE, Or grade 3 irAE that requires hospitalization, IV steroids, or leads to permanent ICI discontinuation. While isolated lab abnormalities (e.g., AST/ALT) that are grade 3 but managed as outpatient and resolve in ≤ 14 days, will not qualify under this category of severe irAE.

- **Dose Holding or Discontinuation Criteria:** Administration of study drugs will be withheld or discontinued in participants who develop Grade 2 irAE persisting > 5 days or Grade ≥3 irAEs or show signs of organ dysfunction suspected to be immune-mediated. Management of irAEs will follow FDA-approved US labeling, as well as ASCO/NCCN guidelines and may include corticosteroids or other immunosuppressants. Grade 4 irAE (except endocrinopathy controlled on hormone replacement) will permanently discontinue ICIs.
- **Grade 3 or 4 LRT complication**: delaying resumption of systemic therapy at least 6 weeks, treat per local standard; resume when ≤ Grade 1 and medically stable, or discontinue if not recovered.
- **For participants who receive LT after the study:** Pre-LT washout: Minimum 4 half-lives (6 weeks) between last durvalumab dose and LT is recommended; shorter intervals are captured for exploratory analysis. Early post-LT period (Day 0–90): graft function tests, RETREAT score, liver

Doppler, and biopsy on clinical indication per transplant unit SOP; data abstracted to study CRFs. Late post-LT (Day 91–365): rejection episodes, and recurrence-free survival recorded at routine transplant clinic visits (exploratory endpoints only; they do not delay primary analysis). As an exploratory safety objective, the study will assess immunologic and molecular markers (e.g., PD-1/PD-L1 expression, T-cell subsets, cytokine profiles, and autoantibody panels) from pre- and post-treatment biopsies to identify predictors of treatment response. Patients who proceed to transplant will be flagged to routine clinical practice for intensified SOC immunologic monitoring post-operatively.

- **Safety Oversight and Escalation:** Refer to Section 7 for safety reporting requirements.

5.6 Concomitant Medications/Treatments

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription (primarily corticosteroid bursts, antibiotics, immunosuppressants) over the counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

No other anti-cancer therapy (chemotherapy, hormonal therapy, radiation therapy, surgery, biologic therapy) or investigational agent may be used from 28 days prior to registration and until the end-of-treatment visit.

5.7 Duration of Study Participation

The anticipated duration of participation for each subject is approximately 16 months, structured as follows:

- **Screening Period (up to 28 days):** Eligibility assessments including history, labs, imaging, and biopsy review.
- **Treatment Period (up to 12 months):** Begins Day 1 of STRIDE regimen. Durvalumab continues until patient is successfully down staged to Milan criteria or reaches 12 months post-treatment (ICI) initiation. Patients with successfully down staged tumor may continue ICI treatment per SOC routine practice until receiving LT under the discretion of the treating physician.
- **Post-Treatment Follow-up Period (3 months after EOT):** Begins at end of treatment and continues for safety monitoring 90 days after last dose.

Additionally, for participants who receive LT after the study, we will review medical records for Post-LT exploratory surveillance, which includes the following timepoints: Pre-LT washout (6 weeks) between last durvalumab dose and LT. Early post-LT period (Day 90) reviewing SOC

graft function tests, RETREAT score, liver Doppler, and biopsy on clinical indication per transplant-unit SOP. Lastly Late post-LT (Day 365) for rejection episodes, and recurrence-free survival recorded at routine transplant clinic visits (exploratory endpoints only; they do not delay primary analysis).

5.8 Removal of Patients from Protocol

Patients will be removed from the study when any of the criteria listed in *Section 6.8* apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed on the Case Report Form. The patient should be followed-up per protocol.

5.9 Evaluability and Subject Replacement

Subjects who withdraw from the study treatment prior to starting study intervention will be replaced. We expect up to enroll up to 45 eligible patients to achieve 41 evaluable subjects.

5.10 Assessment of Response

Participants will undergo tumor assessments (Pathology and mRECIST v1.1) at screening and throughout the study until loss of clinical benefit as determined by the investigator. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations. A baseline liver biopsy must be obtained during the screening period; a historical liver biopsy performed within 3 months prior to enrollment is acceptable and does not need to be repeated. A second liver biopsy must be conducted under the research protocol concurrently when receiving LRT therapy. At the investigator's discretion, other methods of assessment of disease as per mRECIST v1.1 (see Appendix 11.2) may be used. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

6.0 STUDY PROCEDURES

6.1 Screening Visit

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. All screening procedures must be performed within 28 days prior to the Enrollment Visit, unless otherwise stated.

