LUDWIG CANCER RESEARCH

CANCER RESEARCH INSTITUTE

Abstract #3069

Phase 1 Study to Evaluate the Safety and Tolerability of MEDI4736 (Durvalumab) and Tremelimumab in Patients with Advanced Solid Tumors

Margaret K. Callahan[1], Kunle Odunsi[2], Mario Sznol[3], John J. Nemunaitis[4], Patrick A. Ott[5], Patrick Dillon[6], Andrew Park[7], Paul Schwarzenberger[7], Toni Ricciardi[7], Mary Macri[7], Aileen Ryan[7], Ralph R. Venhaus[7], Jedd D. Wolchok[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Roswell Park Cancer Institute, Buffalo, NY; [3]Yale Cancer Center, New Haven, CT; [4]Mary Crowley Cancer Research Center, Dallas, TX; [5]Dana-Farber Cancer Institute, Boston, MA; [6]University of Virginia Division of Hematology and Oncology, Charlottesville, VA; [7]Ludwig Cancer Research, New York, NY

1 Background

DURVALUMAB

- Durvalumab is a human IgG1 mAb that blocks programmed cell death ligand-1 (PD-L1) binding to programmed cell death-1 (PD-1) and CD80, allowing T-cells to recognize and kill tumor cells.
- Inhibition of PD-L1 and CD80 allows T cells to recognize and kill tumor cells without antibody-dependent cell-mediated cytotoxicity activity.
- In preclinical studies, durvalumab blocked the inhibitory effect of PD-L1 on primary human T cells and demonstrated T-cell-dependent antitumor activity *in vitro*.[1]

TREMELIMUMAB

- Tremelimumab is a fully human IgG2 mAb with high specificity for cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).
- Blocking the CTLA-4 negative costimulatory receptor with tremelimumab results in immune activation.

COMBINATION TREATMENT

- Blocking these inhibitory checkpoints has been demonstrated to have antitumor effects.[2,3]
- Targeting both checkpoint pathways provides the potential for additive or synergistic effects, as the mechanisms of activation for PD-1 and CTLA-4 are non-redundant.[4]
- Combined CTLA-4 and PD-1 inhibition using the FDA-approved regimen of nivolumab + ipilimumab demonstrated manageable safety and robust clinical activity in advanced melanoma,[5,6] and the combination is approved by FDA.

2 Study design and objectives

This is an ongoing Phase 1, multicenter, open-label study (NCT01975831) designed to evaluate the safety and efficacy of tremelimumab + durvalumab in patients with selected advanced solid tumors. See Figures 1 and 2.

PRIMARY OBJECTIVE

- Safety and tolerability

SECONDARY OBJECTIVES

- Tumor response assessed by immune-related response criteria (irRC)[7] and Response Evaluation Criteria In Solid Tumors (RECIST) v1.1[8]
- Progression-free survival
- Overall survival

EXPLORATORY OBJECTIVE

- Biological activity of the durvalumab and tremelimumab combination

3 Recruitment

KEY INCLUSION CRITERIA

- Histologic and/or cytologic confirmation of 1 of 5 tumor types (ovarian, colorectal, non-triple-negative breast, renal cell, or cervical cancer) with ≥1 lesion measurable by irRC not previously irradiated
- Age ≥ 18 years
- ECOG performance status 0–2
- Failed to respond, relapsed following, were ineligible for, or refused standard treatment
- Adequate organ function (i.e., normal hemoglobin, absolute neutrophil count, platelet count, total bilirubin, alanine/aspartate aminotransferase, and serum creatinine)

KEY EXCLUSION CRITERIA

- Prior exposure to anti-PD-1, anti-PD-L1, or anti-CTLA-4 agents
- Active, untreated central nervous system metastasis
- Underlying autoimmune disease or immunodeficiency
- Requirement of > 10 mg/day of prednisone or equivalent
- Any prior immune-related AE (irAE, Grade ≥ 3) or any prior corticosteroid-refractory irAE

