Published in final edited form as:

J Immunother. 2009 October ; 32(8): 884–885. doi:10.1097/CJI.0b013e3181affbf0.

No Correlation Between Clinical Response to CTLA-4 Blockade and Presence of NY-ESO-1 Antibody in Patients With Metastatic Melanoma

Stephanie L. Goff, MD, Paul F. Robbins, PhD, Mona El-Gamil, and Steven A. Rosenberg, MD, PhD

Surgery Branch, National Cancer Institute, National Institutes of Health Bethesda, MD

To the Editor:

A recent study by Yuan et al¹ suggested that the blockade of inhibitory cytotoxic T-lymphocyte antigen-4 (CTLA-4) signaling enhanced NY-ESO-1 antigen-specific responses in patients with responding or stable disease. Five of 8 patients experiencing “clinical benefit” from anti-CTLA-4 antibody (ipilimumab) administration had increased serum levels of anti-NY-ESO-1 antibody compared with no antibody detected in 7 clinical nonresponders. We thus conducted an analysis of this association in patients treated in the Surgery Branch, National Cancer Institute (NCI).

Twenty-three objective responders (partial response or complete response by RECIST criteria) were identified from 2 clinical trials performed in the Surgery Branch, NCI.² Nonresponding patients were selected to match age, HLA-A2 status, and protocol assignment.

In Trial 1, 29 HLA-A*0201 patients received anti – CTLA-4 antibody (ipilimumab, Bristol-Myers Squibb/Medarex Inc, Laurenceville and Princeton, NJ) every 3 weeks at 3 mg/kg intravenously over 90 minutes in conjunction with the subcutaneous injection of 1 mg of gp100:209–217(210M) peptide (IMDQVPFSV) emulsified in Montanide ISA-51 in 1 extremity and 1 mg of gp100:280–288(288V) peptide (YLEPGPVTV) similarly emulsified, in another extremity. An additional 27 HLA-A*0201 patients in a second cohort of Trial 1 received an initial dose of 3 mg/kg ipilimumab, followed by subsequent doses every 3 weeks of 1 mg/kg. Ipilimumab was supplied by the manufacturer; peptides and Montanide ISA-51 were supplied by the Cancer Therapy Evaluation Program, NCI

Trial 2 was designed as an inpatient dose-escalation study, and HLA-A*0201-positive patients were randomized to receive ipilimumab every 3 weeks, alone or in conjunction with gp100:209–217(210M) and gp100:280–288(288V) peptides emulsified in Montanide ISA-51. HLA-A*0201-negative patients received ipilimumab alone. Ipilimumab treatment was started at 3 or 5 mg/kg. If after 1 course (2 treatments), patients did not achieve an objective response or a dose-limiting toxicity, the dose was increased to 5 or 9 mg/kg. After another 2 treatments, patients could then be escalated to 9 mg/kg/dose.

Sera collected before the therapy and at a point >6 weeks from first dose of therapy were analyzed when available. NY-ESO-1 specific antibodies were measured by enzyme-linked

immunosorbent assay. In all, 96-well plates were coated with recombinant ESO protein, 0.1 µg/100 µl/well (Novavax, Rockville, MD). Known positive and negative sera and plates coated with phosphate-buffered saline 1% human serum albumin were used as control reagents. Detection antibody was goat anti-human IgG (γ-chain specific)-peroxidase conjugate (Sigma-Aldrich, St. Louis, MO). Positive values were defined as those values greater than the mean plus 3 standard deviations of 6 normal volunteer samples and twice the corresponding human serum albumin plate control.

The 46 patients selected represent a subset of the 139 patients treated with ipilimumab ± peptide vaccination in 2 trials that we have previously reported.² There was no difference in response rate between Trial 1 and Trial 2, and the patients were combined for further analysis. The 23 responders include 3 ongoing complete responders and 20 (9 ongoing) partial responders.

Most patients had no detectable anti-NY-ESO-1 antibody. Of the 5 patients with antibody detection titers of >1:25000, 3 were nonresponders. (Table 1) There was no correlation with seropositivity and response when evaluated pretreatment ($P = 1.0$) or posttreatment ($P = 0.7$) (Table 2).

Three of the 5 patients with the highest observed titers were nonresponders. The patient with the most demonstrable increase in titer after receiving anti-CTLA-4 therapy was a partial responder with a short (9 mo) duration of response. None of the ongoing complete responders had detectable levels of NY-ESO-1 antibody in their sera, pretreatment or posttreatment.