The screening procedures include:

- Informed Consent
- Review subject eligibility criteria

- Medical History review: Relevant medical history, including history of current disease, and information regarding underlying diseases will be recorded at screening.
- Concomitant Medications review
- Demographics: Age, Sex, Race, Ethnicity, Patients may be offered the Inclusive Demographics Questionnaire, which is a standard, non-study-specific document, available on the CS-Link's selection for demographics. Study team to record responses in the subject's OnCore record. Completion is voluntary; patients may decline to complete the Inclusive Demographics Questionnaire.
- Physical exam
- ECOG Performance Status
- Height and Weight
- Vital signs: Temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure will be assessed.
- EKG will be obtained. In cases of clinical suspicion for myocarditis, EKG and cardiac biomarkers (e.g., troponin) will be repeated as clinically indicated.
- Imaging for Tumor Measurements: Participants will undergo tumor assessments at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include triphasic CT scans (with IV contrast: with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, and pelvis.
- Clinical Laboratory Evaluations: Complete Blood Count (CBC), International Normalized Ratio (INR), Liver Function Test (LFT), Thyroid Function Test (TFT), Urinalysis (UA), Hepatocellular Carcinoma Risk Panel (HCC panel), Amylase and lipase will be obtained at baseline and per SOC practice; repeat if clinically indicated for symptoms of pancreatitis, cardiac biomarkers (e.g., troponin) will be repeated as clinically indicated. Urine or Serum Pregnancy Test for SOCBP.
- Liver Biopsy: A baseline liver biopsy must be obtained during the screening period; a historical liver biopsy performed within 3 months prior to initiation of study treatment is acceptable and does not need to be repeated.
- Research Lab collection
- Stool Sample Collection kits, giving participants the kit at screening lets them collect at home within 7 days pre-Day 1 visit.

6.2 Enrollment Visit / Lead-In (Day 1)

- Medical Record Review: To record interval changes in medical history and concomitant medications.
- Review and Confirm Eligibility Criteria
- Physical Examination

- ECOG Performance Status
- Weight
- Vital Signs
- Adverse event assessment: Baseline adverse events will be assessed. See section 7.0 for Adverse Event monitoring and reporting. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).
- Clinical Laboratory Evaluations: As per screening visit assessment (If any assessment test at Screening was completed within 7 days prior to the Enrollment Visit, it does not need to be repeated). Additional (conditional) safety assessments might be performed (see section 5.5)
- Research Lab Kit required only If the screening blood sample is older than 48 hours from Day 1 visit.
- Baseline Stool Sample Collection and kit for Week 6-8 collection.
- Tremelimumab Administration
- Durvalumab Administration

6.3 Week 3 Visit (LRT) (within 6 weeks after Day 1)

- Medical Record Review
- Physical Exam
- ECOG Performance Status
- Weight
- Vital Signs
- Adverse event assessment
- Imaging and Tumor Measurements (at SOC timepoints).
- Clinical Laboratory Evaluations: CBC, INR, LFT, TFT, UA, HCC panel.
- Locoregional Treatment: Locoregional treatment consisting of either TACE, TARE(Y90), and/or local ablation to take place within 6 weeks after initiation of ICI, (LRT may be repeated during the study treatment period per PI discretion).
- Liver Biopsy: Liver biopsy must be performed at date of (or within 7 days after) receiving LRT.

6.4 Each Cycle Day 1 (cycle=28 days), (+/- 7 days from the preceding cycle)

- Medical Record Review
- Physical Exam
- ECOG Performance Status
- Weight
- Vital Signs

- Adverse event assessment
- Imaging and Tumor Measurements (at SOC timepoints)
- Urine or Serum Pregnancy Test for SOCBP
- Clinical Laboratory Evaluations: CBC, INR, LFT, TFT, UA, HCC panel.
- Research Lab Kit (every 6-8 weeks during STRIDE treatment)
- Stool Sample Collection (every 6-8 weeks during STRIDE treatment)
- Durvalumab Administration: Durvalumab treatment cycles will continue until successful downstaging, or up to 12 cycles of treatment; or until any of the criteria in Section 6.8 is met. Subjects who have successful downstaging may continue treatment per treating physician discretion.

6.5 End-of-Treatment (EOT) Visit (+/- 7 days from the end of the preceding cycle)

The end-of-treatment (EOT) visit is to be conducted once the subject reaches Milan criteria or completes 12 cycles of treatment, or at the time when any other criteria in Section 6.8 is met, whichever occurs first.

- Medical Record Review
- Physical Exam
- ECOG Performance Status
- Weight
- Vital Signs
- Adverse event assessment: Following the AE assessment at the EOT visit, adverse events should be re-assessed at 90 days following the last durvalumab administration, via medical record review, in-clinic visit, or phone call to the patient.
- Imaging and Tumor Measurements (at SOC timepoints)
- Clinical Laboratory Evaluations: CBC, INR, LFT, TFT, UA, HCC panel.
- Research Lab Kit
- Stool Sample Collection

6.6 Post Treatment Follow-up safety assessments, 90 days post-last study dose (+/- 28 days).

- Day 90 after EOT Medical Record Review for AEs and safety assessments review per SOC, including survival status (may be assessed by medical record review, phone call, or public records).
- Exploratory Post LT assessments time points (for participant received LT) at Day 90 and Day 365 Post LT time points, Medical Record Review for safety assessments review per SOC, including survival status (may be assessed by medical record review, phone call, or public records).

