Title: A phase II open-label trial of AUY922, an HSP90 inhibitor, in patients with ALK-rearranged, advanced non-small cell lung cancer and acquired resistance or intolerance to prior ALK tyrosine kinase inhibition

NCT01752400

PROTOCOL **12-458**

Protocol Version Date: 1/11/2014

Protocol Version Date: 1/11/2014

NCI Protocol #: N/A

Local Protocol #: 12-458

Title: A phase II open-label trial of AUY922, an HSP90 inhibitor, in patients with ALK-rearranged, advanced non-small cell lung cancer and acquired resistance or intolerance to prior ALK tyrosine kinase inhibition

Principal Investigator:
Alice Shaw, MD, PhD
Massachusetts General Hospital
32 Fruit Street, Yawkey 7B
Boston, MA 02114
Phone: 617-724-4000
[redacted]
Ashaw1@partners.org

Coordinating Center:
Massachusetts General Hospital (MGH) Cancer Center
55 Fruit St
Boston, MA 02114

[redacted]

Agent(s):
AUY922 (IND# 117158), Supplier – Novartis Pharmaceuticals Corporation

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is an open-label phase II study of AUY922 in participants with advanced, anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) who have acquired resistance to prior ALK tyrosine kinase inhibitor (TKI) treatment. Participants who have discontinued ALK TKIs due to intolerance (e.g. pneumonitis) will also be eligible for participation. All participants must have a previously documented ALK translocation or be willing to undergo a fresh biopsy for ALK testing.

Eligible participants will receive AUY922 intravenously at 70 mg/m^2 weekly in a 21 day cycle. This is the established MTD from study [CAUY922A2101]. Efficacy will be evaluated by radiographic assessments using RECIST version 1.1 criteria every 6 weeks. Adverse events will be monitored throughout and reported using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment will continue until disease progression, unacceptable toxicity, participant withdrawal, death or discontinuation from the study for any other reason. Participants will be allowed to continue receiving AUY922 despite disease progression if they are deriving clinical benefit as determined by the Investigator.

Participants with ALK rearrangements may undergo an optional pre-AUY922 biopsy in an attempt to identify the underlying mechanism for TKI resistance at study entry. This is covered under the main study consent. In order to ensure participants start the study without unnecessary delay, the results of the fresh baseline biopsies are not necessary prior to enrollment. Upon disease progression, participants may undergo an optional repeat biopsy in order to evaluate possible mechanisms of AUY922 resistance.

1.2 Primary Objectives

To evaluate the objective response rate (ORR) of AUY922 as assessed by RECIST in participants with advanced, ALK-rearranged NSCLC and acquired resistance or intolerance to prior ALK TKI treatment.

1.2.1 Primary Endpoint

The primary efficacy end point is ORR, defined as partial response (PR) or complete response (CR), occurring at any point post-treatment according to RECIST version 1.1.

1.3 Secondary Objectives

- To estimate overall survival (OS) and progression-free survival (PFS) in participants with advanced, ALK-rearranged NSCLC receiving AUY922.
- To evaluate the disease control rate (DCR) in participants receiving AUY922.
- To determine the safety and tolerability of AUY922.
- To assess the prevalence of concurrent KRAS mutations in a ALK-positive NSCLC population
- To evaluate the impact of different ALK translocation variants on the efficacy of AUY922.
- To investigate mechanisms of AUY922 treatment resistance in pre- and post-therapy tumor tissue.

1.3.1 Secondary Endpoints

- OS, defined as time from study entry to death from any cause.
- PFS, defined as time from study entry to progression or death, whichever comes first.
- DCR, defined as PR, CR, or stable disease (SD) as assessed by RECIST version 1.1.
- Safety parameters: Adverse drug reactions and serious adverse drug reactions, changes in hematology and chemistry values, including those associated with hepatic and renal function, and assessment of physical examination, vital signs, ocular symptoms and cardiac function (i.e. repeated electrocardiograms). CTCAE version 4.02 will be used.
- Mechanisms of treatment resistance: pre- and post-treatment changes in mutational profile of tumor biopsy specimens.

2. BACKGROUND

2.1 Heat Shock Proteins

Heat shock proteins (HSPs) are molecular chaperones, which play a vital role in the maintenance of the proteome. HSPs assist in the structural folding and stabilization of a broad range of proteins within cells, which are commonly referred to as "client proteins." Without active HSPs, these client proteins become misfolded and subject to ubiquitination and degradation within the proteasome.

HSP90, an ATP-dependent molecular chaperone, is the most abundant form of HSPs that accounts for 1-2% of all proteins within the cell (Welch and Feramisco 1982). A vast majority of client proteins within the cell are dependent upon HSP90 (Pratt and Toft 2003), some summarized in Table 1-1, and the list keeps growing every year with more than 200 client proteins identified up to date (Li, Zhang, and Sun 2009). HSP90 consist of three domains, a 24-28 kDa NH_2-terminal region, 33-44 kDa middle region, and a 11-15 kDa COOH domain (Banerji 2009). The primary functions of these domains are ATP binding, client protein binding and dimerization, respectively (Banerji 2009). HSP90 forms multi-chaperone complex with a variety of other co-chaperones and protein kinases to exert its effect on client protein folding and stabilization, a process that is ATP-dependent (Pratt 1998). Pratt and Toft, in their 2003 review article, have elegantly suggested a mechanism involving 5 proteins

(Pratt and Toft 2003). The co-chaperones HSP40 and HSP70 forms a unit which couples with HSP90 through the co-chaperone HOP. In this conformation the complex is able to bind to the client protein and the structure is stabilized by the entry of p23 that binds to HSP90. Recently, it has been discovered that HSP90 binding to p23 is possible through the Sgt-1 co-chaperone. HSP90 and Sgt1-CS couples through the N-domain of HSP90 and forms a closed complex that later interacts with p23/sba1 (Zhang, et al 2008).

Table 2-1 Selected HSP90 client proteins

Cellular process	Client protein
Apoptosis	Apaf-1, P53, RIPK1, AKT, MDM2, Survivin
Cell proliferation	CDC2, CDK4, CDK6, CDK9, CDK11, CHEK1, hTERT, PLK1
Angiogenesis	VEGFR, FLT-3
Oncogenic	HER2, IGF1R, B-RAF, RAF1, BCR-ABL, c-MET, c-Mos, c-SRC, c-KIT, EGFR, NPM-ALK, PIM1, RET, FAK, EML4-ALK
Signal transduction	CAMK1, GRK2, GRK3, GRK5, GRK6, KSR, MAP3K1, MAP3K11, PDK1, HCK, IKKalpha, IKKbeta, LCK, MEK
Transcription factors	AHR, ER, GR, MR, HSF1, HIF1A, RUNX1T1, p53, PPARa, NR1I2, STAT1, STAT3, STAT5
Transporter/ion channel	CFTR, APOB, CX43, KCNH2, SLC12A2, P2X7, ABCB1
Chromatin remodeling	DNMT1, Histones (H1, H2A, H2B, H3, H4)
Others	TPMT, TRKB, ACK2

Most tumors do not depend *de novo* on a single protein abnormality, but on multiple pathway driven processes with redundancies that enable a number of proteins to activate the same pathways for proliferation (Erlichmann 2009). Due to the multitude of client proteins that HSP90 affects, HSP90 inhibitors simultaneously have the potential to disrupt multiple targets in parallel signal transduction pathways by inactivating a large number of oncoproteins, with their crucial targets varying in different cell types. Thus HSP90 inhibitors are expected to have broad utility in oncology. It has been shown that in many tumors HSP90 is either overexpressed and/or exclusively complexed into an activated state with its co-chaperones (Kamal, et al 2003). Many of the HSP90 client proteins are key regulators in cell proliferation, survival and apoptosis. Moreover, oncoproteins are often expressed as mutant forms which depend on HSP90 for proper folding and stability more than their wildtype counterparts. Furthermore, cancer cells present an environment of cellular stress that requires a high level of intact chaperoning activity. By inhibiting HSP90, it is believed, cancer cells will be deprived of key oncogenic proteins for their survival, giving potential HSP90 inhibitors a wide range of molecular targets within cancer cells; a desired outcome in aggressive tumor types such as advanced non small-cell lung cancer (NSCLC). This concept is supported by pre-clinical studies, where HSP90 inhibitors induced cell cycle arrest and apoptosis in a variety of hematological and solid malignancies including lymphomas, sarcomas and NSCLC cell lines.

There are several HSP90 inhibitors currently in development, and 17-AAG (an analogue of geldanamycin, which is a naturally occurring antibiotic) has been the most studied. It should also be noted that geldanamycin has been the choice of agent to identify HSP90 client

proteins *in vitro*. Pre-clinical work with 17-AAG has shown activity in a wide range of cancer models. In osteosarcoma cell lines 17-AAG significantly down regulated cellular proliferation markers such as pAKT, p44Erk, p-mTOR, cyclinD-1 and other proteins (Gazitt, et al 2009). Growth was inhibited, and VEGFR expression was suppressed when 17-AAG was applied to a variety of neuroblastoma cell lines (Jayanthan, et al 2008). Synergistic effects of 17-AAG has also been shown with radiation in esophageal and NSCLC cell lines (Kim 2009, Wu 2009).

17-AAG has been studied extensively in the clinic. It has shown to prolong stable disease in patients with melanoma, lung, prostate and renal cancers (Solit and Rosen 2006). Combination treatment has shown beneficial in some settings. A combination study with trastuzumab resulted in a partial response in a HER2 positive breast cancer patient (Modi, et al 2006). In combination with paclitaxel, a partial response was observed in a lung cancer patient who had previously responded to erlotinib (Solit and Rosen 2006). Responses have also been reported in hematological settings where 17-AAG has shown a partial response in one patient in a 14 patient phase 1 study in multiple myeloma (Mitsiades, et al 2005).

17-DMAG (alvespimycin) is a hydrophobic derivate of 17-AAG that is water soluble with good bioavailability. 17-DMAG does not have the stability and solubility problems as seen with 17-AAG. *In vitro* studies have shown DMAG to be potent, especially in combination with radiotherapy in NSCLC cell lines, NCI-H460 and A549 (Kol, et al 2008). In the clinic, partial responses have been observed in a hormone refractory prostate cancer patient and in a melanoma patient in a 25 patient phase 1 study (Pacey, et al 2009). Combination treatment with 17-DMAG and trastuzumab achieved a partial response in a heavily pretreated HER2 positive metastatic breast cancer patient in a 21 patient phase 1 study (Miller, et al 2007).

With CNF 1010, an oil-in-water nanoemulsion of 17-AAG, 3 minor responses were observed in patients with melanoma, gastric and duodenal cancers (Saif, et al 2006). In a phase I study with the novel HSP90 inhibitor IPI-504, decreased uptake of ^{18}F-FDG in PET scans was observed in 7 out of 18 patients with progressive GIST following imatinib and sunitinib treatment, and 6 patients experienced stable disease for ≥ 4 treatment cycles (Demetri, et al 2007). A recent phase 2 study in advanced NSCLC showed prolonged disease stabilization and partial responses in patients with EGFR wild type, EGFR activating mutations, and EML4-ALK translocations after receiving IPI-504 bi-weekly with a one week rest (Sequist, et al 2010).

Collectively, all these data suggest that targeting HSP90 in various tumors may have anti-neoplastic effects.

2.2 Overview of ALK-rearranged NSCLC

Lung cancer is the leading cause of cancer-related mortality in the United States (Jemal, et al 2008). The disease is traditionally divided into non-small-cell and small-cell variants, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of cases (Herbst, et al 2008). Despite improved therapies, patients with NSCLC often present with an advanced stage, portending a poor long term prognosis (Spira and Ettinger 2004).

Recently, it has been recognized that NSCLC can be further divided into molecularly-defined subsets. This, in turn, has translated into effective new targeted therapies. In 2007, Soda et al. identified the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion oncogene in NSCLC (Soda, et al 2007). This novel oncogene is formed by an inversion in the short arm of chromosome 2, which results in the fusion of exons 1-13 of the EML4 gene and exons 20-29 of ALK (Soda, et al 2007). Multiple variants of EML4-ALK have since been reported. Although the variants preserve the same cytoplasmic portion of ALK, they possess different truncations of EML4 (Choi, et al 2008). Subsequent work has demonstrated that EML4 is not the sole fusion partner for ALK, though it is the most common in NSCLC (Takeuchi, et al 2009). These fusion partners facilitate ligand-independent dimerization of ALK leading to constitutive kinase activation (Shaw and Solomon 2011). ALK translocations have since been recognized to possess potent oncogenic transforming activity in cell lines and transgenic mouse models (Soda, et al 2008).

