CANCER

IIT2020-11-Hendifar-TELAT

A Phase II Study Evaluating Safety and Efficacy of Telatinib in Combination with Keytruda in Subjects with Advanced Stomach and Gastroesophageal Junction Cancers or Hepatocellular Carcinoma

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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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Principal Investigator (PI) Signature **Date**

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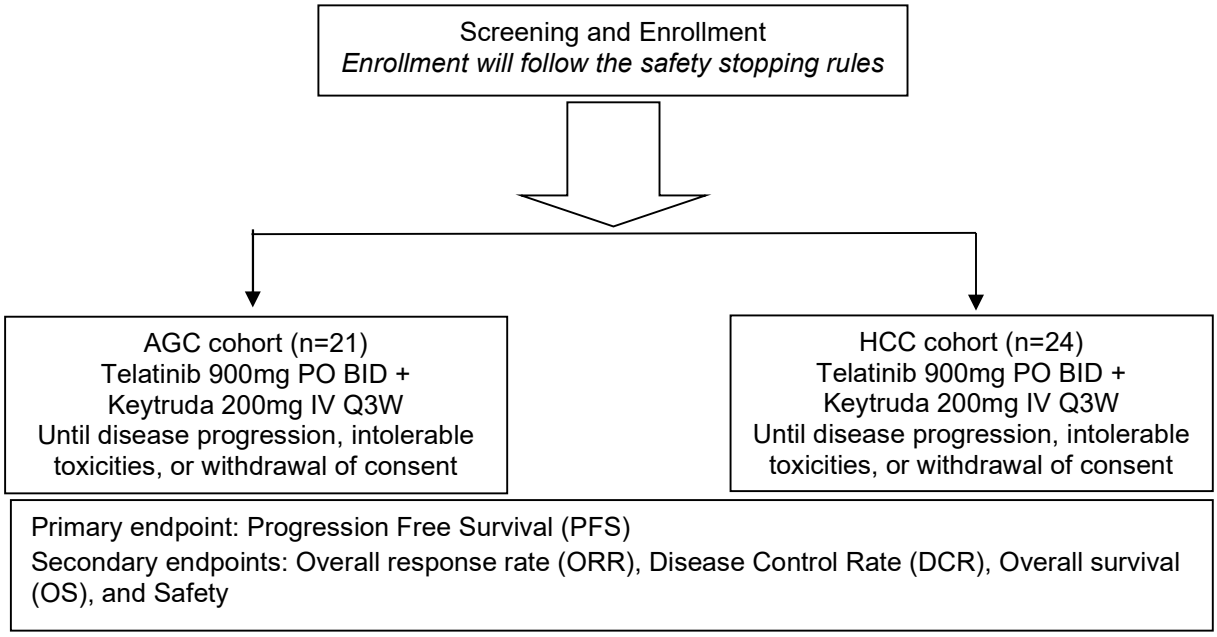
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DARF	Drug Accountability Review Form
DCR	Disease control rate
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
HRPP	Human Research Protections Program
INR	International normalized ratio
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PO	per os/by mouth/orally
PR	Partial Response
PT	Prothrombin time
SAE	Serious Adverse Event
SD	Stable Disease
ULN	Upper limit of normal
WBC	White Blood Cells
WOCBP	Women of childbearing potential

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase II Study Evaluating Safety and Efficacy of Telatinib in Combination with Keytruda in Subjects with Advanced Stomach and Gastroesophageal Junction Cancers or Hepatocellular Carcinoma
Protocol Number	IIT2020-11-Hendifar-TELAT
Phase	Phase II
Methodology	Single arm, open label study with two parallel cohorts
Study Duration	Approximately 30 months (anticipated accrual duration 12 months, with up to an estimated 12 months on-treatment and up to an estimated 6 months follow-up) Stopping rules for safety will be followed.
Study Center	Cedars-Sinai Medical Center and affiliates
Objectives	**Primary:** The primary objective is to assess progression-free survival (PFS) in subjects with advanced gastric cancer or HCC receiving telatinib 900 mg BID in combination with Keytruda. **Secondary:** The secondary objectives are to assess: Overall response rate (ORR), Disease Control Rate (DCR), Overall survival (OS), and Safety **Exploratory:** Time to Progression (TTP) Change in inflammatory cytokines Change in plasma metabolites Change in immune cell profile Change in stool microbiome Change in stool metabolites
Number of Subjects	21 subjects with advanced gastric cancer 24 subjects with advanced hepatocellular carcinoma
Diagnosis and Main Inclusion Criteria	Adult subjects with advanced gastric cancer or HCC who are indicated for Keytruda
Study Product(s), Dose, Route, Regimen	Telatinib 900 mg (3 x 300 mg tablets) will be administered orally, twice daily. Keytruda will be administered IV 200 mg every 3 weeks.
Duration of administration	Until disease progression, intolerable toxicities, or withdrawal of consent
Statistical Methodology	Gastric cancer: PFS will be compared to KEYNOTE-059 with a primary endpoint of improvement in PFS from 2.0 months to 4 months. HCC: PFS will be compared to KEYNOTE-224 with a primary endpoint of improvement in PFS from 4.9 months to 10 months.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

1.1.1 Gastric Cancer

Gastric cancer is the 5th most common cancer and remains the world's third leading cause of cancer mortality [1]. Surgery is the mainstay of curative treatment in stage I to III gastric cancers. However, more than half of the patients at diagnosis are already too advanced for curative resection. Even for those who are resectable upfront, the recurrence rate is still high at around 40–80% [2, 3]. First-line then second-line palliative chemotherapy is the standard of treatment in patients with advanced/metastatic gastric cancer. A Cochrane review and meta-analysis performed by Wagner demonstrated that chemotherapy extended overall survival (OS) by approximately 6.7 months more than best supportive care [4]. Standard front-line therapy includes chemotherapy using fluorouracil (5FU) and platinum agents, with the option of adding anthracycline or taxane group agents. In human epidermal growth factor receptor 2 (Her2) positive advanced gastric cancer, adding trastuzumab to platinum-based chemotherapy (cisplatin/carboplatin + 5FU) showed superior efficacy compared with chemotherapy alone (OS: 13.8 versus 11.1months, HR 0.74; 95% CI 0.60–0.91; p = 0.0046) [5]. Several systematic reviews and meta-analyses had confirmed survival advantage of second-line chemotherapy when compared with BSC alone [6-8]. In Kim and colleagues' meta-analysis, which involved 410 patients, second-line chemotherapy significantly reduced the risk of death when compared with BSC [7]. Standard second-line therapies include irinotecan-based and taxane-based (docetaxel or paclitaxel) chemotherapy. Ramucirumab, a vascular endothelial growth factor receptor (VEGFR) monoclonal antibody, has also been established as monotherapy or in combination with paclitaxel in the second-line setting. Several network meta-analyses have been published to compare these second-line regimes. Combination of paclitaxel plus ramucirumab showed superior efficacy in prolonging OS when compared with single-agent chemotherapy or ramucirumab [9-11].

With the development of new chemotherapies or targeted agents which are potentially more effective and less toxic, many patients can still maintain a good general condition after failing second-line therapies. According to previous studies, around 20–90% patients were able to continue active third-line or further lines of treatment. Established third-line therapies include chemotherapies: irinotecan, taxane and TAS-102, tyrosine kinase inhibitors: apatinib and regorafenib, and immune-checkpoint inhibitors (CPIs): nivolumab and pembrolizumab. Given the expanding options for third-line therapies, there is an unmet need for clinicians to individualize treatment.

Pembrolizumab is a humanized anti-PD-1 monoclonal antibody. In the KEYNOTE-059 Cohort 1, a multicenter, open-label, single-arm phase II trial conducted at 67 sites in 17 countries, 259 patients (after failing two or more lines of chemotherapy including cisplatin and 5FU; patients with Her-2 positive tumors must have received treatment with trastuzumab) received a fixed dose of 200mg pembrolizumab in a 3-weekly cycle [12]. Pembrolizumab showed an objective response rate of 11.6% (95% CI 8.0–16.1%), with complete response of 2.3% (95% CI 0.9–5.0%). The response rate was higher in the patients with PD-L1 positive tumors (PD-L1-positive versus PD-L1-negative: 15.5% versus 6.4%). A total of seven (4%) tumors were microsatellite instable (MSI)-high (H) and the response rates were higher, with an overall response rate of 57.1%. Median PFS was 2.0 months and median OS was 5.6 months. Based on this result, the Food and Drug Administration (FDA) has approved pembrolizumab as the third line treatment for PD-L1-positive gastric adenocarcinoma. Adverse events (AE) of any grade was reported in 60.2% of patients receiving pembrolizumab. The most common any-grade AEs were fatigue, pruritis, rash, hypothyroidism, decreased appetite, anemia, nausea, diarrhea and arthralgia. Grade ≥3 treatment-related AEs occurred in 17.8% patients, with more common AEs including anemia, fatigue and diarrhea. Overall, 17.8% of patients experienced at least one immune-mediated AE of any grade; the most common were hypothyroidism (8.9%), hyperthyroidism (3.5%) and colitis (2.3%).