6.7 Time and Events

Table 6.1: Schedule of Events

	Screening visit	Enrollment Visit / Lead-In	LRT Visit[9]	Each Cycle Day 1	EOT visit[2]	EOS[11] Day 90 Follow-up
Study Windows (Days):	Within 28 days prior to D1	Day 1	3 to 6 weeks after Day 1	Every 28 days (+/- 7days from the preceding cycle)[1]	28 days following last study dose (+/- 7 days from the preceding cycle)	Post last study Treatment dose (+/- 28 days)
Informed Consent	X					
Eligibility Review	X	X				
Medical History Review	X					
Concomitant Medications Review	X	X		X		
Medical Record Review	X	X	X	X	X	X
Demographics Questionnaire	X					
Physical Exam	X	X	X	X	X	
Performance Status (ECOG) and Child-Pugh score (CTP)	X	X[15]	X	X	X	
Height	X					
Weight	X	X	X	X	X	
Vital Signs	X	X	X	X	X	
Adverse Events Assessment[16]		X	X	X	X	X
EKG[14]	X					
Imaging for Tumor Measurements[7]	X[7]			X[7]		
Clinical Laboratory Evaluations[3]	X	X[17]	X[17]	X[17]	X[17]	
Pregnancy Test (urine or serum)	X	X[10]		X		
Liver biopsy	X[4]		X[5]			
Research Labs	X	X[12]		X[6]	X	
Stool Collection[13]		X		X[6]	X	
Tremelimumab		X				
Durvalumab		X		X[1]		
Locoregional Treatment (LRT)			X[8]			
Survival Status						X

1. Treatment continues until subject reaches Milan criteria, or 1 year, or at the time when any other criteria in Section 6.8 is met, whichever occurs first. For subjects who achieve successful downstaging, Durvalumab treatment may continue per treating physician discretion.
2. Once subject reaches Milan criteria, they proceed to the end of treatment (EOT) visit.
3. CBC, INR, LFT, TFT, UA, and HCC panel. Additional safety labs include Thyroid panel including TSH will be obtained at baseline and every 8 weeks (or more frequently as clinically indicated), Cortisol ± ACTH at baseline; repeat if clinically indicated, Amylase and lipase will be obtained at baseline; repeat if clinically indicated for symptoms of pancreatitis, cardiac biomarkers (e.g., troponin) will be collected/repeated as clinically indicated.
4. Baseline Liver Biopsy: Historical liver biopsy conducted within 3 months prior to C1D1 may be used.
5. Liver biopsy must be performed at date of or within 7 days after receiving LRT.
6. Every 6-8 weeks during STRIDE treatment

7. Tumor assessment imaging will include contrast CT or MRI abdomen and pelvis, CT chest every 8 weeks (±1 w) as per SOC practice, Screening imaging is baseline Pre Treatment imaging. Imaging for tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.
8. Locoregional therapy may be repeated per PI's discretion.
9. Locoregional therapy occurs 3 weeks or up to 6 weeks following the Enrollment/Lead-In Visit.
10. If pregnancy test at Screening was completed within 7 days prior to the Enrollment/Lead-In Visit, it does not need to be repeated.
11. If participant receives LT, additional Exploratory Observational Post LT assessments time points at minus 6 weeks' time point prior to LT, Day 90 and Day 365 Post LT time points, Medical Record Review for safety assessments review per SOC, including survival status (may be assessed by medical record review, phone call, or public records). (see section 5.5)
12. Research blood collection required only If the screening blood sample is older than 48 hours from Day 1 visit.
13. Giving participants the Stool Sample Collection kit at screening lets them collect at home within 7 days pre-Day 1 visit.
14. Baseline ECG will be obtained. In cases of clinical suspicion for myocarditis, ECG and cardiac biomarkers (e.g., troponin) will be repeated as clinically indicated.
15. D1 ECOG/CTP may not repeat if screening ECOG/CTP collected within 7 days prior to D1.
16. Any Grade ≥ 2 irAE triggers repeat labs every 48–72 h until improving to ≤ Grade 1.
17. Additional (conditional) safety assessments might be performed (see section 5.5)

6.8 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws (follow-up permitted).
- Patient withdraws consent (termination of treatment and follow-up).
- Patient is unable to comply with protocol requirements.
- Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator).
- Patient experiences toxicity that makes continuation in the protocol unsafe.
- Treating physician determines continuation on the study would not be in the patient's best interest.
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event).
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study.
- Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented. This will be reviewed during an interim data monitoring visit.

7.0 ADVERSE EVENTS (AE), SERIOUS ADVERSE EVENTS (SAE), UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS OR OTHERS (UPIRSO), AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Laboratory test abnormalities

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), is considered an adverse event.

