NCI Protocol #: Not Applicable

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TITLE: A Phase I/II Study of LY3022855 with BRAF/MEK Inhibition in Patients with Melanoma

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Agents:
LY3022855 – Eli Lilly and Company
Vemurafenib – Commercial
Cobimetinib – Commercial

IND #: 130,965

IND Sponsor: Investigator-Initiated Study, Dr. Elizabeth Buchbinder MD

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SUMMARY OF CHANGES

DF/HCC Protocol #: 17-030

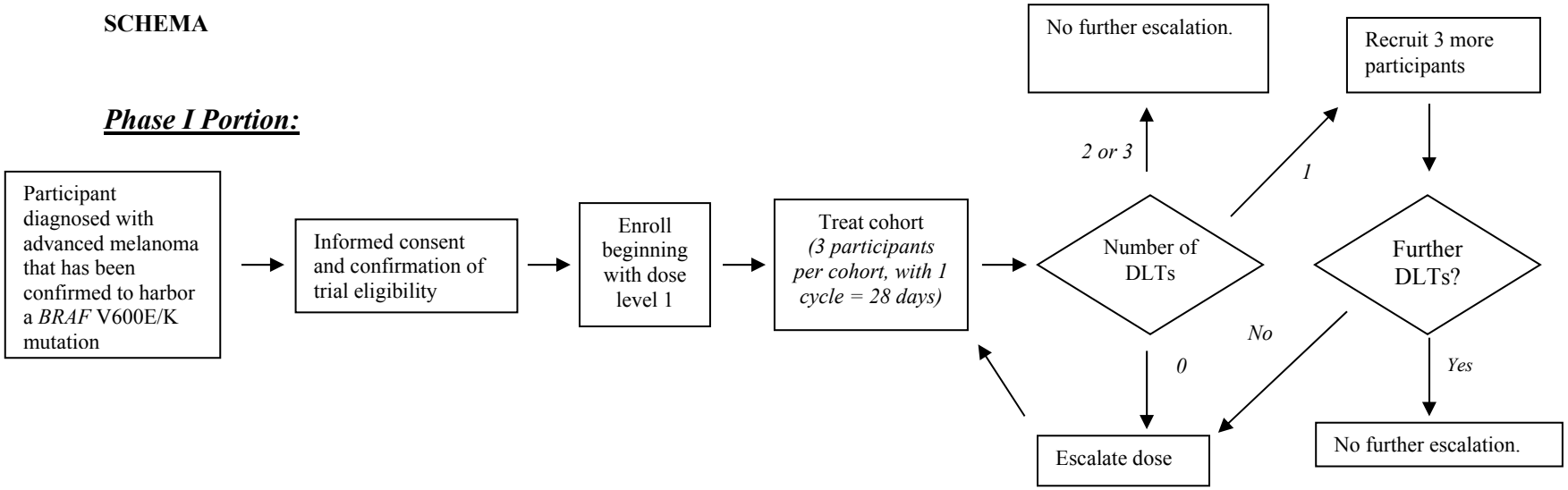
Protocol Date: 31 July 2017

#	Section(s)	Change(s)
1.	TOC; Table 5; Section 2.5.1	Explanation of rationale for flat dosing of LY3022855; update of Table 5 to include non-weight based cohorts for study JSCA; updated Table of Contents and added a List of Figures. Changes per FDA request for further information.
2.	1.3; 2.2.2; 2.3; 2.4; 2.5.1; 2.5.2; 3.1.8; 3.2.13; 5.1; 5.3.1; 5.4; 5.5.2; 5.6; 5,8; 6.2; 6.3; 7.1; 11.1; 13.1	Secondary objective for the phase I portion of the trial further defined per FDA request; Background information on LY3022855 edited per updated IB; Background information on vemurafenib and cobimetinib edited; Rationale for flat-dosing of LY3022855 edited; Eligibility criterion 3.1.8 edited to include additional parameters for defining adequate organ function per FDA request; Strong and moderate CYP3A inhibitors were prohibited for all portions of the trial per FDA request; Definition of the RP2D elaborated to include consideration of toxicity occurring outside of the DLT time window per FDA request,and dose level 3 removed; Hypersensitivity reaction section edited to include suggested medication intervention per FDA request; DLT criteria edited to include Grade 4 anemia and to remove allowance of Grade 3 AST/ALT increases lasting fewer than 8 days per FDA request; Modified criteria for taking participants off therapy to reference unacceptable AEs per FDA request; Clarified that tumor evaluations would continue on schedule in the event of dose delays as per FDA request; Added information that LY3022855 must be reduced as part of the 1st dose reduction for a toxicity and further clarified that patients undergoing intra-patient dose escalation would not be allowed to escalate to a dose level beyond the MTD per FDA request; Added specification that vemurafenib and cobimetinib may be reduced per FDA prescribing information; Edited expected toxicities for clarity; Edited section 11 to include definition of evaluable disease for phase I enrollment purposes; Edited statistical section for clarity that the MTD will be defined in a minimum of 6 patients; General formatting updates to references to Tables/Sections throughout document.

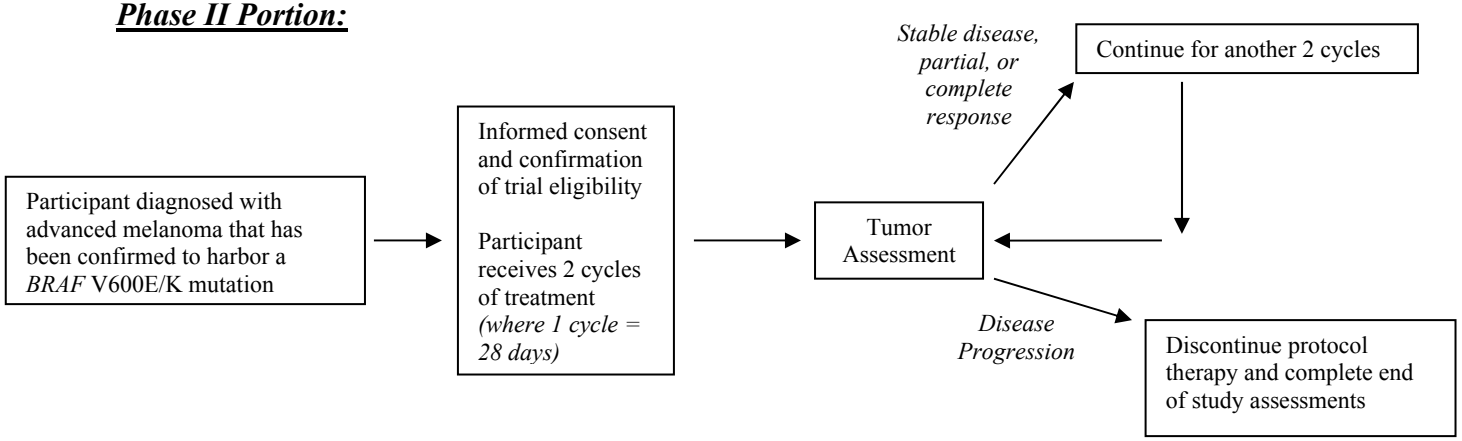
#	Section(s)	Change(s)
3.	Schema; 3.1.3; 5.1; 5.3.1; 13	Schema and Section 5.1 edited to reflect starting dose level of 50 mg for LY3022855 and removal of fallback dose level; Eligibility criterion 3.1.3 edited for clarity; Section 5.3.1 hypersensitivity reaction guidelines edited; Section 13 edited to reflect change in protocol sample size with altered dose levels.
4.	2.5.2; 2.6; 3.1.7; 7.1; 12.1.2; 12.2; Study Calendar	Protocol document edited to comply with DFCI departmental review comments.
5.	3.2.2	Clarification of washout for prior BRAF/MEK inhibitor therapy (applicable only to phase I participants).

SCHEMA

Phase I Portion:



Phase II Portion:



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1. OBJECTIVES

1.1 Study Design

This is an open-label phase I/II study looking at the combination of colony-stimulating factor-1 receptor (CSF-1R) inhibition using LY3022855 with BRAF/MEK inhibitor therapy using vemurafenib and cobimetinib. The BRAF and MEK inhibition will be maintained at standard dosing with the addition of the LY3022855 in a typical 3+3 trial design. Once the maximum tolerated dose (MTD) is reached and a recommended phase II dose (RP2D) is chosen, a single-arm phase II study in patients with *BRAF* mutant melanoma will move forward.

1.2 Primary Objectives

Phase I:

- To determine the MTD and RP2D of the combination of LY3022855 with vemurafenib and cobimetinib.

Phase II:

- To evaluate the progression-free survival (PFS) rate in patients with *BRAF* V600E or V600K mutated melanoma.

1.3 Secondary Objectives

Phase I:

- To evaluate the preliminary overall response rate (ORR) and PFS rate of LY3022855 with vemurafenib and cobimetinib in patients with melanoma harboring *BRAF* V600E or V600K mutations.

Phase II:

- To evaluate the ORR of the combination of LY3022855 with vemurafenib and cobimetinib in patients with *BRAF* V600E or V600K mutated melanoma.
- To evaluate the overall survival (OS) in patients with *BRAF* V600E or V600K melanoma to the combination of LY3022855 with vemurafenib and cobimetinib.
- To continue to evaluate the safety and tolerability of LY3022855 in combination with vemurafenib and cobimetinib.

1.4 Exploratory Objectives

- To investigate the effect of the combination of LY3022855 with vemurafenib and cobimetinib on mitogen-activated protein kinase (MAPK) pathway signaling and the immune tumor microenvironment via collection of blood, archival tumor tissue, and optional pre and on-treatment tissue biopsies obtained during both phases of the trial.
- To investigate the relationship between the levels of tumor DNA in serially collected plasma samples and the observed clinical outcomes during both phases

of the trial.

2. BACKGROUND

2.1 Study Disease

Melanoma is the most deadly form of skin cancer, with over 10,000 deaths estimated in 2016[1]. About 40 - 60% of cutaneous melanomas carry mutations in *BRAF* that lead to constitutive activation of downstream signaling through the MAPK pathway. Approximately 90% of these mutations result in the substitution of glutamic acid for valine at codon 600 (*BRAF* V600E), however other activating mutations are known to occur (e.g., *BRAF* V600K)[2,3].

BRAF inhibitor therapy with vemurafenib or dabrafenib has an improved overall survival in patients with *BRAF* mutations with an even larger effect observed when combined with MEK inhibition using trametinib or cobimetinib[2,4,5]. The response rate to the combination is 64 - 68%; however, these responses are of limited duration. The median PFS for combination BRAF/MEK inhibitor therapy is only 9.9 - 11.4 months. Progression on therapy is thought to occur primarily due to the development of acquired resistance through reactivation of the MAPK pathway[4,5].

2.2 LY3022855

CSF-1R is a receptor tyrosine kinase expressed on monocyte/macrophage and granulocyte cell lineages in normal as well as tumor cells[6,7]. When colony-stimulating factor-1 (CSF-1) or interleukin 34 (IL-34) binds to CSF-1R, the receptor is phosphorylated, initiating downstream signaling events which result in the regulation of proliferation, differentiation, survival and migration of monocytes/macrophages[8-10].

In cancer, increased infiltration of macrophages within and surrounding the tumor mass correlates with increased tumor invasiveness, growth, and poor prognosis. In breast, prostate, ovarian, and cervical cancer, there is a correlation between tumor-associated macrophages (TAMs) and poor prognosis[11-13]. Clinical evidence of TAM participation in tumor growth is corroborated in animal models where CSF-1R/CSF-1 signaling is inhibited or knocked out. Mice with null mutations in the CSF-1 gene have similar initiation rates of virally induced mammary tumors as normal mice, but the tumors do not progress to advanced carcinoma stages and the number of metastases are greatly reduced[14]. In addition to the effects of CSF-1R on macrophages, there are numerous reports of CSF-1R expression on cancer cells. For example breast, ovarian, endometrial, and leukemia cells of myeloid origin express CSF-1R and proliferate in response to CSF-1[6,15-18]. Targeting CSF-1R has the potential to limit cancer progression.

While CSF-1R levels are infrequently increased on tumor cells compared to analogous normal cells, increased CSF-1 ligand in sera of cancer patients is frequently observed and is associated with poor prognosis and severity of disease in multiple cancers[19,20]. This suggests that circulating CSF-1 modulates the stroma (i.e., macrophages) that contribute to tumor progression. For example, in breast cancer, CSF-1 expression correlated with increased leukocytic infiltration,

high tumor grade, and poor clinical outcome[21]. It is hypothesized that the CSF-1 produced by tumor cells suppresses dendritic cell maturation and recruits TAMs that are immunosuppressive, thus promoting angiogenesis and tumor growth[22]. The association of high levels of CSF-1 with poor prognosis in cancer patients may be a consequence of elevated CSF-1 production by tumor cells. Moreover, elevated CSF-1 levels in sera of cancer patients may be an indicator of individuals more likely to benefit from anti-CSF-1R treatment.

A recombinant human immunoglobulin type G1 (IgG1) that targets human CSF-1R, LY3022855 was originally identified from a screen of hybridoma candidates that were generated following immunization of MEDAREX HuMAb™ human immunoglobulin G (IgG)-transgenic mice with human CSF-1R expressing NIH-3T3 cells and soluble CSF-1R protein. The antibody comprises two identical gamma (γ) heavy chains and two identical kappa (κ) light chains.

Since LY3022855 does not inhibit murine CSF-1R, a recombinant rat IgG1 antibody specific for murine CSF-1R (designated as CS7) was developed and utilized as a surrogate antibody to evaluate the effects of targeting CSF-1R on macrophages in murine models of cancer. LY3022855 and CS7 were shown to inhibit the binding of both CSF-1 and IL-34 to human and mouse CSF-1R, respectively. In addition, LY3022855 and CS7 inhibited the phosphorylation both of their respective CSF-1R as well as of downstream signaling molecules. The effects of CS7 were evaluated in several mouse tumor models of cancer established with both human and murine tumor cells. Using CS7 as a single agent to target CSF-1R on macrophages effectively reduced tumor volume in three human xenograft breast cancer models and two syngeneic murine mammary cancer models. In line with the potential utility of LY3022855 as a combination therapy, CS7 increased the antitumor effects of targeted agents such as trastuzumab, doxorubicin, paclitaxel, and docetaxel in preclinical models. When comparing the effect of CS7 in a range of animal models, antitumor efficacy correlated with CSF-1-secreting tumors, supporting the potential use of CSF-1 levels as a predictor of responsiveness to therapy.

On the basis of the above non-clinical findings, LY3022855 was considered to be a candidate for clinical development as a treatment for cancer. A phase I trial to evaluate the safety, MTD, pharmacokinetics (PK), antitumor activity, immunogenicity, and pharmacodynamics (PD) of LY3022855 is currently ongoing.

2.2.1 Non-Clinical Studies

2.2.1.1 Pharmacokinetics

The pharmacokinetics (PKs) of LY3022855 were characterized in mice after a single intraperitoneal injection of 20 mg/kg and in cynomolgus monkeys after a single intravenous (IV) infusion at dose levels of 10, 40, and 140 mg/kg. The PKs of CS7 were evaluated in mice after a single intraperitoneal injection (20 mg/kg). CS7 was produced to validate the strategy of targeting CSF-1R in mouse cancer models because LY3022855 does not cross-react with mouse CSF-1R. The half-life ($t_{1/2}$) of LY3022855 in mice was 110.4 hours, approximately three-fold greater than that of CS7. However, in the IV single-dose cynomolgus monkey study, the $t_{1/2}$ of LY3022855 was greater than that observed in mice, ranging from 183.3 to 275.2 hours (group means). In the primate study, LY3022855 exposure was generally dose proportional. The group means volume of distribution (V_d) in the primate study ranged from 60.8 to 63.6 mL/kg,

indicating that the distribution of LY3022855 is limited to the vasculature. LY3022855 exposure was continuous throughout the duration of the primate study and no sex differences were observed. In the repeat-dose toxicology study, the PK parameters for LY3022855 after the administration of the first dose were consistent with the single-dose study (see **Table 1**).

Table 1: Single-Dose Pharmacokinetics of LY3022855

Study Type	Species	Dose (mg/kg)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (µg/mL)	C_{168hr} (µg/mL)	V_d (mL/kg)	$AUC_{0-168hr}$ (µg × hr/mL)
Single dose (CS7)	CD-1 mouse	20	33.6	24	117	ND	ND	10842[a]
Single dose (LY3022855)	CD-1 mouse	20	110.4	6	120	ND	ND	13956[a]
Single dose (LY3022855)	Cynomolgus monkey	10	183.3	0.26	282.0	83.5	60.8	21278.3
		40	275.2	0.31	1282.5	379.3	63.6	93490.8
		140	222.3	0.25	4010.0	1096.8	63.6	303127.0
Repeat dose (LY3022855)[c]	Cynomolgus monkey	20	NA[b]	0.75	525	136	NA[b]	32316
		60	NA[b]	0.75	1427	354	NA[b]	92053
		80	NA[b]	0.75	4394	1372	NA[b]	319455

Abbreviations: $AUC_{0-\infty}$ = area under the curve from time 0 to infinity; $AUC_{0-168hr}$ = area under the curve from time 0 to 168 hours; C_{168hr} = serum concentration at 168 hours; C_{max} = maximum serum concentration; NA = not applicable; ND = not determined; $t_{1/2}$ = half-life; T_{max} = time to maximum serum concentration; V_d = volume of distribution.

[a] $AUC_{0-\infty}$ (µg × hr/mL).

[b] Not applicable to the short sampling time.

[c] Pharmacokinetic parameters correspond to Dose 1.

