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SUMMARY OF CHANGES – Protocol

NCI Protocol #: 9875
Local Protocol #: 16-712
Protocol Version Date: October 31, 2019

Protocol Title:

Phase 2 Study of AT13387 (onalespib) in ALK+ ALCL, MCL, and BCL-6+ DLBCL

Protocol Version Date: October 31, 2019

#	Section	Comments
1.	**Contacts**	Updated study coordinator.
2.	**4.3.1 Patient Registration**	Updated enrollment status to closed.
3.	**5.1 Agent Administration**	Added end-date of study drug availability.
4.	**5.3 Duration of Therapy**	Added end-date of study drug availability.
5.	**9.1.1.3 Integral Laboratory or Imaging Studies**	Updated sample shipment information.
6.	**9.2.1.3 Exploratory/Ancillary Correlative Studies: Immunoblotting for HSP90 clients**	Updated sample shipment information.
7.	**9.2.1.3 Exploratory/Ancillary Correlative Studies: Whole exome sequencing and transcriptome analysis**	Updated sample shipment information.
8.	**13.1 Study Design and Endpoints**	Updated enrollment status to closed.

NCI Protocol #: 9875

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TITLE: Phase 2 Study of AT13387 (onalespib) in ALK+ ALCL, MCL, and BCL-6+ DLBCL

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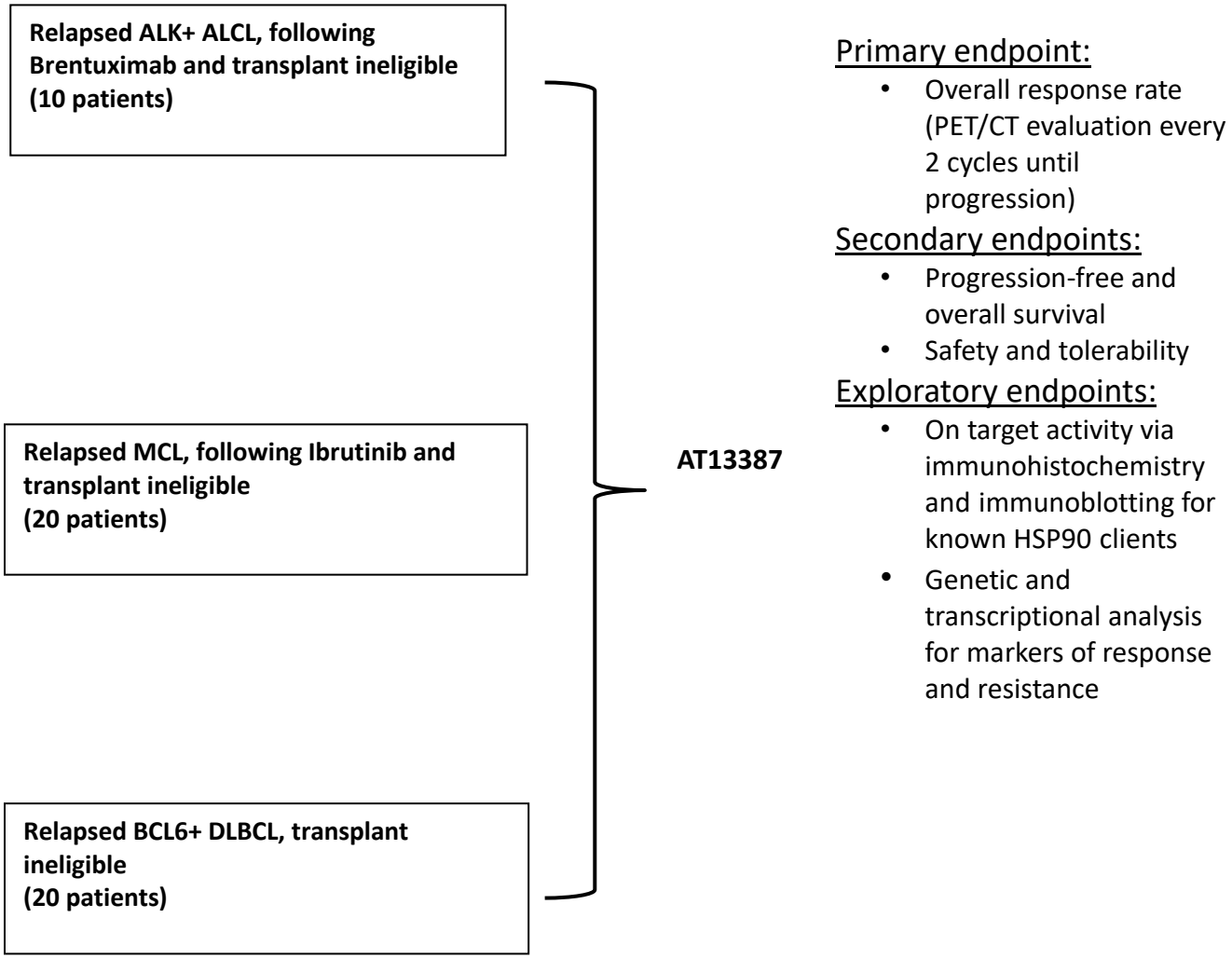
SCHEMA


Relapsed ALK+ ALCL, following Brentuximab and transplant ineligible (10 patients)
Relapsed MCL, following Ibrutinib and transplant ineligible (20 patients)
Relapsed BCL6+ DLBCL, transplant ineligible (20 patients)
AT13387
Primary endpoint:
Overall response rate (PET/CT evaluation every 2 cycles until progression)
Secondary endpoints:
Progression-free and overall survival
Safety and tolerability
Exploratory endpoints:
On target activity via immunohistochemistry and immunoblotting for known HSP90 clients
Genetic and transcriptional analysis for markers of response and resistance

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Overall response rate (ORR) to single agent AT13387 (onalespib) as measured by the proportion of partial and complete responses (PR + CR) in patients with relapsed/refractory ALK+ anaplastic large cell lymphoma (ALCL), mantle cell lymphoma (MCL), and BCL6+ diffuse large B cell lymphoma (DLBCL).

1.2 Secondary Objectives

1.2.1 Progression free survival (PFS) and overall survival (OS), as well as duration of response (DOR) of single agent AT13387 (onalespib) in patients with ALK+ ALCL, MCL, and BCL6+ DLBCL.

1.2.2 Safety and tolerability of single agent AT13387 (onalespib) in patients with ALK+ ALCL, MCL, and BCL6+ DLBCL.

1.3 Exploratory Objectives

1.3.1 Measurement of on-target activity of AT13387 (onalespib) in ALK+ ALCL, MCL, and BCL6+ DLBCL through immunoblotting and immunohistochemistry of pre-treatment, on-treatment, and time of progression tumor biopsies for HSP90 clients.

1.3.2 Determination of genetic and transcriptional markers for response and resistance to AT13387 (onalespib) in patients with ALK+ ALCL, MCL, and BCL6+ DLBCL.

2. BACKGROUND

2.1 ALK+ Anaplastic Large Cell Lymphoma (ALCL), Mantle Cell Lymphoma (MCL), and BCL6+ Diffuse Large B Cell Lymphoma (DLBCL)

2.1.1 ALK+ Anaplastic Large Cell Lymphoma (ALCL)

ALK+ Anaplastic Large Cell Lymphoma (ALCL) is a peripheral T cell lymphoma (PTCL) generally associated with a favorable prognosis compared to other PTCL subtypes. Its hallmark genetic lesion involves translocations or inversions involving the gene for ALK on chromosome 2p23 and results in ALK expression and constitutive activation of this kinase. The most common translocation involves the NPM gene on chromosome 5q23.[1] Expression of the NPM-ALK fusion gene in vitro and in mouse models results in B and T cell lymphoproliferative disorders.[1] Worldwide, ALK+ ALCL accounts for approximately 7% of peripheral T cell lymphomas, although within the United States it represents 16% of cases.[2] As a rare subset of a rare disease, this accounts for 0.25 cases per 100,000 people in the US, affecting men more commonly than women (2:1) and generally affecting younger individuals (median age at diagnosis 34 years).[3] It generally presents with lymphadenopathy and systemic symptoms of fever, night sweats and/or weight loss, although extranodal presentations may occur. The majority of patients will have advanced stage disease at diagnosis (65%).[4] Prognosis is best

predicted by the International Prognostic Index, initially developed from a cohort of patients with diffuse large B cell lymphoma (DLBCL), which identifies older age, elevated LDH, advanced stage, poor performance status, and 2 or more extranodal sites of disease as poor prognostic features.[5] Although patients with ALK+ ALCL generally do better than patients with ALK- ALCL, five year progression free survival (PFS) is only 64% with CHOP chemotherapy and patients with intermediate high- and high-risk disease do especially poorly with a 5 year PFS of only 23-33%.[4,6]

Initial treatment for ALK+ ALCL is generally with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or a CHOP-like regimen, specifically CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone). CHOEP has been associated with improvement in outcomes amongst younger patients with PTCLs, and specifically patients with ALK+ ALCL (3 year event free survival [EFS] 91% versus 57% for CHOEP compared to CHOP in ALK+ ALCL).[6,7] Patients who fail to respond to, or relapse, after their upfront therapy are typically treated with a salvage chemotherapy regimen, often containing gemcitabine, and high dose chemotherapy with autologous stem cell transplant (HDC-ASCT).[4,6] However, for patients who relapse after or are ineligible for autologous stem cell transplant, durable treatment options are limited. The drug-antibody conjugate brentuximab (CD30 conjugated to MMAE) is associated with excellent response rates (86%, with a CR rate of 57%) but the duration of response is 12-14 months.[8] The ALK inhibitor crizotinib has been tested in a small cohort of 11 patients with relapsed/refractory disease with response rate of 100% but a 2 year progression free response of only 64%.[9] Thus, a significant fraction of patients with ALK+ ALCL are not cured with current therapies.

2.1.2 Mantle cell lymphoma (MCL)

Mantle cell lymphoma (MCL) is a mature B cell non-Hodgkin lymphoma (NHL) that is probably best characterized as intermediate between an indolent and an aggressive lymphoma. It accounts for 7% of adult NHL, or 4-8 cases per million person years, in the US and Europe.[10] Like the indolent lymphomas, it is incurable with conventional chemoimmunotherapy and can be retreated at the time of relapse, but its clinical behavior is more aggressive with a markedly shorter median OS. More intensive chemotherapy strategies are associated with longer treatment responses and PFS but not cure.[11-15] While there is a subset of MCL that behaves more indolently, best identified by either a low Ki67, or circulating disease and splenomegaly in the absence of lymphadenopathy, and can be initially observed, the majority of patients will present in advanced stage with symptomatic disease.[16-19] Prognosis is best defined by the MCL International Prognostic Index (MIPI), which uses patient age, performance status, LDH, leukocyte count and Ki67 (the latter for the biologic MIPI only) to identify three risk groups.[20] Overexpression of cyclin D1, as a result of a translocation between the *CCND1* gene on chromosome 11q13 and the immunoglobulin heavy chain gene (*IGH@*) locus on chromosome 14q23, is present in the vast majority of cases, but not sufficient for the pathogenesis of this disease.[21,22] Other molecular and/or genetic events resulting in either cell cycle progression (deletions in INK4a/ARF, expression of SOX11), impaired DNA damage response (TP53 or ATM mutations), and/or enhanced survival (BCL2 overexpression, tonic B cell receptor signaling and/or activation of the PI3K/AKT and NFκB pathways) are also needed.[23-29]

Initial therapy with R-CHOP chemotherapy alone results in poor outcomes with a median PFS of less than two years.[14,30] Consolidation of R-CHOP with HDC-ASCT, or maintenance rituximab for patients who are older and/or ineligible for autologous stem cell transplant, improved outcomes and extended the median PFS to approximately 4 years.[14,31] Regimens that incorporate cytarabine and consolidate with HDC-ASCT have perhaps resulted in the best outcomes, with median EFSs approaching 7 years.[11,12] HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and cytarabine) is associated with a median time to treatment failure (TTF) and PFS of approximately 4-5 years.[13,14] More recently bendamustine, in combination with rituximab, has been identified as a highly effective treatment for MCL with an improvement in PFS compared to R-CHOP (35.4m v 22.1m).[30] The use of bendamustine and rituximab (BR) in combination with cytarabine with or without consolidation HDC-ASCT is being explored.[15]

When MCL patients relapse after initial therapy, additional chemotherapy may be tried but alternative treatment approaches are needed for chemorefractory disease. Targeting Bruton's tyrosine kinase (BTK), which links constitutive B cell receptor (BCR) signaling to PI3K/AKT and NFκB signaling, with ibrutinib has been highly successful in relapsed/refractory MCL, with a response rate of 68% and an 18 month median duration of response.[32] Importantly, between 10-25% have mutations that result in nonclassical NFκB signaling, and thus are refractory to ibrutinib[29]. The use of the proteosome inhibitor, bortezomib, possibly through its activity against NFκB, results in single agent response rates of 30-50%, lasting 7-10 months in relapsed/refractory disease.[33,34] These responses may be enhanced in combination with chemoimmunotherapy. Lenalidomide has been investigated, benefiting about 30% of patients for up to 17 months.[35] Finally, the use of the CDK4/6 inhibitor palbociclib, resulted in disease stabilization for over a year in 5 of 17 patients enrolled in a small proof of concept study.[36] For younger patients with a more aggressive disease course who are able to achieve a minimal disease state with salvage therapies, allogeneic stem cell transplant offers a potentially curative option, with long term disease free survivals of 15-82% depending on the series.[37-39] Most of the remaining patients, both those ineligible for allogeneic transplant and those who relapse after transplant will die from their disease.