7.1.2 Serious Adverse Event (SAE)

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

- Death

- A life-threatening adverse event
- Inpatient hospitalization or 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
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.1.3 Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)

UPIRSOs include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

7.1.4 Immune-related adverse events (irAEs)

• Immune-related adverse events (irAEs) commonly associated with ICI therapy, including but not limited to colitis, hepatitis, pneumonitis, endocrinopathies, and dermatologic reactions, isolated lab abnormalities (e.g., AST/ALT) that are grade 3 but managed as outpatient and resolve ≤ 14 days.

• The composite of (severe-irAE) include any treatment-related grade 4–5 AE, Or grade 3 irAE that requires hospitalization, IV steroids, or leads to permanent ICI discontinuation.

7.2 Principal Investigator Responsibilities for Safety Monitoring

7.2.1 AE Reporting Period

The investigator or designee is responsible for ensuring that all AEs (both serious and non-serious) observed by the clinical team or reported by the subject which after the first dose of and until 90 days following the last dose of the study drug, are fully recorded in the subject's medical records.

7.2.2 AE/SAE Documentation

The investigator, sub-investigator (treating physician if applicable), or study team (according to the responsibilities delegated per the DOA) will document the following for all AEs (both serious and non-serious):

- Event term, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. The CTCAE current version is available at https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

  - the current known adverse events listed in this protocol.
  - the drug package insert; and/or
  - the current Investigator's Brochure

- Grade of toxicity, as per CTCAE v5.0 criteria
- Attribution of relatedness to the investigational agent- (this must be assigned by an Investigator, sub-investigator, or treating physician)
- Attribution categories are as follows:
  - Definite: The AE is clearly related to the study treatment.
  - Probable: The AE is likely related to the study treatment.
  - Possible: The AE may be related to the study treatment.
  - Unlikely: The AE is doubtfully related to the study treatment.
  - Unrelated: The AE is clearly NOT related to the study treatment.
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received concomitant med or other intervention, etc. For the severe-irAE, PI and the DSMC will review context and recommend whether to modify or resume the trial.
- Outcome of event

Source documentation must be available to support all AEs.

7.2.3 Duration of AE monitoring

All patients experiencing an AE of any grade, regardless of its relationship to study drug, will be monitored until:

- the AE resolves or the symptoms or signs that constitute the AE return to baseline
- any abnormal laboratory values deemed an AE has returned to baseline

- there is a satisfactory explanation other than the study drug for the changes observed
- death, or
- until 90 days following the last dose of the study drug

7.3 Safety Reporting Requirements

7.3.1 Reporting to the Principal Investigator

The Principal Investigator (PI) must be notified by study staff or co-investigators within 24 hours of learning of any SAEs, regardless of attribution and expectedness, occurring during the study or within 90 days following the last dose of the study drug.

Contact for Expedited Reporting:
Ju Dong Yang, MD, MS
JuDong.Yang@cshs.org
310-423-6000

Alternate Contact for Expedited Reporting:
Emily Kaymen, MD
Emily.Kaymen@cshs.org
310-888-8680

7.3.2 Reporting to DSMC:

Serious Adverse Events deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g., due to disease progression) are to be reported to the DSMC within 24 hours of awareness. Hardcopies or electronic versions of the MedWatch Form 3500A (Mandatory Reporting) or a narrative report, along with any other supporting documentation available, should be submitted to the DSMC Coordinator. The DSMC Coordinator will forward the information to the DSMC Chair, and/or medical monitor. The DSMC Chair will review all documentation upon receipt from the DSMC Coordinator and determination of whether the following actions are required: 1) takes action immediately, 2) convenes a special DSMC session (physical or electronic), or 3) defers the action until a regularly scheduled DSMC meeting. Reports are to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

7.3.3 Reporting to the Institutional Review Board (IRB)

As per the Cedars-Sinai IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement v.5, the IRB must be notified of all UPIRSOs as soon as possible, but no later than 10 business days from when the study team learned of any of the following events:

1. Any internal SAE, AE or Research-Related Subject Injury (RRSI), which in the opinion of the Principal Investigator was unanticipated or unexpected and has a reasonable possibility of relationship to the research.
2. Any actionable external SAE, AE, SUSAR, development safety update report (DSUR), or FDA MEDWATCH report deemed to be a UPIRSO. An event is considered “actionable” if it warrants a change to the conduct of the study.
3. Any internal or external UADE.
4. Any accidental, unintentional protocol or consent/HIPAA related deviation that may impact subjects’ rights, safety, or welfare. See section 10.8.3.
5. Any planned protocol exception or eligibility waiver. See sections 10.8.2 and 10.8.3.
6. Changes to the research or protocol deviations made without prior IRB approval in order to eliminate apparent immediate hazard to a research subject.(Note: These must be reported to the IRB within 72 hours.)
7. Problems, events, unanticipated incidental findings, billing problems, or other events, outcomes, or new information related to the research (e.g., publication, safety monitoring report, interim findings, product labeling changes, findings generated from preclinical, animal studies) that may adversely affect the rights, safety, or welfare of the subjects or others, put subjects or others at increased risk, compromise the research data, or require/recommend changes to the study conduct.
8. Subject complaints or concerns that cannot be resolved by the research staff to the subject’s satisfaction.
9. Breach or potential breach of confidential or sensitive information.
10. Incarceration of a subject who is enrolled in a study that is not approved by the IRB to include prisoners.