Rearrangements in ALK are identified in approximately 4% of patients with NSCLC (Takeuchi, et al 2008). Patients harboring ALK translocations typically possess unique clinicopathologic features, including young age, never- or light-smoking history, and adenocarcinoma histology (Shaw, et al 2009). Consistent with preclinical studies, this subset of patients is uniquely sensitive to targeted tyrosine kinase inhibition. In an early phase clinical trial of the ALK tyrosine kinase inhibitor (TKI) crizotinib, patients with ALK-rearranged, metastatic NSCLC experienced an overall response rate of 57% and a median progression free survival of 10 months (Kwak, et al 2010, Camidge, et al 2011). Despite its efficacy, as with other forms of targeted therapy, patients acquire resistance to crizotinib (Katayama, et al 2012). Upon disease progression, patients with ALK translocations are typically treated with cytotoxic chemotherapy, which has marginal disease activity in NSCLC.

In addition to the development of acquired resistance, a subset of ALK-positive patients discontinue ALK TKIs due to intolerance. For example, in single-arm studies, severe, treatment-related pneumonitis occurred in 1.6% of patients receiving crizotinib (Crizotinib FDA label). It is recommended that crizotinib be permanently discontinued in this setting. Altogether, treatment-related adverse events leading to permanent discontinuation of crizotinib occurs in ~ 6% of patients (Shaw, et al 2013).

2.3 Overview of AUY922

2.3.1 Mechanism of Action

AUY922, an isoxazole derivative, inhibits the ATPase activity of HSP90 by competitively binding to the ATP binding pocket of the N-Terminal, which causes the dissociation of client proteins, resulting in their ubiquitination and degradation within the proteasome through a cascade of events. This translates into an anti-tumor effect in non-clinical *in vitro* and *in vivo* studies (please see the current AUY922 Investigator's brochure for details). Binding of AUY922 also induces a stress response. When AUY922 binds to HSP90, it

locks the ATP pocket in an ADP-bound confirmation, preventing the step-wise, ATP-dependent binding of p23 described above. This results in dissociation of the chaperone complex and relocation of the protein heat shock factor 1 (HSF-1) to the nucleus of the cell. HSF-1, in turn, binds to the promoter region of the heat shock genes, named heat shock elements (HSE), and induces the transcription of stress-inducible proteins, including HSP70 and HSP27, up to 100 to 1000 fold concentrations in comparison to unstressed base-line levels (McCollum, et al 2008).

2.3.2 Preclinical Pharmacology

2.3.2.1 In vitro Pharmacology

The ATPase activity of AUY922 was measured in a special fluorescence polarization assay and the drug was demonstrated to have potent HSP90 binding activity (IC_{50}: 30 nM).

At the cellular level, AUY922 inhibition of HSP90 induces cell cycle arrest and apoptosis. In turn, this inhibits the proliferation of a range of tumor and non-tumor cell lines at low nanomolar concentrations. In studies involving the breast cancer cell line BT-474, AUY922 was shown to have strong antiproliferative activity (GI_{50}: 2.8 nM). The anticancer activity of AUY922 was also evaluated in 46 primary human tumor samples of 11 different human tumor types (bladder cancer, colon, liver, NSCLC, small cell lung, mammary, ovary, pancreatic and renal cancer, melanoma, pleuramesothelioma) and 3 preparations of hematopoietic stem cells *in vitro* using a clonogenic assay. Recent work completed at UCLA by Dr. Garon and colleagues has shown that AUY922 inhibit a wide range of NSCLC cell lines including ones with EGFR mutations and *KRAS* mutations at concentrations below 100 nM (Garon, et al 2009).

As explained in more detail in the introduction section, a key step in the functioning of HSP90 is the formation of a complex with the co-chaperone protein p23. This action is driven by the binding of ATP to the complex. In the presence of an ATP competitive inhibitor such as 17-AAG, the HSP90-p23 complex was shown to dissociate (Georgakis and Younes 2005). In BT-474 breast cancer cells, AUY922 was shown to destabilize the HSP90-p23 complex in a concentration dependent manner and this mechanistically demonstrated the compound's ability to disrupt HSP90 activity.

With the inhibition of the HSP90 target, the downstream effects of AUY922 inhibition were examined. It was found that a variety of client proteins had been degraded, and a number of signaling pathways disrupted. The effect of AUY922 on the cellular content of several client proteins were analyzed in BT-474 tumor cell and the compound was shown to affect both ErbB2 and p-AKT in a dose dependent manner, confirming that inhibition of HSP90 catalytic activity induces destabilization of HSP90 client proteins, and leads to their degradation within the proteasome.

2.3.2.2 In vivo Pharmacology

The anti-tumor effect of AUY922 was evaluated in a number of tumor xenograft models. AUY922 was administered intravenously (i.v.) on a three times weekly schedule to the

NSCLC cancer xenograft model NCI-H1975. Efficacy in this experiment was assessed by dividing the change in tumor volume with the change in the vehicle group. The experiment demonstrated a cytostatic effect at a dose level of 50 mg/kg, reaching a Treatment vs Control (T/C) ratio of 21 %. In another xenograft model, A549 cell lines, the same dose and treatment schedule was less potent but still showed cytostatic effect with a T/C ratio of 45. For more information about AUY922 xenograft studies on other solid tumors please refer to the current AUY922 Investigators Brochure.

2.3.2.3 Preclinical Safety of AUY922

The preclinical safety profile of AUY922 was studied in rat and dog toxicology studies. Two separate dosing schedules were utilized during toxicology studies. During the 2-week studies in rats and dogs, AUY922 was administered i.v. every other day. During the 4-week studies AUY922 was administered in a once- weekly i.v. schedule.

The main significant findings from both set of toxicology studies in both species were cytotoxic and inflammatory reactions in the intestine, bone marrow, adrenal glands, and lymphoid tissue. A moderate risk of local irritation at the injection site was also noted in rats. All toxicities were reversible. However, there is a risk that participants may experience GI toxicities such as diarrhea following AUY922 treatment. Hence, participants should be followed closely by the diarrhea management plan. No ocular histopathological changes were determined.

In vitro cardiac safety studies demonstrated a pre-clinical signal for QT prolongation, however no effects, such as QTc prolongation or proarrhythmia, were observed in the GLP dog and monkey telemetry studies *in vivo*. Due to potential cardiac toxicity, participants in ongoing clinical studies are undergoing extensive cardiac monitoring. These safety parameters will be monitored in the current study using an intensive ECG and vital signs monitoring schedule. Due to the potential risk of local irritation the infusion site should be monitored carefully during the time of infusion, if a peripheral line is used for the infusion of the study drug.

For a detailed description and results of the pre-clinical safety studies please refer to the current AUY922 Investigator's Brochure.

2.3.3 Clinical Experience

There are several completed and ongoing studies that assessed the efficacy, safety and tolerability of AUY922 in both solid and hematological malignancies. Detailed information on all these studies can be found in the latest version of the Investigator's Brochure. Below is a short summary of the first in human (FIH) phase I study of AUY922 given as a single agent in adult patients with solid malignancies [CAUY922A2101] as well as of an ongoing Phase 2 study of AUY922 in patients with advanced NSCLC treated with at least two prior lines of therapy [CAUY922A2206].

2.3.3.1 **CAUY922A2201**

The FIH phase I study [CAUY922A2101] to determine safety and tolerability of AUY922 as a single agent in adult patients with solid malignancies, has been completed. A total of 101 patients were treated with AUY922 at increasing dose levels from 2 mg/m^2 to 70 mg/m^2. Of the patients enrolled in the two highest dosing cohorts (i.e., 54 and 70 mg/m^2), 5 DLTs were reported. Grade 3 asthenia and grade 3 diarrhea were reported in two patients in the 54 mg/m^2 cohort. In the 70 mg/m^2 cohort, two patients reported grade 3 visual symptoms and one patient experienced grade 3 diarrhea. Based on the available safety profile, the 70 mg/m^2 dose administered intravenously once weekly was declared as the recommended phase II dose (RP2D) (Samuel 2010).

The most common adverse events in the highest dosing cohorts, regardless of AUY922 relationship, included diarrhea, nausea, fatigue, vomiting, decreased appetite, asthenia, abdominal pain, anemia, night blindness, dyspnea, pyrexia, constipation, headache, and hypokalemia. Most toxicities were associated with either the gastrointestinal or visual system.

In the highest dose cohorts of 54 mg/m^2 and 70 mg/m^2, patients reported grade 1-3 visual symptoms including but not limited to: delayed dark to light adaptation, blurred vision, floaters and flashes in peripheral vision, dark or black spots, darkening of visual field, reduced night vision, decreased peripheral vision, decreased color vision and dry eye syndrome. Per investigator follow-up, all visual symptoms suspected to be related to AUY922 resolved after discontinuation or dose reduction of AUY922 treatment.

Detailed information is available in the latest version of the AUY922 Investigator's Brochure.

2.3.3.2 **CAUY922A2206**

The primary purpose of the ongoing study [CAUY922A2206] is to determine the efficacy of AUY922, administered intravenously on a once a week schedule at 70 mg/m^2, in adult patients with advanced NSCLC treated with at least two prior lines of chemotherapy. The study also assesses additional safety, tolerability and pharmacokinetic (PK) profile of AUY922 as secondary objectives. Patients in this study are stratified, retrospectively and prospectively, based on their molecular tumor etiology. All patients are required to have received at least one prior platinum containing regimen with the exception of patients harboring EGFR activating mutation tumors. The following strata are evaluated:

1. Patients with EGFR activating mutation tumors (Note: These patients must have progressed on one prior EGFR TKI containing regimen unless they have documented de novo resistance to EGFR TKI (e.g. T790M or exon 20 insertions)
2. Patients with *KRAS* mutant tumors
3. Patients with EGFR wt and *KRAS* wt tumors
4. Patients with EML4-ALK translocations

5. A fifth stratum is evaluating EGFR mutant patients that are less heavily pre-treated (up to two prior lines), without CNS metastasis. This stratum is termed Modified EGFR mutant stratum

As of January 15, 2012, 118 patients were treated in this study. Of these, data for 114 patients has been entered in the clinical database (median age 60 years; 44% male; 86% adenocarcinoma; 28 patients KRAS mutant stratum [25%]; 35 patients EGFR mutant stratum [31%]; 31 patients EGFR/KRAS/ALK wt stratum [28%]; and 16 patients to the EML4-ALK stratum [28%]. Four patients could not be stratified due to insufficient tumor material submitted for analyses. Most patients were heavily pretreated: 61% had received $\geq$ 3 prior systemic regimens; 64% had WHO PS 1 or 2. Mean duration of exposure was 9.1 weeks (range 1-18+). The most frequent adverse events (AEs, any grade [Gr]) were diarrhea (73%), visual AEs (71%), and nausea (43%). Most AEs were Gr 1/2; Gr 3/4 AE's were rare (all <10%).

Radiological responses, per RECIST, were observed in 15 patients (14%) and 10 of these responses were confirmed with a follow-up scan (at the data cut-off date, follow-up scans for 3 patients were pending) (Garon, et al 2012). Significant responses were seen in the EGFR mutant stratum where 6 patients (17%) had PR. All of these patients had previously been treated with and progressed on EGFR TKI treatment. In addition, 15 patients (43%) achieved SD and receive multiple cycles of treatment. The disease control rate (DCR) was 60% in comparison to 50% for the total number of patients.

2.3.3.3 **Clinical Pharmacokinetics of AUY922**

As of February 18th, 2010, preliminary PK data are available from 100 patients in the first dose escalation clinical trial for AUY922 [CAUY922A2101]. PK profiles of AUY922 and its inactive metabolite BJP762 obtained on Days 1, 22, and 29 for dose cohorts of 2, 4, 8, 16, 22, 28, 40, 54, and 70 mg/m^2 were assessed by noncompartmental analysis.

As of February 18th, 2010, preliminary PK data are available from 20 patients from the second clinical trial at 8, 16, 30, 45, 60 and 70 mg/m^2 [CAUY922A2103] and 16 patients from the third clinical trial at 8, 16, 22, 28, and 40 mg/m^2 (CAUY922A1101).

Following a weekly i.v. infusion (1 hr duration), AUY922 blood concentration followed a bi-exponential decline with a fast phase (t1/2 <10 min) and a slow terminal phase (t1/2~80hr). Peak concentration Cmax occurred at the end of infusion for both AUY922 and BJP762 (Tmax around 1 hr). No apparent drug accumulation for either AUY922 or BJP762 was observed following weekly dosing. AUY922 blood Cmax increased proportionally with dose, though blood AUC was less than dose-proportional. The observed nonlinear blood AUC of AUY922 with dose was likely caused by saturable distribution of AUY922 to red blood cells (RBC). The increase in the exposure ratio of BJP762/AUY922 reached a maximum at a dose of 28 mg/m^2. The dose dependent exposure ratio of BJP762 to AUY922 was also observed, possibly due to the nonlinear distribution of AUY922 to RBC, and the linear distribution of BJP762 to RBC. Both AUY922 blood CL and Vss increased with dose. At 70mg/m^2, the Vss value was over

1000 L, suggesting extensive distribution of AUY922 to the tissues. The observed dose-dependent increases of CL and Vss were consistent with the nonlinear distribution of AUY922 to RBC. The PK results of AUY922 observed thus far are generally consistent between three studies [CAUY922A2101], [CAUY922A2103], and CAUY922A1101.