2.1.3 Diffuse Large B cell Lymphoma (DLBCL)

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults, accounting for approximately 25,000-30,000 new cases each year in the United States.[40] Patients with DLBCL can be stratified into prognostic groups using several factors including age, stage, performance status, lactate dehydrogenase (LDH), and number of extranodal sites by the international prognostic index (IPI).[41] Distinct subtypes of DLBCL have been defined by gene expression profiling, termed germinal center B-cell (GCB) or activated B-cell (ABC) DLBCL. Approximately 60% of DLBCL will be GCB and these carry a more favorable prognosis.[42] In addition, DLBCL with translocations involving both the *MYC* gene locus on chromosome 8 and another oncogenic translocation, most commonly involving the *BCL2* gene on chromosome 18, the so-called "double hit" lymphomas, do especially poorly with long term disease free survival of only 20-30%.[43] Patients with limited stage disease can be effectively treated with combination chemotherapy with or without radiotherapy, achieving very favorable outcomes[44-46]; however a majority of patients present with advanced disease and do not fare as well.[41,47]

Combination chemotherapy with R-CHOP is effective initial therapy, though nearly half of patients will ultimately relapse.[47] Dose escalation, addition of newer agents, and HDC-ASCT have not been able to improve outcomes compared to CHOP.[48-50] The addition of rituximab to CHOP has increased the cure rate in DLBCL by nearly 15%, though a significant number of patients will still relapse and ultimately die of their disease.[51,52] Patients who are primary refractory to, or relapse after, R-CHOP are treated with additional salvage chemotherapy regimens such as dexamethasone, high dose cytarabine, and cisplatin (DHAP), rituximab, ifosfamide, carboplatin, and etoposide (RICE), or rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP).[53-57] While definitive data do not yet exist, there are indications that since the routine inclusion of rituximab with initial combination chemotherapy, relapsing patients may be more difficult to salvage due to selection for more aggressive disease.[58-60] Those able to obtain an objective response are then consolidated with HDC-ASCT resulting in both a progression free and overall survival advantage compared to salvage chemotherapy alone,[53,54,56] though half of patients who undergo stem cell transplant still relapse, highlighting the need for novel therapies.[53,54,56,61] Additionally, a significant number of patients are not eligible to undergo HDC-ASCT due to chemotherapy insensitivity, advanced age, or comorbid disease.

2.2 AT13387 (onalespib)

AT13387 (onalespib) ((2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-1,3-dihydroisoindol-2-yl]-methanone, L-lactic acid salt) is a small molecule inhibitor of HSP90 derived by high-performance liquid chromatography (HPLC) analysis and chosen based on good stability at elevated temperatures, non-hygroscopicity, absence of hydrate formation, and the required aqueous solubility. HSP90 is a chaperone responsible for correctly folding its client proteins into their active confirmation, thereby preventing them from ubiquitination and proteasomal degradation.[62] Inhibition of the ATP-dependent function of HSP90 with small molecule inhibitors results in the degradation of many oncogenes, including BCR-ABL, c-KIT, EGFR, HER2, AKT, BCL6, ALK and cyclin D1.[63-65] Targeting HSP90, then, has the ability to inhibit multiple oncogenic pathways simultaneously. In vitro and in vivo studies of AT13387 (onalespib) have demonstrated its ability to bind to the ATP binding site at the *N*-terminal domain of HSP90, decrease the levels of multiple known HSP90 client proteins important in cell proliferation and survival, and inhibit cell proliferation across a wide panel of tumors at nanomolar concentrations.

AT13387 (onalespib) and other HSP90 inhibitors potently inhibit the *in vitro* growth of mantle cell lymphoma, DLBCL and ALK+ ALCL cell lines and the *in vivo* growth of xenografts (as described in section 2.2.2). Similar sensitivity was observed non-small cell lung cancer (NSCLC) lines, irrespective of sensitivity to the EGFR inhibitor erlotinib or the ALK inhibitor crizotinib, at IC_{50}s of 14-69nM. Exposure to AT13387 (onalespib) (0.03-10μM) resulted in the reduction in levels of wild-type and mutant EGFR, EML4-ALK, and AKT, with associated decreases in levels of phosho-ERK, phospho-AKT, and phospho-S6 when measured by immunoblotting at 24 hours. In xenograft models of both erlotinib sensitive and erlotinib insensitive EGFR mutant NSCLC, AT13387 (onalespib) inhibited tumor growth at doses of both 55mg/kg and 70mg/kg once weekly. Combination of erlotinib and AT13387 (onalespib) in erlotinib sensitive EGFR mutant NSCLC xenografts results in additive efficacy over either agent alone, as did combinations of AT13387 (onalespib) with the antimicrotubule chemotherapeutic

agent paclitaxel. Similar effects were seen in xenograft models of ALK rearranged NSCLC, with better efficacy when AT13387 (onalespib) was combined with crizotinib compared to either agent alone. Furthermore, while there was tumor regrowth observed with single agent AT13387 (onalespib) or single agent erlotinib or crizotinib, there was no tumor regrowth seen with the combinations, suggesting that the combination may delay the emergence of TKI resistance clones. As with erlotinib-resistant EGFR mutant models, AT13387 (onalespib) maintained activity in ALK rearranged NSCLC models that were resistant to crizotinib.

AT13387 (onalespib) was similarly effective against a panel of vemurafenib sensitive and insensitive melanoma cell lines with IC_{50}s of 22-190nM, with depletion of BRAF and CRAF levels as well as AKT and associated decreases in levels of phospo-ERK and phospho-S6. Efficacy was maintained in cell lines that were resistant to both BRAF and MEK inhibitors, with inhibition of MAPK and AKT signaling observed. Xenograft mouse models of both vemurafenib sensitive and insensitive melanoma were sensitive to AT13387 (onalespib). Although there did not appear to be additive efficacy of AT13387 (onalespib) in combination with vemurafenib in the vemurafenib sensitive model, the combination did result in the lack of eventual tumor regrowth seen in mice treated with vemurafenib alone, indicative that the combination may delay the emergence of a resistance clone as was likewise seen in the NSCLC models. Resistant outgrowth tumors demonstrated upregulation of PDGFR and EGFR, both of which were subsequently downregulated following treatment with AT13387 (onalespib), in vitro. After a single dose of AT13387 (onalespib), BRAF, AKT, CRAF, and CDK4 were all downregulated in tumors from these melanoma xenograft models and ERK and AKT pathways were inhibited.

Similar data exists for GIST and hormone-resistant, androgen-receptor positive prostate cancer. Together these data demonstrate the on-target and anti-tumor activity of AT13387 (onalespib) at nanomolar concentrations, and that combination strategies of AT13387 (onalespib) with kinase inhibitors may delay the development of resistance. They also support the development of once or twice weekly dosing schedules, as this dosing was effective and best tolerated in xenograft models.

A CNS safety pharmacology study, conducted in the rat with AT13387 (onalespib) administered by 1-hr IV infusion, demonstrated no adverse CNS effects at doses up to 200 mg/kg in males and 125 mg/kg in females, compared with control vehicle-treated animals. A CV/R safety pharmacology study was conducted in Beagle dogs. Vehicle only or AT13387 (onalespib) (ascending doses of 1, 4 and 15 mg/kg) were administered via a 1-hr IV infusion. A dose-related increase in heart rate was observed at 4 mg/kg and above from 10 minutes after the start of infusion which peaked at the end of infusion and returned to control levels by approximately 5 hours after the end of infusion. The increased heart rate observed at 15 mg/kg was associated with a concomitant decrease in blood pressure (systolic, diastolic and mean arterial). AT13387 (onalespib) did not have any significant effect on QT interval or QTc at any dose level tested. TK data showed good characterization of AT13387 (onalespib) concentration-time profiles achieved for 1-hr IV infusion, and plasma concentration-time profiles were consistent with the IV route of administration. C_{max} was clearly defined by targeting a sample immediately prior to end of the 1-hr infusion. AUC was well characterized as indicated by low % AUC extrapolated (<17%).

AT13387 (onalespib) was essentially completely cleared from plasma by 24 hours (23 hours post-infusion) in both species.

Toxicology studies were done in both rat and dog species. A clear dose-related toxicity was established in dogs, including identification of target organs of toxicity; the NOAEL was 1 mg/kg/dose given 2QWx3 and the nominal HNSTD was 3 mg/kg/dose given 2QWx3. The dog was found to be more sensitive than the rat on a mg/kg and mg/m$_2$ basis, as well as in exposure terms (C_{max} and AUC). The human clinical start dose was calculated on a mg/m$_2$ basis using accepted body surface area conversion factors (FDA, 2005). Given its high sensitivity to AT13387 (onalespib), the dog was deemed an appropriate species for this purpose; therefore, the start dose was estimated as one-sixth of the nominal dog HNSTD (HNSTD = 3 mg/kg = 60 mg/m$_2$), giving a human start dose of 10 mg/m$_2$/dose given 2QWx3. The human start dose calculated from the dog HNSTD is 3-fold lower than would be derived from the rat NOAEL (start dose based on one tenth of the rat NOAEL on a body surface area basis = 30 mg/m$_2$/dose).

2.2.1 Clinical experience

There have been two completed clinical study of AT13387 (onalespib) as monotherapy in advanced solid tumors, and there are three ongoing studies (in combination) with a total of 171 patients having received at least one dose of the drug.[66,67]

2.2.1.1 AT13387 (onalespib) Pharmacokinetics

Sixty-two patients were treated in the first-in-human phase 1 study of AT13387 (onalespib) in advanced solid tumors, either once or twice weekly for 3 weeks every 28 days, at doses up to 310mg/m^2.[66] Blood samples were collected predose and through 72 hours post-infusion on Days 1 and 18 for the twice-weekly regimen, or Days 1 and 15 for the once-weekly regimen. Urine samples were collected for time periods of 0-7 hours, 7-24 hours and 24-48 hours during and after infusion. Concentrations of AT13387 (onalespib) in plasma clinical samples were determined using an analytical method for AT13387 (onalespib)-specific liquid chromatography with mass spectrometric detection (LC-MS/MS). Quantitation of AT13387 (onalespib) was shown to be unaffected by the presence of putative metabolites which were capable of breaking down from parent compounds. Within cohorts, the PK of AT13387 (onalespib) showed inter-individual variability of 2-5 fold for AUC_{0-t} and $t_{1/2}$ but up to 9-fold for C_{max}. The $t_{1/2}$ was dose-independent with mean cohort values ranging from 6.6 to 11.5 hrs. Maximum $t_{1/2}$ observed for any individual profile was 14 hrs. There was no notable accumulation or reduction in exposure between Day 1 and Day 18 of Cycle 1 for the twice-weekly dosing schedule or between Day 1 and Day 15 of Cycle 1 for the once-weekly dosing schedule. Plasma clearance of AT13387 (onalespib) was independent of dose (range 0.96–1.45 L/hour/kg over all 10 cohorts). This high value for plasma clearance is consistent with that predicted from the PK of the drug in nonclinical studies. Measurement of the concentrations of AT13387 (onalespib) excreted in urine showed that renal elimination is of minor importance in the total clearance of the drug. Less than 5% of the administered dose was recovered in the urine during 48 hours post-dose. The volume of distribution was high (9.8-22.9 L/kg).

Limited information on the metabolism, elimination, and safety of AT13387 (onalespib) is currently available. AT13387 (onalespib) appears to be metabolized by the liver and both parent compound and metabolites eliminated by the kidneys. Drug-drug interaction studies in humans have not been conducted with AT13387 (onalespib) administered as a monotherapy or in combination with other cancer therapies.

Results from the first-in-human phase 1 study of AT13387 (onalespib) in advanced solid tumors identified a maximally tolerated dose of 120mg/m^2 twice weekly for 3 weeks every 28 days, or 260mg/m^2 weekly for 3 weeks every 28 days.[66] One dose-limiting toxicity (DLT) of visual disturbance occurred at the 120 mg/m^2 twice-weekly schedule, and accordingly was declared the RP2D on the twice-weekly administration schedule. No formal DLTs occurred on the once-weekly schedule, though multiple severe toxicities, including diarrhea, nausea, vomiting, fatigue, and systemic infusion reactions, led to selection of 260 mg/m^2 as the RP2D on the once-weekly administration schedule. Sixty-two patients with a variety of solid tumors were treated, with one partial response in an imatinib-resistant gastrointestinal stromal tumor (GIST). Stable disease was observed in 36% of patients, one-third of whom experienced disease stabilization for over 4 months.

It has been shown with other HSP90 inhibitors, like ganetespib, that although once weekly dosing results in a prolonged intertumor ½ life, the effect on downregulation of client proteins is short lived, with an initial protein depletion at 24 hours post-dosing followed by a steady increase to normal protein levels at 48-72 hours.[68] Furthermore, once weekly dosing results in a tumor growth delay with a transient reduction in client protein levels, while consecutive daily dosing (5 days in this study) results in tumor regression with a persistent reduction in client protein levels out to 168 hours. It has been difficult to do daily dosing of HSP90 inhibitors over 5 consecutive days in humans due to toxicity, so dosing over 2 consecutive days has been adopted. For AT13387, this dosing schedule was explored in a phase 1 study in solid tumors and the RP2D was 160mg/m2 on d1, 2, 8, 9, 15, an 16 of a 28 day cycles and this dosing schedule was safe and tolerated.[67] Given the high proliferative index of the lymphomas included in this study, the variable sensitivity of their pathogenic HSP90 clients to HSP90 inhibition, and the target suppression advantage of consecutive day dosing, we chose to use this schedule in this lymphoma study.

