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TITLE: Phase II Trial of ERK Inhibition Alone and in Combination with Autophagy Inhibition in Patients with Metastatic Pancreatic Cancer

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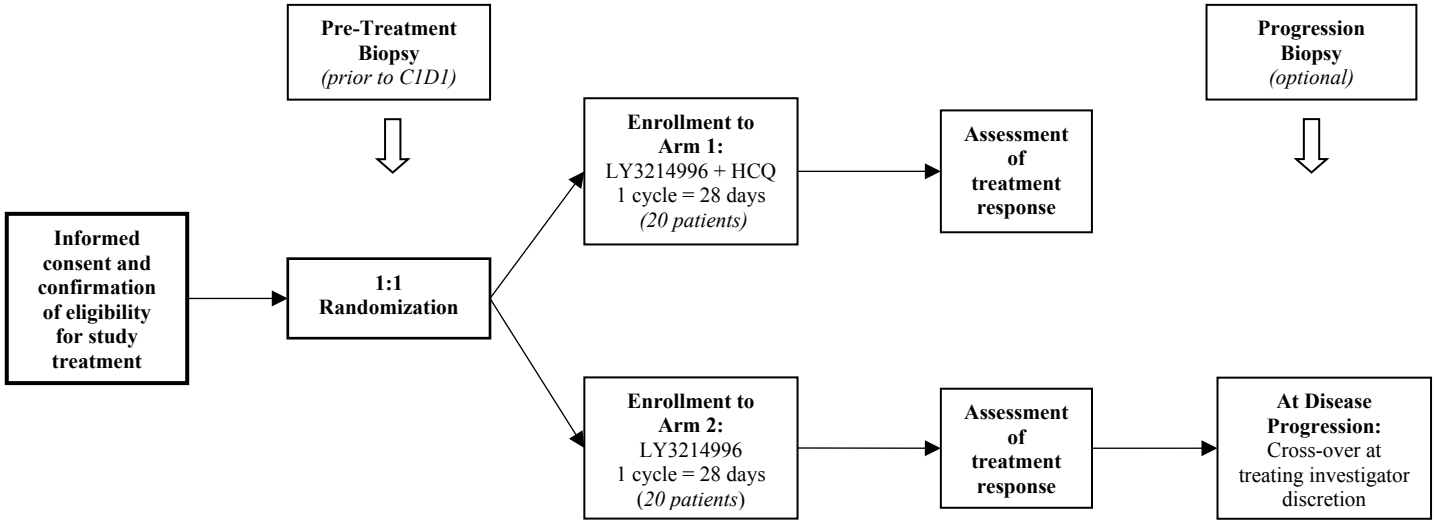
SCHEMA



Note: *The trial will begin with a safety lead-in cohort to evaluate the LY3214996 + HCQ combination. Refer to* ***Section 5.1*** *for details.*

Following discontinuation of study treatment, participants in all arms will be followed for a maximum of 6 months.

Treatment will continue until disease progression, unacceptable toxicity, the participant decides to withdraw, intercurrent illness or condition prevents further administration of study treatment, or subject non-compliance with study requirements. Refer to ***Section 5.5****.*

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1. OBJECTIVES

1.1 Study Design

This is an open label, randomized, two arm, phase II study exploring the anti-tumor activity of the extracellular signal-regulated kinase (ERK) inhibitor LY3214996 with and without hydroxychloroquine (HCQ) in patients with advanced pancreatic cancer. Following completion of a brief combination treatment safety lead-in cohort, participants will be randomized 1:1 for enrollment to one of two treatment arms:

- **Arm 1:** receiving combination treatment with LY3214996 and HCQ
- **Arm 2:** receiving monotherapy treatment with LY3214996

1.2 Primary Objective

Evaluate the anti-tumor activity of LY3214996 alone and in combination with HCQ in patients with metastatic pancreatic tumors. Anti-tumor activity will be measured via disease control rate (DCR), which will be defined as the proportion of patients with complete response (CR), partial response (PR) or stable disease (SD) that persists for ≥ 4 months. Radiologic response will be assessed using RECIST v1.1 criteria.

1.3 Secondary Objective

Examine the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) following treatment in these patient populations.

1.4 Exploratory Objectives

- Develop multivariate predictive models for response to LY3214996 alone and in combination with HCQ via integration of correlative assays, sequencing data, organoid therapeutic response measurements, and clinical data including prior regimens of therapy.
- Explore biomarker indicators of target engagement, response, and resistance.
- Investigate resistance mechanisms via repeat molecular analyses and organoid derivation at the time of progression.
- Assess the pharmacokinetic (PK) properties of LY3214996 when combined with HCQ in this patient population.

2. BACKGROUND

2.1 Study Disease and Rationale

Pancreatic ductal adenocarcinoma (PDAC) is the third-leading cause of cancer-related death in the United States and is projected to become the second leading cause by 2030.[1] Fifteen to twenty percent of PDAC patients are diagnosed with clinically localized disease that is amenable to potentially curative surgical resection.[2,3] Following surgical resection, the majority of patients will have local or distant recurrence and succumb to the disease.[4] Systemic treatment, in the form of neoadjuvant or adjuvant cytotoxic chemotherapy, is used in conjunction with oncologic resection but only adds a modest benefit in survival.[5,6]

Most patients are not surgical candidates and are diagnosed with locally advanced or metastatic disease. Therapeutic options for these patients include the combination chemotherapy regimens gemcitabine/nab-paclitaxel[7] or FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin).[8] Despite therapeutic intervention, median overall survival is 6.7 – 11.1 months (PFS = 3.3 – 6.4) for advanced disease,[7,8] compared to 25 – 28 months (PFS = 13.1 – 13.9) in surgically resected patients.[5] Current therapeutic selection for metastatic pancreatic cancer patients is often based on patient performance status and co-morbidities. This highlights the unmet clinical need to define responsive subgroups to inform treatment selection and to nominate alternative treatment options for patients who are resistant to currently approved treatment regimens.

Approximately 95% of PDAC tumors harbor *KRAS* mutations,[9] and those with wild-type *KRAS* often harbor alterations in other RAS pathway genes such as *BRAF*.[10] Despite this, inhibition of MEK downstream of KRAS hasn't resulted in significant clinical benefit to most patients with PDAC. One promising approach to treatment might be to target ERK alone or in combination with inhibition of the metabolic functions that support the increased energy needs of PDACs.

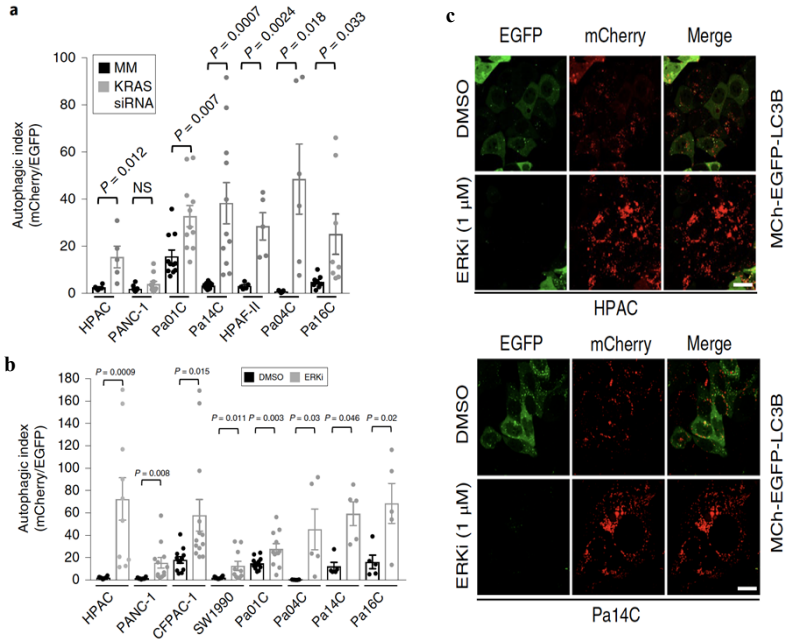


Figure 1: KRAS suppression or ERK inhibition enhances autophagic flux. **a:** PDAC cell lines stably infected with lentiviral vector encoding mCherry-EGFP-LC3B and then transiently transfected with siRNA targeting *KRAS* or a mismatch control oligio (MM) (72 h). Area ratios of mCherry+ punctae to EGFP+ punctae were determined. Mean autophagic index is plotted, each data point representing 1 field containing at least 10 analyzed cells. **b:** PDAC cell lines stably infected with lentiviral vector encoding mCherry-EGFP-LC3B and then treated with ERK inhibitor or DMSO for 24 h. **c:** Representative images of cells described and quantified in **b**, scale bar 20 μm.[9]

Macroautophagy (autophagy) is a lysosome-mediated process that permits cells to degrade organelles and macromolecules and recycle cellular waste. The resulting products are used to sustain cellular metabolic needs.[9,11] Pancreatic tumors have high basal levels of autophagy, and

inhibition of autophagy has been shown to inhibit growth both in cell line and animal models.[11]

Unfortunately, this did not translate clinically when autophagy was inhibited with single-agent hydroxychloroquine (HCQ). HCQ is an FDA approved autophagy inhibitor commonly used in rheumatoid arthritis and as an antimalarial agent. A phase II monotherapy study conducted at Dana-Farber using HCQ in 20 patients with metastatic pancreatic cancer demonstrated negligible therapeutic efficacy. Only two patients were without progressive disease at two months, and median PFS and OS were 46.5 and 69 days, respectively. The trial did identify LC3-II as a candidate clinical pharmacodynamic marker, but otherwise determined that autophagy inhibition alone with HCQ was not sufficient to affect tumor growth.[11]

The theory that RAS pathway signaling regulates autophagy led researchers Bryant and Kinsey to independently explore both the mechanism driving the autophagic flux and the potential combination of MEK/ERK and autophagy inhibition. The authors determined that *KRAS* suppression elevated autophagic flux, and that treatment with a RAF pathway inhibitor phenocopied *KRAS* suppression (**Figure 1**). This elevation serves as a protective mechanism for the survival of the cell in the face of RAF/MEK/ERK pathway inhibition. Consistent with this, both authors reported synergistic anti-proliferative effects with combination treatment both *in vitro* and *in vivo* (**Figure 2**).[9,12]

Based on these discoveries, Kinsey's team went on to compassionately treat a single patient with the MEK inhibitor trametinib (2 mg daily) and HCQ (escalated to 600 mg BID). The patient had failed three prior treatment regimens, with a best response of stable disease with the first two lines and disease progression with the last. Kinsey reported the patient achieved a PR by RECIST 1.1 criteria, with a decrease in tumor burden of approximately 50% at 4 months following initiation of therapy. The patient tolerated the treatment well with only grade 1 rash and fatigue noted, no ocular or cardiac toxicity was observed.[12]

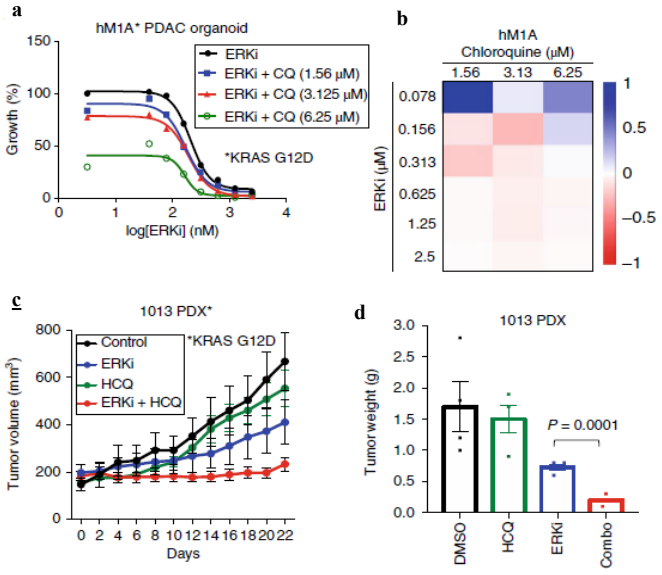


Figure 2: ERK inhibition with HCQ is effective pre-clinically. **a:** hM1A subject-derived organoids grown for 10 days in the presence of indicated concentrations of CQ and ERK inhibitor (0.039 to 2.5 μM). Growth curve is representative of 5 independent experiments. **b:** Heatmap representing BLISS independence scores corresponding to representative growth curve shown in **a. c:** NSG mice implanted with *KRAS*-mutant PDX tumor (AZ1013) were treated with ERK inhibitor alone or in combination with HCQ for 22 days. Mean tumor volume plotted, error bars denote s.e.m. **d:** Quantitation of AZ1013 tumor weights, *P* value is from two-sided, unpaired *t*-test comparing ERK inhibitor-treated to ERK inhibitor + HCQ-treated tumors; error bars denote s.e.m.[9]

Further investigation of the combination of ERK and autophagy inhibition in PDAC is

warranted. The combination may provide significant clinical benefit in a patient population with incredible need.

2.2 LY3214996

LY3214996 is a small molecule that selectively inhibits the extracellular signal-regulated kinase (ERK; ERK1/2), a key downstream node of the RAS/RAF/MEK signaling pathway. The MAPK pathway is a key regulator of cellular proliferation and survival. Abnormalities of the MAPK pathway are common in many cancers, including PDAC, cutaneous melanoma, uveal melanoma, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), breast cancer, ovarian cancer, and many others. Extracellular signal-regulated kinase is a downstream member of this pathway and plays a central role in transmitting extracellular signals from activated receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and others. This pathway is a 3-tiered kinase cascade consisting of the RAF, MEK, and ERK kinases and activation of this pathway begins with activation of RAS, a small guanosine triphosphate hydrolase. Activation of RAS leads to the recruitment of RAF, a serine/threonine kinase, to the cell membrane and its activation. Activated RAF then phosphorylates and activates MEK1/2, which in turn phosphorylates and activates ERK1/2. When activated, ERK1/2 phosphorylates p90 ribosomal S6 kinase 1 (RSK1), and regulates several additional downstream cytoplasmic and nuclear targets involved in the cell cycle, cell proliferation, cell growth, and cell survival.