This study aims to explore the clinical safety and efficacy of combination of Telatinib, a potent oral inhibitor of VEGFR2 tyrosine kinase, and Pembrolizumab within the 3rd line and after treatment of locally advanced and metastatic gastric cancer

1.1.2 Hepatocellular carcinoma (HCC)

Hepatocellular cancer is the sixth most common cancer and the second leading cause of cancer mortality worldwide [13]. Heterogeneity of clinical conditions contributes to the complex management of care for patients with advanced HCC. Recently, the treatment landscape for advanced HCC has expanded rapidly, with the additional FDA approvals of several oral tyrosine kinase inhibitors (lenvatinib, regorafenib, and cabozantinib), as well as immunotherapies such as immune check point inhibitors (nivolumab and pembrolizumab) and the monoclonal IgG1 antibody, ramucirumab.

In 2007, the FDA approved sorafenib, an oral TKI targeting–among others–vascular endothelial growth factor (VEGF), the key mediator of angiogenesis, for the first-line treatment of advanced HCC in light of positive results from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study [14]. This was a multicenter, phase III, double-blind, placebo-controlled trial in treatment-naïve patients with advanced HCC that demonstrated a 2.8-month median overall survival (OS) benefit for sorafenib compared to placebo (10.7 vs. 7.9 months; hazard ratio (HR), 0.69) [14]. A second phase III trial done in the Asia-Pacific region further demonstrated that sorafenib improved median OS compared to placebo (6.5 vs. 4.2 months; HR, 0.68) [15]. Notably, both trials confirmed the antitumor activity of sorafenib in patients with well-preserved liver function (Child–Pugh A) not amenable for surgery or loco-regional therapies.

Pembrolizumab is an IgG4 anti-PD-1 cancer therapeutic that was tested in the KEYNOTE-224 non-randomized, multicenter, open-label, phase II trial [16]. This study aimed to assess the efficacy and safety of pembrolizumab in advanced HCC patients who had progression on or intolerance to sorafenib. The primary endpoint was ORR and from the 104 patients that were treated, 18 (17%) achieved the ORR and 46 (44%) patients had stable disease. Among the 18 patients who responded to pembrolizumab, there was 1 complete response and 17 partial responses. Grade ≥3 treatment-related adverse events occurred in 26% of the patients; the most common adverse events were elevated levels of aspartate aminotransferase (7%), elevated levels of alanine aminotransferase (4%), and fatigue (4%). The efficacy data from the KEYNOTE-224 trial led to the accelerated FDA approval of pembrolizumab as a second-line agent for the treatment of patients with advanced HCC who have previously received sorafenib. However, recent results of the confirmatory phase III trial, KEYNOTE-240, revealed that statistically significant improvement of the co-primary endpoints, OS and PFS, was not achieved [17]. Subsequently, many are left with uncertainty regarding the future of single agent PD-1 immune checkpoint inhibitors in the treatment landscape of advanced HCC.

1.2 Study Agent(s) Background and Associated Known Toxicities

1.2.1 Preclinical Data

Telatinib is an orally bioavailable potent inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase activity with an IC50 of 6 nM when measured in a biochemical assay. It also inhibited platelet-derived growth factor receptor (PDGFR) tyrosine kinase activity with an IC50 of 15 nM. These 2 receptors play key roles in the angiogenic process involving the stimulation of endothelial cells forming the vessel, and PDGFR-expressing pericytes supporting the newly formed vessels. Telatinib is the most selective known VEGFR inhibitor under development and is unique in its ability to discriminate the above targets from other kinase enzymes. As an oral agent, patients can achieve sustained and prolonged inhibition of the intended targets.

The drug product proposed for marketing is formulated as immediate-release tablets of telatinib mesylate for oral dosing. The tablets contain 300 mg of micronized telatinib mesylate (the dose

refers to the free base). Telatinib is administered under a continuous (uninterrupted) dosing regimen.

The pharmacology of telatinib has been extensively characterized in a series of *in vitro* receptor binding and functional assays and *in vivo* efficacy studies assessing the effects of telatinib alone and in combination with standard chemotherapeutic agents. To support the safety in humans, the nonclinical toxicology of telatinib has been evaluated in a series of single and repeat dose studies in mice, rats, rabbits, and dogs involving the oral route of administration. Complementing the toxicology studies, a series of *in vitro* and *in vivo* safety pharmacology studies, the latter in rats and dogs, were also conducted to evaluate the effects of telatinib upon central nervous, respiratory, cardiovascular, gastrointestinal, and renal systems.

1.2.2 Clinical Data

In company-sponsored studies, 185 subjects have been exposed to telatinib as a single agent. In addition, 120 subjects have been exposed to telatinib in combination with other chemotherapeutic or biologic agents in company-sponsored studies. Most subjects received 900 mg bi-daily (bid) dose continuously without interruption. Single agent antitumor activity has been demonstrated in a variety of tumor types including renal, colorectal, hepatocellular and gastric cancer. In an ongoing Phase II study of telatinib in combination with capecitabine (X) and cisplatin (P), >65% of patients have achieved a partial response (>30% reduction in tumor), which is double the expected objective response rate (ORR) from an XP combination. These responses appear durable.

The recommended Phase II dose for single agent telatinib studies is 900 mg bid administered continuously based on biologic effect (decreased serum soluble VEGFR2 levels and PK). The most common adverse events (AEs) at 900 mg bid are gastrointestinal (diarrhea, nausea, hypertension and fatigue). Drug-related AEs of CTCAE Grade 3-4 in subjects treated at a dose level of 900 mg bid continuous were hypertension and diarrhea. In an ongoing Phase II study of telatinib in combination with capecitabine (X) and cisplatin (P), preliminary results indicate the 900 mg bid dose is well tolerated without additive toxicity.

Based on the clinical studies to date, telatinib has the potential as a cancer therapeutic, in particular because of the non-overlapping toxicity profile with fluoropyrimidine, platinum, topoisomerase inhibitors and taxanes. Telatinib has a low incidence of hand-foot syndrome and myelosuppression, attributed to the selectivity of the target. Clinical results to date indicate that the 900 mg bid dose given continuously has side effects that are predictable, reversible and manageable.

1.2.3 Clinical Pharmacokinetics

After oral administration of 14C-labeled telatinib to rats, the absorption of radioactivity from the GI tract was almost complete. In dogs, the mean absorption was 35% and showed high inter-individual variability. Bioavailability was high in rats (about 100%) and low in dogs (2-11%). The low bioavailability in dogs was due to pronounced first-pass metabolism and limited absorption. The PK of telatinib was characterized by low variability in rats. In dogs, however, high variability of the plasma concentration vs. time profiles of telatinib was observed, especially after oral administration. PK of telatinib was almost linear in rats after oral administration in terms of AUC (dose range: 0.075-50 mg/kg). Cmax increased less than dose proportionally. In dogs, an over- proportional increase in AUC was observed after iv infusion of 1 and 3 mg/kg. The Cmax and AUC values increased less than dose proportionally after oral administration in the investigated dose range of 1-500 mg/kg. A pronounced decrease in exposure was observed after repeated oral administration of high doses in rats and dogs. The blood clearance was very low in rats (0.2 L/kg*h) but moderate in dogs (1.1 L/kg*h). The Vss was moderate in both species (0.5-0.8 L/kg).

The terminal plasma elimination half-lives of telatinib were between 2.1 and 3.4 h after oral administration (interval: up to 31 h) in rats. In dogs, the corresponding terminal half-life was about 1 h and was recorded in the interval up to 8 h after administration. Protein binding of telatinib was high and species dependent. The fractions unbound to plasma proteins ranged from 0.2-1.6%

in all investigated species (mouse, rat, rabbit, dog, Rhesus monkey, and human). Albumin was identified as important binding site in human plasma. There was no saturation of plasma protein binding in the investigated concentration range of 1-100 mg/L.

The radioactivity was homogeneously distributed to organs and tissues of rats after intravenous and oral administrations of 14C-labeled telatinib. The CEQmax and the AUC of radioactivity was similar to blood in most of the organs and tissues. Moderate penetration across the blood/brain barrier was observed. Considerable higher radioactivity exposure than in blood was determined in liver, adrenals, and kidneys. The radioactivity concentrations were more than 100 times higher in the eye-wall of the pigmented rats in comparison with the albino rats. This reflects the affinity of radioactivity to melanin-containing tissues. After 7 days, elimination was virtually complete. With the exception of the enrichments of radioactivity in melanin-containing tissues in the pigmented rat, there was no evidence of irreversible binding or retention of radioactivity in organs and tissues of rats.

Incubation of telatinib with liver microsomes of different species revealed Rhesus monkey and Wistar rat as most human-like animals regarding oxidative Phase I biotransformation reactions (Table 9). New Zealand rabbit, Beagle dog, CD-1 mouse, and NMRI mouse were also regarded human-like animals. Hydroxylation of the N-methyl group, leading to metabolite M-1, was distinguished as major primary Phase I reaction followed by N-demethylation leading to M-2. The cleavage of the ether bond leading to metabolite M-3 was found to a minor extent.