2.2.1.2 Safety

Overall, 97.7% of patients having received AT13387 (onalespib) reported any adverse event, and 49.1% of patients report a CTCAE grade 3/4 adverse event. The most common adverse events seen in clinical studies include diarrhea (78%), fatigue (60%), nausea (53%), decreased appetite (40%), vomiting (32%), dizziness (28%), dry mouth (23%), anemia (22%), constipation (21%), headache (21%), abdominal pain (20%), weight loss (19%), insomnia (19%), cough (16%), back pain (15%), muscle spasms (16%), peripheral edema (16%), hypokalemia (15%), visual impairment (15%), increases in aspartate aminotransferase (AST) (12%), chills (13%), dehydration (12%), dyspnea (13%), injection site reactions (12%), dysgeusia (12%), and infusion site pain (11%). The most common serious adverse events, regardless of relationship, were categorized under Gastrointestinal Disorders (18/104; 17%); Infections and Infestations (14/104; 14%); and Respiratory, Thoracic, and Mediastinal Disorders (14/104; 14%). The only individual

event terms reported for >2 subjects were 5/104 (4.8%) for diarrhea (all resolved); 4/104 (3.8%) each for dehydration (3 resolved and 1 resolved with sequelae) and pneumonia (2 resolved and 2 fatal); and 3/104 (2.9%) each for chest pain (2 resolved and 1 not resolved), muscular weakness (1 resolved and 2 not resolved), and dyspnea (3 resolved). There was one unexpected SAE, convulsions (grade 2) that was felt to possibly be related to the study drug, occurring two weeks after the last treatment; the patient had received 2 cycles of treatment in total and did not receive further treatment. Four subjects died within 30 days of receiving treatment with AT13387 (onalespib) from causes not attributed to progression of disease. The causes of all deaths were considered to be not treatment-related.

The one dose-limiting toxicity (DLT) observed on the first-in-human, phase 1 single agent study of AT13387 (onalespib) in advanced solid tumors was visual impairment; one subject developed blurred vision, chloropsia and photopsia on C1D22-23 after receiving AT13387 (onalespib) at 120mg/m2/dose twice weekly for three weeks. An electroretinogram (ERG) on C1D24 showed significant cone suppression (grade 3), the study medication was discontinued permanently, and the visual changes and ERG changes resolved within 21 days of study drug cessation. A range of visual disturbances (collectively grouped under Visual Impairment) have been reported in subjects receiving AT13387 (onalespib) in phase 1-2 trials. These include peripheral flashes (photopsia), blurred or double vision, floaters, color distortion and dimness, difficulties with light/dark accommodation, tunnel vision or other field defects, halos, apparent movement of stationary objects, and complex disturbances. The symptoms were generally Grade 1 in severity. Based on data from Studies AT13387-01 and -02, symptoms were intermittent, reversible and transient, lasting a few seconds to a few minutes and occurring on 1 to 3 days per cycle. The onset was generally in the first cycle, although in some subjects, the onset was in the first half of the second cycle. The symptoms were more frequent in the evening or at night and generally did not interfere with activities of daily living. Visual symptoms were dose-related.

Additional safety analysis was done based on central ECG recording. ECGs were analyzed in 60 subjects who met ECG analysis population criteria (Clinical Cardiac Report, AT13387-01). ECG data revealed no change in heart rate, atrioventricular conduction as measured by the PR interval, or depolarization as measured by the QRS duration. There were no clear signals of any change in morphology or new rhythms. No effect of AT13387 (onalespib) was observed on cardiac repolarization, as measured by the QTcF duration, in the twice-weekly dosing schedule up to a dose of 120 mg/m2. The once-weekly dosing regimen of 220 to 310 mg/m2/dose shows a QTcF increase in the 10-15 ms range, with PK pharmacodynamic analysis showing a predicted change at Cmax of 7 ms (upper confidence interval, 11 ms). This result indicates that AT13387 (onalespib) probably does not affect cardiac repolarization; however, the data do not exclude a small effect, <10 ms in magnitude. An effect of this magnitude is not likely to be clinically relevant.

2.3 Rationale for the use of AT13387 (onalespib) in ALK+ ALCL, MCL and BCL6+ DLBCL

2.3.1 AT13387 (onalespib) in ALK+ ALCL

Oncogenic rearrangements involving ALK are involved in the pathogenesis and survival of more than half of ALCLs. ALK+ ALCL is associated with a better prognosis than ALK- ALCL, but patients with high risk or relapsed/refractory disease do poorly. In addition, among the two patients who had an early relapse after an initial response to crizotinib, deep sequencing of the NPM/ALK fusion gene revealed a mutation in the kinase domain of ALK that preserved ALK signaling. Crizotinib has been similarly effective in EML4-ALK rearranged non-small cell lung cancer (NSCLC) but relapses are frequent and associated with acquired mutations in the ALK kinase domain of the rearranged gene.[69,70]

ALK and its fusion proteins are known clients of HSP90.[71-73] ALK+ ALCL is sensitive to treatment with an older generation HSP90 inhibitor geldanamycin with 50% inhibitory concentration (IC_{50}) between 10-30μM, resulting in G2/M cell cycle arrest and caspase-3-mediated apoptosis.[74] Treatment resulted in a reduction in NPM-ALK protein levels and cleavage of PARP. The HSP90 inhibitor AUY922, which is structurally related to AT13387 (onalespib), results in potent growth inhibition and cell death of the ALK+ ALCL cell line SUDHL-1 with an IC_{50} of <10nM, and this is associated with a reduction in total ALK protein as well as phospho-ALK, AKT, STAT3, and phospho-STAT3.[75] AUY922 was similarly effective *in vivo* in SUDHL-1 mouse xenografts with tumor growth inhibition, early FLT-PET signal reduction, and decreases in Ki67 with evidence of apoptosis determined by caspase-3 staining.[75] HSP90 inhibition with the newer generation HSP90 inhibitor ganetespib exhibited more potent cytotoxic affects against ALK-rearranged NSCLC than crizotinib (IC50 10-13nM v 200-300nM) and was able to suppress tumor growth *in vivo* in ALK-rearranged NSCLC xenograft models. Importantly, HSP90 inhibition was able to overcome acquired crizotinib resistance that resulted from a mutation in the ALK fusion, with evidence of continued destabilization of the mutant fusion gene product.[76,77] Thus, HSP90 inhibition can target multiple tumorigenic pathways and overcome acquired resistance to ALK inhibitors, making it an attractive strategy for the treatment of ALK+ ALCL.

2.3.2 AT13387 (onalespib) in MCL

MCL is characterized by overexpression of cyclin D1, which drives G1/S cell cycle transition through cyclin-dependent kinase 4 (CDK4). A recent study led by our colleague Geoff Shapiro demonstrated that the CDK4 inhibitor PD0332991 led to sustained clinical responses (mostly stable disease) in a subset of patients with MCL.[36] MCL also appears to be reliant on B cell receptor (BCR) signaling, as a subset of MCL has a very restricted immunoglobulin gene repertoire consistent with antigen-driven selection and some of the most abundantly expressed peptides in MCL belong to proteins involved in BCR signaling.[78,79] Inhibition of BTK with ibrutinib has been highly successful in relapsed MCL. However, up to 40% of patients do not respond and progression-free survival among responders averages only 18 months.[32] Intrinsic resistance to ibrutinib has been associated with activation of the non-classical NFκB pathway.[29] Gain-of-function mutations in TRAF2 and TRAF3 that constitutively drive non-classical NFκB

signaling occur in MCL cell lines and primary patient samples.[29] In addition, the BTK C481S mutation that confers resistance to ibrutinib can occur in patients with MCL.[80]

Work in the Weinstock lab has shown that newer-generation heat shock protein 90 (HSP90) inhibitors potently induce apoptosis in primary MCL samples and MCL lines, including lines with constitutive activation of non-classical NFκB, in the 5-300nM range. Specifically, AT13387 (onalespib) has an IC_{50} of 50-130nM in established MCL cell lines. This is associated with degradation of factors essential for MCL survival, including cyclin D1, CDK4, AKT, BTK, and IKKα, with resulting loss of MAP kinase and NFκB signaling. HSP90 inhibitors appear to downregulate both wild-type and BTK C481S *in vitro*. In addition, the HSP90 inhibitor AUY922 was highly active *in vivo* in mice with MCL cell line xenografts and in a patient-derived xenograft of disseminated, ibrutinib-resistant MCL. These mice develop mantle cell lymphoma involving the bone marrow, spleen, lymph nodes, and GI tract that is evident on ^{18}F-FLT-PET scans. HSP90 inhibition resulted in a significant reduction in ^{18}F-FLT uptake in these sites of disease, as well as a reduction in cyclin D1, BTK, and CDK4 by immunoblotting, compared to vehicle treated mice. Thus MCL is an attractive target for HSP90 inhibition, and can overcome both intrinsic and acquired resistance to ibrutinib.

2.3.3 AT13387 (onalespib) in BCL6+ DLBCL

BCL6 is an important oncogene in many DLBCLs. It is normally expressed during the germinal center reaction, where it represses the expression of genes like *TP53* to prevent apoptosis induced by the DNA strand breaks that initiate immuoglobulin class switching and somatic hypermutation.[81] Overexpression of BCL6 can be identified by immunohistochemistry in approximately 60% of DLBCL, and often results from mutations or translocations involving the *BCL6* locus.[82] Overexpression of BCL6 has been associated with BCL6 dependency.[83] HSP90 complexes with BCL6, and inhibition of HSP90 with the newer generation HSP90 inhibitor PU-H71 in BCL6-dependent DLBCL resulted in depletion of BCL6, the upregulation of genes that are downregulated by BCL6 like *ATR* and *TP53*, and cell death[84]. PU-H71 also resulted in a significant reduction in tumor burden and improvement in survival in xenografts derived from BCL-6-dependent DLBCL cell lines. We treated BCL6 dependent DLBCL lines with AT13387 (onalespib), the geldanamycin derivative 17AAG, or ibrutinib. AT13387 (onalespib) was the most potent compound (IC_{50} 10-100nM) and promoted the downregulation of BCL6. Together, these data support the investigation of AT13387 (onalespib) in BCL6-overexpression DLBCLs.

We chose AT13387 (onalespib) for this study as it belongs to a class of newer, more potent HSP90 inhibitors, which generate enhanced tumor cell killing across a variety of cancer types, including lymphoma. The side effect and safety profile to date has shown this to be a well-tolerated drug, with diarrhea, fatigue, nausea/vomiting, abdominal pain, and decreased appetite being among the most commonly reported toxicities. Thus, we do not anticipate any specific safety concerns using AT13387 (onalespib) dosed at 160mg/m^2/dose on days 1,2, days 8,9, and days 15,16 of a 4 week cycle, as the same dosing strategy was previously shown to be tolerated in a phase II trial. We chose this dosing over the once weekly dosing as it has been shown with other HSP90 inhibitors, like ganetespib, that although once weekly dosing results in a prolonged intertumor ½ life, the effect on downregulation of client proteins is short lived, with an initial protein depletion at 24 hours post-dosing followed by a steady increase to normal protein levels

at 48-72 hours.[68] Furthermore, once weekly dosing results in a tumor growth delay with a transient reduction in client protein levels, while consecutive daily dosing (5 days in this study) results in tumor regression with a persistent reduction in client protein levels out to 168 hours. It has been difficult to do daily dosing of HSP90 inhibitors over 5 consecutive days in humans due to toxicity, so dosing over 2 consecutive days has been adopted.[67] Given the high proliferative index of the lymphomas included in this study, the variable sensitivity of their pathogenic HSP90 clients to HSP90 inhibition, and the target suppression advantage of consecutive day dosing, we chose to use this schedule in this lymphoma study.

In summary, we anticipate that AT13387 (onalespib) will demonstrate single-agent activity in this treatment-refractory population and could then be tested in a randomized trial. In addition, we anticipate that correlative studies from this trial will inform both patient selection and our understanding of the determinants of response and resistance to HSP90 inhibition in patients with these subtypes of lymphoma.

2.4 Correlative Studies Background

2.4.1 Immunohistochemical and immunoblotting studies of on-target efficacy

Blood, bone marrow or lymph node biopsy sampling for malignant cells will take place prior to treatment initiation, on cycle 1 day 17-22, and at the time of disease progression for several biomarker studies. These will include immunohistochemical quantification of ALK in ALK+ ALCL, cyclin D1 in MCL, and BCL6 in DLBCL, as well as immunoblotting of tumor samples for known HSP90 clients important to the proliferation and survival of these lymphomas including CDK4, cyclin D1, AKT and pAKT, ERK and pERK, IKKα, BTK (in DLBCL and MCL), HSP70, ALK (in ALCL), BCL6 (in DLBCL), and p53. We will compare protein levels prior to and on treatment and at the time of disease progression. These studies will serve to evaluate if we are achieving on-target activity of the drug and will be correlated with response.

2.4.2 Genetic and transcriptional analysis for markers of disease response and resistance

Samples will also be submitted for whole exome sequencing (with paired germline samples) and RNAseq, and results will be compared between pre-treatment, on-treatment, and time of progression tumor samples for markers of disease response and resistance. For exome sequencing, the ABSOLUTE algorithm will be applied to determine the cancer cell fraction. Variant allele fractions for mutations present in the progression sample can then be compared to those in the pre-treatment sample after adjustment for cancer cell fractions to determine whether AT13387 (onalespib) results in a shift in the clonal architecture of lymphomas.[85] Although HSP90 classically acts at the post-translational level, some evidence indicates that it also can affect transcription.[86] We previously demonstrated in human leukemia cells that transcriptional profiling can highlight downstream pathways that are suppressed or activated in response to the degradation of HSP90 clients.[87] Transcriptional assessment will be performed on specimens obtained prior to beginning treatment, during treatment with AT13387 (onalespib) and then upon progression. In cases with bone marrow or peripheral blood involvement, lymphoma cells will be purified, for example by CD19 selection. Markers of response and progression will be determined by: 1) comparing gene expression patterns using GSEA[88], 2) interrogation of the

Broad Institute Molecular Signatures Database[88] (MSigDB; http://www.broadinstitute.org/gsea/msigdb/index.jsp) and 3) Ingenuity Pathway Analysis[89,90], as we previously performed.[91] In addition, we will interrogate the signature of progression during AT13387 (onalespib) treatment in the Connectivity Map, a database linking gene expression with drug sensitivity.[92] Build 2.0 contains over 7,000 expression profiles representing the effects of 1,309 compounds. Compounds that correlate inversely with the signature, and therefore may abrogate it, are readily available therapeutics to block pathways that bypass HSP90 inhibition. The analysis of these exploratory biomarker studies will be retrospective, with assays performed after response evaluation for biomarker identification.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed, relapsed/refractory ALK+ ALCL (with ALK positivity defined by immunohistochemistry and/or FISH/cytogenetics from any prior biopsy), MCL, or BCL6+ DLBCL (with BCL6 positivity defined by immunohistochemistry from any prior biopsy) and meet the following criteria:

3.1.2 Patients must have measurable disease that has not been previously irradiated, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional imaging or ≥ 10mm with spiral CT scan. If the patient has been previously irradiated, there must be evidence of progression since the radiation. See Section 11 for the evaluation of measurable disease.