Figure 1. Dose-escalation phase

TREATMENT SCHEDULE
(4-week Cycles)

Cohorts 1–3
TRE IV Q4W for the first 6 cycles, then Q12W
DUR IV Q2W for 13 cycles

Cohort 3a
TRE IV Q4W for 4 cycles
DUR IV Q2W for 12 cycles

Cohort 4a
TRE IV Q4W for 4 cycles
DUR IV Q4W for 12 cycles

KEY DESIGN ELEMENTS

- 3 + 3 design
- All patients in a cohort are monitored for dose-limiting toxicity (DLT) for 2 cycles prior to cohort escalation

DOSE SELECTION

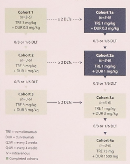
Initial dose selections for dose escalation were based on Phase 1 studies available at the time the study was initiated.

The combination dosing regimen for Cohort 4a was modified by protocol amendment to align with ongoing studies (20 mg/kg Q4W for DUR and 1 mg/kg for TRE) and fixed dosing based on an average body weight of 75 kg (1500 mg, DUR and 75 mg, TRE).

DLTS

There were 3 DLTs:

- *Cohort 2:* Grade 3 colitis
- *Cohort 3:* Grade 3 liver function test abnormal
- *Cohort 3:* Grade 4 hyponatremia (considered secondary to adrenal insufficiency due to hypophysitis)

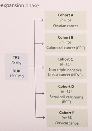

Cohort 1
(n=3-6)
TRE 3 mg/kg
+ DUR 0.3 mg/kg
≥ 2 DLTs
Cohort 1a
(n=3-6)
TRE 1 mg/kg
+ DUR 0.3 mg/kg
0/3 or 1/6 DLT
Cohort 2
(n=3-6)
TRE 3 mg/kg
+ DUR 1 mg/kg
≥ 2 DLTs
Cohort 2a
(n=3-6)
TRE 1 mg/kg
+ DUR 1 mg/kg
0/3 or 1/6 DLT
Cohort 3
(n=3-6)
TRE 3 mg/kg
+ DUR 3 mg/kg
≥ 2 DLTs
Cohort 3a
(n=3-6)
TRE 1 mg/kg
+ DUR 3 mg/kg
0/3 or 1/6 DLT
Cohort 4a
(n=3-6)
TRE 75 mg
+ DUR 1500 mg

TRE = tremelimumab
DUR = durvalumab
Q2W = every 2 weeks
Q4W = every 4 weeks
IV = intravenous
Completed cohorts

Figure 2. Dose-expansion phase

TREATMENT SCHEDULE
(4-week Cycles)
TRE IV Q4W for 4 cycles
DUR IV Q4W for 12 cycles

KEY DESIGN ELEMENTS
Patients are enrolled sequentially in each cohort according to disease type



4 Results

Table 1. Patient Disposition, Safety Analysis Set

	Ovarian cancer	Colorectal cancer	NTNB cancer	Renal cell carcinoma	Cervical cancer	All patients**
Safety Analysis Set	30	19	16	20	16	104
ITT Analysis Set	27	18	16	20	16	99*
Dose Limiting Toxicity n (%)	3 (10.0)	0	0	0	0	3 (2.9)
Continuing Treatment n (%)	5 (16.7)	4 (21.1)	1 (6.3)	12 (60.0)	4 (25.0)	26 (25.0)
Discontinued Treatment n (%)	25 (83.3)	15 (78.9)	15 (93.8)	8 (40.0)	12 (75.0)	78 (75.0)
Adverse Event***	4 (13.3)	0	2 (12.5)	3 (15.0)	1 (6.3)	11 (10.6)
Death	2 (6.7)	0	1 (6.3)	1 (5.0)	0	4 (3.8)
Physician Decision	1 (3.3)	0	0	0	0	1 (1.0)
Progression	14 (46.7)	11 (57.9)	10 (62.5)	4 (20.0)	10 (62.5)	49 (47.1)
Withdrawal by Patient	2 (6.7)	2 (10.5)	0	0	0	5 (4.8)
Other	2 (6.7)	2 (10.5)	2 (12.5)	0	1 (6.3)	8 (7.7)

Percentages are based on the number of patients in the Safety Analysis Set in each column.

