S1400F Phase II

Coordinating Group: SWOG

A Phase II Study of MEDI4736 (Durvalumab) plus Tremelimumab as Therapy for Patients with Previously Treated Anti-PD-1/PD-L1 Resistant Stage IV Squamous Cell Lung Cancer

(Lung-MAP Non-Match Sub-Study)

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

Date Activated:
10/02/2017

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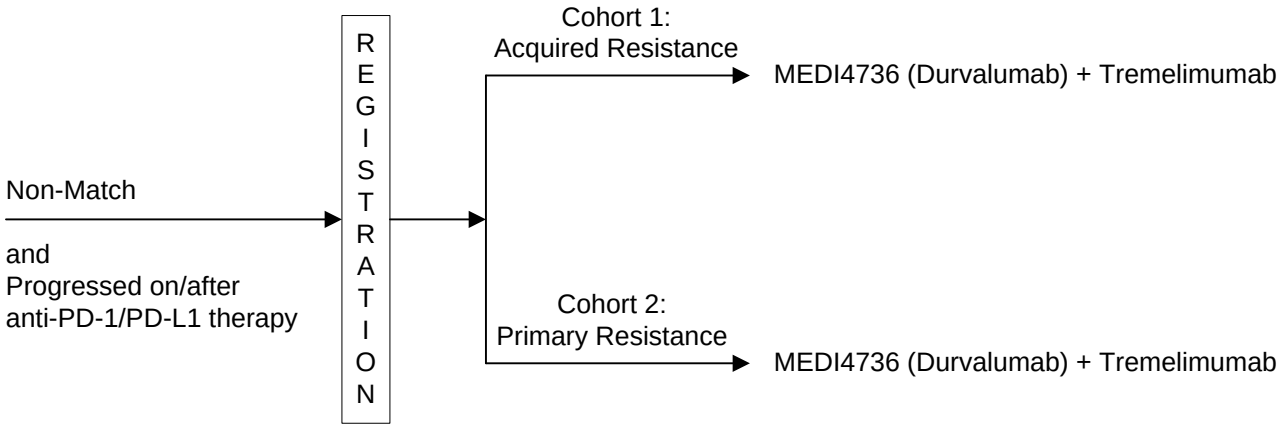
SCHEMA



Objectives

This study will enroll patients into two parallel and independently evaluated cohorts as depicted in the schema:

To evaluate the objective response rate (confirmed and unconfirmed, complete and partial) by RECIST 1.1 among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

To estimate the duration of response (DoR) among patients who achieve a complete response (CR) or partial response (PR) (confirmed and unconfirmed) by RECIST 1.1.

To estimate the duration of response (DoR) per protocol-defined immune-related response criteria among patients who achieve a complete response (CR) or partial response (PR) (confirmed and unconfirmed) by RECIST 1.1.

To evaluate overall survival (OS) among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

To evaluate investigator-assessed progression-free survival (IA-PFS) among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

To evaluate IA-PFS assessed per protocol-defined immune-related response criteria (irRC-IA-PFS) among patients treated with MEDI4736 (Durvalumab) plus tremelimumab.

To evaluate the frequency and severity of toxicities associated with MEDI4736 (Durvalumab) plus tremelimumab.

Patient Population

Patients must have been eligible for the screening study and must have been assigned to the S1400F sub-study based on biomarker profiling results. Patients must have experienced disease progression during or after prior anti-PD-1 or anti-PD-L1 antibody monotherapy as their most recent line of treatment. Patients must have measurable disease by CT or MRI. Patients must not have leptomeningeal disease, spinal cord compression or brain metastases unless both (1) metastases have been locally treated and have remained clinically controlled and asymptomatic for at least 14 days following treatment, and prior to registration, and (2) patient has no residual neurological dysfunction and has been off corticosteroids for at least 24 hours prior to sub-study registration.

Prior exposure to PD-1/PD-L1 in combination with other therapies or CTLA-4 inhibitors is not permitted. Patients must not have received any immunosuppressive medication within 28 days prior to sub-study registration and must not be planning to receive these medications while on protocol therapy. Patients must not have received nitrosoureas or mitomycin-c within 42 days prior to sub-study registration. Patients must not have received any prior systemic therapy within 21 days prior to sub-study registration. Patients must have fully recovered from the effects of surgery at least 14 days prior to sub-study registration. Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment.

Patients must have a Zubrod performance status of 0-1 and adequate hepatic, cardiac, hematologic, thyroid and renal function. Patients must not have experienced a Grade 3 or worse immune-related adverse event (irAE) or any unresolved irAE Grade 2, nor have experienced a toxicity that led to permanent discontinuation of prior anti-PD-1/PD-L1 immunotherapy. Patients must not have any history of organ transplant that requires use of immunosuppressives. Patients must not have clinical signs or symptoms of active tuberculosis infection. Patients must not have received a live attenuated vaccination within 28 days prior to sub-study registration. Patients must not have known HIV, or a known positive test for Hepatitis B virus surface antigen, or Hepatitis C virus ribonucleic acid. Patients with a positive Hepatitis C antibody with a negative viral load are allowed. Patients must not have any prior documented autoimmune or inflammatory disease within three years prior to sub-study registration. Patients with vitiligo, immune-mediated alopecia, Grave's disease, or psoriasis requiring systemic treatment within the past two years are not eligible. Patients with hypothyroidism who are stable on hormone replacement therapy are eligible. Patients must not have any history of primary immunodeficiency.

Stratification/Descriptive Factors

Patients will be stratified into two cohorts:

Acquired resistance: Patients with a history of 24 weeks or more of disease control (complete response, partial response or stable disease) after initiation of single agent anti-PD-1/PD-L1 therapy that have subsequently progressed after 24 weeks.