Please note, this trial includes mandatory tumor biopsies pre-treatment, during cycle 1 and at the time of disease progression of accessible tumor. Having accessible tumor for biopsy is not required for eligibility. We expect that at least 80% of patients will have accessible tumor for these biopsies, however.

3.1.3 Prior therapy

Please note, the washout period for prior therapies cannot *be shortened.*
Please note, prior therapies can be from any time in the past.

3.1.3.1 ALK+ ALCL

Patients must have disease that has relapsed and or is refractory to prior therapy, which must have included a multiagent chemotherapy regimen including an anthracycline, if not contraindicated, and prior brentuximab. Prior crizotinib or other ALK inhibitor therapy, while recommended, is not mandatory. Patients must have relapsed following or be ineligible for, or refuse, autologous stem cell transplant.

3.1.3.2 MCL

Patients must have disease that has relapsed and or is refractory to prior therapy, which must have included a multiagent chemotherapy regimen and prior ibrutinib or other BTK inhibitor therapy. Patients must have relapsed following or be ineligible for, or refuse, autologous stem cell transplant.

3.1.3.3 BCL6+ DLBCL
Patients must have disease that has relapsed and or is refractory to prior therapy, which must have included an anthracycline, if not contraindicated. Patients must have relapsed following or be ineligible for, or refuse, autologous stem cell transplant.

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of AT13387 (onalespib) in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.6 Life expectancy of greater than 3 months

3.1.7 Patients must have normal organ and marrow function, and electrolyte balance (allowing for repletion) as defined below:

– absolute neutrophil count	≥1,000/mcL
– platelets	≥75,000/mcL, unless due to marrow involvement by lymphoma in which case a platelet count of ≥ 30,000/mcL will be used
– total bilirubin	≤ 1.5x ULN, unless due to Gilbert's syndrome or hemolysis, in which case ≤ 3.0x ULN is allowed.
– AST(SGOT)/ALT(SGPT)	≤3.0 × institutional upper limit of normal
– creatinine	≤ 1.5x ULN or a creatinine clearance ≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- Potassium	above the institutional lower limit of normal (supplementation to meet this is allowed)
- Magnesium	above the institutional lower limit of normal (supplementation to meet this is allowed)

3.1.8 HIV+ patients are eligible for the trial provided they meet the other study criteria in addition to the following:

- CD4+ T-cells ≥ 250/mm^3
- HIV sensitive to antiretroviral therapy
- Zidovudine not allowed
- Long term survival anticipated on the basis of HIV alone were it not for the lymphoma
- No concurrent AIDS-defining illness other than the lymphoma

3.1.9 The effects of AT13387 (onalespib) 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, for the duration of study participation, and for 4 months after the completion of AT13387 (onalespib) administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of AT13387 (onalespib) administration.

3.1.10 Although the PK data in humans is still unknown, the potential for drug-interaction cannot be ruled out. Pre-clinical studies suggest that AT13387 (onalespib) is a substrate of P-gp, a moderate inhibitor of BCRP and P-gp, and a strong inhibitor of MATE ½-K. Patients must be willing to not take St. John wort or grapefruit juice while participating in this trial and should avoid drugs that are strong inducers of P-gp, and to switch to alternative drugs when available.

3.1.11 Hepatitis B positive patients are eligible. Prophylactic HBV therapy is recommended but only if there is no circulating virus detectible.

3.1.12 Transformed lymphoma patients are eligible.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Steroids for symptom palliation are allowed but must be either discontinued or on stable doses at the time of initiation of protocol therapy.

3.2.2 Patients who are receiving any other investigational agents. All investigational agents other than ibrutinib must have been discontinued at least 4 weeks prior to beginning treatment. Prior ibrutinib therapy must have been discontinued at least 2 weeks prior to beginning therapy.

3.2.3 Patients with known leptomeningeal or brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Imaging or spinal fluid analysis to exclude CNS involvement is not required, unless there is clinical suspicion by the treating investigator.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AT13387 (onalespib).

3.2.5 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.

There will be no exclusion of patients with known visual impairment or symptoms, including by not limited to peripheral flashes (photopsia), blurred or double vision, floaters, color distortion and dimness, difficulties with light/dark accommodation, tunnel vision or other field defects, halos, apparent movement of stationary objects, and complex disturbances. Patients will have a baseline ophthalmologic exam to serve as a point of comparison and further exams as needed should visual symptoms develop. No pre-treatment eye exam findings or ocular symptoms have been associated with an increased risk of ocular toxicity seen with AT13387.

3.2.6 Pregnant women are excluded from this study because AT13387 (onalespib) has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with AT13387 (onalespib), breastfeeding should be discontinued if the mother is treated with AT13387 (onalespib).

3.2.7 Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study.

3.2.8 Prior history of another malignancy (except for non-melanoma skin cancer or *in situ* cervical or breast cancer) unless disease free for at least three years. Patients with prostate cancer are allowed if PSA is less than 1.

3.2.9 Patients should not receive immunization with attenuated live vaccine within one week of study entry or during study period.

3.2.10 History of noncompliance to medical regimens.

3.2.11 Consistent QTc > 450 msec for men and > 470 msec for women by Fridericia formula, on 3 separate ECGs.

3.2.12 Left ventricular ejection fraction (LVEF) < 50%, regardless of whether there are symptoms of heart failure.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other

circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Both men and women of all races and ethnic groups are eligible for this trial. Accrual of women and minorities to clinical trials in the DF/HCC generally reflects the population of the state of Massachusetts and the New England catchment area. The 2010 census indicated that the population of the state of Massachusetts is 51.6% female and 48.4% male. Additionally, the population is 80.4% white, 6.6% African American, 5.3% Asian, 2.6% of more than one race, and 0.3% Native American. These data were used to generate the planned distribution of subjects table for this trial. The DF/HCC has established the Initiative to Eliminate Cancer Disparities (IECD) to address cancer disparities with regard to recruitment of minorities to clinical trials. We will continue to work closely with the IECD to ensure that we are participating in all of the mechanisms developed through the Initiative to support efforts to enhance diversity in accrual and to address cancer disparities.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are

not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

All ETCTN sites are part of an LAO (Lead Academic Organization), which must use their own funding to participate in any ETCTN trial. Other comprehensive cancer centers can participate in ETCTN trials via the EDDOP program and are awarded funding that can used be to facilitate their participation in NCI-CTEP trials. (https://ctep.cancer.gov/initiativesprograms/eddop.htm)

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9875 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the "By Lead Organization" folder to expand, then select LAO-MA036, and protocol #9875.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 9875 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: https://www.ctsu.org (members' area) → Regulatory Tab

→Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration subtab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Study-wide, new enrollment is permanently closed, as of October 2019.
Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).

- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	***Premedications Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
AT13387 (onalespib)	No premedications are required	160mg/m^2 in 250 cc 5% dextrose or 0.9% NS	IV over 1 hour	Days 1, 2, 8, 9, 15 and 16	28 days (4 weeks)

Patients will be dosed at 160mg/m^2/dose on days 1, 2, days 8, 9, and days 15, 16 of a 4 week cycle. There will be a response assessment by PET/CT and CT scans every 2 cycles. If the CT portion of the PET/CT is of diagnostic quality, then an additional CT scan is not necessary. However, if CT portion of the PET/CT is a low-resolution CT, then a separate CT scan is necessary.

Treatment can be moved up or delayed to accommodate holidays, inclement weather, or other reasons for clinic closures. Patients can continue on treatment as long as they are responding and tolerating treatment. However, all patients will have to come off this study treatment by May 31, 2020, as the study treatment will no longer be available.

5.1.1 AT13387 (onalespib)

The study drug AT13387 (onalespib) will be administered by intravenous infusion via peripheral or central venous access at a dose of 160mg/m^2 (using actual body weight from cycle 1 day 1 to calculate body surface area) over 1 hour. The dosing frequency will be on days 1, 2, 8, 9, 15, and 16 of every 4 week cycle. AT13387 (onalespib) will be provided by CTEP.

On the first day of treatment each week (days 1, 8, and 15), patients must meet the following pre-treatment criteria: ANC $\geq$ 1000/mcL, platelet count $\geq$ 75,000/mcL (or $>$ 30,000/mcL if due to disease), potassium and magnesium above the institutional lower limit of normal (repletion is allowed).

Astex has recommended that vital signs (temperature, heart rate, blood pressure, oxygen saturations) be performed pre-AT13387 (onalespib) infusion. Additional vital signs will be performed during the course of infusion as clinically indicated. No extended post-administration monitoring will be required, except as indicated in the protocol for research-related assays.

5.1.2 Other Modalities or Procedures
N/A

5.2 General Concomitant Medication and Supportive Care Guidelines

All patients receiving treatment with AT13387 (onalespib) may receive antiemetics and anti-motility agents for symptomatic management while on treatment. Both antiemetics and anti-motility agents may be given to alleviate expected drug-related toxicity on an as required basis and gastrointestinal toxicity should not be considered to be dose limiting in the absence of maximal supportive therapy. Patients receiving treatment with a bisphosphonate are not excluded from participating in the trial and bisphosphonate therapy may be initiated while on trial provided the patient does not have disease progression according to RECIST criteria.

5.2.1 Growth factors
The use of white blood cell growth factors (G-CSF) is acceptable for patients who experience grade 4 neutropenia or have a history of febrile neutropenia. For these acceptable circumstances, growth factors can be administered both at the time of the

event and preventively in subsequent cycles. Growth factors should *not* be administered to allow for patient eligibility at screening. Growth factors should *not* be administered on the same day as onalespib; wait 24 hours after an administering onalespib to administer growth factors.

5.2.2 Transfusions

Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (**WWW.ASCO.ORG**).

Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤ 10 x 10^9/L. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50 x 10^9/L.

5.2.3 Electrolyte repletion

Oral and IV potassium and magnesium electrolyte repletion is allowed to meet both study eligibility and treatment criteria.

5.2.4 Antiemetics

Antiemetics will not be administered routinely prior to receiving AT13387 (onalespib). However, if a patient develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metochlopramide, or aprepitant may be given. 5-HT_3 antagonists like ondansetron are not allowed given their prolonging effecting on the QTc interval. In addition, if a patient develops nausea and/or vomiting at any dose level that is Grade 2 or greater, anti-emetics may be instituted prophylactically at the discretion of the investigator. Nausea and vomiting will be considered refractory if it does not resolve to ≤ Grade 1 with treatment with combination antiemetics within 48 hours.

5.2.5 Anti-motility agents

If diarrhea develops and does not have an identifiable cause other than AT13387 (onalespib) administration, anti-motility agents will be administered. Diarrhea will be considered refractory if it does not resolve within 48 hours to ≤ Grade 1 with administration of anti-motility agent(s). If the patient develops blood or mucous in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-motility agents may be discontinued at the discretion of the Principal Investigator and the patient will be treated with intravenous fluids and antibiotics as medically indicated.

5.2.6 Antibiotics

Prophylactic antibiotics are not required on this trial.

5.2.7 Pre-medications

No premedication with acetaminophen, corticosteroids, or antihistamines will be routinely administered.

Local infusion-related irritation and systemic infusion reactions may occur during or shortly after the administration of AT13387 (onalespib). The local infusion adverse events are formulation-related (pH of current formulation is 5.0). Systemic adverse events (e.g.; flushing, itching, rigors, chills, nausea, tachycardia/bradycardia, dizziness) are reversible. If that occurs, slow the infusion rate and/or hydrate. If participants experience an infusion reaction they may subsequently receive acetaminophen (650mg orally), diphenhydramine (25-50mg IV), hydrocortisone (25-100mg IV), +/- famotidien (20mg IV) or equivalent as pre-medications per institutional standard of practice.

5.2.8 Hydration

No pre-hydration or hydration is required with this regimen.

5.2.9 Tumor lysis prevention and management

Participants with bulky disease and/or circulating disease ≥ 15,000 circulating malignant cells/ mm^3 may receive allopurinol 300mg orally daily for 7-10 days starting with the first dose of AT13387 (onalespib). Patients deemed at risk for tumor lysis syndrome (TLS) should have their labs monitored per standard practice. The management of established TLs should also follow standard practice.

5.2.10 Hyperglycemia

AT13387 (onalespib) is known to cause hyperglycemia in patients. Patients with pre-existing diabetes will be asked to keep a log of their fasting and post-prandial blood glucose measurements and adjustments to their diabetes medications will be adjusted accordingly. Referral to an endocrinologist will be made in cases with blood glucose management is challenging.

5.2.11 Potential drug-drug interactions

The potential for AT13387 (onalespib) to inhibit cytochromes P450 (CYP) 1A2, 3A4, 2D6, 2C9, and 2C19 was assessed, and results indicate a low potential for inhibition (IC_{50} > 10 mM), suggesting a low potential for clinically significant drug-drug interactions mediated by these enzymes. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Appendix B presents guidelines for identifying medications/substances that could potentially interact with the study agent(s), as well as a Patient Drug Handout Information and Wallet Card that will be provided to each patient.