The absorption, distribution, metabolism and excretion (ADME) of AUY922 was determined in an open-label, single-center, phase I study following a single intravenous administration of 30 mg [^{14}C]AUY922 in healthy male volunteers [CAUY922A2105]. Mass balance was achieved in this study with ≥ 93.8% of the administered radioactivity being recovered in the excreta of all four patients after 13 days. In feces, 73.0 - 78.7% of the dose was recovered while 15.1 - 23.5% of the dose was recovered in the urine. The most prominent biotransformation pathways for AUY922 in humans was direct glucuronidation at the 2-hydroxy position on the 2,4-dihydroxy-5-isopropyl-phenyl ring of AUY922 to yield M29.7/BJP762 and conversion of the isoxazole ring to a dihydro-pyranone ring by isoxazole ring-opening followed by re-cyclization through the 2-hydroxy group in the adjacent 2,4-dihydroxy-5-isopropyl-phenyl ring to yield M29.1/BGX833. Unchanged AUY922 in urine and feces accounting for 0.39-1.16% and 4.82-27.5% of dose, respectively. The higher total radioactivity exposure observed in blood relative to plasma suggested that the drug-related radioactivity was significantly distributed to blood cells. In contrast to AUY922, metabolite BJP762 does not distribute to blood cells to any significant degree.

2.4 Study Rationale / Purpose

The primary purpose of this study is to determine the efficacy of AUY922 when administered intravenously on a once-weekly schedule at 70 mg/m^2 in adult participants with advanced, ALK-rearranged NSCLC and either acquired resistance or intolerance to ALK tyrosine kinase inhibitor (TKI) therapy. Additional safety and tolerability assessments of AUY922 will be evaluated as secondary objectives. Pre- and post-treatment biopsy specimens, if available, will also be analyzed to determine potential mechanisms of resistance to treatment with AUY922.

There is a strong scientific rationale for the use of the HSP90 inhibitor AUY922 in ALK-rearranged, TKI-resistant NSCLC. Despite the clinical benefits of crizotinib in patients with ALK translocations, patients acquire drug resistance, typically within one year. The earliest reports of acquired TKI resistance identified secondary mutations in the ALK tyrosine kinase domain as well as coactivation of the epidermal growth factor receptor (EGFR) signaling pathway as potential mechanisms of resistance (Choi, et al 2010 and Sasaki, et al 2011). A recent analysis of 18 patients with crizotinib-resistant, ALK-rearranged NSCLC demonstrated that secondary mutations in the ALK tyrosine kinase domain are present in only 22% of cases (Katayama, et al 2012). Additional resistance mechanisms identified in this analysis included ALK gene amplification as well as aberrant activation of bypass tracts, such as KIT and EGFR (Katayama, et al 2012). New strategies are therefore needed across a range of potential ALK TKI resistance mechanisms.

ALK is a client protein of HSP90. Preclinical studies employing HSP90 inhibitors have demonstrated *in vitro* and *in vivo* anti-tumor activity in ALK-rearranged, TKI-naïve models (Chen, et al 2010). HSP90 inhibitors also appear to retain effectiveness in cell lines despite acquired ALK TKI resistance (Normant, et al 2011 and Katayama, et al 2011). Additionally, Katayama and colleagues demonstrated that HSP90 inhibition was highly active against cell lines expressing a range of different secondary mutations in the ALK tyrosine kinase domain (Katayama, et al 2012). In early clinical trials, HSP90 inhibitors have also demonstrated activity in ALK-rearranged NSCLC. In a phase II, open-label trial of the HSP90 inhibitor IPI-504, the overall response rate was 7% among 76 patients with advanced NSCLC. However, among the three patients with confirmed ALK-rearrangements, two had partial responses and the third had prolonged stable disease, suggesting that this subpopulation may be more susceptible to HSP90 inhibition (Sequist, et al 2010). In an ongoing phase II trial using AUY922 in a number of molecularly-defined subgroups of NSCLC, preliminary efficacy data was reported on eight patients with ALK-translocations (Garon, et al 2012). Among these patients treated with AUY922, partial responses were observed in 25% (Garon, et al 2012). More mature follow-up data is now available on a total of 19 patients with ALK translocations treated with AUY922 [CAUY922A2206]. Clinical activity within this group included: partial responses in 7/19 (37%) patients, stable disease in 8/19 (42%) patients and progressive disease in 4/19 (21%) patients. Among the 11 patients in this study previously treated with crizotinib, 3 (27%) experienced partial responses to AUY922 and 4 (36%) demonstrated stable disease [CAUY922A2206].

Taken together, these studies suggest that HSP90 inhibition with AUY922 may be an effective strategy for the treatment of TKI resistant, ALK-rearranged NSCLC. This strategy is likely to be effective across a range of ALK TKI resistance mechanisms. This includes secondary mutations in the ALK tyrosine kinase domain as well as upregulation of bypass tracts such as EGFR, since both are client proteins of HSP90.

2.4.1 Selection of AUY922 dose

AUY922 will be administered intravenously at a dose of 70 mg/m^2 on a weekly schedule. This schedule is in line with the weekly treatment schedule that proved to be effective against human tumor xenograft models in mice. Furthermore, this has been established as the MTD from study [CAUY922A2101] and is the current dose in an ongoing phase II protocol in NSCLC [CAUY922A2206].

2.5 Correlative Studies Background

The mechanisms of ALK TKI resistance are still being elucidated. To date, at least 7 different secondary mutations within the ALK tyrosine kinase domain have been identified, including an amino acid substitution in the gatekeeper residue (Lovely, 2012). However, unlike other subtypes of oncogene-addicted, TKI-sensitive NSCLC (e.g. EGFR mutations), there is no dominant secondary mutation to mediate resistance (Katayama, et al 2012). Additional mechanisms of resistance include up-regulation of bypass signaling tracts, including

activation of EGFR or amplification of c-KIT (Katayama, et al 2012). ALK amplification and emergence of KRAS and EGFR mtuations have also been cited as possible resistance mechanisms (Doebele, et al 2012). Importantly, ALK TKI resistant cell lines demonstrate differential sensitivities to second-generation ALK TKIs and HSP90 inhibitors based upon mechanism of resistance (Katayama, et al 2012). We will therefore incorporate optional biopsies at the time of screening (i.e. time of ALK TKI resistance) and at the time of progression on AUY922. Specimens will be evaluated for ALK gene amplification, secondary mutations in the ALK tyrosine kinase domain, and amplification of bypass tracts in c-KIT and EGFR. Due to the evolving nature of the field, not all of the proteins or genes of interest leading to resistance can be pre-specified in this document.

If sufficient archival tissue is available, we will also perform RT-PCR to identify the specific ALK 5' fusion partner as well as specific EML4-ALK fusion variant. Recent preclinical studies suggest that different ALK fusion genes and EML4-ALK variants possess differences in protein stability within the cell, affecting a variable sensitivity to HSP90 inhibitors (Heuckmann, et al 2012). We will therefore correlate EML4-ALK fusion variants with response rate to AUY922.

3. PARTICIPANT SELECTION

The study population consists of adult participants with histologically or cytologically confirmed advanced NSCLC, which includes stage IIIB (Tx, N3, M0 or T4, N2, M0) and stage IV disease. Participants must have confirmed ALK-translocations or mutations. Prior platinum treatment is not a requirement for participation. Expected number of participants: 20.

3.1 Eligibility Criteria

- Participants with histologically or cytologically confirmed advanced (stage IIIB or stage IV) NSCLC.
- Only participants with tumors characterized by abnormalities in ALK (translocation or mutation) will be enrolled. ALK translocation must be detected by FISH in ≥15% of tumor cells.
- Subjects will be required to provide archival tissue in the form of 5 formalin-fixed paraffin-embedded (FFPE) sections in order to characterize their ALK fusion variant. If no archival tissue is available and the patient is unable to or defers a fresh biopsy, the participant may still be considered for participation at the discretion of the Investigator.

- Participants must have either acquired resistance to treatment with ALK TKIs or intolerance to ALK TKIs as determined by the investigator. Acquired resistance will be defined as:
    - Previous treatment with single agent ALK TKI.
    - Presence of an ALK fusion or documented benefit to prior ALK TKI (CR, PR or 6 months or greater of SD).
    - Systemic progression of disease while on treatment with an ALK TKI.

- All participants must have at least one measurable lesion as defined by RECIST criteria. Previously irradiated lesions are not measurable unless the lesion has demonstrated clear progression after radiation.
- Age ≥ 18 years
- Able to sign informed consent and comply with the protocol.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
- Life expectancy ≥ 12 weeks.
- No restrictions on number of prior therapies.
- Participants must have the following laboratory values:

Hematologic:
- Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
- Hemoglobin (Hgb) ≥ 9 g/dl
- Platelets (Plt) $\geq 100 \times 10^9$/L

Biochemistry:
- Potassium within normal limits or correctable with supplements.
- Total calcium (corrected for serum albumin) within normal limits or correctable with supplements.
- Magnesium within normal limits or correctable with supplements.

Liver and Kidney Functions:
- AST/SGOT and ALT/SGPT ≤ 1.5 x Upper Limit of Normal (ULN)
- AST/SGOT and ALT/SGPT ≤ 2.5 x Upper Limit of Normal (ULN) if AP ≤ 5.0 x ULN if liver metastases are present
- Serum bilirubin ≤ 1.5 x ULN
- Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 ml/min

- Negative serum pregnancy test. The serum pregnancy test must be obtained prior to the first administration of AUY922 (≤ 72 hours prior to dosing) in all pre-menopausal women and women <2 years after the onset of menopause.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

- Participants with symptomatic CNS metastases who are neurologically unstable or require increasing doses of steroids to control their CNS disease. Note: Participants without clinical signs and symptoms of CNS involvement are not required to have an MRI of the brain. **Participants with treated brain metastases or asymptomatic CNS metastases that do not require local anti-neoplastic therapy such as radiotherapy or surgery will be considered eligible for protocol participation at the discretion of the Principal Investigator/Sponsor.**
- Participants who discontinue an ALK TKI within 7 days prior to the first dose of AUY922.
- Unresolved diarrhea ≥ CTCAE (v4.02) grade 1
- Pregnant or lactating women
- Fertile women of childbearing potential (WCBP) not using double-barrier methods of contraception (abstinence, oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly, or surgically sterile). Male participants whose partners are WCBP not using double-barrier methods of contraception.
- Prior anti-neoplastic treatment with any HSP90 or HDAC inhibitor compound.
- Participants who have undergone any major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
- Participants who have received radiotherapy to a large volume (including whole brain radiotherapy) < 2 weeks prior to starting study drug, and participants who have received radiotherapy to a small volume (including stereotactic radiotherapy to the CNS) < 1 week prior to starting study drug.
- Participants who have concurrent or uncontrolled illness that the investigator feels will impede study participation including, but not limited to:
    - Acute or chronic liver disease.
    - Acute or chronic renal disease.
    - Active or ongoing infection.
    - Psychiatric illness/social situations that would limit compliance with study requirements
    - **Note:** Baseline ocular symptoms are NOT an exclusion criteria.
- Participants with known disorders due to a deficiency in bilirubin glucuronidation (e.g. Gilbert's syndrome)
- Participants taking therapeutic doses of warfarin sodium (Coumadin®).

