

# Phase II Study of AUY922 in NSCLC Patients With Exon 20 Insertion Mutations in EGFR

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## 1. OBJECTIVES

### 1.1 Study Design

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<sup>2</sup> in adult NSCLC patients with advanced disease and *EGFR* exon 20 insertion mutations. The design will be a Simon two-stage phase 2 study, with 10 patients enrolled to the first stage and an additional 19 patients enrolled to the second stage provided we observe at least 1 partial or complete response or stable disease lasting  $\geq$  3 months in the first stage. 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 which exon 20 *EGFR* mutations may be most sensitive to Hsp90 inhibition and explore potential mechanisms of resistance to treatment.

### 1.2 Primary Objectives

To evaluate the overall response rate to AUY922 in patients with advanced NSCLC and exon 20 insertion mutations in *EGFR*.

### 1.3 Secondary Objectives

- To estimate progression-free survival (PFS) and overall survival (OS) in the study population
- To determine the safety and tolerability of AUY922
- To explore variance in clinical outcome between different types of exon 20 EGFR mutations

## 2. BACKGROUND

### 2.1 Study Agent: AUY922

#### 2.1.1 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 the 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](#)). There are vast majority of client proteins within the cell that is dependent upon HSP90 ([Pratt and Toft 2003](#)), some summarized in Table 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<sub>2</sub>-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 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 were 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, where in a combination study with trastuzumab a partial response where reported 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 has 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 has 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 <sup>18</sup>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  $\geq 4$  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 translocation kinase after receiving IPI-504 bi-weekly with a one week rest ([Sequist, et al 2010](#)).

Collectively, all these data confirm that targeting HSP90 in various tumors to have anti-neoplastic effect.

## 2.1.2 AUY922

### 2.1.2.1 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 and prevents the step-wise binding of p23 described above, a process that is ATP dependent. This results in the chaperone complex dissociating and the relocation of the protein heat shock factor 1 (HSF-1) to the nucleus of the cell where it 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](#)).

#### 2.1.2.2 *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.

#### 2.1.2.3 *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.

#### 2.1.2.4 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 patients may experience GI toxicities such as diarrhea following AUY922 treatment. Hence, patients 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, patients 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.

#### 2.1.3 Clinical experience

There are several studies assessing the efficacy, safety and tolerability of AUY922 in both solid and hematological malignancies. Detailed information on safety, efficacy, and PK data from patients treated at dose levels from 2 to 70 mg/m<sup>2</sup> can be found in the current AUY922 Investigator's brochure. Below is a brief summary of the relevant clinical experience thus far.

#### CAUY922A2101: A Phase I study of AUY922 in patients with advanced solid tumors

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<sup>2</sup> to 70 mg/m<sup>2</sup>. Of the patients enrolled in the two highest dosing cohorts (i.e., 54 and 70 mg/m<sup>2</sup>), 5 DLTs were reported. Grade 3 asthenia and grade 3 diarrhea were reported in two patients in the 54 mg/m<sup>2</sup> cohort. In the 70 mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> and 70 mg/m<sup>2</sup>, 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.

### CAUY922A2206: A Phase 2 Study of AUY922 in NSCLC Patients

As of April 2012, 121 patients with NSCLC have been treated on this phase 2 study examining the activity of AUY922 in patients with defined molecular subtypes of NSCLC who had received prior chemotherapy. The molecular groups included were those with *EGFR* mutations, those with *KRAS* mutations, those with *EML4-ALK* rearrangements, and those that were wild-type for all 3 driver mutations. Patients were treated at 70mg/m<sup>2</sup> and the primary outcome was rate of partial response (PR) and prolonged stable disease (SD; >18 weeks) within each molecular subgroup. Interestingly, the *EGFR* mutant subgroup had a 20% response rate and the *ALK* rearranged group had a 29% response rate on this phase II study (Garon, 2012), supporting further study of AUY922 in both of these molecularly-defined patients groups.

The most frequent adverse events (AEs, all grades) were visual AEs (77%), diarrhea (74%), and nausea (46%). Overall 7% of patients had a grade 3 or 4 AE involving visual symptoms; most commonly photopsia (20%), visual impairment (19%), vision blurred (18%), night blindness (17%), and visual acuity reduced (17%). These effects were all reversible upon discontinuation of drug.

#### 2.1.4 Pharmacokinetics of AUY922

As of February 18<sup>th</sup>, 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<sup>2</sup> were assessed by noncompartmental analysis.

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

Following a weekly i.v. infusion (1 hr duration), AUY922 blood concentration followed a bi-exponential decline with a fast phase (t<sub>1/2</sub> <10 min) and a slow terminal phase (t<sub>1/2</sub>~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<sup>2</sup>. 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<sup>2</sup>, 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 [<sup>14</sup>C]AUY922 in healthy male volunteers [\[CAUY922A2105\]](#). Mass balance was achieved in this study with  $\geq 93.8\%$  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.

## 2.2 Study Disease: EGFR mutation-positive NSCLC

Non-small cell lung cancer (NSCLC) is the most common cause of cancer mortality in men and women in the U.S. Approximately 170,000 Americans will be diagnosed with NSCLC this year and approximately half of them will have advanced or metastatic disease at presentation, which is not curable. Chemotherapy and biologically targeted agents can extend survival modestly for these patients; however, discovery of novel ways to prolong the disease course is a top research priority.

The epidermal growth factor receptor (EGFR) signaling pathway plays a central role in the neoplastic transformation of NSCLC and promotes cancer cell survival, metastasis, and angiogenesis. The predominance of EGFR signaling in NSCLC makes the pathway an attractive candidate for the development of targeted therapeutics. In the last eight years, the FDA has approved two drugs in this class for salvage treatment of NSCLC, gefitinib (Iressa ®, formerly known as ZD1839) and erlotinib (Tarceva ®, formerly known as OSI-774). Both are small molecule orally-bioavailable tyrosine kinase inhibitors (TKIs) of the EGFR TK domain. Erlotinib improves survival compared to placebo when administered after failure of first line or second line chemotherapy for advanced NSCLC and is currently approved for that indication (Shepherd, 2005). Gefitinib received accelerated approval for salvage treatment of NSCLC based on response to treatment and symptom improvement in phase II clinical trials, but then a randomized placebo-controlled trial failed to demonstrate a survival benefit and gefitinib is no longer available in the US. (Thatcher, Lancet 2005).

