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Table 1. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
APC	Antigen-presenting cell
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BTLA	B- and T-cell Lymphocyte Attenuator
ccRCC	Clear-Cell Renal Cell Cancer
Cmax	Maximum Concentration
CPK	Creatine Phosphokinase
CR	Complete Response
CTL	CD8+ cytotoxic T lymphocyte
CTLA-4	Cytotoxic T Lymphocyte Antigen-4
DN	Dose Normalized
FDA	United States Food and Drug Administration
FMCS	Finding Meaning in Cancer Scale
GI	Gastrointestinal
GLP	Good Laboratory Practice
HGF	Hepatocyte Growth Factor
HIF	Hypoxia-Inducible Factor
HPF	High Power Field
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% maximal inhibitory concentration
irAE	Immune-related Adverse Event
irRC	Immune related Response Criteria
IV	Intravenous
LAG-3	Lymphocyte Activation Gene-3
LFT	Liver Function Test
LMW	Low Molecular Weight
M1 macrophages	Classically activated macrophages
M2 macrophages	Alternatively activated macrophages
mAb	Monoclonal Antibody
MDSC	Myeloid-Derived Suppressor Cell
MERTK	MER Proto-Oncogene Tyrosine Kinase
mRCC	Metastatic Clear-Cell Renal Cell Cancer
MSC	Mesenchymal Stem Cell
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network

NK	Natural Killer cells
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic
PD-1	Programmed Death Receptor-1
PD-L1	Programmed Death-ligand 1
PD-L2	Programmed Death-ligand 2
PDGF	Platelet-Derived Growth Factor
PDGFRA	Platelet-Derived Growth Factor Receptor Alpha Polypeptide
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PO	Per Os (By Mouth)
PR	Partial Response
QOL	Quality of Life
RBC	Red Blood Cells
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
sMET	Soluble MET Ectodomain
SUSAR	Serious Unexpected Suspected Adverse Reaction
$T_{1/2}$	Half Life
T_H1	$CD4^+$ T helper 1 cell
T_H2	$CD4^+$ T helper 2 cell
T_H17	$CD4^+$ T helper 17 cell
TAM receptors	Tyro3, Axl, and Mer receptors
TEN	Toxic Epidermal Necrolysis
TIM-3	T Cell Immunoglobulin and Mucin Protein-3
TKI	Tyrosine Kinase Inhibitor
Tmax	Time of Maximum concentration observed
Tmin	Time of Minimum Observed Concentration
Treg	Regulatory T cell
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR2	Vascular Endothelial Growth Factor Receptor 2
VHL	von Hippel-Lindau
VISTA	V-domain Ig Suppressor of T-cell Activation
WBC	White Blood Cells

1.0 RESEARCH HYPOTHESIS

The receptor tyrosine kinase inhibitor MGCD516 can be safely administered in combination with an anti-PD1 antibody (nivolumab) and augment immunological and clinical responses in patients with metastatic renal cell carcinoma who have been previously treated with drugs targeting the vascular endothelial growth factor (VEGF) pathway.

2.0 OBJECTIVES

Primary objective:

- To determine the toxicities (defined as a grade 3 or 4 NCI CTCAE non-hematologic or hematologic adverse event, within 12 weeks from treatment initiation), and efficacy (defined as achieving complete remission, partial remission, or stable disease within 6 weeks) of MGCD516 when administered PO daily in combination with standard dose nivolumab 240 mg IV every 2 weeks.

Secondary objectives:

- To estimate the overall survival (OS), progression-free survival (PFS) times, objective response rates (ORR), and quality of life (QOL) of patients with advanced clear cell RCC treated with the combination
  of MGCD516 and nivolumab
- Evaluate potential biomarkers for patient stratification and treatment response, including genetic analysis, serum cytokines and chemokines, as well as tumor antigen-specific immune .responses, such as antibody and T cell responses, as surrogates for anti-tumor activity

Extended Access objective (long term extension phase):

- Provide continued access to MGCD516 (sitravatinib) in combination with nivolumab, with continued collection of serious adverse events, for patients enrolled on trial and continue to benefit from this combination regimen.

3.0 BACKGROUND AND RATIONALE

3.1 Introduction

Renal cell cancer (RCC) is the 7th most common cancer in U.S. men and the 9th most common cancer in U.S women. An estimated 61,560 new cases and 14,080 deaths are expected in 2015.[1] Approximately 30% of patients will have metastatic RCC at the time of diagnosis,[2] and a similar proportion of newly diagnosed RCC patients will later on develop metastasis.[3] Clear-cell RCC (ccRCC) is the most common RCC histologic type, comprising 83%-90% of all RCCs.[4,5] An improved understanding of ccRCC tumor biology has led to major advances in the treatment of metastatic ccRCC (mRCC) over the last decade. Subsequently, immunomodulating cytokines such as interleukin-2 and interferon alfa, which were the mainstay therapy for mRCC for two decades, have recently been replaced by agents targeting the VEGF or the mammalian target of rapamycin (mTOR) pathways.[6]

ccRCC is associated with inactivating mutations of the von Hippel-Lindau (VHL) tumor suppressor gene. This leads to upregulation of hypoxia-inducible factors (HIF) and to downstream upregulation of VEGF, resulting in increased angiogenesis, which is commonly noted in ccRCC.[7] Gene mutations that activate the mTOR pathway are also frequently found in

both hereditary and sporadic forms of ccRCC.[8] Tyrosine kinase inhibitors (TKIs) targeting the VEGF pathway that have been approved by the United States Food and Drug Administration (FDA) for use in mRCC include sorafenib, sunitinib, pazopanib, and axitinib. Bevacizumab, a monoclonal antibody that binds to VEGF also has efficacy against mRCC. Two mTOR inhibitors, temsirolimus and everolimus, have received FDA approval for use in mRCC. The most recent targeted agents to improve survival in mRCC are cabozantinib, a TKI that targets the VEGF, Axl and c-MET pathways, and nivolumab, a monoclonal antibody that targets the programmed death-1 (PD-1) immune checkpoint receptor.[9,10]

Although targeted agents prolong survival, resistance eventually develops for most patients. Therefore, there is a clear need for therapies that can produce complete and durable tumor responses with an acceptable toxicity profile. Immune checkpoint inhibition is a new treatment strategy that has garnered much attention after demonstrating impressive durable clinical responses in many solid tumors, including mRCC.[9,11] The interplay between malignant cells and the various components of the immune network can either suppress or foster tumor growth. $CD8^+$ cytotoxic T lymphocytes (CTL), $CD4^+$ T helper 1 cells (T_H1), natural killer (NK) cells and classically activated (M1) macrophages mainly suppress tumor development. However, other immune components such as $CD4^+$ T helper 2 cells (T_H2), $CD4^+$ T helper 17 cells (T_H17), myeloid-derived suppressor cells (MDSC), alternatively activated (M2) macrophages, and $CD4^+CD25^+Foxp3^+$ Induced Regulatory T cells (Treg) can paradoxically protect tumor cells from immunosurveillance.[12] Effective immunotherapies should simultaneously enhance anti-tumor immunity and inhibit tumor-promoting immune factors. Novel combination strategies with other targeted agents may intensify the antitumor effects of immune checkpoint therapy by inducing immunogenic cell death, by sensitizing tumor tissues to killing by effector cells, and by suppressing crucial components of the immune network that hinder immunosurveillance.[12]

3.1 Background on MGCD516

MGCD516 is a potent inhibitor of the catalytic activity of a subset of closely related recombinant human receptor tyrosine kinases (RTKs) including the Axl family, c-MET, KIT, FLT3, RET and the VEGFR, PDGFR, DDR, Trk families as well as selected Eph family members and selected target oncogenic variants (Table 2).[13] To confirm that inhibition of enzymatic activity, as measured using recombinant protein assays, translated into inhibition of target kinases in cells, MGCD516 biochemical specificity was evaluated in cell-based assays with half maximal inhibitory concentration (IC_{50}) values ranging from <10 to 181 nmol/L (Table 2). Many of the targets inhibited by MGCD516 are known driver kinases in mRCC.

Table 2. In vitro kinase inhibition profile of MGCD516[13]

RTK target	Biochemical Specificity (IC_{50} nmol/L)
Axl	1.5
MER	2
c-MET	20

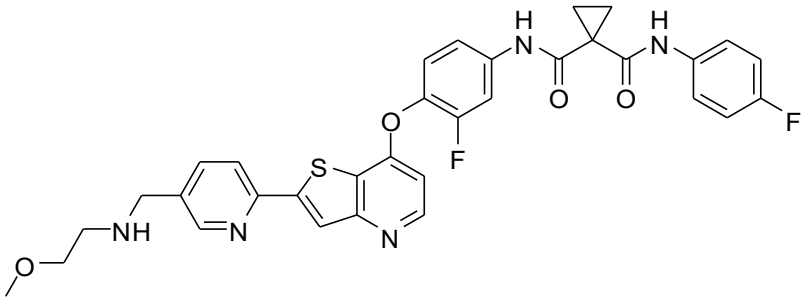
VEGFR2 (KDR)	5
VEGFR1 (FLT1)	6
VEGFR3 (FLT4)	2
FLT3	8
c-KIT	6
PDGFRA	30
DDR1	29
DDR2	0.5
RET	44
TRKA (NTRK1)	5
TRKB (NTRK2)	9
EPHA2	44
EPHA3	1
EPHA4	76
EPHB2	10
EPHB4	12
FYN	339
RON	43
ROS	59
SRC	156
TIE2	274
YES	298
PYK2	364
BTK	304
EPHB3	249
INSR	5550
HCK	1109
FER	1589
fdsLTK	1938
FES	2010
FMS	2290
ABL	2987
IGF1R	3980
ARG	4098
FGFR1	>5000
FGFR2	>5000
FGFR3	>5000
FGFR4	>5000
ITK	>5000
ERBB1	>5000
ERBB2	>5000
ERBB4	>5000
EPHA1	>10000
EPHB1	>10000

FAK	>10000
JAK1	>10000
JAK2	>10000
JAK3	>10000
ALK	>10000
SYK	>10000
ZAP70	>10000

3.1.1 Pharmacology of MGCD516

The following is the chemical name and structure of MGCD516:

MGCD516 Free Base



Chemical Formula: MGCD516 Free Base: $C_{33}H_{29}F_2N_5O_4S$

Molecular Weight: MGCD516 Free Base: 629.68

In MGCD516 toxicity studies in dogs, no target organs were identified, despite overt decreases in body weight and food consumption. In the rat, however, target organs included the adrenal gland, Brunner's glands in the duodenum, femur and sternum (bone and bone marrow), spleen, lymph nodes, thymus, ovaries, kidneys (glomerulopathy, tubular necrosis, increased basophilic tubules), pancreas, and tongue. MGCD516-related microscopic changes in the adrenal gland, Brunner's glands in the duodenum, femur and sternum (bone and bone marrow), spleen, lymph nodes, thymus, ovary, kidney, pancreas, and tongue were consistent with those previously described in rats administered anti-angiogenic (anti-VEGF) compounds in preclinical studies.[14-16] All effects, except those in the kidney and pancreas, either fully resolved or showed partial recovery.

Some of the effects seen preclinically and clinically from VEGF signaling inhibitors include hypertension, proteinuria, impaired wound healing, gastrointestinal (GI) perforation, hemorrhage/thrombosis, posterior reversible leukoencephalopathy, cardiac impairment, thyroid dysfunction, ovarian follicular atresia, and decreased corpora lutea.[17] As noted above, some of the MGCD516 target organs in animal correlate with typical clinical effects seen with VEGF inhibitors. Kidney effects (nephrotic syndrome) have been reported predominantly with bevacizumab and not the small molecule TKIs.[17] Thus, previous experience with other VEGF pathway TKIs indicates that it is unlikely that the adrenal/kidney effects seen in MGCD516-

treated rats (≥ 10 mg/kg/day) will translate into clinical toxicities in patients. Hypertension has been observed with all VEGF pathway inhibitors, and mild increases in intravascular pressure were indeed observed with MGCD516. Decreased corpora lutea and follicular atresia were observed in the ovary, and these effects have also been seen preclinically with sunitinib and bevacuzumab.[15] Cyclic endometrial growth is dependent on its ability to regenerate a vascular capillary network. Therefore, inhibition of the VEGF pathway likely contributes to the effects of MGCD516 on reproductive organs. Genotoxicity studies of MGCD516 indicate a lack of potential to induce point mutations, chromosomal aberrations, or to interact with or damage DNA. Therefore, it is unlikely that MGCD516 poses a genotoxic risk to humans.

The pharmacokinetic properties of MGCD516 have been examined in mice, rats, and dogs, in single-dose pharmocokinetic (PK) studies (Table 3) and in rats and dogs in good laboratory practice (GLP) toxicokinetic studies. Single dose PK studies show that MGCD516 is absorbed, with an absolute oral bioavailability of 20-72%, a half-life ($t_{1/2}$) of 3.6-7.1 hours, and with the maximum concentration (C_{max}) and area under the curve (AUC) increasing generally in a dose-dependent manner.

Table 3. Mean Single Dose Pharmacokinetic Parameters for MGCD516

Route	Parameters Mean (unit)	Mouse (CD-1, Female)	Rat (Sprague-Dawley, Female)	Dog (Beagle, Male)
IV	Dose (mg/kg)	2.5	5.0	1.0
	(n)	(3)	(2)	(2)
	DN C_0 (µmol/L)/(mg/kg) ((µg/mL)/(mg/kg))	0.63 (0.394)	10.6 (6.67)	0.99 (0.620)
	DN AUC_{0-t} (µmol hr/L)/(mg/kg) ((µg.hr/mL)/(mg/kg))	1.11 (0.702)	5.7 (3.59)	0.99 (0.622)
	$t_{½}$ (h)	6.23	3.56	7.11
	CL (L/h/kg)	1.38	0.279	1.49
	V (L/kg)	6.28	0.980	11.1
PO	Dose (mg/kg)	2.0	5.0	5.0
	(n)	(3)	(3)	(2)
	DN C_{max} (µmol/L)/(mg/kg) ((µg/mL)/(mg/kg))	0.081 (0.0511)	0.105 (0.0660)	0.043 (0.0272)
	DN AUC_{0-t} (µmol hr/L)/(mg/kg) ((µg.hr/mL)/(mg/kg))	0.80 (0.505)	0.25 (0.156)	0.50 (0.312)
	t_{max} (h)	6	6	4
	F (%)	72.2	19.6	56.4

Abbreviations: DN C_0 – dose normalized back-extrapolated plasma drug concentration at time zero following bolus intravenous injection; DN AUC_{0-t} – dose normalized area under the plasma concentration versus time curve from

time zero to the time of the last measurable concentration (t=24 h for all reported values except for DN AUC_{0-t} in rats after 2 mg/kg oral dose t=6 h); $t_{½}$ – half life; CL – total clearance; V – volume of distribution; DN C_{max} – dose normalized maximum plasma concentration; F – absolute bioavailability calculated as (DN $AUC_{0-\infty\ oral}$ / DN $AUC_{0-\infty\ IV}$), t_{max} – time to maximum observed concentration.

