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Long term Survival with CTLA-4 blockade Using Tremelimumab

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Abstract

Purpose—One of the hallmarks of cancer immunotherapy is the long duration of responses, evident with cytokines like interleukin-2 or a variety of cancer vaccines. However, there is limited information available on very long term outcomes of patients treated with anti-CTLA-4 antibodies. Tremelimumab is an anti-CTLA-4 antibody of Ig G2 istoype initially tested in patients with advanced melanoma over 12 years ago.

Methods—We reviewed the outcomes of patients with advanced melanoma enrolled in four phase 1 and 2 tremelimumab trials at two sites to determine response rates and long-term survival.

Results—A total of 143 patients were enrolled at two institutions from 2002 to 2008. Tremelimumab administration varied between a single dose of 0.01 mg/kg and 15 mg/kg every 3 months. Median overall survival was 13 months (95% CI, 10–16.6), ranging from less than a month to 12+ years. An objective response rate of 15.6% was observed, with median duration of response of 6.5 years, range of 3 to 136+ months. The Kaplan-Meier estimated 5 year survival rate was 20% (95% CI, 13–26%), with 10 and 12.5 year survival rates of 16% (95% CI, 9–23%).

Conclusions—CTLA-4 blockade with tremelimumab can lead to very long duration of objective anti-tumor responses beyond 12 years.

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Introduction

A well-recognized hallmark of cancer immunotherapy is the long duration of responses, lasting even decades, as evidenced with the use of high dose interleukin-2 or certain cancer vaccines[1, 2]. Only a minority of patients with advanced melanoma attain objective responses with these therapies; however, when reached, the nature of these responses is usually sustained over several years.

Anti-cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) antibodies such as ipilimumab and tremelimumab bind to the inhibitory CTLA-4 receptor on T cells; by blocking the inhibition of costimulatory B7 ligands by CTLA-4, they increase immune stimulation and drive T cell activity [3]. Both drugs are fully human monoclonal antibodies directed against CTLA-4; there are minimal differences between them as ipilimumab is an immunoglobulin IgG1 isotype and tremelimumab is a non-complement-fixing IgG2 isotype [4]. Ipilimumab was approved by the FDA in 2011 for the treatment of patients with unresectable metastatic melanoma based on improvement in overall survival (OS) in two randomized trials [5, 6]. While response rates for ipilimumab in patients with advanced melanoma have ranged from only 10 to 15%[6], the demonstration of long-lasting responses with ipilimumab has stimulated further interest in use of these therapies, with a plateau in the survival curve of 21% beginning at 3 years [7].

As the other anti-CTLA-4 antibody in clinical trials, tremelimumab has also been studied in patients with advanced melanoma and other tumor types [10]. A phase 2 trial of tremelimumab in melanoma compared two dosing regimens at 10 mg/kg once per month and 15 mg/kg once every 3 months [11]. While no difference was seen in the response rate or survival, a dose of 15 mg/kg every 3 month dosing was selected for phase 3 trial testing due to a better toxicity profile. In the phase 3 trial, 655 patients with Stage IIIC or IV and measurable disease were enrolled and randomized to either tremelimumab at 15 mg/kg every three months or chemotherapy with dacarbazine or temozolamide. While no significant statistical differences were observed in the overall response rates (11% with tremelimumab and 10% with chemotherapy; p=0.618) or median OS (12.6 months for tremelimumab and 10.7 months with chemotherapy; p=0.127) between arms, the duration of the anti-tumor responses was significantly different (tremelimumab 35.8 months versus chemotherapy 13.7 months (p=0.0011)[12]. The study design did not allow crossover for patients who progressed to chemotherapy. However, patients in the chemotherapy arm were exposed to ipilimumab (up to 34% of patients who were alive or censored at time of study closure) and the cross-over therapy with the frequent use of a different anti-CTLA-4 antibody in the chemotherapy control arm may have explained the lack of a survival impact [13].

Newer immune checkpoint inhibitors such anti-PD-1 and PD-L1 antibodies have shown response rates ranging between 30–40%, higher than either of the two anti-CTLA-4 antibodies, although long term follow up of patients treated with anti-PD-1/PD-L1 therapies is not yet available [14, 15]. As both ipilimumab and tremelimumab have moved toward combination regimens in clinical trials with other checkpoint inhibitors or immune agonists in advanced melanoma and other tumors [16, 17], we wanted to evaluate the long-term survival in patients with advanced melanoma treated with tremelimumab. We retrospectively

reviewed the records of 143 patients enrolled in four different phase 1 and 2 tremelimumab trials and report on the outcome and follow up of those patients during the past decade.

Methods

Patients

The data presented in this retrospective analysis were obtained from patients enrolled in four clinical trials conducted at UCLA and MD Anderson Cancer Center since these two sites were the initial and highest accruing sites for the early tremelimumab clinical trials. All patients with confirmed stage IIIC or IV melanoma were included. Further details can be found in the original publications of each of the studies [11, 18–20]. The Institutional Review Boards of both participating institutions approved all trials and signed informed consent was obtained from every study participant.

