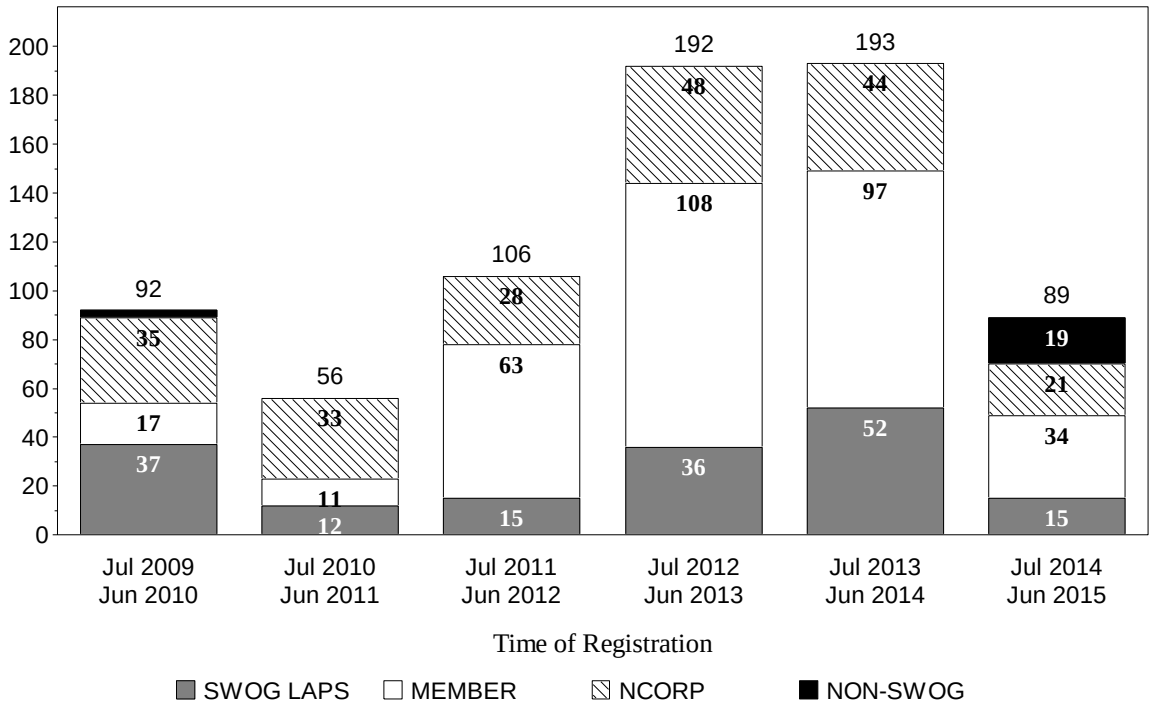
# MELANOMA COMMITTEE

# CONTENTS

# Patient Registrations to Studies

By 12 Month Intervals
**MELANOMA COMMITTEE**




Screening registrations and registrations to Biologic only studies are excluded

# Patient Registrations by Study and Arm

## MELANOMA COMMITTEE

| | Jan 2015<br>Jun 2015 | Jul 2014<br>Dec 2014 | Jan 2014<br>Jun 2014 | All<br>Patients |
|---|---|---|---|---|
| **S1221 Adv, Dabrafenib + Trametinib + GSK2141795** | | | | |
| **Phase I Registrations** | | | | |
| Dabrafenib/GSK2141795 50mg | 0 | 0 | 0 | 3 |
| Dabrafenib/GSK2141795 75mg | 0 | 1 | 6 | 7 |
| Dabrafenib/Tametinib 1.5 mg/GSK2141795 25mg | 4 | 0 | 0 | 4 |
| | 4 | 1 | 6 | 14 |
| **S1320 Adv, BRAF Mut, Intermittent vs Continuous Dabrafenib + Trametinib** | | | | |
| Lead-in Continuous Dosing | 39 | 6 | 0 | 45 |
| **Randomization** | | | | |
| Continuous Dosing | 13 | 0 | 0 | 13 |
| Intermittent Dosing | 13 | 1 | 0 | 14 |
| | 26 | 1 | 0 | 27 |
| **E1609 Adjuvant Ipilimumab vs Interferon*** | | | | |
| Total Registrations | 0 | 36 | 95 | 499 |
| **E2607 Adv, Dasatinib in KIT+ Patients*** | | | | |
| Total Registrations | 0 | 0 | 0 | 0 |
| **E3612 Adv, Ipilimumab ± Bevacizumab*** | | | | |
| Total Registrations | 3 | 0 | 0 | 3 |

* For non-SWOG coordinated studies only SWOG registrations are shown.

# S1204 Surveillance

# A Sero-Epidemiologic Survey and Cost-Effectiveness Study of Screening for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Among Newly Diagnosed Cancer Patients

**Study Chairs:**
S Ramsey, R Loomba, R Chugh, D Hershman, J Hwang

**Statisticians:**
J Unger, K Arnold

**Data Coordinator:**
M Yee

**Date Activated:**
08/29/2013

**Objectives**

Among newly diagnosed cancer patients presenting to SWOG-affiliated community and academic oncology clinics, estimate the prevalence of human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV) infection.

Evaluate known sociodemographic, clinical, and behavioral factors that are significantly associated with previously undiagnosed HIV, HBV, and/or HCV infection in a population of people with newly diagnosed cancer.

Among patients who are identified as having HIV, HBV, and/or HCV, evaluate the timing and type of treatments received, both for the viral infections and the cancers.

Evaluate type and rate of cancer treatment-related adverse events in patients with HIV, HBV, and/or HCV infection.

Determine the cost-effectiveness of (1) routine, universal screening and (2) risk factor-directed screening of newly diagnosed cancer patients for HIV, HBV and/or HCV versus current care.

Create a biorepository of stored serum for future translational medicine studies that may include identifying genomic and viral factors that increase the risk of serious adverse effects among participants infected with HIV, HBV, and/or HCV being treated for invasive cancers.

**Patient Population**

Patients must be presenting for evaluation or treatment for the first diagnosis of a new solid or hematologic cancer malignancy. Confirmed diagnosis date must be within 120 days prior to first clinic visit as a newly diagnosed cancer patient at the registering clinic. Patients presenting for "second opinions" of confirmed malignancies are eligible, including those who have started cancer treatment at other facilities. Patients must be registered within 90 days after their first clinic visit. Patients must not have been diagnosed with a malignancy other than the current malignancy within the past five years, with the exception of basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ breast cancer. Patients must have no evidence of disease for a prior malignancy for at least five years prior to randomization except as noted above.

Patients must be 18 years of age or older. Patients must have had their blood drawn for viral status testing for HIV, HBV and HCV or provide acceptable viral status documentation prior to registration, as defined in the protocol. Note that patients must have blood drawn for testing prior to registration for any of the three viruses not covered by the documentation. Patients are allowed to participate in other clinical trials.

**Accrual Goals**
A total of 3,000 eligible patients will be accrued.

**Summary Statement**
For the current status of this study, please refer to the Cancer Care Delivery chapter.

# S1221 Phase I-II

# Phase I/II Study of the Safety and Efficacy of the AKT Inhibitor GSK2141795 in Combination with Dabrafenib and Trametinib in Patients with BRAF Mutant Cancer

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**Study Chairs:**
A Ribas, A Algazi, B Chmielowski, R Lo

**Statisticians:**
J Moon, M Othus

**Data Coordinator:**
J Barrett

**Date Activated:**
07/12/2013

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**Objectives**

Phase I Portion:

The Phase I portion will be performed in two parts. Part 1 will investigate the doublet combination of dabrafenib and GSK2141795. Part 2 will investigate the triplet combination of dabrafenib, trametinib and GSK2141795.