Toxicokinetic studies using oral MGCD516 dosing were conducted in rats for 7 days (12.5-75 mg/kg/day) and 4 weeks (2.5-25 mg/kg/day) and dogs for 7 days (1-8 mg/kg/day) and 4 weeks (0.3-3 mg/kg/day). The time to maximum observed concentration (T_{max}) ranged between 4 to 12 hours in rats and 2 to 6 hours in dogs. Mean $t_{1/2}$ ranged between 2.96 to 8.65 hours in rats and 3.19 to 6.16 hours in dogs. In all studies, increases in C_{max} and AUC_{0-24} values were roughly dose proportional on Day 1 and at the end of study indicating no accumulation. Female rats had consistently higher C_{max} and AUC_{0-24} values than did males at nearly all dose levels on Day 1, however values were generally comparable at Day 27 at the evaluable dose levels. In dogs, consistent sex differences were not observed. No evidence for accumulation was observed in either rats or dogs.

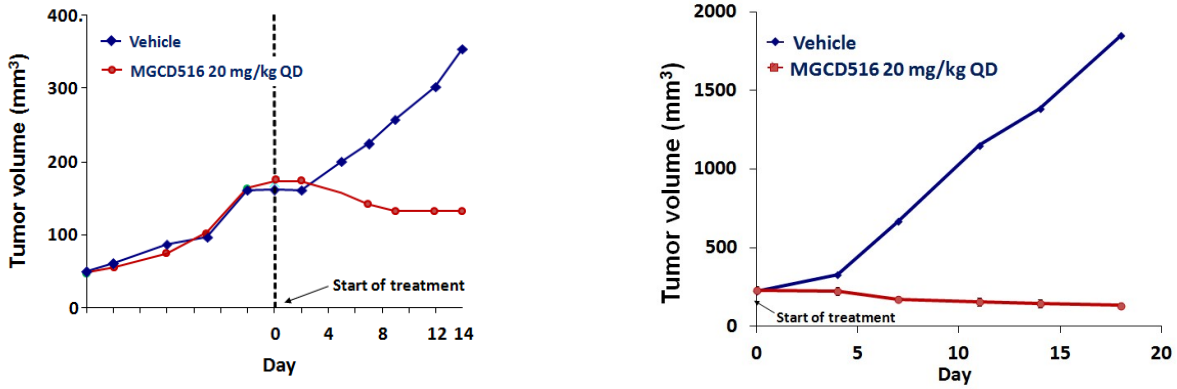
3.1.2 Preclinical efficacy data of MGCD516

A series of *in vivo* experiments with MGCD516 were performed to 1) demonstrate inhibition of its kinase targets (e.g., c-MET, Axl, RET, EPHA2) in tumors and establish the PK and pharmacodynamic (PD) parameters of c-MET inhibition; 2) demonstrate anti-tumor efficacy in rodent models of cancer; 3) demonstrate the dose- and time-dependent relationship of inhibition of RTK targets, such as c-MET, with anti-tumor efficacy.

The anti-tumor efficacy of MGCD516 was evaluated in a variety of human tumor xenograft models (total of 17) representative of cancers known to exhibit dysregulation of RTKs targeted by MGCD516. MGCD516 demonstrated significant anti-tumor efficacy compared with vehicle control across all evaluated models at dose levels ranging from 1.25 to 20 mg/kg/day depending on the model tested (see the Investigator's Brochure for full details). Anti-tumor efficacy was generally dose-dependent for models for which multiple dose levels were evaluated. MGCD516 was generally well tolerated with minimal overt toxicity or weight loss at dose levels up to 20 mg/kg/day for up to 18 days of administration. The 20 mg/kg/day dose level was the maximum dose for comparative purposes across all models utilized for efficacy studies. At this dose, anti-tumor efficacy ranged from stable disease to robust tumor regression, with the minimum proportion of stable tumors observed being 77% (DU145 prostate and HCT-116 colon), which was significantly higher compared with vehicle control. MGCD516 consistently produced either stable disease or tumor response (>90% of cases) in the majority of models evaluated at the 20 mg/kg/day dose with multiple models exhibiting frank tumor regressions at this dose level. Highly sensitive models exhibiting tumor regressions at 20 mg/kg/day MGCD516 included the MKN45 gastric adenocarcinoma model (41% tumor regression), NCI-H1437 lung adenocarcinoma (24% tumor regression), CTG-0838 lung adenocarcinoma (43% tumor regression), and MV4-11 leukemia (minor tumor regression). Interestingly, several of these models have an underlying genetic alteration of at least one MGCD516 RTK target including focal amplification of the *MET* gene (MKN45), linear amplification of a region of chromosome 4, which includes the *PDGFRA*, *KIT* and *KDR* gene loci, along with a R988C *MET* mutation (NCI-H1437), a *KIF5B-RET* oncogenic gene fusion event (CTG-0838); and a *FLT3-ITD* gene

mutation (MV4-11). This observation supports the specificity of MGCD516 for tumors exhibiting genetic alterations in select RTK targets.

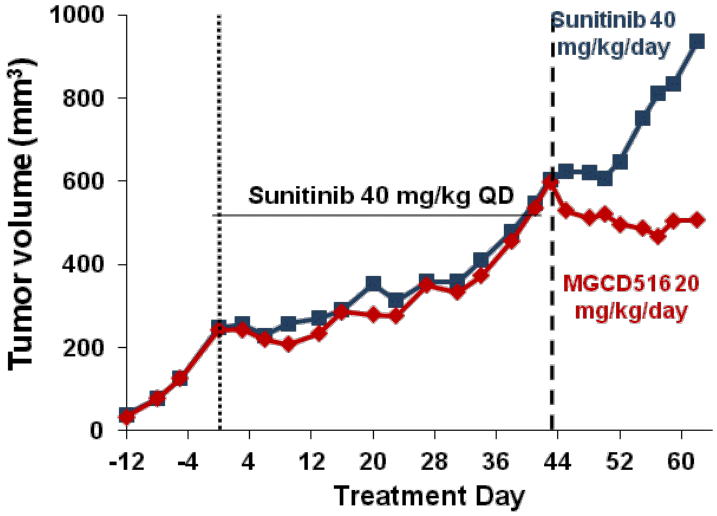
Antitumor Efficacy of MGCD516 in NCI-H1437 (Left Panel) and CTG-0838 (Right Panel) Human Lung Adenocarcinoma Xenograft Models Implanted Subcutaneously in Athymic Mice



Tumor volume reported as median.

In addition, MGCD516 has demonstrated anti-tumor efficacy, including evidence of tumor regression, in the MKN45 gastric adenocarcinoma xenograft model known to be resistant to the VEGF receptor TKI sunitinib (40 mg/kg daily). These data suggest that MGCD516 has the ability to circumvent resistance to clinically used inhibitors of the VEGF pathway likely due to its broader RTK target profile.

Antitumor Efficacy of MGCD516 in the MKN45 Human Gastric Adenocarcinoma Xenograft Model Following Progression During Sunitinib Administration



MKN45 tumors were established at 250 mm^3 and subsequently mice received oral sunitinib at 40 mg/kg/day until tumors progressed to approximately 600 mm^3 at which point mice were randomized into 2 cohorts A) continued treatment with sunitinib at 40 mg/kg/day or B) initiation of oral administration of MGCD516 at 10 mg/kg/day. Tumor volume reported as median.

3.1.3 Dose Rationale for MGCD516

The PK/PD of MGCD516 was evaluated using the c-MET-dependent MKN45 gastric adenocarcinoma tumor model. Plasma concentrations of MGCD516 were determined using liquid chromatography–mass spectrometry, and phosphorylation of c-MET in MKN45 tumors was determined by ELISA at several dose levels and time points on Day 4 of administration. The anti-tumor efficacy of MGCD516 was also evaluated in the MKN45 model over a broad range of doses by calculating the tumor volume change relative to Day 1 in a 14-day repeat-dose study. These studies suggested that the anti-tumor efficacy of MGCD516 in the MKN45 model depended on the extent and duration of c-MET inhibition. This model was further used to define the target plasma concentration, i.e., the projected efficacious plasma level IC_{50} and 90% maximal inhibitory concentration (IC_{90}). The IC_{90} value for inhibiting c-MET phosphorylation corresponded to the IC_{50} values of stable disease or tumor response suggesting that near-complete inhibition of c-MET phosphorylation (> 90%) is needed to inhibit tumor growth (> 50%).

Because the antitumor activity of MGCD516 may be mediated by other RTKs in addition to c-MET, the determination of human target efficacious exposure is based on PK/PD modeling of anti-tumor efficacy as opposed to only c-MET inhibition. In terms of systemic exposure, the daily exposure ($AUC_{0\text{-}24,ss}$) that is associated to 50% maximum tumor growth inhibition was estimated at 2.5 µmol·h/L (1.57 µg·h/mL) which was thus established as the minimum target efficacious exposure in the clinical setting based on this model. The corresponding average plasma concentration at steady-state ($C_{ave,ss}$) was estimated at 0.1 µmol/L (0.0630 µg/mL).

3.1.3.1 Clinical Experience to Date: Data from the Phase 1/1b 516-001 study

The 516-001 trial was a Phase 1/1b dose escalation study that explored the safety, PK, and optimal MGCD516 dose ranges. The following is a summary of experience generated in this first-in-human study. Data collection is ongoing, thus all data reported are preliminary.

The modified toxicity probability interval (mTPI) method[18] was used to guide dose escalation. The assumptions applied in establishing the mTPI methodology were:

- the Maximum Tolerated Dose (MTD) was defined to have a 0.3 probability of dose limiting toxicity; and
- the acceptable variance around the MTD was ± 0.05 (i.e., the region of the MTD was 25% to 35% incidence of dose limiting toxicity).

Dose escalation in cohorts of patients started at 10 mg MGCD516 daily and proceeded through 20, 40, 80, 110, 150 and 200 mg daily. Cohorts included 4 to 7 patients. A total of 32 patients were accrued, and in November 2015, the dose of 200 mg MGCD516 administered daily was determined to exceed the MTD.

The observed safety profile for MGCD516 was manageable and, in most respects, expected for small molecule tyrosine kinase inhibitors that inhibit VEGFR. Adverse events (AEs) reported to

be treatment-related in more than 10% of patients included hypertension, fatigue, diarrhea, nausea, vomiting, rash, and stomatitis. Grade 3 treatment-related AEs reported in one or more patients included hypertension (which was manageable), diarrhea, serum amylase increase, palmar-plantar erythrodysesthesia, decrease in left ventricular ejection fraction (LVEF) and pulmonary embolism. Dose Limiting Toxicities reported during the first cycle of treatment with MGCD516 included Grade 3 palmar-plantar erythrodysesthesia in 1 of 6 evaluable patients enrolled in the 80 mg cohort, as well as Grade 2 intolerable neuropathy, fatigue and stomatitis, each in 1 of 3 patients treated at the 200 mg dose level. In all cases, dosing was interrupted until improvement in the AE and then treatment was restarted with reduction by one dose level. Two Serious Unexpected Suspected Adverse Reaction (SUSAR) have been reported: 1) a patient in the 150 mg dose level cohort developed Grade 3 decrease in LVEF, without clinical symptoms of congestive heart failure, following two cycles of treatment; 2) a patient in the 150 mg dose level cohort who developed Grade 3 diarrhea after two cycles of treatment at 150 mg and 4 cycles of treatment at 110 mg. No other serious adverse events related to MGCD516 treatment were reported.

With regards to the clinical efficacy of MGCD516, as of 11/18/2016, 32 patients were enrolled in the Phase 1 dose escalation portion of the Phase 1/1b 516-001 study, of which 27 patients had at least one imaging study. Of these 27 patients, 17 showed stable disease (SD) and 10 showed progressive disease (PD) as best response. The phase 1b portion is treating patients with a starting dose of 150 mg as the MTD based on the dose escalation portion. It has enrolled 35 patients, of which 25 patients have had at least one imaging study. Of these 25 patients, 4 have shown partial response (PR), 17 have shown SD, and 4 have shown PD as best response. Out of the 4 patients that have demonstrated PR, one has metastatic ccRCC refractory to prior anti-VEGF therapy and has achieved a durable response, one has metastatic castration-resistant prostate cancer, one has refractory breast cancer with RET mutation, one has previously treated non-small cell lung cancer with RET rearrangement. A total of 8 patients with RCC have been treated to date. The majority have had some degree of tumor reduction but only the 1 case mentioned above has achieved PR by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.
The updated Investigator's Brochure (IB) issued on 25 August 2015 includes preliminary PK and PD data collected in the 10 mg to 110 mg cohorts. After single dose administration, MGCD516 reaches peak concentration in a median time of 3 to 9 hours. Exposure parameters (maximum concentration [C_{max}] and area under the curve [AUC]) are dose proportional with doses up to 110 mg. Mean elimination half-life varies between 40 and 53 hours. The steady state PK is reached in a mean time of 11 to 15 days. Drug accumulation is observed after administration of multiple doses and averages 4.2-fold for C_{max} and 4.7-fold for AUC_{0-24}. Preliminary PK data generated since the IB update indicate that increase in exposure continues to be dose proportional through the 200 mg daily dose level, the highest dose administered.

As described in the IB update, the PD effects of MGCD516 treatment are examined by analyzing VEGFA, soluble VEGF-R2 and soluble MET ectodomain (sMET) levels in plasma samples collected before and after MGCD516 administration. Preliminary PD analyses showed a concentration dependent modulation of each biomarker that approached near maximal level (based on historical data for TKIs) for VEGF-A (~300% increase), sVEGF-R2 (~35% decrease),

and sMET (~60% increase). Average MGCD516 steady state concentration values observed in patients receiving 80 mg and 110 mg QD were 64.2 ng/mL and 123 ng/mL, respectively.