The first trial analyzed was the phase 1 study of tremelimumab, which enrolled 34 patients with advanced melanoma from UCLA and MD Anderson from January 2002 until August 2003 [18] (Pfizer A367-1001, not NCI registered). Doses ranged from 0.01 mg/kg up to 15 mg/kg, using a modified Fibonacci dose escalation design. Each patient received a single dose, but patients in the first three cohorts were allowed to re-enter at higher dose levels. WHO criteria were used to assess response in patients who had measurable disease at baseline [21]. Five patients with a non-melanoma diagnosis and four patients with melanoma but no evidence of disease (NED) at baseline were excluded from this analysis. Two patients with metastatic melanoma that were considered to have non-measurable disease at baseline by WHO criteria were included.

The second trial was a combined phase 1/2 study of tremelimumab (NCT00086489) in patients with unresectable melanoma [11]. While 117 patients were enrolled in this trial, the 67 patients who participated at UCLA and MD Anderson were included in this analysis, as these sites had the largest numbers of patients with earliest accrual. These patients were enrolled between August 2003 and October 2005. RECIST 1.0 guidelines were followed for analysis of tumor responses [22]. During the phase 1 stage of the trial, patients were treated at 3, 6 or 10 mg/kg monthly intravenous infusions, while in the phase 2 stage of the trial, patients were assigned to 10 mg/kg monthly or 15 mg/kg every 3 month infusions of tremelimumab.

The third trial was a phase 1 study of tremelimumab in combination with a MART-1 peptide-pulsed dendritic cell vaccine (NCT00090896). Sixteen patients with unresectable stage 3 and stage 4 melanoma expressing MART-1 were enrolled at UCLA from June 2004 to March 2007 [19]. Doses ranged from 3 mg/kg monthly to 15 mg/kg every 3 months; RECIST 1.0 guidelines were used to assess tumor responses.

The fourth trial was a phase 2 study of tremelimumab administered at 15 mg/kg every 3 months with baseline and post-dosing biopsies, with 32 patients with unresectable melanoma enrolled at UCLA from February 2007 to May 2008 (NCT00471887) [20]. As one patient was determined to be a screen failure after enrollment and did not receive

tremelimumab, 31 patients were included in this analysis. The screen-failure patient was alive at last follow-up five years after enrollment.

Tremelimumab administration

The administered doses to all patients included in this analysis varied from a single dose of 0.01 mg/kg of tremelimumab in the phase 1 study (A367-1001), to monthly doses at 10 mg/kg and up to 15 mg/kg every 3 months. With the exception of the dose escalation in the first phase 1 study, treatment was continued until progression of disease or significant toxicity was observed. As above, WHO criteria were used to assess response in the first phase 1 study and RECIST guidelines thereafter.

Statistical analysis

Kaplan-Meier method and Greenwood's formula were used for the estimation of survival probabilities (survival rates and overall survival) and the corresponding 95% confidence intervals (CIs). The objective response rate was reported as proportion along with Clopper-Pearson exact CIs. The chi-square and Fisher's exact test were used to test for differences between groups for categorical variables.

Results

Patient characteristics

A total of 143 patients enrolled between January 2002 and May 2008 were included in this analysis (Table 1). Nineteen patients (13%) had stage IIIC disease, while the remainder had stage IV disease. Approximately 80% of patients received tremelimumab at either 10 mg/kg every month or 15 mg/kg every 3 months. All others received lower doses.

Response rate

One hundred-forty one patients (98%) were assessed for response and 22 patients achieved objective responses (15.6%, 95% Clopper-Pearson CI of 10–22.7%). Eighteen responses were evaluated by RECIST, and four responses were evaluated by WHO criteria in the phase 1 trial (all four of patients who had a response by WHO criteria had a complete response). A total of thirteen complete responses and nine partial responses were observed (Table 2). Only 2 out of 28 patients (7.1%) who received doses ranging from 0.01 up to 6 mg/kg had a response, while 20 out of 114 (18%) who received 10 or 15 mg/kg of tremelimumab had a response, although this was not a statistically significant difference (Supplemental Table 1). There was also no statistically significant difference between the 10 or 15 mg/kg doses.

For the 22 patients with an objective response, the median duration of response was 6.5 years, ranging from 3 to 136+ months (Figures 1 and 2). Of note, 7 of the 22 responders had stage IIIC disease; as expected, these patients were more likely to have a response compared to patients with stage IV melanoma (p=0.004).

Long-term responders and surviving non-complete responders

Of the 22 patients with objective responses (CR or PR), the majority had received prior systemic therapy. All except 3 patients maintained a response for over a year, and 15 patients

had responses lasting at least 5 years (4 PR and 11 CRs), with two patients with PR having subsequent surgery. One patient with a shorter duration of PR (progression free survival of 10 months) had subsequent surgery at a site of progression, and lived 8.5 years without further therapy before dying from colon cancer. Only one patient who achieved a CR has relapsed, which happened after 3 years; at time of relapse, the patient underwent surgical resection, received reinduction with tremelimumab and is alive 11 years later. In the patients who responded to therapy, grade 3 toxicities were observed in eight of 22 (36%) responders, and no grade 4 toxicities were seen. Most of these toxicities occurred during the first year of therapy, except for three patients who had grade 3 toxicities in the fourth, sixth and eight year after onset of tremelimumab.