Our group and others described somatic mutations in the *EGFR* gene that sensitize NSCLC tumors to TKIs, present in about 10% of unselected US patients with NSCLC but in up to 50% of never-smoking NSCLC patients. (Lynch 2004 and Paez 2004). *EGFR* mutations confer a state of “oncogene addiction” on the molecular biology of the tumor, such that the critical downstream signaling pathways are solely controlled by EGFR and are therefore highly susceptible to cell death by blockade of EGFR. Multiple randomized trials have now confirmed a progression-free survival benefit when patients with EGFR mutations are treated with genotype-directed strategies like using first-line gefitinib or erlotinib compared to standard chemotherapy. (Mok 2009, Mitsudomi 2010, Rosell 2012). This targeted strategy has evolved to being considered standard of care for patients with *EGFR* mutations. (Ettinger 2012).

Though *EGFR* mutations primarily consist of overlapping deletion mutations in the LREA region of exon 19 or the point substitution mutation L858R in exon 21, though there are several less common *EGFR* mutations, for example exon 20 insertion mutations of *EGFR*. This class of *EGFR*-mutants seems to have an EGFR-addicted biology, but have historically reaped little benefit from EGFR-directed therapy due to the low affinity of this mutation for direct EGFR inhibitors, especially erlotinib and gefitinib (Yasuda, 2011). Identifying alternative targeted therapeutic options for exon 20 *EGFR* mutation-positive patients is a priority.

### 2.3 Rationale

*EGFR* is a client of Hsp90 and there is strong pre-clinical evidence that Hsp90 inhibition may be preferentially effective in cancers with *EGFR* mutations (Shimamura, 2008 and 2012). However, other Hsp90 inhibitors have disappointingly failed to show significant activity in *EGFR* mutation-positive NSCLC patients, though most of the patients on these studies were treated after acquiring resistance to EGFR tyrosine kinase inhibitors (Sequist, 2010 and Wong, 2011).

As discussed above, in the ongoing phase II [[CAUY922A2206](#)] study of AUY922 in NSCLC, there has been a 20% response rate among patients with *EGFR* mutations, the highest response to Hsp90 inhibition seen in this patient group to date. At least one of the *EGFR*-mutant responders had an exon 20 insertion mutation, an 80 year-old woman with advanced NSCLC who had been treated with first-line erlotinib and had not responded but rather experienced progressive disease after about 4 months of therapy. She went on AUY922 as second-line therapy and achieved a partial response on her first restaging with a 35% reduction in tumor burden, improving to a 42% decrease on her confirmation of response scans 6 weeks later. This type of marked response to therapy and clinical benefit in an *EGFR* exon 20 insertion mutation-positive patient is atypical, provocative, and deserving of further study. This is the basis of the current trial.

AUY922 will be administered intravenously at a dose of 70 mg/m<sup>2</sup> on a weekly schedule. This dose and schedule is the established MTD from study [[CAUY922A2101](#)] and has demonstrated partial responses across a range of genotypes in NSCLC in the ongoing phase II protocol [[CAUY922A2206](#)].

### 3. PARTICIPANT SELECTION

#### 3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

- 3.1.1 Participants must have histologically or cytologically confirmed stage IV or recurrent non-small cell lung cancer with a documented exon 20 insertion mutation in *EGFR* (exon 20 insertion/deletion and deletion mutations will also be allowed)
- 3.1.2 Participants must have measurable disease by RECIST 1.1
- 3.1.3 Patients must have received at least one prior line of therapy for their advanced lung cancer but there is no restrictions on the maximum number of prior therapies allowed.
- 3.1.4 Age  $\geq$  18 years.
- 3.1.5 Life expectancy  $\geq$  12 weeks.
- 3.1.6 ECOG performance status  $\leq$  2 (see Appendix A)
- 3.1.7 Participants must have normal organ and marrow function as defined below:
  - Hematologic:
    - Absolute Neutrophil Count (ANC)  $\geq 1.5 \times 10^9/L$
    - Hemoglobin (Hgb)  $\geq 8 \text{ g/dL}$
    - Platelets (plt)  $\geq 100 \times 10^9/L$
  - Biochemistry:
    - Potassium within normal limits or correctable with supplements
    - Magnesium  $>$  LLN or correctable with supplements
    - Calcium (after correction for albumin level)  $>$  LLN or correctable with supplements
  - Liver and Kidney Functions
    - AST/SGOT and ALT/SGPT  $\leq 3.0 \times$  Upper Limit of Normal (ULN) or  $\leq 5.0 \times$  Upper Limit of Normal (ULN) if liver metastases are present
    - Serum bilirubin  $\leq 1.5 \times$  ULN
    - Serum creatinine  $\leq 1.5 \times$  ULN or 24-hour clearance  $\geq 50 \text{ ml/min}$

3.1.8 The effects of AUY922 on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. In addition, women of child-bearing potential must have a documented negative serum pregnancy test. The serum pregnancy test must be obtained prior to the first administration of AUY922 ( $\leq$  72 hours prior to dosing) in all pre-menopausal women and women  $<2$  years after the onset of menopause.

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

3.1.10 Patients must have a normal baseline ophthalmologic examination or have only clinically-insignificant abnormalities. Patients with significant visual/ocular abnormalities identified during the baseline eye exam may be eligible after discussion with the study PI and it is thought that the abnormalities pose no increased risk with study therapy.

## 3.2 Exclusion Criteria

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

3.2.1 Participants may not have had other anti-neoplastic therapies within the following timelines:

- Radiation within 2 weeks
- Cytotoxic chemotherapy or monoclonal antibodies within 2 weeks, if all treatment-related toxicities have resolved to  $\leq$  grade 1 prior to starting study treatment.
- EGFR tyrosine kinase inhibitor within 2 weeks
- Any other small molecule inhibitor within 2 weeks or 5 half-lives of the compound, whichever is shorter
- Experimental treatment of any type within 30 days

3.2.2 Participants may not be currently receiving any other experimental agents.

3.2.3 No prior treatment with any HSP90 or HDAC inhibitor compound is allowed

3.2.4 Participants with known and untreated brain metastases are excluded. Note: Patients without known prior CNS metastases and without clinical signs and symptoms of CNS involvement are not required to have an MRI of the brain prior to enrollment. **Patients with treated brain metastases**