Yuan et al¹ propose that the detection of NY-ESO-1 immunity may be a marker for a more generalized immune activation that may be part of a clinical response to ipilimumab. It has been demonstrated that one consequence of such generalized immune activation is the development of immune-related adverse events such as dermatitis, enterocolitis, and hypophysitis. These events are highly correlated with the likelihood of response and most can be ameliorated by the use of steroids supporting the theory that an immune activation and a break of self tolerance is likely the mechanism of ipilimumab's action.²⁻⁷

REFERENCES

1. Yuan J, Gnjatic S, Li H, et al. CTLA-4 blockade enhances polyfunctional NY-ESO-1 specific T cell responses in metastatic melanoma patients with clinical benefit. *Proc Natl Acad Sci USA*. 2008;105:20410—20415. [PubMed: 19074257]
2. Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin Cancer Res*. 2007;13:6681—6688. [PubMed: 17982122]
3. Phan GQ, Yang JC, Sherry RM, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proc Natl Acad Sci USA*. 2003;100:8372—8377. [PubMed: 12826605]
4. Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol*. 2005; 23:6043—6053. [PubMed: 16087944]

5. Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J Immunother.* 2007;30:825—830. [PubMed: 18049334]
6. Blansfield JA, Beck KE, Tran K, et al. Cytotoxic T-lymphocyte-associated antigen-4 blockage can induce autoimmune hypophysitis in patients with metastatic melanoma and renal cancer. *J Immunother.* 2005;28:593—598. [PubMed: 16224277]
7. Beck KE, Blansfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol.* 2006;24:2283—2289. [PubMed: 16710025]

TABLE 1.

Titer of NY-ESO-1 Antibody in Patient Sera

ID	Response	Pretreatment Titer	Posttreatment Titer	No. Weeks After First Treatment	Total Dose Received Between Pretreatment and Posttreatment Samples (mg/kg)	Increase in Titer?
MD101	PR	UND	UND	11	6	U
MD111	CR	NT	UND	13	12	—
MD113	CR	UND	UND	12	9	U
MD115	PR	UND	UND	7	4	U
MD119	PR	UND	UND	6	4	U
MD124	PR	UND	UND	12	4	U
MD143	PR	UND	UND	7	6	U
ME001	PR	UND	UND	6	6	U
ME007	PR	UND	1:250	13	6	Y
ME010	PR	1:250	1:25000	6	16	Y
ME031	PR	1:250000	NT	n/a	6	—
ME040	PR	UND	UND	47	n/a	U
ME042	PR	UND	NT	n/a	37	—
ME102	PR	UND	UND	6	n/a	U
ME125	PR	1:250	1:250	14	6	N
ME130	PR	UND	UND	6	20	U
ME131	PR	UND	1:25	6	10	Y
ME133	PR	UND	UND	13	10	U
ME134	PR	UND	UND	7	28	U
ME203	PR	UND	UND	6	10	U
ME204	CR	UND	UND	6	6	U
ME208	PR	UND	UND	6	6	U
ME229	PR	UND	1:25	6	10	Y
MD108	NR	UND	NT	n/a	n/a	—
MD126	NR	1:250,000	1:250,000	6	4	N
MD127	NR	UND	UND	6	4	U
MD128	NR	UND	UND	6	4	U
MD142	NR	UND	UND	6	6	U

ID	Response	Pretreatment Titer	Posttreatment Titer	No. Weeks After First Treatment	Total Dose Received Between Pretreatment and Posttreatment Samples (mg/kg)	Increase in Titer?
MD153	NR	UND	NT	n/a	n/a	—
MD156	NR	UND	1:25	12	12	Y
ME014	NR	UND	UND	6	6	U
ME020	NR	UND	UND	12	16	U
ME023	NR	UND	UND	6	6	U
ME025	NR	1:2500000	NT	n/a	n/a	—
ME030	NR	UND	UND	34	28	U
ME033	NR	UND	NT	n/a	n/a	—
ME101	NR	UND	NT	n/a	n/a	—
ME103	NR	UND	UND	6	6	U
ME127	NR	UND	UND	6	10	U
ME135	NR	UND	UND	6	10	U
ME201	NR	UND	UND	6	6	U
ME206	NR	UND	UND	6	6	U
ME232	NR	UND	UND	6	10	U
ME234	NR	UND	UND	6	5	U
ME235	NR	1:25000	1:2500000	6	5	Y
ME237	NR	1:25	NT	n/a	n/a	—

CR indicates complete response; NR, no response; N, no change or decrease in titer; NT, not tested; PR, partial response; U, undetectable → undetectable; UND, undetectable; Y, increase in titer

TABLE 2.

Presence of NY-ESO-1 Antibody* in Sera of Patients Treated With Anti-CTLA-4

	Responders		Nonresponders		P
Pretreatment	3/22	14%	4/23	17%	1.0
Posttreatment	5/21	24%	3/17	18%	0.71
Weeks after first dose (median)	7		6		
Dose received between samples (mg/kg, median)	6		6		
Relative change					
Undetectable → Undetectable	15/20	75%	14/17	82%	
Increased titer	4/20	20%	2/17	12%	
Decreased or unchanged titer	1/20	5%	1/17	6%	

* All (+) values indicate detection at 1:25 dilution or higher.