Table 9: Metabolite Profiles [% of Radioactivity] in Incubations with Liver Microsomes 3 h After Start of Reaction

Item	Man (mix)	Rhesus Monkey	Wistar Rat (male)	Beagle Dog	NMRI Mouse	New Zealand Rabbit	CD-1 Mouse (male)
M-1	21.6	15.9	19.1	5.9	5.3	15.9	9.1
M-2	5.0	9.7	4.0	2.2	1.0	3.4	2.1
M-3	4.0	6.2	0.9	-	-	-	-
Drug	54.7	47.9	57.9	55.9	83.2	67.5	70.2

Upon incubation of 14C-labeled telatinib with rat hepatocytes, M-2 was detected as a most important metabolite. In addition, metabolite M-1 was found in low amounts. Incubation with dog hepatocytes led to metabolites M-1, M-2, and M-3 in small concentrations and M-7 and M-9 as the 2 major metabolites. The latter were identified as sulfates formed by hydroxylation of the p-chlorophenyl moiety followed by sulfate conjugation. The metabolic profile in human hepatocytes showed 2 N-glucuronides, M-4 and M-5, as major metabolites, whereas metabolites M-1, M-2, and M-3 were present in only low concentrations.

Table 10: Metabolite Profiles [% of Radioactivity] in Incubations with Hepatocytes of Rat, Dog, and Man Cultured by the Sandwich Model

Time [h]	Rat		Dog		Man	
	24	48	24	48	24	48
M-1	5.7	4.0	4.4	-	-	-
M-2	8.9	8.1	6.2	1.7	1.9	-
M-3	2.3	2.5	9.3	10.4	2.8	1.3
M-4	-	-	-	-	42.7	44.9
M-5	-	-	-	-	40.0	38.7
M-7	-	-	12.6	24.0	-	-
M-9	-	-	12.6	30.9	-	-
Drug	61.3	56.1	32.4	2.7	6.4	2.6

Thus, the in vitro data indicated that direct drug glucuronidation may play an important role in the metabolism of telatinib in man. This hypothesis was confirmed after evaluation of the human mass balance study using 14C-labeled telatinib in healthy volunteers.

1.3 Rationale of Combining Telatinib and Pembrolizumab

1.3.1 Telatinib

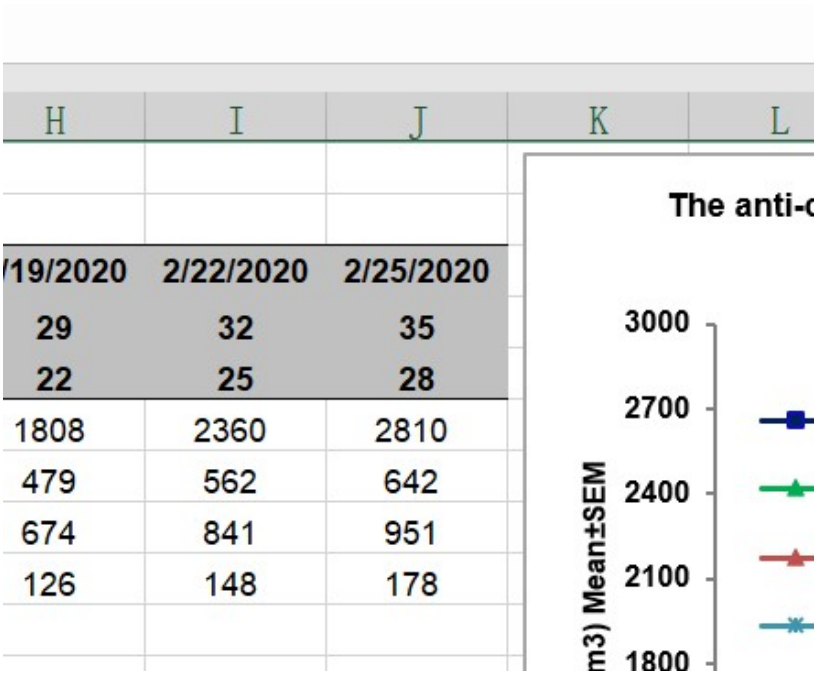
Telatinib, a potent oral inhibitor of VEGFR2 tyrosine kinase, targets the multi-faceted roles of VEGF/VEGFR signaling in immune suppression, including within tumor microenvironment stopping or blocking angiogenesis and hypoxia process, regarding Treg, stopping or blocking Treg proliferation, regarding MDSC, stopping or blocking recruitment and proliferation of MDSC, also regarding cytotoxic T-cells, promoting cytotoxic T-cells recruitment, effector function and trafficking, et al.

1.3.2 Pembrolizumab

Pembrolizumab, as an IgG4 subclass antibody, is preferred over other subclasses as it only induces weakly the complement and cell activation due to low affinity to C1q and Fc receptors. It binds with high affinity to the cell surface receptor programmed cell death protein 1 (PD-1) and it antagonizes its interaction with its known ligands PD-L1 and PD-L2. In normal circumstances, the binding of the ligands of PD-1 to the receptor inhibits the TCR-mediated T cell proliferation and cytokine production. This inhibitory signal seems to be essential for self-tolerance, collateral damage minimizing after immune response against a pathogen and maternal tolerance to fetal tissue. Therefore, the binding of pembrolizumab to PD-1 prevents the inhibitory pathway causing a physiological shift to immune reactivity and enhancing tumor immunosurveillance and anti-tumor immune response.

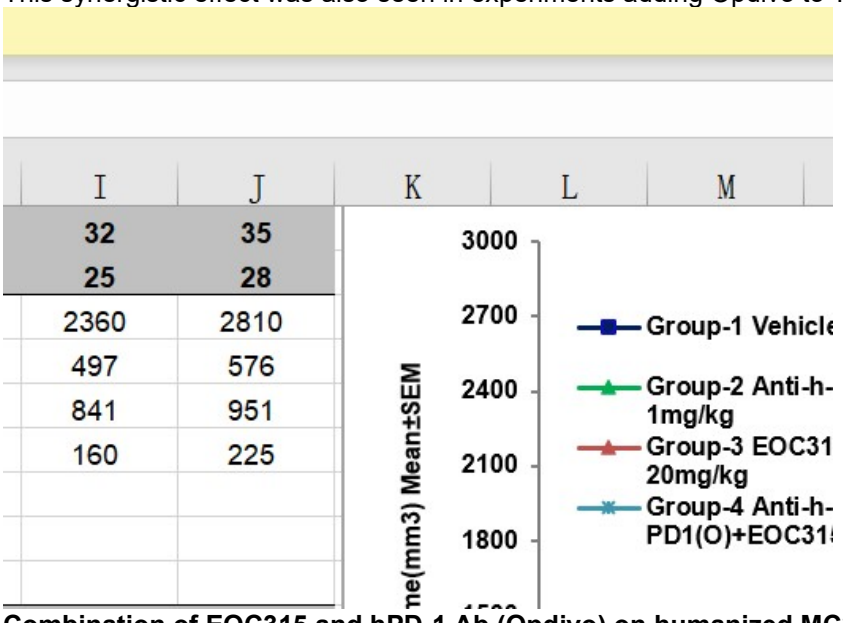
1.3.3 Preclinical data of Telatinib combined with Pembrolizumab

Preclinical data is consistent with excellent synergy with the addition of Telatinib to check point inhibitors. The combination of Telatinib and Keytruda was more active than either agent alone in a humanized MC38 tumor model.



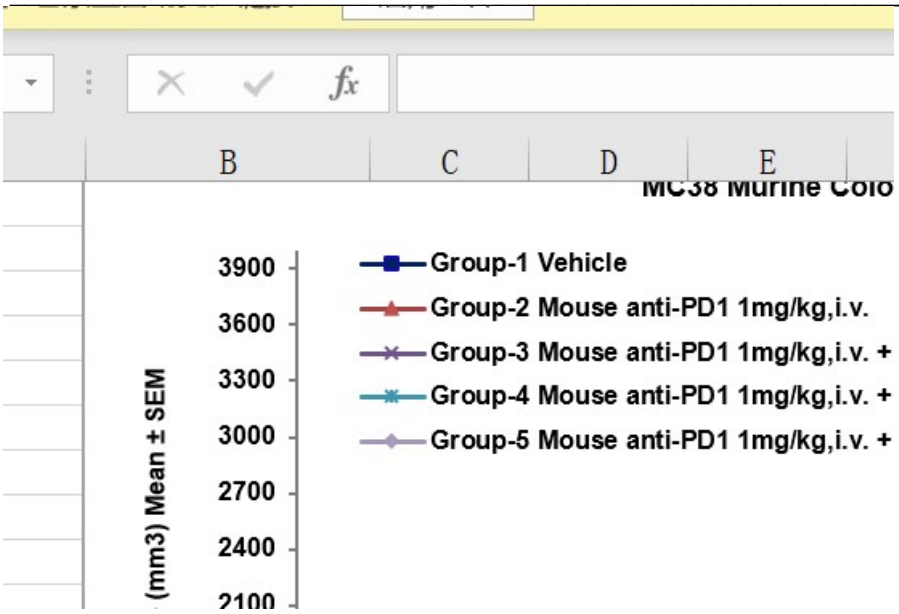
Combination of EOC315 and hPD-1 Ab (Keytruda) on humanized MC38 tumor model

This synergistic effect was also seen in experiments adding Opdivo to Telatinib.



