MELANOMA COMMITTEE

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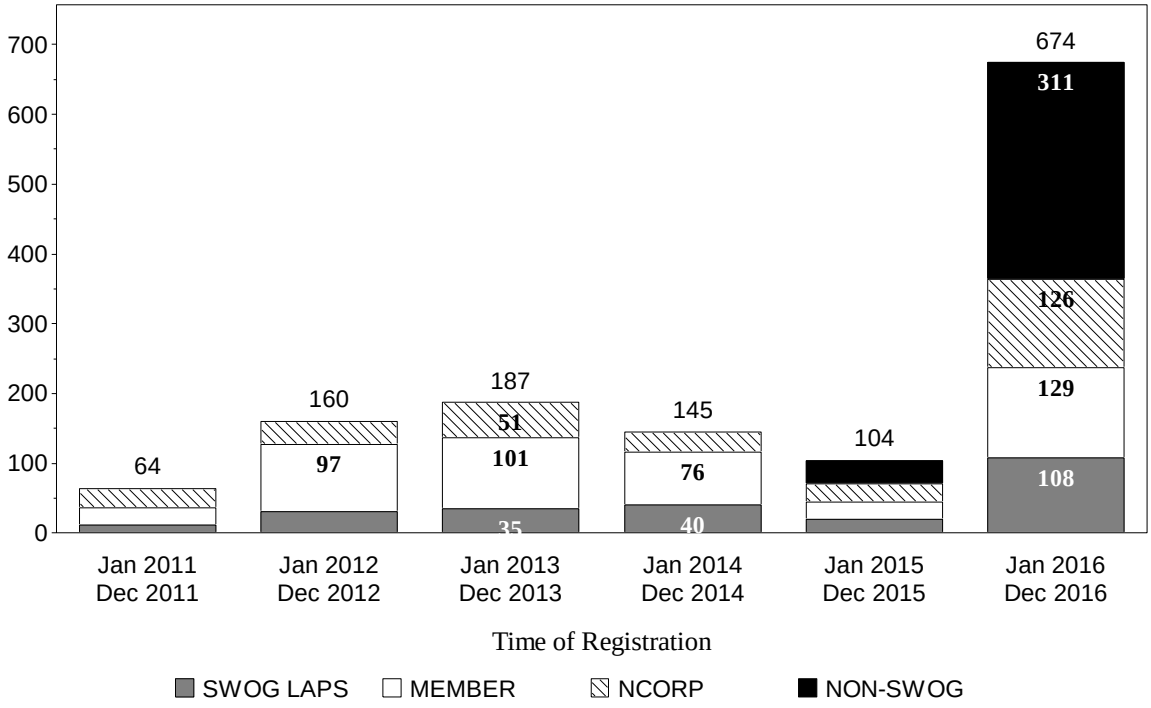
Patient Registrations to Studies

By 12 Month Intervals
MELANOMA COMMITTEE



Screening registrations and registrations to Biologic only studies are excluded

Patient Registrations by Study and Arm

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	Jul 2016 Dec 2016	Jan 2016 Jun 2016	Jul 2015 Dec 2015	All Patients
S1221 Melan, Adv, Dabrafenib + Trametinib + GSK2141795				
Initial Registration				
Dabrafenib/GSK2141795 50mg	0	0	0	3
Dabrafenib/GSK2141795 75mg	0	0	2	9
Dabrafenib + Trametinib 1.5mg + GSK2141795 25mg	0	0	0	4
Dabrafenib + Trametinib 1.5mg + GSK2141795 50 mg	0	0	3	3
Dabrafenib + Trametinib 1.5mg + GSK2141795 75 mg	0	0	3	3
Dabrafenib + Trametinib 2.0mg + GSK2141795 75mg	2	3	0	5
	2	3	8	27
S1320 Melan, Adv, BRAF mut, Intermittent vs Continuous Dabrafenib + Trametinib				
Lead-in Continuous Dosing	23	15	42	125
Randomization				
Continuous Dosing	10	5	23	51
Intermittent Dosing	11	7	20	52
	21	12	43	103
S1404 Melan, Adj, HD-IFN/Ipilimumab vs MK-3475				
Tissue Submission				
Tissue for PD-L1 testing	469	237	8	714
Randomization				
FDA approved regimen	204	97	2	303
MK-3475 (Pembrolizumab)	208	95	2	305
	412	192	4	608
E2607 Melan, Adv, Dasatinib in KIT+ Patients*				
Total Registrations	0	0	1	5
E3612 Melan, Adv, Ipilimumab ± Bevacizumab*				
Total Registrations	1	0	1	5
EA6134 Melan, Adv, BRAF mut, Dabrafenib/Trametinib => Ipilimumab/Nivolumab vs Ipilimumab/Nivolumab => Dabrafenib/Trametinib				
Total Registrations	6	5	2	13
EA6141 Melan, Adv, Nivolumab + Ipilimumab ± GM-CSF*				
Total Registrations	11	4	0	15

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

Non-SWOG Studies with SWOG-Credited Registrations

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Studies with Accrual from July 2015 – December 2016

	SWOG Champion	Date Activated	Date Closed	Total Accrual
E2607 MELAN, Adv, Dasatinib in KIT+ Patients	K Margolin	11/22/11	12/29/15	24
Most Recent Progress Report				
E3612 MELAN, Adv, Ipilimumab ± Bevacizumab		12/13/13		159
Most Recent Progress Report				
EA6134 MELAN, Adv, BRAF mut, Dabrafenib/Trametinib => Ipilimumab/Nivolumab vs Ipilimumab/Nivolumab => Dabrafenib/Trametinib	B Chmielowski	07/13/15		54
Most Recent Progress Report				
EA6141 MELAN, Adv, Nivolumab + Ipilimumab ± GM-CSF	K Kim	03/01/16		152
Most Recent Progress Report				
EAY131 MATCH	V Villalobos	08/12/15		4,121
Most Recent Progress Report				

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

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Study Chairs:
S Ramsey, D Hershman

Statisticians:
J Unger, K Arnold

Data Coordinator:
M Yee

Date Activated:
08/29/2013

Date Closed:
02/15/2017

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.

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 3,061 patients will be accrued to achieve 3,000 eligible patients.

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:
D Salud

Date Activated:
07/12/2013

Date Closed*:
10/31/2016

*Temporary Closure

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 pharmacokinetic 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
Due to the supply of GSK2141795 ending on April 30, 2017, this study was temporarily closed to accrual effective October 31, 2016. All patients currently on treatment will not be able to continue past April 30, 2017. None of the existing cohorts will re-open to accrual. However, a protocol amendment is under development that would replace GSK2141795 with a new AKT inhibitor.

Doublet Regimen:

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.

Nine patients were enrolled to the cohort investigating the two drug combination of dabrafenib and GSK2141795 at the dose level of 75 mg. One patient is currently ineligible, due uncontrolled hypertension. In addition, three eligible patients did not receive any protocol treatment and are not evaluable for any of the study endpoints. Of the remaining five patients, one did not meet the protocol-specified criteria to be considered evaluable for DLTs. There were no DLTs reported for the four evaluable patients on the 75 mg cohort.

Triplet Regimen:

The Phase I portion of this trial investigating the three drug combination of GSK2141795 + dabrafenib + trametinib was activated on February 13, 2015. The first cohort of patients treated at the dose level of 1.5 mg of trametinib and 25 mg of GSK2141795 has been completed. One of these patients did not meet the protocol-specified criteria to be considered evaluable for DLTs and was replaced. No DLTs were observed among the three evaluable patients. Therefore, per protocol, the second cohort of patients to be treated at the dose level of 1.5 mg trametinib and 50 mg GSK2141795 was opened to accrual on August 28, 2015.

The second cohort of three patients treated at the dose level of 1.5 mg trametinib and 50 mg GSK2141795 has been completed. No DLTs were observed. Therefore, per protocol, the third cohort of patients to be treated at the dose level of 1.5 mg trametinib and 75 mg GSK2141795 was opened to accrual on December 15, 2015.

The third cohort of three patients treated at the dose level of 1.5 mg trametinib and 75 mg GSK2141795 has been completed. No DLTs were observed. Therefore, per protocol, the fourth cohort of patients to be treated at the dose level of 2.0 mg trametinib and 75 mg GSK2141795 was opened to accrual on April 15, 2016.

Five patients were enrolled to the fourth cohort. One patient was ineligible due to inadequate hematologic function. Two of the four eligible patients were not evaluable for DLTs. Of the two patients evaluable for DLTs, one patient experienced DLTs due to Grade 3 febrile neutropenia and a Grade 3 Maculo-papular rash that lasted greater than 14 days.