Part 1:

To assess the safety of dabrafenib in combination with GSK2141795 and select the optimal dose of GSK2141795 for the Phase II portion in patients with BRAF mutant cancer.

To explore potential drug interactions between dabrafenib and GSK2141795 via pharmacokinetic sampling of patients enrolled on the Phase I portion.

Part 2:

To assess the safety of dabrafenib and trametinib in combination with GSK2141795 and select the optimal dose of the combination for the Phase II portion in patients with BRAF mutant cancer.

To explore potential drug interactions between dabrafenib, trametinib and GSK2141795 via pharmacokinectic sampling of patients enrolled on the Phase I portion.

Phase II Portion:

The Phase II portion will only investigate the triplet combination of dabrafenib, trametinib and GSK2141795.

To evaluate the objective response rate (confirmed and unconfirmed complete and partial responses) in patients with Stage IV or unresectable Stage III $BRAF^{v600}$ mutant metastatic melanoma who have who have acquired resistance to BRAF inhibitor-based therapy treated with the triplet combination of dabrafenib, trametinib and GSK2141795

To estimate overall survival and progression-free survival.

To assess the toxicity profile of the recommended Phase II dose.

To explore the molecular mechanisms of acquired resistance to BRAF inhibitor therapy in patients with $BRAF^{v600}$ mutant metastatic melanoma.

**Patient Population**

Phase I portion:

Patients may have any type of locally advanced unresectable Stage IIIC or Stage IV cancer, irrespective of the histology or prior therapy. Patients may have measurable or non-measurable disease.

Patients with melanoma must have a serum LDH performed at baseline.

Patients must have a Zubrod performance status ≤ 1.

Phase II portion:

Patients must have histologically confirmed melanoma that is Stage IIIC or Stage IV. Patients must have a serum LDH performed at baseline and must have measurable disease.

Patients must have a Zubrod performance status ≤ 2.

All Patients:

Patients must have $BRAF^{V600}$ mutant metastatic cancer documented by a CLIA-certified laboratory. All patients must have a CT or MRI of the brain. Patients with brain metastases are eligible only if they are asymptomatic or they have been previously treated and are stable (i.e. not requiring corticosteroids).

Patients may have received prior systemic therapy (chemotherapy, immunotherapy, biologic therapy, or combination regimens), surgery, or radiation therapy. Patients must have either progressed on a single agent BRAF inhibitor or BRAF inhibitor plus MEK inhibitor therapy.

Patients must have adequate hematologic, hepatic, renal, cardiac and ocular function. Patients must be able to retain oral medication. Patients who have feeding tubes must be able to take whole capsules without modifying them. Patients must not have an active Hepatitis B or Hepatitis C infection. Patients requiring therapeutic anticoagulation must have approval from physician to use therapeutic dosing of warfarin and they must have close monitoring of PT/INR during the trial. Patients must not be receiving any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8 or P-glycoprotein (Pgp) or breast cancer resistance protein 1 (Bcrp1), or using herbal remedies. Patients must be able to swallow capsules and not have any history of allergic reactions to compounds of similar chemical or biologic composition to dabrafenib or GSK2141795. Patients with HIV are eligible if they are not on antiviral agents and have adequate CD4 counts. Women of childbearing potential must have a negative pregnancy test within 14 days prior to registration.

Patients must have available and must be willing to submit blood and tissue samples as outlined in the protocol.

**Stratification/Descriptive Factors**

Patients enrolled on the Phase I portion can be enrolled on the doublet regimen (dabrafenib and GSK2141795) or the triplet regimen (dabrafenib, trametinib and GSK2141795). Patients with melanoma are encouraged to be enrolled on the triplet regimen.

**Accrual Goals**

The study will be conducted in two sequential parts. Patients enrolled to the Phase I portion will not be included in the analysis of the Phase II portion.

Both the doublet regimen and the triplet regimen will be investigated during the Phase I portion. Within each stratum, patient enrollment will follow the traditional "3+3" algorithm until the MTD for GSK2141795 is reached or the highest dose tested is judged tolerable. At least six patients will be evaluated at the recommended dose within each stratum.

Only the triplet regimen will be investigated in the Phase II portion. A two-stage design will be used. Initially, ten eligible patients will be registered. If at least two responses are observed, an additional 23 eligible patients will be registered.

**Summary Statement**

This study was amended to add a third drug, trametinib, to the two drug combination being investigated. The Phase I portion investigating the doublet combination will continue until its conclusion. Effective February 13, 2015, patients may also be enrolled on the Phase I portion investigating the triplet combination. At the conclusion of the Phase I portion of the triplet combination, the Phase II portion will evaluate the efficacy of the three drug combination. The Phase II evaluation of the two-drug combination will no longer be pursued.

The Phase I portion of this trial, investigating the two drug combination of GSK2141795 + dabrafenib, was activated on July 1, 2013. The first cohort of three patients treated at the dose level of 50 mg GSK2141795 has been completed. No dose limiting toxicities (DLT) were observed. Therefore, per protocol, the second cohort of patients to be treated at the dose level of 75 mg GSK2141795 was opened to accrual on February 3, 2014.

As of June 30, 2015, seven patients have been enrolled to the cohort investigating the two drug combination of dabrafenib and GSK2141795 at the dose level of 75 mg. However, three of these patients did not meet the protocol-specified criteria to be considered evaluable for DLTs, including two eligible patients who did not receive any protocol treatment are not evaluable for any of the study endpoints and another who is not eligible due to uncontrolled hypertension. As of August 7, 2015, there have been no DLTs reported for the first four evaluable patients on the 75 mg cohort. This cohort remains open to accrual until six patients evaluable for DLTs have been enrolled.

As of June 30, 2015, four patients have been registered to the three-drug combination investigating dabrafenib, trametinib at 1.5 mg, and GSK2141795 at 25 mg. One of these patients did not meet the protocol-specified criteria to be considered evaluable for DLTs and was replaced. Accrual to this cohort is temporarily closed while the adverse event data are being assessed.

Institutions are reminded to submit adverse event data in a timely manner.

## Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg |
|---|---|
| Colorado, U of | 4 |
| Ohio State Univ | 4 |
| Los Angeles, U of CA | 3 |
| Prov Portland MC/PCRC NCORP | 2 |
| Michigan, U of | 1 |
| **Total (5 Institutions)** | **14** |

## Registration, Eligibility, and Evaluability

Registrations ending June 30, 2015; Data as of August 7, 2015

| | TOTAL | Dabrafenib + GSK2141795 50mg | Dabrafenib + GSK2141795 75mg | Dabrafenib + Trametinib 1.5mg + GSK2141795 25mg |
|---|---|---|---|---|
| NUMBER REGISTERED | 14 | 3 | 7 | 4 |
| INELIGIBLE | 1 | 0 | 1 | 0 |
| ELIGIBLE | 13 | 3 | 6 | 4 |
| Not Analyzable | 2 | 0 | 2 | 0 |
| BASELINE DISEASE STATUS | | | | |
| Measurable | 9 | 3 | 4 | 2 |
| Too Early | 2 | 0 | 0 | 2 |
| RESPONSE ASSESSMENT | | | | |
| Determinable | 9 | 3 | 4 | 2 |
| Too Early | 2 | 0 | 0 | 2 |
| ADVERSE EVENT ASSESSMENT | | | | |
| Evaluable | 9 | 3 | 4 | 2 |
| Not Evaluable | 1 | 0 | 0 | 1 |
| Too Early | 1 | 0 | 0 | 1 |
| DOSE-LIMITING TOXICITIES | | | | |
| Evaluable | 8 | 3 | 3 | 2 |
| Not Evaluable | 2 | 0 | 1 | 1 |
| Too Early | 1 | 0 | 0 | 1 |