- Participants with the following cardiac criteria:
  - History of long QT syndrome.
  - Mean QTcF ≥ 450 ms during screening ECGs (see Table 6-2)
  - History of clinically manifest ischemic heart disease including myocardial infarction, stable or unstable angina pectoris, coronary arteriography or cardiac stress testing/imaging with findings consistent with infarction or clinically significant coronary occlusion ≤ 6 months prior to study start.
  - History of heart failure or left ventricular (LV) dysfunction (LVEF ≤ 45%) by MUGA or ECHO.
  - Clinically significant ECG abnormalities including one or more of the following: left bundle branch block (LBBB), right bundle branch block (RBBB) with left anterior hemiblock (LAHB). ST segment elevations or depressions > 1mm, or 2nd (Mobitz II) or 3rd degree AV block.
  - Uncontrolled atrial fibrillation or atrial flutter.
  - History of ventricular arrhythmias including ventricular tachycardia or Torsades de Pointes.
  - Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with a hypertensive regimen).
  - Clinically significant resting bradycardia (<50 beats per minute).
  - Participants who are currently receiving treatment with any medication which has a relative risk of prolonging the QTcF interval or inducing Torsades de Pointes (as listed in protocol) and cannot be discontinued or switched to an alternative drug prior to commencing AUY922 dosing.
  - Participants who have a cardiac pacemaker.
- Concurrent malignancies or invasive cancers diagnosed within the past 2 years, except for adequately treated basal cell cancer of the skin or in situ cancers.
- Participants unwilling or unable to comply with the protocol
- Participants known to be HIV positive. Testing is not required in the absence of clinical signs and symptoms suggesting HIV infection.
- Known hypersensitivity to any of the study drugs or their excipients

3.3 Determination of ALK translocation Status

All participants must have ALK translocations or mutations documented previously or be willing to undergo a fresh biopsy for ALK testing. Translocations must be detected by FISH in ≥ 15% of tumor cells. Additionally, participants will be required to submit archival tissue for determination of their specific ALK fusion variant. If archival tissue is unavailable and the patient defers a fresh biopsy, the participant may still be eligible for study participation at the discretion of the Investigator.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at [redacted]

   Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5. TREATMENT PLAN

Treatment phase:
Participant's screening evaluations will commence after the patient signs informed consent and will be concluded within 21 days prior to the first day of dosing.

All participants will receive AUY922 intravenously at 70 mg/m2 weekly in a 21 day cycle. Treatment duration will continue until disease progression (defined by RECIST), unacceptable toxicity, participant withdrawal, death or discontinuation from the study for any other reason.

Efficacy will be evaluated by radiological assessments using RECIST version 1.1 criteria at baseline and after every two cycles.

Follow-up visits:
Participants who discontinue treatment should have a follow-up visit 28 (±7) days after the end of treatment visit to follow-up for adverse events (AEs) and serious adverse events (SAEs) that may occur after discontinuation.

Follow-up period:
Any participant who discontinued study treatment for any reason other than disease progression, death or withdrawal of consent will continue to have tumor assessments every 12 weeks (±7 days) until the participant starts another anti-cancer therapy. This includes surgical procedures for palliative treatment.

All participants will be followed for PFS and OS for a duration of up to a year after the last participant's last visit.

5.1 Agent Administration

5.1.1 AUY922

AUY922 will be administered by a 1 hour (+10 minute window period) intravenous infusion (in 5% glucose/dextrose) at 70 mg/m^2 on days 1, 8, and 15 of each treatment cycle (21 days in duration). A scheduled dose may be administered ± 48 hours of the scheduled day due to public or religious holidays. If a peripheral line is used for the infusion of the study drug, the injection site should be monitored carefully during the time of infusion.

5.2 General Concomitant Medication Guidelines

All medications taken within 4 weeks prior to the initiation of AUY922 and all concomitant therapy administration during the study with reasons for therapeutic use will be recorded as part of this study. All prior chemotherapy, biologic, immunologic or radiation therapy or surgery prior to the administration of AUY922 will also be recorded as part of this study.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant is permitted with the following exceptions:

- Therapeutic doses of warfarin sodium (Coumadin®) are not permitted.
- Preliminary *in vitro* metabolism studies suggest that AUY922 is a moderate CYP2C9, 2C8, 2C19, and CYP3A4 inhibitor. Therefore, drugs known to be metabolized by CYP3A4, CYP2C8, CYP2C9 or CYP2C19 should be used with caution because of the inherent potential risk of either reduced activity or enhanced toxicity of the respective concomitant medication and/or AUY922. Participants using concomitant medications known to be metabolized by these cytochrome p450 isoenzymes will not be excluded from the study. However, the participants must be carefully monitored for potentiation of toxicity due to individual concomitant medications.
- Please refer to a list of known medications that are substrates, inhibitors, and inducers of CYP2C9, CYP2C8, 2C19, and 3A4/5 enzymes in **Appendix A** and avoid co-administration with AUY922 if possible. For the most updated information, please also visit the following website: **medicine.iupui.edu/flockhart/table.htm**
- If, after a participant has been enrolled, he/she requires the concomitant use of any of the medications which may cause QT prolongation, then the patient must be discontinued from the study. Excluded medications which may cause QTc prolongation are also listed in **Appendix A** and updated in web address: **qtdrugs.org/medical-pros/drug-lists/drug-lists.htm**.

The investigator should instruct the participant to notify the study site about any new medications he or she takes after the start of the study drug. All medications (other than the study drug) and significant non-drug therapies (including physical therapy and blood transfusions) will be recorded.

5.3 Duration of Therapy

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

- Disease progression requiring an alternative therapy. Note: In some cases, despite disease progression by RECIST criteria, participants may be continued on study drug if deemed beneficial by the participant and investigators, and if approved by the Principal Investigator/Sponsor.
- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol violation
- Intercurrent illness that prevents further administration of treatment,
- Participant demonstrates an inability or unwillingness to comply with the regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- Death

All cancer medications and/or therapies given to the participant after the last dose of study treatment will be recorded.

5.4 Permitted Treatment

All routine and appropriate supportive care, including blood products, will be provided during this study, as clinically indicated, and in accordance with standard of care practices.

Palliative radiation therapy will be permitted for participants with symptomatic bone metastases or CNS metastases as long as they have demonstrated stability in terms of systemic disease. Disease stability for these purposes will be defined as complete response, partial response, stable disease or clinical benefit in the opinion of the Investigator. For participants undergoing radiation, AUY922 must be held for at least 7 days prior to initiation of radiation. AUY922 may be resumed no sooner than 72 hours after completion of radiation.

5.5 Study Drug Discontinuation

Participants who discontinue study treatment should be scheduled for an End of Treatment Visit within 7 days after discontinuing study treatment, at which time all of the assessments listed for the End of Treatment Visit will be performed. The date and reason for stopping treatment will be recorded.

All participants who discontinue study treatment, including those who refuse to return for the final 28-Day Follow-up Visit, should be contacted for safety evaluations, anti-neoplastic therapies received after discontinuation of study drug, and survival information ≤ 28 days following the last dose of study treatment. Participants should continue to be followed every 12 weeks for the start date of new anti-neoplastic therapies (if not obtained within 28 days of last dose) and survival information until death or one year past the last participant last visit, whichever comes first.

Participants whose treatment is interrupted or permanently discontinued due to a study-related adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4 week intervals, until resolution or stabilization of the event, whichever comes first. If a participant requires a delay of ≥ 21 days since the last dose of AUY922, the participant must be discontinued from study treatment. However, the participant will continue to be followed for toxicity as previously described. In addition, attempts should be made to follow the participant every 12 weeks after discontinuation from the study until disease progression, initiation of other anticancer therapy or study termination.

Participants who discontinue study treatment for reasons other than disease progression will be restaged every 12 weeks (±7 days) until start of another anticancer treatment. An end of study scan is required if the participant is discontinued from treatment for any reason other than disease progression and the last scan was performed ≥ 4 weeks previously.

Participants who discontinue study treatment should be contacted for survival information by telephone every 12 weeks after last participant last visit up to a year.

5.6 Follow-up Assessments and Study Completion

After discontinuation of study drug treatment, participants will continue to be evaluated for safety and survival data. The following visits will be performed:

28 Day Safety Visit: All participants will have a follow-up visit scheduled 28 days (±7 days) after the last dose of study treatment to follow-up for AEs and SAEs. AEs and SAEs that are still ongoing at the time of discontinuation and considered as related to study treatment will continue to be followed weekly until resolution, stabilization of condition, or end of study.

Treatment Follow-up Period: Any participant who is discontinued from study treatment for any reason other than disease progression will continue to have tumor assessments every 12 weeks until progression, death or until a new anti-neoplastic therapy is initiated. The investigator, or his/her designee, will continue to collect information until the first initiation of additional anti-neoplastic therapies for each discontinued participant until one year following last participant last visit.

All participants who have progressed during study treatment or during the Treatment Follow-up Period will be followed every 12 weeks for survival up to 1 year after the last participant is discontinued from the study.

5.7 Treatment Holidays

In general, a 48 hour window is allowed for study drug treatments, unless other restrictions are stated.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

6.1 Anticipated Toxicities

The preclinical safety evaluation showed that the toxicity profile of AUY922 is dominated by cytotoxic and inflammatory reactions in the intestine, bone marrow and lymphoid tissue, as well as a moderate risk of local irritation at the injection site. The observed changes were reversible in the animal experiments. Nevertheless, there is a probability that participants may experience diarrhea following treatment with AUY922. Safety pharmacology studies revealed no effects on CNS or respiratory functions.

Based on *in vitro* and *in vivo* data, a potential for cardiovascular toxicity, such as QTc prolongation or proarrhythmia could not be completely excluded. *In vitro* cardiac safety studies demonstrated a pre-clinical signal for QT prolongation, however, no effects on QT or QTc were observed in the GLP dog and monkey telemetry studies *in vivo*. Due to potential cardiac toxicity, participants in ongoing studies are undergoing careful cardiac monitoring.

No potential for genotoxicity (*in vitro* and *in vivo*) or phototoxicity (*in vitro*) was found in the preclinical safety studies conducted so far.

In conclusion, main target organs for AUY922 are the intestine, bone marrow and lymphoid tissue. There may be a risk of QTc prolongation, and of a local irritative effect. These safety parameters can be monitored in the clinic using an intensive ECG and vital signs monitoring schedule. Detailed instructions for the observation and treatment of diarrhea are also provided in this study protocol.

6.2 AUY922 Dose Modifications / Delays

Toxicity will be assessed using the NCI-CTC for Adverse Events, version 4.02 (CTCAE v4.02)

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug (Tables 6-1). If the participant experiences unacceptable toxicities, treatment with the study drug must be suspended until the toxicities return to ≤ CTCAE grade 1. Special instructions are provided for QTcF, gastrointestinal, and ocular toxicities. The criteria for interruption and re-initiation of AUY922 treatment are outlined in Table 6-1.

Table 6-1 Criteria for interruption, dose reduction and re-initiation of AUY922 study treatment

Recommended dose modifications for AUY922	
Worst toxicity **CTCAE grade* (value)**	**During a cycle of therapy**
No toxicity	Maintain dose level
Hematologic	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Omit dose until resolved to ≤ grade 1 If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, then dose reduce to 54 mg/m^2
Grade 4 (ANC < 500/mm^3)	Omit dose until resolved to ≤ grade 1, then dose reduce to 54 mg/m^2
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then dose reduce to 54 mg/m^2
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Omit dose until resolved to ≤ grade 1 If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, then dose reduce to 54 mg/m^2
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit dose until resolved to ≤ grade 1 If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, then dose reduce to 54 mg/m^2
Grade 4 (PLT < 25,000/mm^3)	Omit dose until resolved to ≤ grade 1, then dose reduce to 54 mg/m^2
Renal	
Serum creatinine	

Recommended dose modifications for AUY922	
Worst toxicity **CTCAE grade* (value)**	**During a cycle of therapy**
Grade 1 (> ULN - 1.5 x ULN; >1 - 1.5x baseline)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN; >1.5 - 3.0x baseline)	Omit dose until resolved to ≤ grade 1, then dose reduce to 54 mg/m^2
Grade 3 (> 3.0 - 6.0 x ULN; >3x baseline)	Omit dose and discontinue patient from study
Grade 4 (> 6.0 x ULN)	Omit dose and discontinue patient from study
Hepatic	
Bilirubin	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1, dose reduce to 54 mg/m^2
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ grade 1, dose reduce to 54 mg/m^2
Grade 4 (> 10.0 x ULN)	Omit dose and discontinue patient from study
AST or ALT	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if liver metastases present), then If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, then dose reduce to 54 mg/m^2
Grade 4 (> 20.0 x ULN)	Omit dose until resolved to ≤ grade 1, then dose reduce to 54 mg/m^2
Cardiac	
Cardiac - prolonged QTcF interval	
During cycle 1: Absolute QTcF < 480msec	Maintain dose level. ECG monitoring assessments should be performed as per visit schedule