The feasibility of pharmacologic inhibition of the MAPK pathway in cancer has been shown through the success of BRAF and MEK inhibitors in the treatment of patients with various cancer subtypes, especially patients who harbor BRAF mutations. However, while BRAF and MEK inhibitors have proven effective in patients with BRAF V600E/K melanoma and BRAFV600E NSCLC, most patients eventually develop drug resistance, which leads to disease relapse.[13,14] Most resistance mechanisms to RAF and MEK inhibitors result in reactivation of ERK1/2;[15] therefore, a blockade of ERK1/2 is directly postulated to overcome many of the current limitations of RAF and MEK inhibitors. In addition, RAF and MEK inhibitors remain ineffective in RAS-mutant cancers. Neurofibromin-1, a tumor-suppressor gene is a negative regulator of RAS. Loss of function of NF1 has been linked to the development of tumors in mice.[16] Neurofibromin-1 deletions and mutations are common in cancers and may recapitulate RAS mutations and represent an attractive target in the MAPK pathway.[16,17]

The current mechanistic paradigm suggests that the drug resistance could be due to reactivation of the MAPK pathway through RAS-/RAF-dependent mechanisms such as activating mutation in NRAS or MEK1,[18,19] expression of truncated forms of BRAF or upregulation of CRAF, or COT1.[20-23] Moreover, the persistent expression of the RTKs PDGFR-β and insulin-like growth factor 1 receptor (IGF-1R) conferred BRAF inhibitor resistance that may involve enhanced phosphatidylinositol 3-kinase (PI3K)/AKT pathway activation.[18,24,25] In addition, RAS-mutant tumors, especially those that harbor KRAS and NRAS mutations that account for a larger proportion of cancer patients, remain refractory to BRAF and/or MEK inhibitors. Loss of MEK function can also be overcome by ERK activation. Therefore, the mechanisms of resistance to ERK inhibitors will be different from those that arise from MEK inhibitors.[13] Furthermore, the

acquired resistance to BRAF and MEK inhibition in BRAF-mutant tumors and the inherent lack of response in RAS cancers present a significant therapeutic challenge. LY3214996 is a potent inhibitor of ERK1/2 kinases that can potentially obviate resistance mechanisms in cancers that harbor BRAF, RAS, NF1, MEK, and other MAPK mutations and alterations.

LY3214996 is being evaluated as monotherapy and in combination in the first-human-dose (FHD) Phase 1 Study I8S-MC-JUAB (hereafter "JUAB") to determine the safety, pharmacokinetic (PK) profile, and pharmacodynamic (PD) relationships of LY3214996 in patients with advanced/metastatic solid tumors refractory to standard therapy. Please refer to the LY3214996 investigator's brochure (IB) for complete background information.

2.2.1 Pre-Clinical Summary

2.2.1.1 Summary of Absorption, Distribution, Metabolism, and Excretion

Please refer to the LY3214996 IB for complete background information. Pharmacokinetic parameters of LY3214996 were examined in mice, rats, and dogs following an oral gavage dose, and in rats and dogs following an intravenous (IV) dose. The data indicate high bioavailability in both rats and dogs. Following infusion, clearance of LY3214996 was low to moderate (i.e., slower than hepatic blood flow) in both rats and dogs.

The plasma toxicokinetics of LY3214996 were evaluated in rats and dogs following single and repeated oral doses for up to 4 weeks. Exposure increased with dose in both species, but the increase was not always dose-proportional. No accumulation in plasma of LY3214996 was noted following repeated dosing to rats and dogs. In the rat, sex differences in exposures were approximately 2-fold, with females showing higher exposure. There was no sex difference in exposure noted in the dog.

In vitro protein binding data indicated low protein binding in all matrices examined. From radiolabel studies conducted in rats and dogs, [^{14}C]LY3214996 was identified as the predominant drug-related peak in plasma, urine, and feces of both species. In the plasma, [^{14}C]LY3214996 accounted for >64% of the systemic exposure (area under the concentration-time curve from time zero till infinity [$AUC_{0-\infty}$]) of the total radioactivity, both in rats and dogs. Minor metabolism, which was primarily oxidative in nature, was observed in both species. Metabolites were identified in rat and dog plasma, bile, urine, and feces. Fecal elimination was the predominant route of excretion (>77%) in both rats and dogs. Excretion of total radioactivity into the urine was approximately 8% in rats and ranged from approximately 11% to 14% in dogs.

2.2.1.2 Summary of Non-Clinical Safety Studies

Please refer to the LY3214996 IB for complete background information. LY3214996 was evaluated in 1-month daily oral-dosing toxicity studies in Sprague-Dawley rats and Beagle dogs (with 1-month reversibility in mid-dose rats and dogs) at tolerated dose levels, as well as at dose levels that exceeded the MTD. Safety pharmacology parameters were evaluated *in vitro* (human ether á-go-go–related gene [hERG]) and as part of the repeat-dose toxicity study in dogs. Genetic toxicity was evaluated in a bacterial mutation (Ames) assay. Results from these studies have allowed for identification of a starting dose that is anticipated to be safe in patients. Based on

nonclinical study findings, potential toxicities include GI inflammation, fecal changes, emesis, dehydration, sores on gums, scabs on skin, and clinical pathology changes, including increased neutrophils and monocytes, decreased lymphocytes, decreases in red cell mass, decreased albumin, increased globulin, and/or increases in serum phosphorus. Injury to the long bones (femur and tibia), female reproductive tract (ovary), and effects in the skin were also observed only in rats. With the exception of effects on skin, bone, and ovaries, all findings either recovered or showed evidence of recovery after a 1-month reversal period.

2.2.1.3 Mechanism of Action

Please refer to the LY3214996 IB for complete background information:

- LY3214996 is an adenosine triphosphate (ATP)-competitive, selective inhibitor of ERK1 (inhibitory constant [K_i] for ERK1-2P=650 pM) and ERK2 (K_i for ERK2-2P=64 pM), with biochemical IC_{50} values of 5 nM for each kinase.
- LY3214996 inhibits cellular phospho-RSK1 (T359/S363) in RAF- and RAS-mutant cancer cell lines with sub-μM potency. It also inhibits transcriptional output mediated by ERK in regulating expression of several target genes. Among 48 genes tested, 16 genes (*EGR1, SPRY4, DUSP6, ETV5, FOSL1, IER3, ETV4, FOS, GPR3, MAFF, DUSP4, GDF15, LIF, IL8, TNFRF12A*, and *PLK3*) were downregulated more than 4-fold and 20 genes (*PHLDA2, ETV1, CCND1, SPRED2, CDC45L, SPRED1, CCNB1, TNC, LNK, JUN, SLC2A1, SPC25, CCNA2, SPRY2, MAD2L1, ETS1, MYC, SLC4A7, HMGA2,* and *MKI67*) were downregulated 2-fold to 4-fold with LY3214996 treatment.

2.2.1.4 *In Vitro* and *In Vivo* Summary

Please refer to the LY3214996 IB for complete background information:

- In CRC BRAF V600E-mutant COLO 205 cells, LY3214996 inhibits cell proliferation with an IC_{50} value of 186 nM *in vitro*, and exhibits significant tumor growth inhibition/regression at 12.5 to 100 mg/kg *in vivo*. LY3214996 may show anti-tumor activity in CRC patients with BRAF V600E mutation.
- In preclinical models, LY3214996 was demonstrated to be active against a vemurafenib-resistant A375 melanoma model with ERK reactivation. These resistance mechanisms include NRAS mutation, BRAF splice variants, CRAF elevations, and FGFR3 activation. Therefore, LY3214996 may show activity in patients who had progressive disease after prior BRAF and MEK inhibitor treatment.
- In preclinical models of NRAS-mutant melanoma, LY3214996 inhibits cell proliferation and induces tumor cell apoptosis, whereas vemurafenib was inactive. Similar activities are also observed for other NRAS-mutant tumor cells, including the AML cell line HL60. LY3214996 has also significantly inhibited SK-MEL-30 (melanoma) and HL-60 (AML) xenograft tumor growth *in vivo* in mice.
- In cancer cell sensitivity profiling of 535 cell lines, cell lines that harbor MAPK pathway mutations are more sensitive to LY3214996 compared to cell lines that do not harbor MAPK pathway mutations.
- In a subsequent, in-house profiling of LY3214996 in a panel of 62 cell lines from colorectal, lung, and pancreatic cancers, mutations of KRAS, NRAS, BRAF, and MEK1 appear to predict cell growth inhibition to LY3214996.

- In a preclinical model of MEK1-mutant SW48 CRC cells, LY3214996 led to better inhibition of cell proliferation and in vivo tumor growth compared to a MEK inhibitor.
- In *in vivo* efficacy studies, LY3214996 demonstrated significant tumor growth inhibition and regression at a 25- to 100-mg/kg once-daily dose schedule in a CRC HCT 116 xenograft model. In xenograft models of KRAS-mutated NSCLC and pancreatic cancer, LY3214996 showed significant tumor growth inhibition at a 50-mg/kg to 100-mg/kg once-daily dose schedule. In an HCT 116 xenograft PD model in mice, LY3214996 demonstrated a dose- and time-dependent inhibition of phospho-RSK1 and a PK/PD correlation with absolute threshold effective dose of 50% inhibition (TED_{50}) and threshold effective dose of 80% inhibition (TED_{80}) of 16 mg/kg and 38 mg/kg, and threshold effective concentration of 50% inhibition (TEC50) and threshold effective concentration of 80% inhibition (TEC_{80}) of 1107 nM and 3758 nM, respectively. In an HCT 116 CRC xenograft PD model in rats, LY3214996 inhibited phospho-RSK with absolute TED_{50} and TED_{80} of 9 mg/kg and 22 mg/kg, and TEC_{50} and TEC_{80} of 559 nM and 2032 nM, respectively. Overall, LY3214996 has demonstrated a PK/PD correlation in HCT 116 xenograft tumors implanted in mice as well as rats. Data suggest that ≥50% phospho-RSK1 (PD biomarker) inhibition for 6 to 8 hours in a once-daily schedule is sufficient to yield significant tumor growth inhibition/regression in BRAF-, KRAS-, or MEK1-mutant models.
- LY3214996 is tolerated in combination with targeted agents such as abemaciclib (cyclin-dependent kinase [CDK]4/6 inhibitor) and chemotherapeutic agents (gemcitabine and paclitaxel), and has shown additive or synergistic effect in 1 or more models.

2.2.2 Clinical Summary

2.2.2.1 Pharmacokinetics

LY3214996 PK data are available from 20 patients after QD dosing and from 9 patients after BID dosing. Please refer to the LY3214996 IB for complete background information.

After oral administration, maximum plasma concentrations of LY3214996 were reached approximately 1 to 2 hours post dose. The mean $t_{1/2}$ was approximately 3 to 5 hours, suggesting little to no accumulation upon multiple QD and BID dosing. Exposures increased with dose from 25 to 400 mg, and AUCτ at steady state on Day 15 was similar to $AUC_{0-\infty}$ on Day 1, suggesting that the PK of LY3214996 did not change with time at these doses. The variability in exposures, assessed by percentage coefficient of variation (%CV), ranged from 3% to 98% for both C_{max} and AUC, and did not display any apparent trend with dose. These variabilities are most likely associated with the all-comer patient population and small numbers of patients per dose level.

2.2.2.2 Distribution

Protein-binding assessments of LY3214996 were conducted in human plasma at concentrations of 0.1, 1, and 10 μM and in human liver microsomes using equilibrium dialysis. The results indicate that LY3214996 is 52.0% to 54.9% bound to plasma proteins over the concentration range investigated. LY3214996 was predominantly bound to albumin to an extent similar to human plasma protein binding, with lower binding to α1-acid glycoprotein (AAG).

2.2.2.3 Metabolism

Exploratory metabolite profiling of human plasma samples collected from patients after single (Day 1) and repeat (Day 15) 200-mg doses of LY3214996 identified LY3214996 as the predominant circulating component based on qualitative assessments (ion peak intensity in mass spectrometry analysis). Eight metabolites, mainly oxidative, were also identified in plasma. The 2 most predominant metabolites observed at C_{max} and $AUC_{0.5\text{-}12hr}$ pools on both Day 1 and Day 15 were a lactam on the morpholine ring (LSN3310162) and a hydroxyl glucuronide.

2.2.2.4 Effect of Other Drugs on the PK of LY3214996

A substrate-depletion approach using recombinant human cytochrome P450s (CYPs) was used to identify CYPs metabolizing LY3214996 and to predict the relative contributions of these CYPs to hepatic CYP-mediated clearance. These studies indicated that CYP2J2, CYP3A4, and CYP3A5, respectively, are responsible for 12%, 88%, and <1% of hepatic CYP-mediated clearance of LY3214996. The magnitude of the contribution of these CYPs toward the overall clearance of LY3214996 is unknown since the *in vivo* clearance pathways of LY3214996 have not yet been determined.

The transport of LY3214996 was evaluated at 5 μM *in vitro* using Madin-Darby canine kidney (MDCK) cells transfected with human of P-glycoprotein (P-gp) or breast cancer-resistance protein (BCRP) transporters. LY3214996 was found to be a substrate of P-gp and BCRP transporters. The clinical relevance of the *in vitro* transport of LY3214996 is currently unknown.

2.2.2.5 Effect of LY3214996 on the PK of Other Drugs

The ability of LY3214996 to reversibly inhibit the metabolism of probe substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A *in vitro* was examined in human liver microsomes over the concentration range 0.15 to 200 μM. The results indicate that LY3214996 reversibly inhibits the metabolism of CYP2C8, CYP2C9, and CYP3A substrates, although at relatively high concentrations of LY3214996 (all IC_{50} values ≥19 μM). To predict the likelihood of a clinically relevant drug-drug interaction (DDI), the predicted ratio of a victim drug (R) was calculated using a static model, $R=1+(I_{max,u}/K_i)$, where $I_{max,u}$ = unbound C_{max} from the 400-mg QD cohort and $K_{i,u}$ is the most potent observed unbound reversible inhibition constant for CYP2C9 at 34.5 μM (K_i×fraction unbound in microsomes = 35.8 μM×0.964). The current C_{max} concentration observed for the 400-mg QD cohort is 1.39 μM. The calculated R value is 1.04. Therefore, the current risk of a DDI mediated by reversible CYP2C9 inhibition is low. Additionally, K_i values for the other CYP enzymes evaluated were higher than that of CYP2C9. Therefore, the risk of a DDI mediated by reversible CYP inhibition of those isoforms is unlikely.