Registration by Institution

Institutions	Total Reg
Los Angeles, U of CA	6
Ohio State Univ	6
Colorado, U of	5
Michigan, U of	5
Prov Portland MC/PCRC NCORP	2
Sutter Cancer RC	2
San Francisco, U-CA	1
Total (7 Institutions)	**27**

Registration, Eligibility, and Evaluability

Patients Enrolled on the Doublet Regimen

Data as of January 18, 2017

	TOTAL	Dabrafenib + GSK2141795 50mg	Dabrafenib + GSK2141795 75mg
NUMBER REGISTERED	12	3	9
INELIGIBLE	1	0	1
ELIGIBLE	11	3	8
Not Analyzable	3	0	3
BASELINE DISEASE STATUS			
Measurable	8	3	5
RESPONSE ASSESSMENT			
Determinable	8	3	5
ADVERSE EVENT ASSESSMENT			
Evaluable	8	3	5
DOSE-LIMITING TOXICITIES			
Evaluable	7	3	4
Not Evaluable	1	0	1

Registration, Eligibility, and Evaluability

Patients Enrolled on the Triplet Regimen

Data as of January 18, 2017

	TOTAL	Dabrafenib + Trametinib 1.5 mg + GSK2141795 25 mg	Dabrafenib + Trametinib 1.5 mg + GSK2141795 50 mg	Dabrafenib + Trametinib 1.5 mg + GSK2141795 75 mg	Dabrafenib + Trametinib 2.0 mg + GSK2141795 75mg
NUMBER REGISTERED	15	4	3	3	5
INELIGIBLE	2	1	0	0	1
ELIGIBLE	13	3	3	3	4
BASELINE DISEASE STATUS					
Measurable	11	3	3	2	3
Non Measurable	2	0	0	1	1
RESPONSE ASSESSMENT					
Determinable	10	3	3	1	3
Not Determinable	1	0	0	1	0
Not Applicable	2	0	0	1	1
ADVERSE EVENT ASSESSMENT					
Evaluable	13	3	3	3	4
DOSE-LIMITING TOXICITIES					
Evaluable	11	3	3	3	2
Not Evaluable	2	0	0	0	2

Patient Characteristics

All Patients Enrolled

Data as of January 18, 2017

	Total (n=21)	
AGE		
Median	58.7	
Minimum	18.5	
Maximum	77.1	
SEX		
Males	13	62%
Females	8	38%
HISPANIC		
No	20	95%
Unknown	1	5%
RACE		
White	20	95%
Unknown	1	5%
PRIOR BRAF INHIBITOR		
Yes	13	62%
No	7	33%
Data pending	1	5%
TYPE OF CANCER		
Melanoma	17	81%
Lung	3	14%
Thyroid	1	5%

Treatment Summary

Patients Enrolled on the Doublet Regimen

Data as of January 18, 2017

	Total
NUMBER ON PROTOCOL TREATMENT	0
NUMBER OFF PROTOCOL TREATMENT	8
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	1
Refusal unrelated to adverse event	0
Progression/relapse	7
Death	0
Other - not protocol specified	0
Reason under review	0
MAJOR PROTOCOL DEVIATIONS	0

Treatment Summary

Patients Enrolled on the Triplet Regimen

Data as of January 18, 2017

	Total
NUMBER ON PROTOCOL TREATMENT	5
NUMBER OFF PROTOCOL TREATMENT	8
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	2
Refusal unrelated to adverse event	0
Progression/relapse	5
Death	1
Other - not protocol specified	0
Reason under review	0
MAJOR PROTOCOL DEVIATIONS	0

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

Patients Enrolled on the Doublet Regimen

Adverse Events Unlikely or Not Related to Treatment Excluded

Registrations ending December 31, 2016; Data as of January 18, 2017

	Total (n=8) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
Alopecia	7	1	0	0	0	0
Anemia	7	0	1	0	0	0
Anorexia	5	2	1	0	0	0
Arthralgia	7	1	0	0	0	0
Chest wall pain	7	1	0	0	0	0
Chills	6	2	0	0	0	0
Constipation	7	1	0	0	0	0
Cough	7	1	0	0	0	0
Diarrhea	7	0	1	0	0	0
Dizziness	6	2	0	0	0	0
Dry skin	7	1	0	0	0	0
Edema limbs	6	2	0	0	0	0
Erythema multiforme	7	1	0	0	0	0
Fatigue	3	5	0	0	0	0
Fever	5	2	1	0	0	0
Flu like symptoms	6	2	0	0	0	0
Flushing	7	1	0	0	0	0
Hand-Foot syndrome	6	2	0	0	0	0
Headache	6	2	0	0	0	0
Hyperglycemia	7	0	0	1	0	0
Hyperhidrosis	7	1	0	0	0	0
Hypernatremia	7	1	0	0	0	0
Hypokalemia	7	1	0	0	0	0

	Total (n=8) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
Hyponatremia	7	0	0	1	0	0
Hypophosphatemia	7	0	1	0	0	0
Hypotension	7	1	0	0	0	0
Inj/poisoning/proced comp-Other	7	1	0	0	0	0
Insomnia	7	1	0	0	0	0
Lymphocyte count decreased	5	2	1	0	0	0
Myalgia	7	1	0	0	0	0
Nail discoloration	7	1	0	0	0	0
Nail ridging	7	1	0	0	0	0
Nausea	4	4	0	0	0	0
Non-cardiac chest pain	7	1	0	0	0	0
Pain	7	1	0	0	0	0
Pain in extremity	7	1	0	0	0	0
Pain of skin	7	1	0	0	0	0
Papulopustular rash	7	1	0	0	0	0
Platelet count decreased	7	1	0	0	0	0
Rash maculo-papular	6	2	0	0	0	0
Renal/urinary disorders-Other	7	1	0	0	0	0
Skin/subq tissue ds-Other	6	1	0	1	0	0
Telangiectasia	7	1	0	0	0	0
Tremor	7	1	0	0	0	0
Vasc disorders-Other	7	0	0	1	0	0
Vomiting	6	2	0	0	0	0
Weight loss	6	1	1	0	0	0
MAX. GRADE ANY ADVERSE EVENT	1	3	2	2	0	0

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

Patients Enrolled on the Triplet Regimen

Adverse Events Unlikely or Not Related to Treatment Excluded

Data as of January 18, 2017

	Total (n=13) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
ALT increased	11	2	0	0	0	0
AST increased	11	2	0	0	0	0
Abdominal pain	12	1	0	0	0	0
Alkaline phosphatase increased	12	1	0	0	0	0
Anorexia	12	0	1	0	0	0
Capillary leak syndrome	12	0	0	1	0	0
Confusion	12	0	1	0	0	0
Constipation	12	1	0	0	0	0
Dehydration	12	1	0	0	0	0
Depression	12	1	0	0	0	0
Diarrhea	11	2	0	0	0	0
Dry skin	12	1	0	0	0	0
Dyspepsia	12	1	0	0	0	0

	Total (n=13) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**
Ear/labyrinth disorders-Other	12	0	1	0	0	0
Fatigue	8	4	1	0	0	0
Fever	9	0	3	1	0	0
Generalized muscle weakness	12	1	0	0	0	0
Headache	11	0	1	1	0	0
Hypertension	11	0	1	1	0	0
Hyponatremia	11	0	0	2	0	0
Joint effusion	12	1	0	0	0	0
Lymphocyte count decreased	11	0	0	2	0	0
Myalgia	12	1	0	0	0	0
Nausea	7	2	4	0	0	0
Neutrophil count decreased	12	1	0	0	0	0
Peripheral sensory neuropathy	12	1	0	0	0	0
Rash acneiform	12	0	1	0	0	0
Rash maculo-papular	9	2	0	2	0	0
Tumor pain	12	1	0	0	0	0
Upper respiratory infection	12	0	1	0	0	0
Vomiting	10	1	1	1	0	0
Weight loss	12	1	0	0	0	0
MAX. GRADE ANY ADVERSE EVENT	1	2	3	7	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)

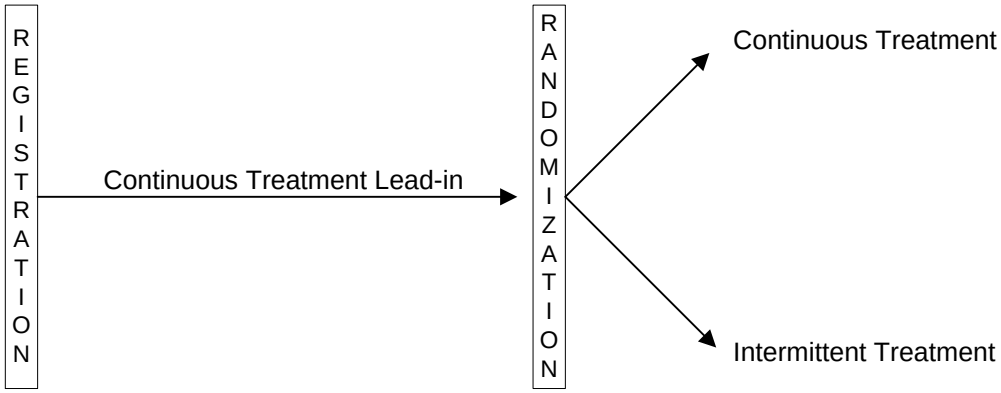
Date Activated:
07/22/2014

Study Chairs:
A Algazi, A Daud, R Lo, J Mehnert (ECOG-ACRIN)

Statisticians:
M Othus, J Moon, M Wu

Data Coordinator:
D Salud

SCHEMA



Objectives

To compare progression-free survival with intermittent dosing versus continuous dosing of dabrafenib and trametinib among patients with metastatic BRAF$^{V600E/K}$ 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). $BRAF^{V600}$ 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

Accrual to this study has been slower then anticipated. In an effort to increase accrual, the protocol has been amended to allow $BRAF^{V600E/K}$ mutation to be documented by any assay as long as it is performed in a CLIA-certified laboratory.