## Patient Characteristics

Registrations ending June 30, 2015; Data as of August 7, 2015

| | Total (n=11) | |
|---|---|---|
| AGE | | |
| Median | 60.8 | |
| Minimum | 40.5 | |
| Maximum | 70.2 | |
| SEX | | |
| Males | 10 | 91% |
| Females | 1 | 9% |
| HISPANIC | | |
| No | 11 | 100% |
| RACE | | |
| White | 11 | 100% |
| PRIOR BRAF INHIBITOR | | |
| Yes | 8 | 73% |
| No | 3 | 27% |
| TYPE OF CANCER | | |
| Melanoma | 8 | 73% |
| Lung | 2 | 18% |
| Thyroid | 1 | 9% |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending June 30, 2015; Data as of August 7, 2015

| | Dabrafenib + GSK2141795 50mg (n=3) Grade | | | | | | Dabrafenib + GSK2141795 75mg (n=4) Grade | | | | | | Dabrafenib + Trametinib 1.5mg + GSK2141795 25mg (n=2) Grade | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** |
| ALT increased | 3 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| AST increased | 3 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Alopecia | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Anemia | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 2 | 0 | 1 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Arthralgia | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Chills | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Dizziness | 2 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Edema limbs | 2 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Fatigue | 1 | 2 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Fever | 1 | 1 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |

| | Dabrafenib + GSK2141795 50mg (n=3) Grade | | | | | | Dabrafenib + GSK2141795 75mg (n=4) Grade | | | | | | Dabrafenib + Trametinib 1.5mg + GSK2141795 25mg (n=2) Grade | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** |
| Flu like symptoms | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Flushing | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Gen disorders/admin site cond | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hand-Foot syndrome | 2 | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Headache | 3 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hyperglycemia | 2 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hyperhidrosis | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hypernatremia | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hypokalemia | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hyponatremia | 2 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hypophosphatemia | 2 | 0 | 1 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hypotension | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Insomnia | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Lymphocyte count decreased | 1 | 1 | 1 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| Myalgia | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Nail ridging | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 1 | 2 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Neutrophil count decreased | 3 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Non-cardiac chest pain | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Pain | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Pain in extremity | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Pain of skin | 2 | 1 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Platelet count decreased | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Rash acneiform | 3 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Renal/urinary disorders-Other | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Skin/subq tissue ds-Other | 2 | 0 | 0 | 1 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Tremor | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Vasc disorders-Other, spec | 2 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 1 | 2 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Weight loss | 2 | 0 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 0 | 1 | 0 | 2 | 0 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |

# S1320 Phase II

## Coordinating Group: SWOG

# A Randomized Phase II Trial of Intermittent versus Continuous Dosing of Dabrafenib (NSC-763760) and Trametinib (NSC-763093) in BRAF$^{V600E/K}$ Mutant Melanoma

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**Participants:**
SWOG, CTSU (Supported by ECOG-ACRIN)

**Study Chairs:**
A Algazi, A Daud, R Lo

**Statisticians:**
M Othus, J Moon, M Wu

**Data Coordinator:**
J Barrett

**Date Activated:**
07/22/2014

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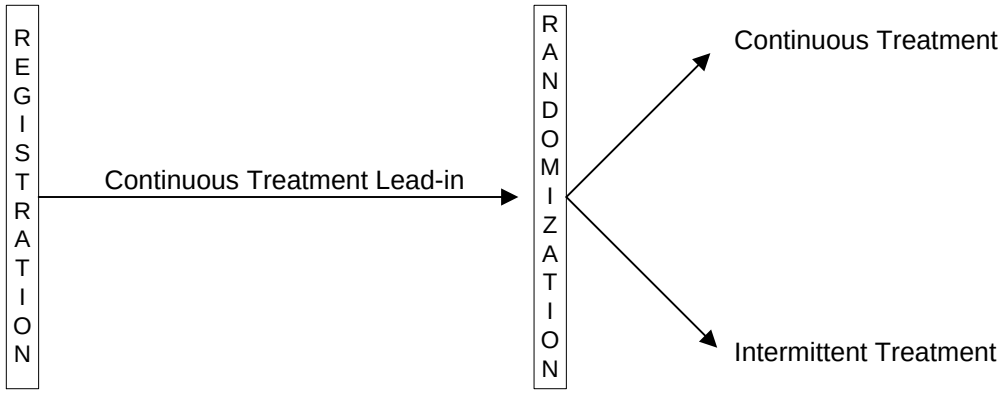
## SCHEMA




**Objectives**

To compare progression-free survival with intermittent dosing versus continuous dosing of dabrafenib and trametinib among patients with metastatic BRAFV600E/K mutant melanoma.

To compare the response rate (complete and partial response, confirmed and unconfirmed), overall survival, and survival after progression between the two dosing schedules.

To compare the frequency and severity of fever greater than Grade 1 per CTCAE 4.0 of the two dosing schedules.

To estimate the frequency and severity of toxicities of the two dosing schedules.

To bank tissue and whole blood in anticipation of future studies to evaluate molecular events associated with clinical benefit and disease progression in

patients treated with continuous versus intermittent dabrafenib and trametinib.

**Patient Population**

Patients must have histologically or cytologically confirmed Stage IV or unresectable Stage III melanoma. Patients must have BRAF mutation-positive melanoma (i.e., V600E or V600K) as determined via Sanger sequencing or an FDA-approved BRAF mutation detection assay. $BRAF^{V600}$ mutant status must be documented by a CLIA-certified laboratory. Patients must have measurable disease as defined by RECIST 1.1. Contrast-enhanced CT scans of the neck, chest, abdomen and pelvis are required. A whole body PET/CT scan with diagnostic quality images and intravenous iodinated contrast may be used in lieu of a contrast enhanced CT of the neck, chest, abdomen and pelvis. Contrast may be omitted if the treating investigator believes that exposure to contrast poses an excessive risk to the patient. Patients must not have brain metastases unless brain metastases have been treated and patient is asymptomatic with no residual neurological dysfunction and has not received enzyme-reducing anti-epileptic drugs or corticosteroids for at least 7 days prior to registration. Patients must have serum LDH obtained prior to registration for treatment randomization stratification and accurate staging.

Patients must not have received a prior BRAF or MEK inhibitor. Prior surgery, radiotherapy, immunotherapy, or chemotherapy are allowed.

Patients must have adequate hematologic, hepatic, cardiac, and renal function and a Zubrod performance status of 0-1. Patients must not have a known history or current evidence of retinal vein occlusion (RVO) or central serous retinopathy (CSR). Patients must not have any predisposing factors for RVO or CSR such as uncontrolled glaucoma, ocular hypertension, uncontrolled systemic hypertension, diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes. An ophthalmic exam is required for all patients. Patients must not have evidence of optic disc cupping, visual field defects, or an intraocular pressure greater than 21 mmHg. Patients must be able to take oral medications and must not have any impairment of gastrointestinal disease that may significantly alter the absorption of protocol treatment. Patients must discontinue treatment with therapeutic warfarin prior to registration. Patients must not have a history of pneumonitis or interstitial lung disease. Patients with known hepatitis B, or hepatitis C are not eligible. Patients known to be HIV positive must have CD4 cells $\geq$ 500 uL, a serum HIV viral load $<$ 25,000 IU/ml and must be able to discontinue antiretroviral therapy. Patients must have a dermatology exam within 28 days prior to registration.

Patients must be offered the opportunity to participate in specimen banking.

**Stratification/Descriptive Factors**

Treatment randomization will be stratified by the following: (1) prestudy serum LDH: elevated (> IULN) vs normal; (2) known prior exposure to immune checkpoint inhibitors targeting CTLA-4, PD-1, or PD-L1: yes vs no.