The potential of LY3214996 to cause time-dependent inhibition of CYP3A4-mediated metabolism was also evaluated *in vitro* using human liver microsomes. The results indicate that LY3214996 is a time-dependent inhibitor of CYP3A4 metabolism. Assuming this is due to mechanism-based inhibition, LY3214996 appears to be a less efficient inhibitor than erythromycin, a known moderate *in vivo* time-dependent inhibitor of CYP3A. The clinical

relevance of this apparent mechanism-based inhibition cannot be fully assessed by this estimate alone, since it is influenced by multiple factors, including the circulating plasma concentrations, protein binding in plasma and microsomes, interactions at the gut wall, and other factors. Therefore, the risk of competitive and mechanism-based inhibition of CYP3A is planned to be clinically evaluated in an Eli Lilly sponsored trial.

An *in vitro* study to investigate the effects of LY3214996 on the expression of CYPs was conducted at concentrations of 0.1 to 10 μM of LY3214996 in 3 individual lots of cryopreserved human hepatocytes. LY3214996 was not an inducer of CYP1A2, CYP2B6, or CYP3A4 messenger ribonucleic acid (mRNA) or activity. LY3214996 was also not an inducer of CYP2C8, CYP2C9, or CYP2C19 mRNA. However, LY3214996 did induce CYP2D6 and CYP3A5 mRNA, but did not induce the activity of CYP2D6. CYP3A5 is considered less responsive to induction than CYP3A4. The clinical relevance of the *in vitro* induction of CYP2D6 and CYP3A5 by LY3214996 is currently unknown.

2.2.2.6 Safety

Please refer to the LY3214996 IB for complete background information. As of 30 June 2018, validated safety data for 39 patients enrolled and treated with LY3214996 were available from ongoing clinical study JUAB.

Dose-Limiting Toxicities

A total of 5 (12.8%) of the 39 patients experienced at least 1 DLT; 2 patients (7.7%) receiving QD dosing (Part A) and 3 patients (23.1%) receiving BID dosing (Part A2). In Part A, DLTs were observed at a dose levels of 400 and 600 mg QD (1 patient, each). These included Grade 3 fatigue and cough at 400 mg QD and Grade 3 dehydration at 600 mg QD. In Part A2, 2 patients at 200 mg BID experienced DLTs of Grade 3 blood creatinine increased, renal failure, and rash maculo-papular and 1 patient at 300 mg BID experienced Grade 3 blood creatinine phosphokinase increased.

Deaths

As of 30 June 2018, 5 deaths (12.8%) were reported in Study JUAB; 3 in Part A and 2 in Part A2. Of these, 4 deaths occurred within 30 days of treatment discontinuation and 1 death occurred after 30 days of treatment discontinuation. All of these deaths were due to patient's disease.

Serious Adverse Events

Four patients (10.3%) experienced a serious adverse event (SAE):

- 1 patient in Part A Cohort 5 (400 mg QD) experienced Grade 3 cellulitis, not considered to be related to the study treatment.
- 2 patients in Part A Cohort 6 (600 mg QD) experienced Grade 3 non-cardiac chest pain and dehydration (n=1). Non-cardiac chest pain was not considered to be related to the study treatment, whereas dehydration was considered to be related to the study treatment.
- 1 patient in Part A2 Cohort 6 (300 mg BID) experienced Grade 3 hepatic enzyme

increased, which was considered to be related to the study treatment. This completely reversed when study drug was discontinued.

Treatment-Emergent Adverse Events

Of the 39 patients, 38 (97.4%) experienced at least 1 treatment-emergent adverse event (TEAE); 17 patients had Grade 3 or higher TEAE. Of the total TEAEs, the most commonly reported TEAEs in 10 or more patients included nausea, vomiting, fatigue, anemia, and rash maculo-papular.

There were 34 patients (87.2%) who experienced at least 1 related TEAE, of whom 8 patients (20.5%) experienced TEAEs that were Grade 3 or above. The commonly reported related TEAEs in 10 or more patients included nausea, rash maculo-papular, and vomiting.

Table 1: LY3214996 Related TEAEs in ≥ 10% of Patients

Preferred Term	Total All Grades N=39 n (%)	Total Grade ≥ 3 N=39 n (%)
Nausea	12 (30.8)	0 (0)
Rash maculo-papular	10 (25.6)	3 (7.7)
Vomiting	10 (25.6)	1 (2.6)
Diarrhea	8 (20.5)	0 (0)
Pruritus	7 (17.9)	1 (2.6)
Dermatitis acneiform	6 (15.4)	0 (0)
Blood creatinine phosphokinase increased	5 (12.8)	1 (2.6)
Rash	4 (10.3)	1 (2.6)
Vision blurred	4 (10.3)	0 (0)
Alanine aminotransferase increased	4 (10.3)	1 (2.6)
Hyperkalemia	4 (10.3)	0 (0)

Discontinuations due to Adverse Events or Death

As of the data cut-off date, 33 patients (84.6%) discontinued the study treatment; 22 patients in Part A and 11 in Part A2. The most common reason for treatment discontinuation was progressive disease (64.1%) followed by AE (12.8%), withdrawal by subject (5.1%), and physician decision (2.6%).

Maximum Tolerated Dose

The MTD for LY3214996 was originally declared to be 600 mg by mouth once daily, or 200 mg by mouth twice daily. Once daily dosing was better tolerated than twice daily dosing, and 600 mg once daily was better tolerated than 300 mg twice daily. In both 600 mg once daily and 300 mg twice daily, 100% pRSK PD inhibition in tumor are observed. PK exposures increased with dose (25 to 800 mg once daily) in a fairly dose-proportional manner. There was no apparent time-dependent inhibition of CYP3A4 up to 800 mg. In a limited set of highly heterogeneous cancer patients, a best overall response of stable disease (SD) was observed with some patients

showing tumor regressions. Tumor regressions were observed in both once daily and twice daily doses, but treatment duration appears to be better in those treated with once daily doses. There were no dose reductions in any patients treated at the once daily dose who achieved SD and 3 participants remain on treatment as of the data cut-off date. The once daily dosing schedule was selected for this trial as once daily dosing was better tolerated.

Eli Lilly has since determined that despite anti-emetic premedication, issues with unexpected toxicity have continued at the 600 mg once daily dose. They have thus advised a reduction in dose to 400 mg once daily.

2.2.2.7 Efficacy

Efficacy has not been established at this time.

2.2.2.8 Marketing Experience

LY3214996 is not approved or marketed in any country.

2.3 Hydroxychloroquine Sulfate

Please refer to the FDA package insert for complete background information on hydroxychloroquine sulfate (HCQ). HCQ is an FDA approved autophagy inhibitor. It has been tested as monotherapy in patients with advanced pancreatic cancer at doses of 400 and 600 mg twice daily. Out of 20 enrolled patients with metastatic pancreatic cancer, 2 (10%) were without progressive disease at 2 months, and median PFS and OS were 46.5 and 69 days, respectively. Grade 3/4 treatment-related adverse events in this patient population included lymphopenia and elevated alanine aminotransferase. Tolerability and efficacy were similar at both doses levels.[11] Subsequent studies in patients with pancreatic cancer have evaluated gemcitabine or gemcitabine and nab-paclitaxel with HCQ at 600 mg PO BID.[26-28]

2.4 Correlative Studies Background

2.4.1 Organoid Culture Generation and Compound Sensitivity Testing

Approaches that predict the most effective chemotherapeutic regimen should improve patient care. To enable precision medicine in PDAC patients at Dana-Farber Cancer Institute (DFCI), a biopsy-based program for genomic and functional characterization of patient specimens was established. It was recently demonstrated that approximately 30% of PDAC patients have clinically relevant genomic lesions that could be used to guide clinical trial selection for molecularly targeted therapies.[10,29,30]

However, additional strategies for therapeutic selection are needed for the majority of patients who do not have clearly actionable genomic lesions. Treatment responsiveness likely represents a multi-factorial phenotype that is not well described by either genomic or transcriptomic assessment alone. We hypothesize that effective prediction of therapeutic responses in a clinically useful manner will require implementation of *ex vivo* functional profiling of PDAC tumor cell sensitivity.

At DFCI, we have established a robust translational pipeline to perform genomic analysis on biopsy specimens and functional therapeutic profiling on patient-derived PDAC organoid models in real-time.[30,31] In ongoing work, we have demonstrated successful whole exome or targeted panel genomic sequencing from small needle biopsies in 90% of patients with advanced PDAC.[30] For patients with previously untreated advanced PDAC, we have demonstrated successful organoid culture and therapeutic sensitivity profiling on 65% of biopsy specimens. Organoids are treated over a 12-point dose range, with estimation of the half maximal inhibitory

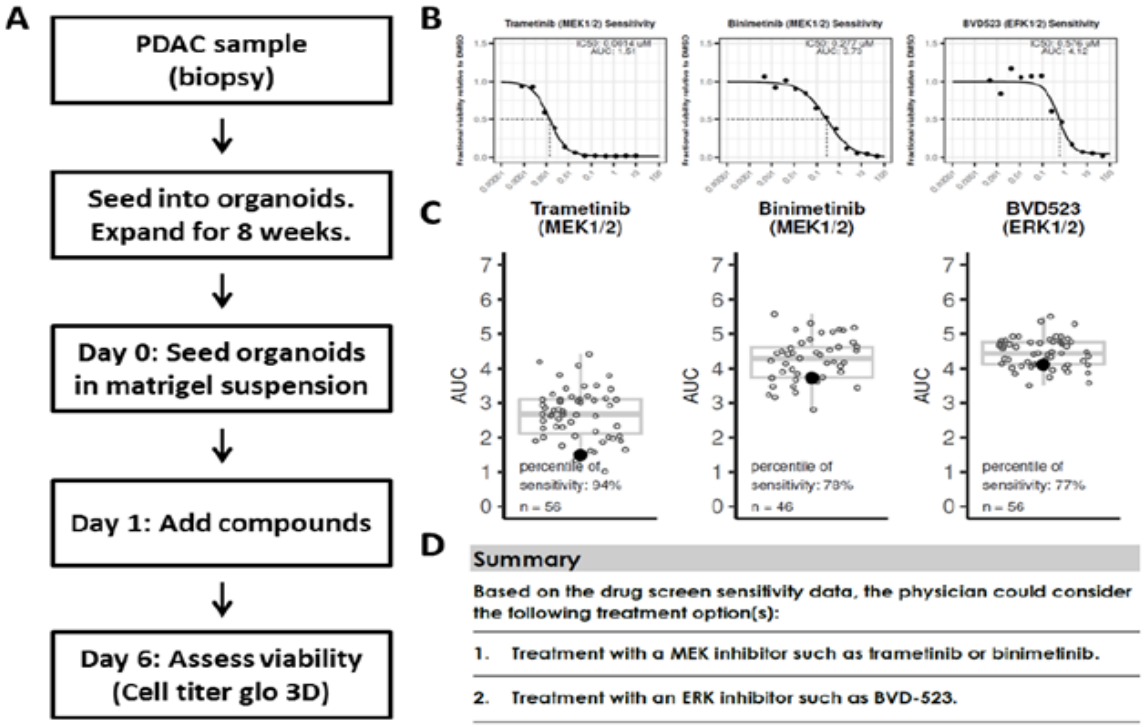


Figure 3: PDAC organoid drug testing protocol and example report. A. Protocol for initiation, expansion, and organoid drug testing. B. Dose-response curves and C. Relative sensitivity to MAPK inhibitors. Each small dot represents a unique patient, and the large dot is the patient of interest. D. Example report summarizing results which suggest sensitivity to MAPK inhibitors.

concentration (IC_{50}) and area under the curve (AUC) from dose response curves (**Figure 3A, 3B**). Treatments are performed with single agent compounds as well as with relevant combinations. Each individual patient's tumor is evaluated in the context of all other patients for whom we have tested therapeutic sensitivity (**Figure 3C**).

Across our initial PDAC organoid cohort of 56 patients, we have identified coherent patterns of

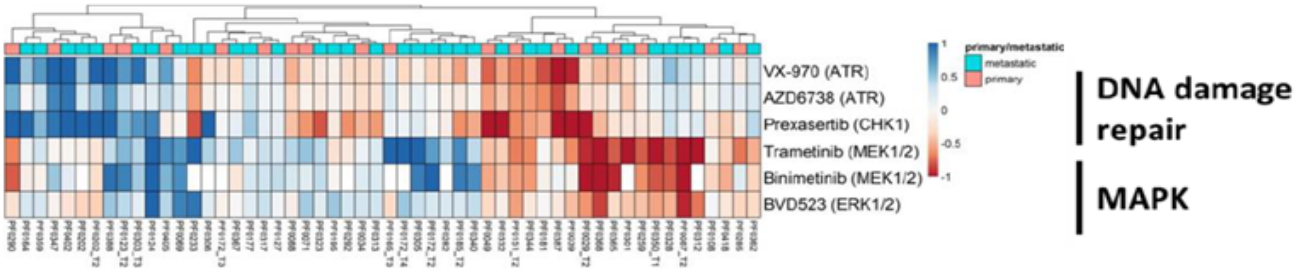


Figure 4. Patient-specific PDAC organoid therapeutic profiling reveals functional subclasses of patients. Heatmap demonstrates variance from mean AUC, with negative variance (red) indicating greater sensitivity.

therapeutic response with two primary clusters of sensitivity to one or more of over 20 drugs that we routinely profile. These two sensitivity clusters include a subset of patients with increased sensitivity to MAPK pathway inhibition with MEK or ERK inhibitors (**Figure 4**). Here, we propose to apply our robust translational infrastructure to correlate observed clinical response to treatment with LY3214996 alone and in combination with HCQ to organoid sensitivity profiling performed on pre-treatment and time of progression biopsy samples. This study will lay the foundation for subsequent PDAC organoid platform trials of novel therapeutic agents.