AT13387 (onalespib) is a substrate of UGT with a relatively low affinity to inhibit UGT1A1, -1A3 and -1A9. Pre-clinical studies suggest that AT13387 (onalespib) is a substrate of P-gp; thus, avoid St. John's wort, rifampin, etc. AT13387 (onalespib) is also a

moderate inhibitor of BCRP and P-gp and a strong inhibitor of MATE1/2-K; thus, use caution with concomitant drugs that are substrates of these enzymes.

5.2.12 QTc prolonging drugs

Every attempt will be made to avoid medications that have been associated with QT interval prolongation or Torsades de Pointes (see Appendix B). Antiemetics and diphenhydramine will be permitted on study with the exception of 5-HT_3 antagonists like ondansetron. Patients who are stable on antidepressants known to prolong QTc will be permitted to continue on their medication at the discretion of the Principal Investigator, provided the QTc at enrollment meets eligibility criteria.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies or until May 31, 2020. All patients must be off this study treatment by May 31, 2020, as the study treatment will no longer be available.

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients who discontinue treatment for reasons other than disease progression will be followed with CT scans at 6 and 12 months or until disease progression or next therapy for PFS and DOR endpoints. Follow-up after treatment discontinuation for progression, or after documented progression following discontinuation of therapy for reasons other than progression initially, will be by phone every 6 months for up to 1 year after the discontinuation of treatment for OS endpoints. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will discontinue study treatment when any of the criteria listed in Section 5.3 applies. Patients will be removed from study after the follow-up period outlined in Section 5.4, or if they decide to withdraw from the study. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Dr. Caron Jacobson at 617-632-5847 or 617-632-3352 (page through operator).

6. DOSING DELAYS/DOSE MODIFICATIONS

There will be up to two dose reductions allowed (120mg/m^2 and 80mg/m^2) for intolerable grade 2 toxicity or the equivalent of dose limiting toxicities. Dose delays up to 14 days will be allowed for any persistent grade 2 adverse events (AE) (with the exception of fatigue, weakness, skin toxicity, and/or laboratory abnormalities) with treatment resumption when the AE resolves to grade 1 or better; AST or ALT > 3x the upper limit of normal, with treatment resumption when the AE resolves to grade 1 or better; and any AE, laboratory abnormality or condition that, in the judgment of the investigator, warrants delaying the dose of study medication.

The dose is determined by the patient's weight on Cycle 1 Day 1, regardless of changes in body weight. The dose can be rounded base on the intuitional guidelines of the treating institution.

Dose Level	**AT13387 (onalespib) Dose**
-2	80 mg/m^2/dose d1,2,8,9,15,16
-1	120 mg/m^2/dose d1,2,8,9,15,16
0	160 mg/m^2/dose d1,2,8,9,15,16

Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia.

Nausea	**Management/Next Dose for AT13387 (onalespib)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >2 weeks should go off protocol therapy.
**Patients requiring > two dose reductions should go off protocol therapy.
Recommended management: antiemetics.

Vomiting	**Management/Next Dose for AT13387 (onalespib)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >2 weeks should go off protocol therapy.
**Patients requiring > two dose reductions should go off protocol therapy.
Recommended management: antiemetics.

Diarrhea	**Management/Next Dose for AT13387 (onalespib)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy

*Patients requiring a delay of >2 weeks should go off protocol therapy.
**Patients requiring > two dose reductions should go off protocol therapy.
Recommended management: Loperamide antidiarrheal therapy
Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours)
Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

Neutropenia	**Management/Next Dose for AT13387 (onalespib)**
≤ Grade 2	No change in dose
Grade 3,4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**

*Patients requiring a delay of >2 weeks should go off protocol therapy.
**Patients requiring > two dose reductions should go off protocol therapy.
Recommended management: G-CSF support.

Thrombocytopenia	**Management/Next Dose for AT13387 (onalespib)**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3,4	Hold* until < Grade 1. Resume at one dose level lower, if indicated.**

*Patients requiring a delay of >2 weeks should go off protocol therapy.
**Patients requiring > two dose reductions should go off protocol therapy.
Recommended management: platelet transfusion support per institutional guidelines.

Visual impairment including peripheral flashes (photopsia), blurred or double vision, floaters, color distortion and dimness, difficulties with light/dark accommodation, tunnel vision or other field defects, halos, apparent movement of stationary objects, and complex disturbances. Symptoms are generally Grade 1, intermittent, reversible, and transient, lasting a few seconds to a few minutes and occurring on 1- 3 days/cycle. Doses may need to be held in the setting of grade 1-2 toxicity, and treatment may need to be discontinued if toxicity is ≥ grade 3.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will

determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting. Adverse events will be assessed at each visit by the clinical trial personnel.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for AT13387 (onalespib)

Below is the CAEPR for AT13387 (Onalespib). *Frequency is provided based on 119 patients.*

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.
>
> **IMPORTANT:** Below is the CAEPR list with the current version of CTCAE terms (version 5.0).

Version 2.1, December 28, 2018[1]

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 5.0 Term) [n= 119]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
EYE DISORDERS			
	Blurred vision		
	Vision decreased		***Vision decreased (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Flatulence		***Flatulence (Gr 2)***
	Gastrointestinal hemorrhage[2]		
	Hemorrhoids		***Hemorrhoids (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		***Fever[3] (Gr 2)***
Injection site reaction[4]			***Injection site reaction[4] (Gr 2)***
	Malaise		***Malaise (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		***Infusion related reaction[3] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased		***CPK increased (Gr 2)***
	Electrocardiogram QT corrected interval prolonged		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		

Adverse Events with Possible Relationship to AT13387 (Onalespib) (CTCAE 5.0 Term) [n= 119]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hyponatremia		***Hyponatremia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		***Muscle cramp (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Hiccups		***Hiccups (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Hyperhidrosis[3]		***Hyperhidrosis[3] (Gr 2)***
	Rash acneiform		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infusion-related reactions may include, tachycardia/bradycardia, hypotension/hypertension, flushing, chills, fever, hyperhidrosis, itching, rigors, and abdominal cramps.

[4]Injection site reaction may include injection site irritation, injection site pain, injection site inflammation or redness, or erythema.

[5]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on AT13387 (Onalespib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AT13387 (Onalespib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Cardiac disorders - Other (atrioventricular block NOS); Left ventricular systolic dysfunction; Palpitations

EYE DISORDERS - Dry eye; Eye disorders - Other (color distortion); Eye disorders - Other (diplopia); Eye disorders - Other (halos); Eye disorders - Other (loss of visual acuity during changes in ambient light levels); Eye disorders - Other (tunnel vision); Eye disorders - Other (visual color darkening); Eye disorders - Other (visual disturbances); Eye pain; Flashing lights; Floaters; Keratitis; Night blindness; Papilledema; Photophobia; Retinopathy
GASTROINTESTINAL DISORDERS - Colitis; Mucositis oral; Oral dysesthesia; Oral pain; Salivary duct inflammation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills[3]; Flu like symptoms
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Creatinine increased; Ejection fraction decreased; Neutrophil count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypoalbuminemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Pruritus; Skin hyperpigmentation
VASCULAR DISORDERS - Hypertension[3]

Note: AT13387 (Onalespib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

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

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration

of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
Investigations	Lymphocyte count decreased	Any			
Investigations	INR increased, aPTT prolonged	2			
Skin and subcutaneous tissue disorders	Alopecia	Any			
Metabolism and nutrition disorders	Hyponatremia, Hypophosphatemia Hypokalemia, Hypomagnesemia, Hypoalbuminemia, Hyperglycemia, Hyperuricemia	2			
Blood and lymphatic system disorders	Anemia	2			

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

8.1 Drug Information

8.1.1 AT13387 (onalespib) (NSC 749712)

The NCI does not provide a pharmacy manual. All drug information and preparation guidelines are provided below.

Chemical Name:	**(**2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-1,3- dihydro-isoindol-2-yl]-methanone, *L*-lactic acid salt
Other Name:	AT13387 (onalespib)AU, AT13387 (onalespib)
Classification:	Heat shock protein 90 (HSP90) inhibitor
Molecular Formula:	$C_{24}H_{31}N_3O_3.C_3H_6O_3$ **M.W.:** 499.61
Mode of Action:	AT13387 (onalespib) is a small molecule inhibitor of HSP90, an enzyme believed to be responsible for supporting malignant transformation of normal cells to tumor cells. HSP90 acts as a "molecular chaperone," stabilizing and preventing the breakdown of key cancer forming (oncogenic) proteins.
How Supplied:	AT13387 (onalespib) is supplied by Astex Pharmaceuticals Inc. and distributed by CTEP, NCI as a 265 mg free base equivalent (as the L-lactic acid salt) vial. The formulation is a sterile white to off-white lyophilized powder with pH 5.0 (red cap vial).
Preparation:	Reconstitute the 265-mg lyophilized powder with 10 mL of Sterile Water for Injection (SWFI) resulting in 25.7 mg/mL concentration (10.3 mL total volume). A sticky mass will be formed. Vigorously shake the vial. Agitate until the contents are fully dissolved (about 5 minutes). Leave the diluted vial at ambient temperature for 15-30 minutes to allow any foam to dissipate. If not used immediately, store the reconstituted vial(s) at 2^0 to 8^0 C to not exceed 8 hours. Withdraw the calculated dose of AT13387 and further dilute it in 250 mL of D5W or 0.9% NS. The prepared IV solution is compatible in PVC or non-PVC infusion bags. Store the prepared IV solution at 2^0 to 8^0 C (up to 8 hours) if not used immediately. When removed from the refrigerator, allows the prepared IV solution to sit at room temperature between 15 to 30 minutes before

	administering to patients. The prepared IV solution must be used within 8 hours -i.e., from the time the drug vial is diluted to the time the IV administration is complete. Protection from light during the infusion period is not required.
Storage:	Store the intact vials at 15^0 to 25ºC (59 to 77ºF). Protect from light. If a storage temperature excursion is identified, promptly return AT13387 to 15^0 to 25ºC (59 to 77ºF) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.
Stability:	Shelf life surveillance of the intact vials is ongoing**.**
Route of administration:	Intravenous
Method of administration:	Infuse over 1 hour through a central line or a well-defined peripheral vein. If using a peripheral line, be sure to aspirate venous blood prior to starting the infusion. The IV infusion does not require a 0.2 micron in-line filter. Check the infusion site every 15 minutes and change the site of infusion should evidence of swelling or discoloration is observed. If patient experiences pain along the infusion site, slow the infusion rate (i.e. > 1 hour duration) and/or infuse D5W through a "Y" connector. The additional volume of D5W dilutes AT13387 (onalespib) concentration at the local site of the infusion and alleviates the irritation.
Potential Drug Interactions:	AT13387 (onalespib) is a substrate of UGT with a relatively low affinity for UGT isoforms. In vitro data demonstrate that AT13387 (onalespib) is a weak inhibitor of UGT1A1, UGT1A3 and UGT1A9. AT13387 (onalespib) is also a weak inhibitor of CYP1A2, -3A4, -2D6, -2C9 and -2C19. AT13387 (onalespib) metabolizes primary via the glucuronidation, sulphation and N-oxidation. Pre-clinical studies suggest that AT13387 (onalespib) is a substrate of P-gp, the efflux ratios was above 2 (ranging from 3.4 to 4.6); a moderate inhibitor of BCRP (35.9% +/- 2%, p=0.0001) and P-gp (31.3% +/- 1.2%, p= 0.0009), and a strong inhibitor of MATE1 (94.6% +/- 0.2%, p=0.0001) and MATE2-K (91.2% +/- 1.2%, p= 0.0002).
Patient Care Implications:	There are no genotoxicity, carcinogenicity, developmental and reproductive studies conducted with AT13387 (onalespib). Women of childbearing potential should not become pregnant or breastfeed and men should not father a child during the study. All subjects must use acceptable contraceptive measures during the treatment of AT13387 (onalespib) and 3 months after the last dose of the investigational drug. Local infusion-related irritation and systemic infusion reactions may occur during or shortly after the administration of AT13387 (onalespib). The local infusion adverse events are a formulation-related (pH of current formulation is 5.0). Systemic adverse events (e.g.; flushing, itching, rigors, chills, nausea, tachycardia/bradycardia, dizziness) are reversible. If that occurs, slow the infusion rate and/or hydrate with D5W. Premedication with dexamethasone, antihistamine and 5HT3 antagonists can also be given.

	Avoid extravasation. For local irritation, apply cold compress or topical pain medication.

A list of the adverse events and potential risks associated with AT13387 (onalespib) administered in this study can be found in Section 7.1.

8.1.2 Availability

AT13387 (onalespib) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.3 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol

8.2 Useful Links and Contacts Related to Drug Information

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines:

http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application:

https://ctepcore.nci.nih.gov/OAOP

- CTEP Identity and Access Management (IAM) account:

https://ctepcore.nci.nih.gov/iam/

- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Blood, bone marrow or lymph node biopsy sampling for malignant cells will take place prior to treatment initiation, on cycle 1 day 17-22, and at the time of disease progression for several biomarker studies. These will include immunohistochemical quantification of ALK in ALK+ ALCL, cyclin D1 in MCL, and BCL6 in DLBCL using established dilutions of CLIA-approved immunostains that have been calibrated to detect changes in protein levels, as well as immunoblotting of tumor samples for known HSP90 clients including CDK4, cyclin D1, AKT and pAKT, ERK and pERK, IKKα, BTK (in DLBCL and MCL), HSP70, ALK (in ALCL), and BCL6 (in DLBCL). Each of these proteins, with the exception of HSP70, are HSP90 clients and thus expected to decrease following treatment with the HSP90 inhibitor AT13387 (onalespib). HSP70 is known to increase in a compensatory fashion upon HSP90 inhibition. Thus, changes in these proteins detected by immunohistochemistry or immunoblotting would be proof of principle that we are indeed depleting expected targets. In addition we will perform whole exome sequencing (on pre-treatment and disease progression samples) and RNASeq (on pretreatment, day 17-22 and disease progression samples) to identify genetic and transcriptional markers of disease response and resistance.