**that are asymptomatic and clinically stable for two weeks will be eligible for protocol participation.**

- 3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AUY922
- 3.2.6 Unresolved diarrhea  $\geq$  CTCAE version 4, grade 1.
- 3.2.7 Pregnant or lactating women
- 3.2.8 Participants who have undergone any major surgery  $\leq$  2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
- 3.2.9 Participants with known disorders due to a deficiency in bilirubin glucuronidation (e.g. Gilbert's syndrome).
- 3.2.10 Participants requiring the use of therapeutic doses of warfarin (Coumadin).
- 3.2.11 Participants with any of the following cardiac conditions:
  - History of long QT syndrome.
  - QTcF  $\geq$  450 ms during screening ECG.
  - 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  $\leq$  6 months prior to study start.
  - History of heart failure or left ventricular (LV) dysfunction (LVEF  $\leq$  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 2<sup>nd</sup> (Mobitz II) or 3<sup>rd</sup> degree AV block.
  - History and presence of atrial fibrillation, atrial flutter or 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 an hypertensive regimen).
  - Clinically significant resting bradycardia (<50 beats per minute).
  - Patients who are currently receiving treatment with any medication which has a relative risk or prolonging the QTc interval or inducing Torsades de Pointes (as listed in protocol section 5.4) and cannot be switched or discontinued to an alternative drug prior to commencing AUY922 dosing.
  - Patients who are on a cardiac pacemaker.

- 3.2.12 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.13 Concurrent malignancies or invasive cancers diagnosed within the past 3 years, except for adequately treated basal cell cancer of the skin or in situ cancer of the cervix.
- 3.2.14 Patients known to be HIV positive, because of the potential for pharmacokinetic interactions with AUY922 and increased risk of life-threatening infections. HIV testing is not required in the absence of clinical signs and symptoms suggesting HIV infection.

### **3.3 Inclusion of Women, Minorities and Other Underrepresented Populations**

Lung cancer affects men and women, and people of all race and socioeconomic class. We do not expect the inclusion and exclusion criteria to negatively affect enrollment of underrepresented populations.

## **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.

#### 4.3 General Guidelines for Other Participating Institutions

N/A

#### 4.4 Registration Process for Other Participating Institutions

N/A

### 5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for AUY922 are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

This is a single-arm, open-label, phase II trial of AUY922. All patients will receive the same dose and schedule of study medication, which is:

**AUY922 intravenously at 70 mg/m<sup>2</sup> once weekly, i.e. days 1, 8 and 15 of every 21-day cycle**

Although it is ideal for patients to receive their study medication on the same day of the week each week, there is a 2-day plus/minus window allowed to be flexible with holidays, inclement weather, transportation difficulties, etc. For patients who are unable to tolerate the protocol-specified dosing schedule, schedule adjustments are permitted. This includes the ability to skip a week of dosing if needed up to once per cycle.

## **5.1 Pre-treatment Criteria**

### **5.1.1 Cycle 1, Day 1**

The patient should continue to meet all eligibility criteria on C1D1, as they did during the screening period.

### **5.1.2 Subsequent treatment days (weekly)**

- Any grade 3 or higher toxicity should have resolved to grade 1 or baseline prior to dosing
- ECG should be reviewed by a clinician to verify QTcF is not prolonged >500ms

## **5.2 AUY922 Administration**

### **5.2.1 How AUY922 is supplied**

Novartis supplies AUY922 in individual vials and/or amber-colored, glass ampoules. Vials will also be available. Each vial is 20mL, each containing nominally 50 mg AUY922 (calculated as free base). The storage conditions for study drug will be described on the medication label. The vials/ampoules should be stored safely and separately from other drugs. Please see handling instructions.

#### **Dosage Forms:**

**Vials:** 20 mL vials, each containing nominally 50 mg AUY922 (calculated as free base).

**Glass ampoules:** 10 mL amber-colored, glass ampoules, each containing 10 ml of a 5 mg/ml active drug substance in 5% aqueous glucose solution.

### **5.2.2 Preparation and storage for AUY922**

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. Note that concentrations within the range of 0.006 mg/ml up to 0.28 mg/ml are acceptable. 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.

Please follow the preparation instruction provided below.

The image is a high-contrast, black-and-white abstract graphic. It features a grid of horizontal bars of varying lengths, primarily black, set against a white background. The bars are arranged in a roughly rectangular frame. On the far left, there is a vertical column of white squares of varying sizes, creating a stepped, staircase-like effect. The overall composition is minimalist and geometric, with a focus on form and space.

**Storage Information:**

### 5.3 Administration of AUY922

- AUY922 will be administered to patients through a 0.2 µm in-line filter.

14. Once the AUY922 Concentrate for Infusion has been compounded in the infusion bag, it should be administered immediately.

15. The infusion set has to be flushed with a carrier solution (5% dextrose) prior administration of the infusion solution.

16. From a microbiological point of view, the aseptic techniques, in-use storage time (60 minutes) and conditions prior to use are the responsibility of the person who is administering the infusion (e.g. hospital pharmacist / nurse).

17. From a chemical - and physicochemical point of view, in-use stability of AUY922 infusion solution has been demonstrated for a maximum of 6 hours at room temperature and at 2-8°C (opening of the Vials until end of infusion).

18. Carefully inspect the final infusion solution prior to administration. The final infusion solution should be a clear solution free from any particles.

19. The final infusion solution must be administered through an integrated or additional 0.2 µm in-line filter.

### 5.4 Definition of Dose-Limiting Toxicity

N/A

### 5.5 General Concomitant Medication and Supportive Care Guidelines

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient 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 with preliminary *in vitro* metabolism studies. Patients using concomitant medications known to be metabolized by these cytochrome p450 isoenzymes will not be excluded from the study. However, the patients 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 and avoid co-administration with AUY922 in *For the most updated information, please also visit the following website: [medicine.iupui.edu/flockhart/table.htm](http://medicine.iupui.edu/flockhart/table.htm)*

If, after a patient 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 and updated in web address: [qtdrugs.org/medical-pros/drug-lists/drug-lists.htm](http://qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). The investigator should instruct the patient to notify the study site about any new medications he or she takes after the start of the study drug.

## 5.6 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 until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- 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.

Patients may continue to receive AUY922 beyond RECIST-defined progression at the discretion of the treating physician if they are continuing to show clinical benefit.

## 5.7 Duration of Follow Up

Participants will be followed for survival every 3 months after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

## 5.8 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Dr. Lecia Sequist, at [REDACTED]

## 6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the recommendations in this section of the protocol. Toxicity assessments will be done using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

### 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 patients 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 patients 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. Patients treated with this medication have had reversible ocular toxicities, see below.

In conclusion, main target organs for AUY922 are the intestine, bone marrow and lymphoid tissue. There may be a risk of QTc prolongation, of visual changes, and of a local irritative effect.