The study was temporarily closed to accrual by CTEP on February 2, 2016 due to drug supply issues for both dabrafenib and trametinib. However, drug supplies were sufficient enough so that enrolled patients could continue to receive protocol treatment. The issue was resolved and the study re-opened to accrual on April 11, 2016.

As of December 31, 2016, 125 patients have been registered. Seven patients are currently ineligible for the following reasons: not having a V600E or V600K BRAF mutation (2), inadequate performance status (1), inadequate cardiac function (1), inadequate hepatic function (1), and untreated brain metastases (1). In addition, one eligible patient who refused protocol treatment and was never randomized, is not evaluable for any of the study endpoints.

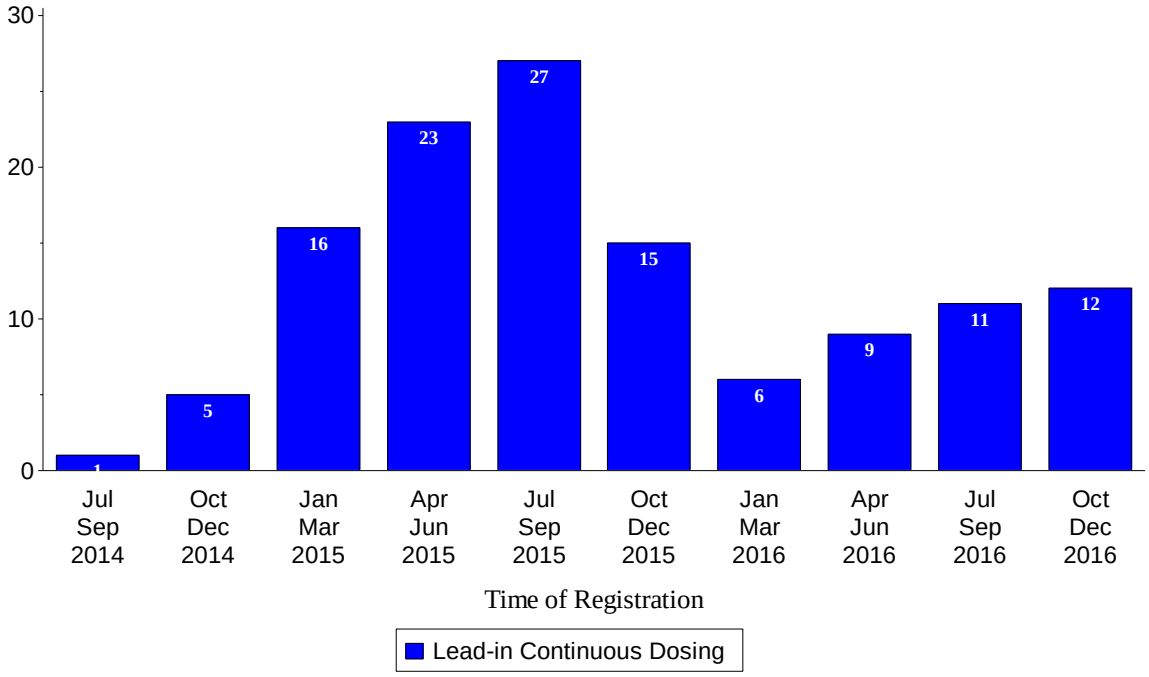
A total of 114 patients have been assessed for adverse events related to lead-in continuous dosing. There has been one treatment-related death due to sepsis. This patient also experienced Grade 4 acute kidney injury and Grade 4 ejection fraction decrease.

A total of 103 patients have been randomized between intermittent and continuous dosing. Four patients are currently ineligible for the following reasons: ineligible for the trial at the initial

registration (3), and disease progression during the lead-in continuous dosing phase (1).

On the continuous dosing arm, 46 patients have been assessed for adverse events. Two patients have experienced Grade 4 treatment-related adverse events, one due to anemia and increases in ALT and AST, and the other due to dyspnea. On the intermittent dosing arm, 43 patients have been assessed for adverse events. Two patients have experienced a Grade 4 treatment-related adverse events, one due to fever, and the other due to increased lipase.

Initial Registrations By 3 Month Intervals



Registration by Institution

Registrations ending December 31, 2016

Institutions	Total Reg	Institutions	Total Reg
ECOG-ACRIN	34	Colorado, U of	2
Kaiser Perm NCORP	14	Los Angeles, U of CA	2
Alliance	10	Michigan, U of	2
San Francisco, U-CA	8	Ozarks NCORP	2
NRG	7	Wichita NCORP	2
Kansas, U of	5	Boston Medical Ctr	1
Ohio State Univ	5	CORA NCORP	1
Utah, U of	5	CRC West MI NCORP	1
Arkansas, U of	4	Lahey Hosp & Med Ctr	1
Loyola University	4	Nevada CRF NCORP	1
Southeast COR NCORP	4	PCRC NCORP	1
Heartland NCORP	3	UF Cancer Center/Arkansas, U of	1
KaiserPermanenteSCAL/Kaiser Perm NCORP	3	**Total (26 Institutions)**	**125**
Arizona MC, U of	2		

Registration, Eligibility, and Evaluability

Lead-In Continuous Dosing

Registrations ending December 31, 2016; Data as of January 26, 2017

	Lead-in Continuous Dosing
NUMBER REGISTERED	125
INELIGIBLE	7
ELIGIBLE	118
Analyzable, Pend. Elig.	2
Not Analyzable	1
ADVERSE EVENT ASSESSMENT	
Evaluable	114
Too Early	3

Treatment Summary

Lead-In Continuous Dosing

Registrations ending December 31, 2016; Data as of January 26, 2017

	Lead-in Continuous Dosing
NUMBER ON PROTOCOL TREATMENT	5
NUMBER OFF PROTOCOL TREATMENT	112
REASON OFF TREATMENT	
Treatment completed as planned	90
Adverse Event or side effects	6
Refusal unrelated to adverse event	1
Progression/relapse	5
Death	2
Other - not protocol specified	0
Reason under review	8
MAJOR PROTOCOL DEVIATIONS	0

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

Lead-In Continuous Dosing

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 December 31, 2016; Data as of January 26, 2017

	Lead-in Continuous Dosing (n=114) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**
AST increased	111	3	0	0
Abdominal pain	113	1	0	0
Acute kidney injury	112	1	1	0
Anemia	113	1	0	0
Anorexia	112	2	0	0
Blood bilirubin increased	113	1	0	0
Blood/lymph disorder-Other	113	1	0	0
Cardiac troponin T increased	113	1	0	0
Constipation	113	1	0	0
Dehydration	109	5	0	0
Diarrhea	112	2	0	0
ECG QT corrected int prolong	113	1	0	0
Ejection fraction decreased	113	0	1	0
Epistaxis	113	1	0	0
Erythema multiforme	113	1	0	0
Fatigue	112	2	0	0
Febrile neutropenia	113	1	0	0
Fever	113	1	0	0

	Lead-in Continuous Dosing (n=114) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**
Fracture	113	1	0	0
Generalized muscle weakness	113	1	0	0
Hypertension	113	1	0	0
Hyponatremia	111	3	0	0
Hypoxia	113	1	0	0
Lipase increased	112	2	0	0
Lymphocyte count decreased	113	1	0	0
Metab/nutrition disorders-Other	113	1	0	0
Mucositis oral	113	1	0	0
Nausea	112	2	0	0
Neutrophil count decreased	111	3	0	0
Proteinuria	113	1	0	0
Rash acneiform	112	2	0	0
Rash maculo-papular	113	1	0	0
Sepsis	113	0	0	1
Skin/subq tissue ds-Other	113	1	0	0
Urinary tract infection	113	1	0	0
Vasc disorders-Other	113	1	0	0
Vomiting	113	1	0	0
MAX. GRADE ANY ADVERSE EVENT	83	30	0	1

Registration, Eligibility, and Evaluability

Randomization

Registrations ending December 31, 2016; Data as of January 26, 2017

	TOTAL	Continuous Dosing	Intermittent Dosing
NUMBER REGISTERED	103	51	52
INELIGIBLE	4	2	2
ELIGIBLE	99	49	50
Analyzable, Pend. Elig.	5	2	3
RESPONSE ASSESSMENT			
Determinable	84	42	42
Too Early	15	7	8
ADVERSE EVENT ASSESSMENT			
Evaluable	89	46	43
Too Early	10	3	7