9.1 Integral Laboratory or Imaging Studies

9.1.1 *Immunohistochemistry for ALK (ALCL), cyclin D1 (MCL) and BCL6 (DLBCL)*

Immunostains on pre-treatment samples are integral assays as they determine patient eligibility for this study (ALK for ALCL, cyclin D1 for MCL, and BCL6 for DLBCL). See Appendix C-E for standard operating procedures (SOPs) for ALK, cyclin D1 and BCL6 respectively. Because this immunostain is diagnostic in this lymphoma, it should by definition be positive in 100% of pre-treatment samples. Because the standard concentration of the stains used for ALK, cyclin D1 and BCL6 is very sensitive for these proteins (i.e., saturating) and therefore not very specific regarding their quantification, we performed several titrations of these immunostains on known ALK+ ALCL, MCL, and BCL6+ DLBCL to determine the lowest concentrations that maintain strong baseline staining but allow for detection of differences in protein levels following treatment with AT13387 (onalespib) and at the time of progression. For ALK, a dilution of

1:24,000 appears to be optimal, while for BCL6 and cyclin D1 optimal staining dilutions would be 1:2000 and 1:160, respectively. We will start with dilutions of 1:24,000 for ALK, 1:2000 for BCL6, and 1:160 for cyclin D1. However, if using those dilutions we are unable to adequately detect antigen in the pre-treatment tumor sample, we will use serial lower dilutions for optimization of that individual tumor specimen, using that same dilution for the subsequent on-treatment and time of progression tumor samples.

The pre-treatment biopsy and the time of progression biopsy are intended to establish a baseline level of staining for comparison and to assess whether these protein levels are again upregulated at the time of treatment progression, and therefore a measure of treatment resistance. We intend to evaluate these immunostains as an early marker of disease response and proof of concept that we are indeed achieving HSP90 inhibition and depleting the expected targets. Given that we see changes in the protein levels of HSP90 clients within 12 hours of exposure to HSP90 inhibitors *in vitro* and after 5 days of treatment with an HSP90 inhibitor *in vivo*, we expect to see differences in HSP90 protein levels early in treatment. The half life of AT13387 (onalespib) is between 6 and 12 hours and the dosing schedule to be used on this study is the twice weekly dosing for 3 weeks with one week off, or dosing on days 1 and 2, 8 and 9, and 15 and 16. We therefore plan to get a biopsy on day 17, within 24 hours of the 6th dose of the drug, but will allow for a biopsy up to day 22 to accommodate scheduling, weekends, and holidays. This biopsy schedule was based on the timing of biopsies done for pharmacodynamic evaluation of AT13387 (onalespib) on the first-in-human phase I study that was recently reported.[66]

We will use an automated Aperio measurement to determine an automated H-score, which previously has been found to be highly concordant with manual H-score determination (R^2= 0.8795 for immunostains for MSI2 in AML for example).[103] Specifically, the assessment of the percentage of tumor cells that is positive for the immunohistochemical stain will be quantitative/continuously distributed from 0 to 100%, whereas the intensity of staining in a given sample will be graded from 0-3+ (0=no staining, 1=weak staining, 2=moderate staining, and 3+=strong staining). An H-score, the product of the percentage of positive tumor cells and the grade of staining intensity, will be calculated (range 0-300).[103] A reduction in the H-score of >50% will be considered meaningful. While the biomarker is integral at diagnosis and study entry, the comparison of quantitative changes in these biomarkers and response is exploratory and our statistical analysis will be descriptive. If there is a correlation between the comparative H-scores and treatment response, this provides a readily available standardized and technically feasible way to predict response to treatment early in a patient's treatment course.

9.1.1.1 Collection of Specimens

Tumor biopsy samples will be obtained by core needle biopsy. A minimum of four, but ideally six, core needle biopsies will be requested: at least 3 for snap freezing for whole exome sequencing, RNA-seq, and immunoblotting, and one for formalin-fixation for immunohistochemistry (see section 9.2). It is recommended that tumor biopsies be collected using an 18 gauge needle, however this us up to the discretion of the Interventional Radiology Team of the treating institution. Standard approaches for formalin-fixation and frozen section will be used (See Appendix F and G). Specimens will be obtained pre-treatment, on-treatment (cycle 1, day 17-22 of a 28 day cycle), and at the time of disease progression.

It is not recommended to use the bone marrow biopsy instead of the tumor biopsy, however it is an option. If a bone marrow biopsy is used, please collect the following samples:

- The 10mL green top (BD Vacutainer Sodium Heparin Tube), which should be ficolled and frozen viably
- The non-heparin syringe that is transferred to a 15mL conical tube (centrifuge tube) should be snap frozen

It is not recommended to collect blood as the source of the tumor biopsy, however it is an option. A bone marrow biopsy or core biopsy are much preferred. Sites should discuss this with Dr. Jacobson prior to proceeding with this option. Please email the DFCI CRC or contact Dr. Jacobson directly if this possibility arises. If blood is used, please collect the following sample:

- whole blood in a Streck cell-free DNA tube, 4-6 mL of plasma obtained and frozen, then sent to CCPM on dry ice

9.1.1.2 Handling of Specimens

Please see the SOPs and IHC templates provided in Appendices D-G.

For formalin-fixed samples, each container should be labeled with:

a. Protocol number (9875)
b. Subject Study Number
c. Pre/on/post treatment
d. Date of collection

For fresh frozen tissue samples, biopsies should be frozen on site within 5-10 minutes of devascularization and one cryomold per specimen should be used and submitted. Each cryomold should we labeled on the bottom with the following:

a. Protocol Number (9875)
b. Subject Study Number
c. Pre/on/post treatment
d. Date of collection

The lip of each cryomold should be labeled with the core #.

9.1.1.3 Shipping of Specimens

Formalin-Fixed Samples should be sent in a securely closed container (one with a screw top/cap), this container should be placed in a secondary container (plastic zip loc bags work well) put a piece of absorbent material in the secondary container with the sample in case of leakage. This entire package along with a Specimen Submission Form (Appendix H) can then be shipped via FedEx (in their appropriate packaging), under current shipping requirements for non-infectious/hazardous human samples. Please keep SSF outside of the secondary container so it does not become wet should the primary container leak. A Specimen Submission Form should be included for each

sample submitted (see Appendix H). An FFPE block of the samples is preferable, however the tissue can be sent in just formalin if needed. Kits for shipment will *not* be provided.

Frozen tissue should be shipped on dry ice in a separate box from Formalin-Fixed tissue. A Specimen Submission Form should be included for each sample submitted.

Shipping container for Frozen Tissue should include:

- Priority Overnight Frozen Material labeling
- Dry Ice UN number
- Class 9 label

Please ship specimens via FedEx Overnight Priority to:
Judy Chen
Dana-Farber Cancer Institute
Dana 950
450 Brookline Avenue
Boston, MA 02215
Re: Protocol 16-712

Please note: packages must be sent for Tuesday through Friday delivery only. Do not ship on Friday or over the weekend/holidays.

For each package, complete and send DFCI Shipping Manifest(s) (Appendix H) as detailed below:

1. Complete one manifest for FFPE samples and a separate manifest for frozen tissue even if shipping on the same day.
2. Email the DFCI Shipping Manifest(s) to CCPM_ResearchOps@dfci.harvard.edu at the time of shipment. This office can also be reached by phone at 617-582-9353.
3. Include a printed copy of the DFCI Shipping Manifest(s) with the package.

9.1.1.4 Site(s) Performing Correlative Study

All immunostains will be performed at the Dana-Farber Cancer Institute/Brigham and Women's Hospital Hematopathology Core Laboratory (a CLIA approved laboratory) under the direction of Dr. Scott Rodig and Dr. Elizabeth Morgan. This lab has extensive experience with these immunostains as they are standardly done on all ALCL, MCL, and DLBCL cases reviewed, respectively.

9.2 Exploratory/Ancillary Correlative Studies

9.2.1 Immunoblotting for HSP90 clients

We have extensive experience in the Weinstock lab with immunoblotting for several HSP90 clients in MCL and DLBCL cell lines before and following exposure to HSP90 inhibitors, and in tissue from MCL cell line and patient derived xenografts treated with either vehicle or drug (see section 2.3.2). These include BTK and pBTK, cyclin D1, CDK4, AKT and pAKT, ERK and pERK, IKKα, p100, p52, and BCL6. Our lab will immunoblot for these HSP90 clients and

others, and compare protein levels semi-quantitatively between pre- and on-treatment lymphoma cells, and at the time of disease progression. We expect to see downregulation of these proteins on treatment, and possibly upregulation of some or all of these proteins at the time of progression on drug.

9.2.1.1 Collection of Specimens

Tumor biopsy samples will be obtained by core needle biopsy. A minimum of four, but ideally six, core needle biopsies will be requested: at least 3 for snap freezing for whole exome sequencing, RNA-seq, and immunoblotting, and one for formalin-fixation for immunohistochemistry (see section 9.1). It is recommended that tumor biopsies be collected using an 18 gauge needle, however this us up to the discretion of the Interventional Radiology Team of the treating institution. Standard approaches for formalin-fixation and frozen section will be used (See Appendix F and G). Specimens will be obtained pre-treatment, on-treatment (cycle 1, day 17-22 of a 28 day cycle), and at the time of disease progression.

It is not recommended to use the bone marrow biopsy instead of the tumor biopsy, however it is an option. If a bone marrow biopsy is used, please collect the following samples:

- The 10mL green top (BD Vacutainer Sodium Heparin Tube), which should be ficolled and frozen viably
- The non-heparin syringe that is transferred to a 15mL conical tube (centrifuge tube) should be snap frozen

It is not recommended to collect blood as the source of the tumor biopsy, however it is an option. A bone marrow biopsy or core biopsy are much preferred. Sites should discuss this with Dr. Jacobson prior to proceeding with this option. Please email the DFCI CRC or contact Dr. Jacobson directly if this possibility arises. If blood is used, please collect the following sample:

- whole blood in a Streck cell-free DNA tube, 4-6 mL of plasma obtained and frozen, then sent to CCPM on dry ice

9.2.1.2 Handling of Specimens

Please see the SOPs and IHC templates provided in Appendices D-G.

For formalin-fixed samples, each container should be labeled with:

a. Protocol number (9875)
b. Subject Study Number
c. Pre/on/post treatment
d. Date of collection

For fresh frozen tissue samples, biopsies should be frozen on site within 5-10 minutes of devascularization and one cryomold per specimen should be used and submitted. Each cryomold should we labeled on the bottom with the following:

a. Protocol Number (9875)
b. Subject Study Number
c. Pre/on/post treatment
d. Date of collection

The lip of each cryomold should be labeled with the core #.

9.2.1.3 Shipping of Specimen(s)

Formalin-Fixed Samples should be sent in a securely closed container (one with a screw top/cap), this container should be placed in a secondary container (plastic zip loc bags work well) put a piece of absorbent material in the secondary container with the sample in case of leakage. This entire package along with a Specimen Submission Form (Appendix H) can then be shipped via FedEx (in their appropriate packaging), under current shipping requirements for non infectious/hazardous human samples. Please keep SSF outside of the secondary container so it does not become wet should the primary container leak. A Specimen Submission Form should be included for each sample submitted (see Appendix H). An FFPE block of the samples is preferable, however the tissue can be sent in just formalin if needed. Kits for shipment will *not* be provided.

Frozen tissue should be shipped on dry ice in a separate box from Formalin-Fixed tissue. A Specimen Submission Form (Appendix H) should be included for each sample submitted.

Shipping container for Frozen Tissue should include:

- Priority Overnight Frozen Material labeling
- Dry Ice UN number
- Class 9 label

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1. Complete one manifest for FFPE samples and a separate manifest for frozen tissue even if shipping on the same day.
2. Email the DFCI Shipping Manifest(s) to CCPM_ResearchOps@dfci.harvard.edu at the time of shipment. This office can also be reached by phone at 617-582-9353.
3. Include a printed copy of the DFCI Shipping Manifest(s) with the package.

9.2.1.4 Site(s) Performing Correlative Study

All immunoblotting will be performed in the laboratory of Dr. David Weinstock at the Dana-Farber Cancer Institute.

9.2.2 Whole exome sequencing and transcriptome analysis

Samples will also be submitted for whole exome sequencing (with paired germline samples) and RNAseq, and results will be compared between pre- and on-, and time or progression tumor samples for markers of disease response and resistance. For exome sequencing, the ABSOLUTE algorithm will be applied to determine the cancer cell fraction. Variant allele fractions for mutations present in the progression sample can then be compared to those in the pre-treatment sample after adjustment for cancer cell fractions to determine whether AT13387 (onalespib) results in a shift in the clonal architecture of lymphomas.[85] Although HSP90 classically acts at the post-translational level, some evidence indicates that it also can affect transcription.[86] We previously demonstrated in human leukemia cells that transcriptional profiling can highlight downstream pathways that are suppressed or activated in response to the degradation of HSP90 clients.[87] Transcriptional analysis by RNAseq will be performed on specimens obtained prior to beginning treatment, during treatment with AT13387 (onalespib) and then upon progression. In cases with bone marrow or peripheral blood involvement, lymphoma cells will be purified, for example by CD19 selection. Markers of response and progression will be determined by: 1) comparing gene expression patterns using GSEA[88], 2) interrogation of the Broad Institute Molecular Signatures Database[88] (MSigDB; http://www.broadinstitute.org/gsea/msigdb/index.jsp) and 3) Ingenuity Pathway Analysis[89,90], as we previously performed.[91] In addition, we will interrogate the signature of progression during AT13387 (onalespib) treatment in the Connectivity Map, a database linking gene expression with drug sensitivity.[92] Build 2.0 contains over 7,000 expression profiles representing the effects of 1,309 compounds. Compounds that correlate inversely with the signature, and therefore may abrogate it, are readily available therapeutics to block pathways that bypass HSP90 inhibition. The analysis of these exploratory biomarker studies will be retrospective, with assays performed after response evaluation for biomarker identification.