Recommended dose modifications for AUY922	
Worst toxicity **CTCAE grade* (value)**	**During a cycle of therapy**
Absolute QTcF ≥480msec and < 500msec	Maintain dose level. ECG monitoring assessments should be performed for 2 additional cycles at the same frequency as in cycle 1. After the second additional cycle, ECGs for subsequent cycles will be performed as follows: If ECG in the additional cycles show no absolute QTcF ≥ 480msec then for subsequent cycles ECG monitoring will be performed as per visit schedule. If ECG is still abnormal (absolute QTcF ≥ 480msec and < 500msec) then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.
During any cycle: Grade 3 or QTcF ≥ 500msec as identified on the ECG by the investigator	Omit dose administration. Monitor patient with hourly ECGs until the QTcF has returned to ≤ 450msec. Perform further monitoring as clinically indicated. Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesemia and blood oxygenation status. Participants who develop hypokalemia or hypomagnesemia during the study should receive electrolyte replacement as soon as possible and should not receive further AUY922 dosing until the respective electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved, participants may be re-treated at 54 mg/m^2 at the investigator's discretion. ECG monitoring must continue throughout the treatment period as follows: ECG monitoring assessments should be performed for 2 additional cycles at the same frequency as in cycle 1. If the ECGs obtained in the first and second additional cycles after dose reduction are without any QTc prolongation, then ECG monitoring in subsequent cycles will continue as per the visit schedule. If the participants had an absolute QTcF ≥ 480msec and < 500msec, then ECG monitoring at the same frequency as in cycle 1 will be continued for all subsequent cycles. Participants who experience absolute QTcF ≥ 500msec after dose reduction to 54 mg/m^2 will be discontinued from study. NB: If Torsades de Points is observed, participant should be discontinued from the study. Whenever QTcF ≥ 500msec is observed, a plasma sample for determination of AUY922 concentration should be obtained with the time of sample collection noted.
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then dose reduce to 54 mg/m^2
Grade 4	Omit dose and discontinue participant from study

Recommended dose modifications for AUY922	
Worst toxicity CTCAE grade* (value)	**During a cycle of therapy**
Diarrhea	
Grade 1	Maintain dose level
Grade 2 (see Section 6.3.1 for recommended treatment algorithm)	Omit dose until resolved to grade 1 or baseline If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, dose reduce to 54 mg/m^2
Grade 3 (see Section 6.3.1 for recommended treatment algorithm)	Omit dose until resolved to grade 1 or baseline, then dose reduce to 54 mg/m^2
Grade 4 (see Section 6.3.1 for recommended treatment algorithm)	Omit dose until resolved to grade 1 or baseline, then dose reduce to 54 mg/m^2 If grade 4 toxicity lasts < 24 hours, then dose reduce to 54 mg/m^2. If grade 4 toxicity recurs, discontinue treatment. In the event grade 4 toxicity lasts > 24 hours despite optimal use of anti-diarrheal, discontinue treatment.
Visual symptoms or signs	
Grade 1	Maintain dose level
Grade 2	Omit dose administration until resolved to ≤ grade 1 (or baseline), then continue treatment with AUY922 at the current dose level If visual symptoms ≥ Grade 2 recur upon re-exposure to AUY922, omit dose until resolution to ≤ Grade 1, then dose reduce to 54 mg/m^2 and maintain this dose level. If visual symptoms ≥ Grade 2 recur at a dose of 54 mg/m^2, then the participant should be discontinued from the study.
Grade 3	Omit dose administration until resolved to ≤ grade 1 (or baseline), then dose reduce to 54 mg/m^2
Grade 4	Omit dose administration and discontinue patient from study
Other adverse events**	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then dose reduce to 54 mg/m^2
Grade 4	Omit dose and discontinue participant from study

Recommended dose modifications for AUY922
Worst toxicity **During a cycle of therapy** **CTCAE grade* (value)**
All dose modifications should be based on the worst preceding toxicity.
Each participant is allowed only one dose reduction. Participants must discontinue treatment with AUY922 if, after treatment is resumed at a lower dose, the same toxicity recurs with the same or worse severity. Similarly, participants who have already required prior dose reduction to 54 mg/m^2 for a given toxicity must be discontinued from treatment with AUY922 if a separate toxicity occurs that would otherwise require dose modification.
If a participant requires a dose interruption of > 28 days from the last dose, then the participant must be discontinued from the study. Participants who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed.
*Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0).
**During the administration of AUY922, the infusion should be stopped if the participant experiences CTCAE grade 2 cardiovascular toxicity or any ≥ CTCAE grade 3 toxicity.

Participants who experience adverse events that require dose reduction will be treated at 54 mg/m^2 upon resolution of the adverse event.

6.3 Toxicity Management

6.3.1 Diarrheal Precautions

Both preclinical toxicology studies and clinical studies have shown AUY922 to cause gastrointestinal toxicities including diarrhea. In the event diarrhea is observed in participants the below management plan should be followed. This treatment algorithm is based on publications on how to manage diarrhea caused by cytotoxic regimens (Wadler 1998, Kornblau 2000).

First report of diarrhea

Please obtain a history of onset and duration of the diarrhea. This should include the description of number of stools from participants and stool composition (e.g. watery, presence of occult blood or mucus in stool etc.) Fever should be assessed and details should be obtained whether participant is also experiencing abdominal pain, cramps, bloating, distension, nausea, vomiting, dizziness and weakness in order to rule out the risk of sepsis, bowel obstruction or dehydration. Please review participant's medication profile and identify any diarrheogenic agents. Please also ask about participant's dietary profile to identify any diarrhea causing foods. Participants should be checked after starting AUY922 to proactively look for start of diarrhea so that anti-diarrheal treatment can be started as soon as possible to limit severity of the diarrheal toxicity. Call participants at home, if necessary, early during the first 8 weeks of AUY922 treatment start. Instruct the participant to call at the first sign of diarrhea.

Management of diarrhea

Participants should be instructed to stop all lactose-containing products and alcohol consumption after starting AUY922 treatment. Participants should also refrain from using laxatives, bulk fiber and stool softeners. Participants should be encouraged to drink 8 to 10 glasses of clear liquids a day and try to eat frequent small meals. High osmolar food supplements such as Ensure Plus® should be avoided.

Participants should be provided with loperamide tablets (or alternative anti-diarrheal agent). It is mandatory that participants are instructed on the use of loperamide in order to manage signs or symptoms of diarrhea at home. All medications that participants take should be recorded. Participants should be instructed to start taking oral loperamide (initial administration of 4 mg, then 2 mg every 4 hours, for a maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. Participants should be reminded of the use of loperamide during each clinic visit.

Treatment of Grade 1 and Grade 2 diarrhea

Grade 1 or grade 2 diarrhea will be treated with standard loperamide regimen (initial administration of 4 mg, then 2 mg every 4 hours, for a maximum of 16 mg/day). If diarrhea resolves within the next 24 hours continue instructions listed above for dietary modification and for participants to gradually introduce solid foods to their diet. Once participant has been event free for 12 hours loperamide use may be discontinued.

If diarrhea does not resolve after 24 hours, opium tincture or dihydrocodeine tartare tablets/injections should be added to the loperamide treatment. Participant should also be monitored to rule out dehydration, sepsis and ileus. Also refer to diarrhea work up section and determine if hospitalization is required. Continue to observe participant for response to antidiarrheal treatment.

If diarrhea resolves within 24 hours following opiate treatment, continue instructions listed above for dietary modification and for participant to gradually introduce solid foods to their diet. Once participant has been event free for 12 hours loperamide and opiate treatment use may be discontinued.

If diarrhea does not resolve after 24 hours after 2x24 hours loperamide treatment and opiates then admit participant to hospital and follow instructions below for grade 3 and grade 4 diarrhea until toxicity is resolved.

Treatment of grade 3 and grade 4 diarrhea

Participants experiencing grade 3 and grade 4 diarrhea must be hospitalized. Upon hospitalization participant should be treated with high dose loperamide (initial 4 mg, then 2 mg every 2 hours with addition of opium tincturate or dihydrocodeine tartrate tablets/injections). Participant should receive i.v. fluids and antiboitics if indicated and should be monitored to rule out sepsis, dehydration or ileus. Participant should be followed per diarrhea workup plan. Continue to observe participant for response to anti-diarrheal treatment.

If diarrhea does not resolve despite all these efforts please follow your institutional guidance for such clinical cases.

Diarrhea workup

The following appropriate tests are based on the following publication (AGA Technical Review on the Evaluation and Management of Chronic Diarrhea 1999).

Spot stool analysis

Collect stool and separate it from urine, use special containers and analyze immediately. If analysis can not be done immediately, freeze samples for later analysis. Examine the collected stool for occult blood and under the microscope examine for fecal leucocytes utilizing Wright staining. The stool should also be examined for C.difficile toxin. Lastly, examine fecal cultures for pathogens such as Shigella and pathogenic E. coli. If it is suspected that the participant might have been in contact with contaminated water, examine fecal cultures for Aeromonas and Pleisiomanas.

Endoscopic examinations

Endoscopic examinations should be only considered **if absolutely necessary.** Participant's bowel is likely to be fragile with evidence of colitis and great care and caution must be exercised in undertaking such an invasive procedure. If endoscopy is undertaken consider gastroscopy to obtain jejunal fluid for assessment of bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis. Also, consider sigmoidoscopy for reassessment of colitis.

6.3.2 Cardiac Safety Management Plan

6.3.2.1 Cardiac function measurements

In telemetry studies in monkeys, no clear effects on the QTc interval have been observed following administration of AUY922. Based upon *in vitro* and *in vivo* data, a potential for cardiovascular toxicity, such as QTcF prolongation or proarrhythmia with AUY922 could not be excluded; therefore, cardiovascular monitoring will be conducted throughout the study.

As part of the screening process, participants will be required to undergo either a MUGA or transthoracic echocardiogram to assess left ventricular ejection fraction (LVEF). Cardiac biomarkers will also be measured at baseline. Participants will also be required to undergo ECG monitoring at baseline. The purpose of this will be to establish an accurate QTc interval. Participants will have a total of 3 ECGs performed at baseline.

Upon initiation of treatment with AUY922, ECGs will be obtained as outlined in Tables 6-1 and 6-2. ECGs will be reviewed by the local investigators or a designee.

6.3.2.2 **Cardiac precautions**

All participants must have an assessment of serum potassium and magnesium within 72 hours of Day 1 dose administration of every treatment cycle (or more frequently if medically indicated). **Note: Participants who develop hypokalemia or hypomagnesemia during the study should receive electrolyte replacement and should not receive further AUY922 dosing until the respective electrolytes are documented to be within normal limits.** On days 1 and 15 of each cycle, the biochemistry results must be reviewed by the investigator before the participant is treated.

6.3.2.3 **Handling algorithm for cardiac changes**

If cardiac changes are observed during the above monitoring, please refer to Table 6-1 for dose modifications.

As AUY922 may have an influence on the QTc interval, ECGs will be the key cardiac assessment in this protocol. 12-lead ECG monitoring will be conducted according to the following schedule:

Table 6-2 ECG schedule

Cycle	Day	12-lead ECG	Timing and details
Baseline	Baseline	X	Three 12-lead ECGs.
1	1	X	A 12-lead ECG should be obtained prior to the infusion (timing not specified) and after infusion (within 5 minutes).
	2	X	A 12-lead ECG should be obtained at approximately 24hrs post end of infusion.
	3	X	A 12-lead ECG should be obtained at approximately 48 hrs post end of infusion.

	8	X	A 12-lead ECG should be obtained at pre-infusion (timing is not pre-specified) and after infusion (within 5 minutes).
	15	X	A 12-lead ECG should be obtained at pre-infusion (timing is not pre-specified) and after infusion (within 5 minutes).
All subsequent cycles	1, 8, 15	X	A 12-lead ECG should be obtained at pre-infusion (timing is not pre-specified) and after infusion (within 5 minutes).

6.3.3 **Ocular Safety Management Plan**

Weekly administration of AUY922 may cause visual symptoms. The visual symptom descriptions from ongoing phase 1 studies have included slow dark-light adaptation or photophobia, blurred vision, floaters and flashes in peripheral vision, dark or black spots, darkening of vision, decreased peripheral vision, color vision disturbances, and dry eye syndrome. The visual symptoms were mostly reported the day after the second or third infusion and typically resolved within a week or two weeks post dose. All visual symptoms were reversible; in some patients the events resolved with omission of a dose or after discontinuation of AUY922 treatment.

Standard ophthalmologic assessments will be required at baseline and follow-up exams will be conducted at the time when visual symptom(s) are reported (if any), at Cycle 3 Day 1 (±2 days) if no visual symptom(s) are reported, and at study discontinuation.

The following standard ophthalmologic assessments are required:

1. Visual acuity test
2. Intraocular pressure test
3. Slit-lamp test
4. Dilated fundus test
5. Color-vision (Ishihara-plate) test

Additional assessments or tests may be conducted as clinically indicated. Ophthalmologic assessments such as electro-retinograms (ERG) may be conducted, if feasible, at the discretion of the site.

Visual symptoms will be graded using NCI CTCAE 4.02. However, for the acuity test (Snellen charts) the following grading should be applied.