Safety Analysis Set includes all patients who received at least one dose of durvalumab or tremelimumab.

Intent-to treat (ITT) Analysis Set includes all patients who received at least one dose of durvalumab or tremelimumab, and had the baseline and at least one post-baseline assessment of any of the efficacy endpoints.

*Five patients not included in ITT = 4 withdrawal by patient and 1 AE.

Patients were enrolled in the escalation phase according to treatment Cohorts 1, 2, 3, 3a, and 4a (see Figure 1), and the respective tumor type was noted. For the expansion phase, patients were enrolled at the expansion dose (see Figure 2) according to tumor type. For the purposes of this report, data for escalation and expansion cohorts are combined and presented according to the 5 expansion phase tumor types.

**For expansion, the NSCLC and head and neck cancer (HNC) tumor types were removed from the study; the 3 patients in these escalation cohorts are included in overall safety, demographics and disposition tables (all patients only). Two patients in the NSCLC cohort are included in the total ITT count, but not included in the remaining efficacy tables and figures.

***With the exception of 2 cases (1 cervical cancer and 1 renal cell carcinoma patient) all were treatment-related AEs.

Enrollment is from 6 sites; dose-escalation complete (n = 28); dose-expansion enrollment complete (n = 76); treatment ongoing.

Data cutoff for this report is 24 February 2017

Table 2. Demographics and Baseline Characteristics, Safety Analysis Set

	Ovarian cancer *(n=30)*	Colorectal cancer *(n=19)*	NTNB cancer *(n=16)*	Renal cell carcinoma *(n=20)*	Cervical cancer *(n=16)*	All patients** *(n=104)*
Age *(years)*						
Mean (StDev)	59.3 (10.12)	52.0 (10.50)	55.4 (14.31)	56.6 (11.63)	52.3 (11.41)	55.5 (11.51)
Median (Range)	60.0 (42–80)	53.0 (33–66)	52.0 (32–78)	57.0 (33–76)	57.5 (30–66)	56.0 (30–80)
Sex n (%)						
Male	0	10 (52.6)	0	17 (85.0)	0	28 (26.9)
Female	30 (100.0)	9 (47.4)	16 (100.0)	3 (15.0)	16 (100.0)	76 (73.1)
Weight *(kg)*						
Mean (StDev)	68.22 (12.946)	78.77 (26.780)	62.26 (11.443)	87.29 (21.221)	65.18 (15.244)	73.05 (20.038)
Median	68.25	75.60	65.00	86.25	65.50	69.55
Range	49.0–103.7	46.7–140.4	40.8–83.5	51.3–128.2	42.2–92.4	40.8–140.4
ECOG Performance Status (n (%))						
0	12 (40.0)	9 (47.4)	6 (37.5)	16 (80.0)	9 (56.3)	52 (50.0)
1	16 (53.3)	10 (52.6)	10 (62.5)	4 (20.0)	7 (43.8)	50 (48.1)
2	2 (6.7)	0	0	0	0	2 (1.9)
Tumor Stage at Study Entry (n (%))						
Unresectable Stage III	6 (20.0)	0	0	1 (5.0)	0	7 (6.7)
Stage IV	24 (80.0)	19 (100.0)	16 (100.0)	19 (95.0)	16 (100.0)	97 (93.3)