The cardiac safety parameters can be monitored in the clinic using an intensive ECG and vital signs monitoring schedule, see Section 6.2.3. Detailed instructions for the observation and treatment of diarrhea and visual toxicities are also provided in this study protocol, Sections 6.2 and 6.3. 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.

## 6.2 Surveillance and Management of Specific Toxicities

Dose modification instructions for general adverse events are found in Section 6.3.

### 6.2.1 Diarrhea Management

In previous studies, AUY922 was shown to induce gastrointestinal toxicities in some patients and therefore there is a substantial risk that patients will develop diarrhea.

Proactively look for occurrence of diarrhea after start of AUY922 treatment. Call patients at home, if necessary, to detect diarrhea early during the first 8 weeks. If no problems occur, instruct the patient to call if and when a problem does arise.

General suggestions:

- Stop all lactose-containing products, and alcohol
- Stop laxatives, bulk fiber (i.e Metamucil®, Procter & Gamble), and stool softeners (docusate sodium; Colace, Roberts)
- Drink 8 to 10 large glasses of clear liquids per day (i.e water, Pedialyte® (Ross), Gatorade (Quaker), broth)
- Eat frequent small meals (bananas, rice, applesauce, Ensure®, toast)
- Stop high-osmolar food supplements such as Ensure Plus and Jevity Plus (with fiber)

It is recommended that patients be provided loperamide tablets and that patients are instructed on the use of loperamide at cycle 1 in order to manage signs or symptoms of diarrhea at home.

Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms.

#### **Treatment of diarrhea grade 1 or 2**

Diarrhea grade 1 or 2 will be treated with loperamide (initial administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool).

#### **24 hours after the start of diarrhea, if:**

##### **Diarrhea resolved**

- Continue dietary modifications
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hour interval without diarrhea
- See Section 6.3 for dose modification recommendations upon re-initiation of AUY922

**Diarrhea unresolved**

- Addition of opium tincture or dihydrocodeine tartrate tablets/injections
- Re-assessment for dehydration, sepsis, ileus
- Medical check and selected work-up to evaluate whether patient does not need hospitalization (see below for recommended diarrhea work-up)

**48 hours after the start of diarrhea, if:**

**Diarrhea resolved**

- Continue dietary modifications
- Gradually add solid foods to diet
- Discontinue loperamide and/or other agents after 12-hour interval without diarrhea
- See Section 6.3 for dose modification recommendations upon re-initiation of AUY922

**Diarrhea unresolved**

- If persistent diarrhea (CTCAE grades 1 or 2) after 2x 24 hours with high dose loperamide and opiates, admit to hospital and follow recommendations for grade 3/4 diarrhea until resolved.

If diarrhea has progressed to CTCAE grades 3 or 4, begin measures outlined below

**Treatment of diarrhea grade 3 or 4**

Severe diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture or dihydrocodeine tartrate tablets/injections. Additionally, intravenous fluids and antibiotics may be given as needed with monitoring of the patient's condition to rule out other causes for diarrhea. Observe for response.

**24 hours after the start of diarrhea, if diarrhea is unresolved:**

- Administer subcutaneous octreotide (100-500 µg TID)
- Consider intravenous fluids and antibiotics as clinically indicated.
- If grade 3 or 4 diarrhea persists, patients should receive opium tincture or dihydrocodeine tartrate by subcutaneous or intra-muscular injection.
- If grade 3 or 4 diarrhea persists despite opium tincture or dihydrocodeine, subcutaneous octreotide (500-1000 µg TID) should be administered.
- See table 5 for dose modifications secondary to diarrhea.

### **Diarrhea work-up**

- History and physical exam.
- Examination of stool for occult blood.
- Examine the stool for fecal leukocytes.
- Examine the stool for *C. difficile* toxin if high clinical suspicion.
- Consider stool cultures for pathogens such as *Shigella* and pathogenic *E. coli*.
- Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

#### **6.2.2 Ocular Toxicity Management**

Weekly administration of AUY922 may cause visual symptoms. The visual symptom descriptions from ongoing phase 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.

The standard recommendation for managing visual toxicities with AUY is to hold the drug if toxicities are grade 2 or higher. See Section 6.3 for dose reduction guidelines.

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 the beginning of cycle 3 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. Visual symptoms will be graded using NCI CTCAE 4.0. However, for the acuity test (Snellen charts) the following grading should be applied.

**Table 2. Visual AE Grading for AUY922 Using Snellen Charts**

| Toxicity         | Grade 1                                | Grade 2     | Grade 3      | Grade 4         |
|------------------|--|-------------|--------------|-----------------|
| Decreased Acuity | Baseline-20/20 despite visual symptoms | 20/30-20/40 | 20/50-20/100 | 20/200 or below |

| Toxicity  | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---------|---------|---------|---------|
| Note: Refers to the visual acuity when a patient wears his or her best eyeglasses.<br>The acuity scores pertains to the better eye. |         |         |         |         |

### 6.2.3 Surveillance for Cardiac Toxicities

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

As part of the screening process, patients will be required to undergo either a MUGA or transthoracic echocardiogram to assess left ventricular ejection fraction (LVEF). Patients will be closely monitored by ECG throughout the study, see schedule below. If cardiac changes are observed during monitoring, please refer to Section 6.3 for dose modifications.

**Table 3. Schedule for 12-lead ECG Monitoring**

| 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 and after infusion.                         |
|                       | 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. |
|                       | 15       | X           | A 12-lead ECG should be obtained at pre-infusion (timing is not pre-specified) and after infusion. |
| 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. |

### 6.3 Dose Modifications/Delays

If the patient experiences unacceptable toxicities, treatment with the study drug should be suspended until the toxicities return to  $\leq$  CTCAE grade 1 (or baseline). Dose modification may be required upon treatment resumption, see below.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value should 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 patient requires a dose delay of  $>21$  days from the intended day of the next scheduled dose, then the patient must discontinue the study. All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of AUY922.

Toxicity will be assessed using the NCI-CTC for Adverse Events, version 4.0 (CTCAE v4.0)

For patients who are unable to tolerate the protocol-specified dosing schedule, schedule adjustments are permitted. This includes the ability to skip a week of dosing if needed up to once per cycle.

Dose reduction levels are listed in Table 4 and specific instructions for holding drug, reducing doses, and managing toxicities are listed in Table 5. Only two dose level reductions are allowed per patient.