**Accrual Goals**

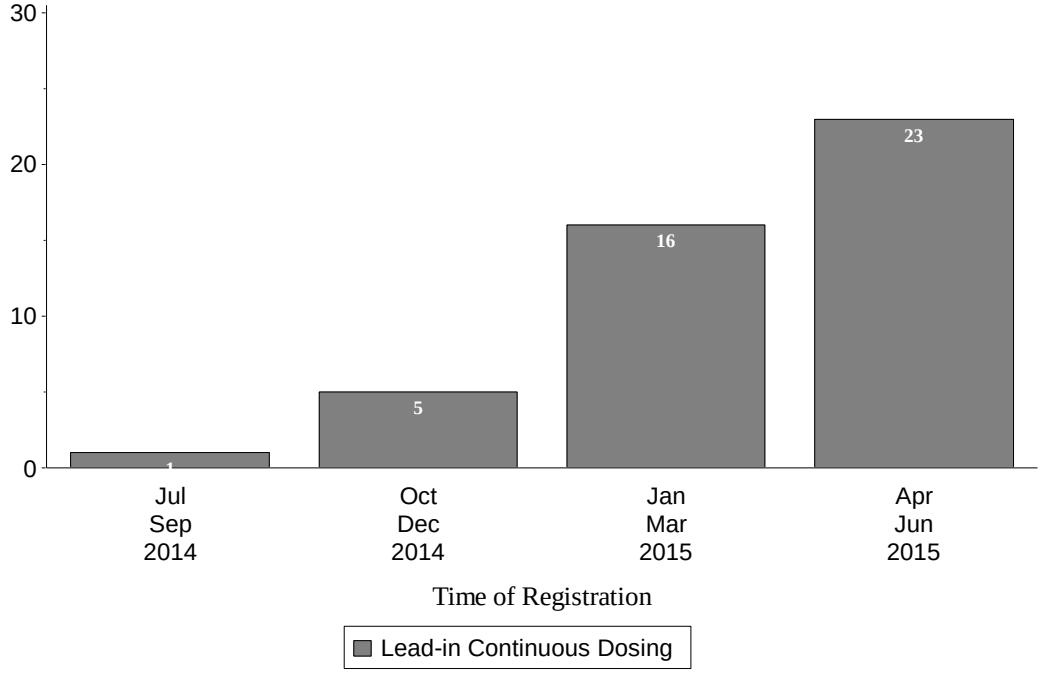
The accrual goal is 226 eligible patients. An interim analysis testing for harm will be performed when 78 progression events have occurred.

**Summary Statement**

As of June 30, 2015, 45 patients have been registered to the continuous lead-in portion of this trial and 27 patients have been randomized between intermittent and continuous dosing. One patient is currently ineligible due to having a Zubrod performance status of 2 at the time of enrollment. In addition, one eligible patient who refused protocol treatment and was never randomized, is not evaluable for any of the study endpoints. Four additional patients never completed lead-in continuous dosing for the following reasons: death (1), disease progression (1), adverse events (1), and patient refusal unrelated to adverse events or side effects (1).

Thirty-five patients have been assessed for adverse events. No adverse events greater than grade 3 have been reported.

## Initial Registrations By 3 Month Intervals




## Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| ECOG-ACRIN | 14 | Utah, U of | 2 |
| San Francisco, U-CA | 7 | Arkansas, U of | 1 |
| Kaiser Vallejo NCORP | 4 | Boston Medical Ctr | 1 |
| KaiserPermanenteSCAL/Kaiser Vallejo NCORP | 3 | Los Angeles, U of CA | 1 |
| NRG | 3 | Michigan, U of | 1 |
| Alliance | 2 | Nevada CRF NCORP | 1 |
| Heartland NCORP | 2 | Wichita NCORP | 1 |
| Loyola University | 2 | **Total (15 Institutions)** | **45** |

## Registration, Eligibility, and Evaluability

Lead-In Continuous Dosing

Registrations ending June 30, 2015; Data as of August 10, 2015

| | Lead-in Continuous Dosing |
|---|---|
| NUMBER REGISTERED | 45 |
| INELIGIBLE | 1 |
| ELIGIBLE | 44 |
| Not Analyzable | 1 |
| ADVERSE EVENT ASSESSMENT | |
| Evaluable | 35 |
| Too Early | 8 |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Adverse Events with No Entries for Grades 3 to 5 or Unknown Have Been Suppressed

Registrations ending June 30, 2015; Data as of August 10, 2015

| | Lead-in Continuous Dosing (n=35) Grade | | | |
|---|---|---|---|---|
| **ADVERSE EVENTS** | **<=2** | **3** | **4** | **5** |
| AST increased | 34 | 1 | 0 | 0 |
| Acute kidney injury | 34 | 1 | 0 | 0 |
| Anorexia | 34 | 1 | 0 | 0 |
| Blood/lymph disorder-Other | 34 | 1 | 0 | 0 |
| Dehydration | 33 | 2 | 0 | 0 |
| ECG QT corrected int prolong | 34 | 1 | 0 | 0 |
| Erythema multiforme | 34 | 1 | 0 | 0 |
| Febrile neutropenia | 34 | 1 | 0 | 0 |
| Hyponatremia | 33 | 2 | 0 | 0 |
| Hypoxia | 34 | 1 | 0 | 0 |
| Lipase increased | 34 | 1 | 0 | 0 |
| Nausea | 34 | 1 | 0 | 0 |
| Neutrophil count decreased | 34 | 1 | 0 | 0 |
| Urinary tract infection | 34 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 27 | 8 | 0 | 0 |

## Registration, Eligibility, and Evaluability

Randomization

Registrations ending June 30, 2015; Data as of August 10, 2015

| | TOTAL | Continuous Dosing | Intermittent Dosing |
|---|---|---|---|
| NUMBER REGISTERED | 27 | 13 | 14 |
| ELIGIBLE | 27 | 13 | 14 |
| Analyzable, Pend. Elig. | 5 | 3 | 2 |
| RESPONSE ASSESSMENT | | | |
| Determinable | 13 | 6 | 7 |
| Too Early | 14 | 7 | 7 |
| ADVERSE EVENT ASSESSMENT | | | |
| Evaluable | 21 | 10 | 11 |
| Too Early | 6 | 3 | 3 |

## Patient Characteristics

Randomization

Registrations ending June 30, 2015; Data as of August 10, 2015

| | Continuous Dosing (n=13) | | Intermittent Dosing (n=14) | |
|---|---|---|---|---|
| AGE | | | | |
| Median | 65.1 | | 66.6 | |
| Minimum | 28.0 | | 26.3 | |
| Maximum | 72.8 | | 80.7 | |
| SEX | | | | |
| Males | 8 | 62% | 10 | 71% |
| Females | 5 | 38% | 4 | 29% |
| HISPANIC | | | | |
| Yes | 0 | 0% | 1 | 7% |
| No | 13 | 100% | 13 | 93% |
| RACE | | | | |
| White | 13 | 100% | 14 | 100% |
| PERFORMANCE STATUS | | | | |
| 0 | 6 | 46% | 9 | 64% |
| 1 | 7 | 54% | 5 | 36% |
| PRIMARY TYPE | | | | |
| Cutaneous | 12 | 92% | 11 | 79% |
| Unknown primary | 1 | 8% | 3 | 21% |
| STAGE | | | | |
| III | 0 | 0% | 2 | 14% |
| IV | 13 | 100% | 12 | 86% |