3.2 Background on Nivolumab (BMS-936558)

3.2.1 Mechanism of Action

Immune checkpoints are regulatory signals that can affect immune activation and self-tolerance. Immune checkpoint signaling is crucial for preventing autoimmunity and for protecting host tissues from immune-mediated collateral damage. Checkpoint inhibitory molecules including cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin protein-3 (TIM-3), B7-H3 (also designated as CD276), B- and T-cell lymphocyte attenuator (BTLA), and the V-domain Ig suppressor of T-cell activation (VISTA) are frequently expressed on tumor-infiltrating T cells.[19] Although the exact signaling pathways associated with these molecules remain to be fully elucidated, it is clear that they regulate immune activity by different mechanisms and at different levels.

PD-1 is the first immune checkpoint receptor to be targeted in clinical practice against mRCC.[9] In contrast to CTLA-4, which is near exclusively expressed on T cells, PD-1 is more broadly expressed and can limit the activity of both T- and B-lymphocytes, NK cells, and certain myeloid cells when bound to either of its two known ligands, PD-L1 and PD-L2.[20] PD-L1 and PD-L2 have distinct expression profiles.[20] PD-L1 is expressed not only on antigen-presenting cells (APCs), but also on non-hematopoietic cells, including tumor cells. Expression of PD-L2 is largely restricted to APCs including macrophages and myeloid dendritic cells, as well as mast cells. PD-L1 can be aberrantly produced in cancer tissues resulting in tumor-induced immune dampening via the PD-1 signaling pathway.[21] Therefore, whereas CTLA-4 regulation occurs mainly in lymphoid tissues, PD-1 is predominantly activated within the tumor microenvironment.

The role of PD-1 as a negative regulator of T cells was demonstrated in PD-1 deficient mice which developed significant autoimmunity with elevated titers of autoantibodies.[22,23] In addition, blocking antibodies against PD-1 activated immune responses that reduced tumor metastasis and tumor growth in a number of experimental tumor models.[24,25] Consistent with the immunosuppressive role of PD-1/PD-L1/2 signaling, forced expression of PD-L1 in murine tumor cell lines allows increased tumor growth *in vivo*, previously kept in check by T cells. This inciting effect of PD-L1 on tumor growth is reversed by blocking anti-PD-L1 antibodies.[26] In ccRCC, high surface expression levels of PD-L1 on tumor cells correlate with tumor aggressiveness.[27,28]

The first anti-PD-1 agent to be approved for clinical use was nivolumab, a fully humanized IgG4 (kappa) isotype anti-PD-1 monoclonal antibody (mAb). It has received accelerated FDA approval for use in metastatic or unresectable melanoma, metastatic non-small cell lung cancer, and metastatic renal cell cancer based on its proven clinical efficacy in these settings.[9,29-32] Immune reactivation by nivolumab produces long-term responses that persist even after treatment cessation.[33] Toxicity data derived from trials of PD-1/PD-L1 blockade suggest that this approach produces less toxicity compared with CTLA-4 targeting.[29-32,34,35] This may be due to

the expression of CTLA-4 in lymphoid organs leading to lower treatment specificity compared with the more localized intratumoral expression of PD-1/PD-L1.

3.2.2 Nivolumab Pharmacokinetics

The PK of single-dose nivolumab was assessed in patients with multiple tumor types in the CA209001 trial, using a dose range of 0.3 to 10 mg/kg. The time of maximum concentration observed (Tmax) across single dose levels ranged from 1.6-3.0 hours with individual values ranging from 0.9 to 7.0 hours. Nivolumab has a linear PK in the range of 0.3 to 10 mg/kg with dose- proportional increase in the maximum concentration observed and in the area under the curve from zero to infinity, with low to moderate inter-subject variability observed at each dose level, i.e., a coefficient of variation ranging from 7%-45%. The geometric mean clearance after a single IV dose of nivolumab ranges from 0.13-0.19 mL/h/kg, whereas the mean volume of distribution ranges from 83-113 mL/kg across doses. The mean terminal half-life of nivolumab is 17-25 days, which is in accordance with the half-life of endogenous IgG4 antibodies, indicating that they share a similar elimination mechanism. The elimination and distribution of nivolumab is dose-independent in the dose ranges studied.

The PK of multiple nivolumab doses is being investigated in the CA209003 trial. A preliminary population pharmacokinetic model has been developed using nonlinear mixed effect modeling using data from 350 patients accrued in the CA209001, CA209002, and CA209003 trials. Dosing based on normalizing by body weight produces relatively constant trough concentrations over a wide range of body weights, and is therefore appropriate for trials of nivolumab.

3.2.3 Nivolumab in Renal Cell Carcinoma

Nivolumab monotherapy has been tested in multiple ongoing and completed trials that accrued patients with mRCC, including the Phase 1 single-ascending dose, dose-escalation CA209001 trial, the Phase 1 multiple-ascending dose, dose-escalation CA209003 study which assessed multiple tumor types (including mRCC), the exploratory CA209009 study which investigated the immunomodulatory activity of nivolumab in mRCC, and the Phase 2 dose ranging CA209010 study. Of note, the efficacy of nivolumab compared with the mTOR inhibitor everolimus was evaluated in the pivotal phase 3 randomized multicenter CheckMate 025 study.[9] In addition, CA209016 is an ongoing phase I dose-escalation study of nivolumab in combination with either sunitinib, pazopanib or the CTLA-4 inhibitor ipilimumab.

3.2.3.1 Safety of Nivolumab in Renal Cell Carcinoma

Patients enrolled in clinical trial CA209001 (n=39) received a single dose of nivolumab with potential retreatment in 3 months. The most common AEs were fatigue (56%), nausea (44%), proteinuria (38%), constipation (33%), back pain (33%), dry mouth (28%), vomiting (28%), rash (26%) and dyspnea (26%). No correlation was identified between nivolumab dose levels (0.3, 1, 3, or 10 mg/kg IV) and AE incidence or severity. All patients had at least one AE, and 32 patients (82%) had Grade 3 or 4 AEs. The three treatment-related severe AEs reported were Grade 2 hypothyroidism, Grade 2 anemia, and Grade 3 colitis. No drug-related deaths were noted.

Nivolumab-related AEs of any grade occurred in 75.2% of patients in the CA209003 trial (n = 306).[36] The most common drug-related AEs occurring in ≥ 5% of patients included fatigue

(28.1%), rash (14.7%), diarrhea (13.4%), pruritus (10.5%), nausea (9%), decreased appetite (9%), and fever (6%). The majority of AEs were low grade, and only 14% of patients developed Grade 3/4 drug-related AEs. The most common Grade 3/4 drug-related AEs occurring in ≥ 1% of patients were fatigue (2%), pneumonitis (1%), diarrhea (1%), and AST/ALT increase (0.3% each). Drug-related serious adverse events (SAEs) occurred in 17% of patients. Grade 3/4 drug-related SAEs occurring in ≥ 1% of patients were pneumonitis (1.3%), and diarrhea (1%). The spectrum, incidence, and severity of nivolumab-related AEs was overall similar across the different dose levels used. Less common drug-related AEs included vitiligo, hepatitis, hypophysitis, and thyroiditis.

Treatment interruption and administration of corticosteroids were used to manage hepatic or gastrointestinal AEs, which overall were fully reversible. Hormone replacement therapy was used to manage endocrine AEs. Several patients with these AEs successfully restarted nivolumab therapy. Drug-related pneumonitis was noted in 3% of patients. Grade ≥ 3 pneumonitis developed in only 3 patients (1%). There was no clear relationship between the occurrence of pneumonitis and dose level, dose number, or tumor type. Low-grade pneumonitis generally resolved with discontinuation of treatment and administration of corticosteroids. Infliximab and/or mycophenolate were used as additional immunosuppressants in 3 patients, but it remains uncertain whether this provided additional benefit. Three drug-related deaths (1%) due to pneumonitis were noted. In two of these cases, early and aggressive intervention such as systemic corticosteroid therapy was not initiated, and this likely significantly contributed to the fatal event, whereas in the 3rd patient, concomittant administration of other anti-cancer agents (erlotinib and vinorelbine) may have aggravated toxicity.

In the CheckMate 025 study using the now established nivolumab dose of 3 mg/kg every 2 weeks, following a median duration of treatment of 5.5 months (range, <0.1 to 29.6), treatment-related AEs of any grade occurred in 319/406 patients (79%). The most frequent treatment-related AEs were fatigue (33%), nausea (14%), and pruritus (14%). Grade 3/4 treatment-related AEs occurred in 19% of patients, with the most common Grade 3/4 AE being fatigue (2%). Treatment-related AEs leading to nivolumab discontinuation were noted in 8% of patients. There were no nivolumab-related deaths.[9]

3.2.3.2 Clinical Activity of Nivolumab in Renal Cell Carcinoma

In the CA209001 trial, partial response (PR) to nivolumab therapy was noted in 3/39 patients (7.7%), one of which had mRCC and was treated at a dose level of 3 mg/kg. The other two partial responders had melanoma and mRCC respectively and were both treated at a dose level of 10 mg/kg. Stable disease (SD) was seen in 10/39 patients (25.6%), and was maintained for > 6 months in 2/10 patients. In the CA209003 trial, 34 patients with pre-treated mRCC received nivolumab and achieved objective response rates of 5/18 (27.8%) and 5/16 (31.3%) for dose levels 1 mg/kg and 10 mg/kg, respectively. The PFS at 24 weeks was 50% in the 1 mg/kg and 67% in the 10 mg/kg dose groups.

In the CheckMate 025 phase 3 trial, patients treated with nivolumab at a dose level of 3 mg/kg every 2 weeks demonstrated a median OS of 25.0 months, which was significantly higher compared with the mTOR inhibitor everolimus (p=0.002). This benefit was retained among different prognostic subgroups. The median PFS in the nivolumab group was 4.6 months. The

objective response rate (ORR) of patients treated with nivolumab was 25%, with PR seen in 24% and CR in 1% of patients respectively. The median time to response was 3.5 months (range, 1.4-24.8) and the median duration of response was 12.0 months (range, 0-27.6).[9]

3.3 Rationale for Combining MGCD516 with Immune Checkpoint Therapy

MGCD516 is a TKI that targets multiple closely related receptor tyrosine kinase pathways including VEGF, platelet-derived growth factor (PDGF), c-KIT, c-MET, and the Tyro3, Axl, and MER (TAM) family. There is a strong rationale for targeting these pathways in mRCC due to their role in aberrant tumor angiogenesis (VEGFR and PDGFR), tumor growth and metastatic progression (c-MET), and evasion of immune surveillance (VEGFRs, c-KIT, TAMs). VEGF, c-KIT, c-MET, and Axl signaling activates cells and molecules that limit the ability of immune checkpoint therapy to fully harness the immune system and achieve consistent, durable anti-tumor activity.

The TAM receptor tyrosine kinases Axl and MER Proto-Oncogene (MERTK) are expressed by selected innate immune cell subpopulations including macrophages and dendritic cells,[37] and cooperate to create an immunosuppressive tumor microenvironment. MERTK suppresses the classically activated (M1) macrophage pro-inflammatory cytokine response involving IL‑ 12, IL 6 and TNF, and enhances M2 macrophage anti-inflammatory cytokine production involving IL‑ 10, IL-4, TGFβ, and HGF.[38,39] The ability to initiate an antitumor M1 macrophage response is impeded by the MERTK-dependent M2 macrophage response within the tumor microenvironment. In addition, Axl is required for the termination of Toll-like receptor dependent inflammatory response in dendritic cells.[40] Studies in TAM receptor null mice have implicated Axl and MERTK in the regulation of innate immune responses mediated by pro-inflammatory signaling.[41] TAM pathway inhibition facilitates the ability of APCs to drive T_H1 responses through increased production of pro-inflammatory cytokines.[42] The inhibition of Axl and MERTK can therefore enhance anti-tumor immunity mediated by CTLs stimulated by T_H1-type cytokines. Accordingly, Axl neutralizing antibodies can attenuate tumor growth by modulating immune cell function in a mouse breast cancer model.[42] In addition, implantation of syngeneic breast and melanoma tumors in MERTK null mice results in decreased tumor growth due to an enhanced innate immune response.[43]

The implantation of MERTK-null bone marrow in irradiated wild-type mice produces a M1-polarized tumor macrophage phenotype that inhibits the growth of breast tumors via immune responses mediated by MERTK-null hematopoetic cells. Both Axl and MERTK are expressed by NK cells and negatively regulate NK cell activity in the tumor microenvironment as part of a feedback regulatory mechanism that decreases NK cell antitumor activity and enhances tumor progression and metastasis in mouse cancer models.[44] Tumors implanted into null mice for the MERTK and Axl ligand Gas6 grow more slowly, likely due to the inhibition of MERTK on macrophages, Axl on dendritic cells, and both Axl and MERTK on NK cells.[45] Collectively, these data implicate Axl and MERTK as key regulators of the innate immune system within the tumor microenvironment, and indicate that inhibition of these TAM RTKs by TKIs such as MGCD516 can reverse tumor-protective immune pathways.

The c-MET RTK also modifies anti-tumor immune responses by regulating APC function and by promoting immunosuppressive pathways within the tumor microenvinronment. c-MET is

expressed by immature $CD14^+$ monocytes which can acquire an immunosuppressive phenotype when exposed to the c-MET ligand hepatocyte growth factor (HGF) secreted by tumor stromal and mesencymal stem cells (MSCs).[46] Depletion of $CD14^+$ monocytes or neutralization of HGF secretion by MSCs reverses the suppression of effector T-cell proliferation and triggers a shift back toward a T_H1-activated T-cell phenotype.[46] MSCs are also implicated in the expansion of immunosuppressive MDSCs which is also dependent on the secretion of HGF.[47] APCs, such as dendritic cells, also express c-MET which can be activated by HGF and subsequently suppress APC function including both antigen presenting capacity and antigen-dependent T-cell responses *in vitro* and *in vivo*.[48-50] HGF neutralization increases APC antigen-presenting capacity and triggers an antigen-mediated and T cell-directed immune response *in vivo* in selected mouse models of inflammatory response.[48,50]

Of all the MGCD516 RTK targets, the most comprehensive preclinical and clinical data demonstrating immunostimulatory activity are available for Vascular endothelial growth factor receptor 2 (VEGFR2) and c-KIT. Inhibition of these receptors results in depletion of immunosuppressive cellular subsets, including Tregs and MDSCs. VEGF neutralizing antibodies and VEGF receptor small molecule inhibitors reduced the percentage of intratumoral Tregs in a syngeneic mouse cancer model.[51] Neutralizing antibodies against VEGFR2 expressed on Tregs attenuate the proliferation of these cells in tumor-bearing mice.[51] Depletion of Tregs in peripheral blood and tumor tissue has also been observed in both mouse models and in clinical trials of VEGF receptor TKIs including sunitinib, sorafenib, and cabozantinib.[51-55] MDSCs notably express both c-KIT and VEGFR1 and the inhibition of these RTKs, using pharmacologic or genetic approaches, reduces MDSC viability *in vitro* and depletes this cell population in mouse tumor models.[52,56,57]

Preclinical data with MGCD516 indicate that it can increase expression of PD-L1 on tumor cells *in vitro* and *in vivo*. Pilot studies in syngeneic mouse tumor models also suggest that MGCD516 increases the proliferation and fraction of systemic/spleen CD4+ and CD8+ T lymphocytes and reduces the number of systemic MDSCs. Additional studies to investigate the effects of MGCD516 in the tumor microenvironment are ongoing.