**Table 4. Does Reduction Levels for AUY922**

| Dose reduction* |                       |                      |                      |
|-----------------|-----------------------|----------------------|----------------------|
|                 | Starting dose level 0 | Dose level – 1       | Dose level – 2       |
| AUY922          | 70 mg/m <sup>2</sup>  | 55 mg/m <sup>2</sup> | 40 mg/m <sup>2</sup> |

\*Dose reduction should be based on the worst toxicity demonstrated at the last dose.  
Dose may be reduced a maximum of 2 times, no further reduction is permitted.

**Table 5. Criteria for Interruption, Dose Reduction and Re-Initiation of AUY922**

| Recommended Dose Modifications for AUY922                                |   |
|--|---|
| Worst Toxicity<br>CTCAE Grade <sup>a</sup> unless otherwise<br>specified | At any time during a cycle of AUY922<br>(including intended day of dosing)  |
| <b>No toxicity</b>   | <b>Maintain dose level</b>  |
| <b>Diarrhea</b>  |   |
| Grade 1 (see Section 6.2 for recommended treatment algorithm)            | Maintain dose level   |
| Grade 2<br>(see Section 6.2 for recommended treatment algorithm)         | Omit dose administration until recovery to Grade 1 or baseline, then continue AUY922 at:<br>- current dose level if grade 2 toxicity persisted ≤ 7 days.<br>- one dose level lower if grade 2 toxicity persisted > 7 days   |
| Grade 3<br>(see Section 6.2 for recommended treatment algorithm)         | Omit dose administration until recovery to Grade 1 or baseline then decrease the next scheduled dose by 1 dose level.   |
| Grade 4<br>(see Section 6.2 for recommended treatment algorithm)         | Omit dose administration until recovery to Grade 1 or baseline then:<br>- if grade 4 toxicity lasted ≤ 24 hours, may resume AUY922 but decrease the next scheduled dose by 1 dose level.<br>- In the event Grade 4 toxicity lasted >24 hours despite maximal medical attention, permanently discontinue treatment.<br><br>If grade 4 toxicity recurs upon re-exposure, permanently discontinue treatment. |

| <b>Recommended Dose Modifications for AUY922</b>  |   |
|---|---|
| <b>Worst Toxicity<br/>CTCAE Grade <sup>a</sup> unless otherwise<br/>specified</b>                                       | <b>At any time during a cycle of AUY922<br/>(including intended day of dosing)</b>  |
| <b>Hematological</b>  |   |
| <b>Neutropenia (ANC)</b><br>Grade 1 (ANC < LLN - $1.5 \times 10^9/L$ ) or<br>Grade 2 (ANC < $1.5 - 1.0 \times 10^9/L$ ) | Maintain dose level   |
| Grade 3 (ANC < $1.0 - 0.5 \times 10^9/L$ )  | Omit dose administration until resolved to $\leq$ grade 1,<br><ul style="list-style-type: none"> <li>• If resolved in <math>\leq</math> 7 days, then maintain dose level</li> <li>• If resolved in <math>&gt;</math> 7 days, then decrease by 1 dose level</li> </ul>       |
| Grade 4 (ANC < $0.5 \times 10^9/L$ )  | Omit dose administration until resolved to $\leq$ grade 1, then<br>decrease by 1 dose level   |
| Febrile neutropenia   | Omit dose administration until resolved, then decrease by 1<br>dose level   |
| <b>Thrombocytopenia</b>   |   |
| Grade 1 (PLT < LLN - $75 \times 10^9/L$ )   | Maintain dose level   |
| Grade 2 (PLT < $75 - 50 \times 10^9/L$ ) or<br>Grade 3 (PLT < $50-25 \times 10^9/L$ )                                   | Omit administration dose until resolved to $\leq$ grade 1, then:<br><ul style="list-style-type: none"> <li>• If resolved in <math>\leq</math> 7 days, then maintain dose level</li> <li>• If resolved in <math>&gt;</math> 7 days, then decrease by 1 dose level</li> </ul> |
| Grade 4 (PLT < $25 \times 10^9/L$ )   | Omit administration dose until resolved, then decrease by 1<br>dose level   |
| <b>Renal</b>  |   |
| <b>Serum creatinine</b><br>( $< 2 \times$ ULN)  | Maintain dose level   |
| ( $2 - 3 \times$ ULN)   | Omit dose administration until resolved to $\leq$ grade 1, then<br><ul style="list-style-type: none"> <li>• If resolved in <math>\leq</math> 7 days, then maintain dose level</li> <li>• If resolved in <math>&gt;</math> 7 days, then decrease by 1 dose level</li> </ul>  |
| Grade 3 ( $>3.0$ baseline; $> 3.0 - 6.0 \times$ ULN) or<br>Grade 4 ( $> 6.0 \times$ ULN)                                | Omit dose administration and permanently discontinue patient<br>from study treatment  |
| <b>Hepatic</b>  |   |
| <b>Bilirubin</b><br>( $< 2 \times$ ULN)   | Maintain dose level   |
| ( $2 - 3 \times$ ULN)   | Omit dose administration until resolved to $\leq$ grade 1, then<br><ul style="list-style-type: none"> <li>• If resolved in <math>\leq</math> 7 days, then maintain dose level</li> <li>• If resolved in <math>&gt;</math> 7 days, then decrease by 1 dose level</li> </ul>  |
| Grade 3 ( $> 3.0 - 10.0 \times$ ULN)  | Omit dose administration until resolved to $\leq$ grade 1, then<br>decrease by 1 dose level   |
| Grade 4 ( $> 10.0 \times$ ULN)  | Omit dose administration and permanently discontinue patient<br>from study treatment  |

| <b>Recommended Dose Modifications for AUY922</b>  |   |
|---|---|
| <b>Worst Toxicity<br/>CTCAE Grade <sup>a</sup> unless otherwise<br/>specified</b>   | <b>At any time during a cycle of AUY922<br/>(including intended day of dosing)</b>  |
| <b>AST or ALT</b><br>Grade 1 (>ULN - 3.0 x ULN) or<br>Grade 2 (Asymptomatic with ALT >3.0 - 5.0 x<br>ULN; >3 x ULN with the appearance of<br>worsening of fatigue, nausea, vomiting, right<br>upper quadrant pain or tenderness, fever,<br>rash, or eosinophilia) | Maintain dose level   |
| Grade 3 (>5.0 - 20.0 x ULN )  | Omit dose administration until resolved to ≤ grade 1 (or ≤ grade 2 in case of liver metastasis), then <ul style="list-style-type: none"><li>• If resolved in ≤ 7 days, then maintain dose level</li><li>• If resolved in &gt; 7 days, then decrease by 1 dose level</li></ul>   |
| Grade 4 (> 20.0 x ULN)  | Omit dose administration until resolved to ≤ grade 1, then decrease by 1 dose level   |
| <b>Cardiac - Prolonged QTcF interval</b>  |   |
| During cycle 1  |   |
| Absolute QTcF ≤ 480msec   | Maintain dose level and ECG monitoring as per visit schedule.   |
| Absolute QTcF ≥ 481msec and, ≤ 500 msec   | 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: <ul style="list-style-type: none"><li>• If ECG in the additional cycles shows no QTcF absolute ≥ 481 msec then, for subsequent cycles ECG monitoring will be performed as per visit schedule.</li><li>• If ECG still abnormal (QTcF absolute ≥ 481 msec and ≤ 500 msec) then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.</li></ul> |