In a repeat-dose monkey toxicology study, LY3022855 was administered to cynomolgus monkeys IV once weekly over four weeks via a 15 minute infusion at four different dose levels: 0 (control), 20, 60, and 180 mg/kg. The serum concentrations of LY3022855 were more sustained over the sampling period after the fourth dose compared with the first dose, with mean concentrations at 168 hours post dose ranging from 23 to 43% of the maximum serum concentration (C_{max}); time to maximum serum concentration (T_{max}) generally occurred by 1 hour post end of infusion. The group means $t_{1/2}$ after the fourth dose was between 158 and 470 hours among recovery animals. The group means V_d for recovery animals was between 29.2 and 51.2 mL/kg and indicated limited distribution beyond the vasculature. Exposure after the fourth dose was moderately higher than after the first dose, with accumulation ratios of approximately two for the area under the curve from time 0 to 168 hours ($AUC_{0-168hr}$) and 1.5 for C_{max}. The exposure parameters for the C_{max} and $AUC_{0-168hr}$ generally increased proportionally with the increase in dose level, and no notable sex differences were apparent (Table 2). Anti-LY3022855 antibodies (anti-drug antibodies [ADA]) were detected in 12 of 30 animals that were evaluated after administration of LY3022855. The apparent concentration of LY3022855 was reduced in two of the 12 animals compared with that of animals from the same dose group that were negative for ADA.

The concentration of CSF-1 increased in animals treated with LY3022855 in a similar manner to that observed in the single-dose primate study. After the first administration of LY3022855,

CSF-1 serum concentrations increased quickly between 0.5 and 24 hours post infusion but then increased only slightly until 168 hours post infusion. CSF-1 concentrations were comparable among all treatment groups after the first and fourth doses, suggesting that maximal increases in CSF-1 were achieved with the lowest dose level studied. The concentrations of CSF-1 were sustained during the study, as high levels were still present prior to the fourth dose administration. After the fourth dose, concentrations generally decreased after approximately 504 hours post infusion in the 20 mg/kg group and after approximately 672 hours post the end of infusion for the 60 mg/kg group. Exposure to CSF-1 was similar during the first and fourth doses, with no notable accumulation or sex differences.

Table 2: Multi-Dose Pharmacokinetics in Cynomolgus Monkeys

Study Type	Dose (mg/kg)	Sex	$t_{1/2}$ (hr)	T_{max} (hr)[c]	C_{max} (µg/mL)	C_{168hr} (µg/mL)	$AUC_{0-168hr}$ (µg × hr/mL)	V_d (mL/kg)
Repeat dose (LY3022855)[a]	20	Male	174	0.75	794	326	73817	29.9
		Female	143	0.5	818	265	61622	28.5
		Mean[b]	158	0.63	806	296	67719	29.2
	60	Male	371	0.75	2243	490	155518	64.7
		Female	116	0.75	2136	560	154775	29.1
		Mean[b]	243	0.75	2190	525	155146	46.9
	180	Male	420	1.25	7702	2924	677203	45.6
		Female	519	0.5	8269	2945	745477	56.8
		Mean[b]	470	1	7985	2935	711340	51.2

Abbreviations: $AUC_{0-168hr}$ = area under the curve from time 0 to 168 hours; C_{168hr} = serum concentration at 168 hours; C_{max} = maximum serum concentration; $t_{1/2}$ = half-life; T_{max} = time to maximum serum concentration; V_d = volume of distribution.

[a] Pharmacokinetic parameters correspond to Dose 4.

[b] Group (sex-combined) mean.

[c] Median value reported for T_{max}.

Metabolism and Disposition

Formal studies to characterize the metabolism and disposition of LY3022855 have not been conducted. As a monoclonal antibody, LY3022855 will be largely confined to the extracellular space, which is supported by data from numerous investigations and is consistent with the PK evaluation of LY3022855. No formal metabolism studies of LY3022855 have been performed because the catabolism of antibodies by mammalian systems is largely understood and formal studies of the metabolic degradation of these molecules are not warranted.

Excretion

Formal excretion studies of LY3022855 have not been conducted.

2.2.1.2 Safety Pharmacology and Toxicology

A standard non-clinical toxicology program for advancement of a monoclonal antibody into clinical trials in oncology indications was conducted to assess the safety and toxicity of

LY3022855. The non-clinical safety assessment of LY3022855 was conducted in cynomolgus monkeys. This species was considered a relevant model for the safety evaluation of LY3022855 based on a preliminary cross-species evaluation of tissue/receptor binding and/or functional *in vitro* pharmacological activity in human and cynomolgus monkey test systems and in a subsequent comprehensive tissue cross-reactivity study using full panels of monkey and human tissues. The toxicology studies conducted with LY3022855 included exploratory single-dose toxicity and toxicokinetic (TK) dose range-finding study and a pivotal four week repeat-dose Good Laboratory Practice toxicity, TK, and immunogenicity study with a six week recovery period.

Animals were administered LY3022855 by IV infusion, the intended clinical method of administration, using the dosing schedule (once weekly) in the planned initial clinical investigations of LY3022855. The pivotal study included evaluations of relevant safety pharmacology parameters. Due to an anticipated effect of LY3022855 on circulating levels of the target ligand, CSF-1, the level of CSF-1 was also measured in the study animals as a potential marker of the PD activity of the antibody. A thorough assessment of peripheral blood and spleen mononuclear cell subsets and an immunohistochemical analysis of CD68+ cells (cellular marker of monocytes/macrophages) in liver and spleen were also included to determine the effects that blockade of the CSF-1R might have on these endpoints.

Tissue Cross-Reactivity

A comprehensive tissue cross-reactivity study was conducted in cryosections of normal human and cynomolgus monkey tissues using a fluorescein isothiocyanate (FITC)-labeled form of LY3022855, designated LY3022855-FITC, applied to cryosections of normal human and cynomolgus monkey tissues at 2 concentrations (5 and 0.5 µg/mL).

The tissue-binding and distribution profile of LY3022855-FITC staining observed in the human and cynomolgus monkey tissue panels was generally consistent with reported sites of CSF-1R expression, and no important unexpected (i.e., off-target) binding was observed. Staining with LY3022855-FITC was present in the cytoplasm, cytoplasmic granules, and membrane granules of mononuclear cells and cells of myeloid and mononuclear phagocytic lineage. In human peripheral blood smears, staining of monocytes was observed. Additionally, staining of the cytoplasm and cytoplasmic granules of hematopoietic precursor cells was observed in one human bone marrow sample. In cynomolgus monkey kidney, cytoplasmic staining of glomerular tuft cells consistent with mesangial cells was present. In human placenta, staining of the cytoplasm, cytoplasmic granules, and membrane of trophoblastic epithelium was observed. Although CSF-1R is expressed mainly by cells of myeloid and mononuclear phagocytic lineage (e.g., macrophages, monocytes, and glomerular mesangial cells), expression has also been reported in cells of neuroepithelial lineage, including trophoblasts[23-25].

Single-Dose Toxicity

Single-dose administration of LY3022855 at dose levels of 10, 40, and 140 mg/kg administered by IV infusion over a 15 minute period was well tolerated in cynomolgus monkeys (two monkeys per sex per group) during the 14 day observation period. Sustained dose-proportional

exposure to LY3022855 was generally observed throughout the 14 day observation period at all dose levels following administration, with no apparent sex differences. A relatively long $t_{1/2}$ was observed for LY3022855, ranging from approximately 183 to 275 hours.

The key toxicological findings after a single administration of LY3022855 were elevations in serum transaminases (ALT and AST) and LDH on days 2, 7, and 15 following dosing. Elevations in ALT were generally minimal at the lowest dose level (10 mg/kg), whereas generally minimal to moderate elevations were observed in ALT at 40 and 140 mg/kg and in AST and LDH across all dose groups. The elevations in ALT, AST, and LDH observed on day 7 generally declined towards baseline levels in most animals by the end of the observation period, suggesting reversibility of these effects. No histological changes in the liver were noted to correlate with the increases in ALT, AST, and LDH, nor were any changes noted in liver functional parameters (i.e., alkaline phosphatase, bilirubin, or coagulation). Based on the small magnitude of the elevations and the absence of histological or functional changes, the increases in ALT, AST, and LDH were not considered adverse. Similar elevations in serum enzyme levels have also been observed when treating with other pharmacological agents targeting CSF-1R[26,27].

No other adverse clinical signs or effects on food consumption, body weight, hematology, or organ weights were associated with administration of LY3022855.

The no-observed-adverse-effect level (NOAEL) in this study was considered to be the highest dose tested, 140 mg/kg. This dose corresponded to a dosing day 1 mean serum concentration at 168 hours (C_{168hr}) of 1097 µg/mL, mean C_{max} of 4010 µg/mL, and mean $AUC_{0\text{-}168hr}$ of 303127 µg·hr/mL for males and females (**Table 3**).

Table 3: Single-Dose Toxicity and Toxicokinetics of LY3022855 in Cynomolgus Monkeys

Doses (mg/kg)	**10**	**40**	**140 (NOAEL)**
No. of animals	**2M / 2F**	**2M / 2F**	**2M / 2F**
C_{max} (µg/mL)[a,b] [M/F]	280.5 / 283.5	1335 / 1230	3820 / 4200
C_{168hr} (µg/mL)[a,b] [M/F]	87.3 / 79.7	370 / 388.5	953.5 / 1240
$AUC_{0\text{-}168hr}$ (µg × hr/mL)[a,b] [M/F]	21309 / 21248	92184 / 94798	284379 / 321875
Mortality	None	None	None
Noteworthy LY3022855-related findings	Non-adverse increase in ALT, AST, and LDH (reversible)	Non-adverse increase in ALT (reversible); Non-adverse increase in AST and LDH (reversible in most animals during the observation phase)	Non-adverse increase in ALT, AST, and LDH (partially reversible during the observation phase)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; $AUC_{0\text{-}168hr}$ = area under the curve from time 0 to 168 hours; C_{168hr} = serum concentration at 168 hours; C_{max} = maximum serum concentration; F = female(s); LDH = lactate dehydrogenase; M = male(s); No. = number; NOAEL = no-observed-adverse-effect level.

[a] Post dose, Day 1.

[b] LY3022855.

Multi-Dose Toxicity

In the pivotal repeat-dose toxicity, TK, and immunogenicity study of LY3022855, doses of 0 (control), 20, 60, and 180 mg/kg/dose of LY3022855 were administered by IV infusion once weekly to cynomolgus monkeys (5 monkeys per sex per group) for four weeks, followed by a six week recovery period. Standard toxicological and relevant safety pharmacology (cardiovascular, central nervous, and respiratory systems) endpoints were assessed. As in the single-dose study, circulating levels of CSF-1 were measured. A thorough assessment of peripheral blood and spleen mononuclear cell subsets and an immunohistochemical analysis of CD68+ mononuclear cells in liver and spleen were also conducted.

IV infusion of LY3022855 was generally well tolerated at all dose levels. Sustained dose-proportional to slightly-greater-than-dose-proportional increases in exposure to LY3022855 were observed, and no sex differences in exposure were apparent. Moderate accumulation (approximately two-fold) of LY3022855 occurred after repeated administration. ADA were detected in 12 of 30 animals treated with LY3022855 (six were positive after the first dose and an additional six were positive after the last dose). In two of the animals with ADA after the last dose, the presence of ADA appeared to decrease the concentration of LY3022855, thus impacting the TK analysis. The ADA in the other animals did not appear to affect serum LY3022855 concentrations.

As noted in the single-dose exploratory study, circulating concentrations of CSF-1 increased shortly after LY3022855 administration. CSF-1 was not detected in any control animals. In contrast to LY3022855, the concentration of CSF-1 did not vary with dose, as comparable maximum levels were reached in all three dose groups. Toward the end of the recovery period, CSF-1 levels generally decreased in the 20 and 60 mg/kg dose groups, but remained elevated in the 180 mg/kg dose group.

The key toxicological findings attributed to LY3022855 administration in this study were periorbital swelling, increases in serum transaminases as noted in the exploratory study, changes in leukocyte populations (monocytes, neutrophils, CD68+ mononuclear cells, natural killer [NK] cells), as well as target organ effects in the liver (Kupffer cell hypertrophy/hyperplasia), spleen (follicular hypertrophy/dendritic cell hyperplasia), and bone marrow (hypercellularity). The immunomodulatory effects on leukocytes, Kupffer cells, spleen, and bone marrow likely reflect an exaggerated pharmacological response to LY3022855, possibly associated with elevations in circulating CSF-1 levels noted during the study.

Elevations in ALT after the last dosing of LY3022855 were generally minimal in the lowest dose group (20 mg/kg) and minimal to moderate at the 60 and 180 mg/kg dose groups. AST levels were minimally to moderately increased in all dose groups. ALT and AST returned to baseline in the 20 mg/kg group and trended toward baseline in the 60 and 180 mg/kg groups during the recovery period, but remained increased in some individual animals compared with baseline. No histological changes in the liver were noted to correlate with the transaminase increases, nor were any changes noted in liver functional parameters (alkaline phosphatase, bilirubin, or coagulation). Based on the small magnitude of the elevations and the absence of histological or functional changes, the increases in ALT and AST were not considered adverse.

Increases in circulating white blood cells due to increases in neutrophils and monocytes were observed in both sexes at 60 and 180 mg/kg. Flow cytometry analysis of spleen and peripheral blood revealed increases in monocytes in spleen and blood at 60 and 180 mg/kg and reductions in splenic NK cells in all LY3022855 treated groups. Variability in NK cell numbers in the peripheral blood of animals in all dose groups (including control) precluded assigning a definitive relationship with LY3022855 treatment. These changes in white blood cell counts, in conjunction with minimal reversible increases in serum globulin concentrations with a corresponding decrease in albumin to globulin ratio, are consistent with the presence of an inflammatory response. However, no histopathological evidence of inflammation was observed. The monocyte, neutrophil, and globulin changes were reversible by the end of the recovery period, while the splenic NK cell reductions were still apparent in some animals. These changes were not considered adverse because of their small magnitude.

Anatomic pathology changes attributed to the administration of LY3022855 at the end of the dosing period included increased spleen weights in females in all dose groups, which generally correlated with splenic follicular hypertrophy (males at 60 and 180 mg/kg; females at 20 and 180 mg/kg), bone marrow hypercellularity (all female dose groups, 1 male at 60 mg/kg), bone marrow lymphoid aggregates (1 male, 1 female at 180 mg/kg), and Kupffer cell hypertrophy/hyperplasia (primarily minimal, all male dose groups, 1 female at 60 mg/kg). Immunohistochemical analyses confirmed the presence of increased size or number of CD68+ Kupffer cells in the liver and increased numbers of CD68+ mononuclear cells in the spleen at all dose levels. The CD68+ cells in the spleen were likely follicular dendritic cells. The immunohistochemical findings in liver and spleen generally correlated with the histopathological diagnoses of Kupffer cell hypertrophy/hyperplasia and splenic follicular hypertrophy. Similar anatomic pathology findings in spleen, liver, and bone marrow were observed after the recovery period. These changes were not considered adverse because of their small magnitude.

Slight to moderate periorbital swelling was observed primarily during the recovery phase in all LY3022855 treated groups (20, 60, and 180 mg/kg/dose). This clinical sign has been reported to occur in humans with another antibody to CSF-1 and may thus represent a delayed response to LY3022855 in the treated monkeys. Watery feces was observed only in the 60 mg/kg/dose animals, but is considered possibly related to the administration of LY3022855. These clinical signs were not considered adverse based on their limited impact to the overall health of the animal. No adverse effects were noted in assessments of the central nervous (neurological behavioral examination), respiratory (rate), or cardiovascular (heart rate, blood pressure, electrocardiogram) systems. In addition, no evidence of an adverse reaction or intolerance attributable to LY3022855 was apparent at the injection sites after IV infusion in the cynomolgus monkey repeat-dose toxicity studies.

Based on the absence of any definitive LY3022855 related adverse findings, the NOAEL for LY3022855 administered via 15 minute IV infusion weekly on four occasions was considered to be 180 mg/kg/dose. The dose corresponded to a dosing day 22 mean C_{max} of 7985 µg/mL, C_{168hr} of 2945 µg/mL, and mean $AUC_{0\text{-}168hr}$ of 711340 µg·hr/mL (**Table 4**).

Table 4: Multi-Dose Toxicity and Toxicokinetics of LY3022855 in Cynomolgus Monkeys

Doses (mg/kg)	20	60	180 (NOAEL)
No. of animals	5M / 5F	5M / 5F	5M / 5F
C_{max} (µg/mL)[a,b] [M/F]	794 / 818	2243 / 2136	7702 / 8269
C_{168hr} (µg/mL)[a,b] [M/F]	326 / 265	490 / 560	2924 / 2965
$AUC_{0\text{-}168hr}$ (µg × hr/mL)[a,b] [M/F]	73817 / 61622	155518 / 154775	677203 / 745477
Mortality	None	None	None
Noteworthy LY3022855-related findings	Periorbital swelling (recovery phase); Minimal non-adverse increase in ALT and AST (reversible); Decreased splenic NK cells; Increased spleen weight; minimal splenic follicular hypertrophy and dendritic cell hyperplasia, Kupffer cell hypertrophy/ hyperplasia, and bone marrow hypercellularity.	Periorbital swelling (recovery phase); watery feces; Minimal to moderate non-adverse increase in ALT and AST (partially reversible); Minimal increase in globulin and decreased A:G ratio (reversible); Increased neutrophils (blood) and monocytes (blood and spleen) [reversible]; Decreased splenic NK cells; Increased spleen weight; minimal splenic follicular hypertrophy and dendritic cell hyperplasia, Kupffer cell hypertrophy/ hyperplasia, and bone marrow hypercellularity.	Periorbital swelling (primarily recovery phase); Minimal to moderate non-adverse increase in ALT and AST (partially reversible); Minimal increase in globulin and decreased A:G ratio (reversible); Increased neutrophils (blood) and monocytes (blood and spleen) [reversible]; Decreased splenic NK cells; Increased spleen weight; minimal splenic follicular hypertrophy and dendritic cell hyperplasia, Kupffer cell hypertrophy/ hyperplasia, and bone marrow hypercellularity/ lymphoid aggregates.