Since MGCD516 and immune checkpoint inhibitors, such as nivolumab, use distinct mechanisms for immune activation we **hypothesize** that combination therapy with MGCD516 plus nivolumab will have acceptable safety profile and may lead to high clinical response rate and long-term survival for patients with mRCC. Treatment of mRCC with MGCD516 may produce rapid tumor cell death and release of tumor associated antigens, as well as simultaneously enhance the ability of APCs to present tumor antigens. This would prime anti-tumor T cell responses, which can then be enhanced and sustained by nivolumab. In addition, because multiple MGCD516 RTK targets are also implicated in the evasion of immune surveillance and resistance to immune checkpoint inhibitors there is a strong mechanistic rationale for the combination of these classes of agents.

3.3.1 Studies Using Other TKIs

Cabozantinib targets multiple RTKs, including the VEGFR family, c-KIT, c-MET, and TAM receptors. Cabozantinib-treated mice exhibit increased splenic $CD4^+$ T cells.[55] Both cabozantinib alone and its combination with a cancer vaccine significantly increase the

percentage of $CD8^+$ T cells. Treatment with cabozantinib also reduces the percentage of splenic Tregs and MDSCs. Cabozantinib-treated Tregs are not able to suppress CD4+ T cell proliferation indicating the normal regulatory function of these cells was eliminated. Collectively, the favorable change in the effector T-cell to Treg/MDSC ratio establishes an immune stimulatory environment.[55] Clinically, a reduction in immunosuppressive immune cell subsets, including Tregs and MDSCs, has also been observed in patients treated with cabozantinib.[58]

Sunitinib blocks the tyrosine kinase activities of multiple receptors including the VEGF receptor family, c-KIT, and the platelet-derived growth factor receptor alpha polypeptide (PDGFRA). Sunitinib increases $CD8^+$ T cells and decreases circulating Tregs and MDSCs *in vivo* thus improving the ratio between $CD8^+$ T effector cells and suppressor cell populations.[51,54,56] Functional analysis studies indicate that sunitinib alone or combined with a vaccine strategy decreases the ability of circulating Tregs[57] and MDSCs to inhibit T $CD8^+$ cell proliferation.[59] In addition, sunitinib in combination with the immunomodulatory molecules IL-12 and/or 4-1BB agonist significantly improved the survival of tumor-bearing mice.[56] The expansion of tumor T effector cell populations and reduction of Tregs and MDSCs by sunitinib has been observed in mRCC and other cancer patients treated with sunitinib.[51-53]

3.4 Updated results from the present protocol

From May 2017 through February 2020, 42 patients were enrolled in the present trial. At data cutoff (September 21, 2020), 12/42 patients (28.6%) continued to receive trial treatment. The median follow-up time was 18.7 months (95% CI 13.5 to 24.3). Sitravatinib (MGCD516) starting doses of 60, 80, 120, and 150 mg daily were selected according to the late-onset efficacy-toxicity (LO-EffTox) design for 0, 15 (35.7%), 24 (57.1%), and 3 (7.1%) patients. Overall, regardless of sitravatinib starting dose, the combination of sitravatinib plus nivolumab yielded an objective response rate (ORR) of 35.7% (15/42 patients) and a disease control rate (DCR) of 88.1% (37/42 patients). Complete response was noted in one patient (2.4%), who received a sitravatinib starting dose of 80 mg. The posterior mean for the median progression free survival (PFS) was 11.7 months [95% credible interval (CrI) 8.2 to 16.6]. Median overall survival (OS) was not reached, and 34/42 patients (80.1%) were alive at the time of data cutoff. Because we designed our trial to reflect the patient population enrolled in the CheckMate 025 phase III trial of nivolumab monotherapy in advanced ccRCC, we performed historical comparisons with CheckMate 025 using conservative Bayesian non-informative priors. Combining the three sitravatinib dose groups, the posterior probabilities that sitravatinib plus nivolumab yielded higher ORR and longer PFS than those reported for nivolumab monotherapy in CheckMate 025 were 96% and 100%, respectively.

Dose-limiting toxicities (DLTs) were noted in all three patients treated with 150 mg daily. The 120 mg dose produced an ORR of 37.5% (9/24 patients) compared with the ORR of 26.7% (4/15 patients) observed with 80 mg. The 80 mg dose was associated with fewer DLTs (4/15 patients; 26.7%) compared with the 120 mg dose (10/24 patients; 41.7%). The estimated EffTox desirability scores were 0.622, 0.787, 0.755, and 0.630 for the 60, 80, 120, and 150 mg doses, respectively. Because the 80 and 120 mg doses had nearly identical estimated trade-off desirability scores, we compared them using additional criteria. The Bayesian posterior probabilities of sitravatinib 120 mg producing a higher ORR and longer PFS, compared with 80 mg were 80.7% and 68.3% respectively. The posterior probabilities of sitravatinib 120 mg yielding lower level of depression, higher quality of life, and higher hope for the future scores at 3 months compared with sitravatinib 80 mg were 92.7%, 82.6%, and 90.5%, respectively. Thus, all metrics favored the sitravatinib

starting dose of 120 mg.

Adverse events (AEs) requiring dose reduction of sitravatinib throughout the treatment course were noted in 22/42 patients (52.4%) . The primary reason for treatment discontinuation was disease progression (25/42 patients [59.5%]). Treatment discontinuation due to AEs was noted in 4/42 patients (9.5%). Death due to toxicity occurred in one patient who developed respiratory failure from myasthenia gravis. High-dose glucocorticoids (prednisone ≥ 40 mg/day or equivalent) for the management of immune-related AEs were administered in 8/42 patients (19%). Additional immunosuppressive strategies such as infliximab were needed in 2/42 patients (4.8%).

In conclusion, this is the first study to evaluate the safety and efficacy of sitravatinib (MGCD516) plus nivolumab in ccRCC. Higher ORR and longer PFS with sitravatinib plus nivolumab in patients with ccRCC that progressed on prior antiangiogenic therapies were seen, compared to historical studies with nivolumab or TKI monotherapies in this setting. Furthermore, we found that the sitravatinib starting dose of 120 mg demonstrated the optimal tradeoff between efficacy, toxicity, and quality of life. The present trial provided a strong rationale for larger ongoing clinical trials utilizing sitravatinib 120 mg in combination with anti-PD1 therapy across multiple tumor types.

4.0 ELIGIBILITY CRITERIA

4.1 Signed written informed consent

1. Patients must give written informed consent prior to initiation of therapy, in keeping with the policies of the institution. Patients with a history of major psychiatric illness must be judged able to fully understand the investigational nature of the study and the risks associated with the therapy.

4.2 Inclusion criteria:

1. Patients with histologically or cytologically confirmed metastatic/advanced clear cell RCC, or RCC with a clear cell component, who have received 1 or 2 prior anti-angiogenic therapy regimens (+/- cytokine therapy with interleukin-2 or interferon-alfa) in the advanced or metastatic setting. Examples of anti-angiogenic agents include, but are not limited to, sorafenib, sunitinib, pazopanib, axitinib, and bevacizumab.

2. There must be evidence of progression on or after last treatment regimen received and within 6 months of enrollment.

3. Patients must have at least one measurable site of disease, defined as a lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) and measures ≥ 15 mm with conventional techniques or ≥ 10 mm with more sensitive techniques such as MRI or spiral CT scan. If the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation.

4. Karnofsky performance status ≥70

5. Age ≥ 18 years

6. Patients must have adequate organ and marrow function prior to study entry as defined below:

• Hemoglobin[a]	≥ 9 g/dl (treatment allowed)
• absolute neutrophil count	≥1,500/μL
• platelets	≥100,000/μL
• total bilirubin	≤ 1.5 mg/dl
• AST(SGOT) or ALT (SGPT)	≤2.5 X institutional uln, except in known hepatic metastasis, wherein may be ≤ 5 x ULN
• Serum Creatinine	≤ 1.5 x ULN (as long as patient does not require dialysis)

[a] May receive transfusion
[b] If creatinine is not <1.5×ULN, then calculate by Cockcroft-Gault methods or local institutional standard and CrCl must be ≥40 mL/kg/1.73 m^2

7. INR and PTT ≤ 1.5 x ULN prior to study entry. Therapeutic anticoagulation with warfarin is allowed if target INR ≤ 3 on a stable dose of warfarin or on a stable dose of low molecular weight (LMW) heparin for > 2 weeks (14 days) at the time of enrollment.

8. Female patients of childbearing potential (not postmenopausal for at least 12 months and not surgically sterile) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) before study entry. Pregnancy test must be repeated if performed > 14 days before starting study drug.

9. Women must not be breastfeeding

10. Patients with a history of major psychiatric illness must be judged (by the treating physician) able to fully understand the investigational nature of the study and the risks associated with the therapy.

11. Patients with controlled brain metastases are allowed on protocol if they had solitary brain metastases that was surgically resected or treated with radiosurgery or Gamma knife, without recurrence or edema for 1 month (4 weeks).

4.3 Exclusion criteria:

1. Patients must not have any other malignancies within the past 2 years except for *in situ* carcinoma of any site, adequately treated (without recurrence post-resection or post-radiotherapy) carcinoma of the cervix or basal or squamous cell carcinomas of the skin, or active non-threatening second malignancy that would not, in the investigator's opinion, potentially interfere with the patient's ability to participate and/or complete this trial. Examples include but not limited to: urothelial cancer grade Ta or T1,

adenocarcinoma of the prostate treated by active surveillance.

2. Patients currently receiving anticancer therapies or who have received anticancer therapies within 2 weeks (14 days) from enrollment into this study (including chemotherapy and targeted therapy) are excluded. Also, patients who have completed palliative radiation therapy more than 14 days prior to the first dose of MGCD516 are eligible.

3. Patients, who have had a major surgery or significant traumatic injury (injury requiring > 4 weeks (28 days) to heal) within 4 weeks (28 days) of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that are expected to require major surgery during the course of the study.

4. Patients who have been previously treated with mTOR inhibitors such as everolimus and temsirolimus, or with c-MET inhibitors such as cabozantinib

5. Patients who have organ allografts.

6. Known or suspected autoimmune disease. Patients with a history of inflammatory bowel disease (including Crohn's disease and ulcerative colitis) and autoimmune disorders such as rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus or autoimmune vasculitis [e.g., Wegener's Granulomatosis] are excluded from this study. Patients with a history of Hashimoto's thyroiditis only requiring hormone replacement, Type I diabetes, or psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are allowed to participate.

7. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
8. Any underlying medical condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of adverse events, such as a condition associated with frequent diarrhea, uncontrolled nausea, vomiting, malabsorption syndrome or small bowel resection that may significantly alter the absorption of MGCD516.

9. Patients must not have received prior anticancer therapy with any immune checkpoint inhibitors such as anti-CLTA-4, anti-PD1, or anti-PD-L1.

10. Patients receiving any concomitant systemic therapy for renal cell cancer are excluded.

11. Patients must not be scheduled to receive another experimental drug while on this study.

12. Patients who are on high dose steroid (e.g., > 10mg prednisone daily or equivalent) or other more potent immune suppression medications (e.g., infliximab). Topical, inhaled, intra-articular, ocular, or intranasal corticosteroids (with minimal systemic absorption) are allowed. A brief course (<48 hours) of systemic corticosteroids for prophylaxis (eg, from contrast dye allergy) is permitted.

13. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Symptomatic congestive heart failure of New York heart Association Class III or IV
    - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
    - severely impaired lung function as defined as 0_2 saturation that is 88% or less at rest on room air
    - uncontrolled diabetes as defined by blood glucose >200 mg/dl (11.1 mmol/l)
    - Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement) despite appropriate antibiotics or other treatment
    - Liver disease such as cirrhosis or chronic active hepatitis; Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.

14. Patients must not have history of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of MGCD516 or nivolumab or that might affect the interpretation of the results of the study or render the subject at high risk from treatment complications.

15. Patients should not receive immunization with attenuated live vaccines within one week (7 days) of study entry or during study period.

16. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.

17. Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 14 days prior to study entry. Pregnancy test must be repeated if performed > 14 days before administration of MGCD516).

18. Any patients who cannot be compliant with the appointments required in this protocol must not be enrolled in this study.

19. Concurrent therapy with medications known to significantly prolong the QT interval and/or associated with increased risk for Torsade de Pointes arrhythmia. The Principal Investigator (PI) is the final arbiter in questions related to eligibility.

20. Patients with LVEF < 40%

4.4 Inclusion of Women and Minorities

This trial is open to women and men and members of all races and ethnic groups.

5.0 TREATMENT PLAN

5.1 Patient Enrollment

All patients or legally acceptable representatives must personally sign and date, and receive a copy of the informed consent form (ICF) before any study specific screening procedures are performed. Standard medical practice procedures (CT, MRI, physical exam, blood tests) performed within the specified screening period may be used for screening.

Patients will be registered by the responsible study nurse or research coordinator. All patients will be registered in the approved Office of Research Administration (ORA) database at MD Anderson.

All patients who sign an informed consent will be identified by a unique patient number. This number will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the entire clinical study.

A patient is considered enrolled when study medication is administered on Day 1.