Patient Characteristics

Randomization

Registrations ending December 31, 2016; Data as of January 26, 2017

	Continuous Dosing (n=49)		Intermittent Dosing (n=50)	
AGE				
Median	59.2		65.3	
Minimum	22.8		26.3	
Maximum	81.3		88.8	
SEX				
Males	32	65%	36	72%
Females	17	35%	14	28%
HISPANIC				
Yes	0	0%	1	2%
No	49	100%	49	98%
RACE				
White	49	100%	49	98%
Multi-Racial	0	0%	1	2%
PERFORMANCE STATUS				
0	29	59%	32	64%
1	19	39%	18	36%
Data pending	1	2%	0	0%
PRIMARY TYPE				
Cutaneous	42	86%	36	72%
Unknown primary	5	10%	13	26%
Data pending	2	4%	1	2%
STAGE				
III	5	10%	6	12%
IV	44	90%	44	88%
SITE(S) OF DISTANT METASTASES				
Bone	8	16%	10	20%
Brain/CNS	3	6%	3	6%
Liver	16	33%	12	24%
Lymph node, skin, soft tissue	29	59%	26	52%
Lung	24	49%	26	52%
Other, visceral	12	24%	13	26%
Other non-visceral	8	16%	7	14%
Data pending	5	10%	6	12%
LDH				
Elevated (>IULN)	20	41%	21	42%
Normal	29	59%	29	58%

	Continuous Dosing (n=49)		Intermittent Dosing (n=50)	
PRIOR IMMUNE CHECKPOINT INHIBITOR				
Yes	12	24%	13	26%
No	37	76%	37	74%
PRIOR BIOLOGIC THERAPY				
No	15	31%	22	44%
Yes	2	4%	2	4%
Data pending	32	65%	26	52%
PRIOR CHEMOTHERAPY				
No	17	35%	20	40%
Yes	2	4%	4	8%
Data pending	30	61%	26	52%
PRIOR IMMUNOTHERAPY				
No	14	29%	17	34%
Yes	9	18%	9	18%
Data pending	26	53%	24	48%
PRIOR RADIATION THERAPY				
No	45	92%	35	70%
Yes	4	8%	15	30%
PRIOR SURGERY				
No	12	24%	10	20%
Yes	37	76%	40	80%

Treatment Summary

Randomization

Registrations ending December 31, 2016; Data as of January 26, 2017

	Total
NUMBER ON PROTOCOL TREATMENT	36
NUMBER OFF PROTOCOL TREATMENT	63
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	8
Refusal unrelated to adverse event	2
Other	4
Reason under review	3
MAJOR PROTOCOL DEVIATIONS	0

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

Randomization

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 December 31, 2016; Data as of January 26, 2017

	Continuous Dosing (n=46) Grade				Intermittent Dosing (n=43) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
ALT increased	45	0	1	0	43	0	0	0
AST increased	43	2	1	0	42	1	0	0
Anemia	45	0	1	0	42	1	0	0
Chills	45	1	0	0	42	1	0	0
Confusion	46	0	0	0	42	1	0	0
Dehydration	45	1	0	0	43	0	0	0
Diarrhea	44	2	0	0	43	0	0	0
Dry skin	45	1	0	0	43	0	0	0
Dyspnea	45	0	1	0	43	0	0	0
Ejection fraction decreased	44	2	0	0	41	2	0	0
Fatigue	42	4	0	0	41	2	0	0
Fever	43	3	0	0	42	0	1	0
Flu like symptoms	45	1	0	0	43	0	0	0
Generalized muscle weakness	44	2	0	0	42	1	0	0
Glucose intolerance	45	1	0	0	43	0	0	0
Hand-Foot syndrome	45	1	0	0	43	0	0	0
Hypercalcemia	46	0	0	0	42	1	0	0
Hyperglycemia	43	3	0	0	42	1	0	0
Hypertension	43	3	0	0	42	1	0	0
Hyponatremia	45	1	0	0	42	1	0	0
Hypotension	46	0	0	0	42	1	0	0
Infections/infestations-Other	46	0	0	0	42	1	0	0
LV systolic dysfunction	45	1	0	0	43	0	0	0
Lipase increased	45	1	0	0	40	2	1	0
Localized edema	45	1	0	0	43	0	0	0
Lymphocyte count decreased	44	2	0	0	43	0	0	0
Mucositis oral	45	1	0	0	43	0	0	0
Neutrophil count decreased	44	2	0	0	43	0	0	0
Platelet count decreased	45	1	0	0	43	0	0	0
Rash acneiform	45	1	0	0	43	0	0	0
Rash maculo-papular	45	1	0	0	43	0	0	0
Resp/thoracic/mediastinal ds	45	1	0	0	43	0	0	0
Retinal detachment	46	0	0	0	42	1	0	0
Serum amylase increased	46	0	0	0	41	2	0	0
Skin/subq tissue ds-Other	45	1	0	0	43	0	0	0
Syncope	45	1	0	0	43	0	0	0
Thromboembolic event	45	1	0	0	43	0	0	0
Tx related secondary malig	46	0	0	0	42	1	0	0
White blood cell decreased	44	2	0	0	43	0	0	0
MAX. GRADE ANY ADVERSE EVENT	28	16	2	0	29	12	2	0

1404 Phase III

Coordinating Group: SWOG

A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma

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

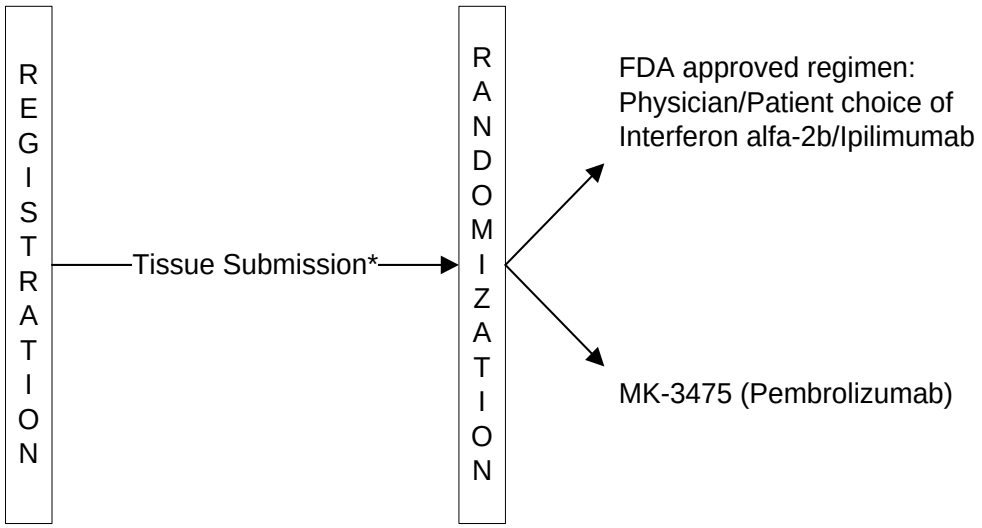
Date Activated:
10/15/2015

Study Chairs:
K Grossmann, S Patel, A Tarhini (ECOG-ACRIN),
T Petrella (CCTG)

Statisticians:
M Othus, H Li, J Moon

Data Coordinator:
D Heaney

SCHEMA



*PD-L1 status determined by central laboratory and blinded to the investigator and patient

Objectives

Co-Primary Objectives:

To compare overall survival (OS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

To compare OS of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab) among patients who are PD-L1 positive.

To compare relapse-free survival (RFS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

To compare RFS of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab) among patients who are PD-L1 positive.

Secondary Objectives:

To estimate OS and RFS for patients who are PD-L1 negative or PD-L1 indeterminate in this population.

To compare OS and RFS between the two arms 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 regimens.

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 basin 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 must have available and be willing to submit adequate tissue for PD-L1 testing.

Patients may have received prior radiotherapy, including after the surgical resection that rendered the patient disease-free. Patients must not have received neoadjuvant treatment for their melanoma. Patients must not have received prior immunotherapy, including but not limited to ipilimumab, interferon alfa-2b, pegylated interferon, high dose IL-2, anti-PD-1, anti-PD-L1 intra-tumoral or vaccine therapies. 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 active autoimmune disease that has required systemic treatment in the past two years.Patients must not have an active infection requiring systemic therapy. Patients must not have pneumonitis or a history of non-infectious pneumonitis that required steroids. 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.

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 indeterminate; (3) planned control arm regimen: high dose interferon vs ipilimumab.

Accrual Goals

The accrual goal of this study is to randomize 1,240 eligible patients. Up to two formal interim analyses of overall survival will be performed when 55% and 85% of the expected deaths across both arms combined have been observed. There will be no interim analyses of relapse-free survival (RFS) and the final analysis of RFS is expected to be one year after the last eligible patients is randomized.