StDev = Standard deviation

** See Table 1

Table 3. Treatment Exposure, Safety Analysis Set

	Ovarian cancer *(n=30)*	Colorectal cancer *(n=19)*	NTNB cancer *(n=16)*	Renal cell carcinoma *(n=20)*	Cervical cancer *(n=16)*	All patients** *(n=104)*
Treatment Duration *(weeks)*						
Mean (StDev)	12.51 (12.757)	10.92 (8.966)	7.47 (8.131)	13.87 (11.053)	12.38 (14.093)	11.42 (11.274)
Median	8.14	8.29	4.79	10.93	8.43	8.14
Range	0.1–46.3	0.1–32.1	0.1–32.1	0.1–50.7	0.1–55.1	0.1–55.1
Number of Treatment Cycles*						
Mean (StDev)	3.9 (3.13)	3.4 (1.83)	2.7 (1.85)	4.2 (2.65)	3.5 (2.80)	3.5 (2.58)
Median	3.0	3.0	2.0	3.0	3.0	3.0
Range	1–13	1–8	1–8	1–13	1–12	1–13
1 Cycle, n (%)	4 (13.3)	2 (10.5)	4 (25.0)	1 (5.0)	2 (12.5)	15 (14.4)
> 1 Cycle, n (%)	26 (86.7)	17 (89.5)	12 (75.0)	19 (95.0)	14 (87.5)	89 (85.6)
Total Dosage of tremelimumab *(mg)*						
Mean (StDev)	350.3 (386.04)	302.1 (264.50)	173.4 (80.86)	346.4 (454.65)	193.1 (77.82)	289.0 (315.57)
Median	225.5	225.0	150.0	262.5	225.0	225.0
Range	73–2158	75–1150	75–300	75–2260	75–300	73–2260
Total Dosage of durvalumab *(mg)*						
Mean (StDev)	4181.9 (4707.37)	4050.5 (2648.82)	4125.0 (2765.86)	4961.1 (3071.41)	4518.8 (2511.10)	4237.4 (3438.66)
Median	3000.0	3000.0	3000.0	4500.0	4500.0	3750.0
Range	82–19800	430–9000	1500–12000	150–10500	1500–12000	82–19800

*Patients are counted as treated for a cycle if they received any study drug during that cycle.

First patient/first visit (escalation) 17 December 2013

First patient/first visit (expansion) 13 May 2016

Last patient/first visit 26 December 2016

** See Table 1

Table 4. Treatment Related Adverse Events (TRAEs) by MedDRA Preferred Term in ≥ 5 (4.8%) Patients and by Maximum CTCAE Grade, Safety Analysis Set