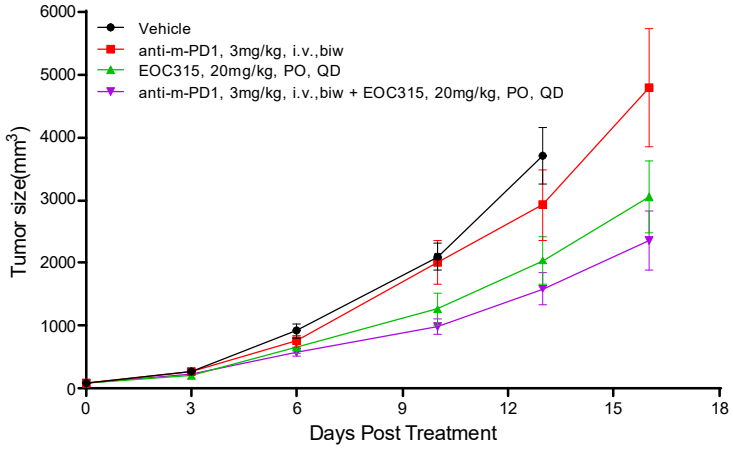
Combination of EOC315 and hPD-1 Ab (Opdivo) on humanized MC38 tumor model

Several *in vitro* models evaluating the combination of checkpoint inhibition to Telatinib also showed a dose response benefit. The combo regimen anti-m PD-1 1mg/kg and Telatinib with different dosage (2mg/kg, 6mg/kg and 20mg/kg) compared with single drug (anti-m PD1), which demonstrated that the combo regimen had better suppressed efficacy for tumor growth according to EOC315 dose escalation.



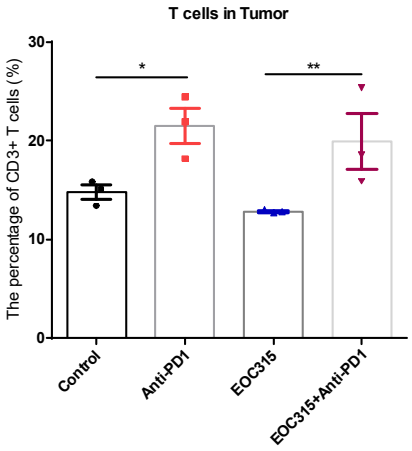
Combination of PD-1 blockage with different dose of EOC315 on MC38 tumor model

The benefit of this combinatorial regimen extended to varying cell-lines and doses of checkpoint inhibition. In the anti-m PD-1 3mg/kg dosage, the tumor model shown tumor growth was inhibited. In the Telatinib 20mg/kg dosage, the tumor model shown tumor growth was inhibited. The combo regimen (anti-m PD-1 3mg/kg and EOC315 20mg/kg) compared with single drug (anti-m PD-1 or EOC315), demonstrated that the combo regimen had better suppression efficacy for CT26 tumor growth.



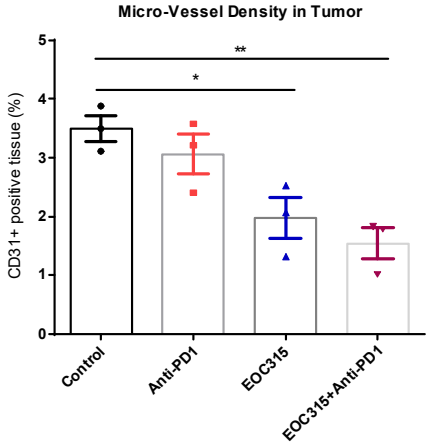
Combination of EOC315 and PD-1 blockage on CT26 tumor model

The addition of telatinib in addition to checkpoint inhibition also increased t-cell infiltration in tumor models. Comparing EOC315 and combination regimen, T cell infiltration ratio was significantly increased in the tumor model(mouse) that received the combination regimen (EOC315 20mg/kg and anti-m PD1 1mg/kg) vs EOC315 alone.



T cell infiltration in tumors treated with Anti-PD-1, EOC315 and combo

Micro-vessel density in tumor was significantly altered when challenged with EOC315. However, checkpoint inhibition had minimal effect on tumor vasculature. There was a substantial increase in CD-8 infiltration in patients with checkpoint inhibitors. The combination of EOC315 20mg/kg and anti-m PD1 1mg/kg compared with single drug (anti-PD-1 or EOC315), resulted in a significant decrease in micro-vessel density. Consequently, the combination regimen had a synergetic effect.



Micro-vessel density in tumors treated with Anti-PD-1, EOC315 and combo

Pre-clinical data suggests that the addition of checkpoint inhibition to Telatinib will provide synergistic improvement in efficacy. This effect is dose responsive with escalating doses of telatinib. The combination regimen improves CD8 T-cell infiltration into the tumor. The combination also reduces tumor micro-vessel density.

1.4 Correlative Studies

Previous studies have demonstrated potential toward the use of plasma biomarkers for prognostic and predictive applications in advanced gastric cancer and HCC. Pro-inflammatory cytokines have been shown to correlate with the development and progression of gastric cancer and HCC tumors [18-20]. It is of interest to determine if telatinib in combination with Keytruda has an impact on inflammatory cytokines associated with advanced gastric cancer or HCC. Plasma metabolites have been studied as potential

biomarkers for gastric cancer and HCC [21-24]. Changes in immune cell profiles have been shown to correlate with treatment response [25-28]. A blood sample will be collected from the patient at the start of each odd cycle of treatment and at the end of the study. Inflammatory cytokines, metabolites, and immune cell profiles as potential biomarkers and prognostic indicators will be measured in the plasma.

Recent evidence suggests that the gut microbiome is associated with cancer progression. This has been demonstrated for both gastric cancer and HCC [29-33]. Stool samples collected at baseline and cycle three, will allow microbiome changes to be investigated. Correlations with favorable treatment responses using telatinib in combination with Keytruda will be further interrogated. Recent studies have begun to look at fecal metabolites as a potential biomarker in cancer [34-36]. We will also investigate the potential for stool metabolites as a biomarker in gastric cancer and HCC. Furthermore, associations of inflammatory cytokines, metabolites, and microbiome changes will provide insight on the mechanistic action of the combination of telatinib and Keytruda.

2.0 STUDY OBJECTIVES

Response will be assessed using RECIST 1.1 criteria. Upon initial radiographic evidence of progression, treatment may continue until repeat imaging is performed 4-8 weeks later (see Section 5.3).

2.1 Primary Objective

The primary objective is to assess progression-free survival (PFS) in subjects with advanced gastric cancer or HCC receiving telatinib in combination with Keytruda.

2.2 Secondary Objectives

2.2.1 Overall response rate (ORR)

2.2.2 Disease control rate (DCR) (CR+PR+SD)

2.2.3 Overall survival (OS)

2.2.4 Safety

2.3 Exploratory Objectives

2.3.1 Time to progression (TTP)

2.3.2 Change in inflammatory cytokines

2.3.3 Change in plasma metabolites

2.3.4 Change in immune cell profile

2.3.5 Change in stool microbiome

2.3.6 Change in stool metabolites

2.4 Endpoints

2.4.1 Primary Efficacy Endpoint

- PFS: Length of time from the start of treatment until the date of first observed disease progression (radiological or clinical, whichever is earlier), or the date of death due to any cause, whichever occurs first

2.4.2 Secondary Efficacy Endpoints

- ORR: Percentage of patients who have a best overall response of partial response (PR) or complete response (CR)
- DCR: Percentage of patients who have achieved complete response, partial response, or stable disease
- OS: Length of time from the start of treatment until death due to any cause

2.4.3 Safety Evaluations

- Incidence and severity of adverse events by CTCAE V5

2.4.4 Exploratory Endpoints

- TTP: Length of time from the start of treatment until the date of first observed disease progression (radiological or clinical, whichever is earlier)
- The effect of immune modulation will be assessed by inflammatory cytokines in subject plasma samples
- Plasma metabolite changes from baseline/C1D1 and over time with treatment
- Immune cell profile (ex. T-cells) from baseline/C1D1 and over time with treatment
- Stool microbiome changes from baseline and over time with treatment, compared to samples collected from subjects on SOC Keytruda through the GI-Bank protocol (IRB# Pro00054363)
- Stool metabolite changes from baseline/C1D1 and over time with treatment, compared to samples collected from subjects on SOC Keytruda through the GI-Bank protocol (IRB# Pro00054363)

3.0 STUDY DESIGN

This is a phase II, single arm, open-label study of two parallel cohorts (AGC and HCC), evaluating the effects of telatinib in combination with Keytruda on progression-free survival.