| | Continuous Dosing (n=13) | | Intermittent Dosing (n=14) | |
|---|---|---|---|---|
| SITE(S) OF DISTANT METASTASES | | | | |
| Bone | 2 | 15% | 2 | 14% |
| Brain/CNS | 1 | 8% | 0 | 0% |
| Liver | 2 | 15% | 3 | 21% |
| Lymph node, skin, soft tissue | 8 | 62% | 4 | 29% |
| Lung | 7 | 54% | 7 | 50% |
| Other, visceral | 5 | 38% | 2 | 14% |
| Other non-visceral | 3 | 23% | 2 | 14% |
| Data pending | 0 | 0% | 2 | 14% |
| LDH | | | | |
| Elevated (>IULN) | 4 | 31% | 5 | 36% |
| Normal | 9 | 69% | 9 | 64% |
| PRIOR THERAPY WITH IMMUNE CHECKPOINT INHIBITOR | | | | |
| Yes | 3 | 23% | 4 | 29% |
| No | 10 | 77% | 10 | 71% |
| PRIOR CHEMOTHERAPY | | | | |
| No | 6 | 46% | 6 | 43% |
| Yes | 0 | 0% | 1 | 7% |
| Data pending | 7 | 54% | 7 | 50% |
| PRIOR IMMUNOTHERAPY | | | | |
| No | 5 | 38% | 5 | 36% |
| Yes | 1 | 8% | 2 | 14% |
| Data pending | 7 | 54% | 7 | 50% |
| PRIOR RADIATION THERAPY | | | | |
| No | 13 | 100% | 10 | 71% |
| Yes | 0 | 0% | 4 | 29% |
| PRIOR SURGERY | | | | |
| No | 4 | 31% | 2 | 14% |
| Yes | 9 | 69% | 12 | 86% |

# Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending June 30, 2015; Data as of August 10, 2015

| | Continuous Dosing (n=10) Grade | | | | | | Intermittent Dosing (n=11) Grade | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** |
| ALT increased | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| AST increased | 9 | 0 | 0 | 1 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| AV block first degree | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Alkaline phosphatase increased | 8 | 2 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Alopecia | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Anemia | 7 | 2 | 1 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Anorexia | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 1 | 0 | 0 | 0 |
| Chills | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Constipation | 9 | 1 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Creatinine increased | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Dehydration | 7 | 2 | 0 | 1 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 8 | 2 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Dizziness | 9 | 1 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Dry mouth | 9 | 0 | 1 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Dry skin | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Dysgeusia | 9 | 1 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Dyspepsia | 8 | 2 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| ECG QT corrected int prolong | 9 | 1 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Edema face | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Edema limbs | 9 | 1 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Ejection fraction decreased | 9 | 0 | 1 | 0 | 0 | 0 | 8 | 0 | 2 | 1 | 0 | 0 |
| Fatigue | 6 | 1 | 3 | 0 | 0 | 0 | 6 | 3 | 2 | 0 | 0 | 0 |
| Fever | 6 | 2 | 1 | 1 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Flu like symptoms | 9 | 0 | 0 | 1 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Gen disorders/admin site cond | 10 | 0 | 0 | 0 | 0 | 0 | 9 | 2 | 0 | 0 | 0 | 0 |
| Generalized muscle weakness | 9 | 0 | 1 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Headache | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Hyperglycemia | 10 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 2 | 0 | 0 | 0 |
| Hypersomnia | 9 | 1 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Hypoalbuminemia | 9 | 0 | 1 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Hypocalcemia | 9 | 1 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Hyponatremia | 9 | 1 | 0 | 0 | 0 | 0 | 10 | 1 | 0 | 0 | 0 | 0 |
| Hypophosphatemia | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 1 | 0 | 0 | 0 |
| Lipase increased | 10 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 1 | 1 | 0 | 0 |
| Lymphocyte count decreased | 9 | 0 | 1 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 7 | 2 | 1 | 0 | 0 | 0 | 9 | 2 | 0 | 0 | 0 | 0 |
| Neutrophil count decreased | 8 | 1 | 0 | 1 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Pain | 9 | 1 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Personality change | 9 | 0 | 1 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Platelet count decreased | 9 | 0 | 0 | 1 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Proteinuria | 9 | 0 | 1 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Pruritus | 10 | 0 | 0 | 0 | 0 | 0 | 8 | 3 | 0 | 0 | 0 | 0 |
| Rash acneiform | 9 | 1 | 0 | 0 | 0 | 0 | 9 | 2 | 0 | 0 | 0 | 0 |
| Rash maculo-papular | 9 | 0 | 1 | 0 | 0 | 0 | 9 | 2 | 0 | 0 | 0 | 0 |
| Serum amylase increased | 10 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 1 | 0 | 0 | 0 |
| Skin/subq tissue ds-Other | 9 | 1 | 0 | 0 | 0 | 0 | 9 | 2 | 0 | 0 | 0 | 0 |

| | Continuous Dosing (n=10) Grade | | | | | | Intermittent Dosing (n=11) Grade | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ADVERSE EVENTS** | **0** | **1** | **2** | **3** | **4** | **5** | **0** | **1** | **2** | **3** | **4** | **5** |
| Vomiting | 9 | 1 | 0 | 0 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Weight loss | 9 | 1 | 0 | 0 | 0 | 0 | 10 | 0 | 1 | 0 | 0 | 0 |
| White blood cell decreased | 7 | 1 | 1 | 1 | 0 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 3 | 1 | 3 | 3 | 0 | 0 | 1 | 2 | 6 | 2 | 0 | 0 |

# S1404 Phase III

## Coordinating Group: SWOG

# A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma

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**Participants:**
SWOG, CTSU (Supported by ECOG-ACRIN)

**Study Chairs:**
K Grossmann, S Patel, A Tarhini (ECOG-ACRIN)

**Statisticians:**
M Othus, J Moon, H Li

**Data Coordinator:**
J Barrett

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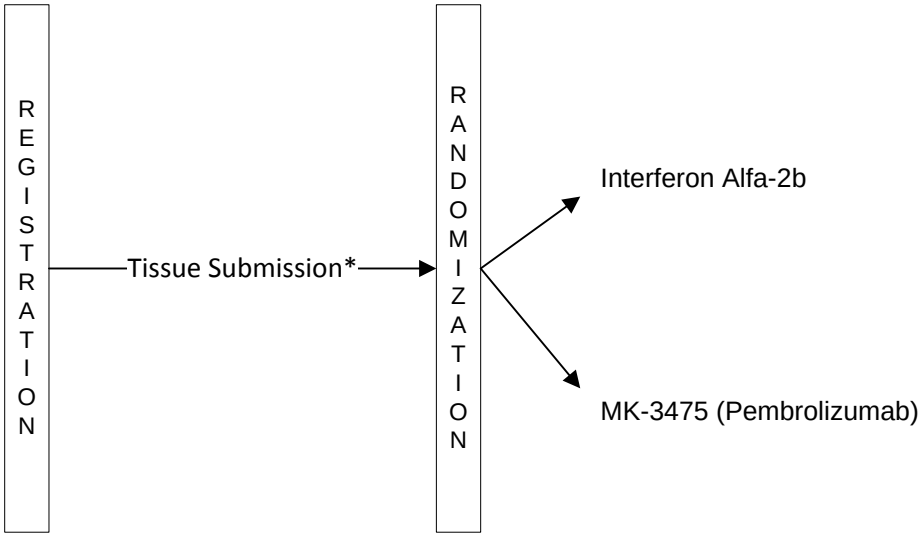
## SCHEMA




*PD-L1 status determined by central laboratory

**Objectives**

Co-Primary Objectives:

To compare overall survival of patients with resected Stage III and IV melanoma treated with high dose interferon alfa-2b versus MK-3475 (pembrolizumab).

To compare overall survival between the two regimens within the PD-L1 positive subgroup in this population.

To compare relapse-free survival between the two regimens among all patients and within the PD-L1 positive subgroup in this population.

Secondary Objectives:

To estimate overall survival and relapse-free survival for patients who are PD-L1 negative or PD-L1 indeterminate in this population.

To compare overall survival and relapse-free between the two regimens within the PD-L1 positive and PD-L1 negative subgroups and to investigate the interaction between PD-L1 status (positive versus negative) and treatment arm.