Abbreviations: A:G = albumin to globulin (ratio); ALT = alanine aminotransferase; AST = aspartate aminotransferase; $AUC_{0\text{-}168hr}$ = area under the curve from time 0 to 168 hours; C_{168hr} = serum concentration at 168 hours; C_{max} = maximum serum concentration; F = female(s); M = male(s); NK = natural killer (cells); No. = number; NOAEL = no-observed-adverse-effect level.

[a] Post dose, Day 22.

[b] LY3022855.

2.2.1.3 Efficacy Pharmacology

A series of *in vitro* studies determined the pharmacodynamic (PD) properties of LY3022855 toward its target, CSF- 1R. LY3022855 bound in a dose-dependent manner to human CSF-1R and blocked CSF-1 and IL-34 binding in a solid-phase ligand-blocking assay. In addition to blocking ligand-induced receptor phosphorylation, LY3022855 inhibited ligand-induced phosphorylation of the downstream-signaling molecules AKT and MAP kinase in a CSF-1R transfected cell line. *In vitro* studies further demonstrated that LY3022855 inhibited monocyte proliferation and monocytic-to-macrophage differentiation.

LY3022855 does not cross-react with murine CSF-1R, and thus cannot be used in efficacy

studies in mice to explore the effects of targeting TAMs as a mechanism of inhibiting tumor growth. Therefore the surrogate rat monoclonal antibody CS7, which antagonizes murine CSF-1R, was identified. CS7 binds murine CSF-1R with high affinity (K_d = 0.8nM) and neutralizes CSF-1 binding activity in a solid-phase ligand-blocking assay. Cell-based assays utilizing RAW264.7 cells, a murine macrophage-like cell line, showed CS7 blocked activation of CSF-1R in a dose-dependent manner with similar efficacy to LY3022855. In addition, in the presence of CS7, monocytes failed to differentiate into macrophages and had reduced proliferative properties. Thus, CS7, by neutralizing activation of CSF-1R, can inhibit the proliferation and differentiation of murine monocytes into macrophages in a manner similar to LY3022855 acting on human monocytes/macrophages and is an appropriate surrogate antibody for *in vivo* studies.

Non-clinical PD studies with CS7 demonstrated the potential for CSF-1R targeted therapy in oncologic indications by reducing the number of TAMs in the tumor stroma and inhibiting the growth of tumor cells. Animal tumor model studies focused initially on breast cancer models because scientific literature indicates that breast cancers have high macrophage infiltration of the tumor stroma[28]. Also, CSF-1 is often highly secreted in breast cancer, and elevated circulating CSF-1 is an indicator of poor prognosis and high tumor grade[28]. Therefore, the hypothesis that the growth of tumors established with cell lines that secrete significant amounts of CSF-1 would be inhibited by an antibody targeting mouse CSF-1R (CS7) to a greater extent than tumors established with cell lines that express very little or no detectable CSF-1 was investigated. Two human breast cancer cell lines, MDA-MB-231LP-OSPT and HCC1954, were chosen for xenograft animal models because of their high CSF-1 secretion levels. In both tumor models, CS7 showed a statistically significant dose-dependent suppression of tumor growth over those animals treated with the rat IgG control antibody.

Staining of the tumor and surrounding stroma with a macrophage-specific antibody revealed a dramatic decrease in macrophage infiltration in both MDA-MB-231LP-OS-PT and HCC1954 tumor stroma. Thus, treatment of tumor-bearing animals with CS7 leads to a decrease in macrophage infiltration, as anticipated. Similarly, non-tumor bearing Balb/c mice treated with CS7 demonstrated a decrease in Kupffer cells (tissue-resident macrophages in liver) within two weeks of thrice-weekly administration.

To estimate target serum concentrations for efficacy in initial clinical investigations, trough concentrations associated with efficacy were determined in human breast cancer (HCC1954) and human leukemia (NKM-1) models established in mice. LY3022855 was evaluated in the leukemia model established following IV injection of CSF-1R expressing NKM-1 cells. The rat surrogate, CS7, was used in the breast cancer model established following subcutaneous injection of CSF-1R negative HCC1954 cells. The results from the two studies identified markedly different efficacious concentrations for the antibodies in the different models. The human NKM-1 model appeared very sensitive to the anti-tumor effect of LY3022855, as efficacy was achieved at mean trough concentrations down to 0.2 µg/mL. For CS7, notably higher doses and concentrations were required to inhibit human HCC1954 breast cancer tumor growth, as a mean trough concentration of 425 µg/mL was associated with efficacy. Because the initial clinical investigation was in solid tumors, the higher concentration is regarded as a conservative target concentration for efficacy.

2.2.2 Clinical Studies

As of 28 January 2016, data are available from 43 patients who have received treatment in two Lilly-sponsored phase I studies of LY3022855 (Study I5F-IE-JSCA hereby referred to as JSCA and Study I5F-MC-JSCB hereby referred to as JSCB), as summarized in Table 5. A third Lilly-sponsored phase Ia/Ib study of LY3022855 (JSCC) will be initiated in 2016; no patients have been treated as of 28 January 2016. Please refer to the most recent investigator's brochure (IB) for further information.

Table 5: Lilly-Sponsored Clinical Studies

Study Number and Title	Study Design	Treatment Regimen	Number of Patients Treated and Study Status
15F-IE-JSCA (JSCA) Phase I Study of LY3022855, a Monoclonal Antibody Targeted to the CSF-1 Receptor (CSF-1R), in Patients With Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Is Available	Phase I, single-agent (monotherapy), dose-escalation study	LY3022855 administered by IV infusion at the following dosages: Part A (weight-based dosing): **Cohort 1** - 2.5 mg/kg weekly **Cohort 2** - 0.3 mg/kg weekly **Cohort 3** - 0.6 mg/kg weekly **Cohort 4** - 1.25 mg/kg every 2 weeks **Cohort 5** – 1.25 mg/kg weekly Part B (non-weight based dosing): **Cohort 6a** – 100 mg weekly (completed) **Cohort 7a** – 150 mg weekly (ongoing)	Study is ongoing.
I5F-MC-JSCB (JCSB) Phase I Study to Identify the Immunomodulatory Activity of LY3022855 (IMC-CS4) in Patients with Advanced, Refractory Breast or Prostate Cancer	Phase I, single-center, open-label, nonrandomized, noncontrolled study	LY3022855 administered by IV infusion at the following dosages: **Dosage A** - 1.25 mg/kg every 2 weeks **Dosage B** - 1 mg/kg on weeks 1, 2, 4, and 5 of every 6 week cycle	Study is ongoing.
15F-MC-JSCC A Phase Ia/Ib Trial Investigating the CSF-1R Inhibitor LY3022855 in Combination with Durvalumab (MEDI4736) or Tremelimumab in Patients with Advanced Solid Tumors	Phase 1a/1b, multicenter, nonrandomized, open-label, dose-escalation study followed by dose expansion (5 disease specific expansion cohorts) of IV LY3022855 in combination with IV	In Part A (Dose Escalation, Phase 1a) of the study, LY3022855 QW, in combination with Durvalumab Q2W or Tremelimumab Q4W (after 6 doses, tremelimumab Q12W until discontinuation), is planned. Part B (Disease-Specific Expansion, Phase 1b) of the study will include 5 expansion cohorts. Patients will be treated at the MTD identified for each combination in	Study is ongoing.

	durvalumab or IV tremelimumab in patients with advanced cancer.	Part A, unless otherwise specified by the sponsor.	

2.2.2.1 Pharmacokinetics

As of 28 January 2016, LY3022855 serum concentrations for non-compartmental analysis were available from 27 patients enrolled in Study JSCA within 5 Cohorts: 0.3 mg/kg QW (n=4), 0.6 mg/kg QW (n=3), 1.25 mg/kg QW (n=5), 1.25 mg/kg Q2W (n=9), and 2.5 mg/kg QW (n=6), and from 14 patients enrolled in Study JSCB within 2 Cohorts: 1.25 mg/kg Q2W (n=9) and 1 mg/kg on Weeks 1, 2, 4, and 5 of every 6-week cycle (n=5). Note that for patients in Study JSCA Cohort 4 and Study JSCB, only nominal time data (i.e., the intended sample collection time, rather than the actual collection time) were available.

In addition to non-compartmental analysis, LY3022855 PK data were analyzed using a PK modeling approach. LY3022855 in cancer patients exhibited moderate total body clearance (CL) (mean values on Day 1 ranged from 0.0378 to 0.0651 L/h), low volume of distribution at steady state (V_{ss}) (mean values on Day 1 ranged from 2.85 to 4.93 L) and moderate $t_{1/2}$ (mean values on Day 1 ranged from 30.8 to 92.2 hours).

While the values for CL and $t_{1/2}$ appeared to be slightly larger and smaller, respectively, than those typically observed for an IgG1 monoclonal antibody, the estimates of both CL and $t_{1/2}$ were likely confounded by the limited sampling period (between 168 hours and 336 hours, dependent on dosing frequency), and the high incidence of samples reported as below the quantifiable lower limit of the assay (BLQ) at lower doses.

By comparison of the non-compartmental PK parameters across each dose cohort, the CL ofLY3022855 appeared to be non-linear with respect to LY3022855 concentration, with higherdoses of LY3022855 exhibiting lower CL values. Non-linearity of LY3022855 CL with respect to concentration was also observed in the model structure used for the PK/PD modeling analysis. However, this apparent non-linearity was confounded by the high incidence of concentrations reported as BLQ which could artificially inflate the calculated CL at lower doses.

The intra-patient accumulation ratio (R_A) for the 2.5-mg/kg QW regimen (1.97) was approximately twice that observed for the 1.25-mg/kg Q2W regimen (0.998). While this was approximately equal to the difference in the theoretical calculated accumulation index for a molecule with a 7-day $t_{1/2}$ which was dosed QW versus Q2W, the 2 cohorts also received different dose levels, and thus the potential effect of dose non-linearity in CL on this difference in R_A could not be disregarded.

An apparent lack of relationship between patient body weight and LY3022855 CL resulted in an amended dose escalation plan for Study JSCA to evaluate the safety, PK, and immunogenicity of LY3022855 using a flat dosing approach (i.e., mg as opposed to mg/kg). Please see IB for further information.

2.2.2.2 Pharmacodynamics

All patients receiving LY3022855 in Study JSCA exhibited elevated serum CSF-1 and IL-34 levels, suggesting CSF-1R target engagement across a 0.3 to 2.5-mg/kg dose range. The extent of serum CSF-1 and IL-34 elevation increased with increasing dose. The duration of serum CSF-1 and IL-34 elevation was dependent on dosing frequency, where dosing every week yielded increased and sustained serum CSF-1 and IL-34 elevations over dosing every 2 weeks. At higher serum concentrations of LY3022855 (i.e., higher doses and earlier time points), inter-individual variability in patient CSF-1 PD response was reduced.

In addition, inhibition of non-classical $CD14^{dim}CD16^{bright}$ monocytes occurred with increasing dose and was sustained with increased dosing frequency, where dosing every week yielded increased and sustained suppression of $CD14^{dim}CD16^{bright}$ monocytes over dosing every 2 weeks. This indicated that sustained target engagement yielded sustained biological response, as measured by inhibition of $CD14^{dim}CD16^{bright}$ monocytes.

2.2.2.3 Pharmacokinetic/Pharmacodynamic Model

Patients receiving LY3022855 across the dose range tested (0.3 to 2.5 mg/kg) exhibited increased levels of serum CSF-1 after single and multiple doses of LY3022855, with the extent of CSF-1 elevation increasing with increasing dose level and dosing frequency. Since CSF-1 is a ligand of CSF-1R, it is thought that the increase in serum concentrations of this marker showed evidence of CSF-1R target engagement. A PK/PD model was therefore developed to quantify the relationship between LY3022855 dose, LY3022855 serum concentrations, and serum CSF-1 levels.

The PK/PD dataset comprised PK and CSF-1 data which were available as of 28 January 2015. This dataset included 24 patients enrolled on Study JSCA: 2.5 mg/kg QW (n=6), 0.3 mg/kg QW (n=4), 0.6 mg/kg QW (n=3), 1.25 mg/kg Q2W (n=6) and 1.25 mg/kg QW (n=5). Rich sampling was performed for both PK and CSF-1 across single and multiple doses of LY3022855.

The PK of LY3022855 was characterized by a two-compartment model with non-linear clearance. The Michaelis-Menten constant (K_M) for non-linear LY3022855 clearance was approximately equal to 30 µg/mL, corresponding to doses above 1.25 mg/kg. However, this apparent non-linearity in CL may have been confounded by the high incidence of concentrations reported as BLQ which could have artificially inflated the calculated CL at lower doses.

LY3022855-mediated elevations of CSF-1 were best described by an indirect response model, where the action of LY3022855 was incorporated as inhibition of CSF-1 elimination. The model indicated potent and complete inhibition of CSF-1 elimination by LY3022855, and a steep concentration-response curve. The model-estimated LY3022855 concentration at which 50% inhibition of CSF-1 elimination occurs (IC_{50}) (approximately equal to 1.4 µg/mL) was lower than the PK assay limit of quantification, and thus the lowest dose that could sustain this LY3022855 concentration across the dosing period is not known, but is predicted to be as low as 0.3 mg/kg QW. However, model simulations showed that, of the doses tested, the 1.25-mg/kg QW dose was the lowest dose associated with sustained CSF-1 elevation across the dosing interval in the majority of patients.

Although the PK/PD model suggests complete inhibition of CSF-1 elimination by LY3022855, the extent of serum CSF-1 elevation continued to increase with increasing dose. The model suggests that this phenomenon is due to continued production of serum CSF-1, rather than insufficient inhibition of the target, CSF-1R.

2.2.2.4 Safety

Study JSCA

As of 09 September 2016 total of 369 patients have received LY3022855 in the phase I dose escalation study of LY3022855 in advanced solid tumors (study JSCA). This study is currently ongoing.

In cohort 1, two of the first three patients experienced Common Terminology Criteria for Adverse Events (CTCAE) grade 2 elevations of serum CPK, AST (Grade 1 - 2) and LDH. Due to these serum enzyme elevations and the general conditions of the patients involved, two of the first three patients enrolled did not complete cycle 1.

Per protocol, three additional patients were treated in cohort 1. These additional patients also exhibited elevated levels of CPK, AST, and LDH. In one patient, serum levels of CPK and AST reached grade 3; however, this was not classified as a dose-limiting toxicity (DLT) upon comprehensive clinical evaluation of the patient due to the lack of clinical signs and symptoms of organ toxicity. Furthermore, enzyme levels decreased upon discontinuation of LY3022855, indicating that these effects were reversible.

Since pre-clinical studies with LY3022855 in monkeys demonstrated a dose-response correlation between the dose of LY3022855 and the increase in serum enzyme levels, continued dose escalation in the JSCA trial was considered likely to result in a DLT. Therefore, it was considered medically prudent not to dose escalate beyond cohort 1 with the originally planned dosage schedule, which was 5, 10, 20, and 30 mg/kg once weekly. In order to better characterize the LY3022855 dose-response effect on the monocyte/macrophage system and on various serologic and hematologic parameters, the dosing scheme and schedule for study JSCA were revised to reflect dose reductions and prolonged administration intervals.

Under the revised dose-escalation plan, the dosages for subsequent dose explorations were as follows: cohort 2 (0.3 mg/kg QW), cohort 3 (0.6 mg/kg QW), Cohort 4 (1.25 mg/kg Q2W), Cohort 5 (1.25 mg/kgQW), and Cohort 6 (2.5 mg/kg Q2W). The addition of every-2-week dosing was considered appropriate based on the relatively long $t_{1/2}$ observed in cynomolgus monkeys.

In cohort 4, a DLT for LY3022855 was declared in one patient with a history of cardiac dysfunction who developed a grade 3 left ventricular systolic dysfunction after one dose of LY3022855. Two DLT events were observed in cohort 5: one patient developed grade 4 rhabdomyolysis and acute renal failure and one patient developed grade 3 pancreatitis. The original recommended phase II dose for LY3022855 was determined to be 1.25 mg/kg every 2

weeks. However, subsequent analysis of clinical data suggested sub-maximal target engagement on a Q2W schedule as opposed to QW dosing. Additionally, exploratory graphical analysis of the PK of LY3022855 in weight-based dosing Cohorts 1 to 5 indicated no clear relationship between body weight and drug clearance. Therefore, additional cohorts were added (Part B of the study) in a protocol amendment, Version 7.0, to evaluate safety, PK, and PD of non-weight based dosing of LY3022855 administered on a weekly schedule.

Study JSCB

Study JSCB is a Phase 1 study to identify the immunomodulatory activity of LY3022855 in patients with advanced, refractory breast or prostate cancer. As of the data cut-off date, 28 January 2016, 9 patients have been treated with 1.25 mg/kg LY3022855 Q2W of every 6-week cycle and 5 patients have been treated with 1 mg/kg LY3022855 on Weeks 1, 2, 4, and 5 of every 6-week cycle. Patients treated with 1.25 mg/kg LY3022855 Q2W were observed to have elevated CK, AST, and LDH levels. In 1 patient, serum levels of CK reached Grade 3 on 2 occasions. For each of these occasions, study drug was subsequently held and the event resolved. Please refer to the IB for more information. Enrollment to this study is ongoing.

Deaths

As of the data cut-off date of 28 January 2016, three deaths occurred on the JSCA study or within 30 days after the last dose of LY3022855. One death each, due to progressive disease, occurred in patients enrolled in the 0.3 mg/kg weekly dose cohort (cohort 2), 0.6 mg/kg weekly dose cohort (cohort 3), and 1.25 mg/kg weekly dose cohort (cohort 5). In addition, two deaths were reported post completion of the study. The patients died after more than 30 days of receiving the last dose of LY3022855 due to progressive disease. One of the patients was enrolled in the 0.3 mg/kg weekly dose cohort (cohort 2), and the other in the 1.25 mg/kg every 2 weeks dose cohort (cohort 4).No deaths occurred while patients were on study treatment in trial JSCB or within 30 days after the last dose of LY3022855, and no deaths were reported post completion of study participation.