Several recent studies have demonstrated that drug sensitivity testing in organoid models correlates with clinical responses to standard-of-care therapies. Vlachogiannis and colleagues recently reported that patient-derived organoids modeled the treatment response of metastatic gastrointestinal cancers. The team grew organoids from a total of 110 fresh biopsies obtained from 71 patients with metastatic colorectal cancer (mCRC), metastatic gastroesophageal cancer (mGOC), and cholangiocarcinoma. Organoids were grown from 70% of biopsies with a cellularity of 2+ and above, and their establishment rate correlated strongly with tumor cellularity of the parental biopsy (χ^2 test, $P < 0.0001$). All the organoids were established as part of a co-clinical trial, allowing for direct comparison between clinical and pre-clinical response.[32]

Histological comparison confirmed notable morphological similarities between the organoids and parental biopsies, routine immunohistochemistry markers (CDX-2 and CK7) verified that the parental tumor's expression pattern was maintained in the organoids, and the results of next generation sequencing (NGS) demonstrated a 96% overlap in mutation spectrum between the organoids and parental biopsies. The team examined the predictive value of organoids in 21 comparisons of clinical response observed in patients with *ex vivo* response data available (**Figure 5**). Overall, the organoids that were analyzed had a 100% sensitivity, 93% specificity, and 88% positive predictive value in forecasting treatment response to targeted agents or chemotherapy in patients (Fisher's exact test, $P < 0.0001$).[32]

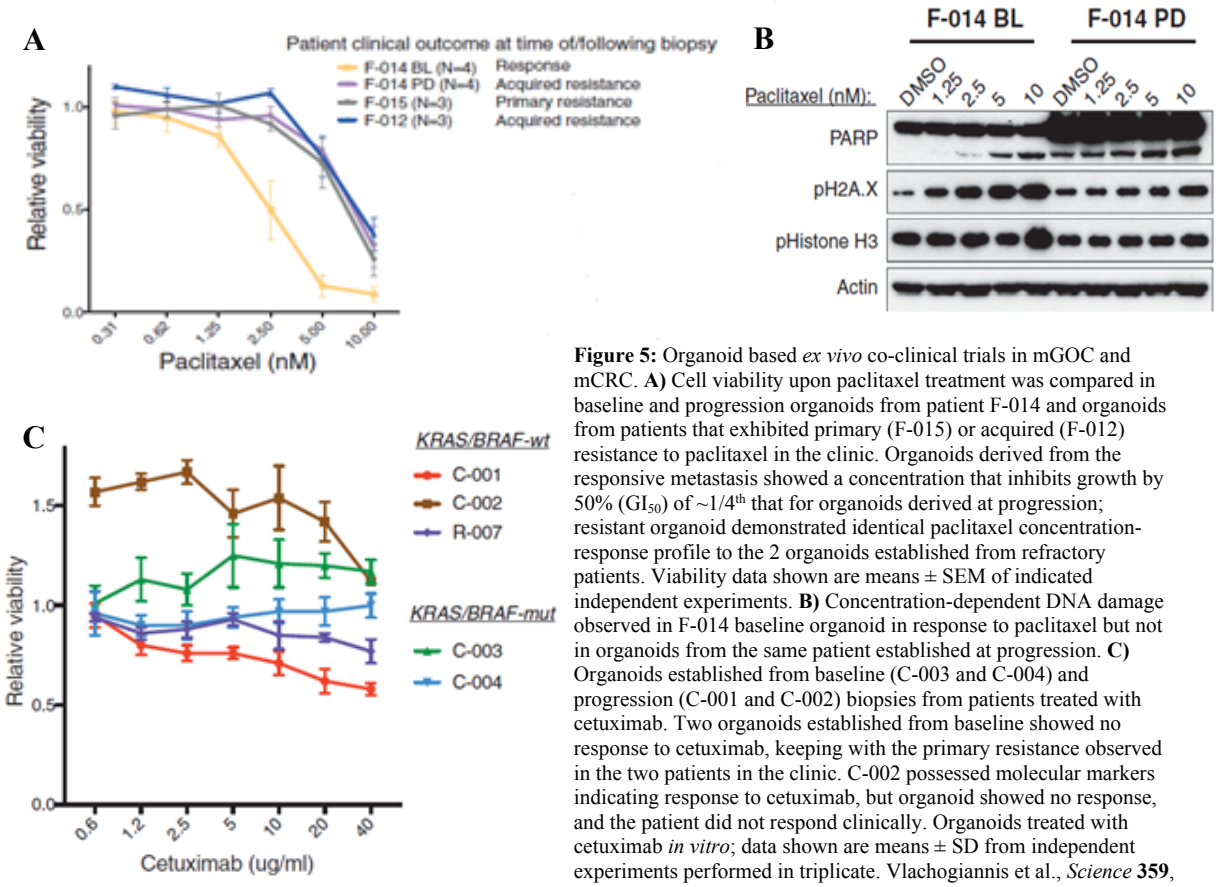


Figure 5: Organoid based *ex vivo* co-clinical trials in mGOC and mCRC. **A)** Cell viability upon paclitaxel treatment was compared in baseline and progression organoids from patient F-014 and organoids from patients that exhibited primary (F-015) or acquired (F-012) resistance to paclitaxel in the clinic. Organoids derived from the responsive metastasis showed a concentration that inhibits growth by 50% (GI_{50}) of ~1/4th that for organoids derived at progression; resistant organoid demonstrated identical paclitaxel concentration-response profile to the 2 organoids established from refractory patients. Viability data shown are means ± SEM of indicated independent experiments. **B)** Concentration-dependent DNA damage observed in F-014 baseline organoid in response to paclitaxel but not in organoids from the same patient established at progression. **C)** Organoids established from baseline (C-003 and C-004) and progression (C-001 and C-002) biopsies from patients treated with cetuximab. Two organoids established from baseline showed no response to cetuximab, keeping with the primary resistance observed in the two patients in the clinic. C-002 possessed molecular markers indicating response to cetuximab, but organoid showed no response, and the patient did not respond clinically. Organoids treated with cetuximab *in vitro*; data shown are means ± SD from independent experiments performed in triplicate. Vlachogiannis et al., *Science* **359**, 920-926 (2018).

Correlation of organoid results and clinical response was also reported by Tiriac et al. in PDAC. The team obtained 159 biopsy samples from primary tumors and metastases in 138 patients for generation of organoids. A total of 114 organoid cultures were successfully generated from 101 patients (73% of patients). Whole genome sequencing (WGS) was performed on a subset of PDAC organoids and matched primary tumor (bulk), both were germline corrected with normal tissue (n = 13). An average of 97.43% of the mutations detected in the parental tumor specimen were also detected in the organoids. In 11 of the 13 cases, the organoid cultures completely recapitulated the core mutation profile found in the patient, and the primary tumor specimens from the two sample pairs that did not overlap had extremely low purity (<15%) and no alterations in PDAC core genes were detected in the parental biopsies.[31]

The team generated drug sensitivity signatures by correlating organoid transcriptional profiles with pharmacotyping results. For each chemotherapeutic agent, the Spearman correlation was computed between organoid gene expression and the AUC for each drug, defining distinct transcriptional signatures. The signatures were refined to include genes that increased in expression when AUC decreased (negative rho value), which is indicative of increased drug sensitivity. By clustering the organoid cultures using the individual drug response signatures, the organoids could be grouped into sensitive or non-sensitive classes for each individual chemotherapeutic signature. This signature was then used to evaluate patient response in a

subgroup of 55 patients who received gemcitabine monotherapy, and it was determined that patients with enrichment for the gemcitabine sensitivity signature had a significantly better progression free survival (772 v. 373 days, HR = 0.54, *P* = 0.04) and a trend toward improved overall survival.[31]

In the proposed study, patient-derived pancreatic tumor organoids will be grown from tumor tissue obtained from mandatory pre-treatment and optional time of progression biopsies following published protocols.[33] After several rounds of organoid expansion, sensitivity will be evaluated to LY3214996, as well as additional RAS-MAPK pathway inhibitors. Additionally, organoid sensitivity to HCQ alone or in combination with LY3214996 will be evaluated. For each single agent, 12-point dose response curves measured in triplicate, as illustrated in **Figure 3**. Moreover, combination therapy with LY3214996 and HCQ will be investigated through measuring dose response curves across a range of LY3214996 and HCQ in a 10-day assay with patient-derived organoid models.[9] Determinations of synergy will be assessed by Bliss independence scores, as previously described.[9]

AUCs will calculated from the dose response curves, and these AUC estimates are used for comparison with other patients' samples as a measure of relative sensitivity to each agent (**Figure 6**). The percent sensitivity statistic is a measure of where the patient's AUC measurement for each drug occurs within the population tested (n), with higher percentages indicating greater sensitivity to that particular agent. This trial will retrospectively assess the correlation of organoid drug sensitivity screening with ERK inhibition ± HCQ clinical treatment response.

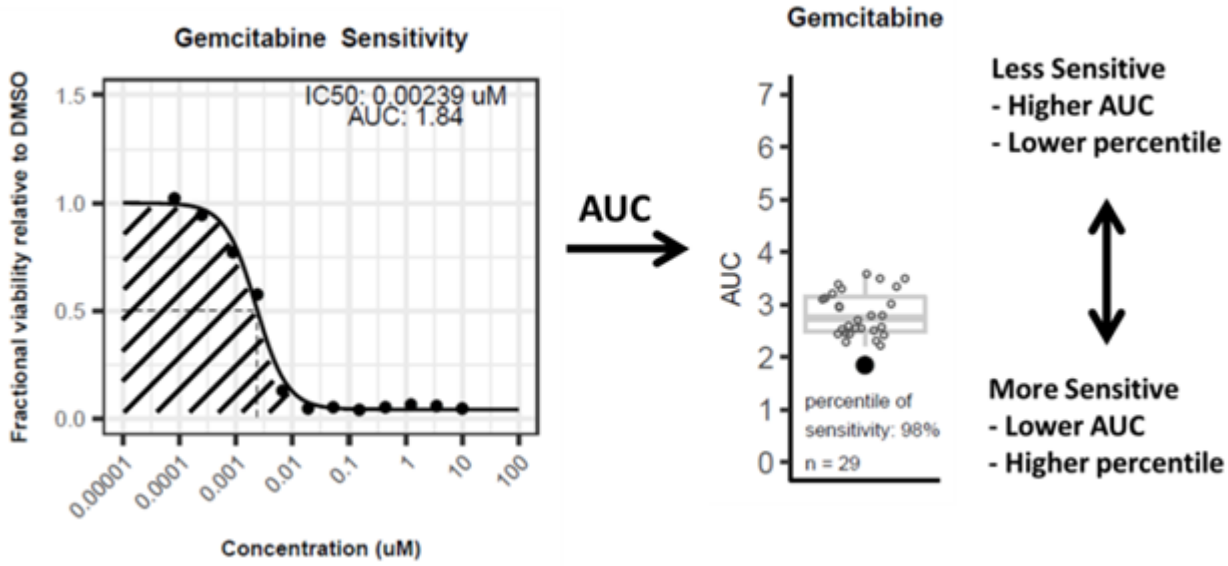


Figure 6: Example Drug Sensitivity Profiling. AUC estimates are used for comparison with other patients' samples as a measure of relative sensitivity to each agent.

2.4.2 Targeted DNA Sequencing

Next generation sequencing will be performed at the Center for Advanced Molecular Diagnostics

(CAMD) at Brigham and Women's Hospital (BWH). CAMD has developed a cancer genomic assay to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples. The OncoPanel assay surveys exonic DNA sequences of over 440 cancer genes and over 190 regions across approximately 60 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer.

The pre-treatment biopsy will be submitted for OncoPanel testing. Somatic genetic alterations in oncogenes and tumor-suppressor genes contribute to the pathogenesis and evolution of human cancers. These alterations can provide prognostic and predictive information and stratify cancers for targeted therapeutic information.[34]

2.4.3 Whole Transcriptome Sequencing

Each patient enrolled on the study will have whole transcriptome sequencing (WTS) by RNA-sequencing (RNAseq) performed on their pre-treatment biopsy and organoid specimens to assess for baseline transcriptional signatures that may correlate with treatment response. RNA will be obtained from tumor cellular material using standard operating procedures, and RNAseq will be performed at the Broad Institute as previously described.[30] Multiple transcriptional subtypes have been described for pancreatic cancer, and these subtypes may have prognostic and predictive therapeutic implications.[10,31,35-38] Of notable importance to this ERK inhibitor based trial, these pancreatic cancer transcriptional subtypes have previously been shown to correlate with differences in dependency on KRAS and MAPK signaling.[38] RNA-sequencing will enable a comprehensive analysis of RNA expression features in human tumor samples in both parental tumor biopsies as well as organoid cultures to investigate the fidelity of organoid cultures to represent subtype-specific transcriptional signatures. Furthermore, using our patient-specific organoid models, we will also perform RNA-sequencing on post-treatment samples to measure transcriptional signatures 24 hours after treatment with LY3214996 ± HCQ to investigate the ability of dynamic expression changes to serve as a biomarker for therapeutic response. In these analyses, we will employ our own RAS-MAPK pathway transcriptional signatures,[39] as well as other published signatures[40] and those defined by colleagues at Eli Lilly (see above, section 2.2.1.3). The identification of dynamic alterations in RAS-MAPK transcriptional signatures in post-treatment early passage organoid samples may enable early identification of patients who are likely to respond to treatment with LY3214996 ± HCQ. Thus, these data may fuel additional prospective utilization of organoid-based transcriptional profiling, in addition to conventional viability testing, as a potential biomarker-driven strategy for stratification onto future LY3214996-based clinical trials.

2.4.4 Evaluation of Resistance Mechanisms

Participants will be offered an optional biopsy at the time of disease progression. Time of progression biopsies will undergo repeat molecular analyses and organoid derivation to investigate mechanisms of resistance using organoid-based sensitivity profiling as well as DNA and RNA sequencing as noted above.

2.4.5 Confirmation of Target Engagement

Wolpin et al. identified LC3-II in peripheral lymphocytes as a candidate pharmacodynamic marker to monitor autophagy inhibition.[11] Tumor tissue and serial blood samples will be collected from all study participants to evaluate LC3-II levels at the Wolpin Laboratory at Dana-Farber Cancer Institute, additional or alternate markers may be explored as considered appropriate at the time of analysis.

2.4.6 Immunohistochemistry

During the pre-screening and post-treatment biopsy, an additional core will be obtained following standard institutional procedures. FFPE samples from this core will be evaluated for target inhibition including ERK inhibition (pERK, pRSK, MYC) and autophagy inhibition (p62 and LC3B) via immunohistochemistry (IHC).

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the pancreas.

3.1.2 Age ≥ 18 years.

3.1.3 ECOG performance status ≤ 1 (see **Appendix A**)

3.1.4 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. See **Section 11** for the evaluation of measurable disease.

3.1.5 Participants must have received at least one but no more than two prior lines of systemic therapy for metastatic pancreatic cancer. Perioperative treatment (chemotherapy and/or radiation) is not considered a prior line of therapy.