Table 6-3 Visual AE grading for AUY922 using Snellen charts

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Decreased Acuity	Decrease of 1 line or less of visual acuity from baseline in either eye despite visual symptoms	Decrease of 2-3 lines of visual acuity from baseline in either eye	Decrease of 4 or more lines of visual acuity from baseline in either eye	20/200 or below

Note: Refers to the visual acuity when a participant wears his or her best eyeglasses. The acuity scores pertain to the better eye.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 AUY922

7.1.1 How AUY is Supplied

Novartis supplies AUY922 in individual 10 mL amber-colored, glass ampoules, each containing 10 ml of a 5 mg/ml active drug substance in 5% aqueous glucose solution. Medication labels will comply with the legal requirements of each country and be printed in the local language. The labels will not supply any information about the participant. The storage conditions for study drug will be described on the medication label. The vials should be stored safely and separately from other drugs.

7.1.2 Preparation and Storage

AUY922 is intended for IV infusion and should be diluted to the appropriate concentration (according to patient body surface area) in a 500ml infusion bag containing 5% dextrose or glucose (with a maximum infusion volume of 500 ml) prior to administration. AUY922 has a pH of 4.2 ± 0.5. The drug may be administered using a central line or via peripheral vein. If a peripheral line is used, the injection site should be monitored carefully during the time of infusion and at subsequent follow-up visits. Irritations at the injection site were observed in one preclinical animal model; thus, an irritant potential for AUY922 can not be excluded. AUY922 is not considered a vesicant.

Novartis has confirmed the compatibility of AUY922 with a variety of US and European infusion systems across a range of concentrations.

Please follow the preparation instruction provided below.

Important notes:

- **The vials have an under-fill/over-fill tolerance of -0.4/0.5+ ml.**
- **Each vial is for a single dose and may not be used for multiple doses.**
- **All preparation steps must be performed under aseptic conditions.**
- **Do not infuse the concentrated solution directly into the participant.**
- **AUY922 must not be administered by intramuscular or subcutaneous route.**

- **In the event of extravasation, institutional standard of care should be followed. The infusion should be immediately stopped and the affected extremity should be elevated.**

7.1.3 Pharmacy Handling Instructions for AUY922

7.1.4 Treatment Arms

This is a single-arm, open-label phase II trial of AUY922 in participants with advanced, ALK-rearranged NSCLC and acquired resistance to prior ALK TKI treatment. All participants will receive the same dose and schedule of study medication, which is AUY922 intravenously weekly at 70 mg/m^2.

7.1.5 Administration

AUY922 will be administered by a 1 hour (+10 minute window period) intravenous infusion (in 5% glucose/dextrose) at 70 mg/m^2 on days 1, 8, and 15 of each treatment cycle (21 days in duration). A scheduled dose may be administered ± 48 hours of the scheduled day due to public or religious holidays. If a peripheral line is used for the infusion of the study drug, the injection site should be monitored carefully during the time of infusion.

8. STUDY CALENDAR AND ASSESSMENTS

Table 8-1 lists all of the assessments and indicates with an "X" the visit when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. For assessment window periods, please refer to Table 8-1 as well as Sections 8.1.5 – 8.1.11.

Table 8-1 Visit evaluation schedule

	Baseline	Cycle 1					Cycle 2			Subsequent cycles			End of Treatment	28 Day Safety Visit	Treatment Follow-up Period	End of Study
Day of Cycle	-21 to -1	1	2	3	8	15	1	8	15	1	8	15	Within 7 days of last dose	28 days of last dose (±7 days)		
Informed consent	X															
Demographics	X															
Inclusion/Exclusion Criteria	X															
Relevant medical history/current medical conditions	X															
Diagnosis and extent of tumor	X															
Prior anti-neoplastic therapies	X															
Smoking history	X															
Vitals signs[1]	X	X			X	X	X	X	X	X	X	X	X			
Weight and BSA	X	X			X	X	X	X	X	X	X	X	X			
Height	X															
Physical Exam	X	X				X	X		X	X		X	X			
ECOG Performance Status	X	X			X	X	X	X	X	X	X	X	X			
12-lead ECG[2-4]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Cardiac imaging (MUGA or ECHO)	X												X			
Hematology	X	X				X	X		X	X		X	X			

	Baseline	Cycle 1					Cycle 2			Subsequent Cycles			End of Treatment	28 Day Safety Visit	Follow-up	End of Study
Day of Cycle	-21 to -1	1	2	3	8	15	1	8	15	1	8	15	Within 7 days of last dose	28 days of last dose (±7 days)		
Coagulation	X	X				X	X			X			X			
Biochemistry	X	X				X	X		X	X		X	X			
Serum Pregnancy Test[5]	X									X						
Cardiac Enzymes	X												X			
Urinalysis	X	X					X			X			X			
Eye Exam[6]	X[6]									X[6]			X[6]			
AUY922 IV infusion		X			X	X	X	X	X	X	X	X				
Concomitant Medications	X	Ongoing											X			
Adverse Events	X	Ongoing											X	X		
Radiological assessment of tumor – CT/MRI[7]	X									X					X[8]	
Tumor biopsy[9]	X												X			
Anti-neoplastic therapy														X	X	
Survival[10]														X	X	X
1. Vital sings – During treatment period, vital signs will be performed pre- and immediately post-dose infusion. Assessments to include oral temperature, respiratory rate, sitting blood pressure and sitting pulse.																
2. ECG- At baseline, all participants will be required to undergo three 12-lead ECGs.																
3. ECG – Please refer to Table 6-2 for ECG window periods.																

	Baseline	Cycle 1					Cycle 2			Subsequent Cycles			End of Treatment	28 Day Safety Visit	Follow-up	End of Study
Day of Cycle	-21 to -1	1	2	3	8	15	1	8	15	1	8	15	Within 7 days of last dose	28 days of last dose (±7 days)		
4. ECG – At end of treatment, ECGs can be obtained at any time.																
5. A serum pregnancy test must be obtained prior (within 72 hours) to the first administration of AUY922. The test should be repeated prior to D1 of every subsequent odd numbered cycle (within 72 hours) or if pregnancy is suspected.																
6. Standard ophthalmologic assessments will be required at baseline and follow-up exams will be conducted at the time when visual symptoms are reported (if any), at cycle 3 day 1 (±2 days) if no visual symptoms are reported, and at study discontinuation (±7 days).																
7. A CT scan with contrast of the chest, abdomen, and pelvis will be performed on participants at baseline (screening) -21 to -1 days prior to study drug administration. The same type of imaging modality (CT with contrast or MRI) used at screening must be used for all subsequent follow-up assessments. Follow-up CT/MRI scans will be performed every 6 weeks (±7 days) from start of study treatment.																
8. In the event that a participant is discontinued from treatment for any reason other than disease progression, an end of treatment CT/MRI is recommended to be performed if the last scan was conducted ≥ 4 weeks previously. Such participants who discontinue study treatment for reasons other than disease progression will be re-staged every 12 weeks (±7 days) until start of another anti-cancer treatment. A partial or complete response warrants confirmation assessment no sooner than 4 weeks and no later than 6 weeks after its initial observation. An end of study scan is required if the participant is discontinued from treatment for any reason other than disease progression and the last scan was performed ≥ 4 weeks.																
9. In consented participants, an optional biopsy will be performed at baseline and again at the end of treatment.																
10. Participants will be followed for survival every 12 weeks after discontinuing the trial. Follow-ups may be conducted over the telephone.																

8.1 Assessments

8.1.1 Participant Demographics / Baseline Characteristics

The data that will be collected on participant characteristics at baseline include general demographics, relevant medical history, smoking history, the diagnosis and extent of tumor(s) and details regarding prior anti-neoplastic therapy.

8.1.2 Efficacy

Throughout the trial, modified RECIST criteria (See Section 9) must be applied to CT/MRI imaging data when assessing any responses to AUY922 treatment. All complete and partial responses must be confirmed by a second assessment at least 4 weeks later but no more than 6 weeks later.

The CT/MRI scans should be contiguous throughout the chest, abdomen and pelvis, with the same window setting at each visit. An adequate amount of contrast agent should be given, such that the tumor lesions appear with good resolution. All known measurable lesions, up to 10 lesions in total and up to 5 lesions per organ, should be selected as target lesions at screening. All other lesions not included as target lesions should be identified as non-target lesions and recorded at baseline – excess measurable and all non-measurable lesions. For subsequent scans in the same participant, the radiologist must account for all lesions that were present at screening and must use the same technique

Tumor assessment for RECIST criteria will be performed by independent central review through the DFCI/HCC Tumor Imaging Metrics Core (TIMC). These reviews will be used only for determining response by RECIST criteria, and do not need to be used for clinical decision making in real time.

Note: Any lesions that have been previously treated with radiation therapy should not be used as target lesions for tumor assessment. Exceptions will be considered if there has been documented tumor progression.

8.1.3 Safety

Safety assessments should consist of monitoring and recording of all adverse events (AEs), including serious adverse events (SAE). Safety assessments will also include the regular monitoring of hematology, serum chemistry, urinalysis, vital signs (heart rate, blood pressure, and body temperature), weight, ECOG performance status, chest CT scans, and physical condition.

Toxicity will be assessed using the NCI-CTC Common Terminology Criteria for Adverse Events, version 4.02 (CTCAEv4.02, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

8.1.4 Adverse Events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s).

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.02. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, **or** grades 1 - 4, will be used. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment. Please see Section 10 for further details on safety monitoring and reporting of adverse events and serious adverse events.

8.1.5 Physical examination, weight and height

Physical examinations will be conducted at baseline and during the study (see Table 8-1). These examinations will be performed according to the standards at each institution.

Weight will be measured at baseline, each day of study treatment (days 1, 8, and 15 of each cycle) and then upon end of treatment. Height will be recorded at baseline.

Physical examinations and weight will be performed on the scheduled day, even if study medication is held. More frequent examinations may be performed at the investigator's discretion, if medically indicated. If these baseline examinations are performed ≤ 72 hours prior to the first infusion of AUY922, they need not be repeated on day 1 of cycle 1. For the follow-up visits, examinations in most cases can be performed within 48 hours prior to visit day. Information about the physical examination and vital signs must be present in source documentation at the study site.

8.1.6 Vital signs

Vital signs will consist of oral temperature, respiratory rate, sitting blood pressure, and sitting pulse). Vital signs will be performed at the following times:

- Baseline (≤ 72 hours prior to first infusion)
- Every study drug infusion day (pre and post dose)
- End of treatment

Vital signs should be assessed on the scheduled day, even if study medication is held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

8.1.7 ECOG Performance Status

ECOG performance status will be documented at:

- Baseline (≤ 72 hours prior to first infusion)
- Days 1*, 8, and 15 of each treatment cycle (≤ 48 hours prior to infusion)
- End of treatment

Assessment of ECOG Performance Status will be performed on the scheduled day, even if study medication is held.

*Note: If the baseline assessment was performed ≤ 72 hours prior to the first infusion of AUY922, then it does not need to be repeated on day 1 of cycle 1.

Table 8-2 ECOG Performance Status Scale

Grade 0	Fully active, able to carry on all pre-disease performance without restriction
Grade 1	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)
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Grade 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

8.1.8 Laboratory Evaluations

The standard clinical laboratory analyses described below are to be performed by the study site's local laboratories according to the Visit Schedule (Table 8-1). More frequent examinations may be performed at the investigator's discretion if medically indicated.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g. any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g. cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded.

8.1.8.1 Hematology

Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell count (RBCs) a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count.

Hematology must be performed at:

- Baseline (≤ 72 hours prior to first infusion)
- Day 1* and 15 of each treatment cycle (≤ 48 hours prior to infusion)
- End of treatment

*Note: If the baseline assessment was performed ≤ 72 hours prior to the first infusion of AUY922, then it does not need to be repeated on day 1 of cycle 1.

8.1.8.2 Coagulation

Coagulation studies will include prothrombin time or INR, activated partial thromboplatin time and fibrinogen.

A coagulation profile must be performed at:

- Baseline (≤ 72 hours prior to first infusion)
- Day 1* of each treatment cycle (≤ 48 hours prior to infusion)
- End of treatment

*Note: If the baseline assessment was performed ≤ 72 hours prior to the first infusion of AUY922, then it does not need to be repeated on day 1 of cycle 1.

8.1.8.3 **Biochemistry**

Biochemistry includes the following parameters: urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, magnesium, phosphorous, glucose, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT), uric acid and LDH.

Biochemistry analysis must be performed at:

- Baseline (≤ 72 hours prior to first infusion)
- Day 1* and 15 of each treatment cycle (≤ 48 hours prior to infusion)
- End of treatment

*Note: If the baseline assessment was performed ≤ 72 hours prior to the first infusion of AUY922, then it does not need to be repeated on day 1 of cycle 1.

Note: Participants who develop hypokalemia or hypomagnesemia during the study should receive electrolyte replacement as soon as possible and should not receive further AUY922 dosing until the respective electrolytes are documented to be within normal limits. On treatment days 1 and 15, the biochemistry results must be reviewed by the investigator before the participant is treated.