Serious Adverse Events

As of the data cut-off date of 28 January 2016, Nine patients who received at least one dose of LY3022855 in study JSCA experienced a total of 15 treatment-emergent serious adverse events (SAEs): grade 2 toxicity to various agents and tremor, and grade 3 ascites (cohort 2, 0.3 mg/kg QW); grade 3 tachycardia, pneumothorax, and hypotension and grade 5 sudden death (cohort 3, 0.6 mg/kg QW); grade 3 left ventricular dysfunction, confusional state, and small intestinal obstruction (cohort 4 and the MTD expansion cohort, 1.25 mg/kg Q2W); and grade 2 fatigue and mental status changes, grade 3 pancreatitis, and grade 4 rhabdomyolysis and acute renal failure (cohort 5, 1.25 mg/kg QW).

Of these 15 SAEs, 8 SAEs reported in 5 patients were considered at least possibly related to LY3022855: tachycardia, hypotension, and sudden death (1 patient, Cohort 3); left ventricular dysfunction (1 patient, Cohort 3); rhabdomyolysis and acute renal failure (1 patient, Cohort 5); pancreatitis (1 patient, Cohort 5); and confusional state (1 patient, MTD expansion cohort). The

sudden death occurred after the patient had completed the DLT assessment period (i.e., had received all scheduled treatments for cycle 1 and completed the observation period, as needed). The treating investigator felt that the death was most likely related to disease progression of the underlying sarcoma.

In study JSCB, two patients with breast cancer who received at least 1 dose of LY3022855 (1.25 mg/kg Q2W) experienced 8 treatment-emergent SAEs: anemia, cardiomyopathy, confusional state, encephalopathy, femur fracture, hemorrhage, pain, and pain in the extremity (all Grade 3). Of the 8 SAEs, 2 SAEs (cardiomyopathy and encephalopathy) reported in 1 patient were considered by the investigator to be at least possibly related to LY3022855.

Treatment-Emergent Adverse Events

As of 28 January 2016, 28 of the 29 patients (96.6%) treated with LY3022855 in study JSCA experienced at least one treatment-emergent adverse event (TEAE). Please refer to the IB for a comprehensive list of adverse events. Of the 29 patients treated with LY3022855, 22 patients (75.9%) experienced at least one AE considered at least possibly related to treatment with LY3022855. This data is summarized below. The most commonly reported possibly study drug-related TEAEs (≥ 20% of patients) regardless of grade were fatigue, AST increased, and blood CPK increased, and nausea. Among all grade 3 and grade ≥ 4 AEs, the following AEs reported in a total of 7 patients (24.1%) were considered related to LY3022855: grade 3 AST increased and blood CPK increased (cohort 1); grade 3 hypotension, subcutaneous abscess, and tachycardia (cohort 3); grade 5 sudden death (cohort 3); grade 3 confusional state and left ventricular dysfunction (cohort 4 and the MTD expansion cohort); grade 3 hypophosphatemia and pancreatitis (cohort 5); and grade 4 acute renal failure and rhabdomyolysis (cohort 5).

In study JSCB, all 14 participants treated with LY3022855 experienced at least 1 TEAE. Twelve of 14 patients experienced at least 1 AE considered at least possibly related to treatment with LY3022855. The most common TEAEs considered to be at least possibly study drug-related (≥20% of patients), regardless of grade, were: fatigue, nausea, blood CPK increased, decreased appetite, diarrhea, lipase increased, and periorbital edema. The following Grade 3 AEs reported in 5 of 14 patients were considered at least possibly related to LY3022855: amylase increased, blood alkaline phosphatase increased, blood CPK increased, cardiomyopathy, and encephalopathy, and fatigue.

Of the 29 patients treated with LY3022855, 4 patients (13.8%) were discontinued from study drug due to AEs. One patient treated with LY3022855 at the weekly dose of 2.5 mg/kg (cohort 1) was discontinued from study drug due to the AEs of elevated CPK, AST, and LDH; all AEs were considered probably related to the study drug. One patient was discontinued from study drug due to cognitive disorder (considered unrelated to the study drug). Two patients treated with LY3022855 at the weekly dose of 1.25 mg/kg (cohort 5) discontinued study therapy due to acute renal failure (as a consequence of rhabdomyolysis) and pancreatitis that were probably and possibly related to study drug, respectively.

In study JSCB, no patient was discontinued from LY3022855 due to AEs.

Table 6: Related TEAEs by Cohort for Study JSCA Occurring in ≥ 2 Patients (N = 29)

	Cohort 1 (2.5 mg/kg QW) N = 6 n (%)			Cohort 2 (0.3 mg/kg QW) N = 4 n (%)			Cohort 3 (0.6 mg/kg QW) N = 3 n (%)			Cohort 4 (1.25 mg/kg Q2W) N = 11[a] n (%)			Cohort 5 (1.25 mg/kg QW) N = 5 n (%)			All Cohorts N = 29 n (%)		
Preferred Term	All Grades	Gr 3	Gr 4	All Grades	Gr 3	Gr 4	All Grades	Gr 3	Gr 4	All Grades	Gr 3	Gr 4	All Grades	Gr 3	Gr 4	All Grades	Gr 3	Gr 4
Patients with any AE	6 (100.0)	1 (16.7)	0	2 (50.0)	0	0	3 (100.0)	0	1 (33.3)	8 (72.7)	2 (18.2)	0	3 (60.0)	2 (40.0)	1 (20.0)	22 (75.9)	5 (17.2)	2 (6.9)
Fatigue	2 (33.3)	0	0	1 (25.0)	0	0	2 (66.7)	0	0	4 (36.4)	0	0	1 (20.0)	0	0	10 (34.5)	0	0
Aspartate aminotransferase increased	4 (66.7)	1 (16.7)	0	0	0	0	2 (66.7)	0	0	2 (18.2)	0	0	1 (20.0)	0	0	9 (31.0)	1 (3.4)	0
Blood creatine phosphokinase increased	4 (66.7)	1 (16.7)	0	0	0	0	1 (33.3)	0	0	2 (18.2)	0	0	0	0	0	7 (24.1)	1 (3.4)	0
Nausea	1 (16.7)	0	0	1 (25.0)	0	0	1 (33.3)	0	0	2 (18.2)	0	0	1 (20.0)	0	0	6 (20.7)	0	0
Decreased appetite	1 (16.7)	0	0	1 (25.0)	0	0	1 (33.3)	0	0	0	0	0	1 (20.0)	0	0	4 (13.8)	0	0
Diarrhoea	1 (16.7)	0	0	1 (25.0)	0	0	1 (33.3)	0	0	0	0	0	1 (20.0)	0	0	4 (13.8)	0	0
Hypoalbuminaemia	0	0	0	0	0	0	1 (33.3)	0	0	2 (18.2)	0	0	1 (20.0)	0	0	4 (13.8)	0	0
Blood lactate dehydrogenase increased	2 (33.3)	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	3 (10.3)	0	0
Lipase increased	0	0	0	0	0	0	0	0	0	2 (18.2)	0	0	1 (20.0)	0	0	3 (10.3)	0	0
Lymphopenia	1 (16.7)	0	0	0	0	0	0	0	0	1 (9.1)	0	0	1 (20.0)	0	0	3 (10.3)	0	0
Weight decreased	0	0	0	2 (50.0)	0	0	1 (33.3)	0	0	0	0	0	0	0	0	3 (10.3)	0	0
Hypophosphataemia	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (20.0)	1 (20.0)	0	2 (6.9)	1 (3.4)	0
Acute kidney injury	0	0	0	0	0	0	0	0	0	1 (9.1)	0	0	1 (20.0)	0	1 (20.0)	2 (6.9)	0	1 (3.4)
Amylase increased	0	0	0	0	0	0	0	0	0	1 (9.1)	0	0	1 (20.0)	0	0	2 (6.9)	0	0
Anaemia	0	0	0	0	0	0	1 (33.3)	0	0	1 (9.1)	0	0	0	0	0	2 (6.9)	0	0
Face oedema	2 (33.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (6.9)	0	0
Hypertension	2 (33.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (6.9)	0	0
Hypocalcaemia	1 (16.7)	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	2 (6.9)	0	0
Hyponatraemia	1 (16.7)	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	2 (6.9)	0	0
Muscular weakness	1 (16.7)	0	0	0	0	0	1 (33.3)	0	0	0	0	0	0	0	0	2 (6.9)	0	0
Pyrexia	0	0	0	0	0	0	1 (33.3)	0	0	1 (9.1)	0	0	0	0	0	2 (6.9)	0	0
Vomiting	1 (16.7)	0	0	1 (25.0)	0	0	0	0	0	0	0	0	0	0	0	2 (6.9)	0	0
White blood cell count decreased	2 (33.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (6.9)	0	0

[a] Includes 6 patients in Cohort 4 and 5 patients in an MTD expansion cohort at the same dose as Cohort 4.

Table 7: Related TEAEs by Cohort for Study JSCB Occurring in ≥ 2 Patients (Safety Population, N = 14)

	1.25 mg/kg Q2W (Breast Cancer) (N = 6) n (%)		1.0 mg/kg Weeks 1, 2, 4, and 5 (Breast Cancer) (N = 5) n (%)		1.25 mg/kg Q2W (Prostate Cancer) (N = 3) n (%)		Total (N = 14) n (%)	
Preferred Term	**All Grades**	**Gr 3**	**All Grades**	**Gr 3**	**All Grades**	**Gr 3**	**All Grades**	**Gr 3**
Patients with any AE	6 (100.0)	4 (66.7)	3 (60.0)	0	3 (100.0)	1 (33.3)	12 (85.7)	5 (35.7)
Fatigue	1 (16.7)	0	1 (20.0)	0	3 (100.0)	1 (33.3)	5 (35.7)	1 (7.1)
Nausea	2 (33.3)	0	0	0	2 (66.7)	0	4 (28.6)	0
Blood creatine phosphokinase increased	1 (16.7)	1 (16.7)	0	0	2 (66.7)	0	3 (21.4)	1 (7.1)
Decreased appetite	2 (33.3)	0	0	0	1 (33.3)	0	3 (21.4)	0
Diarrhoea	1 (16.7)	0	1 (20.0)	0	1 (33.3)	0	3 (21.4)	0
Lipase increased	2 (33.3)	0	0	0	1 (33.3)	0	3 (21.4)	0
Periorbital oedema	2 (33.3)	0	1 (20.0)	0	0	0	3 (21.4)	0
Alanine aminotransferase increased	2 (33.3)	0	0	0	0	0	2 (14.3)	0
Aspartate aminotransferase increased	2 (33.3)	0	0	0	0	0	2 (14.3)	0
Weight decreased	1 (16.7)	0	0	0	1 (33.3)	0	2 (14.3)	0

Abbreviations: AE = adverse event; Gr = grade; QW = once weekly; Q2W = once every 2 weeks; TEAE = treatment-emergent adverse event; N = number of patients in a specified cohort; n = number of patients with the event.

There were no Grade ≥4 related TEAEs reported.

2.2.2.5 Efficacy

No efficacy information is available as of 28 January 2016.

2.2.2.6 Drug Interactions

No formal drug interaction studies have been performed with LY3022855 in humans.

2.3 Vemurafenib

Vemurafenib is a low molecular weight, orally available inhibitor of some mutated forms of *BRAF* serine threonine kinase, including *BRAF* V600E. Vemurafenib also inhibits other kinases *in vitro* such as *CRAF, ARAF*, wild-type *BRAF, SRMS, ACK1, MAP4K5*, and *FGR* at similar concentrations. Some mutations in the *BRAF* gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated *BRAF* V600E.

Vemurafenib has been FDA approved for patients with unresectable or metastatic melanoma with a *BRAF* V600E mutation and is commercially available. Please reference the FDA package insert for background information. Agent will be administered per standard of care guidelines in accordance with institutional standards and the FDA prescribing information.

2.4 Cobimetinib

Cobimetinib (Cotellic) is a reversible inhibitor of MAPK/ MEK1 and MEK2. MEK proteins are upstream regulators of the extracellular signal related kinase (ERK) pathway, which promotes cellular proliferation. *BRAF* V600E and K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. In mice implanted with tumor cell lines expressing *BRAF* V600E, cobimetinib inhibited tumor cell growth.

Cobimetinib and vemurafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared to either drug alone, co-administration of cobimetinib and vemurafenib resulted in increased apoptosis *in vitro* and reduced tumor growth in mouse implantation models of tumor cell lines harboring *BRAF* V600E mutations. Cobimetinib also prevented vemurafenib-mediated growth enhancement of a wild-type *BRAF* tumor cell line in an *in vivo* mouse implantation model.

Cobimetinib has been FDA approved for patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation and is commercially available. Please reference the FDA package insert for background information. Agent will be administered per standard of care guidelines in accordance with institutional standards and the FDA prescribing information.

2.5 Rationale

The tumor microenvironment is known to play a role in innate or acquired resistance to BRAF inhibition[29,30]. Tumor cells can control the surrounding milieu by producing cytokines that suppress cytolytic T-cells and recruit immunosuppressive cells, and CSF-1 is one such cytokine that is secreted by melanoma. CSF-1 induces the proliferation and differentiation of immunosuppressive myeloid cells, such as M2 polarized macrophages and myeloid-derived suppressor cells (MDSCs), by binding to CSF-1R on the surface of the cell. This results in the ability of the tumor cell to evade the immune response and allows for subsequent metastasis[31].

Pre-clinical data by Mok et al. showed a dramatic reduction in tumor infiltrating myeloid cells when treated with CSF-1R inhibition. When this was combined with BRAF inhibition superior antitumor responses and increased tumor-infiltrating lymphocytes were observed[31]. Inhibitors to CSF-1R have been shown to deplete certain populations of TAMs and in established tumors, the combination of CSF-1R inhibitors with chemotherapy has been shown to dramatically enhance responses[32].

Additional pre-clinical data from Wang et al. demonstrated that macrophages play a role in resistance to BRAF inhibitor therapy through paradoxical activation of the MAPK pathway leading to increased production of vascular endothelial growth factor (VEGF). Targeting macrophages in a pre-clinical model led to increased tumor activity of BRAF inhibition in mouse and human tumor models[33]. These data together suggest that targeting macrophages in combination with BRAF inhibition in patients with melanoma may reduce baseline resistance and increase efficacy. Prior BRAF inhibition has also been shown to lead to increased TAMs, suggesting a potential role of combination therapy in patients with acquired resistance[34].

2.5.1 LY3022855 Flat Dosing Rationale

LY3022855 was initially dosed per body weight. However, Study JSCA (Version 7.0) was amended to explore a non-weight based dosing scheme based upon clinical data.

As of 14 August 2016, LY3022855 serum concentrations for non-compartmental analysis were available from 33 patients enrolled in Study JSCA within 7 cohorts: 0.3 mg/kg QW (N=4), 0.6 mg/kg QW (N=3), 1.25 mg/kg QW (N=5), 1.25 mg/kg every 2 weeks (Q2W) (N=11), 2.5 mg/kg QW (N=6), 100 mg QW (N=3), and 150 mg QW (N=1). The non-compartmental PK parameters stratified by dosing regimen and day of PK sample collection for Study JSCA are provided in **Table 8**. Mean LY3022855 serum concentration-time profiles on Day 1 and on Day 15 or 22 for Study JSCA are presented in **Figure 1.**

Table 8: Summary of Non-compartmental PK Parameters Following IV Infusion of Weight-Based and Non-Weight-Based of Dosing LY3022855 in Cancer Patients during Cycle 1 for Study JSCA

Geometric Mean (CV%)

Treatment	0.3 mg/kg QW	0.6 mg/kg QW	1.25 mg/kg QW	1.25 mg/kg Q2W		2.5 mg/kg QW		100 mg QW		150 mg QW
Cohort	2	3	5	4		1		6a		7a
Day	1	1	1	1	15	1	22	1	84 or 99	1
N	4	3	5	11	10	6	4	3	2	1
Parameter										
C_{168h}, µg/mL	NC	NC	(5.68 and 3.41)[a]	3.32 (11)[b]	3.35 (22)[c]	14.4 (34)	50 (25)[d]	(1.77 and 6.11)[a]	7.71[e]	NC
$C_{max,}$ µg/mL	6.83 (32)	13.5 (33)	26.0 (14)	30.7 (24)	30 (25)	69.2 (13)	92.7 (23)	34.6 (25)	(42.8 and 31.2)	42.7
t_{max}[f], h	0.01 (0.01-1.02)	2.02 (0.01-2.08)	1.01 (0.01-21.6)	0.01 (0.01-2)	1.00 (0.01-2)	0.75 (0.01-8.00)	0.97 (0.50-2.00)	0.960 (0.01-2)	(0.01 and 1.07)	2.02
$t_{1/2}$[g], h	30.9[d] (25.2-44)	30.8 (23.6-36.2)	58.3 (45.5-85.3)	41.4 (21.5-67.3)	46.9[h] (24.3-109)	85.0 (56.6-126)	196 (132-346)	48.2 (35.9-69.9)	82.8[e]	38.7
$C_{av,\tau}$, µg/mL	1.53[d] (15)	2.91 (24)	10.8 (21)	4.72 (50)	5.06[h] (49)	29.9 (18)	55.8 (41)	10.5 (28)	18.9[e]	13.2
$AUC_{(0-\infty)}$, h·µg/mL	264[d] (17)	500 (24)	2130 (28)	1600 (50)	1730[h] (52)	6860 (26)	21200 (73)	1970 (37)	4150[e]	2330
$AUC_{(0-\tau)}$[i], h·µg/mL	257[d] (15)	489 (24)	1810 (21)	1590 (50)	1700[h] (49)	5030 (18)	9370 (41)	1770 (28)	3170[e]	2220
CL, L/h	0.107[d] (21)	0.0720 (30)	0.0561 (31)	0.0559 (33)	0.0516[h] (36)	0.0378 (25)	0.0203 (34)	0.0566 (28)	0.0315[e]	0.0676
V_{ss}, L	4.71[d] (9)	3.15 (10)	4.72 (12)	3.39 (22)	3.37[h] (20)	4.67 (37)	5.70 (19)	3.88 (23)	3.68[e]	3.77
R_A	NC	NC	NC	NC	1.04[h, j] (18)	NC	1.82[c, k] (27)	NC	2.29[e, l]	NC

Abbreviations: $AUC_{(0-\tau)}$ = area under the concentration versus time curve from time zero to τ; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from time zero to ∞; C_{168h} = serum concentration collected 168 hours following the start of infusion; $C_{av,\tau}$ = average serum concentration over dosing interval calculated using $AUC_{(0-\tau)}$; CL = total body clearance; C_{max} = maximum

Table 8: Summary of Non-compartmental PK Parameters Following IV Infusion of Weight-Based and Non-Weight-Based of Dosing LY3022855 in Cancer Patients during Cycle 1 for Study JSCA

	Geometric Mean (CV%)									
Treatment	**0.3 mg/kg QW**	**0.6 mg/kg QW**	**1.25 mg/kg QW**	**1.25 mg/kg Q2W**		**2.5 mg/kg QW**		**100 mg QW**		**150 mg QW**
Cohort	2	3	5	4		1		6a		7a
Day	1	1	1	1	15	1	22	1	84 or 99	1
N	4	3	5	11	10	6	4	3	2	1

serum concentration; CV = coefficient of variation; h = hours; N = number of patients; NC = not calculable; Q2W = once every 2 weeks; QW = once weekly; R_A = intrapatient accumulation ratio; $t_{1/2}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration; V_{ss} = volume of distribution at steady-state.