4.0 PATIENT ELIGIBILITY

Enrollment will follow the safety stopping rules described in Section 9.4, with interim looks after completion of the first cycle of treatment for the 6^{th} subject in each cohort, and again after completion of the first cycle of treatment for the 15^{th} subject in each cohort. Any enrollment holds deemed necessary for the evaluation of stopping rules will be at the discretion of the PI.

4.1 Inclusion Criteria

4.1.1 *Diagnosis:*

4.1.1.1 Histologically confirmed gastric/esophagealgastric adenocarcinoma, recurrent, locally advanced or metastatic, PD-L1-positive disease (CPS ≥1), progressed on at least two prior lines of therapy and/or discontinued second line therapy for intolerance, indicated for Keytruda therapy.

OR

4.1.1.2 Hepatocellular carcinoma, with diagnosis confirmed by histologic or cytologic analysis or clinical features according to the American Association for the Study of Liver Diseases criteria for patients with cirrhosis, unresectable disease not amenable to locoregional therapy with disease progression after at least one prior line of systemic therapy or discontinued first line therapy for intolerance.

4.1.2 At least 1 measurable metastatic lesion that has not been irradiated. The lesion will be measured according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and be documented by radiological evaluation within 28 days prior to registration. ***For subjects with locally advanced disease:*** at least one measurable lesion that has not been irradiated, documented by radiological evaluation within 28 days prior to registration.

4.1.3 Any prior radiation therapy must be completed at least 28 days prior to C1D1.

4.1.4 Eighteen years of age or older.

4.1.5 Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, or 2.

4.1.6 Adequate bone marrow, liver, and renal function as assessed by:

4.1.6.1 Hemoglobin ≥ 9.0 g/dL

4.1.6.2 Absolute neutrophil count (ANC) ≥1500/mcL

4.1.6.3 Total bilirubin ≤ 3.0 times the upper limit of normal (ULN)

4.1.6.4 Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5.0 x ULN in the presence of liver metastasis; ALT and AST ≤ 3.0 x ULN in the absence of liver metastasis

4.1.6.5 International normalized ratio for prothrombin time (PT/INR) ≤ 1.5 and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the subject has been on a stable dose of anticoagulants for at least two weeks before C1D1.

4.1.6.6 Serum creatinine ≤ 1.5 times the ULN

AND/OR

Calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault formula. Subjects with a calculated creatinine clearance below 60 mL/min may be eligible if a measured creatinine clearance (based on 24-hour urine collection or per institutional standards) is ≥ 60 mL/min.

Calculated Creatinine Clearance = ((140 – Age in years) / (serum creatinine)) * (Weight in kg / 72) * 0.85 (if female)

4.1.7 Negative urine or serum pregnancy test for women of childbearing potential.

4.1.8 Women of childbearing potential and men must agree to use adequate contraception (examples include condom, intrauterine device (IUD), oral contraceptive, double-barrier method, etc.), prior to registration, for the duration of study participation and until 4 months after the last study drug dosing.

4.1.9 Able and willing to sign a written informed consent. A signed informed consent must be appropriately obtained prior to any study specific procedures.

4.1.10 Able to comply with study procedures and other protocol requirements and, receive outpatient treatment, laboratory monitoring and follow-up examinations at the institute that administers the study drug.

4.1.11 Able to swallow and agree to take the prescribed tablets twice daily.

4.2 Exclusion Criteria

4.2.1 Clinical or radiographic evidence of current brain metastasis. History of treated brain metastases is allowable.

4.2.2 Cardiac disease defined by:

a) Congestive heart failure > class II New York Heart Association (NYHA), or

b) Unstable angina (anginal symptoms at rest), or new-onset angina (began within the last 12 months), or myocardial infarction within the 12 months prior to registration, or

c) Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy or

d) Atrial fibrillation or atrioventricular heart block

4.2.3 Uncontrolled hypertension (defined as persistent elevation of systolic blood pressure >150 mmHg or diastolic pressure > 100 mmHg; if screening BP measurement exceeds these parameters, BP measurement must be repeated at least one day later during the screening period; if repeat BP measurement exceeds these parameters, the subject should be excluded; if repeat measurement does not exceed these parameters, the subject is not excluded.)

4.2.4 Any (including pulmonary) hemorrhage/bleeding event Grade 3 or greater by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V5 within 28 days prior to C1D1.

4.2.5 Major surgery, open biopsy, or significant traumatic injury within 42 days prior to C1D1.

4.2.6 Current serious, nonhealing wound, ulcer, or bone fracture within 42 days prior to C1D1.

4.2.7 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to C1D1.

4.2.8 Presence of an uncontrolled infection or infection that required IV antibiotics, antifungals, or antivirals within 14 days of C1D1.

4.2.9 Known human immunodeficiency virus (HIV) infection. HIV-infected subjects on effective anti-retroviral therapy are eligible if the most recent viral load test performed within six

months of screening (based on medical chart review) is negative. The safety of telatinib in this subject population has not been studied.

4.2.10 Known chronic hepatitis B, unless receiving antiviral treatment.

4.2.11 Known Child-Pugh Score B or C liver cirrhosis.

4.2.12 Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment or has been diagnosed with an autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Patients that require replacement therapy (e.g., thyroxine [T4], insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) may be enrolled.

4.2.13 History of (non-infectious) pneumonitis that required steroids, or current pneumonitis, or has a history of interstitial lung disease.

4.2.14 Has received a live-virus vaccination within 30 days of planned treatment start.

4.2.15 Known history of proteinuria > 1gr/24 hours.

4.2.16 Previous or concurrent cancer that is distinct in primary site or histology from the current stomach or liver cancer. Subjects with cervical cancer in-situ, treated basal cell carcinoma, superficial bladder tumors (Ta and Tis) or any cancer curatively treated are not excluded.

4.2.17 Anti-cancer therapy (chemotherapy, hormonal therapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) or investigational agent within 28 days prior to C1D1.

4.2.18 Known or suspected allergy to any component of telatinib or Keytruda

4.2.19 Prior or current history of substance abuse, or medical, psychological, or social condition that in the opinion of the investigator may interfere with the subject's participation in the study or evaluation of the study result.

4.2.20 Women who are pregnant or breastfeeding.

4.2.21 Prior history of thromboembolic disease, e.g., deep vein thrombosis (DVT), pulmonary emboli (PE), within 6 months of C1D1 that has required continued medical intervention.

4.2.22 Baseline peripheral neuropathy of Grade 2 or greater.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Telatinib will be self-administered orally twice daily. Subjects will complete a dosing diary throughout the study treatment period. Oral compliance will be determined through review of the DARF. Oral compliance for Telatinib is 50%. Less than 50% compliance is considered a deviation reportable to the IRB.

Pembrolizumab will be administered at a dose of 200mg as a 30 minute IV infusion Q3W. Effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given

the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Drug	Dose/Potency	Dose/ Frequency	Route of Administration	Regimen/ Treatment Period
Telatinib	900 mg	BID	Orally	Daily (each cycle = 3 weeks)
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle

5.2 Toxicities and Dosing Delays/Dose Modifications

Telatinib known toxicities include:

- Nausea, vomiting, and diarrhea: Antiemetics and antidiarrheal agents may be administered to prevent or control symptoms.
- Hypertension
- Fatigue
- Liver injury
- Proteinuria/renal injury
- Hand and foot syndrome: Symptomatic therapy may be provided if necessary.
- Hypokalemia: Potassium treatment should be given in the event of hypokalemia.
- Hemorrhage
- Gastrointestinal perforation
- Cardiac function abnormality

Please refer to the telatinib IB for more details.

Toxicities may be treated symptomatically per standard of care/investigator discretion. Telatinib administration may be held at the investigator's discretion for any reason. Dose modifications are permitted. Any dose holds or modifications will be documented in the research record.

Dose Modifications and Delays for Telatinib
General dose reductions for telatinib are outlined in the following table.

Dose Level	0	-1	-2
Telatinib	900 mg BID (3 tablets twice a day)	600 mg BID (2 tablets twice a day)	300 mg BID (1 tablet twice a day)

If a dose reduction of telatinib is required and the toxicity resolves and no additional toxicities are seen after 6 weeks of treatment at the reduced dose (2 cycles), then telatinib may be increased to the dose prior to the reduction, not to exceed the original dose of 900mg (3 tablets) BID.

Any clinical event that requires dose reduction must be recorded as an AE and recorded in the CRF. For any dose that is not administered according to the protocol, the reason for the omission must be recorded in the CRF.