Summary Statement

As of December 31, 2016, a total of 714 patients have been registered to the PD-L1 status screening

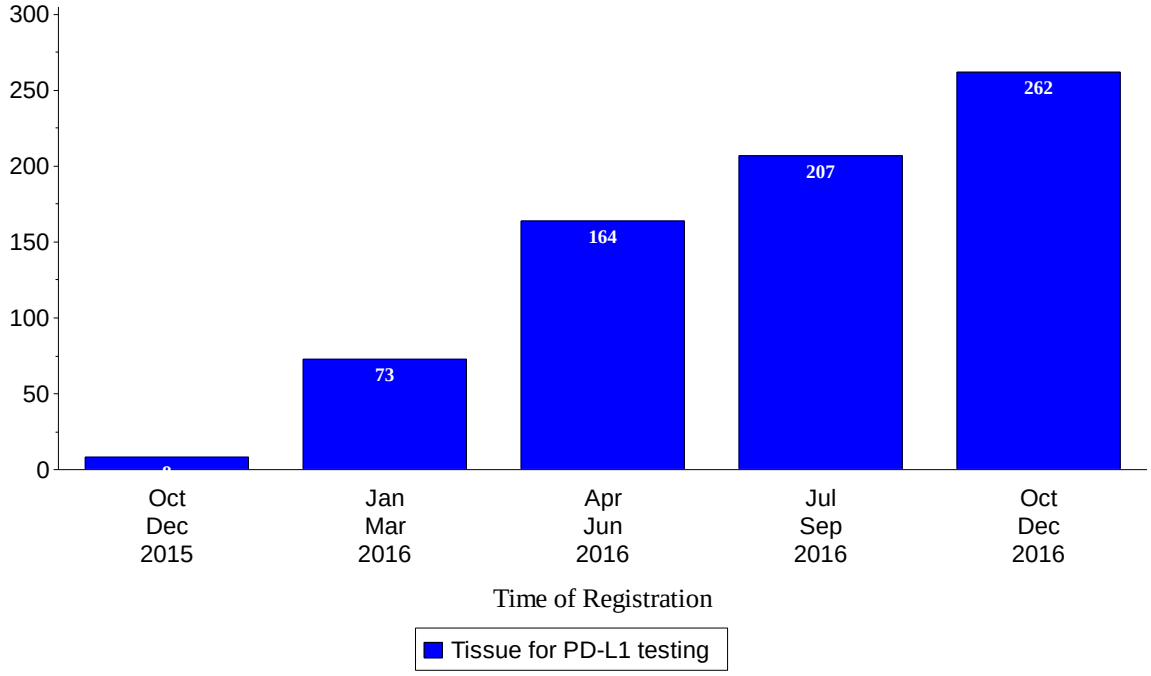
step. Five patients are currently ineligible. Two due to incorrect stage of disease, two due to incomplete resection of disease, and one due to lack of adequate tissue for PD-L1 testing.

A total of 608 patients have been randomized, including one who was ineligible at the screening step. Thirty-three patients, 29 of them randomized to the control arm, did not receive any protocol treatment, coded as major protocol deviations, and are not evaluable for adverse events.

On the control arm, 209 patients have been assessed for adverse events. There have been two treatment related deaths, one due to enterocolitis, the other due to respiratory failure along with Grade 4 sepsis; both patients were receiving ipilimumab. An additional 14 patients have experienced treatment-related Grade 4 adverse events. These included seven patients who received high-dose interferon: increased CPK (1), increased AST and ALT (1), and hematologic adverse events (5), and seven patients who received ipilimumab: one due to pancreatitis, colitis and an autoimmune disorder (autoimmune coltis), one due to increased CPK, one due to increased ALT, one due to hyponatremia, one due to peripheral motor and sensory neuropathy, one due to colitis, and one due to increased lipase.

On the pembrolizumab arm, 245 patients have been assessed for adverse events. Two patients have experienced treatment-related Grade 4 adverse events due to bronchial infection, dyspnea, wheezing and bronchospasm, the other due to episcleritis (coded as "Eye disorders, other").

Initial Registrations By 3 Month Intervals



Registration by Institution

Initial Registration

Registrations ending December 31, 2016

Institutions	Total Reg	Institutions	Total Reg
ECOG-ACRIN	161	PCRC NCORP	6
Alliance	90	Wichita NCORP	6
NRG	53	Columbus NCORP	5
CCTG	46	Oregon Hlth Sci Univ	5
Kaiser Perm NCORP	34	Southeast COR NCORP	5
H Lee Moffitt CC	27	Wayne State Univ	5
Colorado, U of	25	Arizona MC, U of	4
Utah, U of	24	CORA NCORP	4
MD Anderson CC	22	Northwest NCORP	4
Ohio State Univ	21	Rochester, Univ of	4
Heartland NCORP	14	TX Oncology-Central/San Antonio, U of TX	4
Kansas, U of	14	Cincinnati MC, U of	3
Cleveland Clinic OH	13	Lahey Hosp & Med Ctr	3
Los Angeles, U of CA	13	Mt Sinai Med Ctr	3
CRC West MI NCORP	12	San Diego, U of CA	3
Georgia NCORP	10	UF Cancer Center/Arkansas, U of	3
Michigan, U of	10	Montana NCORP	2
Baylor Univ Med Ctr	9	Ozarks NCORP	2
Northwestern Univ	9	Sutter Cancer RC	2
Cedars-Sinai Med Ctr	6	Yale University	2
City of Hope Med Ctr	6	All Other Institutions	8
Dayton NCORP	6	**Total (51 Institutions)**	**714**
New Mexico MU-NCORP	6		

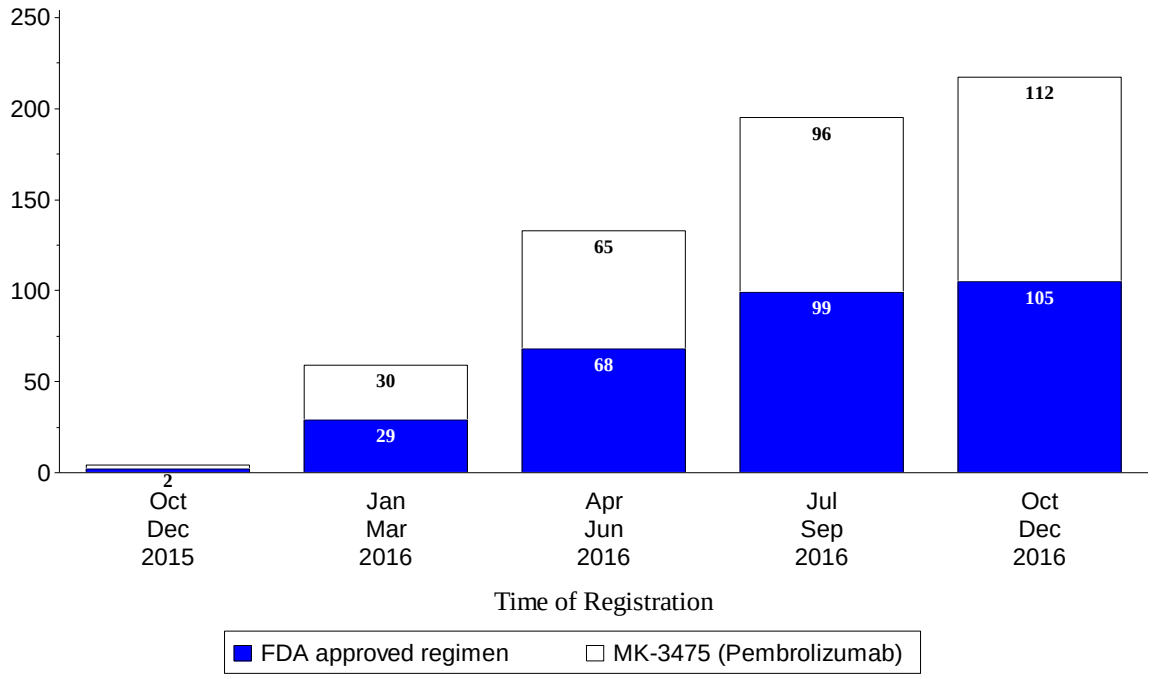
Registration, Eligibility, and Evaluability

Initial Registration

Registrations ending December 31, 2016; Data as of January 26, 2017

	Tissue for PD -L1 testing
NUMBER REGISTERED	714
INELIGIBLE	5
ELIGIBLE	709
Analyzable, Pend. Elig.	132