| <b>Recommended Dose Modifications for AUY922</b>  |  |
|---|--|
| <b>Worst Toxicity<br/>CTCAE Grade <sup>a.</sup> unless otherwise<br/>specified</b>                | <b>At any time during a cycle of AUY922<br/>(including intended day of dosing)</b>   |
| During any cycle<br>Grade 3 or QTcF $\geq$ 501 msec as identified by the investigator on the ECG. | <p>Omit dose administration. Monitor patient with hourly ECGs until the QTcF has returned to <math>\leq</math> 450 msec. Further monitoring as clinically indicated. Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesemia and blood oxygenation status<sup>b</sup>.</p> <p>Once QTcF prolongation has resolved, patients may be re-treated at one lower dose level at the investigator's discretion. ECG monitoring must continue throughout the treatment period as follows:</p> <ul style="list-style-type: none"><li>• ECG monitoring assessments should be performed for 2 additional cycles at the same frequency as in cycle 1</li><li>• If the ECGs obtained in the first and second additional cycle (after dose reduction) are without any QTcF prolongation, then ECG monitoring in subsequent cycles will be continued as per the visit schedule.</li><li>• If the patient had an absolute QTcF <math>\geq</math> 481 msec and <math>\leq</math> 500 msec, then ECG monitoring at the same frequency as in cycle 1 will be continued for all subsequent cycles.</li><li>• Patients who experience absolute QTcF <math>\geq</math> 501 msec after one dose reduction will be discontinued from study.</li></ul> <p>Note: If Torsades de Pointes are observed in a patient, the patient will be discontinued from the study.</p> |

| <b>Recommended Dose Modifications for AUY922</b>  |   |
|---|---|
| <b>Worst Toxicity<br/>CTCAE Grade <sup>a</sup> unless otherwise<br/>specified</b>   | <b>At any time during a cycle of AUY922<br/>(including intended day of dosing)</b>  |
| <b>Other adverse events</b>   |   |
| Grade 1 or 2  | Maintain dose level   |
| Grade 3   | Omit dose administration until resolved to ≤ grade 1, then decrease by 1 dose level   |
| Grade 4   | Omit dose administration and permanently discontinue patient from study   |
| <b>Eye disorders (see section 6.2 for Grading Table)</b>  |   |
| 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<br>If visual symptoms ≥ Grade 2 recur upon re-exposure to AUY922, omit dose until resolution to ≤ Grade 1, then decrease 1 dose level |
| Grade 3   | Omit dose administration until resolved to ≤ grade 1 (or baseline), then decrease 1 dose level  |
| Grade 4   | Omit dose administration and permanently discontinue patient from study   |
| All dose modifications should be based on the worst preceding toxicity.   |   |
| If a patient requires a treatment interruption of > 21 days from the last dose of AUY922, then the patient must be discontinued from the study treatment. Patients who discontinue from the study for a study-related adverse event or an abnormal laboratory value must be followed as per protocol.   |   |
| - Up to two dose reductions are allowed. In case the patient had clinical benefit and needs more than two dose reduction, it will be discussed case by case with the sponsor  |   |
| <sup>a</sup> Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)   |   |
| <sup>b</sup> Exclude other causes of QTc prolongation such has hypokalemia, hypomagnesemia and blood oxygenation status. Patients 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. |   |

## 7. CORRELATIVE/SPECIAL STUDIES

Patients with available tumor tissue will have EGFR exon 20 analyzed by direct sequencing if they have not already had this testing. The purpose of this is to know the exact exon 20 mutation for all patients on the study, variations in outcome by mutation type can be explored. Some of the participating institutions use direct sequencing already as their clinical test to identify these patients, while some use a sizing assay that does not provide the exact insertion or insertion/deletion mutation. Patients without available tumor tissue will be eligible to participate in the study and will not have to undergo a biopsy.

## 7.1 Pharmacokinetic Studies

N/A

## 8. STUDY CALENDAR

### Table 6. Required Data

|  | Baseline       | Cycle 1 |   |   | Cycle 2 |    |   | Subsequent cycles |    |                 | End of Treatment | 28 Day Safety Visit | Tumor FU              | Survival FU               | End of Study |     |
|--|----------------|---------|---|---|---------|----|---|-------------------|----|-----------------|------------------|---------------------|-----------------------|---------------------------|--------------|-----|
| Day of Cycle   | -21 to -1      | 1       | 2 | 3 | 8       | 15 | 1 | 8                 | 15 | 1               | 8                | 15                  | ≤ 7 days of last dose | 28 (±7) days of last dose | N/A          | N/A |
| Informed consent   | X              |         |   |   |         |    |   |                   |    |                 |                  |                     |                       |                           |              |     |
| Inclusion/Exclusion Criteria                                     | X              |         |   |   |         |    |   |                   |    |                 |                  |                     |                       |                           |              |     |
| Collection of baseline required demographic and clinical data    | X              |         |   |   |         |    |   |                   |    |                 |                  |                     |                       |                           |              |     |
| Vitals signs and ECOG Performance status <sup>1</sup>            | X              | X       | X | X | X       | X  | X | X                 | X  | X               | X                | X                   |                       |                           |              |     |
| Physical Exam  | X              | X       | X | X | X       | X  | X | X                 | X  | X               | X                | X                   |                       |                           |              |     |
| 12-lead ECG <sup>2</sup>   | X              | X       | X | X | X       | X  | X | X                 | X  | X               | X                | X                   |                       |                           |              |     |
| Cardiac imaging (MUGA or ECHO)                                   | X              |         |   |   |         |    |   |                   |    |                 |                  |                     | X                     |                           |              |     |
| Hematology and biochemistry labs <sup>3</sup>                    | X              | X       | X | X | X       | X  | X | X                 | X  | X               | X                | X                   |                       |                           |              |     |
| Coagulation labs   | X              | X       |   |   |         | X  |   |                   |    | X <sup>10</sup> |                  | X                   |                       |                           |              |     |
| Urinalysis   | X              | X       |   |   |         | X  |   |                   |    | X <sup>10</sup> |                  | X                   |                       |                           |              |     |
| Eye Exam <sup>4</sup>  | X <sup>4</sup> |         |   |   |         |    |   |                   |    | X <sup>4</sup>  |                  | X <sup>4</sup>      |                       |                           |              |     |
| AUY922 IV infusion <sup>5</sup>                                  | X              |         | 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 <sup>6</sup>           | X              |         |   |   |         |    |   |                   |    |                 |                  |                     | X <sup>7</sup>        |                           |              |     |
| Survival <sup>8</sup>  |                |         |   |   |         |    |   |                   |    |                 |                  |                     | X                     | X                         | X            |     |
| Tumor sample for mutation and amplification testing <sup>9</sup> | X              |         |   |   |         |    |   |                   |    |                 |                  |                     | X                     | X                         | X            |     |