	Ovarian cancer *(n=30)*		Colorectal cancer *(n=19)*		NTNB cancer *(n=16)*		Renal cell carcinoma *(n=20)*		Cervical cancer *(n=16)*		All patients** *(n=104)*	
	All	*Gr 3**	*All*	*Gr 3**	*All*	*Gr 3**	*All*	*Gr 3**	*All*	*Gr 3**	*All*	*Gr 3**
Any treatment related adverse events n (%)	**23** (76.7)	**6** (20)	**13** (68.4)	**1** (5.3)	**12** (75.0)	**3** (18.8)	**16** (80.0)	**3** (15.0)	**12** (75.0)	**2** (12.5)	**79** (76.0)	**15** (14.4)
Gastrointestinal disorders	**11** (36.7)		**8** (42.1)		**9** (56.3)		**4** (20.0)		**5** (31.3)		**38** (36.5)	
Diarrhea	7 (23.3)	1 (3.3)	6 (31.6)	0	6 (37.5)	0	1 (5.0)	0	4 (25.0)	1 (6.3)	25 (24.0)	2 (1.9)
Nausea	2 (6.7)	0	3 (15.8)	1 (5.3)	2 (12.5)	0	3 (15.0)	0	0	0	11 (10.6)	1 (1.0)
Vomiting	3 (10.0)	0	2 (10.5)	1 (5.3)	1 (6.3)	0	1 (5.0)	0	0	0	7 (6.7)	1 (1.0)
Skin and subcutaneous tissue disorders	**11** (36.7)		**5** (26.3)		**4** (25.0)		**8** (40.0)		**4** (25.0)		**33** (31.7)	
Rash/Pruritus	13 (43.3)	0	5 (26.3)	0	4 (25.0)	0	11 (55.0)	0	4 (25.0)	1 (6.3)	38 (36.5)	1 (1.0)
General disorders/ administration site conditions	**8** (26.7)		**4** (21.1)		**5** (31.3)		**5** (25.0)		**4** (25.0)		**27** (26.0)	
Fatigue	6 (20.0)	0	2 (10.5)	0	3 (18.8)	0	5 (25.0)	0	1 (6.3)	0	17 (16.3)	0
Pyrexia	1 (3.3)	0	2 (10.5)	0	1 (6.3)	0	0	0	1 (6.3)	0	5 (4.8)	0
Investigations	**5** (16.7)		**2** (10.5)		**4** (25.0)		**4** (20.0)		**2** (12.5)		**18** (17.3)	
AST increased	1 (3.3)	1 (3.3)	0	0	2 (12.5)	1 (6.3)	2 (10.0)	0	1 (6.3)	0	7 (6.7)	2 (1.9)
ALT increased	1 (3.3)	1 (3.3)	0	0	1 (6.3)	0	2 (10.0)	0	1 (6.3)	1 (6.3)	6 (5.8)	2 (1.9)
Endocrine disorders	**5** (16.7)		**4** (21.1)		**1** (6.3)		**1** (5.0)		**1** (6.3)		**12** (11.5)	
Hypothyroidism	3 (10.0)	0	3 (15.8)	0	1 (6.3)	0	1 (5.0)	0	0	0	8 (7.7)	0
Hyperthyroidism	3 (10.0)	0	1 (5.3)	0	0	0	0	0	1 (6.3)	0	5 (4.8)	0

NCI CTCAE scale Version 4.03. Adverse events are coded using the MedDRA Dictionary Version 16.0.

Treatment related adverse events are those determined by the investigator to be possibly, probably or definitely related to study drug. The relationship to study drug could refer to the regimen or a specific drug within the combination. Patients who experienced the same event at more than one severity level are counted only for each unique SOC and PT once under the maximum severity of CTCAE Grade experienced.

* There was one Grade 4 TRAE in the study: this patient (escalation Cohort 3, ovarian) experienced a CTC Grade 4 TRAE of hyponatremia. One patient in the NTNB cancer cohort was reported to have died overseas due to multi-organ failure (CTC Grade 5), which was most likely caused by progression, but an immune-related etiology cannot be entirely excluded.

** See Table 1

Table 5. Interim Tumor Response Based on Immune-related Response Criteria (irRC), ITT Analysis Set

	Ovarian cancer *(n=27)*	Colorectal cancer *(n=18)*	NTNB cancer *(n=16)*	Renal cell carcinoma** *(n=20)*	Cervical cancer *(n=16)*	All patients*** *(n=97)*
Best Overall Tumor Response						
irPartial Response (irPR), n (%)	2 (7.4)	2 (11.1)*	1 (6.3)	3 (15.8)	2 (13.3)	10 (10.5)
95% CI	0.9, 24.3	1.4, 34.7	0.2, 30.2	3.2, 37.9	1.6, 38.3	5.1, 18.1
irStable Disease (irSD), n (%)	10 (37.0)	2 (11.1)	2 (12.5)	11 (57.9)	5 (33.3)	30 (31.6)
95% CI	19.4, 57.6	1.4, 34.7	1.6, 38.3	31.5, 76.9	11.0, 58.7	21.9, 41.1
irProgressive Disease, n (%)	15 (55.6)	14 (77.8)	13 (81.3)	5 (26.3)	7 (46.7)	54 (56.8)
95% CI	35.3, 74.5	52.4, 93.6	54.4, 96.0	8.7, 49.1	19.8, 70.1	45.2, 65.8
Not evaluable or missing, n	0	0	0	1	2	3
Disease Control Rate (DCR), n (%)	12 (44.4)	4 (22.2)	3 (18.8)	14 (70.0)	7 (43.8)	40 (41.2)
95% CI	25.5, 64.7	6.4, 47.6	4.0, 45.6	45.7, 88.1	19.8, 70.1	31.3, 51.7
Duration of Response (days), n	2	2	1	3	2	10
Median	322.5	75.0	52.0	57.0	37.0	54.5
Range	168–477	29–121+	52	29–399+	26–48+	26–477

