Phase II Anti-PD1 Epigenetic Therapy Study in NSCLC.

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT01928576	RECRUITING	AUGUST 26, 2013	APRIL 28, 2020

STUDY DESCRIPTION

Brief Summary

Response Rate

Condition or Disease: Non-Small Lung Cancer, Epigenetic Therapy

Intervention/treatment: Drug: Azacitidine
Drug: Entinostat
Drug: Nivolumab

Phase: Phase 2

DETAILED DESCRIPTION

Objective response rate to Nivolumab preceded by epigenetic priming. Response will be assessed by RECIST 1.1 criteria, baseline scans for this assessment will be the baseline scans done within 4 weeks of enrollment.

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 120 participants

Intervention Model : Parallel Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: A Phase II Study of Epigenetic Therapy With Azacitidine and Entinostat With Concurrent Nivolumab in Subjects With Metastatic Non-Small Cell Lung Cancer.

Study Start Date: August 2013

Estimated Primary Completion Date: August 2022

Estimated Study Completion Date: August 2022

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Arm D Anti-PD-1/PD-L1 treatment naïve patients only Every 28 days for 6 cycles Azacitidine 40mg/m2 days 1-5 and 8-10 Entinostat 5mg Days 3 and 10 Nivolumab 3mg/kg Days 1 and 15 Followed by: Nivolumab 3mg/kg every 2 weeks until progression	Drug: Azacitidine Drug: Entinostat Drug: Nivolumab
Experimental: Arm E Patients must have had refractory (Arm E=less than 24 weeks from first dose of anti-PD-1/PD-L1) disease during or after anti-PD-1 or anti-PD-L1 therapy and, in the opinion of the investigator, must be unlikely to benefit from nivolumab monotherapy. Every 28 days for 6 cycles Azacitidine 40mg/m2 days 1-5 and 8-10 Entinostat 5mg Days 3 and 10 Nivolumab 3mg/kg Days 1 and 15 Followed by: Nivolumab 3mg/kg every 2 weeks until progression	Drug: Azacitidine Drug: Entinostat Drug: Nivolumab
Experimental: Arm F Patients must have had recurrent (Arm F=more than 24 weeks from first dose of anti-PD1/PD-L1) disease during or after anti-PD-1 or anti-PD-L1 therapy and, in the opinion of the investigator, must be unlikely to benefit from nivolumab monotherapy. Every 28 days for 6 cycles Azacitidine 40mg/m2 days 1-5 and 8-10 Entinostat 5mg Days 3 and 10 Nivolumab 3mg/kg Days 1 and 15 Followed by: Nivolumab 3mg/kg every 2 weeks until progression	Drug: Azacitidine Drug: Entinostat Drug: Nivolumab
Experimental: Arm C Nivolumab 3mg/kg every 2 weeks until progression	Drug: Nivolumab

OUTCOME MEASURES

Primary Outcome Measures: 1. Objective Response [Time Frame: 2 years]
Percentage of participants with response to combination Nivolumab and epigenetic therapy. Response will be assessed by RECIST 1.1 criteria, where complete response (CR)= disappearance of all target lesions, partial response (PR) is =>30% decrease in sum of diameters of target lesions, progressive disease (PD) is >20% increase in sum of diameters of target lesions, stable disease (SD) is <30% decrease or <20% increase in sum of diameters of target lesions.

Secondary Outcome Measures:	1. Time to Progression [Time Frame: 2 years] Number of months from the time nivolumab begins until radiologic (per RECIST 1.1) or clinical progression is noted. 2. Overall survival [Time Frame: 2 years] Number of months from the time of randomization until death. Estimation will be by the Kaplan-Meier method. 3. Safety and tolerability as assessed by number of participants with adverse events [Time Frame: 2 years] Number of participants who experience adverse events as defined by CTCAE v4.0. 4. Progression free survival [Time Frame: 2 years] Number of months from the time of randomization until radiologic (per RECIST 1.1) or clinical progression or death, whichever comes first.

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 to 100 Years (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
- Patients must have histologically proven stage IIIB, IV or recurrent non-small cell lung cancer. Patients must be willing to undergo a pre-treatment biopsy, either core needle biopsy or equivalent amount or via excisional specimen. (cytology specimen not acceptable for this purpose).
- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm with conventional techniques or as >10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.
- Age >18 years. Because no dosing or adverse event data are currently available on the use of azacitidine with entinostat, or of Nivolumab, in patients 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum-doublet regimen given to treat the recurrences, are eligible and do not count as another line of therapy for advanced disease.
- Subjects who received pemetrexed, bevacizumab, or erlotinib as maintenance therapy (nonprogressors with platinum-based doublet chemotherapy) and subsequently progressed after maintenance therapy, are eligible and do not count as a line of therapy. However, subject who received a tyrosine kinase inhibitor after failure of a prior platinum-based therapy, that tyrosine kinase inhibitor therapy would count as an additional line of therapy.
- Patients who have been treated with prior standard of care PD-1/L1 agents, alone or in combination with chemotherapy, are eligible. Patients previously treated on clinical trials with non PD-1/PD-L1 immunotherapy agents are eligible. Patients who have been treated with a PD-1/L1 agent in more than 1 line of therapy (as standard of care or in clinical trial) are not eligible.
- Arm-specific eligibility criteria
- Arm D: Anti-PD-1/PD-L1 treatment naïve patients only
- Arm E & F: Anti-PD-1/PD-L1 treatment experienced patients: Patients must have had refractory (Arm E=less than 24 weeks from first dose of anti-PD-1/PD-L1) or recurrent (Arm F=more than 24 weeks from first dose of anti-PD-1/PD-L1) disease during or after anti-PD-1 or anti-PD-L1 therapy and, in the opinion of the investigator, must be unlikely to benefit from nivolumab monotherapy.
- Patients must have disease amenable to biopsy at the time of enrollment as biopsies are required for study participation.

Exclusion Criteria:
- Any active history of a known autoimmune disease. Subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a history of interstitial lung disease that has required intubation in the past (i.e. such as Asthma or COPD).
- Patients who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.
- Patients who are receiving any other anticancer therapy.
- Patients with uncontrolled brain metastases. Patients with brain metastases must have stable neurologic status following local therapy (surgery or radiation) for at least 2 weeks without the use of steroids or on stable or decreasing dose of 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Patients with malabsorption in the small intestine or other conditions that would preclude administration of oral medication.
- Prior therapy with DNA methyltransferase therapy or HDAC inhibitor therapy.

CONTACTS AND LOCATIONS

Contacts

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Locations

United States, California	University of Southern California	Los Angeles
United States, District of Columbia	Sibley Memorial Hospital	Washington
United States, Maryland	Julie Brahmer, MD	Baltimore
United States, Maryland	Julie Brahmer, MD	Baltimore
United States, Pennsylvania	UPMC Cancer Center- Hillman Cancer Center	Pittsburgh

Sponsors and Collaborators

Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Rising Tide Foundation

Stand Up To Cancer

Bristol-Myers Squibb

Celgene

Syndax Pharmaceuticals, Inc.

Rhone-Poulenc Rorer

Investigator

Principal Investigator :	Julie Brahmer, MD	Johns Hopkins University

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MORE INFORMATION

Responsible Party :	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
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Other Study ID Numbers :	J1353, NA_00084192, 119134, 117207, 121445, 119134, CA209-117
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