8.0 CORRELATIVES/SPECIAL STUDIES

8.1 Assay Methodology

We will test checkpoint molecules (Tim3, CTLA4, PD1, PDL1) IFNg, IL27 in circulation/serum, in tumor/liver CD8 cytotoxic cells (cell numbers, markers of exhaustion, markers of cytotoxicity (Granzymes, Perforin), IFNg, markers of activation Innate cytotoxic cells (NK, ILC1; cell numbers, markers of exhaustion, markers of cytotoxicity (Granzymes, Perforin) Neutrophils (long-lived= tumor promoting neutrophils) Tumor associated macrophages/DC (pro-inflammatory (former M1) vs anti-inflammatory (former M2); cDC1 vs cDC2 B cells (Bregs (IL10+)-poor prognosis; B cells -good prognosis) Tregs (numbers, suppressor functions, conversion to effect cells (by scRNAseq trajectory analyses) Microbiota analysis (if we go this way). Proposed correlative study will involve 1)scRNA seq of biopsies vs PBMC 2) spatial analyses (biopsies) 3) multi-color FACS 4)cytokine multiplex 5) microbiota 16s seq-> metabolomics.

8.2 Sample Collection / Specimen Banking

Study will use consistent institutional laboratory method throughout study. Blood and stool sample will be collected for the study as outlined below:

Research stool samples will be collected at Screening, Day 1, Every treatment cycle, and End of treatment visits, we will obtain stool samples using a stool collection kit. This kit will be provided during the research visit by the research team along with instructions on the stool collection process. You will have the option to collect the stool during the study visit or at home. If you collect the stool sample at home, then you may return the stool sample to the site by mail or in person.

Research blood samples will be collected at Screening, Day 1, Every treatment cycle, and End of treatment visits, four (4) 8.5 mL (two purple tops, one red top, and one yellow top ACD tube) will be provided in a research kit from the Yang lab and will be used when collecting blood from patients.

A baseline liver biopsy must be obtained during the screening period; a historical liver biopsy performed within 3 months prior to initiation of study treatment is acceptable and does not need to be repeated. A second liver biopsy must be conducted under the research protocol concurrently when receiving LRT therapy, research biopsy with be performed at Cedars Sinai imaging facility (Ultrasound Guided Liver biopsy), and read by Cedars Sinai radiologist, remnant liver tissue for biopsy may be retained for further future analysis.

All collected study biospecimens will be processed, and bio banked at CSMC Dr Yang lab space.

9.0 STATISTICAL CONSIDERATIONS

9.1 Design and Sample size

This is a single arm Phase-II study focused on the preliminary efficacy of administering ICI and LRT combination therapy to downstage patients with (intermediate to advance stage) HCC to Milan Criteria within 12 months of enrollment. Simon two-stage design will be used to test for efficacy [20]. Due to the use of standard treatments and enrichment for compliant patients who are eligible for liver transplantation, we anticipate a low drop-off rate of 10%. Thus, our target patient accrual is 41 with an addition of 4 patients if replacement is required.

Using the Simon's two-stage design we will test the following hypothesis $H_0: P \leq 0.25 \ \ vs \ H_1: P \geq 0.50$. The trial will be carried out in two stages. In stage I, a total number of 15 patients will be enrolled. If there are 4 or fewer downstages among these 15 patients, the study will be stopped early for futility. Otherwise, the study will enroll additional 26 patients in stage II, resulting in a total number of sample size of 41. The null hypothesis will be rejected if 15 or more HCC patients downstage to MILAN criteria. The design attains a one-sided type-I error rate of 0.028 and power of 90.2% when the true response

rate is 50%. The probability of early termination under the null hypothesis is 68.6%. When the null hypothesis is true, the expected sample size is 23 patients. The sample sizes are calculated using admissible design [21].

9.2 Stopping Rules:

We will conduct safety assessment during the phase II trial using Bayesian sequential monitoring. Let Pt be the true probability of grade 3 or more irAE during the study treatment (defined as grade 4–5, or grade 3 irAE requiring hospitalization, IV steroids, or permanent ICI discontinuation; endocrinopathies controlled on replacement therapy are excluded). The trial will stop if there is statistical evidence that Pt>30%. We will use Bayesian design to check whether Pt > 30% after 15, 25, 35 and 41 patients complete the study treatment (up to 12 months). The trial will stop if the posterior probability that Pt>0.30 is 0.948 or more, i.e. Pr (Pt >0.30 | data)>0.948. Using a non-informative Jeffery's prior distribution for Pt, Table 1 shows the stopping rules at each interim look. The column 2 shows the maximum number of patients with grade 3 or more irAE allowed for trial to continue. For example, if 8 patients develop grade 3 or more irAE after enrolling first 15 patients, the trial stops. The third column gives the probability to stop the trial when true Pt =0.30. The target type I probability was set at 0.10. Enrollment will continue uninterrupted during interim assessments (after 15 evaluable patients). These reviews are intended for monitoring only and will not require suspension of accrual.
Safety stopping rules will be based on Grade ≥3 adverse events occurring within one cycle (4 weeks). Enrollment will not be halted at the 15-, 25-, or 35-patient reviews; these checkpoints are intended solely for ongoing safety monitoring.