To assess the safety and tolerability of the two regimens.

To bank tissue and whole blood.

To evaluate PD-L1 expression through immunohistochemistry assay.

To compare treatment-related side effects that may have an impact on the health-related domains of quality of life between the two regimens using the FACT-BRM and the EQ-5D-3L.

To evaluate exposure-response analyses for activity and efficacy, potential pharmacodynamic biomarkers, and safety of MK-3475 (pembrolizumab) by performing pharmacokinetic (PK) and anti-drug antibody (ADA) testing on patients randomized to receive MK-3475 (pembrolizumab).

**Patient Population**

Patients must have histologically confirmed selected Stage III (IIIA-N2a, IIIB, IIIC) or Stage IV melanoma of cutaneous or mucosal origin or unknown primary. Patients must not have melanoma of ocular origin. Patients are eligible for this trial either at initial presentation of their melanoma, at time of first detected nodal, satellite/in-transit, distant metastases or recurrent disease in prior lymphadenectomy or distant site. Patients must not have a history of brain metastases. Patients who have multiple regional nodal basin involvement are eligible. Gross or microscopic extracapsular nodal extension is permitted. All disease must have been completely resected with negative pathologic margins and no clinical, radiologic, or pathologic evidence of any incompletely resected melanoma.

Patients may have received prior radiotherapy, including after the surgical resection that rendered the patient disease-free. Patients must not have received prior therapy with interferon alfa-2b, pegylated interferon, or any anti-PD-1 or anti-PD-L1 agents. Patients may have received other forms of treatment for melanoma, including chemotherapy, immunotherapy, interleukins, ipilimumab, or anti-tumor vaccine provided these were last received at least 42 days prior to enrollment and prior to the surgery(s) performed to render the patient free of disease. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

Patients must have a Zubrod performance status of 0-1, and have adequate renal, hepatic, hematologic, and cardiac function. Patients must not have autoimmune disorders, conditions of immunosuppression or treatment with corticosteroids. Patients known to be HIV positive must have adequate CD4 counts and low viral load. Patients must not have known active hepatitis B or C infections. Patients must not have received live vaccines within 42 days prior to enrollment. Women of childbearing potential must have a negative pregnancy test within 28 days prior to randomization.

Patients must have available and be willing to submit adequate tissue for PD-L1 testing. The results of the PD-L1 testing will be used to stratify treatment randomization. Patients must be willing to have blood draws for PK/ADA analysis should the patient be randomized to receive MK-3475 (pembrolizumab). Patients must be offered the opportunity to participate in specimen banking

**Stratification/Descriptive Factors**

Treatment randomization will be stratified by the following: (1) surgically resected AJCC stage: IIIA(N2a) vs IIIB vs IIIC vs IV; (2) PD-L1 status: positive vs negative vs indeterminant. The patient's PD-L1 status will be blinded.

**Accrual Goals**

The accrual goal of this study is to randomize 1,240 eligible patients. Up to two formal interim analyses will be performed when 55% and 85% of the expected deaths across both arms combined have been observed. The final analysis of relapse-free survival will be performed when all patients are off protocol therapy (expected to be one year after the last eligible patients is randomized) and 100% of expected events for relapse-free survival have been observed.

# E1609 Phase III SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

# A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapies Versus High-Dose Interferon Alfa-2b for Resected High-Risk Melanoma

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**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
06/08/2011

**Study Chairs:**
A Tarhini (ECOG-ACRIN), L Flaherty (SWOG)

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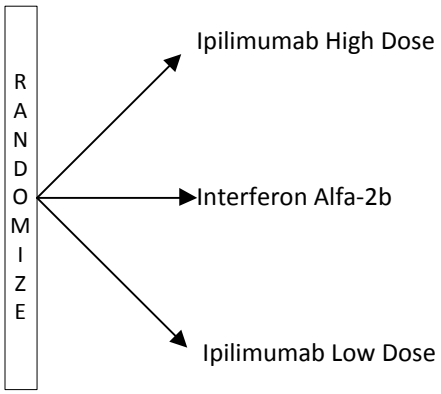
## SCHEMA




**Objectives**

First co-primary endpoint:

To evaluate recurrence-free survival (RFS) between patients randomized to receive post-operative adjuvant ipilimumab given at either 10 mg/kg (high dose ipilimumab; HIP) or 3 mg/kg (low dose ipilimumab; LIP) versus those randomized to receive high dose interferon alfa-2b (HDI) utilizing a hierarchical design assessing HIP versus HDI first and LIP versus HDI second (if the first comparison is significant).

Second co-primary endpoint:

To evaluate overall survival (OS) between patients randomized receive post-operative adjuvant HIP or LIP versus those randomized to receive HDI utilizing a hierarchical design assessing HIP versus HDI first and LIP versus HDI second (if the first comparison is significant).

Secondary endpoints:

To evaluate safety and tolerability of post-operative adjuvant ipilimumab therapy given at either 10 mg/kg or 3 mg/kg.

Among patients enrolled by CCOPs, to compare the global QOL between the ipilimumab arms versus HDI using FACT-G form and to evaluate the effect of treatment-related side effects that may have an impact on the health-related domains of QOL using FACITD and FACT-BRM.

**Patient Population**

Patients must have one of the following: selected Stage III (IIIB/IIIC) or selected Stage IV (M1a/M1b) melanoma of cutaneous origin; unknown primary melanoma presenting with cutaneous, subcutaneous, nodal and/or lung metastases with LDH within the institutional upper limit of normal; recurrence in a regional lymph node basin following resection of an original cutaneous primary; recurrence in the form of satellite/in-transit, distant skin/subcutaneous, nodal or lung metastases following resection of an original cutaneous primary or unknown primary melanoma; recurrence in a regional lymph node basin following a prior complete lymph node dissection and resection of an original cutaneous primary or unknown primary melanoma. All disease must be completely resected with free margins. Patients rendered free of disease by non-surgical means are not eligible. Patients with disease recurrence are eligible provided all relapsed disease has been completely resected with free margins. Patients must be randomized within 12 weeks of their most recent surgical procedure required to render the patient disease-free.

Patients must not have received any adjuvant treatment (chemotherapy, biotherapy, or limb perfusion). Previous radiation is allowed, including radiation following complete resection of disease. Patients must not have received any prior treatment with anti-CTLA4 monoclonal antibodies, CTLA-4 inhibitors/agonists, CD137 agonists, or interferon-alpha. Other forms of prior treatment for melanoma (e.g. IL-2, anti-tumor vaccine, chemotherapy) are allowed if completed prior to the resection(s) performed to render the patient free of disease.

Patients must have adequate hematologic, renal, and hepatic function and an ECOG performance status of 0-1. All females of childbearing potential must have a blood test or urine study to rule out pregnancy. Patients must not have any active infections requiring current treatment with parental antibiotics, autoimmune disorders or conditions that require ongoing treatment with systemic corticosteroids, or a documented history of inflammatory bowel disease (including ulcerative colitis and Crohn's disease) or diverticulitis. Patients must not have had any infectious disease vaccination (e.g. standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) within the past four weeks prior to randomization. Patients must not have active or chronic infection with HIV, hepatitis B, or Hepatitis C. All patients must have negative testing for HIV, HBV, and HCV within four weeks prior to randomization.

Patients must submit tissue samples for central pathology review.

**Stratification/Descriptive Factors**

Treatment randomization will be stratified by AJCC Stage: IIIB vs IIIC vs M1a vs M1b.

**Accrual Goals**

A total of 1,500 patients will be enrolled.

**Summary Statement**

This study is open to accrual of adolescent patients (ages 12-17), but remains permanently closed to adult patients after meeting the protocol specified accrual goals for that subgroup. As of June 30, 2015 there have been 1,673 registrations to this study, which include 499 registrations from SWOG institutions. The complete summary of this study from ECOG-ACRIN is available on the SWOG web site.

# Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| H Lee Moffitt CC | 41 | Irvine, U of CA | 7 |
| Arkansas, U of | 37 | Wayne State Univ | 7 |
| Ohio State Univ | 32 | Cleveland Clinic OH | 6 |
| Sutter Cancer RC | 28 | Loyola University | 6 |
| Baylor Univ Med Ctr | 26 | Montana NCORP | 6 |
| Colorado, U of | 25 | Ozarks NCORP | 6 |
| Los Angeles, U of CA | 22 | Sinai Hospital/San Antonio, U of TX | 6 |
| Arizona MC, U of | 18 | Southeast COR NCORP | 6 |
| Kaiser Vallejo NCORP | 17 | KaiserPermanenteCOL/Kaiser Vallejo NCORP | 5 |
| Utah, U of | 12 | Oregon Hlth Sci Univ | 5 |
| Michigan, U of | 11 | Lahey Hosp & Med Ctr | 4 |
| Cincinnati MC, U of | 10 | Mem Hosp, Co Springs/Colorado, U of | 4 |
| Kansas, U of | 10 | Virginia Mason MC/Northwest NCORP | 4 |
| PCRC NCORP | 10 | Yale University | 4 |
| Rochester, Univ of | 10 | Boston MC MBCCOP | 3 |
| St Luke's Mt State/PCRC NCORP | 10 | Greenville NCORP | 3 |
| Thompson Ca Surv Ctr/San Antonio, U of TX | 10 | Hawaii MU-NCORP | 3 |
| CRC West MI NCORP | 9 | Kansas City NCORP | 3 |
| Carolinas Med Ctr/San Antonio, U of TX | 8 | San Diego, U of CA | 3 |
| Highlands Onc Group/Arkansas, U of | 8 | St Charles Hlth Sys/PCRC NCORP | 3 |
| Northwest NCORP | 8 | All Other Institutions | 35 |
| UF Cancer Center/Arkansas, U of | 8 | **Total (69 Institutions)** | **499** |

# E2607 Phase III SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

# A Phase II Trial of Dasatinib in KIT-Positive Patients with Unresectable Locally Advanced or Stage IV Mucosal, Acral and Vulvovaginal Melanomas

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**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
11/22/2011

**Study Chairs:**
D Lawrence (ECOG-ACRIN), K Margolin (SWOG)

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**Objectives**

To estimate the objective tumor response rate for dasatinib monotherapy in treatment-naive or previously treated KIT-positive patients with advanced or metastatic acral or mucosal melanoma.

To estimate the response duration for dasatinib monotherapy in this patient population.

To estimate the progression-free survival for dasatinib monotherapy.

To evaluate the safety profile of this treatment.

To evaluate the PDGFR expression, and activation of Src Family Kinases in tumor samples and correlate these parameters with response to treatment.

**Patient Population**

Patients must have histologically or cytologically confirmed unresectable Stage IV melanoma that is one of the following subtypes: acral (defined as occurring on the palms, soles, or subungual sites), mucosal, or arising from the vagina and/or vulva. Patients with ocular primaries are not eligible. Patients with a history or clinical evidence of brain metastases must have completed radiation therapy or surgical treatment of brain lesions and have no evidence of CNS progression. Patients must have measurable disease as defined by RECIST. Patients must be c-KIT positive as determined by local assessment or by central review. See protocol for specific instructions.

Patients may have had prior systemic therapy with the exception that prior treatment with targeted therapies directed to c-KIT/PDGFR are not allowed (e.g. imatinib or sunitinib). Patients may have had prior limb perfusion or radiation therapy.

Patients must have adequate hematologic, renal, hepatic, and cardiac function with a performance status of 0-1. Females of childbearing potential are required to have a pregnancy test. Patients must not be taking cytochrome P450 enzyme-inducing antiepileptic drugs. Patients must have adequate blood coagulation with or without therapeutic warfarin.

**Accrual Goals**

A two-stage design will be used. Initially 15 KIT-positive patients will be enrolled. If three or more confirmed responses are observed, an additional 15 KIT-positive patients will be enrolled. To enroll 30 KIT-positive patients will require that approximately 250 patients be screened.

**Summary Statement**

SWOG's support of this study began after it was amended in November, 2011 with a new design which restricted the patient population to c-KIT positive patients. As of June 30, 2015, 22 c-KIT positive patients have been enrolled, including four registrations by SWOG institutions. The complete summary of this study from ECOG-ACRIN is available on the SWOG web site.

# Registration by Institution

Registrations ending June 30, 2015

| Institutions | Total Reg |
|---|---|
| Hawaii MU-NCORP | 2 |
| Kansas City NCORP | 1 |
| Michigan, U of | 1 |
| **Total (3 Institutions)** | **4** |

# EA6134 Phase III SWOG Supported CTSU Study

**Coordinating Group: ECOG-ACRIN**

# A Randomized Phase III Trial of Dabrafenib plus Trametinib followed by Ipilimumab plus Nivolumab at Progression versus Ipilimumab plus Nivolumab followed by Dabrafenib plus Trametinib at Progression in Patients with Advanced $BRAF^{v600}$ Mutant Melanoma

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**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
07/13/2015

**Study Chairs:**
M Atkins (ECOG-ACRIN), B Chmielowski (SWOG)

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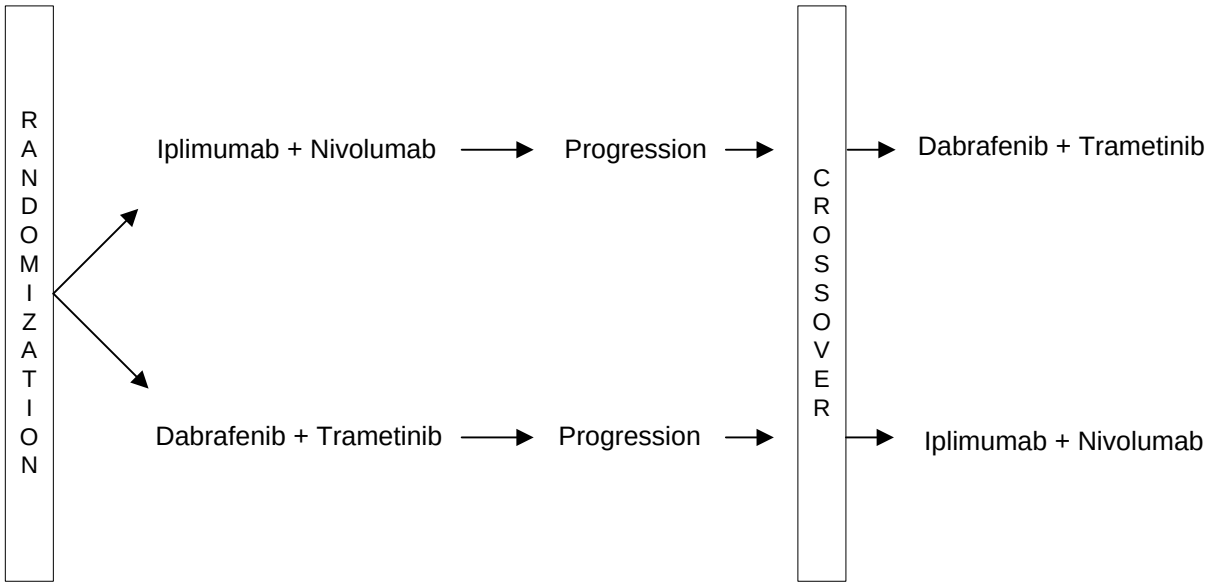
## SCHEMA




**Objectives**

To determine whether initial treatment with either combination ipilimumab + nivolumab (with subsequent dabrafenib in combination with trametinib) or dabrafenib in combination with trametinib (with subsequent ipilimumab + nivolumab) significantly improves two-year overall survival (OS) in patients with unresectable stage III or stage IV $BRAF^{V600}$ mutant melanoma.