5.2 Data Collection

Data will be entered into MD Anderson institutionally approved and compliant database(s) Prometheus and CORe. The database(s) have secure portal that requires users to login with validated credentials, uses approved encryption protocols as defined by institutional information security standards. Systems have granular data access controls to ensure that the minimal amount of information required to complete a task is presented, can handle de-linking and de-identification of patient information to maintain patient confidentiality if necessary. The system(s) are 21 CFR 11 compliant. Standard data collection, storage procedures, and quality assurance procedures will be followed, to ensure integrity and auditability of all information entered.

All patients will be registered in the University of Texas M. D. Anderson Cancer Center CORe database. Registration will occur following informed consent process and prior to initiation of investigational intervention(s). All eligibility criteria must be satisfied.

5.3 Study Design and Duration

This is a phase I–II dose-finding trial to determine the optimal dose of the targeted oral agent MGCD516 when combined with immunotherapy via intravenous Nivolumab at fixed dose 240 mg IV every 2 weeks, in patients with metastatic renal cell carcinoma with a clear cell component who have progressed following treatment with anti-VEGF agents. The goal of the study is to determine an optimal oral MGCD516 dose level among the four levels 60, 80, 120

and 150 mg/day given orally daily until toxicity or progressive disease. Dose-finding will be done using the sequentially adaptive phase I-II late-onset EffTox (Lo-EffTox) trade-off-based design of Jin et al.[60-62] To determine the optimum dosage, efficacy is defined as achieving complete response (CR), partial response (PR), or stable disease (SD) within 6 weeks, and the occurrence of any of the following toxicities within 12 weeks from the start of therapy will be considered a dose-limiting **toxicity** (DLT), if judged by the Investigator to be clinically relevant and related (possibly or probably) to administration of either or both study drug(s):

- Hematologic DLTs:
  - Grade ≥ 3 febrile neutropenia (ANC < 1.0 x 10^9/L with either a single temperature≥ 38.3ºC or a sustained temperature of ≥ 38ºC for more than 1 hour)
  - Grade 3 thrombocytopenia (platelets < 50.0 x 10^9/L ≥ 25.0 x 10^9/L) if associated with:
    - A bleeding event that requires an elective platelet transfusion, OR
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
  - Grade 4 thrombocytopenia (platelets < 25.0 x 10^9/L)

- Non- Hematologic DLTs:
  - Any Grade 4 non-hematological toxicity
  - Grade ≥ 2 drug-related uveitis that does not respond to topical therapy OR requires systemic treatment
  - Grade 3 overlapping toxicities of nivolumab and MGCD516, including diarrhea, rash, fatigue, or elevation of serum amylase/lipase, lasting > 3 days despite optimal supportive care with the exception of:
    - Grade 3 fatigue lasting ≤5 days
    - Grade 3 rash that resolves to ≤ Grade 1 within 3 weeks
    - Grade 3/4 elevation in serum amylase and/or lipase that are not associated with clinical or radiological evidence of pancreatitis
  - Any other Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care with the exception of:
    - Grade 3 tumor flare (defined as local pain, irritation or rash localized at sites of known or suspected tumor)
    - A transient (resolves within 6 hours of onset) Grade 3 infusion-related AE
    - Grade 3 hypertension that can be controlled with medical therapy
  - Any clinically meaningful Grade 3 non-hematologic laboratory value if:
    - Medical intervention (other than electrolyte repletion) is required to treat the patient, OR
    - The abnormality leads to hospitalization, OR
    - The abnormality persists for > 1 week.

Beginning on day 1 of the study, patients will each be treated with a pre-specified daily oral dose of MGCD516 determined by the Lo-EffTox method. Following 2 weeks of MGCD516 monotherapy, nivolumab will additionally be initiated at a dose of 240 mg intravenously (IV) every 2 weeks. Patients who have received at least 6 infusions of nivolumab 240 mg IV every 2 weeks with no DLTs related to nivolumab, will be allowed as an option to transition to the nivolumab schedule of 480 mg IV every 4 weeks. No other dose or schedule modifications will be allowed for nivolumab. A maximum of 60 patients will be treated in up to 20 cohorts of size 3, with the first cohort treated at the pre- specified dose of 80 mg of MGCD516 per day. All

successive doses will be chosen by the Lo- EffTox method, and no untried dose level will be skipped when escalating. The Lo-EffTox design will be implemented using the specialized computer program developed by Jin et al.[60] The study biostatistician Peter Thall, Ying Yuan, or Xuemei Wang in the Biostatistics Department should be consulted as necessary during trial conduct. Secondary outcomes will include progression-free survival (PFS) time, overall survival (OS) time, objective response rate (ORR), and quality of life (QOL).

Patients will receive baseline staging studies with CT or MRI and be assessed for treatment response (RECIST 1.1) by CT or MRI at week 6 (+/- 7 days) as detailed on Sections 9 and 10 of the protocol.

Patients will continue to receive combination therapy of MGCD516 plus nivolumab on protocol until disease progression or unacceptable treatment-related toxicity. Patients will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1-defined progression if they are deemed by the investigator to be deriving clinical benefit and tolerating study drug(s), as described in Section 8.3.

6.0 STUDY MEDICATIONS

6.1 Nivolumab (Anti-PD1)

Nivolumab is a fully human, IgG4 (kappa) isotype, monoclonal antibody that binds PD-1. Nivolumab will be supplied in vials of 100 mg (10 mg/mL) and packaged in an open-label fashion. Ten nivolumab vials (each 10 mL) will be packaged within a carton. The vials are not subject specific although there will be specific vial assignments by subject distributed by the Pharmacy in order to track drug usage and re-supply.

6.1.1 Dose Calculation of nivolumab

Nivolumab will be 240 mg (every 2 weeks) or 480 mg (every 4 weeks), flat dose per infusion. Dose adjustment is not allowed.

6.1.2 Preparation and Dispensing of Nivolumab

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Investigator Brochure. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. Nivolumab will be obtained through commercial sources as the trial is being conducted in the salvage setting that nivolumab is FDA-approved for and its use is in accordance with the National Comprehensive Cancer Network (NCCN) guidance. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 60 +/- 15 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution 1 mg/ml to 10 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

6.1.3 Administration of nivolumab

Each treatment cycle will last 2 weeks (or 4 weeks if the patient is switched to the nivolumab schedule of 480 mg IV every 4 weeks). During the first treatment cycle, patients will be treated with MGCD516 only. The 1st infusion of nivolumab will be given on day 1 of the 2nd treatment cycle. Patients will receive nivolumab as a 60 +/- 15 minute IV infusion on Day 1 of a treatment cycle every 2 weeks until disease progression or intolerability. There will be no nivolumab dose escalations or reductions allowed. Patients may be dosed no less than 12 days from the previous dose. If a subject cannot receive a following dose of the cycle within the designated time frame, it will be omitted and the next dose received will be considered Day 1 of the next cycle.

Nivolumab should be administered under the supervision of a physician experienced in the use of IV agents. Nivolumab is administered as an IV infusion only.

Patients may receive nivolumab at the MDACC local Regional Cancer Centers or local physician office. However, initial screening, workup, the first dose of nivolumab, restaging, and biological sample collection must be done at the MDACC main campus. The participating oncologists will be advised to order pre- and post-treatment evaluations according to the protocol with a written memo. Patients with local physicians who agree to manage standard infusions must agree to perform required tests, send all related medical records to MDACC, and allow the MDACC investigator to direct dose adjustments. The patients are required to return to MDACC for evaluation at weeks 4 (+/- 3 days), 6 (+/- 3 days) from the day of study treatment initiation, and then at least every 12 weeks (+/-7 days) for those that are progression-free during the first 2 years, and then every 6 months for those that progression-free for more than 2 years.

All study related treatment decisions will be made by the MD Anderson PI or designee.

Calculate **Total Infusion Volume** as follows:

(Total nivolumab dose in mg ÷ 10 mg/mL) + dilution volume = total infusion volume in mL

Calculate **Total Drug Concentration** as follows:

Total nivolumab dose in mg ÷ Total infusion volume nivolumab dose in ml = total infusion volume in mg/mL.
Total concentration cannot be below 1 mg/mL.

Calculate **Rate of Infusion** as follows:
Total infusion volume in mL ÷ 60 minutes = rate of infusion in mL/min.

6.1.4 Patient Monitoring During Infusion

Patients will be monitoring by standard of care vital signs during nivolumab infusion.

6.1.5 Treatment of nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations for nivolumab related infusion reactions are provided below and may be modified based on MD Anderson treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated):
Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):
Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: Diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms [Severe reaction, Grade 3: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates), Grade 4: life-threatening; pressor or ventilatory support indicated]:
Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Institutional guidelines will be followed for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids).

6.2 MGCD516

MGCD516 is an orally-available, potent small molecule inhibitor of a closely related spectrum of tyrosine kinases including MET, Axl family, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members. MGCD516 targets several clinically validated ccRCC pathways including VEGF and c-MET.

6.2.1 Formulation and Packaging

MGCD516 will be provided by Mirati as 10 and 40 mg unit dose strength capsules. Please refer to the drug label for formulation and handling information. The composition of the drug product consists of a blend of MGCD516 free base drug substance, microcrystalline cellulose (Avicel® PH302) and polysorbate 80 (Tween® 80). The blend is filled into either Size 1 Light Blue Opaque (10 mg strength) or Size 1 Swedish Orange Opaque (40 mg strength), hard gelatin capsules.

MGCD516 drug product is packaged in 30 count, high-density polyethylene (HDPE), white opaque, round bottles. The 1 mg unit dose capsules are packaged into 30 cc bottles while the 2, 10 and 40 mg unit dose capsules are packaged into 60 cc bottles. A tamper-proof heat induction seal and a child-resistant closure are used for all 4 dosage strengths. Each bottle is labeled with contents, product lot number, required storage conditions, and regional specific cautionary statement “New Drug-Limited by Federal Law to Investigational Use.”

The drug will be provided free of charge by Mirati Therapeutics. Up to 2 or 3 month drug supply will be provided to patients in long term extension phase. Depending on the return appointment.

6.2.2 Dose

Beginning on day 1 of the study, each patient will be treated with a daily oral dose of MGCD516 determined by the Lo-EffTox method[60] among the four levels 60, 80, 120 and 150 mg/day. The first cohort will be treated at the pre-specified dose of **80 mg** of MGCD516 per day. All successive doses will be chosen by the Lo-EffTox method, and no untried dose level will be skipped when escalating. Patients

will continue to receive MGCD516 daily until disease progression or unacceptable treatment- related toxicity.

6.2.3 Administration of MGCD516

MGCD516 will be self-administered by the patients. The investigator will instruct the patient to take the study drugs exactly as specified in the protocol. MGCD516 will be administered orally as a once daily dose. MGCD516 capsules should be taken in the fasted state, at least 2 hours after the previous meal and 1 hour before the next meal.

6.2.4 Compliance

Patients will be required to return all empty bottles of study medication at the beginning of every other cycle, for destruction. Patients will keep a drug diary to document administration compliance. The completed diaries will be brought to clinic for review. Self-administered medications must be accounted for and destroyed per applicable Institutional and Departmental policy. Instructed intervals and dosing will be documented in the medical record. Compliance (individual drugs) within 80% of instructed dose and schedule is expected of participants during each cycle. Variations in dosing within expected compliance will not constitute a protocol deviation or violation. Missed dosed may be documented in the electronic case report form.

6.2.5 Drug Storage and Drug Accountability

The investigator, or an approved representative, e.g. pharmacist, will ensure that all study medications are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of this protocol. Bottles of MGCD516 are to be stored at room temperature (suggested range is 15- 30°C or 59-86°F).

The investigator must maintain adequate records documenting the receipt, use, loss, or other deposition of the investigational product. The records must identify the investigational product, including batch or code numbers, and account for its disposition on patient-by-patient basis, including specific dates and quantities.

6.2.5.1 MGCD516 Destruction

Investigational MGCD516 (expired or end of study) should be destroyed on site according to the institution's standard operating procedure.

6.2.6 Management of MGC516 toxicity

6.2.6.1 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to study drug should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with study drug as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt

water (0.9%) mouth wash several times a day until resolution. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

2. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

3. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of metabolism of study drug, thereby leading to higher drug level exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI CTCAE for adverse events, version 4.0.

6.3 Concomitant Therapies

The following considerations apply during the entire duration of the study:

- No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biologic agents, hormone therapy or immunotherapy except for bisphosphonates. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another therapeutic clinical trial is not allowed.
- No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Surgery or radiation therapy for palliation purposes or management of intercurrent illness which, in the judgement of the treating physician, is not related to disease progression. After the patient has received at least 2 infusions of nivolumab and 6 weeks (42 days) of oral MGCD516 then further therapy on protocol can be held for up to 4 weeks (28 days) to allow for recovery from surgical or other interventions.
- Growth factors (e.g.G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the investigator for rescue from severe hematologic events, if this is thought to be appropriate.
- No chronic treatment with systemic steroids or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- Live vaccines should be avoided while a patient is on protocol.
- The co-administration of MGCD516 and oral warfarin is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).
- Patients who develop venous thromboembolism (pulmonary embolisms or deep venous thrombosis) may be treated as indicated by LMW heparin and stay on protocol at the discretion of the treating physician.
- The patient will provide a list of concurrent medications related to co-morbidity (e.g. hypertension, diabetes, etc.), including over the counter agents, taken prior to enrollment. The list will be updated during clinic visits while on treatment and will be maintained in the medical record.

- In vitro experiments indicate that MGCD516 is a potential inducer of CYP 2B6 and 3A4, as well as a potential inhibitor of CYP 2C8, 2D6, and 3A4, though neither time dependent nor metabolism dependent inhibition has been observed. Medications that are substrates for CYP 2C8, 2D6 or 3A4 and are either sensitive substrates or have a narrow therapeutic index should be used with caution during treatment with MGCD516.
- In vitro experiments in microsomes and recombinant human P450 enzymes suggest that MGCD516 is metabolized by several cytochromes including CYP 3A4, 2B6, 2D6, and with a low risk of any one CYP demonstrating a disproportionate contribution to its metabolism. Caution should therefore be used when administering MGCD516 to patients taking medications that are strong inhibitors or inducers of the cytochrome P450 system.
- The solubility of MGCD516 is pH dependent. For this reason, medications that are associated with sustained increase in gastric pH should be avoided during treatment with MGCD516. Patients requiring gastric pH medications should switch from use of proton pump inhibitors or H_2 antagonists to use of antacids.
- MGCD516 is an inhibitor of BCRP and P-gp transporters based on in vitro studies. Medications that are substrates for BCRP or P-gp transporters should be avoided during treatment with MGCD516.
- Medications with QTc Prolonging Activity: The risk of QTc prolongation in patients receiving sitravatinib has not been characterized. Use of medications known to prolong QTc and pose risk of Torsades de Pointes (listed in Appendix E) is to be avoided.