8.1.8.4 **Urinalysis**

Urinalysis includes macroscopic (protein, glucose, blood and specific gravity) exam. A microscopic (WBC per high powered field, RBC per high powered field, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

Urinalysis must be performed at the following times unless otherwise specified:

- Baseline* (≤ 72 hours prior to first infusion)
- Day 1** of each treatment cycle (≤ 48 hours prior to infusion)
- End of treatment

*Note: If greater than 1+ protein is obtained at baseline, then a 24-hour urine sample will need to be collected and analyzed for protein excretion and creatinine clearance.
**If the baseline assessment was performed ≤72 hours prior to the first infusion of AUY922, then it does not need to be repeated on day 1 of cycle 1.

8.1.8.5 Pregnancy Test

All females of childbearing potential should have a serum pregnancy test (beta-HCG) at the following time unless otherwise specified:

- Baseline (within 72 hours of initial administration of AUY922)
- ≤72 hours prior to Day 1 of each subsequent odd numbered cycle or if pregnancy is suspected.

Note: Postmenopausal women must have been amenorrheic for ≥ 24 months in order to be considered "of non-childbearing potential". This should be documented appropriately in the participant's medical history.

To ensure participant safety, each pregnancy in a participant on study drug must be reported to the Principal Investigator, who will in turn communicate this to Novartis. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

8.1.9 Radiological Assessments

The radiological examinations should be conducted as required by the protocol or clinically indicated. For each participant, if an initial radiological assessment is conducted using one imaging modality, all radiological assessments in subsequent cycles should always be conducted using the same technique.

All sites of tumor lesions must be assessed using CT or MRI imaging; however, CT is the preferred imaging modality to be used in this study. Each lesion that is measured at baseline must be measured by the same method throughout the study to ensure that a comparison between each scan can be made. If at baseline a participant has a medical contraindication to CT intravenous contrast or develops a contraindication during the trial, a non-contrast CT of the chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of the abdomen and pelvis is acceptable.

While the participant is enrolled in the study, follow-up CT/MRI scanning should occur at the frequency indicated in the visit assessment schedule, or as clinically indicated. In the event that a participant is discontinued from treatment for any reason other than disease progression, an end of study CT/MRI is recommended to be performed if the last scan was obtained ≥ 4 weeks previously. In addition, attempts should be made to assess response in these participants every 3 months (i.e. every 12 weeks ± 7 days) after discontinuation from the study until disease progression, initiation of other anticancer therapy or study termination.

Throughout the trial, modified RECIST must be applied when assessing any responses to AUY922

Baseline CT/MRI scans are to be performed within twenty-one (21) days prior to the date of first dose of study treatment. After baseline scheduled CT/MRI scans on or after day 1 of cycle 3 are allowed a window of assessment of ± 7 days.

8.1.10 Cardiac Assessments

The following cardiac assessments should be conducted as required by the protocol or when clinically indicated. In pre-clinical *in vitro* studies, AUY922 showed potential cardiac toxicity. Although ongoing clinical studies have not revealed significant cardiac toxicity signals, extra attention should be paid for potential cardiac toxicity.

8.1.10.1 Electrocardiogram

As AUY922 may have an influence on the QTc interval, ECGs will be the key cardiac assessment in this protocol. 12-lead ECG monitoring will be conducted according to the schedule on Table 6-2.

8.1.10.2 Cardiac Enzymes

Cardiac enzymes include troponin-I or troponin-T, creatine phosphokinase (CK), and the MB isoenzyme of CK (CK-MB). Cardiac enzymes need only be assessed at baseline (unless otherwise clinically indicated) and at the end of treatment.

8.1.10.3 Cardiac Imaging

A MUGA or trans-thoracic echocardiogram should be performed at baseline and end of treatment (±7 days) to assess the left ventricular ejection fraction (LVEF). These assessments may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity.

8.1.11 Ophthalmology Assessments

Standard ophthalmologic assessments will be required at baseline and follow-up exams will be conducted at the time when visual symptom(s) are reported (if any), at cycle 3 day 1 (±2 days) if no visual symptom(s) are reported, and at the end of treatment.

The following standard ophthalmologic assessments are required:

- Visual acuity test
- Intraocular pressure test
- Slit-lamp test
- Dilated fundus test
- Color-vision (Ishihara-plate) test

Additional assessments or tests, such as electro-retinograms (ERG), may be considered if clinically indicated and feasible, at the discretion of the site.

8.1.12 Biopsy collection (optional)

Tumor tissue (an incisional biopsy or 18 gauge core biopsy) will be collected under bronchoscopy, endobronchial ultrasound or other imaging guidance according to the table below if participants provide consent.

Table 8-3 Tumor collection details (optional)

Visit	Details
Baseline	A baseline biopsy at the time of disease progression on ALK TKI prior to treatment with AUY922 will be collected if feasible, accessible and agreed to by the participant.
End of Treatment	Collect when feasible and accessible.

An optional baseline biopsy at the time of disease progression on crizotinib or alternative ALK TKI will be offered to participants. The purpose of this optional study is to perform repeat molecular analysis on the specimen, assessing for the continued presence of the ALK fusion transcript as well as investigating possible resistance mechanisms to ALK TKI (e.g. ALK amplification, secondary mutations within the ALK kinase domain).

A second optional biopsy will be offered to participants at the end of study. The purpose of this biopsy is to investigate potential resistance mechanisms to AUY922.

8.1.13 Potential predictive markers and exploring markers of resistance

Tumor samples will be analyzed for the presence of mutations in KRAS to determine the prevalence of concurrent ALK translocations and KRAS mutations. Additionally, we will investigate whether individuals with both mutations are more or less likely to respond to AUY922 treatment. These studies will be carried out in all participants, in archival and/or fresh pre-treatment tumor samples.

Archival tissue will also be examined to determine the specific ALK translocation variant present. If no archival tissue is available, then fresh pre-treatment tumor samples may be used. This information will be used to assess how different ALK translocation variants impact the efficacy of AUY922.

Since all participants are required to have received an ALK TKI within 30 days of enrollment, pre-AUY922 treatment biopsy specimens, when available, will be analyzed for potential mechanisms of resistance to ALK tyrosine kinase inhibition. These specimens will be evaluated for ALK gene amplification, secondary mutations in the ALK tyrosine kinase domain, and amplification of bypass tracts in c-KIT and EGFR in order to determine whether certain populations of TKI-resistant, ALK-rearranged participants respond more favorably to AUY922. These studies will be carried out in all participants when tumor samples are available.

In addition, end of treatment biopsy specimens, if available, will be analyzed for potential mechanisms of resistance of AUY922. Specimens will again be evaluated for ALK gene amplification, secondary mutations in the ALK tyrosine kinase domain, and amplification of bypass tracts in c-KIT and EGFR. Due to the evolving nature of the field, not all of the proteins or genes of interest leading to resistance can be pre-specified in this document.

9. MEASUREMENT OF EFFECT

Participants will be assessed by RECIST version 1.1 criteria. For the purposes of this study, participants should be reevaluated every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained no sooner than 4 weeks and no later than 6 weeks following initial documentation of an objective response.

9.1 Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al, 2009) guideline. Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

9.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective 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 response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.}

9.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

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/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

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. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions. All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

9.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or 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 when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Participants should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Participants should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult participants. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent participant preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

9.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node 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 with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

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.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: 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 (ex: new bone lesions may be 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.

Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

*Definition of New Lesion: 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 (ex: new bone lesions may be 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.

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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response for 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	

* 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.

9.1.5 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 recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

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 recurrent disease is objectively documented.

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.

9.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study enrollment to time of objective disease progression or death from any cause.

10. ADVERSE EVENT REPORTING REQUIREMENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

10.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more sever form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

10.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

10.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

10.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

10.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

10.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

10.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

10.4 Reporting to the Study Sponsor

10.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 10.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Alice Shaw, MD, PhD
Ashaw1@partners.org
Phone: 617-724-4000
[redacted]

AND

[redacted]

AND

Novartis Pharmaceuticals Integrated Medical Safety Department
[redacted]

AND

FDA via MedWatch 3500A. Please fax to phone number listed on the MedWatch form

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

10.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

10.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Alice Shaw, MD, PhD
Ashaw1@partners.org
Phone: 617-724-4000
[redacted]

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

10.6 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

10.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

10.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11. DATA AND SAFETY MONITORING

11.1 Data Reporting

11.1.1 Method

The QACT will collect, manage, and monitor data for this study.

11.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. 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 Principal Investigator and study team.

The DSMC will meet quarterly and/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 for Phase I or II protocols; for gene transfer 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.

11.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

12. REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This study will enroll participants with ALK-rearranged, advanced (stage IIIB or IV) NSCLC with acquired resistance or intolerance to ALK TKI therapy. Participants will receive AUY922 on a weekly basis with radiographic assessments of response performed every 6 weeks. Response will be scored by RECIST version 1.1 criteria and consist of partial responses and complete responses. Treatment with AUY922 will continue until disease progression, unacceptable toxicity, participant withdrawal, death or discontinuation from the study for any other reason.

In order to investigate the preliminary efficacy of AUY922 in participants with acquired resistance or intolerance to ALK TKIs, the primary endpoint for this cohort is the best overall response rate using RECIST version 1.1 criteria. If at least 4 of 20 participants were to achieve a complete or partial response, AUY922 will be considered to have promising clinical activity in this molecularly defined population. The decision rule is associated with 89% power if 30% of participants in this population truly were to have tumors responsive to AUY922. In contrast, the probability of type 1 error is only 13% if the underlying rate of overall response were 10%, indicating a minimal level of anti-tumor activity.

13.2 Sample Size/Accrual Rate

Our estimated sample size is 20 participants. ALK translocations are identified in approximately 4-5% of patients with NSCLC. At MGH alone, approximately 500 patients with NSCLC undergo genotyping annually. Since a majority of these cases are likely to be ALK TKI naïve our study population is likely to be smaller. Across all participating institutions, we hope to enroll 1 participant per month.

13.3 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed for exploratory purposes only. Participants with ALK TKI resistance and those with ALK TKI intolerance will be analyzed collectively and as distinct cohorts for all endpoints.

Disease Control Rates: Disease control rates (DCR) will be scored according to RECIST version 1.1 criteria and consist of complete response, partial response, and stable disease.

Progression-free and Overall Survival Rates: Progression-free survival (PFS) will be defined as the time from the date of study enrollment to the date of first documented progression or death due to any cause. Overall survival will be defined as the time from study enrollment to death from any cause.

Safety: Toxicity will be assessed using CTC v4.02 criteria. All participants who receive any amount of study drug will be evaluable for toxicity.

KRAS Mutations: Concurrent KRAS mutations will be reported as frequencies. Descriptions of the specific KRAS mutations will also be reported.

ALK Translocation Variant: Exploratory, hypothesis-generating analysis will be performed to correlate different ALK translocation variants with response to treatment with AUY922.

Mechanisms of Resistance: Exploratory, hypothesis-generating analyses will be performed to correlate any findings from the various potential biomarker studies listed in Section 8 with the primary and secondary study endpoints above.

13.4 Reporting and Exclusions

13.4.1 **Evaluation of toxicity.** All participants will be evaluable for toxicity from the time of their first treatment.

13.4.2 **Evaluation of response**. Participants who received no study treatments will not be evaluated for response to treatment. All other participants included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

All of the participants who met the eligibility criteria and were enrolled, except participants who did not receive any study medication, will be included in the main analysis of the response rate and calculation of survival.

14. PUBLICATION PLAN

It is anticipated that the results of this study will first be reported in abstract form, followed by presentation in a peer-reviewed manuscript.

15. REFERENCES

AGA Technical Review on the Evaluation and Management of Chronic Diarrhea (1999) Gastroenterol; 116:1464-86.

Banerji U (2009) Heat Shock Protein 90 as a Drug Target: Some like it Hot. Clin Cancer Res; 15(1): 9-14.

Biamonte MA, Van de Water R, Arndt JW et al (2010) Heat Shock Protein 90: Inhibitors in Clinical Trials. J Med Chem; 53: 3-17.

Camidge DR, Bang Y, Kwak EL, et al (2011) Progression-free survival (PFS) from a phase I study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol; 29 (Suppl):2501

Chen Z, Sasaki T, Tan X, et al (2010) Inhibition of ALK, PI3K/MEK, and HSP90 in murine lung adenocarcinoma induced by EML4-ALK fusion oncogene. Cancer Res; 70(23):9827-36.

Chène P (2002) ATPases as drug targets: learning from their structure. Nature Rev. Drug Discov. 1: 665-73.

Choi YL, Soda M, Yamashita Y, et al (2010) EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med; 363(18):1734-39.

Choi YL, Takeuchi K, Soda M, et al (2008) Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. Cancer Res; 68(13):4971-6.

Demetri GD, von Mehren M, Blanke CD, et al (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med; 347:472-80.