If new health information about inherited traits is found on research testing, the study doctor will let the participant know about this and the participant will then be able to choose whether or not to receive this information.

9.2.2.1 Collection of Specimens

Tumor biopsy samples will be obtained by core needle biopsy. A minimum of four, but ideally six, core needle biopsies will be requested: at least 3 for snap freezing for whole exome sequencing, RNA-seq, and immunoblotting, and one for formalin-fixation for immunohistochemistry (see section 9.1). It is recommended that tumor biopsies be collected using an 18 gauge needle, however this us up to the discretion of the Interventional Radiology Team of the treating institution. Standard approaches for formalin-fixation and frozen section will be used (See Appendix F and G). Specimens will be obtained pre-treatment, on-treatment (cycle 1, day 17-22 of a 28 day cycle), and at the time of disease progression.

It is not recommended to use the bone marrow biopsy instead of the tumor biopsy, however it is an option. If a bone marrow biopsy is used, please collect the following samples:

- The 10mL green top (BD Vacutainer Sodium Heparin Tube), which should be ficolled and frozen viably
- The non-heparin syringe that is transferred to a 15mL conical tube (centrifuge tube) should be snap frozen

It is not recommended to collect blood as the source of the tumor biopsy, however it is an option. A bone marrow biopsy or core biopsy are much preferred. Sites should discuss this with Dr. Jacobson prior to proceeding with this option. Please email the DFCI CRC or contact Dr. Jacobson directly if this possibility arises. If blood is used, please collect the following sample:

- whole blood in a Streck cell-free DNA tube, 4-6 mL of plasma obtained and frozen, then sent to CCPM on dry ice

9.2.2.2 Handling of Specimens

Please see the SOPs provided in Appendices F and G

For formalin-fixed samples, each container should be labeled with:

a. Protocol number (9875)
b. Subject Study Number
c. Pre/on/post treatment
d. Date of collection

For fresh frozen tissue samples, biopsies should be frozen on site within 5-10 minutes of devascularization and one cryomold per specimen should be used and submitted. Each cryomold should we labeled on the bottom with the following:

a. Protocol Number (9875)
b. Subject Study Number
c. Pre/on/post treatment
d. Date of collection

The lip of each cryomold should be labeled with the core #.

9.2.2.3 Shipping of Specimens

Formalin-Fixed Samples should be sent in a securely closed container (one with a screw top/cap), this container should be placed in a secondary container (plastic zip loc bags work well) put a piece of absorbent material in the secondary container with the sample in case of leakage. This entire package along with a Specimen Submission Form (Appendix H) can then be shipped via FedEx (in their appropriate packaging), under current shipping requirements for non-infectious/hazardous human samples. Please keep SSF outside of the secondary container so it does not become wet

should the primary container leak. A Specimen Submission Form should be included for each sample submitted (see Appendix H). An FFPE block of the samples is preferable, however the tissue can be sent in just formalin if needed. Kits for shipment will *not* be provided.

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3. Include a printed copy of the DFCI Shipping Manifest(s) with the package.

9.2.2.4 Sites Performing Correlative Study

Whole exome sequencing and RNASeq will be done at the Broad Institute.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays, including LVEF evaluation, must be done $\leq$6 weeks prior to the start of therapy and bone marrow biopsy must be done $\leq$ 6 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

		Cycle 1								Cycle 2+		
	Pre-Study[a]	D 1	D 2	D 8	D 9	D 15	D 16	D 17	D 18	D 1,8,15	D 2,9,16	Off Treatment[i]
AT13387 (onalespib)		A	A	A	A	A	A			A	A	
Informed consent	X											
Demographics	X											
Medical history	X											
Detailed eye exam[b]	X											
Concurrent meds	X	X----------X										
Physical exam	X	X		X		X				X		X
Vital signs	X	X	X	X	X	X	X			X	X	X
Height	X											
Weight	X	X	X	X	X	X	X			X	X	X
Performance status	X	X		X		X				X		X
CBC w/diff, plts	X	X		X		X		X		X		X
Serum chemistry[c]	X	X		X		X		X		X		X
EKG[d]	X	X		X		X				X[d]		X
LVEF evaluation (TTE or MUGA)	X											
Adverse event evaluation[e]		X----------X										X
Bone marrow biopsy	X	.										X[f]
Blood sample for germline sequencing[g]	X											
Radiologic evaluation												
FDG-PET/CT scans	X								FDG-PET/CT should be performed every 8 weeks +/- 3 days			X
CT chest/abdomen/pelvis	X								CT scans should be performed every 8 weeks +/- 3 days			X[j]
B-HCG[h]	X											
Tumor biopsy[k]	X							X				X

A: AT13387 (onalespib): 160mg/m2/dose as assigned

a: All screening must take place within 2 weeks of the start of therapy, except for scans, which must occur within 6 weeks, and the screening bone marrow biopsy, which must occur within 6 weeks, prior to the start of therapy.

b: All patients will have a detailed eye exam by an ophthalmologist during screening to be used as a baseline eye exam for comparison, should ocular toxicity later develop. There are no protocol-specific tests required for this eye exam. If patients develop eye symptoms during treatment, an additional eye examination may be conducted at the investigator's discretion. See appendix I for an example of an eye exam work-up. Using this eye exam form is *not* required.

c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, magnesium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid.

d: Cycle 2 and on, electrocardiograms (EKGs) will be done on day 1 of each cycle. EKGs should be done per standard of care at the treating institution. EKGs are not required to be in triplicate, but if there is an issue with a QTc value on the single EKG, an average CTc is acceptable on three triplicate EKGs if it makes a patient eligible for treatment.

e: Adverse event and concomitant medication evaluation will be assessed at each visit by the clinical trial personnel.

f: If bone marrow biopsy is negative at screening, it does not need to be repeated. If the bone marrow biopsy is involved at baseline, it must be repeated in order to confirm a complete response (CR).

g: To be collected in 1 x 4 mL purple top EDTA tube. However, a minimum of 1 mL of blood is needed so any tube size that meets this 1 mL minimum is acceptable. This can be shipped along with the frozen tissue.

h: Serum pregnancy test (women of childbearing potential).

i: Off-treatment evaluation. Patients who come off treatment for progression will have telephone follow-up every 6 months for up to 1 year

for OS endpoints. Patients who come off treatment for reasons other than progression will have CT scans (see below) at 6 and 12 months, or until the time of progression or next therapy, for PFS and DOR endpoints.

j: CT scans will be repeated at 6 and 12 months, or until the time of progression, for patients who come off study for reasons other than disease progression.

k: Biopsy or sample of most accessible tissue, which may be bone marrow, body fluid, lymph node, or other tumor site. The sample should be from the same tumor source (ie body fluid, bone marrow, lymph node, or other tumor site) at each timepoint. This is distinct from the bone marrow biopsy required at screening for lymphoma staging. However, if the bone marrow is involved at screening, this can be used as the site of tumor biopsy for patients during pre-treatment, cycle 1 and at the time of progression. Biopsies during cycle 1 should optimally be done on day 17, but can be done between days 17-22.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

All patients will have a baseline PET/CT scan within 6 weeks prior to the start of therapy. For the purposes of this study, patients should be re-evaluated for response by PET/CT scans every 8 weeks. In addition, a bone marrow aspirate and biopsy are required within 6 weeks before the 1st treatment for all patients. If the initial marrow shows involvement, repeat marrow is required to confirm a CR. If the initial marrow is negative, further bone marrow biopsy is not required. The marrow should be sent for aspirate, core pathology, flow cytometry, and cytogenetics.

Response and progression will be evaluated in this study using the International Harmonization Project for lymphoma criteria.[104]

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AT13387 (onalespib).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.1.2 Response Criteria

11.1.2.1 Evaluation of Disease

Complete Response (CR): Disappearance of all evidence of disease. For FDG-avid or PET positive sites of disease prior to therapy, a mass of any size is permitted if PET negative; for variably FDG avid or PET negative lesions, regression to normal size on CT is necessary. The spleen or liver must also be nonpalpable with disappearance of any nodules, and the bone marrow, if initially involved, must be cleared on repeat biopsy.

Partial Response (PR): Regression of measurable disease and no new sites of disease. This is defined as a $\geq$ 50% decrease in the sum of the diameters of the up to 6 largest dominant masses with no increase in size of other masses. If the sites of disease were

PET positive at baseline, there must be at least one previously involved site that remains PET positive. For disease involving the spleen or liver, there must be a ≥ 50% decrease in the sum of the diameters of nodules (of if a single nodule, ≥ 50% reduction in its greatest transverse diameter) and/or no increase in size of the liver or spleen.

Progressive Disease (PD): Any new lesion or an increase by ≥ 50% of previously involved sites from nadir. This includes the appearance of any new lesion(s) > 1.5cm in any axis, a ≥ 50% increase in the sum of diameters of > 1 site of disease or ≥ 50% increase in the longest diameter of a previously identified node >1cm in short axis. If the sites of disease were PET positive at baseline, they must remain PET positive.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. If sites of disease were FDG avid or PET positive prior to therapy, they remain PET positive with no new sites of disease. If sites of disease were variably FDG avid or PET negative, there has been no change in the size of previous lesions.

11.1.2.2 Evaluation of Best Overall Response

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

11.1.3 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

11.1.4 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.5 Response Review

For determination of response rate and response duration, central review of the PET/CT scans obtained at baseline, after every 2 cycles of therapy, and at final response evaluation is required.

These scans should be burned onto CD and sent via FedEx to the head study coordinator (refer to study contact list at the beginning of the protocol) at DFCI.

The CDs should be labeled with the following information:

1. Patient initials
2. Study number
3. Patient date of birth
4. **Type of scan – please make sure you specify this**
5. Date of scan
6. Timepoint (baseline, post cycle 2 etc.)

The CDs should be sent to the following address:

[Insert DFCI Study Coordinator's name] #16-712
Dana-Farber Cancer Institute
450 Brookline Avenue, LG100
Boston, MA 02215

The scan will then be reviewed at the Tumor Imaging Metrics Core at DFCI. We will accept the decision of the treating investigator and local radiology review of scans, however, to determine if a patient remains on study in real time at the time of response assessment.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug. The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For this Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officers to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second

stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician through IWRS and Medidata Rave.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, RAVE CRA, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or RAVE CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site

audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and

disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase II, multi-center study of an Hsp90 inhibitor in non-Hodgkin lymphomas. Study-wide, new enrollment is permanently closed, as of October 2019. The study is comprised of three patient populations (cohorts) with the following designs:

ALK+ ALCL: The primary objective of this cohort is objective response rate in relapsed ALK+ ALCL patients. Given the rarity of refractory disease in this patient population, we will aim for a sample size of ten patients and deem the treatment worthy of further consideration if at least three patients respond while on study. The 90% exact binomial confidence limits for three responses in ten patients is 9-61%. We will consider a response rate of 5% unworthy of further study for this patient population, and note the 3 responses in 10 patients is the smallest number of

responses that excludes a 5% response rate based on 90% exact binomial confidence. This cohort is now closed to new enrollment, as of February 2019.

MCL: The primary objective of this arm is objective response rate in MCL patients who have failed multiple lines of therapy. This arm will follow a Simon two-stage design to allow for early termination due to a lack of efficacy. We will consider a response rate of 25% worthy of further study and a response rate of 5% as unworthy of further study. The first stage will enroll ten patients and assess response rate, and if zero responses are seen in the first ten patients, the study will stop early for lack of efficacy. However, if one or more responses are seen, we will enroll an additional ten patients for a total of 20. If three or more out of the 20 respond, we will consider this regimen worthy of further study. The study will be stopped early with a probability of 60% if the true response rate is 5% or with a probability of 5.6% if the true response rate is 25%. The regimen will be considered worthy of further study with a probability of 6.9% if the true response rate is 5% or with a probability of 88% if the true response rate is 25%. Therefore, this study has an overall type-I error rate of 6.9% and an overall power of 88%. This cohort is now closed to new enrollment, as of February 2019.

BCL6+ DLBCL: The primary objective of this arm is objective response in relapsed BCL6+ DLBCL. We will consider a response rate of 25% worthy of further study in this patient population while a 5% response rate is unworthy. We will employ a Simon two-stage plan designed to allow for early study termination if the regimen lacks efficacy. We will distinguish between a response rate of 5% which will be considered unworthy of further study and a response rate of 25% which will be considered worthy of further study. According to this design, if none of the first ten patients respond, we will stop early for lack of efficacy. If one or more patients respond, we will accrue ten additional patients for a total of 20. If three or more of the 20 respond, we will consider this regimen worthy of further study. The study will stop early with a probability of 60% if the true response rate is 5% or with a probability of 5.6% if the true response rate is 25%. The regimen will be considered worthy of further study with a probability of 6.9% if the true response rate is 5% or with a probability of 88% if the true response rate is 25%. Therefore, this study has an overall type-I error rate of 6.9% and an overall power of 88%.