Randomization By 3 Month Intervals



Registration by Institution

Randomization

Registrations ending December 31, 2016

Institutions	Total Reg	Institutions	Total Reg
ECOG-ACRIN	138	Wichita NCORP	6
Alliance	79	Cedars-Sinai Med Ctr	5
NRG	42	New Mexico MU-NCORP	5
CCTG	35	Arizona MC, U of	4
Kaiser Perm NCORP	31	Columbus NCORP	4
H Lee Moffitt CC	25	CORA NCORP	4
Utah, U of	20	Northwest NCORP	4
Ohio State Univ	19	Oregon Hlth Sci Univ	4
Colorado, U of	18	Rochester, Univ of	4
MD Anderson CC	17	Southeast COR NCORP	4
Kansas, U of	12	Wayne State Univ	4
Los Angeles, U of CA	12	Cincinnati MC, U of	3
Heartland NCORP	11	Lahey Hosp & Med Ctr	3
Cleveland Clinic OH	10	San Diego, U of CA	3
Baylor Univ Med Ctr	9	TX Oncology-Central/San Antonio, U of TX	3
CRC West MI NCORP	9	UF Cancer Center/Arkansas, U of	3
Georgia NCORP	9	Montana NCORP	2
Michigan, U of	9	Ozarks NCORP	2
Northwestern Univ	7	Sutter Cancer RC	2
City of Hope Med Ctr	6	Yale University	2
Dayton NCORP	6	All Other Institutions	7
PCRC NCORP	6	**Total (49 Institutions)**	**608**

Registration, Eligibility, and Evaluability

Randomization

Registrations ending December 31, 2016; Data as of January 26, 2017

	TOTAL	FDA approved regimen	MK-3475 (Pembrolizumab)
NUMBER REGISTERED	608	303	305
INELIGIBLE	1	1	0
ELIGIBLE	607	302	305
Analyzable, Pend. Elig.	59	34	25
ADVERSE EVENT ASSESSMENT			
Evaluable	454	209	245
Not Evaluable	33	29	4
Too Early	120	64	56

Patient Characteristics

Randomization

Registrations ending December 31, 2016; Data as of January 26, 2017

	FDA approved regimen (n=286)		MK-3475 (Pembrolizumab) (n=293)	
AGE				
Median	56.8		56.7	
Minimum	18.3		21.4	
Maximum	86.4		81.4	
SEX				
Males	159	56%	163	56%
Females	127	44%	130	44%
HISPANIC				
Yes	8	3%	12	4%
No	268	94%	271	92%
Unknown	10	3%	10	3%
RACE				
White	273	95%	278	95%
Black	2	1%	2	1%
Asian	0	0%	1	0%
Unknown	11	4%	12	4%
STAGE				
IIIA	26	9%	32	11%
IIIB	144	50%	146	50%
IIIC	96	34%	97	33%
IV	20	7%	18	6%
PERFORMANCE STATUS				
0	239	84%	253	86%
1	47	16%	40	14%

Treatment Summary

Randomization

Registrations ending December 31, 2016; Data as of January 26, 2017

	Total
NUMBER ON PROTOCOL TREATMENT	396
NUMBER OFF PROTOCOL TREATMENT	211
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	99
Refusal unrelated to adverse event	36
Other	9
Reason under review	27
MAJOR PROTOCOL DEVIATIONS	33

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

Randomization

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 December 31, 2016; Data as of January 26, 2017

	FDA approved regimen (n=209) Grade				MK-3475 (Pembrolizumab) (n=245) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
ALT increased	193	14	2	0	242	3	0	0
AST increased	197	11	1	0	241	4	0	0
Abdominal pain	207	2	0	0	245	0	0	0
Acidosis	208	1	0	0	245	0	0	0
Acute kidney injury	208	1	0	0	245	0	0	0
Adrenal insufficiency	208	1	0	0	244	1	0	0
Alkaline phosphatase increased	208	1	0	0	245	0	0	0
Anemia	209	0	0	0	244	1	0	0
Anorexia	208	1	0	0	245	0	0	0
Anxiety	207	2	0	0	245	0	0	0
Arthralgia	208	1	0	0	245	0	0	0
Atelectasis	208	1	0	0	245	0	0	0
Atrial fibrillation	208	1	0	0	245	0	0	0
Atrial flutter	209	0	0	0	244	1	0	0
Autoimmune disorder	208	0	1	0	245	0	0	0
Blood/lymph disorder-Other	208	1	0	0	245	0	0	0
Bone pain	208	1	0	0	245	0	0	0
Bronchial infection	209	0	0	0	244	0	1	0
Bronchospasm	209	0	0	0	244	0	1	0
CPK increased	205	2	2	0	244	1	0	0
Cardiac disorder-Other	208	1	0	0	245	0	0	0
Cardiac troponin T increased	208	1	0	0	245	0	0	0
Colitis	204	3	2	0	243	2	0	0

	FDA approved regimen (n=209) Grade				MK-3475 (Pembrolizumab) (n=245) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Confusion	209	0	0	0	244	1	0	0
Cough	209	0	0	0	244	1	0	0
Dehydration	208	1	0	0	245	0	0	0
Depression	206	3	0	0	245	0	0	0
Diarrhea	194	15	0	0	242	3	0	0
Dizziness	208	1	0	0	245	0	0	0
Dyspnea	205	4	0	0	244	0	1	0
Encephalopathy	209	0	0	0	244	1	0	0
Endocrine disorders-Other	208	1	0	0	244	1	0	0
Enterocolitis	207	1	0	1	245	0	0	0
Eye disorders - Other	209	0	0	0	244	0	1	0
FEV1 decreased	209	0	0	0	244	1	0	0
Fatigue	195	14	0	0	245	0	0	0
Flu like symptoms	208	1	0	0	245	0	0	0
GI disorders-Other	208	1	0	0	245	0	0	0
Generalized muscle weakness	207	2	0	0	245	0	0	0
Headache	205	4	0	0	244	1	0	0
Hepatitis viral	208	1	0	0	245	0	0	0
Hyperglycemia	206	3	0	0	245	0	0	0
Hypersomnia	208	1	0	0	245	0	0	0
Hypertension	205	4	0	0	245	0	0	0
Hypertriglyceridemia	205	4	0	0	245	0	0	0
Hypokalemia	207	2	0	0	245	0	0	0
Hyponatremia	205	3	1	0	245	0	0	0
Hypophosphatemia	207	2	0	0	244	1	0	0
Hypoxia	207	2	0	0	245	0	0	0
Infusion related reaction	208	1	0	0	245	0	0	0
Insomnia	208	1	0	0	245	0	0	0
Leukocytosis	208	1	0	0	245	0	0	0
Lipase increased	207	1	1	0	245	0	0	0
Lung infection	209	0	0	0	244	1	0	0
Lymphocyte count decreased	203	6	0	0	244	1	0	0
MS/connective tissue disorder	209	0	0	0	244	1	0	0
Myalgia	208	1	0	0	245	0	0	0
Myositis	208	1	0	0	244	1	0	0
Nausea	203	6	0	0	245	0	0	0
Neutrophil count decreased	181	23	5	0	245	0	0	0
Pain	208	1	0	0	245	0	0	0
Pain of skin	209	0	0	0	244	1	0	0
Pancreatitis	208	0	1	0	244	1	0	0
Peripheral motor neuropathy	208	0	1	0	245	0	0	0
Peripheral sensory neuropathy	208	0	1	0	245	0	0	0
Pleural effusion	208	1	0	0	245	0	0	0
Proteinuria	209	0	0	0	244	1	0	0
Pruritus	205	4	0	0	245	0	0	0
Rash maculo-papular	203	6	0	0	244	1	0	0
Rash pustular	208	1	0	0	245	0	0	0
Respiratory failure	208	0	0	1	245	0	0	0
Sepsis	208	0	1	0	245	0	0	0
Sinus tachycardia	208	1	0	0	245	0	0	0

	FDA approved regimen (n=209) Grade				MK-3475 (Pembrolizumab) (n=245) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**	**<=2**	**3**	**4**	**5**
Skin infection	208	1	0	0	245	0	0	0
Skin/subq tissue ds-Other	208	1	0	0	245	0	0	0
Syncope	207	2	0	0	245	0	0	0
Vomiting	206	3	0	0	245	0	0	0
Weight loss	208	1	0	0	245	0	0	0
Wheezing	209	0	0	0	244	0	1	0
White blood cell decreased	198	9	2	0	245	0	0	0
MAX. GRADE ANY ADVERSE EVENT	105	88	14	2	225	18	2	0

S1512 Phase II

A Phase II and Pilot Trial of PD-1 Blockade with MK-3475 (Pembrolizumab) in Patients with Resectable or Unresectable Desmoplastic Melanoma (DM)

Study Chairs:
K Kendra, S Hu-Lieskovan, A Cochran

Date Activated:
10/20/2016

Statisticians:
M Wu, J Moon

Data Coordinator:
D Heaney

Objectives

This study will enroll two separate cohorts to assess the efficacy of MK-3475 (pembrolizumab) in desmoplastic melanoma (DM). Cohort A will evaluate MK-3475 (pembrolizumab) as neoadjuvant therapy for patients with DM that is deemed resectable by the treating investigator; including primary DM, locally advanced DM, and locally recurrent DM. Cohort B will be a pilot study to evaluate the use of MK-3475 (pembrolizumab) for patients with DM that is deemed unresectable by the treating investigator, including metastatic DM.