Table 9.1: Safety Stopping Rule* (15 Patients) and Ongoing Monitoring Checkpoints (25, 35, 41 Patients)

Number of Patients	Maximum number of patients with undesirable events at which trial will continue	Probability to Stop	Cumulative Probability to stop
15	7	0.0500	0.0500
25	11	0.0217	0.0717
35	15	0.0117	0.0834
41	17	0.0103	0.0938

• The stopping rule applies only at the 15-patient interim analysis. The 25-, 35-, and 41-patient reviews are safety monitoring checkpoints only and do not mandate trial suspension unless recommended by Data and Safety Monitoring Committee (DSMC).

Table 9.1 shows the design operating characteristic under different values of the true probability of P_t with the probability of stopping the trial under alternative hypothesis, the expected sample size and the average sample size given that the trial is stopped. For example, if the true value of P_t is 0.4, then there is a 45.98% chance that the trial will be stopped early, and the average sample size is about 33. When the true P_t is 0.1, the chance of stopping the trial is very low <0.1%.

Table 9.2: Design operating characteristics under different true probability of P_t

True value of P_t	Probability to Stop	Expected N		Expected N given the trial stopped
0.1	< 0.001	41		15.27
0.3	0.0938	39.28		22.68
0.4	0.4598	33.23		24.1
0.6	0.9912	17.91		17.71

9.3 Primary endpoint

Proportion of patients who meet Milan criteria by mRECIST within 12 months of first STRIDE dose.

9.4 Primary Analysis

The downstaging rate and exact Clopper-Pearson 95 % CI will be reported. Operating characteristics of the two-stage design (stop probability under H_0/H_1, expected sample size) will accompany the results.

9.5 Secondary Analysis

The Incidence and grade of treatment-emergent AEs and hepatic decompensation events summarized descriptively; cumulative incidence curves for first severe irAE.

The ORR at Months 3, 6 and 12 with 95 % CIs; PFS and TTP estimated by Kaplan Meier, censored at 12 months. The PFS will be analyzed similarly as well. Rate and grade of hepatic decompensation events will be summarized descriptively.

9.6 Exploratory analysis

Post-LT outcomes (RETREAT score, allograft rejection and time to rejection) will be analyzed descriptively using mean, SD, median and IQR. RFS will be estimated with Kaplan Meier estimator along with 95% confidence interval. Associations with ICI washout interval will be assessed either using Cox or logistic regression. Correlative biomarker changes (immune profiling, microbiome shifts) versus clinical outcomes will be analyzed appropriately using bi-variate analysis, e.g. LMM or GEE. Omics endpoints will be tested using two-sided t-test or Mann-Whitney test at 10% False discovery rate using Benjamini-Hochberg adjustment. All analyses will be conducted either in SAS or R

9.7 Safety and Data Sets Analyzed

All eligible patients who are enrolled into the study and receive at least one dose of a study agent will be included in the efficacy and safety analysis.

The safety profile of ICI and locoregional treatment combination is well known in HCC. Grade 3,4 AE were reported up to 70s% in HCC trials thus, we will closely monitor unexpected or severe irAEs (e.g., grade 4 hepatitis, grade 3 pneumonitis needing oxygen, grade 3 colitis requiring IV steroids). Please refer to the safety plan described in Section 5.5.

A potential risk of this study is allograft loss due to rejection after liver transplantation, which will be reported descriptively as a exploratory endpoint as there are retrospective evidence suggesting safety of ICI treatment as long as there is an adequate washout period (at least 6 weeks or longer)(see Section 9.3.2).

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated and prior to the shipment of study supplies to participating sites, if applicable. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Registration/Enrollment Procedures

All patients will be tracked following written informed consent. Those patients who are consented to participate in the clinical trial but do not meet one or more criteria required for participation during the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study teams will track all subjects who sign consent using OnCore. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a three-digit numeric ID that follows the standard CSCC format (001, 002, etc.).

A) Eligibility Verification

Prior to registration/enrollment, all subjects must undergo eligibility verification by the Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC). The following documents will be organized into an eligibility packet, scanned as a pdf, and emailed to GroupCCTOQMC@cshs.org for review:

- QMC approved Eligibility Checklist signed by investigator and 2 members of the study team (or equivalent)
- Source documents substantiating eligibility that cannot be located in the subject's CS Link medical record
- Signed consent form with Subject's Bill of Rights, HIPAA authorization form, consent progress note, and any optional consent forms, as applicable, if not available in CS Link

B) Registration

After eligibility is verified, each site will assign the subject a study number and site staff will then register the patient in OnCore®.