Suggested Dose Modifications for Telatinib-Associated Toxicities

Toxicity	Non-hematologic	Hematologic
Grade 1	● Continue at the same dose level	● Continue at the same dose level
Grade 2	● Continue at the same dose level	● Continue at the same dose level
Grade 3*	● Withhold dose until toxicity is grade ≤2, then resume treatment at the same dose level.	● Continue at the same dose level

	● If subject experiences a second grade 3 toxicity, withhold dose until toxicity is grade <1, then reduce 1 dose level and resume treatment	
Grade 4**	● Withhold dose until toxicity is grade ≤2, then reduce 1 dose level and resume treatment, or discontinue at the discretion of Investigator	● Withhold dose until toxicity is grade ≤2, then reduce 1 dose level and resume treatment, or discontinue at the discretion Investigator

*Subjects who develop grade 3 fever/chills, grade 3 elevation of hepatic transaminases with ALT and AST <10X ULN, grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, grade 3 hypophosphatemia, grade 3 leukopenia, or grade 3 lymphopenia may continue telatinib without interruption at the discretion of the Investigator. NOTE: Refer to CTCAE v 5.0 for grade definitions.
**Subjects with grade 3 or 4 allergic reactions to telatinib should be removed from treatment. Subjects with grade 2 allergic reactions should be carefully assessed for potential risk of serious or life-threatening reactions following re-exposure to telatinib.

Pembrolizumab
Pembrolizumab toxicities and dosing delays/dose modifications will be managed per standard of care, the package insert, and investigator discretion. Pembrolizumab is associated with immune-related adverse events and infusion reactions. Please refer to the package insert for more details.

In the event that pembrolizumab is discontinued, treatment with telatinib may continue.

5.2.1 Treatment-Related Serious Adverse Events

Non-hematologic serious adverse events, graded 3 or 4 per CTCAE v5, deemed probably related or related to telatinib (alone or in combination), occurring within the first cycle of treatment, will be monitored throughout the study for safety stopping rules (see Section 9.4). Serious adverse events deemed probably related or related to Keytruda alone will not count toward safety stopping rules.

5.3 Treatment Duration and Confirmation of Progression

Subjects will continue treatment until disease progression, intolerable toxicities, or withdrawal of consent.

In patients with initial disease progression substantiated by radiographic imaging per RECIST 1.1, study treatment may continue until repeat imaging is conducted, at least 4 weeks and no later than 8 weeks later, under the following conditions:

- No worsening of ECOG Performance Status
- No clinically relevant increases in disease-related symptoms thought to be associated with disease progression
- No requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

5.4 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, 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, immunotherapy, biologic therapy, or tumor embolization) or investigational agent may be used from 28 days days prior to C1D1 until study treatment discontinuation.

5.5 Duration of Study Participation

The study duration per subject will be up to 28 days of screening, up to an estimated 12 months on treatment (until disease progression, intolerable toxicities, or withdrawal of consent), and 30 days of follow-up. Survival follow-up will continue until death (estimated approximately 6 months).

5.6 Removal of Patients from Protocol

Patients will be removed from the study when any of the criteria listed in *Section 6.5* 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.

5.7 Evaluable for toxicity

Any patient who receives at least one dose of investigational product (telatinib) is evaluable for toxicity and will be included in the safety analysis.

5.8 Subject Replacement

Subjects who withdraw from the study prior to starting study treatment (telatinib) will be replaced.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

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 C1D1 unless otherwise stated. Baseline procedures not used for eligibility verification may occur on C1D1 of treatment. The screening/baseline procedures include:

6.1.1 Informed Consent

6.1.2 Medical history and record review

Relevant medical history, including history of current disease and information regarding underlying diseases, will be recorded at Screening.

6.1.3 Demographics

Age, sex, race, ethnicity

6.1.4 Review subject eligibility criteria

6.1.5 Physical exam including weight, height, vital signs, and ECOG Performance Status

6.1.6 Adverse event assessment

Baseline symptoms will be assessed at Screening. 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).

6.1.7 Concomitant Medications Review

6.1.8 Laboratory Evaluations

- Hematology (Complete blood count (CBC) with differential)
- Serum chemistries (Comprehensive metabolic panel (CMP)), including: glucose, sodium, potassium, chloride, carbon dioxide, anion gap, blood urea nitrogen, creatinine, calcium, total bilirubin, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase
- Tumor markers
  - HCC: AFP, CA19-9
  - Gastric: CEA, CA19-9
- Thyroid panel (T3 Free, T4 Free, thyroid stimulating hormone)
- Coagulation (PT, INR, aPTT)
- Urinalysis (including urine protein)

6.1.9 Pregnancy Testing for WOCBP (urine or serum)

6.1.10 Imaging (CT chest/abdomen/pelvis and/or MRI) (within 28 days prior to *registration*)

6.1.11 ECG

6.1.12 Research stool sample collection and completion of 24-hour food recall and stool survey

May be collected up to 4 weeks prior to C1D1 or on C1D1. The 24-hour food recall and stool survey should be completed on the same day as the stool sample collection, if feasible (not required).

6.2 Procedures During Treatment

6.2.1 Prior to Each Treatment Cycle

- Physical exam, weight, vital signs, ECOG Performance Status
- Hematology
- Serum chemistries
- Urinalysis

6.2.2 Each Cycle Day 1

- Pembrolizumab administration
- Adverse events assessment
- Concomitant medications review
- Tumor markers
- Thyroid panel (TSH with reflex to T3 and T4 if TSH is abnormal) (even cycles only)

- Fasting research blood collection (odd cycles only beginning with C1D1) (patients must fast for 8 hours prior to blood collection, water is allowed)
- Research stool sample collection, completion of 24-hour food recall, and stool survey (C3D1 only). The 24-hour food recall and stool survey should be completed on the same day as the stool sample collection, if feasible (not required).

6.2.3 Throughout the treatment period

- Telatinib self-administration and completion of dosing diary
- Drug supply and dosing diary will be returned at the next Cycle Day 1 (or for the last cycle, at the end-of-treatment visit) for compliance diary review and pill count.
- Imaging as per standard of care or every 9 weeks for response assessment (RECIST 1.1)
  - Upon initial radiographic disease progression per RECIST 1.1, treatment may continue until confirmation of progression at least 4 weeks and no later than 8 weeks later (see Section 5.3).

6.2.4 30 days after treatment termination (+/- 7 days)

- Physical exam, vital signs, weight, ECOG Performance Status
- Hematology
- Serum chemistries
- Tumor markers
- Adverse events assessment
- Concomitant medications review
- *If indicated:* Imaging (CT or MRI) with response assessment (RECIST 1.1)
- Fasting research blood collection (patients must fast for 8 hours prior to blood collection)

6.3 Follow-up Procedures

Patients will be followed every 12 weeks (+/- 14 days) after completion of (or early withdrawal from) study treatment until death for survival and progression assessment via medical record review, telephone contact, or in-clinic contact.

6.4 Time and Events Table

Procedure	Screening/ Baseline (Within 4 weeks of C1D1)	Each Cycle Day 1 (+/- 3 days) (each cycle = 3 weeks / 21 days)	End of Treatment	Survival Follow-up
			30 days after drug discontinuation (+/- 7 days)	Every 12 Weeks (+/- 14 days) until death
Informed Consent	X			
Medical History and record review	X			
Demographics	X			
Review subject eligibility criteria	X			
Physical Exam	X	X	X	
Height (at screening only) and weight	X	X	X	
Vital signs	X	X	X	
ECOG Performance Status	X	X	X	
Adverse Event Assessment	X	X	X	
Concomitant Medications	X	X	X	
Hematology	X	X	X	
Chemistry	X	X	X	
Tumor markers	X	X	X	
Thyroid panel (TSH with reflex to T3 and T4 if TSH is abnormal)	X	X (even cycles only)		
Coagulation (PT, INR, aPTT)	X			
Urine or serum pregnancy test	X			
Urinalysis	X	X		
ECG	X			
CT Scan (Chest, Abdomen, Pelvis) and/or MRI	X[1]	As per standard of care (or every 9 weeks for response assessment by RECIST 1.1)[2]		
Pembrolizumab Administration		X		
Telatinib Administration and Dosing Diary completion		X (continuous throughout treatment period)[3]		
Telatinib Dosing Diary Review and pill counts[3]		X	X	

Procedure	Screening/ Baseline (Within 4 weeks of C1D1)	Each Cycle Day 1 (+/- 3 days) (each cycle = 3 weeks / 21 days)	End of Treatment	Survival Follow-up
			30 days after drug discontinuation (+/- 7 days)	Every 12 Weeks (+/- 14 days) until death
Research blood collection		X[4]	X	
Research stool sample collection, completion of 24-hour food recall and stool survey[5]	X[5]	X[5]		
Survival and progression assessment (by medical record review, phone call, or clinic visit)				X

[1] Screening/baseline imaging to be conducted within 28 days prior to *registration.*

[2] Upon initial radiographic disease progression, treatment may continue until repeat imaging is conducted 4-8 weeks later (see Section 5.3).

[3] Subjects will be given a telatinib dosing diary at Cycle 1 Day 1, and at Day 1 of each subsequent cycle while taking telatinib. The completed diary and remaining drug supply will be collected at the next cycle Day 1 (or for the last cycle, at the end-of-treatment visit) for a pill count and diary review.