1. Vital signs – During treatment period, vital signs will be performed pre-dose (including temperature, respiratory rate, blood pressure, pulse, weight and ECOG PS) and immediately post-dose infusion (including temperature, respiratory rate, blood pressure and pulse).
2. ECG- Please refer to Table 3 for detailed schedule of ECGs.
3. In women of child-bearing potential, a serum pregnancy test must be obtained prior (within 14 days) to the first administration of AUY922. CHEMISTRY: BUN, Creatinine, Glucose, Total Protein, Albumin, AST/SGOT, ALT/SGPT, Total Bilirubin, Alkaline Phosphatase, Magnesium, Calcium, Sodium, Potassium, Phosphorous. HEMATOLOGY: CBC with differential
4. 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 if no visual symptoms are reported, and at study discontinuation. There is a +/- 7 day window allowed for eye exam at Cycle 3 day 1
5. One should aim to administer AUY922 on the same day each week, but there is a +/- 2 day window allowed to account for holidays, inclement weather, transportation difficulties, etc. For patients who are unable to tolerate the protocol-specified dosing schedule, schedule adjustments are permitted. This includes the ability to skip a week of dosing if needed up to once per cycle. Patients who continue treatment beyond progression can skip up to two infusions per cycle if needed after discussion between the treating MD and the overall PI of the study.
6. A CT scan with contrast of the chest, abdomen, and pelvis will be performed on patients at baseline (screening) -30 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 ( $\pm$ 7 days) from registration.
7. In the event that a patient 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  $\geq$  4 weeks previously. Such patients who discontinue study treatment for reasons other than disease progression should be re-staged every 12 weeks ( $\pm$ 7 days) until start of another anti-cancer treatment.
8. Patients will be followed for survival every 3 months after discontinuing the trial. Follow-ups may be conducted over the telephone.
9. If available, tumor samples will be sequenced for EGFR exon 20 mutation.
10. For patients who miss a D1 visit of any cycle (as allowed per protocol,) any missed day 1 assessments (for example, coagulation studies and urinalysis) will be performed at the next clinic visit.

## 9. MEASUREMENT OF EFFECT

### 9.1 Treatment Efficacy

For the purposes of this study, participants should be re-evaluated for response every 6 weeks. 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). Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

#### 9.1.1 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  $\geq 20$  millimeters (mm) using conventional techniques (CT, MRI, x-ray) or  $\geq 10$  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).

**Reminder:** 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  $\geq 15$  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  $\geq 10$  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  $\geq 15$  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  $\geq 10$  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.

### 9.1.2 Methods for Evaluation of Measurable Disease

The same method of assessment (CT or MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

### 9.1.3 Response Criteria

#### 9.1.3.1 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.

#### 9.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. 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.

**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 and /or 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.

#### 9.1.3.3 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.

**Table 7. Evaluation of Best Overall Response**

| Target Lesions | Non-Target Lesions          | New Lesions | Overall Response | Best Overall Response for when Confirmation is Required: |
|----------------|-----------------------------|-------------|------------------|--|
| CR             | CR                          | No          | CR               | $\geq 4$ wks confirmation                                |
| CR             | Non-CR/Non-PD               | No          | PR               |  |
| CR             | Not evaluated               | No          | PR               | $\geq 4$ wks confirmation                                |
| PR             | Non-CR/Non-PD/Not evaluated | No          | PR               |  |
| SD             | Non-CR/Non-PD/Not evaluated | No          | SD               | Documented at least once $\geq 4$ 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.

#### 9.1.4 Duration of Response

**Duration of overall response:** The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that 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.

#### 9.1.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

### 9.1.6 Response Review

Restaging imaging will be assessed at the DF/HCC Tumor Imaging Metrics Core to provide unbiased formal RECIST measurements

## 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 severe 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 Investigator's Brochure or is included in the informed consent document as a potential risk.

##### 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 Investigator's Brochure 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:

- Related – The AE is clearly or may possibly be related to the study treatment.

- Unrelated – The AE is unlikely or clearly not related to the study treatment.

## 10.2 Procedures for AE and SAE Recording and Reporting

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 CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting, and can be found on the CTEP website at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

## 10.3 Reporting Requirements

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.

## 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 Dr. Sequist (who is the Study Sponsor) 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 that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while 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:

Lecia V. Sequist, MD, MPH  
Massachusetts General Hospital Cancer Center

[REDACTED]  
[REDACTED]  
Email: [LVSequist@partners.org](mailto:LVSequist@partners.org)

and

Elizabeth (Beth) A. Kennedy

[REDACTED]  
[REDACTED]  
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).

### **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 Novartis**

All SAEs should be reported, by FAX [REDACTED], to Novartis Pharmaceuticals Integrated Medical Safety Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 1 working day.

## **10.8 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.

## **10.9 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. Electronic case report forms (eCRFs) will be used.

#### 11.1.2 Data Submission

**Table 8. Schedule for completion and submission of eCRFs to the QACT**

| 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 and by Novartis prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator 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](http://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](http://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](http://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](http://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](http://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](http://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

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<sup>2</sup> in adult NSCLC patients with advanced disease and EGFR exon 20 insertion mutations. The design will be a Simon two-stage phase 2 study, with 10 patients enrolled to the first stage and an additional 19 patients enrolled to the second stage provided we observe at least 1 partial or complete response or stable disease lasting  $\geq 3$  months in the first stage.

The Primary Objective is:

- To evaluate the overall response rate to AUY922 in patients with advanced NSCLC and exon 20 insertion mutations in *EGFR*.