Cohort A

To evaluate the pathologic complete response rate in patients with resectable desmoplastic melanoma treated with neoadjuvant MK-3475 (pembrolizumab).

To estimate the nine week response rate (unconfirmed complete and partial responses).

To estimate the median overall survival.

To evaluate safety and tolerability of MK-3475 (pembrolizumab) in the neoadjuvant setting.

Cohort B

To evaluate the complete response rate (confirmed and unconfirmed) in patients with unresectable desmoplastic melanoma treated with MK-3475 (pembrolizumab).

To estimate the median progression-free survival.

To estimate the median overall survival.

To evaluate safety and tolerability of MK-3475 (pembrolizumab) in this setting.

Patient Population

Patients must have histologically or cytologically confirmed primary desmoplastic melanoma. Patients with disease that, in the judgment of the surgeon is deemed completely resectable resulting in free surgical margins, are eligible for Cohort A. Patients with unresectable disease are eligible for Cohort B. All patients must have measurable disease. Patients must not have known brain metastases unless brain metastases have been treated and patient is asymptomatic with no residual neurological dysfunction without receiving enzyme-reducing anti-epileptic drugs or corticosteroids.

Patients must not have received prior systemic therapy for desmoplastic melanoma. Patients must not have received radiation therapy, non-cytotoxic

agents or investigational agents or systemic corticosteroids within 14 days prior to registration. Patients may have received prior surgery.

Patients must have adequate hematologic and hepatic function with a Zubrod performance status of 0-2. Patients must not have known, active non-infectious pneumonitis, an active infection requiring systemic therapy, or an active autoimmune disease that has required systemic treatment in the past two years. Patients must not have received live vaccines within 42 days prior to registration. Patients known to be HIV positive must have stable and adequate CD4 counts, a serum viral load below 52,000 IU/ml and must be on stable anti-viral therapy. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to registration.

Stratification/Descriptive Factors

Patients will be stratified by Cohort: A (resectable) vs B (unresectable).

Accrual Goals

Accrual to this study will proceed in two independent cohorts: A and B.

Cohort A will accrue approximately 51 patients to achieve 41 eligible patients. Initially, 21 eligible patients will be enrolled. If two or more pathologic complete responses are observed, an additional 20 eligible patients will be enrolled.

Cohort B will accrue approximately 26 patients to achieve 21 eligible patients.

Summary Statement

This study was activated on October 20, 2016. As of December 31, 2016, no patients have been registered.

S1607 Phase II

A Phase II Study of Combining Talimogene Laherparepvec (T-VEC) (NSC-785349) and MK-3475 (Pembrolizumab) (NSC-776864) in Patients with Advanced Melanoma Who Have Progressed on Anti-PD/L1 Based Therapy

Study Chairs:
S Hu-Lieskovan, A Ribas

Statisticians:
M Wu, J Moon

Data Coordinator:
D Salud

Objectives

To evaluate the durable response rate of treatment with talimogene laherparepvec (T-VEC) in combination with MK-3475 (pembrolizumab) following progression on prior anti-PD-1 or anti-PD-L1 therapy alone or in combination with other agents different from talimogene laherparepvec (T-VEC).

To estimate the response rate (confirmed and unconfirmed, complete and partial responses) in the injected lesions.

To estimate the response rate in the non-visceral, non-injected lesions.

To estimate the response rate in the visceral lesions.

To estimate the overall objective response rate per RECIST 1.1, progression-free survival, and overall survival within each cohort.

To evaluate whether adding talimogene laherparepvec (T-VEC) to PD1 blockade can increase T-cell infiltration into tumors and whether change in T-cell infiltration is associated with response.

To evaluate whether adding talimogene laherparepvec (T-VEC) to PD1 blockade can increase TCR clonality in tumors and in peripheral blood and whether increased TCR clonality is associated with response.

To evaluate whether intra-tumoral injection of talimogene laherparepvec (T-VEC) is associated with the tumor immune microenvironment.

To evaluate whether tumor mutational load and mutations in the IFN pathway is associated with response to talimogene laherparepvec (T-VEC) plus MK-3475 (pembrolizumab) therapy in the anti-PD1/L1 therapy refractory melanoma patients.

Patient Population

Patients must have pathologically confirmed Stage IV or unresectable Stage III melanoma with cutaneous, mucosal or unknown primary. Patients with uveal primary are not eligible. Patients will be enrolled onto one of two independent cohorts: for Cohort A, patients must have at least one measurable visceral lesion, defined as any solid organ except for skin, lymph node, or musculoskeletal tissue; for Cohort B, patients must have at least one measurable non-visceral lesion and no evidence of visceral disease. Patients must not have known active central nervous system (CNS) metastases. Patients with a history of CNS metastases must have been adequately treated with no evidence of progression for at least 28 days prior to registration and must be asymptomatic without requiring steroids for at least

14 days prior to registration. Patients must, in the opinion of the treating investigator, be candidates for intralesional administration into cutaneous, subcutaneous, or nodal lesions. Patients must have at least two injectable lesions

Patient must have had prior treatment with anti-PD-1 or anti-PD-L1 agents and have documented disease progression on these agents prior to registration. Patient must have received anti-PD-1 or PD-L1 based therapy as the immediate previous line of treatment and within 56 days prior to registration. Patients must not have had surgery, chemotherapy, biologic therapy, hormonal therapy, or radiation therapy within 14 days prior to registration. Patients must not have had an investigational agent or monoclonal antibodies, except anti-PD1/L1 antibodies, within 28 days prior to registration. Patients must not have received prior treatment with talimogene laherparepvec (T-VEC) or other oncolytic virus agents. Patients must not have had any infectious disease vaccination within seven days prior to registration.

Patients must have adequate hematologic, hepatic, and renal function and a Zubrod performance status of 0+2.Patients must not have severe autoimmune disease requiring systemic corticosteroids or ongoing immunosuppression. Patients must not have a known history of HIV, hepatitis B, or hepatitis C, or pneumonitis, Patients must not have an active infection requiring systemic therapy nor a viral-infection requiring intermittent treatment with an antiherpatic drug,and must not have active herpatic skin lesions or prior complications of herpatic infection which require treatment with an anti-herpatic drug. Patients must not have organ allografts, or a history of autoimmune disease, or clinically significant immunosuppression. Women of reproductive potential must have a negative serum pregnancy test within seven days prior to registration.

Patients must have tissue available and must be willing to submit blood and tissue specimens for the translational medicine objectives. Patients must be offered the opportunity to participate in specimen banking.

Stratification/Descriptive Factors

Patients will be stratified based on presence of visceral lesions: one or more vs none.

Accrual Goals

The study will accrue to two independent cohorts.

Cohort A, patients with at least one visceral lesion, will use a two-stage design. Initially 18 patients will be enrolled. If at least one response is observed, then an additional 14 patients will be enrolled for a total of 32 patients.

Cohort B, patients with no visceral lesions, will use a modified two-stage design. Initially 18 patients will be enrolled. If at least one response is observed, considering only responses among visceral target lesions, then an additional 14 patients will be enrolled for a total of 32 patients.

S1609 Phase II

Coordinating Group: SWOG

DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors

Participants:
SWOG, CTSU

Date Activated:
01/13/2017

Study Chairs:
S Patel, Y Chae

Statisticians:
M Othus, C Ebnesajjad

Data Coordinator:
C McLeod

Objectives

To evaluate the RECIST 1.1 overall response rate (ORR) in subsets of patients with advanced rare cancers treated with ipilimumab plus nivolumab combination immunotherapy.

To evaluate toxicities in each cohort.

To estimate overall survival (OS), progression-free survival (PFS), clinical benefit rate; and to estimate immune-related ORR (irORR), and immune-related PFS (irPFS) by unidimensional immune-related response criteria.

To collect specimens for banking for use in future correlative biomarker research studies.

Patient Population

Patients must have enrolled in EAY131, NCI-MATCH, and were either not matched to a molecularly-guided therapy or progressed on molecularly-matched therapy and have no further molecularly-matched treatment recommendations per EAY131. Patients must have measurable disease and histologically confirmed rare cancer and/or cancer of unknown primary specified on the list of eligible rare cancer histologic cohorts in the S1609 protocol. Patients who do not qualify for one of the histologic cohorts may be considered for registration in the "Not Otherwise Categorized" Rare Tumors cohort with confirmation of the study chairs.

Patients must not have received prior anti-PD-1 or anti-PD-L1 therapy. Other immunotherapy is permitted, provided that it is completed at least seven days prior to registration. Patients who had prior immune-related adverse event with prior immunotherapy are not eligible. Patients with brain metastases or primary brain tumors must have completed treatment, surgery or radiation therapy ≥ 28 days prior to registration and have stable disease at time of registration. Patients with metastatic brain parenchymal disease must have been treated and patients must be off steroids for seven days prior to registration. Patients must have been off all other systemic anti-cancer therapy at least seven days prior to registration and any therapy-induced toxicity must have recovered to ≤ Grade 1.