3.1.6 Participants must have adequate organ and marrow function as defined below:

Absolute Neutrophil Count	≥ 1,500/mcL
Platelet Count	≥ 100,000/mcL
Total Bilirubin	≤ 1.5 × institutional upper limit of normal (ULN)
AST (SGOT) / ALT(SGPT)	≤ 2.5 × institutional ULN, **OR**
AST (SGOT) / ALT (SGPT)	≤ 5 × institutional ULN if elevation is a result of metastases
Creatinine	≤ 1.5 × institutional ULN, **OR**

Creatinine Clearance	≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above 1.5 × institutional normal (calculated via the Cockcroft-Gault equation)

3.1.7 The effects of LY3214996 or HCQ on the developing human fetus are unknown. For this reason and because anti-cancer agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of LY3214996 or HCQ administration.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 Ability to swallow and retain oral medication.

3.1.10 Baseline QTcB of ≤ 470 msec on screening EKG.

3.1.11 Participants must be able and willing to undergo the pre-treatment biopsy procedure, and have a cancer site amenable to biopsy.

3.2 Exclusion Criteria

3.2.1 Participants with pancreatic histologies other than adenocarcinoma or poorly differentiated carcinoma, such as neuroendocrine or acinar cell carcinoma.

3.2.2 Participants who have received a prior MAPK pathway inhibitor, including but not limited to LY3214996.

3.2.3 Participants who have had systemic chemotherapy, other investigational therapy, or immunotherapy within 3 weeks prior to the first dose of study medication.

3.2.4 Participants who have received oral tyrosine kinase inhibitors (TKIs) within 5 half-lives of the first dose of study medication.

3.2.5 Participants who have received radiation therapy within 2 weeks prior to the first dose of study medication.

3.2.6 Participants who have had major surgery within 4 weeks prior to the first dose of study medication.

3.2.7 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to LY3214996 or HCQ.

3.2.9 Individuals with a history of a different malignancy are ineligible with the following exceptions: individuals who have been treated and are disease-free for a minimum of 3 years prior to study enrollment, or individuals who are deemed by the treating investigator to be at low risk for disease recurrence. Additionally, individuals with the following cancers are eligible if diagnosed and curatively treated within the past 3 years: basal or squamous cell carcinomas of the skin, and breast or cervical carcinomas *in situ*.

3.2.10 Uncontrolled intercurrent illness including, but not limited to: ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.11 Pregnant women are excluded from this study because LY3214996 and HCQ are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with LY3214996 or HCQ, breastfeeding should be discontinued if the mother is treated with LY3214996 or HCQ. A negative serum pregnancy test is required for women of childbearing potential prior to the first dose of study medication.

3.2.12 Participants who are known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B or C.

3.2.13 Participants with a history or findings of central or branch retinal artery or venous occlusion with significant vision loss, or other retinal diseases causing visual impairment or would likely cause visual impairment over the time period of the study, as assessed by an ophthalmologist.

3.2.14 Participants with a known personal or family history of long QT syndrome.

3.2.15 Participants with known glucose-6-phosphate dehydrogenase (G6PD) deficiency.

3.2.16 Participants who are known at the time of trial enrollment to require concomitant treatment with strong CYP3A4 inhibitors or inducers. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1.1 For Enrollment to Arm 1 or Arm 2 (Randomized Trial Arms)

The eligibility checklist(s) and all pages of the consent form(s) will be faxed to the ODQ at 617-632-2295. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30 am – 5 pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Non-DF/HCC Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager or Study Coordinator. The required forms can be found in **Section 4.4.**

Following registration, participants should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not

receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Non-DF/HCC Investigative Sites

To register a participant, the following documents should be completed by the participating site and faxed or e-mailed to the Study Coordinator/Project Manager:

- Signed participant consent form
- HIPAA authorization form
- Eligibility checklist
- Screening provider note including the medical/surgical history, ECOG performance status, vital signs, and physical exam findings
- Pathology report confirming adenocarcinoma or poorly differentiated carcinoma of the pancreas
- Laboratory reports including:
    - CBC with differential
    - Chemistry panel
    - Pregnancy test (if applicable)
- Screening imaging report (CT and/or MRI scans)
- Screening ophthalmic exam report
- Screening EKG

To complete the registration process, the Project Manager or Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The registering party will fax or email the participant study number and assigned arm or dose treatment level to the participating site.

NOTE: Registration can only be conducted during the regular business hours of 8:30 AM to 4:30 PM Eastern Standard Time Monday through Friday, holidays excluded. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Project Manager or Study Coordinator.

5. TREATMENT PLAN

5.1 Treatment Regimen

A treatment cycle will be defined as 28 consecutive days. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**.

5.1.1 Safety Lead-in Cohort

To confirm the safety of the LY3214996 and HCQ combination, a lead-in cohort will be conducted. The first six participants will enroll to **Dose Level 0**, as depicted in the table below. Enrollment to the dose level can occur in parallel with no observation period or delay between

the start of therapy for each enrolled participant.

Table 2: Safety Lead-in Cohort Dose Plan		
Dose Level	**LY3214996 Dose (mg PO QD)**	**Hydroxychloroquine (HCQ) Dose (mg PO BID)**
-1 *(Fallback Dose)*	400*	200*
0	400	400
*: At the discretion of the overall principal investigator, the fallback dose of LY3214996 may be reduced to 200 mg PO QD instead of or in addition to a reduction of the HCQ dose level. The principal investigator determined dose level -1 to be LY3214996 200 mg PO QD and HCQ 400 mg PO BID		

Participants will be observed during the first cycle of therapy for toxicity consistent with a dose-limiting toxicity (DLT) definition, defined in **Section 5.1.2**. If ≤ 1 DLT is observed among the six participants, the randomized two arm portion of the trial will begin with enrollment to Arms 1 and 2 (see **Section 5.1.3**).

If **Dose Level 0** is found intolerable (with ≥ 2 participants experiencing a DLT), **Dose Level -1** will be evaluated. If **Dose Level -1** is also not tolerable, the cohort will be closed with no further combination treatment enrollment and the trial will proceed as a single arm evaluation of LY3214996 as monotherapy.

Table 3: Dose Escalation Decision Criteria for Safety Lead-in Cohort	
Number of Participants with DLT at a Given Dose Level	**Escalation Decision Rule**
≤ 1	Proceed with enrollment to the randomized two arm portion of the trial.
≥ 2	Enrollment to the dose level will be stopped. This dose level will be declared the MAD (highest dose administered). Proceed with enrollment of six participants to the fallback dose level if at **Dose Level 0**. If at **Dose Level -1,** enrollment to combination treatment will be stopped.

Participants enrolled to the safety lead-in portion of the trial will be required to have received at least 75 percent of their assigned doses of LY3214996 and HCQ during the first cycle to be considered evaluable for DLT purposes. Participants will be replaced if they do not meet these parameters during cycle 1 for reasons other than toxicity (e.g. withdrawal of consent for participation, or rapid disease progression and subsequent removal from the trial).

5.1.2 Dose-Limiting Toxicities (Applicable for Safety Lead-in Cohort Only)

DLTs will be defined as toxicities experienced by participants enrolled in the safety lead-in that are considered at least possibly related to the treatment regimen, occur during the first cycle of treatment, and fit at least one of the following criteria:

- Grade 4 absolute neutrophil count (ANC) decrease of greater than 7 days duration, or ANC decrease that necessitates the use of growth factor support
- Febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding, or that requires transfusion support
- Grade 4 thrombocytopenia
- Grade 4 anemia
- Intolerable Grade 2 nausea or vomiting that is unresponsive to maximal medical management (see **Section 5.4** for anti-emetic regimen information).
- Any ≥ Grade 3 non-hematologic toxicity, with the following exceptions:
    - Grade 3 gastrointestinal toxicities (nausea, vomiting, diarrhea, or constipation) that were not optimally managed. Grade 3 gastrointestinal toxicities will only be considered dose-limiting if refractory to treatment, defined as a failure to resolve to ≤ Grade 2 or baseline within 48 hours of instituting appropriate supportive care.
    - Grade 3 rash that resolves to ≤ Grade 2 within 7 days and remains tolerable may not be considered a DLT if agreed upon with the overall principal investigator.
    - Grade 3 asymptomatic electrolyte abnormalities that resolve to ≤ Grade 2 or baseline within 48 hours of repletion/clinical intervention.
- Any death not clearly due to underlying disease or extraneous causes.
- Any toxicity that results in the participant receiving < 75% of the **assigned** doses of LY3214996 or HCQ during cycle 1.

Management and dose modifications associated with the above adverse events are outlined in **Section 6**.

5.1.3 Arm 1 and Arm 2

If combination dosing with LY3214996 and HCQ is found tolerable (≤ 1 DLT among 6 participants enrolled to the dose level), the randomized two arm portion of the trial will commence. Participants will be randomized 1:1 to enroll to either **Arm 1** or **Arm 2.**

5.1.3.1 Arm 1 Treatment: LY3214996 + HCQ

If **Dose Level 0** was found tolerable, enrollment to **Arm 1** will initiate with LY3214996 at a dose of 400 mg PO daily and HCQ at 600 mg PO BID. Following accrual of six evaluable participants to **Arm 1**, enrollment to **Arm 1** will be paused for an assessment of safety of the increased dose of HCQ.

The safety assessment will occur after all six participants on **Arm 1** have completed at least one cycle of dosing with the combination. Participants must have received at least 75% of their assigned doses of LY3214996 and HCQ to be considered evaluable for this safety analysis, unless dosing was held or reduced due to toxicity. If one or more of the first six participants enrolled does not meet this parameter for a reason other than toxicity (e.g. rapid disease progression and subsequent removal), **Arm 1** will continue to accrue as many participants as needed to have six evaluable participants for safety assessment. ***Participants will be replaced in***

the randomized portion of the trial if they withdraw consent for participation before initiating protocol therapy or rapid disease progression limits their ability to receive any therapy per protocol. All participants accrued to the arm who start protocol treatment will be considered evaluable for efficacy endpoints, regardless of whether they meet criteria to be considered evaluable for assessment of safety of the increased dose of HCQ.

The overall principal investigator will review applicable adverse event data and determine if enrollment should continue with HCQ at the 600 mg dose level. At the discretion of the overall principal investigator, the dose level may be reduced for all participants remaining to be accrued to the arm.

If **Dose Level 0** was not tolerable, but **Dose Level -1** was tolerable, enrollment to **Arm 1** will be initiated with LY3214996 200 mg PO QD and HCQ600 mg PO BID. An interim safety assessment will still occur in this scenario. If **Dose Level -1** was also not tolerable, **Arm 1** will not move forward. The trial will proceed with enrollment to **Arm 2** only, evaluating LY3214996 as monotherapy.

At the conclusion of the safety lead-in cohort, on March 26, 2021 findings demonstrated that Dose Level 0 was not tolerable, but Dose Level -1 was tolerable. Therefore, patients enrolling to the randomized two arm portion of the trial will receive:

Arm 1 LY3214996 200 mg QD and 600 mg HCQ BID and
Arm 2 LY3214996 400 mg QD

5.1.3.2 Arm 2 Treatment: LY3214996

Participants enrolled to **Arm 2** will receive treatment with LY3214996 at the recommended phase II dose of 400 mg PO once daily.

5.1.4 Treatment Cross-Over

Participants who are enrolled to **Arm 2** who experience radiologic disease progression on monotherapy will have the option to cross-over to receive treatment with the combination. Cross-over will occur at the treating investigator's discretion following consultation and approval from the overall principal investigator. Participants who cross-over must meet all of the following criteria:

1. The participant does not meet any other investigational product discontinuation criteria (see **Section 5.5**).
2. ECOG performance status is ≤ 1.
3. Absence of rapid disease progression or threat to vital organs/critical anatomical sites (e.g. spinal cord compression) requiring urgent alternative medical intervention.
4. The participant must have a tumor imaging assessment and EKG prior to initiating cross-over treatment (within 28 days of the start of combination dosing). All subsequent assessments will continue with the same frequency defined in the **Study Calendar** and **Section 11**.

5. Participants must re-consent prior to treatment cross-over.

The treating investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities indicating that continuing treatment will not benefit the patient. Participants should be made aware of the potential risks of initiating combination therapy by the treating investigator and must provide re-consent prior to the beginning of cross-over therapy.

Participants who cross-over will receive LY3214996 and HCQ at the dose being administered to **Arm 1** participants. Under no circumstances may a participant crossing-over receive treatment with HCQ at a dose level higher than what is being evaluated on **Arm 1**. Participants enrolled to **Arm 2** who cross-over will not be considered one of the six required participants for the safety analysis of **Arm 1** (see **Section 5.1.3.1**). In the event combination dosing was not found tolerable during the safety lead-in, no treatment with HCQ will be permitted.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

If screening laboratory assessments were completed ≤ 7 days prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 values. If cycle 1 day 1 laboratories are performed, the values do not need to re-meet eligibility criteria, participants will be allowed to initiate treatment at the treating investigator's discretion.

5.2.2 Subsequent Cycles

Management guidelines for toxicities associated with study treatment are located in **Section 6**.

5.3 Agent Administration

Table 4: Treatment Regimen Description

Study Arm	Agent	Precautions	Dose	Route	Schedule	Cycle Length
Safety Lead-in, Arm 1 & Cross-Over	LY3214996	Participants should fast for 1 hour prior to each dose, and continue fasting for 1 hour following each dose Refer to **Section 5.4** for anti-emetic regimen information	Variable	Oral	Once Daily	28 Days (4 weeks)

Table 4: Treatment Regimen Description						
Study Arm	**Agent**	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
	Hydroxychloroquine (HCQ)	Participants should take HCQ with a meal (or within 30 minutes of eating) or a glass of milk		Oral	Twice Daily	
Arm 2	LY3214996	Participants should fast for 1 hour prior to each dose, and continue fasting for 1 hour following each dose Refer to **Section 5.4** for anti-emetic regimen information	400 mg	Oral	Once Daily	

5.3.1 LY3214996 Administration

Instructions for administration of LY3214996:

- LY3214996 will be administered by mouth once daily continuously throughout each treatment cycle.
- Participants should be advised to take their dose at approximately the same time each day, a ± 4 hour dosing window is allowed. Doses that would occur outside of this time frame should be considered missed and should not be administered.
- Participants should be advised to fast for at least 1 hour prior to each dose, and to continue fasting for at least 1 hour after each dose. Water is permitted during the fasting period.
- If a participant vomits following a dose, the dose should not be re-taken. The participant should be advised to continue with their next regularly scheduled dose as clinically appropriate.
- LY3214996 should be swallowed whole, capsules should not be opened, chewed, or crushed.
- Refer to **Section 5.4** for anti-emetic regimen information.