6.4 Dose Modifications and Interruptions

There will be no intra-subject dose reduction or escalation of nivolumab during the study. Patients will continue to receive MGCD516 daily along with nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable treatment-related DLT. Patients who have received at least 6 infusions of nivolumab 240 mg IV every 2 weeks with no DLT related to nivolumab, will be allowed to transition to the equivalent nivolumab schedule of 480 mg IV every 4 weeks. If one agent (MGCD516 or nivolumab) is interrupted or discontinued, administration of the other agent may continue at the discretion of the Investigator and patient.

There are four possible dose levels for MGCD516 in this study: 60, 80, 120, and 150 mg per day. Depending on safety observations, the MGCD516 dose during subsequent cycles of treatment may be reduced to the next lower dose level at the discretion of the Investigator and patient. Specifically, for grade $\geq$ 3 hematologic and non-hematologic DLTs or Grade $\geq$ 2 drug-related uveitis that does not respond to topical therapy OR requires systemic treatment (as described in section 5.3) attributed to MGCD516 then treatment should be held until resolution to $\leq$ Grade 1 or baseline, and then MGCD516 can be restarted at the next lower dose level. If toxicity recurs (second time or third time) at Grade $\geq$3 (or Grade $\geq$ 2 drug-related uveitis that does not respond to topical therapy OR requires systemic treatment), then hold MGCD516 until resolution to $\leq$ Grade 1 or baseline and restart at next lower dose level. If the patient develops a DLT related to MGCD516 at the 60 mg dose level then MGCD516 should be discontinued. Dose reductions of MGCD516 will also be allowed on a case-by-case basis at the discretion of the Investigator and patient in patients with toxicity related to MGCD516 that does not meet the DLT criteria outlined in section 5.3. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis. If the administration of MGCD516 is interrupted for reasons other than toxicity, then treatment with MGCD516 may be resumed at the same dose. Only the data from the originally planned MGCD516 dose will be used for the dose-finding late-onset EffTox (Lo-EffTox) calculations, described in section 14.

Dosing interruptions > 4 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 4

weeks, the UTMDACC IND Office must be notified. Tumor assessments should continue as per protocol even if dosing is interrupted.

As described above, after the patient has received at least 2 infusions of nivolumab and 6 weeks (42 days) of oral MGCD516 then further combination treatment can be held for up to 4 weeks (28 days) to allow for recovery from surgery, radiation therapy, or other interventions for palliation purposes or management of intercurrent illness which, in the judgement of the treating physician, is not related to disease progression.

Immune-related Adverse Events (irAEs) are defined in the nivolumab label as those occurring during nivolumab therapy, often necessitate immunosuppression and have no other alternate etiology. The nivolumab package insert (http://packageinserts.bms.com/pi/pi_opdivo.pdf) provides detailed evaluation and management guidelines for the following types of ir-AEs: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, rash, and encephalitis. As a general principle, nivolumab should be withheld or permanently discontinued in patients with moderate or severe irAEs. Depending on the nature of the irAE, it should be managed with corticosteroids and/or hormone-replacement therapy. The corticosteroids should be tapered down upon improvement of the irAE to Grade ≤1. Depending on the severity of the irAE, restarting of nivolumab may be considered. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 28 days, the UT MDACC IND Office must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

Patients experiencing any Grade 4 non-hematological toxicity should be taken off study. MGCD516 can be held in patients experiencing, despite optimal supportive care, persistent non- overlapping toxicities attributed to MGCD516, such as hypertension, palmar-plantar erythrodysesthesia, peripheral neuropathy, or stomatitis. The Principal Investigator must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 4 weeks.

With regards to the management of potential overlapping toxicities of the two drugs:

- Patients experiencing Grade 3 fatigue for > 5 days despite optimal supportive care should be taken off study with discontinuation of the combination therapy.
- In patients experiencing Grade 3 rash or Grade 2/3 diarrhea, both oral MGCD516 and nivolumab should be held until improvement to Grade ≤1. Topical and/or systemic steroids can be given as needed. If no improvement to ≤ Grade 1 after combination treatment has been held for >3 weeks then the patient should be taken off study. Dosing interruptions for prolonged steroid tapers >6 weeks to manage drug-related adverse events are allowed. The Principal Investigator must be consulted prior to re-initiating treatment in a patient with a dosing interruption lasting > 4 weeks.
- Patients experiencing Grade 3/4 elevation in serum amylase and/or lipase levels associated with clinical or radiological evidence of pancreatitis, with no other alternate etiology, should be taken off study with discontinuation of the combination therapy.

Discontinuation criteria for nivolumab and MGCD516 are described in sections 8.1 and 8.2, respectively.

6.5 Quality of Life Evaluation

Measuring quality of life (QOL) outcomes in cancer patients has become an important mandate for clinical trials. It is especially important to assess QOL in phase II cancer clinical trials that are likely to

move into the phase III setting. The extent to which treatment impairs QOL is information the patients need when making treatment decisions. It is also important to try and identify factors that are associated with better adjustment to help us identify patients at risk for adjustment problems and translate this information into the clinical setting to individualize intervention programs. In addition, elucidating protective and risk factors will help identify individuals at greater risk for medical complications, disease progression, and recurrence.

Patients will experience somewhat different symptoms when they receive the different therapies. In order to assess the effects of combining these treatments, we will assess multidimensional aspects of QOL over the treatment course.

QOL evaluations will not be performed during the long term extension phase of the trial.

6.5.1 Assessment Schedule

All patients will complete a full assessment battery at baseline, *prior* to treatment. Patients will then complete a brief assessment battery at week 2, week 4, week 6, and then every 12 weeks (see Table 4).

Table 4: Data collection sessions for psychosocial measures

BASELINE	FOLLOW-UP
• FACT • SF-12 • Depression (CES-D) • Social Provisions Scale • History of depression • FMCS	• FACT • SF-12 • CES-D • FMCS

Several measures used previously in our work on chronic stress and QOL will be used in the proposed study. In all cases, they have proven to be useful and sensitive measures of stress and QOL, have proven to be stable, reliable, and valid with groups of people who are and are not suffering from major depression or other psychiatric disorders. All surveys will be completed electronically using e-tablets and response data will be collected using the HIPAA-compliant Qualtrics software platform.

Quality of Life:

The Functional Assessment of Cancer Therapy (FACT) is a cancer-specific measure of *health-related quality of life*. This instrument was able to discriminate between individuals with metastatic and non-metastatic disease, as well as between patients at different stages of illness. The scale has been found to have good concurrent validity, high internal consistency (0.89), and good test re-test reliability (0.82 to 0.88). The FACT will be completed at each assessment.

General QOL – General QOL will be assessed using the Medical Outcomes Study 12-item short-form survey (SF-12). Responses are based on a Likert-type scale. The SF-12 is a health-related QOL measure that is responsive to minor versus major medical problems as well as psychiatric problems. It has good test-retest reliability (coefficients for various subscales range from 0.60 to 0.81) and good internal consistency (coefficients range from 0.78 to 0.93). The SF-12 will be completed at each assessment.

Depression:

Depression will be assessed using the Centers for Epidemiologic Studies - Depression (CES-D) (3). The CES-D is a well-validated 20-item self-report measure of depression that focuses on affective components of depression. Cut-off scores of 16 for screening clinical depression have been recommended. Internal consistency is high in the general population and in patient populations. It also has been demonstrated to possess adequate convergent validity with other measures of depression. The CES-D will be completed at baseline and at each subsequent assessment.

Lifetime history of Major Depressive Disorder (MDD) will be measured using the two cardinal items from the Structured Clinical Interview for DSM-IV Disorder (SCID) that assess lifetime presence of depressed mood or anhedonia for two weeks or more. Patients are considered to have lifetime MDD if they endorse one or both of the items. These two questions will only be completed at the first assessment.

Social Support:
Perceived availability of social support will be measured using the 24-item Social Provisions Scale that includes subscales for attachment, social integration, opportunity for nurturance, reassurance of worth, reliable alliance, and guidance. The SPS will only be completed at baseline.

Hope for the future:
Finding meaning in cancer will be measured using the Finding Meaning in Cancer scale (FMCS). This 17-item scale assesses benefits in different domains, including accepting life's imperfections, changing priorities, and developing a sense of purpose in life. The scale is scored as a single factor, has good internal consistency (0.95), and has shown moderate association with psychological well-being.

7.0 CORRELATIVE STUDIES

We will perform immune monitoring, including but not limited to the evaluation of CD4 and CD8 T cells in available tumor tissue and peripheral blood samples as previously published.[63-66] Peripheral blood and tumor tissue samples (optional) will be obtained within 14 days pretreatment, 2 weeks after MGCD516 monotherapy, following 2 infusions of Nivolumab, and upon disease progression. All samples will be collected and analyzed per a separate IRB-approved protocol. In addition, another IRB-approved protocol, separate from the aforementioned immunotherapy analyses, will be used to investigate in the blood and tumor tissues, a panel of cytokines, chemokines, cell-free DNA, and other relevant angiogenic factors, biological receptors, ligands, nucleotides and proteins.

Up to one hundred (150) ml of blood will be drawn at the visits outlined in Sections 9 and 10. These samples will be labeled with confidential identification numbers and provided to the Immunotherapy platform for immunological assessments. A detailed laboratory manual highlighting the blood collection and processing procedures will be prepared. All blood collection will be compliant with institutional safety standards and will not exceed the maximum blood draw per venipuncture policy.

Blood and tissue collections for correlative studies will not be performed during the long term extension phase of the trial. The only exception is optional collection of blood or tissue samples for those patients taken off therapy due to disease progression to assess causes of disease progression.

8.0 DISCONTINUATION OF THERAPY

Patients MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapies is not in the best interest of the subject
- Termination of the study by MD Anderson Cancer Center
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Progressive disease: Patients, who develop rapidly progressive disease (clinically or by RECIST) before the scheduled evaluations, may be taken off protocol treatment at the discretion of the investigator. Patients can continue to receive their assigned targeted agent, even if they develop progressive disease radiographically, as long as in the judgment of the treating physician, they are benefitting from their targeted agent.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to study drug must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. This may be done by telephone correspondence. If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If one agent (MGCD516 or nivolumab) is interrupted or discontinued, administration of the other agent may continue at the discretion of the Investigator and patient.

8.1 Discontinuation Criteria of Nivolumab

Nivolumab administration should be discontinued for the following:

- Any Grade ≥ 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related bronchospasm, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5- 10x upper limit of normal (ULN) for > 2 weeks
      - AST or ALT > 10x ULN
      - Total bilirubin > 5x ULN
      - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
  - Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the PI for Grade 4 amylase or lipase abnormalities.
- Any dosing interruption lasting > 4 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 4 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 4 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 4 weeks, the UTMDACC IND Office must be notified. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin: Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the PI for Grade 3 amylase or lipase abnormalities.
- Any Grade 3 colitis, neurologic toxicity, symptomatic pancreatitis, or pneumonitis.
- Any Grade ≥3 Stevens-Johnson Syndrome of Toxic Epidermal Necrolysis (TEN).

8.2 Discontinuation Criteria of MGCD516

General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator. Patients may discontinue from study treatment or from the study at any time at their own request, or they may be discontinued at any time at the discretion of the investigator for safety, or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Criteria that may be used to discontinue patients from receipt of study medication will include, but will not be limited to:

- Objective disease progression according to RECIST 1.1 as determined by the investigator, (patients who may derive clinical benefit may continue on treatment at the discretion of the investigator);
- Global deterioration of health status requiring discontinuation;
- Adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Refusal for further treatment;
- Study terminated by Sponsor;

- Death.

Reasons for discontinuation from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. At least 2 attempts should be made to contact the patient and each attempt should be recorded in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return for a final visit, and if applicable follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study treatment, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The investigator may retain and continue to use any data collected before such refusal for further follow-up.

8.3 Continued Treatment beyond Progression of Disease

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease.[67] For this reason, patients will be permitted to continue study therapy beyond initial investigator- assessed RECIST 1.1-defined progression as long as they meet the 2 criteria listed below.

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression must be discussed with the MDACC IND Office and documented in the study records.

Patients should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, patients who continue treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

9.0 PRE-TREATMENT EVALUATION

9.1 Within 28 days of study entry

- Signed and dated informed consent.
- Physical Exam and updated medical history
- Updated evaluation of concurrent non-malignant diseases and recent medical therapy (within the thirty days prior to the evaluation).
- Imaging: CT scan of chest, abdomen, and pelvis (MRI of abdomen and pelvis may substitute CT abdomen/pelvis). CT scan or MRI of the brain.
- Plain films of bones/skeletal survey and bone scan will be ordered only if clinically indicated
- 12-lead ECG

9.2 Within 14 days (+/- 3 days) of study entry

- Confirmation of the eligibility of patients (see Section 4 for detailed Inclusion/Exclusion criteria)
- Histologic diagnosis/confirmation of RCC with clear cell component
- Baseline signs and symptoms
- Current medications
- Interim history
- Assessment of Karnofsky performance status, weight, temperature, blood pressure, heart rate, respiratory rate, oxygen (O_2) saturation
- Physical Examination
- Laboratory testing:
  - CBC with differential & platelets
  - Chemistry panel including electrolytes (Na, K, Cl, CO_2), albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine,
    Phosphorus
  - INR/PTT
  - Lipid profile
  - Blood glucose
  - Serum amylase and lipase,
  - Serum free T4 and TSH.
  - Serum ACTH and Cortisol
  - Blood samples for Immune Testing and Correlative Studies
  - Urinalysis: Gross examination including specific gravity, protein, glucose, and
    blood; microscopic examination including white blood cells / high power field
    (WBC/HPF), red blood cells / high power field (RBC/HPF) and any additional findings.
    - If urine protein ≥ 100 mg/dL then obtain random urine protein/creatinine ratio
  - Serum or urine pregnancy test for females of childbearing potential
- Collect fresh biopsy (optional / up to 14 days prior)
- Complete e-tablet QOL assessments (FACT, SF-12, CES-D, Social Provisions Scale, FMCS, History of Depression)

9.3 Within 6 months (180 days) of study entry

- Doppler echocardiogram

9.4 Treatment can not start until at least 1 week after any minor surgical procedure, excluding placement of a vascular access device and core biopsies.