[4] Fasting research blood collection will occur every odd cycle beginning with C1D1 and at the end-of-treatment visit. (patients must fast for 8 hours prior to blood collection, water is allowed)

[5] Research stool sample collection and completion of 24-hour food recall and stool survey will occur at screening/baseline (within 4 weeks of C1D1 or on C1D1) and C3D1 (to be collected +/- 3 days of cycle start).

6.5 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:

6.5.1 Patient voluntarily withdraws (follow-up permitted);

6.5.2 Patient withdraws consent (termination of treatment and follow-up);

6.5.3 Patient is unable to comply with protocol requirements;

6.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

6.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

6.5.6 Treating physician determines continuation on the study would not be in the patient's best interest;

6.5.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

6.5.8 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;

6.5.9 Lost to follow-up. *If a research subject cannot be located to document survival after a period of 1 year, the subject may be considered "lost to follow-up." All attempts to contact the subject during the one year must be documented. This will be reviewed during an interim data monitoring visit.*

7.0 ADVERSE EVENTS (AE)

7.1 Definitions

7.1.1 Adverse Event

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

7.1.1.1 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 Events (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.
- In-patient 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 to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research).

7.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected unexpected serious adverse reactions (SUSARs) include adverse events that are deemed unexpected, serious, and as having a reasonable possibility of a causal relationship with the study drug.

7.2 Principal Investigator Responsibilities for Safety Monitoring

The investigator or designee is responsible for ensuring that adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur from treatment administration on Cycle 1 Day 1 and until 30 days following the last dose of the study drug or until initiation of a new anticancer therapy (whichever occurs first), are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

7.2.1 AE Documentation

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), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will document the following for all adverse events (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 http://ctep.cancer.gov/reporting/ctc.html
- 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
- 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 conmed or other intervention, etc.
- Outcome of event

Source documentation must be available to support all AEs.

7.2.2 Duration of AE monitoring

All patients experiencing an adverse event, 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 value deemed an AE as per section 7.1.1.1, has returned to baseline
- there is a satisfactory explanation other than the study drug for the changes observed
- death, or
- until 30 days following last dose of study drug or until initiation of a new anticancer therapy (whichever occurs first)

7.2.3 Pembrolizumab

As pembrolizumab is FDA-approved for this indication and used in accordance with the package insert, only events determined to be unexpected and at least possibly related to pembrolizumab will be recorded in the eCRF.

7.3 Safety Reporting Requirements

7.3.1.1 Reporting to the Principal Investigator

The Principal Investigator must be notified by study staff or co-investigators within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug or until initiation of a new anticancer therapy (whichever occurs first).

Contact for Expedited Reporting:
Andrew Hendifar, MD, MPH
310-423-2217; Andrew.Hendifar@cshs.org

Alternate Contact for Expedited Reporting:
Jun Gong, MD
310-423-5776; Jun.Gong@cshs.org

7.3.1.2 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 to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

7.3.1.3 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, 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: Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.

- Any internal AE, SAE 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.
- 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.
- Any accidental, unintentional protocol or consent/HIPAA related deviation that may impact subjects’ rights, safety, or welfare. See section 10.8.3.
- Any planned protocol exception or eligibility waiver. See sections 10.8.2 and 10.8.3.

- 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 5 business days.)
- 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.
- Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
- Breach or potential breach of confidential or sensitive information.
- Subject complaints or concerns that cannot be resolved by the research staff to the subject's satisfaction.
- Incarceration of a subject who is enrolled in a study that is not approved by the IRB to include prisoners.

7.3.1.4 Reporting to the Food and Drug Administration

The sponsor-investigator of the IND, or designee must submit all reported SUSARs to the FDA on FDA Form 3500A (MedWatch).

The sponsor-investigator of the IND must notify the FDA as soon as possible but no later than:

- **7 calendar days** after the sponsor-investigator's initial receipt of the information in a written IND safety report of any **fatal or life-threatening SUSARs**.
- **15 calendar days** after the sponsor-investigator's initial receipt of the information in a written IND safety report of any **non-fatal / non-life-threatening SUSARs**.

Copies of IND Safety Reports will be kept in the Trial Master File in the SOCCI CCTO.

7.3.1.5 Reporting to EOC Pharma

SUSARs reported to the FDA as per Section 7.4.2.4 will be sent to EOC Pharma within 3 days of awareness via the MedWatch FDA Form 3500A, and emailed to eoc.pv@eocpharma.com.

8.0 CORRELATIVES/SPECIAL STUDIES

The effect of immune modulation will be assessed by inflammatory cytokines in subject plasma samples. Changes in metabolites and inflammatory biomarkers will also be assessed in plasma. Changes in the stool microbiome will be assessed by 16s and/or shotgun metagenomics analysis. Stool metabolites will also be measured by MS-based quantitation. Stool microbiome and metabolites will be compared to samples collected from subjects on SOC Keytruda collected through the GI-Bank protocol (IRB# Pro00054363).

8.1 Plasma and PBMC Collection / Specimen Banking

Immune modulation will be assessed by FACS from PBMCs, inflammatory cytokines and metabolites will be assessed in the plasma.

- A fasting morning research plasma sample will be collected at odd cycles during the study and at the end-of-treatment visit.
- Samples will be processed in the CSMC CCTO lab or Biobank.

- Samples will be stored indefinitely in Dr. Hendifar's Biobank rental freezer.

8.2 Stool Specimen Collection / Banking

8.2.1 Materials/ Sample Collection

- A research stool sample will be collected at screening/baseline and C3D1. A stool collection kit will be given to the patient during the physical exam, where the patient will be advised to follow the instructions on the kit and bring their sample into laboratory within 4 weeks prior to Cycle1/Day1 or on Cycle 1 Day 1, and at C3D1 (+/- 3 days). Microbiome analysis will be measured from the collection of stool sample.

8.2.2 Process

- Patients will be advised to keep the stool sample frozen until transport to the clinic. Upon receipt of the sample at the investigator site, site personnel should verify that the collection date and subject ID is written on a paper in a biohazard bag with the stool container.

8.2.3 Storage of Stool Sample/ Specimen Banking

- The stool sample will be transported to the CCTO laboratory for short term storage.
- Samples will be stored indefinitely in Dr. Hendifar's Biobank rental freezer.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size

For the AGC cohort, the median PFS in the KEYNOTE-059 trial (Fuchs et al. 2020) is 2.0 months. Assuming an accrual time of 12 months and 6 months follow-up, 21 patients are needed to improve median PFS from 2 months to 4 months or HR = 0.5 with 80% power using a two-sided one sample log-rank test at the 0.05 level of significance. Time to progression was assumed to follow an exponential distribution.

For the HCC cohort, the median PFS in the KEYNOTE-224 trial (Zhu et al. 2018) is 4.9 months. Assuming an accrual time of 12 months and 10 months follow-up, 24 patients are needed to improve median PFS from 4.9 months to 10 months or HR = 0.49 with 80% power using a two-sided one sample log-rank test at the 0.05 level of significance. Time to progression was assumed to follow an exponential distribution.

9.2 Data Sets Analyzed

All eligible patients who receive at least one dose of telatinib (the Safety Population) will be included in the safety analysis.

All patients who receive at least one dose of telatinib will be included in the efficacy analysis. Patients who drop before disease progression will be right censored.

9.3 Data Analyses/Study Endpoints

9.3.1 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects entered into the study at Cycle 1 Day 1.

The primary efficacy endpoint will be Progression-Free Survival. For each cohort, the log-rank test will be used to test the null hypothesis that the median PFS is less than or equal to 2 months for the AGC cohort and 4.9 months for the HCC cohort under exponential distribution assumption for time to progression. If this assumption is violated, bootstrap methods will be used to construct a 95% confident interval for the median.

Kaplan-Meir (KM) curves with 95% confidence bands will be constructed for PFS of each cohort. For the secondary endpoints, exact 95% confidence intervals for ORR, DCR will be constructed and KM curves for OS will be reported. For the exploratory objectives, 95% confidence intervals for change in mean values of biomarkers such as inflammatory cytokines, plasma metabolites will be constructed.

9.3.2 Safety Analysis

All subjects who receive at least one dose of telatinib will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail.

9.3.3 Interim Analysis

There will be no interim analysis for futility or early efficacy due to the small sample size in the AGC cohort and fast enrollment in the HCC cohort with hypothesized median PFS of 10 months under the alternative hypothesis.

9.4 Stopping Rules

Let P_T be the true probability that a patient experiences a treatment-related SAE (as defined in Section 5.2.1) within the first cycle of treatment in the AGC cohort. The trial will stop if there is statistical evidence that P_T exceeds 30%. We will use a Bayesian sequential design by checking whether P_T exceeds this threshold value after 6, 15, and 21 patients are evaluable for SAEs. The decision rule is to stop the trial if the posterior probability that P_T exceeds 0.30 is 0.97 or more; $P(P_T > 0.3 \mid \text{data}) > 0.97$. A noninformative prior distribution for P_T will be used.