5.3.2 Hydroxychloroquine (HCQ) Administration

Only participants enrolled to the **Safety Lead-in Cohort**, **Arm 1,** or who cross-over on **Arm 2** will receive treatment with HCQ. Instructions for administration of HCQ:

- HCQ will be administered by mouth twice daily continuously throughout each treatment cycle.
- Participants should be advised to take their doses approximately 12 hours apart, a ± 4 hour dosing window is allowed. Doses that would occur outside of this time frame should be considered missed and should not be administered.
- Participants should be advised to take each dose with a meal (or within 30 minutes of

eating) or with a glass of milk.
- If a participant vomits following a dose, the dose should not be re-taken. The participant should be advised to continue with their next regularly scheduled dose as clinically appropriate.
- HCQ should be swallowed whole, tablets should not be dissolved, chewed, or crushed.
- Order of administration of HCQ and LY3214996 does not matter but note the different administration requirements regarding food. It may be easier for participants to take their dose of LY3214996 in the morning prior to taking HCQ, and to take HCQ with breakfast after the 1 hour fasting period for LY3214996 is completed.

5.4 General Concomitant Medication and Supportive Care Guidelines

No investigational or commercial agents or therapies other than LY3214996 or HCQ may be administered with the intent to treat the participant's malignancy, with the exception of palliative radiation treatment with the overall principal investigator's agreement. Study treatment should be held for the duration of the radiation therapy and may be resumed when adverse events associated with the radiation treatment have resolved to ≤ Grade 1 or baseline. Bisphosphonate use is permitted.

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to anti-emetics (see **Section 5.4.8** below), anti-diarrheals, and blood product transfusion.

5.4.1 Granulocyte Colony-Stimulating Factor

Growth factor support may be initiated per ASCO or local institutional guidelines at the treating investigator's discretion during or following the first occurrence of neutropenia or neutropenic fever.

5.4.2 Participants Receiving HCQ: Hypoglycemia

HCQ has been shown to cause hypoglycemia including loss of consciousness that could be life threatening in patients treated with or without antidiabetic medications. Patients treated with HCQ should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia (e.g. shakiness, palor, anxiety, sweating, an irregular heart rhythm, confusion, etc.) during treatment with HCQ should have their blood glucose checked and treatment reviewed as necessary. Please also refer to **Section 6.3.**

5.4.3 Participants Receiving HCQ: Medications Known or Suspected to Cause Prolonged QTc Intervals or Torsades de Pointes

HCQ may prolong the QT interval. Ventricular arrhythmias and Torsades de Pointes have been reported in patients taking HCQ. Patients should avoid taking concomitant medications that are known or suspected to cause prolonged QTc or Torsades de Pointes (see **Appendix B**). If possible, alternative agents should be considered.

5.4.4 Participants Receiving HCQ: Other Concomitant Medication Guidelines

Please also refer to the FDA package insert for complete information:

- Digoxin: Concomitant HCQ and digoxin therapy may result in increased serum digoxin levels. Serum digoxin levels should be closely monitored in patients receiving combined therapy.
- Insulin or antidiabetic drugs: As HCQ may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.
- Mefloquine and other drugs known to lower the convulsive threshold: HCQ can lower the convulsive threshold. Co-administration of HCQ with other antimalarials known to lower the convulsion threshold (e.g., mefloquine) may increase the risk of convulsions.
- Antiepileptics: The activity of antiepileptic drugs might be impaired if co-administered with HCQ.
- Cyclosporin: An increased plasma cyclosporin level was reported when cyclosporin and HCQ were co-administered.

5.4.5 LY3214996: Drug-Drug Interactions (DDIs)

Investigators should avoid the use of concomitant therapy with sensitive substrates of CYP3A4 (e.g. simvastatin, lovastatin, buspirone, etc.) and drugs cleared by CYP3A4 that have a narrow therapeutic range when clinically feasible. LY3214996 is a time-dependent inhibitor of CYP3A4 metabolism. Assuming this is due to mechanism-based inhibition, LY3214996 appears to be a less efficient inhibitor than erythromycin, a known moderate *in vivo* time-dependent inhibitor of CYP3A. The clinical relevance of this apparent mechanism-based inhibition is currently unknown.

Caution should be used when using concomitant therapy with CYP2D6 and CYP3A5 substrates as the metabolism of such drugs may be induced. *In vitro*, LY3214996 was an inducer of CYP2D6 and CYP3A5 messenger ribonucleic acid. The clinical relevance of the *in vitro* induction of CYP2D6 and CYP3A5 by LY3214996 is currently unknown. Use caution with drugs metabolized by CYP2C9 because LY3214996 is a reversible CYP2C9 inhibitor.

Participants should avoid any concomitant medications that are moderate or strong inhibitors (e.g. grapefruit juice, ketoconazole, etc.) or inducers of CYP3A4 when clinically feasible. *In vitro* data indicates that the major cytochrome P450 involved in the clearance of LY3214996 is CYP3A (~88%).

5.4.6 Prohibited Foods

The consumption of grapefruit or grapefruit juice is prohibited while receiving LY3214996 therapy.

5.4.7 Rash Management Guidelines

Both LY3214996 and HCQ have been associated with rash or dermatologic reactions. Please

refer to **Appendix C** for rash management guidelines.

5.4.8 LY3214996 Anti-Emetics

Approximately 90% of patients have experienced nausea and/or vomiting due to LY3214996 when dosed at 600 mg daily (which is above the maximum dose evaluated in this study). In a limited number of cases this has led to more severe adverse events (i.e., dehydration, acute kidney injury). Anti-emetic treatment for participants receiving LY3214996 will be at the discretion of the treating investigator.

Anti-emetic medication will be prescribed and administered according to local standards. Recommended anti-emetic treatment follows the National Comprehensive Cancer Network 2018 (v. 3) guidelines. Anti-emetic treatment consists of a 5-HT3 receptor antagonist and should be given 30 – 60 minutes prior to the LY3214996 dose as needed:

- Ondansetron 16 mg (total dose) by mouth once. Repeat 8 mg every 8 hours as needed for nausea. Do not exceed more than 24 mg daily.

In the event use of ondansetron is contraindicated in a participant, an alternative agent may be used. Breakthrough or additional treatment may also be given by adding an agent from a different drug class to the current regimen (e.g., olanzapine 5 – 10 mg by mouth daily, dexamethasone 12 mg by mouth or IV daily).

5.4.9 LY3214996 Dehydration

Patients must be instructed to maintain adequate oral hydration at home, in order to prevent dehydration secondary to vomiting or diarrhea. During clinic visits, patients should be evaluated for signs and symptoms of dehydration and, if necessary, intravenous hydration should be implemented at the discretion of the treating investigator.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (except in the case of participants on **Arm 2** LY3214996 monotherapy who are going to cross-over to combination treatment)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6 Duration of Follow Up

Participants will be followed for 30 days after removal from protocol therapy or until death for serious adverse events, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. After completion of the 30 day follow up period, participants will continue to be followed for 6 months after removal from protocol therapy or until death for survival status only.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Completion of the survival follow up period
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Dosing Delays

The study agents may be held for a maximum of 28 days to allow for recovery of toxicity. Participants requiring a longer delay should be removed from protocol therapy. Participants who are deriving clinical benefit who require a longer hold may be allowed to continue treatment

following discussion and agreement with the overall principal investigator.

If attribution of the toxicity is known, study medications may be held independently of each other. For example, a participant may continue dosing with LY3214996 while holding HCQ at the treating investigator's discretion. If attribution of the toxicity is unknown or the combination of study agents may be contributing to the toxicity, both study agents must be held.

In the event of a dose hold due to toxicity, the counting of cycle days and protocol assessment schedule will continue without interruption. For example, a participant who holds dosing of LY3214996 on Cycle 4 Day 15 to Cycle 4 Day 18 for toxicity will resume dosing on Cycle 4 Day 19 and proceed with their next scheduled clinic visit as previously planned (Cycle 5 Day 1). Interim visits may be conducted as clinically necessary to manage toxicity; however, the cycle will not restart and doses will not be "made up" in the event of dosing delays.

6.2 Dose Modifications

Dose reductions may be made in accordance with the tables below. Once a participant's dose of HCQ or LY3214996 has been reduced, it may be re-escalated to the previous dose level if the toxicity has resolved to baseline or ≤ Grade 1 with agreement from the overall principal investigator. If the toxicity recurs necessitating another dose reduction, the dose may not be re-escalated.

Table 5: HCQ Dose Reductions

Original HCQ Dose (PO BID)	HCQ Dose Reduction (PO BID)
600 mg	1st Reduction: 400 mg
	2nd Reduction: 200 mg
	3rd Reduction: Discontinue
400 mg	1st Reduction: 200 mg
	2nd Reduction: Discontinue
200 mg	Discontinue

Table 6: LY3214996 Dose Reductions

Original LY3214996 Dose (PO Daily)	LY3214996 Dose Reduction (PO Daily)
400 mg	1st Reduction: 200 mg
	2nd Reduction: 100 mg
	3rd Reduction: Discontinue
200 mg	1st Reduction: 100 mg
	2nd Reduction: Discontinue

If attribution of the toxicity is known, dose reductions may occur independently of each other. For example, the dose of HCQ may be reduced while maintaining the dose of LY3214996. If toxicity attribution is unknown or the combination of study agents may contribute to the toxicity,

both agents must be dose reduced.

If attribution of the toxicity is known, discontinuation of study medications may also occur independently of each other with agreement from the overall principal investigator. For example, participants who cannot tolerate HCQ may be allowed to continue to receive LY3214996 if the overall principal investigator agrees. If toxicity attribution is unknown or the combination of study agents may contribute to the toxicity, the participant should be removed from protocol therapy.

6.3 Toxicity Management Guidelines

Management of toxicity considered ***at least possibly related*** to HCQ and/or LY3214996 is detailed in the tables below.

Table 7: Hematologic Toxicity Management

Event Terms	CTCAE Grade	Management Guidelines
Neutrophil count decreased	≥ Grade 3	Hold study agent(s) until recovery to ≤ Grade 2, resume with one dose level reduction.
Febrile neutropenia	≥ Grade 3	Hold study agent(s) until resolution, resume with one dose level reduction.
Platelet count decreased	≥ Grade 3	Hold study agent(s) until recovery to ≤ Grade 2, resume with one dose level reduction.

Table 8: Non-Hematologic Toxicity Management

Event Terms	CTCAE Grade	Management Guidelines
Ocular Toxicity	≤ Grade 2	Ocular toxicity is associated with HCQ, and blurred vision has been observed in patients receiving LY3214996. Participants experiencing new or worsening visual disturbances or suspected ocular toxicity of any grade while receiving study treatment should be referred for ophthalmic examination. In the case of mild or moderate ocular toxicity (i.e. CTCAE Grade 1 or Grade 2), the treating investigator may hold and/or dose reduce the study agent(s) at their discretion.
Ocular Toxicity	≥ Grade 3	Ocular toxicity is associated with HCQ, and blurred vision has been observed in patients receiving LY3214996. Participants experiencing new or worsening visual disturbances or suspected ocular toxicity of any grade while receiving study treatment should be referred for ophthalmic examination. Hold study agent dosing until resolution to ≤ Grade 2 or baseline. Resume with one dose level reduction.

Table 8: Non-Hematologic Toxicity Management		
Event Terms	**CTCAE Grade**	**Management Guidelines**
Hypoglycemia	≥ Grade 3 **-OR-** Symptomatic (ANY GRADE)	HCQ has been shown to cause severe hypoglycemia that has included loss of consciousness and can be life-threatening. Implement appropriate supportive care. Hold dosing until resolution to ≤ Grade 2 or baseline, AND participant is asymptomatic. Resume with one dose level reduction.
Skin Rash	≤ Grade 2[1]	Dermatologic reactions have been associated with both LY3214996 and HCQ. No change in dosing. Implement supportive care as appropriate (e.g. topical steroids, antibiotics).[3]
Skin Rash	Grade 3	Dermatologic reactions have been associated with both LY3214996 and HCQ. Hold dosing until resolution to ≤ Grade 2 or baseline. Implement appropriate supportive care (e.g. topical steroids, antibiotics).[3] **With first occurrence**, if there is resolution to ≤ Grade 2 or baseline in ≤ 7 days, study agent(s) may be resumed at the same dose level.[2] If toxicity does not improve in ≤ 7 days, upon resolution reduce dose by one dose level. If toxicity **recurs** despite appropriate supportive care (e.g. topical steroids, antibiotics), upon resolution to ≤ Grade 2 or baseline reduce dose of by one dose level.
Skin Rash	Grade 4	Dermatologic reactions have been associated with both LY3214996 and HCQ. Hold dosing and implement appropriate supportive care.[3] Permanently discontinue protocol therapy.
Any other non-hematologic toxicity	≤ Grade 2[1]	No change in dosing. Implement supportive care as appropriate.
Any other non-hematologic toxicity	≥ Grade 3	Hold dosing until resolution to ≤ Grade 2 or baseline. Upon resolution, resume with one dose level reduction. Exceptions: • Grade 3 nausea, vomiting, diarrhea, or constipation that was not medically managed: appropriate medical management should be initiated, and study medication should be held until resolution to ≤ Grade 2 or baseline. Upon resolution, study medication may be resumed at the same dose level or with one dose level reduction at the treating investigator's discretion. • Asymptomatic laboratory abnormalities that resolve to ≤ Grade 2 or baseline within 48 hours of repletion or treatment: study medication should be held until resolution to Grade 2 and may be resumed at the same dose level or with one dose level reduction at the treating investigator's discretion. Treatment and resumption of study medication dosing may occur on the same day. • Asymptomatic laboratory abnormalities considered non-clinically significant: participants may continue dosing at the treating investigator's discretion.

1. At the treating investigator's discretion, participants experiencing intolerable grade 2 toxicities may hold and/or dose reduce LY3214996 and/or HCQ.
2. At the treating investigator's discretion, dose of LY3214996 and/or HCQ may be reduced by one dose level.
3. Please refer to **Appendix C** for rash management guidelines.

6.4 Overdose

There is currently no specific treatment in the event of overdose with LY3214996 and possible symptoms of overdose are not established. In the event of an overdose, the participant should be monitored and adverse reactions associated with the overdose should be treated symptomatically.