Secondary Objectives include:

- To estimate progression-free survival (PFS) and overall survival (OS) in the study population
- To determine the safety and tolerability of AUY922
- To explore variance in clinical outcome between different types of exon 20 EGFR mutations

## 13.2 Sample Size/Accrual Rate

A Simon two-stage design will be used. In this design we will consider a rate of response plus SD lasting  $\geq 3$  months that is no greater than 5% as evidence that AUY922 is ineffective as a monotherapy in patients with exon 20 insertion mutations in *EGFR*, and 20% will be the target rate of effectiveness. In other words,  $H_0=0.05$  and  $H_a=0.20$ .

This design requires that 10 patients will be initially enrolled (the first stage of the Simon design). If there are no responses or patients with SD lasting  $\geq$  3 months in these 10 patients then AUY922 will be considered ineffective in *EGFR* exon 20 insertion mutation patients. If at least 1 PR or SD lasting  $\geq$  3 months is noted, then an additional 19 patients will be enrolled (the second stage of the Simon design).

If the total number of responses plus SD lasting  $\geq$  3 months in the entire set of 29 patients is 4 or more, then AUY922 will be considered for further evaluation, likely in a randomized setting. If the number of responses of PR or SD lasting  $\geq$  3 months is 3 or fewer in the entire set of 29 patients, then AUY922 will be considered potentially ineffective and further investigation may be unwarranted.

Using this design, if AUY922 is actually not effective, there is a 0.047 probability of concluding that it is (the target for this value was 0.050, the  $\alpha$ -level). If the drug is actually effective, there is a 0.199 probability of concluding that it is not (the target for this value was 0.200, the beta-level [80% power]). The power and  $\alpha$ -level are slightly different from the nominal values due to the discrete nature of the binomial distribution of response.

Among the three participating clinics (MGH, DFCI and BIDMC), we expect to enroll approximately 1.5 patients per month. Therefore, assuming full enrollment to 29 patients, accrual should be complete within 20 months.

### **13.3 Patient Disposition**

A detailed description of patient disposition will be provided. It will include:

- A definition of patient enrollment
- A summary of data regarding patient discontinuation of study treatment
- A summary of data regarding patient inclusion and exclusion in efficacy and safety analyses

### **13.4 Patient Characteristics**

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Baseline tumor molecular characteristics
- Significant medical history and co-morbidities
- Concomitant therapies
- Other characteristics as appropriate

### **13.5 Safety of Treatment**

A summary of the adverse events and their attributed relatedness to treatment will be provided. All patients will be included in the safety analyses

### **13.6 Analysis of Response Rate**

Response rate will be assessed as per RECIST, see Section 9.1. Results will be reported with 95% confidence intervals. All patients will be evaluable for response rate.

### **13.7 Analysis of Progression-Free and Overall Survival**

Progression-Free Survival (PFS) will be defined as the duration of time from start of treatment to time of objective disease progression or death. Overall survival (OS) will be defined as the duration of time from start of treatment until death. Analysis will be performed using the Kaplan-Meier method. All patients will be evaluable for survival endpoints.

## **14. PUBLICATION PLAN**

At the end of the study, the results will be analyzed and a manuscript submitted for peer review within 24 months of the end of data collection.

## 15. REFERENCES

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.

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

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.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumors: Revised RECIST guidelines (version 1.1). *Eur J Cancer*:45(2);228-47.

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

Ettinger D, et al (2012). Non-small cell lung cancer, version 3.2012. NCCN Clinical Practice Guidelines in Oncology. Accessed at [www.nccn.com](http://www.nccn.com)

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 G, et al (2012). Phase II study of the HSP90 inhibitor AUY922 in patients with previously treated, advanced non-small cell lung cancer (NSCLC). Presented at the 2012 Annual Meeting of the American Society of Clinical Oncology. *J Clin Oncol* 30, 2012 (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.

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 microenvironment. *J Exp Ther Oncol*; 7(3): 183-93.

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.

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.

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.

Lynch TJ, Bell DW, Sordella R, et al (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *N Engl J Med* 350(21):2129-39.

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, bronchioloalveolar carcinoma subtype, predict response to erlotinib. *J Clin Oncol*; 26(9):1472-8.

Mitsudomi T, Moriata S, Yatabe Y (2009). Gefitinib versus cisplatin plus docetaxel in patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (WJTOG3405):an open label, randomized, phase 3 trial. *Lancet Oncol*; 11(2):121-8.

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.

Mok T, Wu YL, Thongprassert S, et al (2009). Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*; 361(10):947-57.

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.

Paez JG, Janne PA, Lee JC, et al (2004). EGFR mutations in lung cancer: correlation with clinical response to gefitinib. *Science*; 304(5676):1497-500.

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.

Rosell R, Carcereny E, Gervais R, et al.(2012). Erltinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small cell lung cancer (EURTAC): a multicenter, open-label, randomized phase III trial. *N Engl J Med*:13(3):239-46.

Saif MW, Erlichman C, Dragovich T, et al (2006) Phase I study of CNF1010 (lipid formulation of 17-(allylamo)-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).

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

Sequist LV, Gettinger S, Senzer NN (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):4953-60.

Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al (2005). Erlotinib in previously treated non-small cell lung cancer. *N Engl J Med*; 353(2):123-32.

Shimamura T, Li D, Ji H, et al (2008). Hsp90 inhibition suppresses mutant EGFR-T790M signaling and overcomes kinase inhibitor resistance. *Cancer Res*; Jul 15;68(14):5827-38.

Shimamura T, Perera SA, Foley KP, et al (2012). Ganetespib (STA-9090), a Non-Geldanamycin HSP90 Inhibitor, has Potent Antitumor Activity in In Vitro and In Vivo Models of Non-Small Cell Lung Cancer. *Clin Cancer Res*; 2012 Jul 17 (epub ahead of print).

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

Thatcher N, Chang A, Parikh P, et al (2005). Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomized, placebo-controlled multicenter study (Iressa Survival Evaluation in Lung Cancer). *Lancet*; 366(9496):1527-37.

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

Wong K, Koczywas M, Goldman JW, et al. (2011). An open-label phase II study of the Hsp90 inhibitor ganetespib (STA-9090) as monotherapy in patients with advanced non-small cell lung cancer (NSCLC). Presented at the 2011 Annual Meeting of the American Society for Clinical Oncology. *J Clin Oncol* 29: 2011 (suppl; abstr 7500).

Yasuda H, Kobayashi S, Costa DB (2012). EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncology*; 13(1):e23-31.

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: Performance Status Criteria

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