Table 1 gives the stopping rules for the design at each look and column 2 gives the maximum number of patients with treatment-related SAEs in order for the trial to proceed. For example, if 4 or more treatment-related SAEs are observed after enrolling 6 patients, the trial stops. The third column gives the probability of stopping the trial when in fact, the true $P_T = 0.30$. This is the equivalent of the Bayesian type I error probability. The target type I error probability was set at 0.10.

Number of Patients	Number to Continue	Probability to Stop	Cumulative Probability to Stop
6	3	0.070	0.070
15	7	0.028	0.098
21	10	0.006	0.104

Table 1. Stopping rules based on three interim looks. Number to continue is the maximum number of treatment-related SAEs for not stopping the trial.

Table 2 gives the design operating characteristics under selected values of the true probability P_T. It gives the probability of stopping the trial under the alternative hypothesis, the expected sample size, and the average sample size given that the trial stopped. For example, if the true value of P_T is 0.5, then there is an 63.6% chance that the trial is stopped early, and the average sample size is about 14.5. On the other hand, there is a small chance of stopping the trial if P_T is small; 1.9% chance of stopping the trial when in fact $P_T = 0.2$.

True Value of P_T	Probability to Stop	Expected N	Expected N given that we Stopped

0.20	0.0197	20.73	7.3
0.30	0.1043	19.78	9.2
0.40	0.3212	17.66	10.6
0.50	0.6362	14.50	10.8

Table 2. Design operating characteristics under different scenarios for the true probability of toxicity P_T.

Similar stopping rules are used for the HCC cohort with a target probability of treatment-related SAEs not to ne exceeded equal to 0.3. Tables 3 and 4 present the operating characteristics of this stopping rules for HCC arm.

Number of Patients	Number to Continue	Probability to Stop	Cumulative Probability to Stop
6	3	0.070	0.070
15	7	0.028	0.098
24	11	0.010	0.108

Table 3. Stopping rules based on three interim looks. Number to continue is the maximum number of treatment-related SAEs for not stopping the trial.

True Value of P_T	Probability to Stop	Expected N	Expected N given that we Stopped
0.20	0.0198	23.67	7.46
0.30	0.1087	22.48	10.03
0.40	0.3480	19.79	11.90
0.50	0.6866	15.79	12.05

Table 4. Design operating characteristics under different scenarios for the true probability of toxicity P_T.

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. The IRB should approve the consent form and protocol.

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 Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass 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 team 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 SOCCI format (001, 002, etc.).

A) Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the SOCCI 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 GroupSOCCICROQMC@cshs.org for review:

- Registration form (or equivalent), if applicable
- Copy of applicable source documents
- QMC-approved eligibility checklist (signed by investigator and 2 members of the study team)
- Signed patient consent form with Subject's Bill of Rights, HIPAA authorization form, consent progress note and any optional consent forms, as applicable

B) Registration

After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Assign the patient a dose 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 and Quality Control and Reporting

The data will be entered into a HIPAA-compliant database. 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.

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 Data Monitoring and Quality Assurance

High Risk Monitoring
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). In addition, the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct internal monitoring visits and audits for data quality and protocol adherence. QMC reports will be forwarded to the SOCCI Data and Safety Monitoring (DSMC). Refer to the DSMC Charter for more details. For any protocol, QMC has the authority to request more frequent reviews or focused safety monitoring if it is deemed appropriate for any reason.

QMC will also conduct the following:

1. Central eligibility verification for all subjects enrolled as described in protocol section 10.3.
2. Central review by the SOCCI CCTO Medical Director or designee of all eligibility exception requests and waiver requests to assess appropriateness, to ensure quality data and subject safety protections for investigator-initiated research.

10.5.2 Safety Monitoring

High Risk Monitoring
Oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. Adverse events and unanticipated problems are not expected, but if they occur, they will be documented and reported according to CS-IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known, the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly. It is the responsibility of the principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, this protocol will utilize the SOCCI Data and Safety Monitoring Committee to provide another layer of data and safety oversight. DSMC membership and responsibilities are governed by the committee charter. Every three (3) months 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 may increase or decrease the frequency of study review, at their discretion. Refer to the DSMC Charter for details of the DSMC review.

10.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, 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 per local guidelines.

10.7 Adherence to 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 SOCCI Medical Director and CSMC IRB, 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 10 days from the investigator's awareness of the event.

10.7.2 Protocol Exceptions and Eligibility Waivers

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 impact an eligibility criterion, 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 SOCCI (CCTO) Medical Director and the IRB. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents to the SOCCI CCTO Medical Director for review and further instructions on IRB reporting.

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. Once approved by the medical director, the deviation or exception request must be submitted to the IRB for review and approval prior to implementation.

Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be forwarded to the SOCCI CCTO Medical Director for assessment prior to submission to the IRB for approval.

The CCTO Medical Director will review the case and contact the investigator if additional information is needed or further discussion is warranted. The CCTO Medical Director will provide a written assessment/recommended course of action. The CCTO Medical Director's assessment must be uploaded into CS-IRB with the waiver request for IRB review and consideration. The CCTO Medical Director may recommend future protocol changes.

Eligibility Waiver and Exception Request Submission Process

The PI and/or treating physician will provide a written request for an eligibility waiver including case history and justification for prospective deviation from the study design, to the SOCCI CCTO Medical Director. The "IIT Monitoring – Eligibility Waivers and Exception Requests (EW/ER) Form" must be completed then submitted, along with any applicable supporting documents, by email to QMC (GroupSOCCICROQMC@cshs.org) to request an eligibility exception or waiver request from the CCTO Medical Director. This is only a requirement for studies with a DSM category of moderate or high. An assessment from the CCTO Medical Director or designee must be done prior to submission to the IRB for review.

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 SOCCI 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 SOCCI CCTO's Standard Operating Procedure 12: *Deviation and Noncompliance Reporting*. In this case, a Protocol Deviation report must be submitted in CS-IRB, per 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.

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12.0 APPENDICES

12.1 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 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 disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension (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

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- **Target Lesions** - all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
  - Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
  - A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- **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 all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm).
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions from the smallest sum of the LD recorded since the treatment started; the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of ≥1 new lesion is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non- pathological in size (<10 mm short axis)
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions*

* Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

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	
Any	Any	Yes	

(Eisenhauer et al. 2009)

12.2 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.

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

12.3 Study Drug Dosing Diary: Attached as a separate document

12.4 24-HR RECALL FORM: Attached as a separate document

12.5 STOOL SURVEY: Attached as a separate document

12.6 Instructions for Stool Collection: Attached as a separate document

12.7 SUMMARY OF CHANGES

Protocol version 2 dated 25AUG2021

- Addition of Kevin Scher, MD as a consenting Investigator
- Section 1.4, Correlative Studies: Update to timing of stool collection. Sample collection is required at baseline and the start of cycle 3.
- Section 4.1.1.2: Revise inclusion criteria to allow for intolerance to standard therapies
- Section 4.2.8: Revise HIV exclusion criteria to allow enrollment of patients who have an undetected viral load
- Section 4.2.9: Updated the Hepatitis B exclusion criterion to specify that patients with chronic hepatitis B are excluded unless they're receiving antiviral treatment and HBV DNA test performed within six months of screening (based on medical chart review) is <2000 IU/mL.
- Section 4.2.10: Specified that patients with known Child-Pugh Score B or C liver cirrhosis are ineligible to participate
- Section 6.1.12 & 6.2.2: Clarified that the stool survey and 24-hour food recall should occur on the same day as the stool sample collection, if feasible
- Section 7.4.2.5: Clarified that SUSARs will be sent to EOC Pharma within 3 days of awareness
- Section 8.2.2: Clarified that the baseline stool sample should be collected 4 weeks prior to C1D1 or on C1D1. In addition a window (±3 days) was added for the C3D1 stool collection. This section was revised to be consistent with the Schedule of Events table.
- Removal of Appendix 12.2 Application of iRECIST

Protocol version 3 dated 27JUL2022

- Section 4.0, Patient Eligibility: Clarified that enrollment holds deemed necessary for the evaluation of stopping rules is understood to be the responsibility of the PI.
- Section 4.1.6.6, Inclusion Criteria: Revised the creatine criterion to require either serum creatinine or CrCL (not both).
- Section 4.2.10, Exclusion Criteria: Corrected formatting error for HBV criterion. Removed requirement for HBV screening test results within 6 months and viral load threshold.
- Section 7.0, Adverse Events: Clarified that AE assessment occurs after the patient has started study treatment.
- Section 7.1, Adverse Event Monitoring: Clarified the timeframe for adverse event monitoring. Added a bullet to indicate that monitoring should occur "until 30 days following last dose of study drug or until initiation of a new anticancer therapy (whichever occurs first)."

Protocol version 4 dated 02SEP2022

- Cover page: Updated sites and Investigators
- Sec 7.3.1.3: Updated IRB reporting requirements to indicate the AE is reportable if it "has a reasonable possibility of relationship," per local guidelines.