In the event of overdosage of HCQ, management should be in accordance with institutional standards of practice and the FDA package insert. Please refer to **Section 7** for adverse event reporting requirements.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (**Section 7.1**) and the characteristics of an observed AE (**Section 7.2** and **7.3**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Expected Toxicities for HCQ

The table below summarizes treatment-emergent adverse events considered expected for HCQ serious adverse reaction reporting. Please refer to the FDA package insert for detailed information.

Table 9: HCQ Toxicities Considered Expected

System Organ Class	Event Preferred Term
Blood and lymphatic system disorders	Leukopenia *(including white blood cell decreased)*
	Thrombocytopenia *(including platelet count decreased)*
	Anemia *(including hemoglobin and hematocrit decreased)*
	Bone marrow failure
	Aplastic anemia
	Agranulocytosis
Cardiac disorders	Cardiomyopathy
Ear and labyrinth disorders	Vertigo
	Tinnitus
	Nystagmus
	Nerve deafness
	Deafness (*including hearing impaired*)
Eye disorders	Irreversible retinopathy with retinal pigmentation changes (*includes retinopathy*)
	Visual field defects, paracentral scotomas

Table 9: HCQ Toxicities Considered Expected	
System Organ Class	**Event Preferred Term**
	Visual disturbances (*includes vision decreased*)
	Maculopathies, macular degeneration
	Decreased dark adaptation
	Color vision abnormalities
	Corneal changes, corneal edema, corneal opacities, corneal deposition of drug with or without symptoms (halo around lights, photophobia, blurred vision)
Gastrointestinal disorders	Nausea
	Vomiting
	Diarrhea
	Abdominal pain
General disorders and administration site conditions	Fatigue
Hepatobiliary disorders	Hepatic failure
Investigations	Electrocardiogram QT corrected interval prolonged
	Liver function tests abnormal (*includes aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased*)
	Weight decreased (*includes weight loss*)
Immune system disorders	Angioedema
	Bronchospasm
	Urticaria
Metabolism and nutrition disorders	Decreased appetite (*includes anorexia*)
	Hypoglycemia
	Porphyria
Musculoskeletal and connective tissue disorders	Abnormal nerve conduction
	Depression of tendon reflexes
	Sensorimotor disorder
	Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups
Nervous system disorders	Ataxia
	Dizziness
	Extrapyramidal disorders such as dystonia, dyskinesia, and tremor
	Headache
	Seizure
Psychiatric disorders	Affect/emotional lability
	Irritability
	Nervousness (*includes anxiety)*
	Nightmares
	Psychosis
	Suicidal behavior

Table 9: HCQ Toxicities Considered Expected	
System Organ Class	**Event Preferred Term**
Skin and subcutaneous tissue disorders	Rash
	Pruritis
	Pigmentation disorders in skin and mucous membranes
	Hair color changes
	Alopecia
	Dermatitis bullous eruptions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis
	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
	Photosensitivity
	Dermatitis exfoliative
	Acute generalized exanthematous pustulosis (AGEP)
	Psoriasis

7.1.2 Expected Toxicities for LY3214996

Please refer to the most recent LY3214996 IB for detailed information. Recently identified expected serious adverse drug reactions (SADRs) for LY3214996 include the following:

- Nausea
- Vomiting
- Diarrhea
- Renal failure

One patient experienced itching of hands and feet, swelling of lips and tongue, and itching in ear, followed by a hive-like rash on the upper legs and lower abdomen two days later. The symptoms were believed to be secondary to an allergic reaction. As this has not been described in any other patient who has received this drug, it remains a possible though not yet expected toxicity.

Any fatal or life-threatening events (i.e. events posing an immediate risk of dying) will always be considered unexpected for the purposes of suspected unexpected serious adverse reaction (SUSAR) reporting.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event

varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment that results in one of the following outcomes:

- Death
- Hospitalization for greater than 24 hours
- Prolonging an existing inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

Previously planned (prior to signing the informed consent form) surgeries, and non-disease related elective surgeries planned during the course of the study, should not be reported as SAEs unless the underlying medical condition has worsened or appeared during the course of the study. Events that occur prior to the first administration of study medication should not be reported as SAEs.

Preplanned hospitalizations or procedures for pre-existing conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (e.g., for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Death due to disease progression should not be reported as an SAE unless the investigator deems it to be related to the use of study drug.

Study site personnel must alert Eli Lilly of any SAE as soon as possible and no later than 1

business day of the investigator receiving notification of the SAE experienced by a patient participating in the study. The SAE reports should be on a standard reporting form (e.g. CIOMS, local institutional SAE form, MedWatch 3500a, or similar) and are to be sent to Eli Lilly via email: MAILINDATA_GSMTINDY@LILLY.COM.

7.4 Adverse Event Reporting

7.4.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.4.2 Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.3 For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4.4 DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable Adverse Events(AEs)			
	Gr. 2, 3, & 4 AE Expected#	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days	24 hours*
# Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.				
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.				

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.5 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

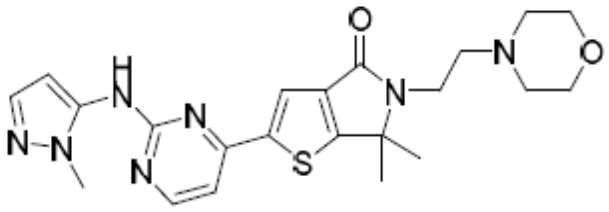
8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational administered in this study can be found in **Section 7.1**.

8.1 LY3214996

Chemical Name: 4H-Thieno[2,3-c]pyrrol-4-one, 5,6-dihydro-6,6-dimethyl-2-[2-[(1-methyl-1H-pyrazol-5-yl)amino]-4-pyrimidinyl]-5-[2-(4-morpholinyl)ethyl]-

Chemical Structure:



Structure of LY3214996.

Molecular Weight: 453.57

Molecular Formula: $C_{22}H_{27}N_7O_2S$

Description: White to light brown powder

Solubility: Water: 0.06 mg/mL; Methanol: 7.8 mg/mL

8.1.1 **Form**

The drug product is supplied as capsules. Each capsule contains LY3214996 equivalent to 25 mg or 100 mg of the base compound, with no inactive ingredients.

8.1.2 **Storage and Stability**

The drug product should be stored at room temperature (10˚C to 30˚C).

8.1.3 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.4 **Availability**

LY3214996 is an investigational agent that will be supplied by Eli Lilly and Company.

8.1.5 **Administration**

LY3214996 administration instructions:

- LY3214996 will be administered by mouth once daily continuously throughout each treatment cycle.
- Participants should be advised to take their dose at approximately the same time each day, a ± 4 hour dosing window is allowed. Doses that would occur outside of this time frame should be considered missed and should not be administered.
- Participants should be advised to fast for at least 1 hour prior to each dose, and to continue fasting for at least 1 hour after each dose. Water is permitted during the fasting period.
- If a participant vomits following a dose, the dose should not be re-taken. The participant should be advised to continue with their next regularly scheduled dose as clinically appropriate.
- LY3214996 should be swallowed whole, capsules should not be opened, chewed, or crushed.
- Refer to **Section 5.4** for anti-emetic regimen information.

8.1.6 **Ordering**

LY3214996 will be ordered by site pharmacy personnel from Eli Lilly and Company.

8.1.7 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

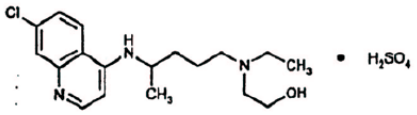
8.1.8 **Destruction and Return**

Expired, returned, or unused supplies of LY3214996 should be destroyed according to local institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2 Hydroxychloroquine Sulfate (HCQ, Plaquenil®)

Chemical Name: 2-[[4-[(7-Chloro-4-quinolyl) amino]pentyl] ethylamino]ethanol sulfate (1:1)

Chemical Structure:



Molecular Weight: 433.95

Molecular Formula: $C_{18}H_{26}ClN_3O.H_2SO_4$

Description: White or practically white, crystalline powder

Solubility: Freely soluble in water, practically insoluble in alcohol, chloroform, and in ether

8.2.1 **Form**

Please refer to the FDA package insert. HCQ tablets contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration. Inactive Ingredients: Dibasic calcium phosphate USP, hypromellose USP, magnesium stearate NF, polyethylene glycol 400 NF, polysorbate 80 NF, corn starch, titanium dioxide USP, carnauba wax NF, shellac NF, black iron oxide NF.

8.2.2 **Storage and Stability**

Please refer to the FDA package insert.

8.2.3 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent in a self-contained and protective environment in accordance with local institutional standards of practice.

8.2.4 Availability

HCQ is an FDA approved drug that is commercially available.

8.2.5 Administration

Only participants enrolled to the **Safety Lead-in Cohort**, **Arm 1,** or who cross-over on **Arm 2** will receive treatment with HCQ. Instructions for administration of HCQ:

- HCQ will be administered by mouth twice daily continuously throughout each treatment cycle.
- Participants should be advised to take their doses approximately 12 hours apart, a ± 4 hour dosing window is allowed. Doses that would occur outside of this time frame should be considered missed and should not be administered.
- Participants should be advised to take each dose with a meal (or within 30 minutes of eating) or with a glass of milk.
- If a participant vomits following a dose, the dose should not be re-taken. The participant should be advised to continue with their next regularly scheduled dose as clinically appropriate.
- HCQ should be swallowed whole, tablets should not be dissolved, chewed, or crushed.

8.2.6 Ordering

HCQ is an FDA approved commercially available agent that should be ordered by site pharmacy personnel per local institutional standards of practice. The cost of HCQ will be covered by the research trial, it will not be billed to patient insurance.

8.2.7 Accountability

HCQ accountability will be handled in accordance with local institutional standards of practice.

8.2.8 Destruction and Return

Expired, returned, or unused supplies of HCQ should be destroyed according to local institutional policies.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Tumor Biopsy Collection

Core needle, incisional, or excisional biopsies may be obtained for analysis at the time points indicated below. Biopsy procedures will be performed following standard institutional procedures. The tissue collection goal is 3 – 6 core biopsy samples collected using an 18 - 20 gauge needle. Less than the goal amount of tissue is acceptable and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure. In the event tissue is insufficient for analysis it will not be considered a protocol violation.

- Biopsy #1 (Pre-Treatment): A mandatory fresh tumor tissue biopsy will be obtained pre-treatment from all participants.
    - The pre-treatment fresh tumor biopsy may be obtained any time before the participant's Cycle 1 Day 1 visit.
- Biopsy #2: An additional optional biopsy at the time of disease progression will be offered to all participants.
    - The time of progression biopsy should be obtained prior to the initiation of another anti-cancer therapy when possible. In the event this is not feasible, the time of progression biopsy may be obtained up to 30 days after the date that disease progression was determined. The date of progression may be considered either the date the radiological scan was performed, or the date the treating investigator judged the participant to have progressed.
    - In the event a participant enrolled to **Arm 2** crosses-over to combination treatment, the time of progression biopsy may be collected prior to cross-over and/or upon progression on combination treatment. A tumor biopsy is not required prior to the initiation of cross-over treatment.

Please refer to the protocol laboratory manual for specific handling and shipping instructions.

9.2 Pharmacodynamic Marker Collection

Serial blood sampling will be performed for pharmacodynamic assessments on all patients. A total of 30 - 40 mL of blood will be collected at the following time points:

- Cycle 1 Day 1 prior to dosing with the study agent(s)
- Cycle 1 Day 15 at any time during the study visit
- Day 1 of all subsequent cycles at any time during the study visit
- At the off treatment visit

Please refer to the protocol laboratory manual for specific collection and handling instructions.

9.3 Pharmacokinetic (PK) Sample Collection

Limited PK blood sampling will be performed on participants enrolled to the **Safety Lead-in Cohort** and the first 6 evaluable participants enrolled to **Arm 1**. The PK sampling will serve to

evaluate the plasma concentration-time profiles of LY3214996 when combined with HCQ. Refer to the table below.

Please refer to the protocol laboratory manual for specific collection and handling instructions.

Table 10: Pharmacokinetic Blood Sample Collection[1,2]		
Visit Day	**Time**	**Sample Number**
Cycle 1 Day 1	Any time prior to first doses of LY3214996 and HCQ	PK-00
Cycle 1 Day 1	1 hour post-LY3214996 dosing (± 15 minutes)	PK-01
Cycle 1 Day 1	2 hours post-LY3214996 dosing (± 15 minutes)	PK-02
Cycle 1 Day 1	4 hours post-LY3214996 dosing (± 15 minutes)	PK-03
Cycle 1 Day 1	8 hours post-LY3214996 dosing (± 30 minutes)	PK-04
Cycle 1 Day 2	Any time on Cycle 1 Day 2 prior to the Cycle 1 Day 2 doses of LY3214996 and HCQ	PK-05
Cycle 2 Day 1	Any time prior to the Cycle 2 Day 1 doses of LY3214996 and HCQ	PK-06
Cycle 2 Day 1	2 hours post-LY3214996 dosing (± 15 minutes)	PK-07
1. Approximately 3 – 4 mL of blood will be collected at each time point. Refer to the protocol laboratory manual for specific collection and handling instructions. 2. Applicable only to participants enrolled to the **Safety Lead-in Cohort** or the first 6 evaluable participants enrolled to **Arm 1**.		

10. STUDY CALENDAR

Screening evaluations are to be conducted within 14 days prior to the start of protocol therapy, with the exception of obtaining the informed consent, imaging, and ophthalmic exam, which may be obtained up to 28 days prior to the start of protocol therapy. Assessments must be performed prior to administration of the study agent.