10.0 EVALUATION DURING TREATMENT

10.1 A cycle of treatment is defined as 2 weeks (+/- 3 days), or 4 weeks +/- 3 days if the

patient is switched to the nivolumab schedule of 480 mg IV every 4 weeks. The following must be performed on Day 1 of each course. If assessment and tests were completed within 7 days of Course 1 Day 1, procedures will not be repeated. Patients are required to come to MD Anderson at the beginning of every course.

- Interim history
- Assessment of Karnofsky performance status, weight, temperature, blood pressure, heart rate.
- Physical examination
- Assessment of all concomitant medications and treatments taken since the last assessment. Concurrent medications related to co-morbidity (e.g. hypertension, diabetes, etc.) will be recorded in the database. The name, dose, date start and stop (as accurately as possible) along with indication of the medication will be collected.
- Assessment of adverse events and tumor-related signs and symptoms
- Assessment of treatment related toxicities
- Laboratory testing:
  - CBC with differential & platelets
  - Chemistry panel including electrolytes (Na, K, Cl, CO_2), alkaline phosphatase, ALT, AST, calcium, total bilirubin, BUN, creatinine
  - Blood for correlative studies
  - Tissue sample

10.2 After 2 weeks (± 3 days) of MGCD516 monotherapy: collect blood samples as well as optional fresh biopsy for immune testing and correlative studies to assess treatment response to MGCD516 monotherapy.

10.3 The following labs will additionally be obtained at 6 weeks (42 days +/- 3 days), 12 weeks (84 days +/- 7 days), and every 12 weeks (84 days +/- 7 days)for as long as patients are receiving therapy on protocol :

- Lipids
- Blood glucose
- Serum amylase and lipase
- Serum free T4 and TSH.
- Serum ACTH and Cortisol
- Chemistry panel including electrolytes (Na, K, C1, CO_2), albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus
- Urinalysis: Gross examination including specific gravity, protein, glucose, and blood; microscopic examination including white blood cells / high power field (WBC/HPF), red blood cells / high power field (RBC/HPF) and any additional findings.
  - If urine protein ≥ 100 mg/dL then obtain random urine protein/creatinine ratio.
- Optional: on the 4th week (± 3 days) of therapy on protocol (following at least 1 infusion of nivolumab): collect blood samples for immune testing and correlative studies to assess treatment response to combination therapy.

10.4 Imaging scans (CT of chest and CT scan or MRI of abdomen/pelvis) will be performed to determine disease response at 6 weeks (42 days)(+/- 3 days), 12 weeks (84 days +/- 7 days), and every 12 weeks (84 days +/- 7 days), for as long as patients are receiving therapy on protocol. A follow-up CT or MRI of the brain will only be ordered if clinically indicated.

10.5 Echocardiogram will be obtained on the 12th week (± 14 days) of therapy on protocol and then repeat every 6 months (± 1 month) or as clinically indicated.

10.6 Complete e-tablet QOL assessments (FACT, SF-12, CES-D, FMCS) at 2 weeks (± 7 days), 6 weeks (± 7 days), 12 weeks (± 7 days) and every 12 weeks (± 7 days) thereafter.

10.7 End of Treatment Evaluation: Adverse events and tumor-related signs and symptoms will be assessed. For patients who develop toxicity related to study drug necessitating discontinuation of protocol therapy before restaging to assess tumor response, physicians treating these patients will make every effort to repeat the appropriate imaging studies if feasible and indicated to assess tumor response at the time the patients are taken off protocol treatment. For patients taken off protocol therapy due to disease progression, blood samples and tumor biopsy (optional at the physician's discretion) will be collected within 28 days from the time that disease progression is first confirmed and used for immune testing and correlative studies.

10.8 Long-term Follow-Up: Patients will be followed for survival every 3 months (90 days ± 1 month or 28 days) by record review or telephone correspondence. Patients in long term follow up at the time of Long Term Extension Phase approval will be assessed for survival every 6 months (180 days +/- 1 month or 28 days)

10.9 Long term Extension Phase

Upon analysis of primary endpoints, the Investigator, sponsor and supporter may agree to notify patients of the status of the clinical trial and allow patients on study medication if they agree and consent. The supporter will continue to supply the MGCD516 (sitravatinib) drug until the treating physician determines to withdraw study medication due to adverse events progression or patient decision.

Data collection will include visit date, assessment of compliance per patient statement, preferable with a medication recorded on study calendar. Patients who choose not to record doses on a medication calendar will not constitute a deviation or violation of the protocol. Patients will be asked to return to MD Anderson every 2 to 3 months (8 to 12 weeks) for resupply of study medication. The return appointment timing is at the discretion of the treating physician. MGCD516 will not be mailed except when acts of nature make it impossible to travel, such as hurricanes, other natural storms (such as snowstorms) or in the case of manmade disasters such as fire. Patients may remain on MGCD516 even if nivolumab is withdrawn. As the nivolumab is per standard of care dose and schedule the infusions may be scheduled locally with the instruction of a local physician letter (“dear doctor” letter). Serious adverse events will be reported and assessed by the MD Anderson study team.

STUDY CALENDAR

	Pre-Study	**Day +1**	**Day+15 (C2D1)**	**Each 14 or 28 day cycle (+/- 3 days)[z]**	**4 weeks (28 days)(+/- 3 days) from day+1**	**6 weeks (42 days)(+/- 3 days) from day+1**	**Every 12 weeks (84 days +/- 7 days)**	**End of treatment**
Informed Consent	X[m]							
Confirmation of eligibility	X[n]							
Histologic diagnosis/confirmation	X							
Medical History	X[m]							
Interim History	X[n]			X		X	X	X
Physical Examination	X[n]			X		X	X	X
Imaging	X[b,m]					X[b]	X[b]	X[j]
Echocardiogram	X[a]						X[u]	
Weight, temperature, blood pressure, heart rate and respiratory rate	X[n]			X[h]		X	X	
O2 saturation	X[n]							
CBC with differential & platelets	X[c,n]			X[c]		X[c]	X[c]	
Chemistry Panel	X[d,n]			X[g]		X[d]	X[d]	
INR/PTT	X[d,n]							
Serum Free T4 + TSH	X[n]					X	X	
Serum ACTH and	X[n]					X	X	
Urinalysis	X[n,o]					X[o]	X[o]	
Pregnancy Test	X[n,f]							
Lipid Profile	X[n]					X	X	
Blood glucose	X[n]					X	X	
Amylase and Lipase	X[n]					X	X	
12-Lead ECG	X[m]							
Karnofsky Performance Status	X[n]			X		X	X	X
Concomitant Medications	X[n]			X		X	X	X
Adverse Events				X		X	X	X
Initiate daily oral MGCD516		X[p]						
Initiate IV nivolumab			X[q]					
QOL assessment	X[n,x]		X[y]			X[y]	X[y]	
Long Term Follow Up								X[k]
Optional Procedures								
Blood for correlative studies	X[n]		X[e]		X[r]	X[s]	X	X[v]
Tissue Sample	X[n,i]		X[l]			X[t]		X[w]

a. During Pre-Study, must be within six months of study entry.

b. CT scan of chest, CT scan or MRI of abdomen/pelvis at 6 weeks (42 days)(+/- 3 days) from study day 1, then every 12 weeks (84 days)(+/- 7 days) after day 1. CT scan or MRI of the brain only at baseline (within 28 days of study entry), and can be repeated if clinically indicated. Plain films of bones/skeletal survey and bone scan will not be ordered routinely on all patients but only if clinically indicated; any follow-up CT scan or MRI will be ordered if clinically indicated.
c. Differentials include neutrophils, lymphocytes, monocytes, eosinophils and basophils
d. Includes electrolytes (Na, K, Cl, Co2), albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, glucose, INR/PTT (pre-study only)
e. After 2 weeks (± 3 days) of MGCD516 monotherapy: collect blood sample for correlative studies to assess treatment response to MGCD516 monotherapy
f. Only for women of childbearing potential. May be serum or urine.
g. Only includes electrolytes (Na, K, Cl, Co2), alkaline phosphatase, ALT, AST, calcium, total bilirubin, BUN, and creatinine
h. Only blood pressure and heart rate
i. Optional fresh biopsy at the physician's discretion (up to 14 days prior)
j. For patients who develop toxicity related to study drug necessitating discontinuation of protocol therapy before restaging to assess tumor response, physicians treating these patients will make every effort to repeat the appropriate imaging studies if feasible and indicated to assess tumor response at the time the patients are taken off protocol treatment.
k. Patients will be followed for survival every 3 months (90 days ± 1 month or 28 days) by record review or telephone correspondence. Patients in long term follow up at the time of Long Term Extension Phase approval will be assessed for survival every 6 months (180 days +/- 1 month or 28 days)
l. After 2 weeks (± 3 days) of MGCD516 monotherapy: collect fresh biopsy (optional at the physician's discretion) to assess treatment response to MGCD516 monotherapy
m. Within 28 days of study entry
n. Within 14 days (+/- 3 days) of study entry
o. If urine protein ≥ 100 mg/dL on urinalysis then obtain random urine protein/creatinine ratio
p. Patients will continue to receive MGCD516 daily until disease progression or unacceptable treatment-related toxicity
q. Patients will receive nivolumab as a 60 +/- 15 minute IV infusion on Day 1 of a treatment cycle every 2 weeks until disease progression or intolerability. Patients may be dosed no less than 12 days from the previous dose. Patients who have received at least 6 infusions of nivolumab 240 mg IV every 2 weeks with no DLTs related to nivolumab, will have the option to transition to the equivalent nivolumab schedule of 480 mg IV every 4 weeks.
r. On the 4th week (± 3 days) of therapy on protocol (following at least 1 infusion of nivolumab): collect blood sample (optional at the physician's discretion) for correlative studies to assess treatment response to combination therapy
s. On the 6th week (± 3 days) of therapy on protocol (following at least 2 infusions of nivolumab): collect blood sample for correlative studies to assess treatment response to combination therapy
t. On the 6th week (± 3 days) of therapy on protocol (following at least 2 infusions of nivolumab): collect fresh biopsy (optional at the physician's discretion) to assess treatment response to combination therapy
u. Obtain an echocardiogram on the 12th week (±14 days) of therapy on protocol and then repeat every 6 months (±1 month)
v. In patients taken off therapy due to disease progression, collect blood sample for correlative studies to assess causes of disease progression
w. In patients taken off therapy due to disease progression, collect fresh biopsy (optional at the physician's discretion) to assess causes of disease progression.
x. Complete e-tablet QOL assessments (FACT, SF-12, CES-D, Social Provisions Scale, FMCS, History of Depression) within 14 days (+/- 7 days) of study entry
y. Complete e-tablet QOL assessments (FACT, SF-12, CES-D, FMCS) at 2 weeks (± 7 days), , 6 weeks (± 7 days), 12 weeks (± 7 days) and every 12 weeks (± 7 days) thereafter
z. patients who switch to nivolumab 480mg will, from that time onwards, have physical exam, CBC and chemistry panel every 4 weeks (28 days +/- 3 days) instead of every 2 weeks (14 days +/- 3 days)

Long Term Extension Phase Schedule of Events

Event	Every 8 to 12 weeks (56 to 84 days +/- 7 days)	End of treatment Plus 30 days post last dose
Follow up exam with physician or delegated advance practice provider	X	X
Assessment of serious adverse events	X	X
Disease assessment per the discretion of the treating physician	X	X
daily oral MGCD516		
IV nivolumab *every 4 weeks per standard of care	X*	X
Routine laboratory assessment per the discretion of the treating physician		
Blood and tissue for correlative studies		X[a]

[a] In patients taken off therapy due to disease progression, collect optional blood and tissue sample for correlative studies to assess causes of disease progression

11.0 CRITERIA FOR RESPONSE OR PROGRESSION

11.1 Efficacy Assessments

Progression-free survival (PFS) and objective response rate (ORR), each based on RECIST 1.1 criteria, are two of the primary efficacy assessments of this study.

Evaluation of response will follow the Response Evaluation Criteria in Solid Tumors (RECIST). All tumor measurements must be recorded in centimeters.

- 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 (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum of longest diameters will be used as the reference by which the objective tumor response is characterized.

- Non-target Lesions:
  All other lesions (or sites of disease) up to 2 lesions per site and 5 lesions in total 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.

11.2 Evaluation of Target Lesions:

- Complete Response (CR):
  The disappearance of all target lesions.
- Partial Response (PR):
  At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
- Progressive Disease:
  At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.
- Stable Disease:
  Insufficient shrinkage to qualify for partial response, or insufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

11.3 Evaluation of Non-target Lesions:

- Complete Response:
  The disappearance of all non-target lesions.
- Incomplete Response/Stable Disease:
  The persistence of one or more non-target lesion(s)
- Progressive Disease:
  The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

11.4 Evaluation of Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Evaluation of Best Overall Response (RECIST)

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

CR= complete response; PR= partial response; SD= stable disease; and PD= progressive disease

11.5 Immune related Response Criteria (irRC)

New, measurable lesions	Incorporated into tumor burden
New, non- measurable lesions	Do not define progression (but precludes irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance is required
Complete response (CR)	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
Partial response (PR)	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
Stable disease (SD)	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
Progression of disease (PD)	≥25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

Note: According to the irRC, disease progression of non-index lesions or appearance of new non-measurable lesions will not classify the subject as PD, and therefore the subject may stay in the study if it is the in the subject's best interest. A confirmatory tumor assessment may be performed no less than 4 weeks after the first indication of progression to provide additional data for the investigator to decide if the subject should stay in the trial or be discontinued due to clinical progression based on the investigator's decision.

11.6 Time -to- Event Assessment of Response

Time to Response: From the start of study drug to the first observation of a response (the first of two confirmatory measurements).

Duration of Response: From the first observation of a response (the first of the two confirmatory statements) to the first observation of progressive disease, or to death due to any cause, or early discontinuation of treatment due to progressive disease.

Time to Progression: From the start of study drug to the first evidence of progression.

Progression-free survival (PFS): Time from the start of the study drugs until disease progression (based on RECIST 1.1 criteria) or death

Survival: Survival will be calculated from the start of the study drugs to death due to any cause.