[a] N=2; reported as individual parameter estimates.

[b] N=5.

[c] N=4.

[d] N=3.

[e] N=1; reported as individual parameter estimate.

[f] Median (Minimum – Maximum).

[g] Geometric Mean (Minimum – Maximum).

[h] N=9.

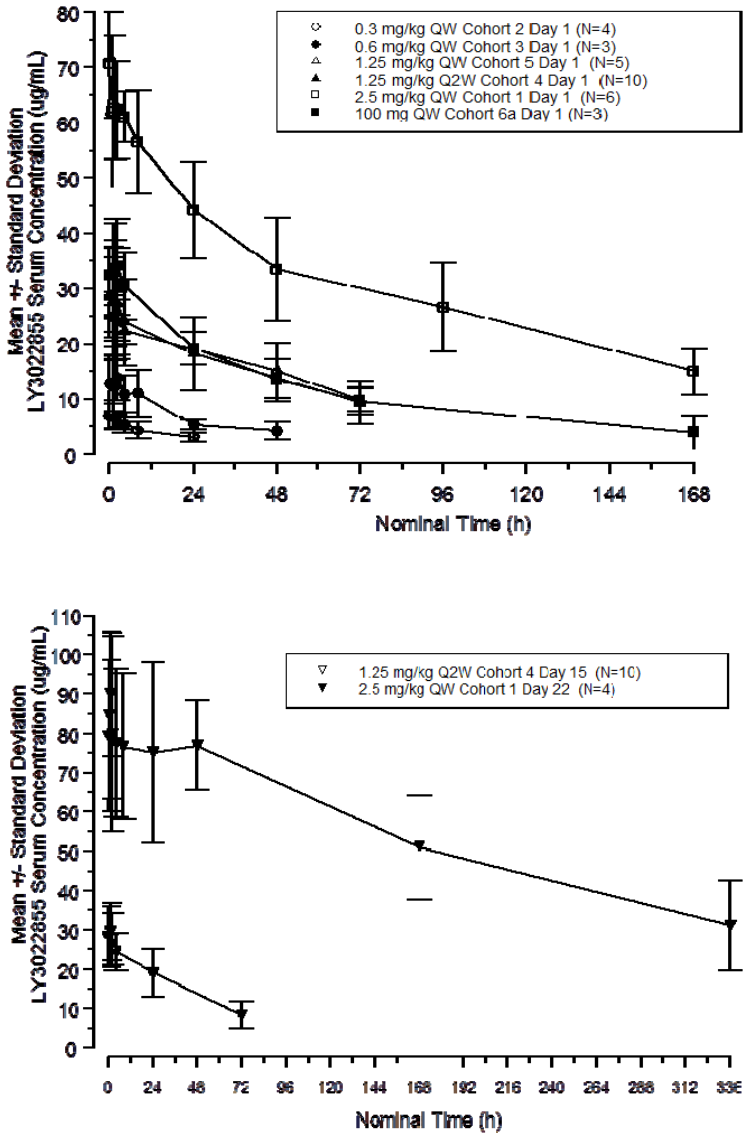
[i] τ = 168 h for QW regimen; τ = 336 h for Q2W regimen.

[j] $R_A = AUC_{(0\text{-}\tau),\text{day 15}} / AUC_{(0\text{-}\tau),\text{day 1}}$.

[k] $R_A = AUC_{(0\text{-}\tau),\text{day 22}} / AUC_{(0\text{-}\tau),\text{day 1}}$.

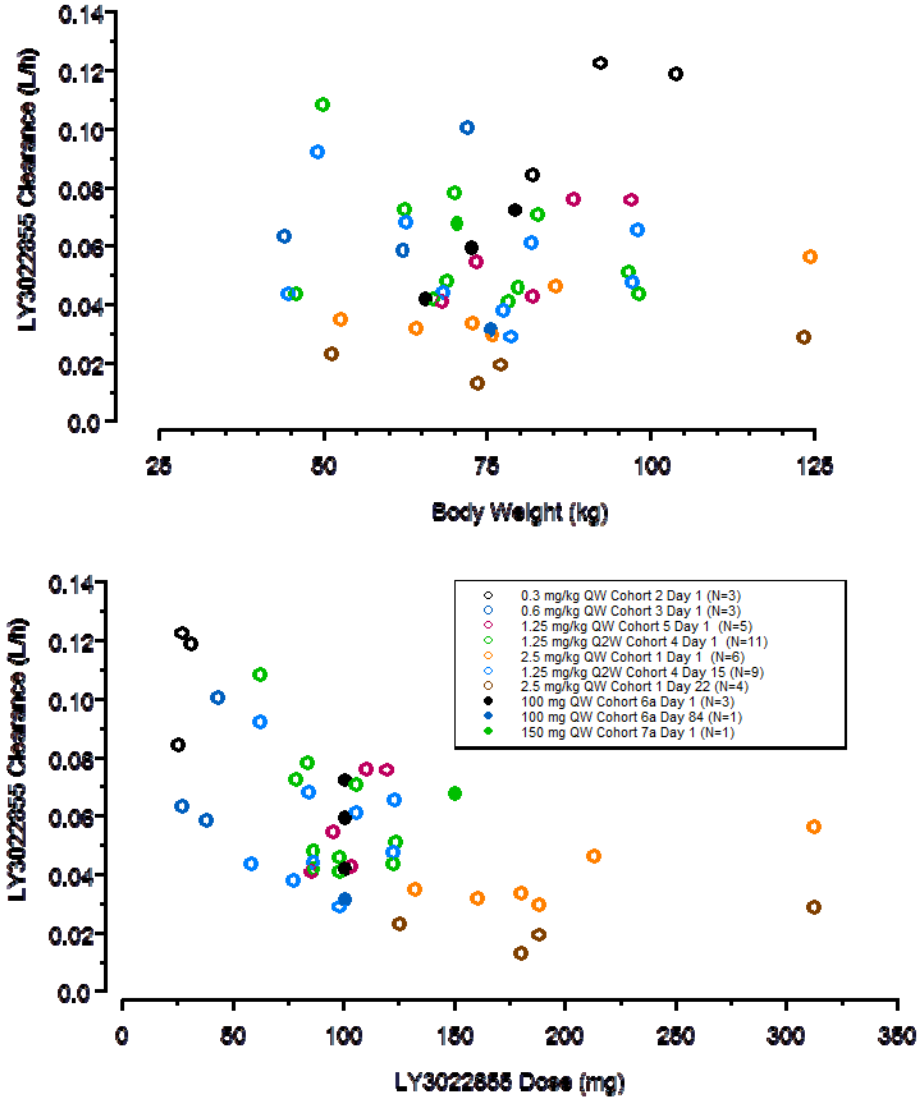
[l] $R_A = AUC_{(0\text{-}\tau),\text{day 84 or day 99}} / AUC_{(0\text{-}\tau),\text{day 1}}$.

LY3022855 in cancer patients exhibits pharmacokinetic properties consistent with those typically expected for an IgG1 antibody, with mean total body clearance (CL) after a single dose ranging from 0.0378 to 0.107 L/h, mean volume of distribution at steady state (V_{ss}) after a single dose ranging from 3.15 to 4.72 L, and mean half life ($t_{1/2}$) after a single dose ranging from 30.8 to 85.0 hours. LY3022855 CL appears to be non-linear with respect to dose, with higher doses of LY3022855 exhibiting lower CL values (**Figure 2**). These results are in accordance with the previous PK analysis for Cohorts 1 to 5, as detailed in the Investigator's Brochure.



Abbreviations: h = hours; N = number of patients treated; QW = once weekly; Q2W = once every 2 weeks.

Figure 1: Mean concentration-versus-time profiles for LY3022855 following intravenous administration to patients with cancer on Day 1 (upper panel) and on Days 15 and 22 (lower panel) for Study JSCA.



Abbreviations: N = number of patients treated; QW = once weekly; Q2W = once every 2 weeks.

Figure 2: Individual observed clearance versus patient body weight (upper panel) and LY3022855 dose (lower panel) for Study JSCA.

These updated results indicate an apparent lack of relationship between patient body weight and LY3022855 CL (**Figure 2**), consistent with previous analyses. Moreover, the PK of LY3022855 in patients receiving a non-weight-based dose of 100 mg QW (Cohort 6a) and the weight-based dose of 1.25 mg/kg QW (Cohort 5) appears comparable (**Figure 1**). The $AUC_{(0-\tau)}$, C_{max}, t_{max}, and $t_{1/2}$ values are consistent between the 2 cohorts, further demonstrating a lack of a relationship between patient body weight and serum LY3022855 concentration exposure. Taken together, these analyses provide support for the exploration of LY3022855 using a non-weight-based dosing approach.

Similar findings with monoclonal antibodies have been reported by others[35-38]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based

dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies[36]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/pharmacodynamic parameters[37].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens.

2.5.2 LY3022855 Flat Dosing Safety

Updated safety analyses for patients treated in the flat dosing cohorts for Study JSCA (data cut off date of 06 September 2016) are available; including 3 patients treated in Cohort 6a (100 mg weekly [QW]) and 3 patients treated in Cohort 7a (150 mg QW).

LY3022855 administered at a flat dose on a weekly schedule has not resulted in any adverse events that led to permanent discontinuation of study treatment. Only one patient who received flat weekly dosing of LY3022855 experienced an AE (elevated lipase) resulting in a dose reduction. The most common treatment emergent adverse events (all grades, with a minimum incidence of 33%) for patients treated with flat weekly dosing were: anemia (4 – 67%), nausea (3 – 50%), fatigue (3 – 50%), constipation (2 – 33%), lipase elevation (2 – 33%), hypoalbuminemia (2 – 33%), hypocalcemia (2 – 33%), and back pain (2 – 33%). The majority of these TEAEs were Grade 1 or 2. The incidence of Grade 3 events were: anemia (2 – 33%), nausea (0%), fatigue (2 – 33%), constipation (0%), lipase elevation (1 – 17%), hypoalbuminemia (0%), hypocalcemia (0%), and back pain (0%). A summary of all-cause serious treatment-emergent adverse events for flat doses are presented in the table below. Two patients treated at a dose of 100mg QW experienced 4 serious treatment-emergent AEs. One patient experienced an SAE of pulmonary hemorrhage (Medical Dictionary for Regulatory Activities Preferred Term [MedDRA PT]), and the second patient, experienced SAEs of abdominal discomfort, C-reactive protein increased, and upper gastrointestinal (GI) hemorrhage (all are MedDRA PTs).

No DLT events were reported for patients treated at a dosage of 100mg QW. One out of three patients treated at a dosage of 150mg QW experienced a DLT event of Grade 3 serum creatine kinase (CK) elevation associated with elevated urine and serum myoglobin. As a result of this one DLT, 3 additional patients are planned to be enrolled to the 150mg QW dose level.

Dose levels for LY3022855 in this protocol are detailed in **5.1** and are not planned to exceed the 100 mg weekly dose that has thus far been shown to be tolerable in study JSCA. As a result 50 mg QW is an appropriate initial dose for LY3022855 for this study.

Table 9: Study JSCA: Summary of Serious Treatment-Emergent Adverse Events for Flat Doses

Summary of Serious Treatment-Emergent Adverse Events for Flat Dose. - Study I5F-IE-JSCA/CP24-1001
Safety Population 13:51 07SEP2016
TDTM

	100 mg weekly (N=3) n(%)			150 mg weekly (N=3) n(%)		
SOC/Preferred Term	All Grades	Grade =3	Grade >=4	All Grades	Grade =3	Grade >=4
Patients with any AE	1 (33.3)	0	0	1 (33.3)	1 (33.3)	0
Gastrointestinal disorders	0	0	0	1 (33.3)	1 (33.3)	0
ABDOMINAL DISCOMFORT	0	0	0	1 (33.3)	1 (33.3)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	0	0	0	1 (33.3)	1 (33.3)	0
Investigations	0	0	0	1 (33.3)	0	0
C-REACTIVE PROTEIN INCREASED	0	0	0	1 (33.3)	0	0
Respiratory, thoracic and mediastinal disorders	1 (33.3)	0	0	0	0	0
PULMONARY HAEMORRHAGE	1 (33.3)	0	0	0	0	0

Note 1: For each SOC and Preferred Term, each patient was counted only once according to the worst grade of the TEAE.
Note 2: All Grades column includes patients with missing CTC grades as well.
Data cut-off date: September 6, 2016.

2.6 Correlative Studies Background

Use of immune and targeted therapies in patients with genomically complicated tumors presents a variety of confounding variables that could contribute to success or failure of the therapy. Correlative studies are designed to both enable better understanding of the possible reasons that LY3022855 in combination with vemurafenib and cobimetinib may prove to be effective or ineffective in individual patients, and to enable the development of more effective targeting strategies in the future.

Collection of Tumor Tissue

In order to retrospectively explore the determinants of response and resistance to LY3022855 combination therapy, archival tumor tissue will be collected at baseline from all patients enrolling to the trial. In addition, optional fresh tumor biopsies will be obtained from patients enrolled to either the phase I or phase II portion of the trial. These biopsies will be obtained on-treatment and again at the time of disease progression. The genetic and immune characteristics identified in the tumor tissue will be correlated to clinical outcome.

Analysis of tumor tissue samples taken at distinct points enables addressing of key questions including: (1) the genomic lesions and immune cell presence at baseline in samples studied and their potential impact upon response, (2) the identification of immediate pathways/gene expression programs activated by tumors following LY3022855 combination therapy, and (3) mechanisms of acquired resistance to therapy.

The first correlative question relates to the genetic and immune diversity of the patients enrolled in this study. It is the anticipation that most patients on this study will have had their tumor genomically characterized by either the OncoPanel test at DFCI/BWH (a custom hybrid capture panel which via next-generation sequencing will identify mutations and copy-number alterations in cancer associated genes) or via another CLIA-certified method at the time of enrollment. The archival tissue collected will be analyzed to look at the TAMs present at baseline. Macrophages are among the most abundant normal cells in the tumor microenvironment. Substantial evidence has indicated that macrophages adopt a pro-tumoral phenotype, suppressing T cell response and promoting tumor progression via angiogenesis, tumor cell invasion, motility, intravasation, and promotion of persistent growth[32]. The levels of certain TAMs present at baseline can be correlated to the clinical response observed with the combination therapy, and this data may enable us to identify immune characteristics that may also impact clinical response.

Another key rationale for performance of biopsies in patients after initiating drug therapy is to address mechanisms of resistance to LY3022855 combination therapy. The emergence of resistance to therapy is a profound problem in oncology. Such resistance can follow not only acquisition of secondary mutations but also from the ability of cancer cells to activate immediate compensatory signaling tracts following targeted inhibition of a key pathway[39]. Identification of these compensatory reactions is a necessary step in order to design subsequent rational therapies that may lead to even more durable and long-lasting clinical benefit. The optional on-treatment tissue samples will be examined for changes in MAPK activation as well as levels of TAMs and tumor immune infiltrates.

Optional biopsies obtained at the time of disease progression will be used to characterize the change in the tumor at the time of resistance. Such changes could stem from the acquisition of novel genomic alterations, from activation of other signaling pathways, or the production of anti-inflammatory and immunosuppressive mediators. Biopsies obtained at progression will be analyzed for MAPK reactivation, other mechanisms of resistance (e.g., alternate kinase domain mutations), and tumor immune infiltrates. The information collected from these biopsies will be vital to understanding the methods of resistance to the combination therapy and planning subsequent treatment strategies in this population.

Collection of Blood

Cell-free DNA (cfDNA) will be collected and analyzed for *BRAF* V600E or V600K mutations. Levels of tumor DNA will decline longitudinally over time if there is a response to the treatment administered. To further assess this concept, plasma will be collected from participants to evaluate whether circulating free plasma DNA declines with the administration of LY3022855, vemurafenib, and cobimetinib and this information will be compared to clinical outcome.