Percentages are based on the number of patients in the ITT Analysis Set in each column. CI=Confidence Interval. 95% CI is calculated based on the binomial distribution.

There were no patients meeting criteria of irComplete Response.

Disease Control Rate (DCR) is defined as percentage of patients meeting criteria of Complete Response, Partial Response, or Stable Disease and have been treated for at least 4 weeks without progression.

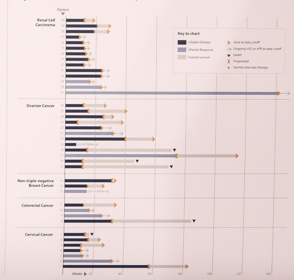
Duration of response is calculated for responders only. + indicates ongoing response.

*irPR for CRC: one patient had MSI-high status and the other had unknown MSI status.

**RCC: 70% = clear cell histology; 30% = other rare histologies.

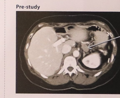
***See Table 1, Footnote **

Figure 3. Survival in Patients with Best Overall Response irPR and irSD

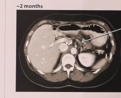

Patient
Renal Cell Carcinoma
Ovarian Cancer
Non-triple-negative Breast Cancer
Colorectal Cancer
Cervical Cancer
Key to chart
irStable Disease
irPartial Response
Overall survival
Alive at data cutoff
Ongoing irSD or irPR at data cutoff
Death
Progressed
Started alternate therapy

Tumor Imaging for Ovarian Patient #21 in Figure 3

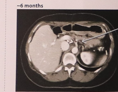
Pre-study



~2 months



~6 months



5 Conclusions

- Treatment is reasonably well tolerated, with a safety profile consistent with that reported for checkpoint therapy including other studies with tremelimumab and durvalumab.
- No new toxicities have been identified with the durvalumab and tremelimumab combination therapy.
- Early evidence of efficacy was observed with responses seen in all expansion cohorts. Final conclusions cannot be drawn from this ongoing study, because some patients still have a chance to respond and the overall number of patients in each cohort is small. However, these interim data do support continued study of the combination in all of the tumor types included in the expansion cohorts.
- Of the two CRC patients who achieved partial responses, one had MSI-high status and the other had unknown MSI status.
- Study is ongoing with 25% of patients on treatment as of the cutoff date. Efficacy data will be updated as data mature.
- Exploratory studies are ongoing.

Acknowledgments

We gratefully acknowledge the patients in the study and their families, and the Study Investigators and their teams.

This study is sponsored by Ludwig Cancer Research with grant funding and support from MedImmune and grant funding from Cancer Research Institute.

Statistical analysis was provided by Prometrika LLC, Cambridge, MA.

References

1 Khleif SN, et al. Eur Cancer Congress. 2013.
2 Hodi FS, et al. N Engl J Med 2010;363:711-23.
3 Topalian SL, et al. N Engl J Med 2012;366:2443-54.
4 Sharma P and Allison JP. Cell 2015;161:205-14.
5 Wolchok JD, et al. N Engl J Med 2013;369:122-33.
6 Postow MA, et al. N Engl J Med 2015;372:2006-17.
7 Wolchok JD, et al. Clin Cancer Res 2009;15:7412-20.
8 Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47.

Poster Presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, Illinois, USA, June 2–6, 2017.

Contact: Margaret Callahan, MD, PhD | callaham@mskcc.org