	Table 11: Study Calendar for the Safety Lead-in Cohort, Arm 1, and Cross-Over Participants										
	Screening[∞]	Cycle 1 Day 1[a]	Cycle 1 Day 2	Cycle 1 Day 8[b]	Cycle 1 Day 15[b]	Cycle 1 Day 22[b]	Cycle 2+ Day 1[c]	Cycle 2 Day 15[b]	Off Treatment[d]	Every Month Following Treatment Discontinuation	EDC Timepoints[¥]
Informed consent	X										N/A
Demographics	X										Screening
Medical history	X										Screening
Physical exam	X	X		X	X	X	X	X	X		N/A
Vital signs[e]	X	X		X	X	X	X	X	X		N/A
Height	X										N/A
Weight	X	X		X	X	X	X	X	X		N/A
ECOG performance status	X	X					X		X		Screening, Day 1 of every cycle, Off Treatment
CBC w/diff, plts	X	X		X	X	X	X	X	X		N/A
Serum chemistry[f]	X	X		X	X	X	X	X	X		N/A
Serum β-HCG[g]	X										N/A
EKG[h]	X			X	X	X	X				N/A
Adverse event evaluation		X----------X							X		All Visits
Radiologic evaluation[i]	X	Radiologic measurements should be performed every 8 weeks (± 7 day scheduling window)							X		Screening, Every 8 weeks, Off Treatment
Tumor Biopsy[j]	X								X		Screening, Off Treatment
PD Marker[k]		X			X		X		X		Screening, Day 1 of all cycles, C1D15, Off Treatment
Standard ophthalmic exam[l]	X						X				N/A

	Table 11: Study Calendar for the Safety Lead-in Cohort, Arm 1, and Cross-Over Participants										
	Screening∞	Cycle 1 Day 1[a]	Cycle 1 Day 2	Cycle 1 Day 8[b]	Cycle 1 Day 15[b]	Cycle 1 Day 22[b]	Cycle 2+ Day 1[c]	Cycle 2 Day 15[b]	Off Treatment[d]	Every Month Following Treatment Discontinuation	EDC Timepoints¥
PK Collection[m]		X	X				X				C1D1, C2D1
LY3214996[n]		As described in **Section 5.3**									Day 1 of every cycle
HCQ[n]		As described in **Section 5.3**									Day 1 of every cycle
Telephone or Care Provider Contact[o]										X	Every month following treatment discontinuation × 6 months

∞: Cross-over participants do not need to re-screen but must provide re-consent prior to initiating cross-over treatment. First day of combination treatment will be considered C1D1 of cross-over. See **Section 5.1.4.**

¥: Note: column relevant only for CRF builders.

a. Please refer to **Section 5.2.1**.
b. A ± 3 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
c. A ± 7 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
d. Off treatment evaluation. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment.
e. Heart rate, respiratory rate, temperature, blood pressure, and oxygen saturation; to be performed prior to study agent dosing.
f. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, creatinine phosphokinase (CPK).
g. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35μIU/mL).
h. EKG to be collected during screening, C1D8, on C1D15, C1D22, C2D1, and C3D1 at any time during the study visit, and as clinically indicated. Single EKG to be collected at each time point. QTc to be calculated using Bazett's formula.
i. Radiologic imaging of any disease-involved site**.**
j. A tumor biopsy is mandatory at baseline for all participants, and optional at the time of disease progression for all participants. Tumor biopsies to be collected as per **Section 9.1**. A repeat screening tumor biopsy is not required for cross-over participants (i.e. participants are not required to have a biopsy prior to crossing-over).
k. Blood samples to be collected as per **Section 9.2**.
l. To be performed by an ophthalmologist. Exam required during screening and on Cycle 3 Day 1 (± 7 day window). In addition, exam required if participant experiences new or worsening visual disturbances or suspected ocular toxicity while receiving trial treatment.
m. PK sample collection only required on participants enrolled to the **Safety Lead-in Cohort** and the first six evaluable participants enrolled to **Arm 1**. Refer to **Section 9.3** for details.
n. Adequate supply of the study agents should be dispensed to account for any pre-planned scheduling delays.
o. Following treatment discontinuation, participants will continue to be followed for survival status only for 6 months or until death, whichever occurs first. Survival status may be verified via medical record review, contact with care providers, or telephone contact with the patient. A ±14 day window is allowed for survival status verifications.

Table 12: Study Calendar for Arm 2 Participants

	Screening	Cycle 1 Day 1[a]	Cycle 1 Day 8[b]	Cycle 1 Day 15[b]	Cycle 1 Day 22[b]	Cycle 2+ Day 1[c]	Cycle 2 Day 15[b]	Off Treatment[d]	Every Month Following Treatment Discontinuation	EDC Timepoints[¥]
Informed consent	X									N/A
Demographics	X									Screening
Medical history	X									Screening
Physical exam	X	X	X	X	X	X	X	X		N/A
Vital signs[e]	X	X	X	X	X	X	X	X		N/A
Height	X									N/A
Weight	X	X	X	X	X	X	X	X		N/A
ECOG performance status	X	X				X		X		Screening, Day 1 of every cycle, Off Treatment
CBC w/diff, plts	X	X	X	X	X	X	X	X		N/A
Serum chemistry[f]	X	X	X	X	X	X	X	X		N/A
Serum β-HCG[g]	X									N/A
EKG[h]	X	As clinically indicated								N/A
Adverse event evaluation		X----------X						X		All Visits
Radiologic evaluation[i]	X	Radiologic measurements should be performed every 8 weeks (± 7 day scheduling window)						X		Screening, Every 8 weeks, Off Treatment
Tumor Biopsy[j]	X							X		Screening, Off Treatment
PD Marker[k]		X		X		X		X		Screening, Day 1 of all cycles, C1D15, Off Treatment

Table 12: Study Calendar for Arm 2 Participants

	Screening	Cycle 1 Day 1[a]	Cycle 1 Day 8[b]	Cycle 1 Day 15[b]	Cycle 1 Day 22[b]	Cycle 2+ Day 1[c]	Cycle 2 Day 15[b]	Off Treatment[d]	Every Month Following Treatment Discontinuation	EDC Timepoints[¥]
Standard ophthalmic exam[l]	X	As clinically indicated								N/A
LY3214996[m]		As described in **Section 5.3**								Day 1 of every cycle
Telephone or Care Provider Contact[n]									X	Every month following treatment discontinuation × 6 months

¥: Note: column relevant only for CRF builders.

a. Please refer to **Section 5.2.1**.
b. A ± 3 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
c. A ± 7 day scheduling window is allowable to account for holidays, adverse weather, vacations, or any other scheduling issues.
d. Off treatment evaluation. Note: for IND trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment.
e. Heart rate, respiratory rate, temperature, blood pressure, and oxygen saturation; to be performed prior to study agent dosing.
f. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, phosphorus, creatinine phosphokinase (CPK).
g. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with a documented plasma follicle-stimulating hormone level >35µlU/mL).
h. Single EKG to be collected during the screening period. QTc to be calculated using Bazett's formula.
i. Radiologic imaging of any disease-involved site**.**
j. A tumor biopsy is mandatory at baseline for all participants, and optional at the time of disease progression for all participants. Tumor biopsies to be collected as per **Section 9.1**.
k. Blood samples to be collected as per **Section 9.2**.
l. To be performed by an ophthalmologist. Repeat exam required if participant experiences new or worsening visual disturbances or suspected ocular toxicity while receiving trial treatment.
m. Adequate supply of the study agent should be dispensed to account for any pre-planned scheduling delays.
n. Following treatment discontinuation, participants will continue to be followed for survival status only for 6 months or until death, whichever occurs first. Survival status may be verified via medical record review, contact with care providers, or telephone contact with the patient. A ±14 day window is allowed for survival status verifications.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks (± 7 day scheduling window). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

For patients who discontinue protocol treatment prior to disease progression, they will continue to undergo restaging scans every 8 weeks ± 7 days or earlier if clinically indicated, until the documentation of disease progression.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

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

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

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.5 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.6 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.7 Evaluation of Best Overall Response

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

Table 13: For Participants with Measurable Disease (*i.e.*, Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table 14: For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.8 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.9 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.10 Response Review

Confirmation of scan results will be done centrally using the Tumor Imaging Metrics Core (TIMC) at DF/HCC, however treatment decisions may be made based on local scan interpretation.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 7.0** (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in **Appendix D**.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open label, randomized, two arm, phase II study evaluating LY3214996 alone and in combination with HCQ in participants with advanced pancreatic cancer. Following completion of a brief combination treatment safety lead-in cohort (N=6 patients), participants will be randomized 1:1 for enrollment to one of two treatment arms:

- **Arm 1:** receiving combination treatment with LY3214996 and HCQ
- **Arm 2:** receiving monotherapy treatment with LY3214996

13.2 Sample Size, Accrual Rate and Study Duration

The safety lead-in cohort will enroll a maximum of 12 patients. For the randomized component of the trial, a total of 20 patients will be enrolled to each treatment arm of the trial, for an overall maximum total of 52 patients. Participants will be replaced in the randomized portion of the trial if they withdraw consent for participation before receiving any protocol treatment or rapid disease progression limits their ability to receive any therapy per protocol. We will enroll up to 54 subjects in order to obtain 52 evaluable cases. We expect to complete trial enrollment within 24 months. An additional 4 months will be required to observe the response of the last

participant accrued, for a total length of approximately 28 months for determination of the primary endpoint of DCR. OS is a secondary endpoint of the trial, and participants will continue to be followed for survival status for 6 months following treatment discontinuation or until death.

13.3 Analysis of Primary Endpoint

13.3.1 Safety Lead-in Cohort

The probability to escalate dose in the safety lead-in phase is presented in the table below. The randomized portion of the trial will proceed if there are < 2 DLTs observed among participants accrued to **Dose Level 0**. If **Dose Level 0** is found intolerable (with ≥ 2 participants experiencing a DLT), **Dose Level -1** will be evaluated. If **Dose Level -1** is also not tolerable, the cohort will be closed with no further combination treatment enrollment and the trial will proceed as a single arm evaluation of LY3214996 as monotherapy.

Table 15: Safety Lead-in Probability Table

True Toxicity Rate	Probability for Dose Escalation in the Safety Lead-in Phase
0.01	>0.99
0.05	0.97
0.1	0.89
0.2	0.66
0.4	0.23

13.3.2 Randomized Arms

The randomized arms will be treated independently, not directly compared. Anti-tumor activity will be measured via disease control rate (DCR), which will be defined as the proportion of patients with complete response (CR), partial response (PR) or stable disease (SD) that persists for ≥ 4 months. Radiologic response will be assessed using RECIST v1.1 criteria. With 20 subjects in each treatment arm, there is 79% power using a one-sided alpha of 0.1 to differentiate between an unacceptable DCR of 5% and a desirable DCR of 20%. Observing at least 3 patients with disease control in a treatment arm will be sufficient for the rejection of the null hypothesis in favor of the desirable DCR of 20% and suggesting that further evaluation of this treatment arm is warranted.

While treatment cross-over will be permitted (see **Section 5.1.4**), participants who cross-over will not be considered in the primary endpoint analysis of combination treatment.

13.4 Analysis of Secondary Endpoints

Point estimates and exact binomial 90% confidence intervals will be provided for binary secondary endpoints such as ORR. The method of Kaplan and Meier will be used to estimate overall survival in all patients; and duration of response in those that achieve OR.

13.5 Analysis of Exploratory Endpoints

All participants will have a mandatory pre-treatment biopsy, and an optional time of progression biopsy will be offered to all participants. Non-parametric paired analysis will be conducted to assess the significance of changes between pre-treatment and time of progression samples.

Concordance of drug sensitivity and WTS results will be analyzed. The percentage of pre-treatment biopsies with that are above a 66% sensitivity threshold for organoid sensitivity will be determined. With a sample size of 20 per arm, we will obtain a 95% confidence interval of (36.1%, 80.9%) if we observe 60% (or 12) of the pre-treatment biopsies that are above the threshold.

Agreement between the two biopsies will be analyzed using the Kappa statistics.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All patients will be evaluable for evaluation of toxicity from the time of their first dose of study medication.

13.6.2 Evaluation of the Primary Efficacy Endpoint

All eligible patients included in the study who receive study medication will be assessed for response, even if there are major protocol therapy deviations. Patients who are replaced due to not receiving any protocol therapy will not be included in efficacy analyses.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B LIST OF DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S. ®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Ondansetron*	Zofran®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

*when administered intravenously at high dose (32 mg).

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: http://www.crediblemeds.org/. This list is not meant to be considered all inclusive. See website for current list.

APPENDIX C RASH MANAGEMENT GUIDELINES

Rash is a common on target toxicity associated with the treatment of MAPK inhibitors including ERK inhibitors and is also commonly observed with HCQ treatment. Grade 3 rash lasting for > 7 days has been observed in ongoing sponsored trials of LY3214996. The following guidelines are suggested to help mitigate rash.

Once a patient starts on the trial, patients should be instructed to initiate the use of a moisturizer with no scents added. In addition, patients should be directed to limit sun exposure or to apply sunscreen protection before going outdoors (PABA-free, SPF 15 or higher) if appropriate.

A prescription for topical antimicrobials and steroidal agents based on institutional practice or guidelines should be provided by appropriate medical staff to the patient. The patient should be instructed to immediately fill the prescription for the topical agents and to start it immediately at the first onset of a grade 1 rash. If the rash escalates further, then the patient should be instructed to call the study investigator(s) / nurse(s) and additional interventions per institutional practice or guidelines for oral steroids, oral antimicrobials or dose reductions per investigator discretion may be implemented.

Suggested Topical and oral agents for use (additional or alternate agents may be used as based on availability, investigator discretion, and institutional standards of practice):

i. clindamycin 1% solution or lotion
ii. hydrocortisone valerate 0.2% or hydrocortisone cream 1%
iii. Moisturizer (e.g. Cetaphil or Lubriderm) with no scents added
iv. Steroids (e.g. Medrol dose pack or pulses of prednisone 40 mg BID for 5 – 7 days if non-responsive).

APPENDIX D DF/HCC MULTI-CENTER DATA AND SAFETY MONITORING PLAN

DFCI IRB Protocol #: TBD

APPENDIX D

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

15. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

15.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

15.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc.) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

16. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

16.1 DF/HCC Sponsor

The DF/HCC Sponsor, Brian Wolpin, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA, as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

16.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.

- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting pPolicy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

16.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.

- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

17. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

17.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

17.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

17.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

17.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

17.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

17.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

17.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

17.7 DF/HCC Multi-Center Protocol Registration Policy

17.7.1 Participant Registration and Randomization

Please refer to **Protocol Section 4.4.**

17.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

17.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement.

17.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

17.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these

requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

17.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

17.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

17.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy 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

by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

17.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in **Protocol Section 7**.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

17.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

17.10 Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web based training for all eCRF users.

17.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

18. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of the investigational agents is specified in the **Protocol Section 8**.

Participating Institutions should order their own agent regardless of the supplier (i.e., pharmaceutical company or commercial supply).

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

19. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

19.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Frequency of teleconferences may be increased or decreased based on research needs and patient accrual but will not occur less than quarterly. “Newsletters” highlighting overall protocol progress and important announcements will be distributed regularly.

Remote Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions

will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participant's complete medical record and source documents for source documentation verification (SDV) during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments, provided that the minimum monitoring frequencies are adhered to.

19.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

19.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

A minimum of 3 patients per site annually is expected.

20. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

20.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

20.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

20.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

20.4 Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.