Blood samples will also be collected to look at circulating immune cells including MDSCs. MDSCs are a heterogeneous group of myeloid-derived cells which are greatly expanded in experimental models of cancer. Studies in humans carried out thus far have reported an increased frequency as well as immune-suppressive activity in some of the myeloid-derived subsets of MDSCs present in the peripheral blood of patients with cancer. In the case of metastatic melanoma, both monocytic as well as granulocytic blood MDSCs with immune-suppressive function have been studied independently and proposed to exert an immune-regulatory role[40]. To further explore the relationship of circulating immune cells including MDSCs and their potential correlation to clinical outcomes, peripheral blood levels will be serially collected from patients enrolled to the trial.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, echocardiogram, ophthalmologic exam, and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

3.1.1 For enrollment to the phase I portion: participants must have a histologically confirmed melanoma with a *BRAF* V600E or *BRAF* V600K mutation (identified via NextGen sequencing using the DFCI/BWH OncoPanel or any CLIA-certified method) that is metastatic or unresectable and for which standard curative measures do not exist or are no longer effective.

3.1.2 For enrollment to the phase II portion: participants must have a histologically confirmed melanoma with a *BRAF* V600E or *BRAF* V600K mutation (identified via NextGen sequencing using the DFCI/BWH OncoPanel or any CLIA-certified method) and cannot have received prior BRAF or MEK inhibitor therapy.

3.1.3 Participants enrolling to the phase I portion of the trial must have evaluable or measurable disease (see **11** for definitions).

3.1.4 Participants enrolling to the phase II portion of the trial 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 ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. See **11** for the evaluation of measurable disease.

3.1.5 Age ≥ 18 years. As no dosing or adverse event data are currently available in participants < 18 years of age, children are excluded from this study but will be eligible for future pediatric trials.

3.1.6 ECOG performance status 0 - 1 (see **APPENDIX A** PERFORMANCE STATUS CRITERIA).

3.1.7 Participants must have normal organ and marrow function as defined below:

– Absolute neutrophil count	≥ 1.5 K/uL
– Platelets	≥ 100 K/uL
– Hemoglobin	≥ 9 g/dL
– Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤ 2.5 × institutional ULN
– Serum creatinine	≤ 1.5 × institutional ULN
– PT-INR	≤ 1.5 × institutional ULN (for participants on anticoagulation therapy, ≤ 1.5 × their baseline value)
– aPTT	≤ 1.5 × institutional ULN (for participants on anticoagulation therapy, ≤ 1.5 × their baseline value)

3.1.8 Participants must have a left ventricular ejection fraction (LVEF) ≥ 50%.

3.1.9 Participants must have a QTc of ≤ 470 msec on the screening EKG.

3.1.10 The effects of LY3022855 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 4 months after completion of LY3022855 administration.

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

3.1.12 Participants must have archival tumor tissue available. Participants without archival tissue may be enrolled at the discretion of the principal investigator.

3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy, radiotherapy, biologic therapy, major surgery, or another investigational agent within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

3.2.2 For enrollment to the phase I portion: there is no required washout period for BRAF or MEK inhibitor therapy.

3.2.3 Participants who have not recovered to ≤ CTCAE grade 1 or baseline from toxicity as a result of previous cancer treatment prior to entering the study (with the exception of alopecia and peripheral neuropathy which can be ≤ grade 2).

3.2.4 For enrollment to the phase II portion: participants who have received prior BRAF or MEK inhibitor therapy.

3.2.5 Participants with known untreated 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. Participants with a history of brain metastases that have been treated, are no longer taking corticosteroids, and have been stable on imaging for ≥ 4 weeks following the last date of treatment are permitted.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to LY3022855, vemurafenib, or cobimetinib.

3.2.7 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.

3.2.8 Pregnant women are excluded from this study because LY3022855 is an anti-cancer agent 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 LY3022855, breastfeeding should be discontinued if the mother is treated with LY3022855. These potential risks may also apply to the other agents used in this study.

3.2.9 Participants with a known history of HIV are ineligible because of the potential for pharmacokinetic interactions with LY3022855, vemurafenib, and cobimetinib with antiretroviral agents. In addition, these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

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

3.2.11 Participants with a history of a second primary malignancy. Exceptions include: patients with a history of malignancies that were treated curatively and have not recurred within 3 years prior to study entry; resected basal and squamous cell carcinomas of the skin, and completely resected carcinoma *in situ* of any type.

3.2.12 Participants with impairment of GI function or GI disease that may significantly alter the absorption of vemurafenib and cobimetinib in the opinion of the treating investigator (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

3.2.13 Participants who are unable to swallow or retain oral medication.

3.2.14 Participants that require co-administration of strong or moderate CYP3A inhibitors, as these medications may alter vemurafenib and cobimetinib concentrations.

3.2.15 Participants who require treatment with medications that are strong or moderate CYP3A inducers, as these medications may alter the concentration of cobimetinib.

3.2.16 Participants with evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy (CSCR), retinal vein occlusion (RVO), or neovascular macular degeneration.

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 protocol therapy. Any participant not registered to the protocol before protocol therapy 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 therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Not Applicable.

4.4 Registration Process for Other Investigative Sites

Not Applicable.

5. TREATMENT PLAN

5.1 Treatment Regimen

The starting dose for the phase I portion of the trial will be dose level 1: LY3022855 50 mg IV weekly, vemurafenib 960 mg by mouth twice per day (BID), and cobimetinib 60 mg by mouth once daily on days 1-21 of the cycle. The dose escalation scheme is depicted in **Table 10**. One cycle is 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 **6.3**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy, with the exception of palliative radiation therapy or surgical resection to non-target lesions with prior permission from the principal investigator. Bisphosphonate use is permitted.

Table 10: Phase I Dose Escalation Schedule

Dose Level	Dose

	LY3022855	Vemurafenib	Cobimetinib
1 (Starting Dose Level)	50 mg IV weekly	960 mg BID	60 mg daily (taken on days 1-21)
2	75 mg IV weekly	960 mg BID	60 mg daily (taken on days 1-21)
3	100 mg IV weekly	960 mg BID	60 mg daily (taken on days 1-21)

Three patients will be enrolled to dose level 1. The maximum dose of LY3022855 to be evaluated in the triplet combination will not exceed the recommended phase 2 flat dose of singe-agent LY3022855. Enrollment to the dose level can occur in parallel with no observation period or delay between the start of therapy for each enrolled patient. The patients will be observed during the first cycle of therapy for toxicity consistent with a dose-limiting toxicity (DLT) definition, located in **5.4**.

Dose escalation will proceed in a standard 3+3 fashion according to the scheme in **Table 11**.

Table 11: Phase I Dose Escalation Decision Criteria

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the RP2D. At least 6 participants must be entered at the RP2D.

The maximally administered dose (MAD) of the study medications will be defined as the dose

level where at least two participants develop toxicities consistent with a DLT definition. In this situation, the dose level immediately below the MAD will be defined as the MTD. In the event that dose level 1 is found to be intolerable (with either 2/3 or ≥ 2/6 patients experiencing a DLT), the trial will be discontinued. In the situation where none of the dose levels have ≥ 2 DLTs, the MTD will be the highest dose administered (i.e. dose level 3). The MTD will be defined in a minimum of six patients.

In the event that dose level 3 is found tolerable (with ≤ 1 of 6 participants experiencing DLT); subsequent higher dose levels may be explored following a full protocol amendment as long as the LY3022855 dose does not exceed the identified RP2D of LY3022855 single-agent therapy. Upon declaring the MTD, the Overall Principal Investigator will review safety data generated during the phase 1 portion of the trial to decide the RP2D of the combination. This review will include a review of the DLTs that occurred among the dose levels in conjunction with toxicities experienced among participants beyond the DLT time frame. Once the RP2D has been defined, the phase II portion of the trial will begin with enrollment of 25 patients with either *BRAF* V600E or V600K mutant melanoma. Patients enrolling into the phase II portion of the trial will be treated at the RP2D for the combination identified during the phase I portion of the study.

Patients enrolled to the phase I dose escalation portion of the trial will be required to have received at least 75 percent of their doses of vemurafenib and cobimetinib, and must complete at least three of the four LY3022855 infusions during the first cycle to be considered evaluable for DLT purposes. Patients who do not meet these parameters during cycle 1 for reasons other than toxicity (for example, withdrawal of consent for participation on the trial, or rapid disease progression and subsequent removal from the trial) will be replaced.

Participants will be requested to maintain a study medication diary that will indicate each dose of oral medication taken to illustrate treatment compliance. The medication diary should be returned to appropriate research staff for review at the end of each treatment cycle.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Patients who completed screening assessments > 72 hours prior to cycle 1 day 1 should have cycle 1 day 1 laboratory values that re-meet eligibility criteria. If screening assessments were completed ≤ 72 hours 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.

5.2.2 Subsequent Cycles

Management of specific toxicities considered at least possibly related to the study regimen is outlined in **6.1**.

5.3 Agent Administration

5.3.1 LY3022855

LY3022855 will be given once per week on day 1, 8, 15, and 22 of the 28 day cycle. On days where LY3022855, vemurafenib, and cobimetinib are all to be given, order of administration does not matter.

LY3022855 will be administered via IV infusion. The first infusion should be scheduled to occur over 90 minutes (± 5 minute infusion window). If no infusion-related reaction occurs, the second infusion can be scheduled to occur over 60 minutes (±5 minute window). If no infusion-related reaction occurs, the third and all subsequent infusions can be given over 30 minutes (± 5 minute window).

Please see guidance regarding hypersensitivity reactions below. In the event that the infusion time takes longer than the above guidance (in the setting of a LY3022855 infusion-related reaction), this will not be considered to be in violation of the protocol; however, in all cases the infusion **must be completed within 4 hours of preparation**. The exact infusion time should be accurately recorded.

Only 0.9% normal saline should be used for dilution and post-infusion flushing of the infusion line. Post-infusion, the infusion line must be flushed with 0.9% normal saline, with a volume equal to or greater than the hold-up volume of the infusion line.

DO NOT FREEZE AND/OR SHAKE PREPARED LY3022855 DOSING SOLUTION FOR INFUSION.

LY3022855 should be handled according to standard procedures and precautions consistent with a cytotoxic anti-cancer drug.

Hypersensitivity Reactions

As with other monoclonal antibodies, infusion-related reactions may occur during or following LY3022855 administration. As a precaution, during the first cycle of treatment with LY3022855 patients should be monitored by the medical staff for signs and symptoms of an infusion-related reaction from the start of the infusion until at least one hour after the end of the infusion. Monitoring should occur in an area where resuscitation equipment and other agents (e.g., epinephrine, prednisolone or equivalents) are available. After completion of the first cycle, if no infusion-related reactions have occurred the post-infusion observation period may be discontinued.

Patients will not be premedicated prior to the first infusion of LY3022855. In the event of an infusion-related reaction, institutional guidelines for managing infusion reactions should be followed. In the case of a grade 1 infusion-related reaction, the infusion rate should be decreased by 50% for the duration of the infusion. In the event of a grade 2 infusion-related reaction, the infusion must be stopped until resolution to ≤ grade 1; the infusion may then be resumed at 50% of the prior infusion rate. Note that the infusion must be completed within 4 hours of preparation. Patients should be monitored for worsening of condition in case of a grade 1 or 2 infusion-related reaction. Once the

infusion rate has been reduced for a grade 1 or 2 infusion-related reaction, it is recommended to maintain the lower infusion rate for all subsequent infusions.

If the patient experiences a grade 1 or grade 2 infusion-related reaction, premedication should be provided prior to subsequent infusions. The exact premedication regimen will be per institutional standards and investigator discretion, and should include use of diphenhydramine hydrochloride 50 mg IV (or equivalent) administered prior to the infusion.

Patients who experience a ≥ grade 3 infusion-related reaction will be discontinued from protocol therapy.

5.3.2 Vemurafenib

Vemurafenib will be given as per package instructions. Vemurafenib should be taken orally every 12 hours. A missed dose can be taken up to 4 hours prior to the next dose. Doses that would be administered outside of that timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Vemurafenib can be taken with or without food. On days where LY3022855, vemurafenib, and cobimetinib are all to be given, order of administration does not matter.

5.3.3 Cobimetinib

Cobimetinib will be given as per package instructions. Cobimetinib should be taken orally once daily on days 1-21 of every 28 day cycle. For the purposes of this trial, there is a +/- 4 hour dosing window. Doses that would occur outside of this timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Cobimetinib can be taken with or without food. On days where LY3022855, vemurafenib, and cobimetinib are all to be given, order of administration does not matter.

5.4 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicity is based on version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). DLT refers to toxicities experienced during the first cycle of treatment that are possibly, probably, or definitely related to the study medication regimen. A DLT will be defined as follows:

- ≥ Grade 3 non-hematological toxicity. Exceptions will be made for:
  - Nausea, vomiting, diarrhea, or constipation that can be controlled with appropriate care. Grade 3 and grade 4 nausea, vomiting, diarrhea, or constipation should be considered a DLT if persisting more than 48 hours despite maximum supportive intervention.
  - Grade 3 rash or photosensitivity lasting fewer than 8 days, or that can be controlled with appropriate care. Grade 3 rash or photosensitivity should be considered a DLT if it persists for more than 8 days and cannot be managed despite maximum supportive

intervention.
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia
- ≥ Grade 3 febrile neutropenia
- Grade 4 anemia
- Holding of any study medication due to toxicity for a period of greater than 8 consecutive days or two separate periods of any duration during the first cycle.
- Any other significant toxicity deemed by the principal investigator to be dose limiting (for example, any toxicity that is at least possibly related to the study medication regimen that results in the withdrawal of the patient from the study during cycle 1).

Management and dose modifications associated with the above adverse events are outlined in **6.1**, **6.2**, and **6.3**.

5.5 General Concomitant Medication and Supportive Care Guidelines

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to antiemetics, antidiarrheals, and blood product transfusion.

Photosensitivity has occurred with use of both vemurafenib and cobimetinib. Patients on trial should be advised to avoid sun exposure, wear protective clothing, and use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors.

5.5.1 LY3022855 Guidelines

No formal drug interaction studies have been performed with LY3022855.

5.5.2 Vemurafenib Guidelines

CYP3A4 Inhibitors or Inducers: Vemurafenib is a substrate of CYP3A4 based on *in vitro* data; therefore, co-administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole).

Concurrent use of strong or moderate CYP3A inducers is prohibited at any point during the trial due to their effects on cobimetinib (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital).

CYP1A2 Substrates: Concomitant use of vemurafenib with drugs with a narrow therapeutic window that are predominantly metabolized by CYP1A2 is not recommended as vemurafenib may increase concentrations of CYP1A2 substrates. If co-administration cannot be avoided, monitor closely for toxicities and consider a dose reduction of concomitant CYP1A2 substrates.

P-gp Substrates: Co-administration of vemurafenib with digoxin, a sensitive P-gp

substrate, increased digoxin systemic exposure by 1.8-fold. Avoid concurrent use of P-gp substrates known to have narrow therapeutic indices. If use of these medications is unavoidable, consider dose reduction of P-gp substrates with narrow therapeutic indices.

Concentration-dependent QT prolongation occurred in an uncontrolled, open-label vemurafenib QT substudy in previously treated patients with *BRAF* V600E mutation-positive metastatic melanoma. Patients that require medications that are known to prolong the QTc interval should be changed to alternative drugs whenever possible. If in the opinion of the treating investigator, co-administration cannot be avoided, patients should be closely monitored for QT prolongation.

5.5.3 Cobimetinib Guidelines

CYP3A Inducers: Co-administration of cobimetinib with a strong CYP3A inducer may decrease cobimetinib systemic exposure by more than 80% and reduce its efficacy. For this reason, concurrent use of strong or moderate CYP3A inducers is prohibited at any point during the trial (medications including but not limited to phenytoin, carbamazepine, efavirenz, rifampin, and St. John's Wort).

CYP3A Inhibitors: Co-administration of cobimetinib with itraconazole (a strong CYP3A4 inhibitor) increased cobimetinib systemic exposure by 6.7-fold. During the phase I portion of the trial, co-administration of strong or moderate CYP3A inhibitors is prohibited. Following the phase I portion of the trial, avoid concurrent use of cobimetinib and strong or moderate CYP3A inhibitors where possible. If concurrent short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable for patients who are taking cobimetinib 60 mg, reduce cobimetinib dose to 20 mg. After discontinuation of a moderate CYP3A inhibitor, resume cobimetinib at the previous dose. Use an alternative to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of cobimetinib.

5.6 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 indefinitely or until one of the following criteria applies:

- Disease progression, unless the patient is deriving clinical benefit as agreed upon with the principal investigator
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) including those described in **5.4** and **6.1**
- 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.

For Centralized Subject Registrations, the research team submits a completed Off Treatment form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Dr. Elizabeth Buchbinder at DFCI pager number 40221.

5.7 Duration of Follow Up

Participants will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

5.8 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- 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).

For Centralized Subject Registrations, the research team submits a completed Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Specific Toxicity Management

Dose delays and modifications due to toxicity considered at least possibly related to LY3022855, vemurafenib, and/or cobimetinib will be made as indicated in the following tables. Please also see **6.2** and **6.3** for further guidance on allowed treatment delays and dose modifications:

Table 12: Management of Elevated AST/ALT

AST (SGOT) and/or ALT (SGPT) Increase	Medication Management
≤ Grade 2	No change.
Grade 3, ***increase lasting less than 8 days without evidence of other hepatic injury***	Hold study medications until resolution to ≤ grade 1 or baseline. Resume study medications at the same dose level.
Grade 3, ***increase lasting 8 or more days without evidence of other hepatic injury*** ***-OR-*** **Grade 4,** ***without evidence of other hepatic injury***	Hold study medications until resolution to ≤ grade 1; resume study medications with one dose level reduction.
≥ Grade 3, ***with evidence of other hepatic injury***	Discontinue protocol therapy.