Doebele RC, Pilling AB, Aisner DL, et al (2012) Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res. 18(5):1472-82.

Erlichmann C (2009) Tanespimycin: the opportunities and challenges of targeting heat shock protein 90. Expert Opin Investig Drugs;18(6): 861-68.

Garon EB, Finn RS, Dering J, et al (2009) Identification of predictors of response to NVP-AUY922, an HSP90 inhibitor, in an *in vitro* panel of human non-small-cell lung cancer (NSCLC) cell lines [abstract]. 13th World Conference on Lung Cancer. PD13.5.5.

Garon EB, Moran T, Barlesi F, et al (2012) Phase II study of the Hsp90 inhibitor AUY922 in patients with previously treated, advanced non-small cell lung cancer. J Clin Oncol (suppl; abstr 7543).

Gazitt Y, Kolaparthi V, Moncada K, et al (2009) Targeted therapy of human osteosarcoma with 17AAG or rapamycin: characterization of induced apoptosis and inhibition of mTOR and Akt/MAPK/Wnt pathways. Int J Oncol; 34(2): 551-61.

Georgakis GV, Younes A (2005) Heat-shock protein 90 inhibitors in cancer therapy: 17AAG and beyond. Future Oncology; 1(2):273-81.

Herbst RS, Heymach JV, Lippman, SM (2008) Lung Cancer. N Engl J Med; 359(13):1367-80.

Heuckmann JM, Balke-Want H, Malchers F, et al (2012) Differential protein stability and ALK inhibitor sensitivity of EML4-ALK fusion variants. Clin Cancer Res; 18(17):1-9.

Jackman D, Pao W, Riely GJ, et al (2010) Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. J Clin Oncol; 28(2):357-60.

Jakob U, Buchner J (1994) Assisting spontaneity: the role of Hsp90 and small Hsps as molecular chaperones. Trends Biochem Sci.; 19; 205-11.

Jayanthan A, Fowler J, Hawkins L, et al (2008) Effects of Hsp90 inhibition in neuroblastoma: analysis of drug sensitivity, target modulation and the influence of bone marrow microenviroment. J Exp Ther Oncol; 7(3): 183-93.

Jemal A, Siegel R, Ward E, et al (2008) Cancer Statistics, 2008. CA Cancer J Clin; 58:71-96.

Kamal A, Thao L, Sensintaffar J, et al (2003) A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. Nature; 425: 407-10.

Katayama R, Khan TM, Benes C, et al (2011) Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. Proc Natl Acad Sci USA; 108(18):7535-40.

Katayama R, Shaw AT, Khan TM, et al (2012) Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med; 4(120):120ra17.

Kim WY, Oh SH, Woo JK, et al (2009) Targeting heat shock protein 90 overrides the resistance of lung cancer cells by blocking radiation-induced stabilization of hypoxia-inducible factor-1alpha. Cancer Res; 69(4): 1624-32.

Kol TT, Feiss SS, Wright MH, et al (2008) HSP90 inhibitor, DMAG, synergizes with radiation of lung cancer cells by interfering with base excision and ATM-mediated DNA repair. Mol Cancer Ther; 7: 1985-92.

Kornblau S, Bensen AB, Catalano R, et al (2000) Management of cancer treatment-related diarrhea: Issues and therapeutic strategies. Journal of Pain and Symptom Management; 19:118-129.

Kwak EL, Bang YJ, Camidge DR, et al (2010) Anaplastic lymphoma kinase inhibition in non-small cell lung cancer. N Engl J Med; 363(18):1693-703.

Li Y, Zhang T, Sun D (2009) New Developments in Hsp90 inhibitors as anti-cancer therapeutics: mechanisms, clinical perspective and more potential. Drug resist updat. 12(1-2):17-27.

Lovely CM, Pao W (2012) Escaping ALK inhibition: Mechanisms of and Strategies to Overcome Resistance. Sci Tranl Med: 4(120):120ps2.

McCollum AK, Lukasiewicz KB, Teneyck CJ, et al (2008) Cisplatin abrogates the geldanamycin-induced heat shock response. Mol Cancer Ther; 7(10):3256-64.

Mitsiades C, Chanan-Khan A, Alsina M, et al (2005) Phase I Trial of 17-AAG in Patients with Relapsed Refractory Multiple Myeloma [abstract]. J Clin Oncol; 23(16 Suppl):3056.

Miller K, Rosen LS, Modi S, et al (2007) Phase I trial of alvespimycin (KOS-1022; 17-DMAG) and trastuzumab (T) [abstract]. J Clin Oncol; 25(18 Suppl):1115.

Miller VA, Riely GJ, Zakowski MF, et al (2008) Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, brochioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol; 26(9):1472-8.

Modi S, Stopeck A, Gordon M, et al (2006) Phase I dose escalating trial of KOS-953 (Heat shock protein 90 inhibitor) and Trastuzumab [abstract]. AACR Annual Meeting Abstract, Washington DC, April 1-5.

Normant E, Paez G, West KA, et al (2011) The HSP90 inhibitor IPI-504 rapidly lowers EML4-ALK levels and induces tumor regression in ALK-driven NSCLC models. Oncogene; 30:2581-6.

Pacey SC, Wilson R, Walton M, et al (2009) A phase 1 trial of the HSP90 inhibitor, alvespimycin (17-DMAG) administered weekly, intravenously, to patients with advanced, solid tumours [abstract]. J Clin Oncol; 27(15suppl): 3534.

Pratt WB (1998) The hsp90-based chaperone system: involvement in signal transduction from a variety of hormone and growth factor receptors. Proc Soc Exptl Biol Med; 217:420-34.

Pratt WB, Toft DO (2003) Regulation of signaling protein function and trafficking by the hsp90/hsp70-based chaperone machinery. Exp. Biol. Med.; 228; 111-33.

Powers, M.V. and Workman, P. (2006) Targeting of multiple signalling pathways by heat shock protein 90 molecular chaperone inhibitors. Endocr Relat Cancer 13 (Suppl. 1), S125-S135.

Prodromou C, Pearl LH (2003) Structure and functional relationships of Hsp90. Curr Cancer Drug Targets 3(5):301-23.

Saif MW, Erlichman C, Dragovich T, et al (2006) Phase I study of CNF1010 (lipid formulation of 17-(allylamino)-17-demethoxygeldanamycin: 17-AAG) in patients with advanced solid tumors [abstract]. J Clin Oncol; 24(18 Suppl):10062.

Samuel TA, Sessa C, Britten C, et al (2010) AUY922, a novel HSP90 inhibitor: Final results of a first-in-human study in patients with advanced solid malignancies. J Clin Oncol 28:15s, (suppl; abstr 2528).

Sasaki T, Koivunen J, Ogino A, et al (2011) A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. Cancer Res; 71(18):6051-60.

Sequist LV, Gettinger S, Senzer NN, et al (2010) Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small cell lung cancer. J Clin Oncol; 28(33):4953-4960.

Sequist LV, Lynch TJ (2008) EGFR tyrosine kinase inhibitors in lung cancer: an evolving story. Annu Rev Med; 59:429-442.

Shaw AT, Solomon B (2011) Targeting anaplastic lymphoma kinase in lung cancer. Clin Cancer Res; 17(8):2081-6.

Soda M, Choi YL, Enomoto M, et al (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature; 448:561-6.

Soda M, Takada S, Takeuchi K, et al (2008) A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A; 105:19893-7.

Solit DB, Rosen N (2006) Hsp90: a novel target for cancer therapy. Curr Top Med Chem; 6(11):1205-14.

Spira A, Ettinger DS (2004) Multidisciplinary management of lung cancer. N Engl J Med; 350:379-92.

Takeuchi K, Choi YL, Soda M, et al (2008) Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts. Clin Cancer Res; 14(20):6618-24.

Takeuchi K, Choi YL, Togashi Y, et al (2009) KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK positive lung cancer. Clin Cancer Res; 15(9):3143-9.

Wadler S, Benson AB, Engelking C, et al (1998) Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J Clin Oncol; 16:3169-78.

Welch WJ, Feramisco JR (1982) Purification of the major mammalian heat shock proteins. J Biol Chem; 257(24):14949-59.

Zhang M, Boter M, Li K, et al (2008) Structural and functional coupling of Hsp90- and Sgt1-centered multi-protein complexes. The EMBO journal; 27:2789-98.

16. APPENDICES

Appendix A

Excluded Medications

The use of any concomitant medication deemed necessary for the care of the participant is permitted, with the following exceptions.

- Therapeutic doses of warfarin sodium are not permitted (>2 mg/day)
- If, after a participant has enrolled, he/she requires the concomitant use of any of the medications listed in Table 1-1 which may cause QT prolongation, then the participant must be discontinued from the study. Excluded medications which may cause QTc prolongation are also listed and updated in website: **qtdrugs.org/medical-pros/drug-list/drug-lists.htm.**
- Participants whose cancer has progressed while receiving HSP90 or HDAC inhibitors should be excluded from entering the study.

Table 1-1 List of Excluded Medications

Drug Name	Drug Class	Reason for Exclusion
17-AAG	HSP90 Inhibitor	Known to have HSP90 inhibition
17-DMAG	HSP90 Inhibitor	Known to have HSP90 inhibition
Amitriptyline	Antidepressant	May prolong QTc
Apicidin	Cyclic Peptid	Known to have HDAC inhibition
Arsenic trioxide	Miscellaneous	May prolong QTc
Bepridil	Miscellaneous	May prolong QTc
CBHA	Hydroxamic Acids	Known to have HDAC inhibition
CGI 242	HSP90 Inhibitor	Known to have HSP90 inhibition
Chloroquine	Anti-malarial	May prolong QTc
Chlorpromazine	Anti-psychotic	May prolong QTc
CI-944	Benzamides	Known to have HDAC inhibition
Cisapride	Miscellaneous	May prolong QTc
CNF 1010	HSP90 Inhibitor	Known to have HSP90 inhibition
Depsipeptide/FK228	Cyclic Peptid	Known to have HDAC inhibition
Desipramine	Antidepressant	May prolong QTc
Dolasetron	Anti-emetic	May prolong QTc
Domperidone	Miscellaneous	May prolong QTc
Doxepin	Antidepressant	May prolong QTc
Droperidol	Miscellaneous	May prolong QTc
Gatifloxacin	Antibiotic	May prolong QTc
Halofantrine	Anti-malarial	May prolong QTc
Imipramine	Antidepressant	May prolong QTc
IPI-504	HSP90 Inhibitor	Known to have HSP90 inhibition
Itraconazole	Antifungal	May prolong QTc and CYP3A4 inhibitor
Ketoconazole	Antifungal	May prolong QTc and CYP3A4 inhibitor
KOS-953	HSP90 Inhibitor	Known to have HSP90 inhibition
LAQ824	Hydroxamic Acids	Known to have HDAC inhibition
Maprotiline	Antidepressant	May prolong QTc
Mesoridazine	Anti-psychotic	May prolong QTc
Methadone	Miscellaneous	May prolong QTc
Moxifloxacin	Antibiotic	May prolong QTc
MS-275	Benzamides	Known to have HDAC inhibition
Ondansetron	Anti-emetic	May prolong QTc

Pentamidine	Miscellaneous	May prolong QTc
Pimozide	Anti-psychotic	May prolong QTc
Risperidone	Anti-psychotic	May prolong QTc
SAHA	Hydroxamic Acids	Known to have HDAC inhibition
Sodium butyrate	Hydroxamic Acids	Known to have HDAC inhibition
Sparfloxacin	Antibiotic	May prolong QTc
SRN 005	HSP90 Inhibitor	Known to have HSP90 inhibition
Stresgenin B	HSP90 Inhibitor	Known to have HSP90 inhibition
Thioridazine	Anti-psychotic	May prolong QTc
Tropisetron	Anti-emetic	May prolong QTc
TSA	Hydroxamic Acids	Known to have HDAC inhibition
Venlafaxine	Antidepressant	May prolong QTc
Ziprasidone	Anti-psychotic	May prolong QTc

Medications to be Used with Caution

The *in vitro* metabolism studies suggest that AUY922 is a moderate inhibitor of CYPs 2C8, 2C9, 2C19, and 3A4. Therefore, drugs known to be metabolized by or act as inducers or inhibitors of CYPs 2C8, 2C9, 2C19, and 3A4 should be used caution because of the risk of either reduced or enhanced activity / toxicity of the respective concomitant medication. Participants using concomitant medications known to be metabolized by these CYP isoenzymes or to interact with these enzymes will not be excluded from the study; however, the participants must be carefully monitored for potentiation of toxicity. For an up to date list of concomitant medications that are metabolized by or act as inducers/inhibitors of CYPs 2C8, 2C9, 2C19 and 3A4, please see:

http://medicine.iupui.edu/clinpharm/ddis/table.aspx