Primary resistance: Patients with a history of disease progression within 24 weeks of initiation of single agent anti-PD-1/PD-L1 therapy.

Accrual Goals

Total accrual goal is 66 patients per cohort to achieve 60 eligible patients per cohort. The study design includes interim analyses within each cohort upon 20 and 40 patients evaluable for response.

Summary Statement

As of December 31, 2018, 159 patients (34% of patients screened to S1400 while S1400F has been open) have been assigned to S1400F and 49 patients have been enrolled.

Of the 110 who did not register, 67 patients were not eligible, seven patients were based on investigator decision, seven patients were not eligible for the screening study, six patients refused, five patients had symptomatic deterioration, three patients passed away, one for previous treatment on S1400I, one was registered by accident, and one could not delay treatment any longer. The remaining twelve patients have not yet submitted the Notice of Intention Not to Register.

Of the 49 registered, two are ineligible as they received another therapy other than anti-PD-L1 monotherapy as their most recent line of treatment and one additional patient is ineligible due to creatinine clearance outside of protocol-specified range. Additionally, two patients are not analyzable due to withdrawing consent prior to receiving any treatment and passing away prior to receiving any treatment (1 each). Thus, these five will not be included in any analysis.

Forty-four patients have been assessed for adverse events. In the acquired resistance cohort, there has been one treatment-related death due to pneumonitis. This patient also experienced Grade 4 dyspnea. Additionally, one patient experienced treatment-related Grade 4 decreased white blood cells.

Registration by Institution

Registrations ending December 31, 2018

Institutions	Total Reg	Institutions	Total Reg
Georgia NCORP	4	Oregon Hlth Sci Univ	1
Heartland NCORP	4	PIH Health Hosp/Irvine, U of CA	1
Southeast COR NCORP	4	Providence Hosp	1
MAVERIC	2	Rochester, Univ of	1
Colorado, U of	1	VAMC Kansas City	1
Harrington CC	1	Wichita NCORP	1
Kentucky, U of	1	Yale University	1
MD Anderson CC	1	ALLIANCE	9
Michigan CRC NCORP	1	ECOG-ACRIN	6
Michigan, U of	1	NRG	6
New Mexico MU-NCORP	1	**Total (21 Institutions)**	**49**

Registration, Eligibility, and Evaluability

Classified by Cohort

Registrations ending December 31, 2018; Data as of February 22, 2019

	TOTAL	Acquired	Primary
NUMBER REGISTERED	49	28	21
INELIGIBLE	3	1	2
ELIGIBLE	46	27	19
Analyzable, Pend. Elig.	1	1	0
Not Analyzable	2	0	2
RESPONSE ASSESSMENT			
Determinable	42	26	16
Not Determinable	1	0	1
Too Early	1	1	0
ADVERSE EVENT ASSESSMENT			
Evaluable	44	27	17

Patient Characteristics

Classified by Cohort

Registrations ending December 31, 2018; Data as of February 13, 2019

	Acquired (n=27)		Primary (n=17)	
AGE				
Median	67.6		67.5	
Minimum	46.6		49.7	
Maximum	82.5		89.8	
SEX				
Males	15	56%	11	65%
Females	12	44%	6	35%

	Acquired (n=27)		Primary (n=17)	
HISPANIC				
Yes	3	11%	1	6%
No	23	85%	16	94%
Unknown	1	4%	0	0%
RACE				
White	23	85%	13	76%
Black	3	11%	3	18%
Native American	0	0%	1	6%
Unknown	1	4%	0	0%
PRIOR LINES OF TREATMENT FOR STAGE IV DISEASE				
0	1	4%	0	0%
1	10	37%	5	29%
2	11	41%	8	47%
3	4	15%	2	12%
4	1	4%	2	12%
PERFORMANCE STATUS				
0	11	41%	5	29%
1	16	59%	12	71%
WEIGHT LOSS PAST 6 MONTHS				
< 5%	20	74%	14	82%
5 - < 10%	5	19%	2	12%
10 - < 20%	2	7%	1	6%

Treatment Summary

Classified by Cohort

Registrations ending December 31, 2018; Data as of February 13, 2019

	TOTAL	Acquired	Primary
NUMBER ON PROTOCOL TREATMENT	9	7	2
NUMBER OFF PROTOCOL TREATMENT	35	20	15
REASON OFF TREATMENT			
Treatment completed as planned	0	0	0
Adverse Event or side effects	7	3	4
Refusal unrelated to adverse event	0	0	0
Progression/relapse	25	15	10
Death	3	2	1
Other - not protocol specified	0	0	0
Reason under review	0	0	0
MAJOR PROTOCOL DEVIATIONS	0	0	0
LOST TO FOLLOW-UP	0	0	0
CONSENT WITHDRAWAL AFTER TREATMENT INITIATION	0	0	0

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 Have Been Suppressed

Registrations ending December 31, 2018; Data as of February 13, 2019

	MEDI4736 + Tremelimumab (n=44) Grade			
ADVERSE EVENTS	**<=2**	**3**	**4**	**5**
Chills	43	1	0	0
Dehydration	42	2	0	0
Diarrhea	40	4	0	0
Dyspnea	41	2	1	0
Encephalopathy	43	1	0	0
Fatigue	43	1	0	0
Febrile neutropenia	43	1	0	0
Hyperglycemia	43	1	0	0
Hypoxia	42	2	0	0
Lung infection	43	1	0	0
Nausea	43	1	0	0
Neutrophil count decreased	43	1	0	0
Platelet count decreased	43	1	0	0
Pneumonitis	42	1	0	1
Vomiting	43	1	0	0
White blood cell decreased	43	0	1	0
MAX. GRADE ANY ADVERSE EVENT	32	10	1	1