Our primary investigation of exploratory/correlative laboratory assays in this study involve comparisons between baseline, on treatment, or time of progression protein levels of ALK in ALK+ ALCL; cyclin D1 in MCL; and BCL6 in DLBCL. These are primary endpoints of the laboratory component because they are biomarkers which are anticipated to be positive at study entry based on eligibility criteria, and our goal is to identify changes with the administration of AT13387 (onalespib), and, further, to examine the association between the magnitude of change and response to therapy. We will use an H-score for each of these assays (IHC intensity grade [0-3+] multiplied by the proportion of IHC positive tumor cells [0-100%]). Because of the limited sample size in ALK+ ALCL, these results (at each time point and as changes as a proportion of baseline levels) will be reported descriptively. For changes in cyclin D1 levels in MCL, as well as for changes in BCL6 in DLBCL, we will investigate these markers in two ways. First, we will characterize the changes between baseline, on study, and at the time of progression and present them descriptively both as differences and as differences at the referenced time point as a proportion of the baseline levels. We will present both mean and standard deviation, and median and IQR/range. We will use the Wilcoxon rank sum test to compare these changes

between responders to non-responders. If there are 3 responders, we will have 84% power to detect a 1.5 standard deviation difference in the changes, testing at the 0.10 one-sided significance level. If there are 6 clinical responses, we will have 75% power to detect a one standard deviation difference. We use a one-sided significance level because we hypothesize that activity of AT13387 (onalespib) leading to response will reduce the protein levels of these markers. Other biomarkers (immunoblotting, whole exome sequencing, RNASeq) are exploratory, and we can only investigate changes in those cases in which the marker is positive/measurable at study entry. Statistics for these endpoints will be descriptive. This cohort is now closed to new enrollment, as of October 2019.

13.2 Sample Size/Accrual Rate

For ALK+ ALCL, we expect accrual of 0-1 patients/month, with an estimated time to accrual of all ten patients of 18 months. For DLBCL and MCL, we expect accrual of 1-2 patients/month, with an estimated time to accrual of all 20 patients of 12-18 months.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	2	0	0	5
White	18	17	1	1	37
More than one Race	2	1	1	1	5
Total	24	22	2	2	50

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Accrual of women and minorities to clinical trials in the DF/HCC generally reflects the population of the state of Massachusetts and the New England catchment area. The 2010 census indicated that the population of the state of Massachusetts is 51.6% female and 48.4% male. Additionally, the population is 80.4% white, 6.6% African American, 5.3% Asian, 2.6% of more than one race, and 0.3% Native American. These data were used to generate the planned distribution of subjects table for the AT13387 (onalespib) trial. The DF/HCC has established the Initiative to Eliminate Cancer Disparities (IECD) to address cancer disparities with regard to recruitment of minorities to clinical trials. We will continue to work closely with the IECD to ensure that we are participating in all of the mechanisms developed through the Initiative to support efforts to enhance diversity in accrual and to address cancer disparities.

13.3 Stratification Factors

All three cohorts will enroll simultaneously and independently. There will be no stratification.

13.4 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed at the same time as the primary endpoint and assessed for each cohort separately and overall. Due to the small sample size in each cohort and all patients combined, secondary endpoints will be descriptive unless otherwise noted. All eligible patients who receive at least one dose of treatment will be included in efficacy endpoints, and all patients regardless of eligibility who receive at least one dose of treatment will be included in toxicity assessments.

Patients receiving any treatment regardless of eligibility or study completion will be assessed for toxicity from the time of their first treatment. At each toxicity evaluation, patients with unacceptable toxicities will be removed from study but remain in safety evaluations. Toxicities will be summarized with counts and proportions within each cohort and overall.

Time-to-event endpoints of progression-free and overall survival (PFS and OS, resp.) will be characterized using the Kaplan-Meier method. OS is defined from the date of study entry until the date of death by any cause. PFS will be measured from the date of study entry until documentation of first progression or death from any cause. Median follow-up time will be assessed using the reverse Kaplan-Meier method.

Duration of response (DOR) is defined as the time from first objective response (PR or CR) until the first date of documented progression using [the response criteria] or death due to any cause. For patient who remain alive without progression, the DOR will be censored on the date of their last response assessment. Patients who begin a subsequent therapy without prior documented progression will be censored at the last response assessment prior to initiation of non-protocol therapy. DOR will be evaluated only in patients who respond with either a PR or CR while on study.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with AT13387 (onalespib)

13.5.2 Evaluation of Response

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

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B__PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **AT13387 (onalespib).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that your prescriber needs to know:

Pre-clinical data show that AT13387 (onalespib) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

The enzymes in question are UGT1A1, UGT1A3, UGT1A9 and CYP 1A2, 3A4, 2D6, 2C9, and 2C19.

- AT13387 (onalespib) is metabolized by UGT1A1 and UGT1A3 and may be affected by other drugs that inhibit or induce these enzymes.
- AT13387 (onalespib) is a "weak" inhibitor of UGT1A1, UGT1A3, UGT1A9 and CYP 1A2, 3A4, 2D6, 2C9, and 2C19 and may affect the metabolism of other drugs.
- The proteins in questions are P-gp, BCRP, MATE-1, and MATE2-K. AT13387 (AT13387 (onalespib) is a P-gp substrate and may be affected by other drugs that inhibit/induce P-gp. AT13387 is a "moderate inhibitor" of BCRP and P-gp, and a "strong inhibitor" of MATE1 and MATE2-K and may affect transport of other drugs in and out of cells.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

AT13387 (onalespib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.
Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:
AT13387 (onalespib) must be used very carefully with other medicines that need certain liver enzymes or transport proteins to be effective or to be cleared from your body. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to

review any medicines and herbal supplements that are considered "strong/moderate inhibitor/inducer or substrate of UGT1A1, UGT1A3, BCRP, P-gp, MATE1 and MATE2-K, CYP1A2, -3A4, -2D6, -2C9, and -2C19."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is: _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **AT13387 (onalespib).** This clinical trial is sponsored by the NCI. AT13387 (onalespib)) interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- AT13387 (onalespib) interacts with drugs that are processed via UGT1A1, UGT1A3. It may also interact with transport proteins (P-gp, BCRP, MATE1, and MATE2K) and liver enzymes (CYP 1A2, -3A4, -2D6, -2C9, and -2C19); thus, it must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong or moderate inducers/inhibitors" of these enzymes and protein transporters.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX C ANTI-ALK IMMUNOHISTOCHEMISTRY STANDARD OPERATING PROCEDURE, BRIGHAM AND WOMEN'S HOSPITAL HEMATOPATHOLOGY, CLIA CERTIFIED CORE LABORATORY

Immunohistochemical staining of ALK (D5F3, Cell Signaling Technologies) was performed manually following the manufacturer's protocols. 4um thick paraffin-embedded sections were pre-baked in 60 °C oven for one hour. ALK (D5F3) immunostaining was performed with 1:100 dilution using Dako Antibody diluent with Background reducing reagents. Slides were first dewaxed and rehydrated. Heat induced antigen retrieval was performed in Decloaking Chamber (Biocare Medical). Slides were incubated in Peroxidase Block (Dako) for 5 minutes, followed by Protein Block (Dako) for 5 minutes. Primary antibody was incubated overnight at 4°C. Slides were then incubated with Envision+ Rabbit Polymer-HRP (Dako) for 30 minutes at ambient temperature. Slides were developed with Diaminobenzene (Dako) for 5 minutes then counterstained with hematoxylin, dehydrated and coverslipped.

APPENDIX D ANTI-CYCLIN D1 IMMUNOHISTOCHEMISTRY STANDARD OPERATING PROCEDURE, BRIGHAM AND WOMEN'S HOSPITAL HEMATOPATHOLOGY, CLIA CERTIFIED CORE LABORATORY

Immunohistochemical staining of Cyclin D1 (SP4, Neomarkers) was performed using an automated staining system (Bond III, Leica Biosystems, Buffalo Grove, IL) following the manufacturer's protocols. 4um thick paraffin-embedded sections were pre-baked in 60 °C oven for one hour. Adhesive labels for each protocol were printed and applied to slides. Slides were then loaded onto Bond III with "Bond Universal Covertiles" (Leica Biosystems). Cyclin D1 (SP4) immunostaining was performed with 1:40 dilution using Bond Primary Antibody Diluent (Leica). The following steps were performed online. Slides were first dewaxed and rehydrated. Heat induced antigen retrieval was performed using ER2 solution (pH8) (Leica Biosystems) for 20 minutes. Primary antibody was incubated for total of 30 minutes, followed by 10 minutes of horseradish peroxidase-labeled polymer, 5 minutes of peroxidase block, and 10 minutes of DAB developing. Slides were counterstained by hematoxylin for 10 minutes. All reagents were components of the Bond Polymer Refine detection system (Leica Biosystems). Slides were then taken off the autostainer, dehydrated and coverslipped.

APPENDIX E ANTI-BCL6 IMMUNOHISTOCHEMISTRY STANDARD OPERATING PROCEDURE, BRIGHAM AND WOMEN'S HOSPITAL HEMATOPATHOLOGY, CLIA CERTIFIED CORE LABORATORY

Immunohistochemical staining of BCL6 (GI191E/A8, Cell Marque) was performed using an automated staining system (Bond III, Leica Biosystems, Buffalo Grove, IL) following the manufacturer's protocols. 4um thick paraffin-embedded sections were pre-baked in 60 °C oven for one hour. Adhesive labels for each protocol were printed and applied to slides. Slides were then loaded onto Bond III with "Bond Universal Covertiles" (Leica Biosystems). BCL6 (GI191E/A8) immunostaining was performed with 1:500 dilution using Bond Primary Antibody

Diluent (Leica). The following steps were performed online. Slides were first dewaxed and rehydrated. Heat induced antigen retrieval was performed using ER2 solution (pH8) (Leica Biosystems) for 20 minutes. Primary antibody was incubated for total of 30 minutes, followed by 10 minutes of postprimary reagent, followed by 10 minutes of horseradish peroxidase-labeled polymer, 5 minutes of peroxidase block, and 10 minutes of DAB developing. Slides were counterstained by hematoxylin for 10 minutes. All reagents were components of the Bond Polymer Refine detection system (Leica Biosystems). Slides were then taken off the autostainer, dehydrated and coverslipped.

APPENDIX F PROCEDURES FOR FORMALIN FIXATION

Cores biopsies (skin or tumor) should be fixed in formalin. The minimum fixation time in formalin is 4 hours prior to processing in pathology. The maximum fixation time in formalin is 36 hours, so that phospho-epitopes are not compromised. (Therefore, sites should not plan on procuring samples on Fridays. It is also best not to ship on Fridays as well).

Ideally, after 24 hours, the core should be transferred to 70-80% ethanol for longer term storage and transport.

Samples should be sent in 70 to 80 percent ethanol in a securely closed container (one with a screw top/cap), this container should be placed in a secondary container (plastic zip loc bags work well) put a piece of absorbent material in the secondary container with the sample in case of leakage. This entire package along with any requisition/ paperwork can then be shipped via FedEx (in their appropriate packaging), under current shipping requirements for non-infectious/hazardous human samples. Please keep the requisition outside of the secondary container so it does not become wet should the primary container leak.

APPENDIX G PROCEDURES FOR SNAP FREEZING

1. Each cryomold is labeled with the unique patient identifier and date of procedure.
    a. Please note: intermediate size (15 x 15 x 5 mm) cryomold is preferred.
2. The labeled cryomold is filled half way with OCT medium and placed on dry ice for 10 minutes.
3. The tissue is placed directly on the frozen OCT cryomold.
4. The tissue is fully covered with additional OCT compound and place on dry ice for an additional 10 minutes.
5. Once the blocks are fully frozen, the frozen tissue can be stored in a -80 degree Celsius freezer until shipment. (A -70 degree Celsius freezer is also acceptable).

APPENDIX H 9875 Specimen Submission Form

(on next page)

Please provide a copy of the completed form with your specimen shipment to Dana-Farber Center for Cancer Precision Medicine

SITE INFORMATION

Contact person:_____ **Phone number:** _____

Site Location: _____ **Date and time of procedure:** _____

PATIENT INFORMATION

Patient identifier (Subject Study #): _____ **Birth Year:** __ __ __ __

Study Timepoint: ☐ Pre-treatment ☐ On-treatment ☐ Post-progresssion

SAMPLE INFORMATION

Site of Tumor Tissue Biopsy/Resection (Check One): ☐ Primary ☐ Metastatic

Tissue Collection: ☐ Surgical Resection ☐ Excisional Biopsy ☐ Core Biopsy (_____gauge) ☐ Fine Needle Aspirate

For FORMALIN-FIXED TISSUE, please fill out following section:

SPECIMEN SITE		
1. _____	block number: _____	number of slides: _____
2. _____	block number: _____	number of slides: _____
3. _____	block number: _____	number of slides: _____

For FROZEN TISSUE, please fill out following section:

SPECIMEN SITE	**TISSUE SIZE**	**SAMPLE MEDIA**
1. _____	___x___x___ cm	☐ OCT ☐ Other _____
2. _____	___x___x___ cm	☐ OCT ☐ Other _____
3. _____	___x___x___ cm	☐ OCT ☐ Other _____
4. _____	___x___x___ cm	☐ OCT ☐ Other _____

APPENDIX I Example Ophthalmologic Examination Worksheet

Date of Examination: _____

	Right Eye	**Left Eye**
Refraction		
Visual Acuity	_ _ / _ _ _ Abnormal / Normal: _____	_ _ / _ _ _ Abnormal/ Normal: _____
Slit Lamp Examination		
Conjunctiva	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Cornea	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Anterior Chamber	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Iris	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Lens	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Other (specify)	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
	Clinical relevant abnormalities only	**Clinical relevant abnormalities only**
Intraocular Pressure	_____mmHg	_____mmHg
Fundoscopy		
Vitreous	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Optic disc	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Macula	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Peripheral retina	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Blood vessels	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
Other (specify)	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
	Clinical relevant abnormalities only	**Clinical relevant abnormalities only**
Additional Ophthalmologic Examinations:		
_____	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
_____	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
_____	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____
_____	Not Done/ Abnormal / Normal: _____	Not Done/ Abnormal / Normal: _____

Examination performed by: _____
Signature of person performing examination: _____
Date: _____

(Form Version 1.0 dated 6 September 2016)