Patients in Long Term Extension Phase will not have formal RECIST measurements. The treating physician will evaluate patient for overall continued benefit.

12.0 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT

- Progressive disease: Patients, who develop rapidly progressive disease (clinically or by RECIST) before the scheduled evaluations, may be taken off protocol treatment at the discretion of the investigator. Patients can continue to receive their assigned targeted agent, even if they develop progressive disease radiographically, as long as in the judgment of the treating physician, they are benefitting from their targeted agent.
- Intercurrent illness that prevents continuation of treatment.
- Unacceptable adverse event(s), or delay of treatment for > 4 weeks due to treatment-related toxicity. Note: Patients who require emergency surgery (e.g. for appendectomy or because of trauma complications) or who require a procedure (e.g. Kyphoplasty/vertebroplasty) may remain on trial, even if administration of the targeted agent is interrupted, as long as the targeted agent is resumed within 4 weeks from date of interruption.
- Death
- Patient non-compliance with therapy.
- Decision of the patient to withdraw from the study
- Lost to follow-up
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

13.0 SAFETY ASSESSMENTS AND REPORTING REQUIREMENTS

13.1 All patients will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. All adverse events encountered after the patient has provided informed consent and until 4 weeks after the patient has stopped treatment will be evaluated according to the NCI Common Toxicity Criteria (CTCAE) version 4.0. Prior treatment associated toxicities present at the time of informed consent but before study treatment initiation, will be recorded as baseline abnormalities and graded according to NCI CTCAE version 4.0 criteria.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and reported as described in the data submission schedule

Reporting Responsibilities of Investigators under 21 CFR 312.64(b) and Sponsors under 21 CFR 312.32(c)(1)(i) for Serious and Unexpected Suspected

Adverse Reactions

Term	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious (or life-threatening)	Yes (Investigator must report all serious adverse events to the sponsor immediately)	Yes	An event is considered serious or life-threatening, based on **either** the investigator's or sponsor's opinion.
Unexpected	No (No requirement to assess "expectedness")	Yes	The **sponsor** is responsible for determining whether event meets the definition of "unexpected," based on whether the event is listed in the investigator brochure; or if an investigator brochure is not required or available, is not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.
Suspected Adverse Reaction – (causality assessment standard - "reasonable possibility")	Yes (Investigator must provide sponsor with an assessment of causality)	Yes (Sponsor's assessment determines reportability, regardless of investigator's assessment)	The sponsor is responsible for determining whether there is a reasonable possibility that the drug caused the adverse event, taking into consideration the investigator's assessment.

↓

The *sponsor* reports serious and unexpected suspected adverse reaction to the FDA and all participating investigators.

13.2 Serious Adverse Event Reporting (SAE)

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

outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalized 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 a serious adverse drug experience when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline**,** progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

13.3 Reporting to FDA

- Serious adverse events will be forwarded to FDA by the IND MD Anderson (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

13.4 For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

13.5 Pregnancies

Any pregnancy that occurs during study participation should be reported. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

13.6 Long Term Extension Phase

Patients will continue to be assessed for serious adverse events in the long term extension. Routine and expected AEs will not be collected in the case report form. Reporting of events to sponsor and supporter will remain as above.

14.0 STATISTICAL CONSIDERATIONS / DATA ANALYSIS

14.1 Phase I-II Dose-Finding Design

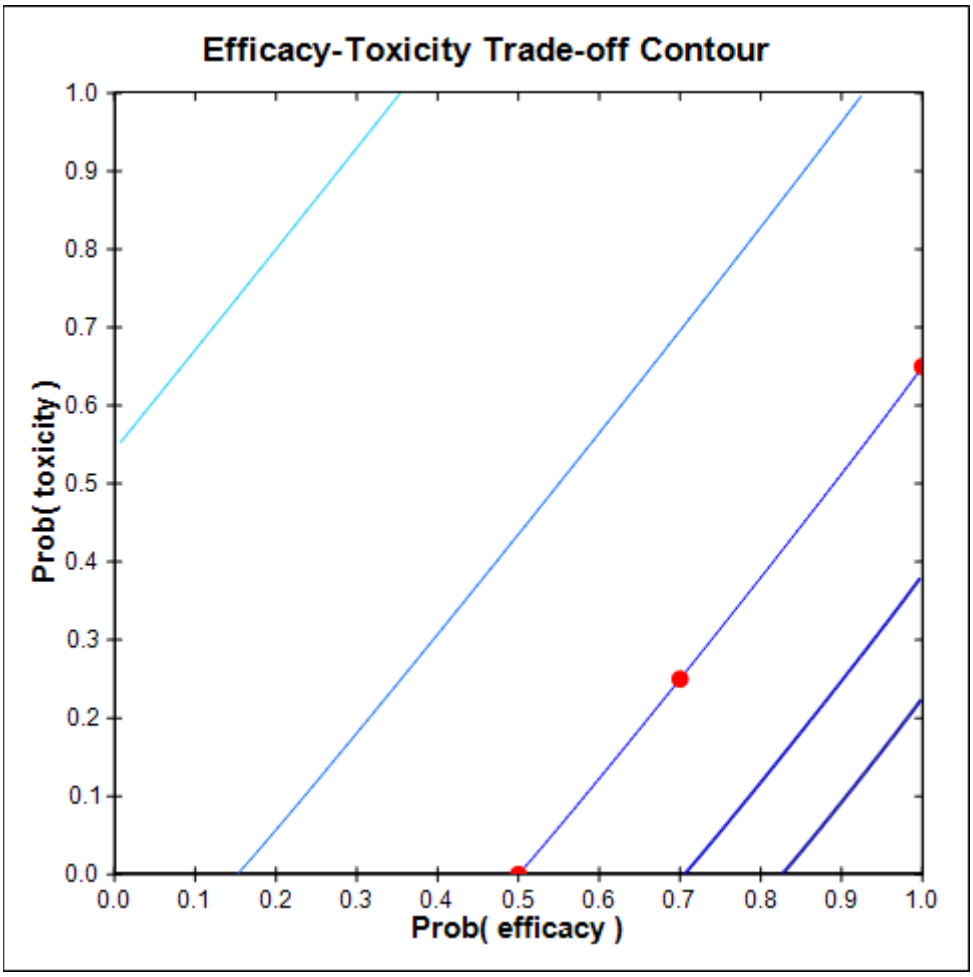
This is a phase I–II dose-finding trial to determine the optimal dose of the targeted oral agent MGCD516 when combined with immunotherapy via Nivolumab at fixed dose 240 mg IV every 2 weeks, in patients with metastatic renal cell carcinoma with clear cell component who have had prior treatment with anti-VEGF agents. The scientific goal of the trial is to determine an optimal MGCD516 dose level among the four levels **60, 80, 120, 150** mg/day given orally each day until toxicity of progressive disease. Dose-finding will be done using the sequentially adaptive phase I-II late-onset EffTox (Lo-EffTox) trade-off-based design of Jin et al.[60-62] For the goal of determining an optimum dose, dose limiting Toxicity within 12 weeks from the start of therapy is defined as described in section 5.3, and Efficacy is defined as achieving CR, PR, or stable disease within 6 weeks. Patients who have received at least 6 infusions of nivolumab 240 mg IV every 2 weeks with no DLTs related to nivolumab, will have the option to transition to the equivalent nivolumab schedule of 480 mg IV every 4 weeks. Because such a change will occur after at least 12 weeks from study initiation the endpoints are not affected for the purpose of dose escalation and de-escalation.

Each cohort will include no more or less than 3 patients. A maximum of 60 patients will be treated in up to 20 cohorts of size 3, with the first cohort treated at **80** mg/day, all successive

doses chosen by the Lo-EffTox method, and no untried dose level skipped when escalating. Enrollment will continue without delay except, we also require at least one patient's toxicity outcome to have been observed at the current dose (which takes a maximum of 12 weeks) before enrolling the next cohort of patients. For the two Lo-EffTox dose acceptability rules, the upper limit on the probability of toxicity is .40, the minimum probability of Efficacy .50, and cut-offs .10 will be used for both stopping probability criteria. If the lowest dose level is found to be unacceptable in terms of either high toxicity or low efficacy, the trial will be terminated and no dose level will be selected. The three equivalent trade-off probability pairs used for computing the trade-off contours are (.50, 0), (.70, .25), (1, .65). The prior hyper-parameters were computed based on the assumed prior means Prob(Efficacy | dose) = .25, .30, .35, .50 and Prob(Toxicity | dose) = .20, .25, .30, .40. respectively, at the four MGCD-516 dose levels. The overall prior effective sample size = 1.

The Lo-EffTox design will be implemented using the specialized computer program developed by Jin et al.[60] The study biostatistician Peter Thall, Ying Yuan, or Xuemei Wang in the Biostatistics Department should be consulted as necessary during trial conduct. Secondary outcomes will include progression-free survival (PFS) time, overall survival (OS) time, objective response rate (ORR), and quality of life (QOL). Unadjusted distributions of the time-to-event outcomes will be estimated using the method of Kaplan and Meier[68] and their relationship to prognostic covariates will be evaluated by Bayesian piecewise exponential survival regression.[69]

A Toxicity/Efficacy Summary will be submitted to IND Office Medical Monitor; every three patients, after the first twelve weeks of study therapy or administration is discontinued, whichever comes first, until 60 patients have completed study therapy.



14.2 Design Operating Characteristics

Operating characteristics of the design are summarized below, based on simulations with1000 replications per scenario. In the simulations, it is assumed that the times to toxicity and efficacy follow Weibull distributions, the percentage of toxicity (or efficacy) events occurring in the later half of each evaluation interval is 50%, and the accrual rate is 2 cohorts per month.

Scenario		**Dose (mg/day)**				
		60	80	120	150	None
1						
	True pT, pE	.20, .25	.30, .45	.40, .70	.50, .95	-
	Trade-off Value	-0.83	-0.58	-0.24	0.12	-
	% selected	0	11.5	41.0	41.0	6.5
	# Patients Treated	3.5	8.7	18.8	27.6	-
2						
	True pT, pE	.20, .40	.30, .65	.60, .70	.90, .75	-
	Trade-off Value	-0.53	-0.18	-0.55	-0.91	-
	% selected	8.4	75.5	1.4	0	14.7
	# Patients Treated	8.0	31.1	10.6	6.2	-
3						
	True pT, pE	.30, .65	.60, .72	.65, .75	.70, .78	-
	Trade-off Value	-0.18	-0.51	-0.52	-0.54	-
	% selected	78.4	10.3	0.1	0	11.2
	# Patients Treated	27.5	18.5	6.8	3.9	-
4						
	True pT, pE	.10, .15	.15, .20	.20, .25	.25, .30	-
	Trade-off Value	-0.87	-0.85	-0.83	-0.81	-
	% selected	0	0	0	3.8	96.2
	# Patients Treated	3.2	3.3	4.3	22.2	-
5						
	True pT, pE	.50, .25	.60, .35	.70, .45	.80, .56	-
	Trade-off Value	-1.30	-1.26	-1.21	-1.14	-

	% selected	0	0	0	0	100
	# Patients Treated	4.2	6.2	4.9	5.4	-

14.3 Additional analyses

Demographics: For each treatment group (control, experimental), summary statistics will be provided for age, baseline disease status and prior treatments.

Toxicity: Adverse effects that will be evaluated include, but are not limited to infections, renal toxicity, hepatic toxicity, and pulmonary toxicity. Methods of assessment will include monitoring blood counts, and performing laboratory tests as indicated by clinical signs and symptoms. Evidence of toxicity or adverse events will be recorded at all clinic visits. All observed adverse effects will be graded for all patients and the degree of association of each with therapy assessed.

Quality of Life: Prior to inferential procedures, extensive descriptive analyses will be conducted for each of the measures obtained at each session. Descriptive statistics (e.g., means, ranges, standard deviations) will be computed, together with ninety-five percent confidence intervals for the means. Proportions of subjects falling outside normative ranges for the stress and QOL measures will also be calculated. Values for the standardized scales will be compared to normative data and patients receiving other types of cancer therapy. Graphical methods (e.g., boxplots and histograms) will be employed to more closely examine the distributions of the measures at each time point. Change scores for the stress and QOL measures will be computed as the simple differences between the baseline measure and subsequent evaluations. Bivariate associations between the raw scores, the change scores, optimism, social support, and demographic variables will be evaluated using Pearson's product moment correlation coefficients together with scatterplots where appropriate. These procedures will allow us to thoroughly characterize the stress and QOL profiles of this patient population across the sessions.

In this study, numerous models will be constructed to analyze the data and, therefore, the results will be treated as hypothesis generating and interpreted with caution. Inferential statistics will comprise paired t-tests of the stress and QOL measures. Significant test results ($p < .05$) will be interpreted as indicating significant changes in stress and QOL associated with the treatment. Linear regression analyses will then be used to construct prediction models using a composite stress and QOL score. In these analyses, the composite stress and QOL score will be regressed onto spirituality and social support at the start of the trial, and interaction terms will be calculated to determine whether these factors moderate stress and quality of life. Potential confounders include the stress and QOL measures obtained at baseline and demographic and treatment characteristics. Backwards step-wise regression will be employed to construct the final models, with a rejection criteria of $p > .05$. Multivariate methods, including repeated measures analyses, will be employed to further explore the potential changes in the stress and QOL measures over time. Standard residual based diagnostic procedures will be used to evaluate model assumption and normalizing transformation made as appropriate.

15.0 DATA AND PROTOCOL MANAGEMENT

Protocol Compliance: All required interim and pretreatment data should be available, and the physician must assess tumor response and must provide a detailed description of toxicity, when appropriate. If dose modifications or treatment interruptions are necessary, the details must be carefully documented. Performance status must be documented at each toxicity assessment.

Data Capture: Data will be entered in the MD Anderson institutionally approved database(s). Registration data entry will occur prior to initiation of therapy. All eligibility criteria must be satisfied.

Accuracy of Data Collection: The MD Anderson Principal Investigator will be the final arbiter of response and toxicity, should a difference of opinion exist.

Monitoring: The trial will be monitored throughout the study with the assistance of the MD Anderson IND office. The study will be performed in accordance with ethical principles and follow federal, institutional, and departmental policy and or regulation. Every effort will be made to maintain patient confidentiality in accordance with federal regulation and institutional policy.

Chain of custody of biological samples: The chain of custody will be maintained for all samples throughout to completion and close out of the trial. A record of storage location will be documented. Records will be available for monitoring and audit as requested.

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