Liver transaminase elevations have been associated with all three study medications in previous clinical trials. Patients should be monitored for increases in their liver function tests and for other signs of possible hepatic injury as clinically appropriate and as indicated in the Study Calendar – **Table 23**.

Table 13: Management of Neutropenia

Neutrophil Count Decrease	Medication Management
≤ Grade 2	No change.
Grade 3, ***no associated fever or infection*** ***-OR-*** **Grade 4,** ***decrease lasting less than 8 consecutive days***	Hold study medications until recovery to ≤ grade 2. Upon recovery, restart at the same dose level.
≥ Grade 3, ***associated with a fever or infection*** ***-OR-*** **Grade 4,** ***decrease lasting 8 or more consecutive days***	Hold study medications until recovery to ≤ grade 2. Upon recovery, resume with one dose level reduction.

Table 14: Management of Thrombocytopenia

Platelet Count Decrease	Medication Management
≤ Grade 2	No change.
Grade 3, *no clinically significant bleeding*	Hold study medications until recovery to ≤ grade 2. Upon recovery, restart at the same dose level.
Grade 3, *associated with clinically significant bleeding* ***-OR-*** **Grade 4**	Hold study medications until recovery to ≤ grade 2. Upon recovery, resume with one dose level reduction.

Table 15: Management of Rash or Photosensitivity

Rash or Photosensitivity	Medication Management
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., topical or oral antibiotics or steroids, use of protective clothing/sunscreen).
Grade 3, *not optimally managed or lasting fewer than 8 consecutive days*	Implement appropriate supportive care (e.g., topical or oral antibiotics or steroids). Hold study medications until recovery to ≤ grade 2. Upon recovery, restart at the same dose level.
Grade 3, *optimally managed or lasting 8 or more consecutive days* ***-OR-*** **Grade 4**	Hold study medications until recovery to ≤ grade 2. Upon recovery, resume with one dose level reduction.
**If a patient is experiencing intolerable grade 2 rash or photosensitivity despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.*	

Table 16: Management of QTc Increase (Associated with Vemurafenib)

QTc Interval Prolonged	Vemurafenib Management
≤ Grade 2	No change.
Grade 3, *increase is ≤ 60 msec from pre-treatment value*	Hold vemurafenib until recovery to ≤ grade 2. Upon recovery, restart with one dose level reduction.
Grade 3, *increase is > 60 msec from pre-treatment value* ***-OR-*** **Grade 4**	Discontinue vemurafenib.

Table 17: Management of Nausea

Nausea	Medication Management
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., antiemetics) as clinically indicated.
Grade 3, *not optimally managed*	Hold study medication and implement appropriate supportive care (including antiemetics and IV hydration if indicated). Upon resolution to ≤ grade 2, resume study medication at the same dose level.
≥ Grade 3, *optimally managed* ***-OR-*** **Grade 4**	Hold study medication until resolution to ≤ grade 2; resume study medication with one dose level reduction if ≥ grade 3 nausea persisted for more than 48 hours despite maximum supportive intervention.
**If a patient is experiencing intolerable grade 2 nausea despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication can be dose reduced at the treating investigator's discretion.*	

Table 18: Management of Vomiting

Vomiting	Medication Management
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., antiemetics) as clinically indicated.
Grade 3, *not optimally managed*	Hold study medication and implement appropriate supportive care (including antiemetics and IV hydration if indicated). Upon resolution to ≤ grade 1, resume study medication at the same dose level.
≥ Grade 3, *optimally managed* ***-OR-*** **Grade 4**	Hold study medication until resolution to ≤ grade 1; resume study medication with one dose level reduction if ≥ grade 3 vomiting persisted for more than 48 hours despite maximum supportive intervention.
**If a patient is experiencing intolerable grade 2 vomiting despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.*	

Table 19: Management of Diarrhea

Diarrhea	Medication Management
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., antidiarrheals) as clinically indicated.

Diarrhea	Medication Management
Grade 3, *not optimally managed*	Hold study medication and implement appropriate supportive care (including antidiarrheals and IV hydration if indicated). Upon resolution to ≤ grade 1, resume study medication at the same dose level.
≥ Grade 3, *optimally managed* ***-OR-*** **Grade 4**	Hold study medication until resolution to ≤ grade 1; resume study medication with one dose level reduction if ≥ grade 3 diarrhea persisted for more than 48 hours despite maximum supportive intervention.
**If a patient is experiencing intolerable grade 2 diarrhea despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.*	

Table 20: Management of Constipation

Constipation	Medication Management
≤ Grade 2	No change.* Implement appropriate supportive care (e.g., laxatives) as clinically indicated.
Grade 3, *not optimally managed*	Hold study medication and implement appropriate supportive care (including laxatives and enemas if indicated). Upon resolution to ≤ grade 2, resume study medication at the same dose level.
≥ Grade 3, *optimally managed* ***-OR-*** **Grade 4**	Hold study medication until resolution to ≤ grade 2; resume study medication with one dose level reduction if ≥ grade 3 constipation persisted for more than 48 hours despite maximum supportive intervention.
**If a patient is experiencing intolerable grade 2 constipation despite optimal medical management, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study medication may be dose reduced at the treating investigator's discretion.*	

Table 21: Management of Other Toxicity

Other Toxicity	Medication Management
≤ Grade 2	No change.*§
≥ Grade 3	Hold study medication. Upon resolution to ≤ grade 2, resume study medication with one dose level reduction. **
**If a patient is experiencing intolerable grade 2 toxicity, their study medication may be held at the treating investigator's discretion. Upon resolution to grade 1 or baseline, the study*	

medication can be dose reduced at the treating investigator's discretion.
***Patients who experience a ≥ grade 3 infusion-related reaction should be discontinued from protocol therapy.*
§If a patient is experiencing a new grade 2 or greater increase in CPK, both urine and serum myoglobin laboratory tests should be performed. Additional tests may also be performed or repeated at the treating investigator's discretion.

6.2 Treatment Delays

The study medications may be held for toxicity for up to four weeks before the participant must be removed from the study. Exceptions to this requirement are possible should the principal investigator agree that the patient may continue despite the length of time off drug.

Study medications may be held independently of each other if toxicity is felt by the treating investigator to be attributed to one or two of the three medications (e.g., a patient may continue to receive their LY3022855 on schedule while holding their vemurafenib and/or cobimetinib).

If the study medication(s) is/are placed on hold for toxicity, the counting of cycle days and assessment schedule will continue without interruption. For example, a patient who does not receive their cycle 2 day 15 infusion of LY3022855 due to toxicity will proceed with their next scheduled infusion and visit (cycle 2 day 22). Additional interim visits will be conducted as clinically necessary to manage toxicity. The cycle will not restart for dosing delays due to toxicity. Exceptions to this are possible for significant treatment delays (≥ 2 weeks) after a discussion with the principal investigator. If an exception is made to restart the cycle for a participant in the phase II portion of the trial, tumor evaluations should continue as previously scheduled (tumor evaluations should not be delayed).

6.3 Dose Modifications

The first dose reduction for any toxicity must include a reduction in LY3022855. Further dose reductions will be based on the offending medication(s) according to the schedule outlined in **Table 22**. In the event the treating investigator feels all three medications are responsible for the toxicity, all medications can be reduced. Dose reductions below 25 mg once per week of LY3022855 will not be permitted. Reductions below 480 mg BID of vemurafenib or 20 mg daily of cobimetinib will not be permitted.

A maximum of two dose reductions will be allowed with any one of the medications. If a patient requires more than two dose reductions with any one of the study medications, they should be discontinued from protocol therapy. Exceptions are possible in the event a patient is not tolerating the vemurafenib and/or cobimetinib despite maximal dose reductions but is deriving clinical benefit. In this circumstance, a patient may be allowed to continue on protocol therapy and receive LY3022855 either alone or in combination with just the vemurafenib or cobimetinib if agreed upon with the principal investigator.

Patients undergoing dose reductions for toxicities may not be re-escalated.

Participants enrolled to the phase I portion of the trial may undergo intra-patient dose escalation if subsequent higher dose levels are proven safe as per the guidelines in **5.1** and **5.4**. Participants may only undergo dose escalations to a dose level where ≤ 1 DLT have been observed among 6 patients, two dose levels below a dose level where < 1 out of 3 patients have experienced DLTs, or the dose level that has been declared the RP2D. Under no circumstances may a patient escalate to a dose level above the MTD. Patients must have been on study for at least two cycles with no DLTs or DLT-equivalent toxicity to be eligible for dose escalation.

Table 22: Dose Modifications

Original Dose Level	LY3022855 Reduction	Vemurafenib Reduction*	Cobimetinib Reduction*
1	1st Reduction: 25 mg weekly	1st Reduction: 720 mg BID	1st Reduction: 40 mg once daily
	2nd Reduction: Discontinue protocol therapy	2nd Reduction: 480 mg BID	2nd Reduction: 20 mg once daily
2	1st Reduction: 50 mg weekly	2nd Reduction: 720 mg BID	1st Reduction: 40 mg once daily
	2nd Reduction: 25 mg weekly	2nd Reduction: 480 mg BID	2nd Reduction: 20 mg once daily
3	1st Reduction: 75 mg weekly	1st Reduction: 720 mg BID	1st Reduction: 40 mg once daily
	2nd Reduction: 50 mg weekly	2nd Reduction: 480 mg BID	2nd Reduction: 20 mg once daily
*: Vemurafenib and cobimetinib may be reduced as per the FDA prescribing information			

6.4 Overdose management

There are no known antidotes for over-dosage of LY3022855, vemurafenib, or cobimetinib. In the case of suspected overdose, monitor hematologic parameters, serum chemistry, vital signs, cardiac function, and provide supportive care as necessary.

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 (**7.1**) and the characteristics of an observed AE (**7.2** and **7.3**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

Please refer to the FDA prescribing information for vemurafenib and cobimetinib, along with the IB for LY3022855 for the most comprehensive information regarding expected toxicities associated with treatment.

Reasonably anticipated serious adverse events for patients with advanced melanoma who receive LY3022855 include:

- Fatigue
- Nausea/vomiting/anorexia
- Diarrhea
- Elevation of hepatic transaminases
- Increases in LDH
- Increases in blood creatine phosphokinase
- Lymphopenia

Fatigue has been the most frequent toxicity reported following treatment with LY3022855, followed by elevation in hepatic transaminases and increases in blood creatine phosphokinase (CPK). Increased creatinine has been the most frequently reported AE for patients treated with the combination of vemurafenib and cobimetinib, followed by increased CPK, and liver transaminase increases.

Reasonably anticipated overlapping toxicities for the combination may include hepatotoxicity, CK elevations, and cardiomyopathy.

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 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 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 during this study 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.

Preplanned hospitalizations or procedures for preexisting 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 24 hours of the investigator and/or institution receiving notification of the SAE experienced by a

patient participating in the study. The SAE reports are to be sent to Eli Lilly via fax at 1-866-644-1697.

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) 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.

7.4.2 DF/HCC Expedited 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.

7.5 Expedited 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 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to 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 also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

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

8.1 LY3022855

8.1.1 **Description**

Molecular Structure: LY3022855 is an anti-CSF-1R recombinant human monoclonal antibody of the IgG1 class, composed of 4 polypeptide chains: 2 identical heavy (γ) chains consisting of 450 amino acids each, and 2 identical light (κ) chains consisting of 214 amino acids each. The heavy chain subunit contains 1 consensus glycosylation site for N-linked oligosaccharides at position N^{300} in the Fc region. There are no O-linked glycosylation sites.

Molecular mass: 148 kDa

pH: 6.0 at a concentration of 5 mg/mL

Osmolality: 293 mmol/kg

The LY3022855 active ingredient is an aqueous solution at a pH of approximately 6.0 at a concentration of 5 mg/mL. The monomeric purity of LY3022855 is > 90% by size-exclusion chromatography.

LY3022855 drug product is a sterile, preservative-free injection for infusion of LY3022855 formulated in an aqueous solution at a concentration of 5 mg/mL (100 mg/20 mL vial). The buffer contains 10mM histidine, 100mM glycine, 100mM arginine, and 0.01% polysorbate 80. LY3022855 drug product is a clear or slightly opalescent liquid, without visible particles. All excipients used for the manufacture of LY3022855 drug product are of pharmacopeial grade. No animal-derived components are used in the manufacture of LY3022855 drug product excipients.

8.1.2 **Form**

LY3022855 drug product is supplied in single-use, 20 mL nominal volume, United States Pharmacopeia (USP) Type I glass vials. Each vial contains 100 mg of LY3022855 at a concentration of 5 mg/mL in a sterile, preservative-free solution. Each vial is stoppered with a coated chlorobutyl latex-free rubber stopper and sealed with an aluminum seal and a flip-off cap.

8.1.3 **Storage and Stability**

LY3022855 Drug Product

The drug product must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) with protection from direct light. **DO NOT FREEZE AND/OR SHAKE LY3022855 DRUG PRODUCT.** Stability studies have demonstrated that the drug product can withstand transient excursion to room temperature without adverse effect; however, storage at this temperature is not recommended.

LY3022855 Prepared Dosing Solution for Infusion

Chemical and physical in-use stability for the prepared LY3022855 dosing solution has been demonstrated for up to 24 hours below 25°C (77°F). However, it is recommended that the prepared dosing solution be used immediately in order to minimize the risk of microbial contamination. If not used immediately, the prepared LY3022855 dosing solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 24 hours. If the prepared solution is held at room temperature (below 25°C [77°F]) it must be used within 4 hours. Store protected from light. Brief exposure to ambient light is acceptable while preparation and administration is taking place. **DO NOT FREEZE AND/OR SHAKE PREPARED LY3022855 DOSING SOLUTION FOR INFUSION.**

8.1.4 Compatibility

The following have been found to be compatible for LY3022855 drug product infusion:

- A polyethylene-lined PVC infusion set with a 0.22-µm downstream high-pressure, protein-sparing in-line filter made of polyethersulfone of 10-cm^2 surface area
- A PVC (with di(2-ethylhexyl)phthalate) infusion set with a 0.2-µm protein-sparing filter made of polyethersulfone of 4.2-cm^2 surface area
- A polyethylene-lined PVC infusion set with a 0.2-µm protein-sparing in-line filter made of polyethersulfone of 10-cm^2 surface area
- A polyurethane infusion set with a 0.2-µm protein-sparing in-line filter made of polyethersulfone of 10-cm^2 surface area
- A polybutadiene tubing with 0.2-µm in-line filter made of polysulfone of 9-cm^2 surface area

Only 0.9% normal saline should be used for dilution and post infusion flushing of the infusion line.

8.1.5 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.

8.1.6 Availability

LY3022855 is an investigational agent that will be supplied by Eli Lilly and Company.

8.1.7 **Preparation**

The dose of LY3022855 should be aseptically withdrawn from the vial and transferred to a sterile IV container. LY3022855 is compatible with infusion containers composed of polyolefin, polyvinyl chloride (PVC), ethylene vinyl acetate, and evacuated glass (USP Type II or local equivalent). An infusion bag composed of polyolefin, polypropylene, and polyethylene prefilled with 0.9% sodium chloride injection, such as AVIVA, may also be used.

To administer using pre-filled IV infusion containers:
Calculate the respective dose and remove the corresponding volume of 0.9% normal saline from the prefilled 250 mL container of the correct composition. Aseptically transfer the calculated dose of LY3022855 drug product to the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix.

To administer using empty IV infusion containers:
Aseptically transfer the calculated dose of LY3022855 drug product into an empty IV container of the correct composition and add a sufficient quantity of sterile normal saline (0.9% weight/volume) to the container to bring the total volume to 250 mL. Gently invert the container to mix.

For dose volumes greater than 250 mL, the addition of sterile normal saline is not required. Only 0.9% normal saline should be used for dilution and post infusion flushing of infusion line. Post infusion, the infusion line must be flushed with 0.9% normal saline, with a volume equal to or greater than the hold-up volume of the infusion line.

Different lot numbers of LY3022855 must not be mixed in a single infusion.

8.1.8 **Administration**

LY3022855 will be given once per week on day 1, 8, 15, and 22 of the 28 day cycle. On days where LY3022855, vemurafenib, and cobimetinib are all to be given, order of administration does not matter.

LY3022855 will be administered via IV infusion. The first infusion should be scheduled to occur over 90 minutes (± 5 minute infusion window). If no infusion-related reaction occurs, the second infusion can be scheduled to occur over 60 minutes (±5 minute window). If no infusion-related reaction occurs, the third and all subsequent infusions can be given over 30 minutes (± 5 minute window).

Only 0.9% normal saline should be used for dilution and post-infusion flushing of the infusion line. Post-infusion, the infusion line must be flushed with 0.9% normal saline, with a volume equal to or greater than the hold-up volume of the infusion line.

DO NOT FREEZE AND/OR SHAKE PREPARED LY3022855 DOSING SOLUTION FOR INFUSION.

LY3022855 should be handled according to standard procedures and precautions consistent with a cytotoxic anti-cancer drug.

8.1.9 Ordering

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

8.1.10 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.)

8.1.11 Destruction and Return

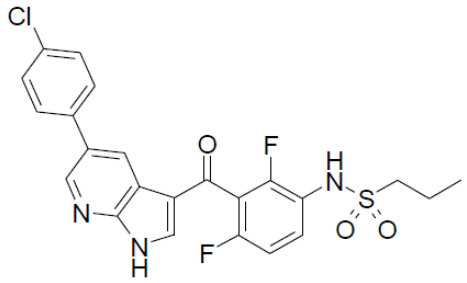
Expired supplies of LY3022855 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. At the end of the study, unused supplies of LY3022855 should also be destroyed according to institutional policies and destruction will be documented in the Drug Accountability Record Form.