Patients must have a Zubrod performance status of 0-2 and have adequate hematologic, hepatic, renal, thyroid, and adrenal axis function. Patients must not have active autoimmune disease that has required systemic treatment in past two years or any uncontrolled intercurrent illness. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection at time of registration. Patients with HBV or HCV that have an undetectable viral load, or in the opinion of the treating investigator is well controlled, are eligible.

Patients who are known to be HIV-positive at registration are eligible if they meet the conditions outlined in the protocol.

Stratification/Descriptive Factors
Patients will be described by histologic cohorts.

Accrual Goals

The accrual goal for this study is 334 patients to achieve 300 eligible patients. A two-stage design will be used. Initially, six eligible patients will be registered to each histologic cohort. If at least one response is observed within a cohort, an additional 10 eligible patients will be registered to that cohort.

Summary Statement
For the current status of this study, please refer to the Early Therapeutics and Rare Cancers chapter.

S1616 Phase II

Coordinating Group: SWOG

A Phase II Randomized Study of Nivolumab (NSC-732442) with Ipilimumab (NSC-748726) or Ipilimumab Alone in Advanced Melanoma Patients Refractory to an Anti-PD-1 or Anti-PD-L1 Agent

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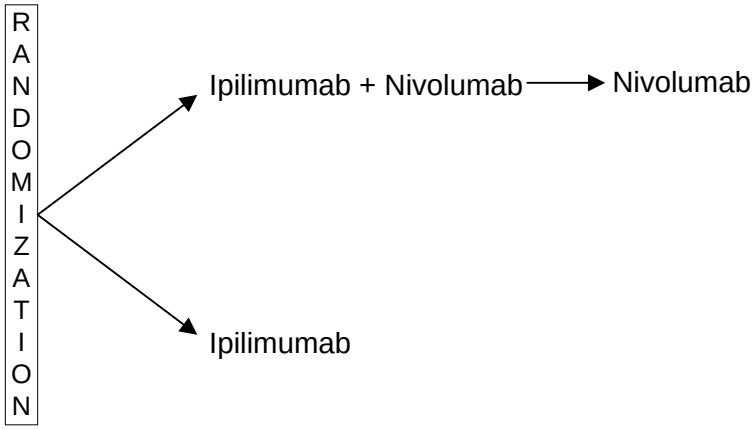
Participants:
SWOG, CTSU

Study Chairs:
A VanderWalde, A Ribas

Statisticians:
J Moon, M Wu

Data Coordinator:
D Salud

SCHEMA



Note: For every one patient randomized to receive single agent ipilimumab, three will be randomized to receive the combination of ipilimumab and nivolumab

Objectives

To compare progression free survival (PFS) of patients with advanced melanoma refractory to an anti-PD-1 or anti-PD-L1 agent, treated with combination therapy ipilimumab plus nivolumab versus ipilimumab alone.

To estimate difference in T-cell infiltrate between on-study biopsy samples of patients who respond to combination therapy (including confirmed and unconfirmed, complete and partial response per RECIST 1.1) as compared to those who do not respond.

To evaluate the objective response rate (ORR) (confirmed and unconfirmed complete or partial responses) in each treatment arm.

To evaluate overall survival in each treatment arm.

To evaluate the toxicity profile of patients in each treatment arm.

Patient Population

Patients must have pathologically confirmed melanoma that is either Stage IV or unresectable Stage III. Patients may have primaries of cutaneous, mucosal, or unknown origin. Patients with uveal (ocular) primary are not eligible. Patients must have measurable disease. If the only measurable disease is cutaneous or subcutaneous, lesions must be at least 10 mm in greatest dimension and able to be serially recorded using calipers and photographs. Patients must not have central nervous system metastases unless adequately treated and patient is asymptomatic without requiring steroids for at least 14 days prior to registration.

Patients must have had prior treatment with anti-PD-1 or anti-PD-L1 agents and had documented disease progression either while on these agents or after stopping therapy with these agents without intervening therapy. Patients must not have achieved a confirmed partial or complete response to the anti-PD-1 or anti-PD-L1 agents prior to progression. Patients must not have had any systemic therapy within 21 days prior to registration. Patients must not have had prior radiation therapy within 14 days prior to registration. Patients must not have had prior treatment with ipilimumab or other CTLA-4 antagonists.

Patients must be at least 18 years of age and have a Zubrod performance status of 0-2 with adequate hepatic, renal, and hematologic function. Patients with a known history of HIV must have an adequate CD4 count. Patients must not have a known active Hepatitis B, or Hepatitis C infection. Patients must not have received systemic treatment with corticosteroids or other immunosuppressive medications within 14 days prior to registration. Patients must not have organ allografts or a history of immune-mediated pneumonitis or colitis that required steroid treatment. Women of reproductive potential must have negative serum pregnancy test within two days prior to registration.

Patients must be willing to undergo biopsies and submit tissue and blood for the translational medicine objectives.

Accrual Goals

Patients will be randomized using a 3:1 ratio to receive combination therapy ipilimumab and nivolumab versus single therapy ipilimumab. In other words, will be randomized with 63 patients will be randomized to receive the combination regimen and 21 will be randomized to receive the single agent regimen Assuming an ineligibility rate of 10% the total accrual goal is 94 patients to achieve 84 eligible patients.

EAY131 Master Protocol / Phase II

Coordinating Group: ECOG-ACRIN

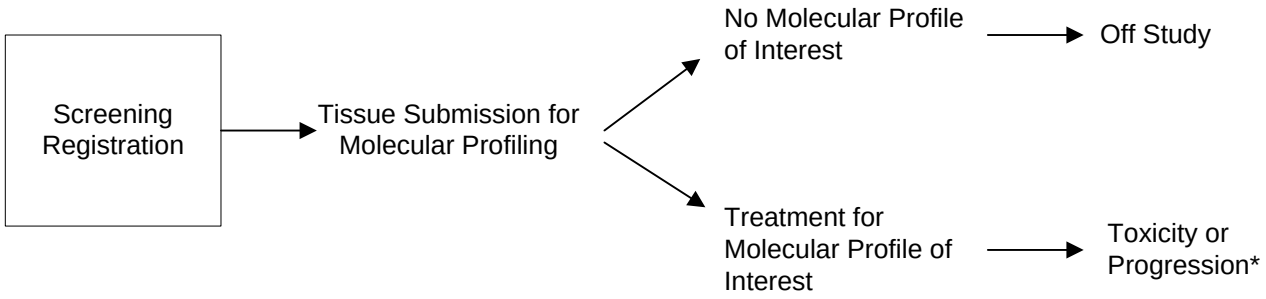
NCI-MATCH: Molecular Analysis for Therapy Choice

Participants:
ECOG-ACRIN, CTSU

Date Activated:
08/12/2015

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

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/multiple myeloma.

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/multiple myeloma.

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 protein and imaging-based assessment platforms.

To assess whether radiomic phenotypes obtained from pre-treatment imaging and changes from pre- through post-therapy imaging can predict objective response and progression-free survival and to evaluate the association between pre-treatment radiomic phenotypes and targeted gene mutation patterns of tumor biopsy specimens.

Patient Population

Patients must have histologically documented solid tumors or histologically confirmed diagnosis of lymphoma or multiple myeloma 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 and meet one of the criteria in the protocol regarding tissue procurement.

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 start of treatment. Patients must not require the use of full dose coumarin-derivative anticoagulants. Factor X inhibitors are permitted. Patients may receive non-protocol treatment after biopsy (if clinically indicated) until they receive notification of results, but patients may not enroll in another investigational study during this time and the therapy cannot be an arm in this trial.

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. Patients must not have any uncontrolled intercurrent illness. 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 reach 25 patients by the time the overall study screening accrual goal is met, and if 13 patients have been treated and no responses have been observed, then the steering committee may consider terminating accrual in that subgroup due to lack of feasibility. After 500 patients are screened, the study design will be reassessed to assure its appropriateness. 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 January 26, 2015, with 10 subprotocols included in the activation. Only sites utilizing the CIRB as their IRB of record are able to participate in the trial. The study was temporarily closed to accrual on November 11, 2015, after rapid accrual of 795 patients to the screening step in only three months, including 119 SWOG registrations. This pause in patient enrollment for assessment of study design appropriateness was lifted on May 31, 2016, when this study reopened to enrollment with an additional 14 new subprotocols. As of November 16, 2016, accrual to subprotocol N has been suspended due to drug supply shortage.

ECOG-ACRIN reported a total of 4,121 screened patients and 368 molecularly matched patients as of December 31, 2016. This includes 512 screened and 46 molecularly matched SWOG registrations. The complete Spring 2016 summary of this study from ECOG-ACRIN is available on the SWOG web site.