To evaluate the impact of initial treatment on overall survival.

To evaluate the anti-tumor activities (RECIST-defined response rate, median progression-free survival) and safety profiles of ipilimumab + nivolumab and dabrafenib + trametinib.

To evaluate the activity (response rate, PFS) and safety of dabrafenib + trametinib in patients who have had disease progression on ipilimumab + nivolumab and in comparison to its activity and safety in ipilimumab + nivolumab naïve patients.

To evaluate the activity of ipilimumab + nivolumab (response rate, PFS) and safety in patients who have had disease progression on dabrafenib + trametinib and in comparison to its activity and safety in dabrafenib + trametinib naïve patients.

To assess the feasibility of crossover to the alternative treatment strategy.

This study also includes objectives related to translational medicine and patient-reported outcomes. Please refer to the protocol for details.

**Patient Population**

Patients must have histological or cytological confirmation of melanoma which is stage IV or unresectable stage III and clearly progressive. Patients must have $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations, identified by an FDA-approved test at a CLIA-certified lab. Patients must have measurable disease as defined by RECIST 1.1. Patients must not have currently active CNS metastases. Patients may have treated brain metastases (with either surgical resection or stereotactic radiosurgery (SRS)) that have been stable on head MRI or contrast CT scan for at least four weeks following treatment and within four weeks prior to randomization, provided they have not have taken any steroids for the purpose of managing their brain metastases for at least 14 days prior to randomization. Patients with only whole brain irradiation for treatment of CNS metastases are ineligible. Patients with a history of RAS mutation-positive tumors are not eligible. Patients must have aggressive melanoma that results in a serum LDH of more than 10 times the institutional upper limit of normal.

Patients may have had prior systemic therapy in the adjuvant setting; however this adjuvant treatment must not have included a CTLA4 or PD1 pathway blocking antibody or a BRAF/MEK inhibitor. Patients must not have received any prior systemic therapy for stage IV disease. Patients may have received prior radiation therapy or surgery.

Patients must have adequate hematologic, hepatic, and renal function and an ECOG performance status of 0-1. Patients must not have any ongoing or active infections requiring parenteral antibiotics. Patients must not have a history of bleeding diathesis or need for concurrent anticoagulation. Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR. Patients must not have a history of or evidence of cardiovascular risks. Patients must not have evidence of active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection. Patients must not be known to be HIV infected. Patients must not have active autoimmune disease or a history of autoimmune disease that might recur. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), are eligible provided they do not require systemic immune suppression treatment. Patients must not be taking any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8. Patients must not have evidence of interstitial lung disease or pneumonitis, or a history of retinal vein occlusion (RVO) or malabsorption, swallowing difficulty, or other conditions that would interfere with the ingestion or absorption of dabrafenib or trametinib. All females of childbearing potential must have a pregnancy test.

**Stratification/Descriptive Factors**

Treatment randomization will be stratified by the following: (1) ECOG performance status: 0 vs 1; (2) serum LDH: normal vs elevated.

**Accrual Goals**

The accrual goal is 270 eligible patients.

**Summary Statement**

This study was activated on July 13, 2015.

# EAY131 Master Protocol / Phase II

## Coordinating Group: ECOG-ACRIN

## NCI-MATCH: Molecular Analysis for Therapy Choice

---

**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
08/12/2015

**Study Chairs:**
K Flaherty (ECOG-ACRIN), P O'Dwyer (ECOG-ACRIN), A Chen (NCI), B Conley (NCI)

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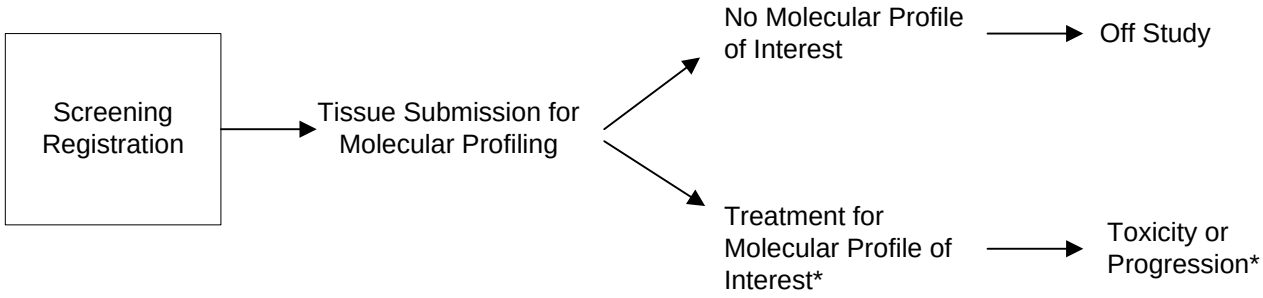
## SCHEMA




*Upon progression or inability to tolerate protocol treatment, patients may be re-screened for additional molecular profiles of interest and corresponding protocol treatment.

**Objectives**

To evaluate the proportion of patients with objective response (OR) to targeted study agent (s) in patients with advanced refractory cancers/lymphomas.

To evaluate the proportion of patients alive and progression free at six months of treatment with targeted study agent in patients with advanced refractory cancers/lymphomas.

To evaluate the time until death or disease progression.

To identify potential predictive biomarkers beyond the genomic alteration by which treatment is assigned or resistance mechanisms using additional genomic, RNA and protein-based assessment platforms.

**Patient Population**

Patients must have histologically documented solid tumors or histologically confirmed diagnosis of lymphoma that has progressed following at least one line of standard systemic therapy and/or for whose disease no standard treatment exists that has been shown to prolong survival. Patients must have measurable disease, have tumor amenable to image guided or direct vision biopsy, and be willing and able to undergo biopsy for molecular profiling.

Patients must not currently be receiving any other investigational agents. Any prior therapy, radiotherapy (except palliative radiation therapy of 30 Gy or less), or major surgery must have been completed at least four weeks prior to treatment on NCI-MATCH and patient must be recovered from adverse events due to prior therapy (except alopecia and lymphopenia). Palliative radiation therapy must have been completed at least two weeks prior to enrollment on a NCI-MATCH treatment subprotocol, and patient must have recovered from any adverse events of this therapy. Patients with brain metastases or primary brain tumors must have completed treatment , surgery, or radiation therapy at least four weeks prior to initial registration. Patients must not require the use of full dose coumarin-derivative anticoagulants such as warfarin. Low molecular weight heparin is permitted for prophylactic or therapeutic use.

Patients must be at least 18 years of age, have an ECOG performance status of 0 or 1 and must be able to swallow tablets. Patients must have adequate hematologic, hepatic, renal, cardiac and marrow function. HIV-positive patients are eligible provided they meet protocol criteria. Each subprotocol will have additional eligibility criteria that will be outlined in Section 2.0 of the agent-specific subprotocol.

**Accrual Goals**

The target screening accrual for this study is approximately 3,000 patients, with the goal of accruing 35 patients in each treatment subprotocol. If after screening 500 patients, the total number of patients with actionable tumor alteration (therefore qualifying for treatment) is below 50, results will be presented to the steering committee for consideration of terminating the trial. Within any given subprotocol, if rate of enrollment is such that it is unlikely accrual can be completed in 7.5 years, then the steering committee may consider terminating accrual in that subgroup due to lack of feasibility. An interim analysis of the assay results will be performed after biopsies from approximately the first 200 patients are processed.

**Summary Statement**

This study activated on August 12, 2015, with ten subprotocols included in the activation. Only sites utilizing the CIRB as their IRB of record will be able to participate in the trial.