8.2 Vemurafenib

8.2.1 Description

Chemical Name: propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide

Chemical Structure:



Molecular Weight: 489.9

Molecular Formula: $C_{23}H_{18}ClF_2N_3O_3S$

Solubility: Insoluble in aqueous media

The inactive ingredients of the tablet core are hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and hydroxypropyl cellulose. The ingredients of the coating are poly (vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.

8.2.2 Form

Vemurafenib is available as 240 mg film-coated tablets with VEM debossed on one side.

8.2.3 Storage and Stability

Store at room temperature between 20°C–25°C (68°F–77°F); excursions permitted between 15°C and 30°C (59°F and 86°F), See USP Controlled Room Temperature. Store in the original container with the lid tightly closed.

8.2.4 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.

8.2.5 Availability

Vemurafenib is commercially available.

8.2.6 Administration

Vemurafenib will be given as per package instructions. Vemurafenib should be taken orally every 12 hours. A missed dose can be taken up to 4 hours prior to the next dose. Doses that would be administered outside of that timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Vemurafenib can be taken with or without food.

8.2.7 Ordering

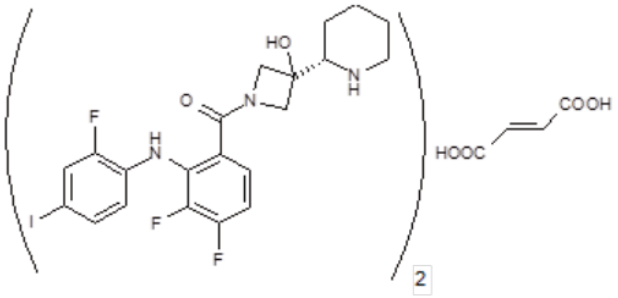
Vemurafenib is commercially available. The investigator or designated study personnel are responsible for maintaining dispensing records of vemurafenib per institutional standards.

8.3 Cobimetinib

8.3.1 **Description**

Chemical Name: (*S*)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate

Chemical Structure:



Molecular Weight: 1178.71 as a fumarate salt

Molecular Formula: $C_{46}H_{46}F_6I_2N_6O_8$ (2 $C_{21}H_{21}F_3IN_3O_2$. $C_4H_4O_4$)

The inactive ingredients of the tablet core are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. The inactive ingredients of the tablet coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc.

8.3.2 **Form**

Cobimetinib is available as 20 mg white, round, film-coated tablets with COB debossed on one side. Each 20 mg tablet contains 22 mg of cobimetinib fumarate, which corresponds to 20 mg of the cobimetinib free base.

8.3.3 **Storage and Stability**

Store at room temperature below 30°C (86°F).

8.3.4 **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.

8.3.5 **Availability**

Cobimetinib is commercially available.

8.3.6 **Administration**

Cobimetinib will be given as per package instructions. Cobimetinib should be taken orally once daily on days 1-21 of every 28 day cycle. For the purposes of this trial, there is a +/- 4 hour dosing window. Doses that would occur outside of this timeframe should be considered missed and should not be taken. Tablets should not be crushed or chewed. A vomited dose should not be retaken, patients should continue with the next scheduled dose. Cobimetinib can be taken with or without food.

8.3.7 **Ordering**

Cobimetinib is commercially available. The investigator or designated study personnel are responsible for maintaining dispensing records of cobimetinib per institutional standards.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Collection of Archival Tissue

Archival tumor tissue will be collected on all patients enrolling to the trial as described in **2.6 -** Correlative Studies. Patients who do not have archival tissue available will be allowed to enroll at the discretion of the principal investigator.

Depending on availability, 10 - 20 unstained slides will be collected. Less than the goal amount of tissue is acceptable if archival tissue is limited. The slide collection should be labeled with the protocol number and study subject number. Slides should be mailed to the following address for analysis:

ATTN: CIO Laboratory Manager
Center for Immuno-Oncology Laboratory
Jimmy Fund Building Room 406
1 Jimmy Fund Way
Boston, MA 02115

9.2 Exploratory Fresh Tumor Biopsies

Optional fresh tumor biopsies will be obtained from patients enrolled during either phase of the trial, as described in **2.6** – Correlative Studies. The biopsies will only be obtained if the treating investigator believes the biopsy to be clinically feasible and if the patient is willing to undergo the biopsy procedures.

The optional on-treatment biopsy can be collected anytime between Cycle 1 Day 15 and Cycle 2 Day 1. An additional optional biopsy at the time of disease progression will also be offered to patients if deemed clinically feasible. Preferably, time of progression biopsies should be obtained prior to the initiation of another cancer treatment. However, in the event that it is not possible to

perform the biopsy before another treatment is begun, the biopsy can be obtained up to 30 days after the last dose of LY3022855.

Core biopsy samples should be obtained for analysis. Three-to-four biopsy passes utilizing a 16-18 gauge needle are preferable, but a 20 gauge core needle biopsy is also acceptable. Less than the goal amount of tissue is acceptable for the biopsy procedures, and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure.

Biopsy samples should be formalin-fixed and paraffin embedded per institutional standards.

Both the pre and on-treatment tumor biopsy samples should be labeled with the protocol number and study subject number, and should be sent to the CIO lab for analysis:

ATTN: CIO Laboratory Manager
Center for Immuno-Oncology Laboratory
Jimmy Fund Building Room 406
1 Jimmy Fund Way
Boston, MA 02115

9.3 Laboratory Correlative Studies

A cell-free DNA (cfDNA) plasma sample and a circulating immune cell (CIC) sample will be collected at baseline (prior to the first dose of LY3022855, vemurafenib, and cobimetinib), at visits immediately following restaging scans (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.), and at the off study visit. Samples collected on days where study medication dosing will occur can be collected anytime pre-dosing.

9.3.1 Cell-free DNA (cfDNA) and Circulating Immune Cell (CIC) Sample Collection Procedure:

1. Blood samples should be labeled with the protocol number, study subject number, date of the draw, and the label, “cfDNA/CIC.”
2. Draw venous blood into three 10 mL EDTA tubes, immediately gently invert the tube 3-4 times.
3. Send tubes to the CIO lab for processing within 6 hours of blood draw (tubes sent outside of this window due to shipping or scheduling difficulties will not be considered protocol violations):

   ATTN: CIO Laboratory Manager
   Center for Immuno-Oncology Laboratory
   Jimmy Fund Building Room 406
   1 Jimmy Fund Way
   Boston, MA 02115

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, echocardiogram, ophthalmologic exam, and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

Assessments must be performed prior to administration of any study agent.

	Table 23: Study Calendar										
	Pre-Study[L]	**Cycle 1 Day 1**	**Cycle 1 Day 8[M]**	**Cycle 1 Day 15[M]**	**Cycle 1 Day 22[M]**	**Cycle 2+ Day 1[N]**	**Cycle 2+ Day 8[M]**	**Cycle 2+ Day 15[M]**	**Cycle 2+ Day 22[M]**	**Off Treatment[O]**	**Every 3 Months after Discontinuing**
Informed Consent	X										
Archival Tumor Tissue Collection[A]	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X								X	
Physical exam	X	X	X	X	X	X		X		X	
Vital signs[B]	X	X	X	X	X	X	X	X	X	X	
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X		X		X		X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	
C-Reactive Protein (CRP)	X	*Repeat as clinically indicated.*									
PT-INR, PTT	X	*Repeat as clinically indicated.*									
Serum chemistry[C]	X	X	X	X	X	X	X	X	X	X	
EKG[D]	X			X		X					
Echocardiogram[E]	X					X					
Dermatologic Evaluation	X	*Dermatologic evaluations to be performed to assess for suspicious skin lesions every 2 months while on vemurafenib/cobimetnib therapy or as per institutional standards. Evaluation can be performed and documented by treating investigator or by dermatologist.*								X	
Adverse event evaluation		X----------X								X	

	Table 23: Study Calendar										
	Pre-Study[L]	**Cycle 1 Day 1**	**Cycle 1 Day 8[M]**	**Cycle 1 Day 15[M]**	**Cycle 1 Day 22[M]**	**Cycle 2+ Day 1[N]**	**Cycle 2+ Day 8[M]**	**Cycle 2+ Day 15[M]**	**Cycle 2+ Day 22[M]**	**Off Treatment[O]**	**Every 3 Months after Discontinuing**
Radiologic evaluation	X	*CT or MRI imaging of any disease-involved site. Radiologic measurements should be performed at the end of cycle 2 (Cycle 2 Day 28) and at the end of every 2 cycles of treatment thereafter (i.e., Cycle 4 Day 28, Cycle 6 Day 28, and so on). There is a +/- 7 day scheduling window on imaging evaluations.*								X	
Serum β-HCG[F]	X										
Ophthalmologic examination	X	*To be conducted at baseline, on cycle 2 day 1, and as clinically indicated – to be done at the treating investigator's discretion based on institutional standards and the presence of symptoms.*									
cfDNA Sample[G]		X	*Samples to be collected at visits immediately following restaging scan visits (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.)*							X	
Plasma CIC Sample[H]		X	*Samples to be collected at visits immediately following restaging scan visits (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.)*							X	
Fresh Tumor Tissue Biopsy[I]				X						X	
LY3022855 Administration		X	*LY3022855 to be administered as described in **5.3.1**.*								
Vemurafenib Administration[J]		X	*Vemurafenib to be administered as described in **5.5.2** and as per institutional standards.*								
Cobimetinib Administration[J]		X	*Cobimetinib to be administered as described in **5.3.3** and as per institutional standards.*								
Telephone or Care Provider Contact[K]											X

A. Participants must have archival tumor tissue available for enrollment. Participants without archival tissue may be enrolled at the discretion of the principal investigator. See **9.1** for further detail.
B. Vital signs to include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation (O_2 sat).
C. Serum chemistry to include: sodium, potassium, chloride, CO_2, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT], globulin, phosphorus, magnesium, calcium, and creatinine phosphokinase (CPK). Other tests may be ordered as clinically indicated. If a patient experiences a new grade 2 or greater increase in CPK, a urine and serum myoglobin should also be obtained.
D. EKG to be performed during screening, at anytime pre-dose on Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 day 1. EKGs to be collected every 3 months thereafter (i.e., Cycle 6 Day 1, Cycle 9 Day 1, and so on). EKGs can be performed more frequently as clinically indicated or as per institutional standards.
E. Echocardiogram (echo) to be performed during screening, on Cycle 2 day 1, and then every 3 cycles thereafter (i.e., Cycle 5 Day 1, Cycle 8 Day 1, and so on). Echo can be performed more frequently if clinically indicated.
F. 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).
G. cfDNA plasma genotyping sample to be obtained anytime pre-dose on Cycle 1 Day 1. The exact time of the sample should be recorded. Additional samples to be collected at visits immediately following restaging scans (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.), and at the off treatment visit. Please see **9.3.1** for more detail.

	Table 23: Study Calendar										
	Pre-Study[L]	**Cycle 1 Day 1**	**Cycle 1 Day 8[M]**	**Cycle 1 Day 15[M]**	**Cycle 1 Day 22[M]**	**Cycle 2+ Day 1[N]**	**Cycle 2+ Day 8[M]**	**Cycle 2+ Day 15[M]**	**Cycle 2+ Day 22[M]**	**Off Treatment[O]**	**Every 3 Months after Discontinuing**

H. Plasma CIC sample to be obtained anytime pre-dose on Cycle 1 Day 1. The exact time of the sample should be recorded. Additional samples to be collected at visits immediately following restaging scans (i.e., cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.), and at the off study visit. Please see Section 9 for more detail.

I. Optional fresh tumor tissue biopsy to be obtained anytime between cycle 1 day 15 and cycle 2 day 1. An additional optional biopsy at the time of disease progression may be obtained up to 30 days after the last dose of LY3022855. Please see **9.2** for more detail.

J. Vemurafenib and cobimetinib to be dispensed and administered as described in **5.3.2** and **5.3.3** and as per institutional standards.

K. Participants will be followed until death or withdrawal of consent after removal from protocol therapy for survival status only. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

L. Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, echocardiogram, ophthalmologic exam, and baseline tumor imaging which may be obtained up to 28 days prior to the start of protocol therapy.

M. A +/- 1 day scheduling window exists to accommodate holidays, adverse weather, vacations, or other scheduling requests.

N. The start of a subsequent cycle may be delayed by up to 7 days to allow for vacations or other scheduling requests.

O. Off-treatment evaluation to be completed within 30 days of the last dose of LY3022855. Note: Follow up visits or other contact is required in order to identify SAEs during the 30 days following the end of study treatment.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of the phase I portion of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every eight weeks. In addition to a baseline scan, confirmatory scans will also be obtained not less than four weeks following initial documentation of an objective response.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every eight weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than four weeks following initial documentation of objective response.

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.

Participants enrolling to the phase I portion of the trial who do not have measurable disease at baseline per RECIST 1.1 guidelines may be enrolled if they have evaluable disease. Evaluable disease includes non-measurable disease: small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses that cannot be accurately measured by CT or MRI are all considered non-measurable. For the purposes of the phase I portion of the trial a participant who exhibits one or more non-measurable disease parameters but does not meet the definition for measurable disease may be enrolled assuming that they meet the other eligibility requirements of the protocol.

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.

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.

11.1.3.1 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.

11.1.3.2 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).

11.1.3.3 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.

11.1.3.4 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 24: 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 25: 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		

11.1.4 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.

11.1.5 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.

11.1.6 Response Review

Evaluation of scans will be done centrally at the DFCI using the Tumor Metrics Core.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **7.1** (Adverse

Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The 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 InForm application designed by CTRIO according to the schedule set by CTRIO.

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 clinical specialists with experience in oncology and who have no direct relationship with the study. 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 or more often if required to review toxicity and accrual data. 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.

13. STATISTICAL CONSIDERATIONS

A standard 3+3 design is planned for the dose finding phase I portion of the trial. The phase I portion of the trial will require a minimum of six and a maximum of 18 patients to determine the MTD and RP2D. Following identification of the MTD and RP2D, a single-arm phase II trial will commence. A total of 25 patients with metastatic melanoma harboring a *BRAF* V600E or V600K mutation will be enrolled to the phase II portion of the trial.

13.1 Study Design/Endpoints

Primary Endpoints:

For the phase I portion of the trial:

A conventional algorithm (3+3 design) will be used to identify the MTD, escalating on 0/3 or 1/6

DLTs, and de-escalating if two DLTs are encountered. The MTD will be the highest dose level at which $\leq 1/6$ subjects experience a DLT. If dose level 1 is discovered to be intolerable (with 2/3 or $\geq 2/6$ subjects experiencing a DLT), the trial will be discontinued. The probabilities of escalation if the true but unknown DLT rates are 10, 20, 30, 40, and 50% are 91, 71, 49, 31, and 17%, respectively.

Data will be summarized using descriptive statistics for continuous variables and frequencies, percentages for discrete variables, and presented by dose group, as appropriate.

For the phase II portion of the trial:

Primary Endpoint:

For the phase II portion of the trial, the primary endpoint will be PFS, defined as the time from study enrollment until the identification of disease progression by RECIST 1.1 criteria or death. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be progression-free.

Power is based on the Wald test of the log failure rate. We assume uniform accrual for 12 months, 12 additional months of follow-up, and a null median PFS of 10 months. A sample of 25 subjects, with 12 observed PFS events, will have 85% power to detect an alternative median PFS of 20 months (hazard ratio = 2), The design assumes a one-sided, type-I error of 10%. The null median PFS of 10 months will be rejected if the observed median PFS is at least 14.5 months.

Secondary Endpoints:

Overall response rate (ORR) will be assessed by RECIST 1.1 criteria and will be graded as complete response, partial response, stable disease and progressive disease. Overall survival (OS) will be defined as the time from study enrollment to death from any cause. Patients who are alive at the time of analysis will be censored at the date of last vital status.

Toxicity will be assessed using the CTCAE version 4.03.

Exploratory Endpoints:

Data from correlative studies will be summarized using descriptive statistics. Associations between MAPK signaling, TAMs, and immune infiltrates will be compared to clinical outcome and will be summarized by descriptive methods and may be explored graphically.

Additionally, tumor DNA levels obtained from the serial collection of cfDNA samples will be examined to explore whether clinical outcome correlates to fluctuations following the administration of LY3022855 combination therapy.

13.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is between six and 18 patients in the phase I portion of the trial, and 25

patients in the phase II portion of the trial, for a total of 31 to 43 patients. The planned accrual rate is approximately 5 patients per quarter. Up to an additional one year of follow-up will be required for the last participant accrued to observe the patient's response and survival following therapy, for a total study length of about four years. Participants will be identified via targeted NextGen sequencing using the DFCI/BWH OncoPanel or another CLIA-certified method for genotyping.

Table 26: Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	0	+	1	=	1
Not Hispanic or Latino	15	+	27	=	42
Ethnic Category: Total of all subjects	15	+	28	=	43
Racial Category					
American Indian or Alaskan Native	0	+	1	=	1
Asian	0	+	0	=	0
Black or African American	0	+	0	=	0
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	15	+	27	=	42
Racial Category: Total of all subjects	15	+	28	=	43

13.3 Analysis of Primary and Secondary Endpoints

The primary and secondary analyses will include all eligible patients who started assigned therapy. The phase II evaluations will not include the patients enrolled to the phase I portion of this trial. The exception to this includes the planned analysis of toxicity data, which will include all patients who received study drug regardless of eligibility.

Overall response rate will be presented with a 90% exact binomial confidence interval. For a sample of size 25, the confidence interval will be no wider than 0.35. The distributions of overall survival and progression-free survival will be described using the method of Kaplan-Meier. Median PFS and OS will be summarized with 90% confidence intervals estimated using log (-log(endpoint)) methodology.

In the event that there are missing data points, no imputation of the missing data will be conducted.

13.4 Reporting and Exclusions

13.4.1 Evaluation of Toxicity

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

13.4.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study will be assessed for response, even if there are major protocol therapy deviations. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

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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16. 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.