Registration is completed as follows:

- Assignment of a patient study number
- Assignment to the patient a dose/treatment arm as determined through communication with Biostatistics and the principal investigator, if applicable

- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

Oversight by the principal investigator is required throughout the entire registration process.

10.4 Data Management, Quality Assurance, Quality Control and Reporting

REDCap is the Cedars-Sinai Cancer institutional choice for the electronic data capture of case report forms for CSCC Investigator Initiated Trials. REDCap, a HIPAA-compliant database, will be used for electronic case report forms in accordance with institutional requirements, as appropriate for the project. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. See also Section 10.6.2, Monitoring.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

10.5 Data and Safety Monitoring

10.5.1 Safety Oversight

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. It is the responsibility of the principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, safety oversight and efficacy data will be reviewed by the CSCC Data and Safety Monitoring Committee (DSMC). The DSMC will review this trial commensurate with the assigned risk class as categorized by the PRMC. The DSMC membership and responsibilities are governed by the committee charter. The DSMC findings and recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC outcome letters will be furnished to the FDA, as applicable. Refer to the DSMC Charter for details of the DSMC review.

10.5.2 Monitoring and Auditing

The CSCC Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct internal monitoring visits to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and

verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The Cedars-Sinai IRB and Office of Research Compliance & Quality Improvement (ORCQI) may conduct auditing activities to ensure compliance with institutional policies, procedures, applicable laws, regulations and codes designed to protect the rights, safety and welfare of human subjects.

Refer to the DSMP for details pertaining to the type, frequency, and extent of auditing and monitoring that will be performed.

10.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, records of study drug receipt, dispensation, destruction and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file in accordance with all applicable federal guidelines and local guidelines.

Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request.

10.7 Adherence to Protocol

It is the responsibility of the Investigator-sponsor to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at CSCC are all performed as specified in the protocol. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the IRB of record, the study shall be conducted exactly as described in the approved protocol.

10.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 72 hours from the investigator’s awareness of the event.

10.7.2 Protocol Exceptions and Eligibility Waivers

Moderate Risk or High Risk

A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.* A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior approval from the IRB. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents for IRB review.

Study team should refer to the IRB *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement* guidelines to determine which deviations and exception requests meet reporting guidelines. The deviation or exception request must be submitted to the IRB for review and approval prior to implementation.

Special considerations for Eligibility Waivers (EW)

Subjects who do not meet the eligibility requirements should not be enrolled. Eligibility waivers are not permitted.

10.7.3 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the subject's research record or deviation log as described in the CSCC CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the CSCC CCTO's Standard Operating Procedure 12: *Deviation and Noncompliance Reporting* (or local policy, for multi-site studies). In this case, a Protocol Deviation report must be submitted

in CS-IRB, per CSMC IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

10.7.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted, and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.9 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor-investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

11.0 APPENDICES

- **Summary of Changes**
- **Modified RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (mRECIST VERSION 1.1) for Hepatocellular Carcinoma**
- **ECOG Performance Status Scale**
- **Child-Pugh Score**
- **Milan Criteria**
- **UCSF Criteria**
- **Retreat Score**
- **BCLC Staging**

11.1 Summary of Changes

11.2 Response Evaluation Criteria in Solid Tumors mRECIST Version 1.1

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable lesions - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

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

Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- For special considerations regarding lesion measurability for bone lesions, cystic lesions and lesions with prior local treatment, consult the RECIST 1.1 guidelines.
- 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 beginning of 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, either a CT scan or documentation by color photography, including a ruler to estimate the size of the lesion, is to be done.

Methods of Measurement

Optimization of image acquisition protocol and consistence in the use of the same protocol throughout follow-up examinations are key proper application of mRECIST. Patients can be followed with either contrast-enhanced spiral computed tomography (CT) – preferably with use of multislice scanners – or contrast-enhanced dynamic magnetic resonance imaging (MRI). The administration of intravenous contrast is recommended for all CT or MRI studies if not medically contraindicated. In contrast-enhanced studies, it is mandatory to obtain a dual-phase imaging of the liver. Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. Delayed imaging obtained in the equilibrium phase may be useful, but it is not mandatory and should only be done if it is part of clinical practice. For multidetector CT scanners that are capable of acquiring very thin slices, it is necessary to keep in mind that it is mandatory to use contiguous slices for image read and interpretation, to avoid missing small lesions. For example, the analysis of contiguous slices with traditional 5 mm reconstruction interval is acceptable; however, the analysis of 2.5 mm thickness sliced at 5 mm intervals is not acceptable.

According to RECIST, tumor lesions are categorized at baseline as follows: measurable (lesions that can be accurately measured in at least one dimension as ≥1 cm with a spiral CT scan) or nonmeasurable [all other lesions, including small lesions (longest diameter <1 cm with spiral CT scan) and truly nonmeasurable lesions]. The original RECIST publication states that 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. The recent 1.1 release of RECIST has reduced the number of lesions to select as target lesions to a maximum of two lesions per organ and five lesions in total (Eisenhauer et al., 2009). In fact, analyses on a large prospective database has shown that assessment of five versus 10 lesions per patient did not affect the overall response rate, and that progression-free survival was only minimally affected (Bogaerts et al., 2009) Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements. All other lesions (or sites of disease) should be identified as nontarget 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.

It is our understanding that the measurement of the longest viable tumor diameter for the assessment of response according to mRECIST can be only applied in case of typical lesions. Conversely, for non- enhancing atypical lesions, as well as for any extrahepatic neoplastic niches, the measurements of the longest overall tumor diameter as per conventional RECIST should prevail.

To be selected as a target lesion using mRECIST, an HCC lesions should meet all the following criteria:

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

Non-target lesions - 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.

Response Criteria Evaluation of Target Lesions

Complete Response (CR):	Disappearance of any intratumoral arterial enhancement in all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Progressive Disease (PD):	At least a 20% increase 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 (SD):	Any cases that do not qualify for either partial response or progressive disease

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
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).

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.

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.

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.

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.

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 8) 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 4-8 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 4-8 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.

Definition of CT tumor response by RECIST 1.1 criteria:

The following table outlines the response categories by RECIST 1.1 criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Complete Response (sum of diameters=0 mm)	Complete response	No	Complete Response
Complete Response	Non-complete response, non-progressive disease	No	Partial Response
Complete Response	Not evaluated	No	
Partial Response (decrease in sum of target lesions by ≥30%)	Non-progressive disease OR Not evaluated	No	
Stable Disease	Non-progressive disease OR Not evaluated	No	Stable Disease
Not all evaluated	Non-progressive disease	No	Not Evaluable
Progressive Disease (increase in sum of target lesions by ≥ 20% with an absolute increase in summed diameters by 5mm)	Any	Yes or No	Progressive Disease
Any	Progressive Disease	Yes or No	

(Eisenhauer et al. 2009; Lencioni et al. 2010)

11.3 ECOG Performance Status Scale

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

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11.4 Child-Pugh Scoring

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

11.5 UCSF vs Milan Criteria

Milan Criteria (Mazzaferro et al, 1996)

- Single tumor ≤ 5 cm, or
- 2-3 tumors none exceeding 3 cm, and
- No vascular invasion and/or extrahepatic spread

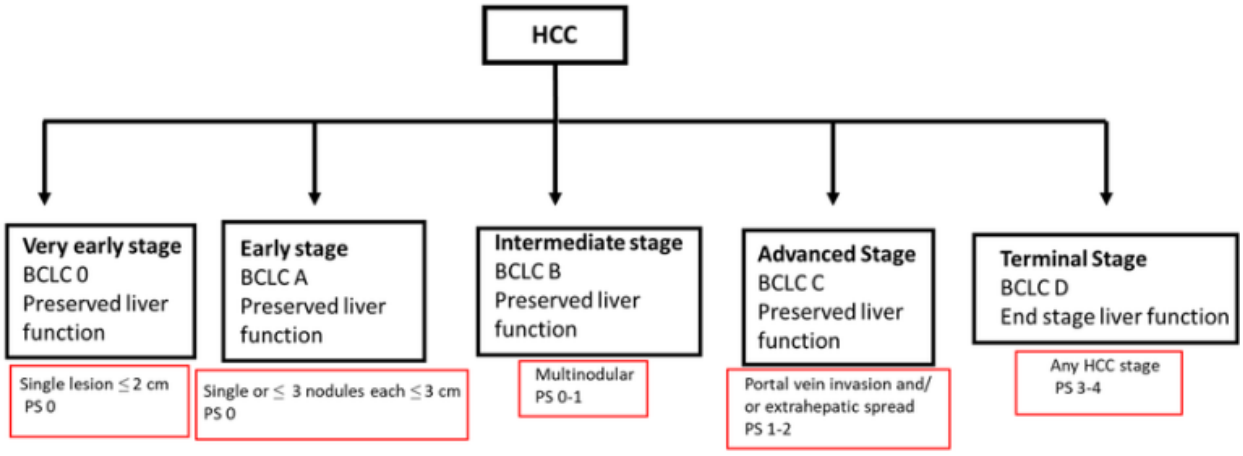
UCSF Criteria (Yao et al, 2001)

- Single tumor ≤ 6.5 cm, or
- 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter ≤ 8 cm
- No vascular invasion and/or extrahepatic spread

11.6 RETREAT Score

RETREAT score predictors	RETREAT points
AFP at LT (ng/mL)	
0 to 20	0
21 to 99	1
100 to 999	2
>1000	3
Microvascular invasion	2
Largest viable tumor diameter (cm)	
0	0
1.1 to 4.9	1
5.0 to 9.9	2
>10	3

11.7 BCLC Staging



BCLC HCC staging 2022. BCLC, Barcelona clinic liver cancer staging system; HCC, hepatocellular carcinoma; PS, performance status score.

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