There were 9 additional patients who did not have an objective response to therapy but were alive over 5 years or longer (Supplemental Table 2). Two of these patients had no measurable disease at baseline and thus were not assessable for response. However, one patient with brain metastases who progressed after 2 months on study had subsequent resection of bowel metastasis and radiofrequency ablation of a liver metastasis, and has been alive without further therapy for over 12 years. Four patients had stable disease as best response on therapy, including one patient who was considered to have stable disease for over 7 years with no other therapy besides tremelimumab, and who died due to unrelated reasons.

Long-term survival

At the September 2014 cut off for data analysis, all 143 patients analyzed had enrolled in the four tremelimumab trials at least six years ago. Seventy-two patients were alive at 12 months with a Kaplan-Meier 1-year survival rate of 50% (95% CI, 42–59%). Thirty-nine of 143 patients were alive at 36 months confirming a 3-year survival rate of 27% (95% CI, 19–34%), and 27 patients were alive at least 60 months with an estimated 5 year survival rate of 20% (95% CI, 13–26%). Seventy-five of the 143 patients had enrolled more than 10 years before time of survival analysis. Thirteen out of total 143 patients were alive ≥120 months, with Kaplan-Meier estimated 10-year and 12.5-year survival probability of 16% with 95% CI, 9–23%.

Overall survival

A median overall survival of 13 months (95% CI, 10–16.6%) was observed; no difference in survival was observed in association with the site of study enrollment. Survival ranged from less than 1 month to 150+ months (12.5+ years, Figure 3). Median OS was longer in the 18 patients with stage IIIC disease (median 46.4 months) compared to the 125 patients with stage IV disease (13 months, $p < 0.001$). Median OS was also much shorter (2 months) in the four patients who received 0.01, 0.1 or1 mg/kg doses compared to the rest of the patients who received higher doses (median OS 14 months, $p=0.03$). There were no significant differences in survival between the 3, 6, 10 or 15 mg/kg dosing regimens. There was no correlation between patients' age or gender with response rate or overall survival.

Discussion

Our data suggest that CTLA-4 blockade with tremelimumab induces durable responses in patients with advanced melanoma, with a plateau of the survival curve observed. The combined long term follow up data with ipilimumab and tremelimumab provide compelling evidence that CTLA-4 blockade therapy can lead to very long duration of responses, which most likely represent cures from their advanced melanoma in a small subset of patients. Long term follow up with ipilimumab treatment has been provided from three published studies; of 177 patients, 14 out of 15 patients with a complete response continued responding with a median follow up of 7 years [8]. In an analysis of four phase 2 trials, five-year survival rates ranged from 16.5% for previously treated patients to 26.8% for treatment-naive patients who received ipilimumab at the 3 mg/kg dose [9]. A pooled analysis of 1861 patients with advanced melanoma treated with ipilimumab showed a median OS of 11.4 months; for the 254 patients who could be followed for overall survival for 3 years, a 3-year OS rate of 22% was observed [7].

In the tremelimumab phase 3 study, 3-year survival rate was 21% [12]; in the current analysis the 3-year survival was 27%, with a majority of these patients continuing to be alive at 5 years with an estimated 20% survival rate. Furthermore, there was a 16% survival estimate at 10 and 12.5 years. There were no long term toxicities among the patients followed for over one decade. Although four patients with a partial response eventually progressed and received other systemic therapies, the majority either underwent surgery with no subsequent therapy, or were eventually taken off tremelimumab with no progression of their disease.

There also appears to be a small subset of patients who do not meet criteria for objective response, but still have many years of stable disease, including two patients who had initially progressive disease per RECIST guidelines within 2 months after starting tremelimumab, but subsequently remained disease free over 12 years with no other systemic therapy. A prior analysis of tumor biopsies in seven patients in this series demonstrated massive intratumoral infiltrates of CD8+ cytotoxic T lymphocytes in those with an objective response as confirmed by WHO or RECIST guidelines [23, 24]. However, as observed in another study with ipilimumab, in some patients the tumor lesions may become heavily infiltrated by immune and inflammatory cells, resulting in an apparent increase in the size of lesions [25]; this may be due to infiltration by tumor immunotherapy–recruited cells as opposed to a progressive growth of cancer cells [24]. Thus, a lesion may qualify as progressive disease by WHO or RECIST guidelines, but the patient may potentially be a responder using immune-related response criteria [26].

Despite identical 21% 3-year survival rates in the phase 3 tremelimumab and ipilimumab trials [6, 12], tremelimumab is unlikely to ever obtain FDA approval for single-agent use in advanced melanoma as the phase 3 trial study did not meet its primary endpoint of overall survival benefit. This may have been be due to patients on the chemotherapy arm receiving ipilimumab when they came off study; overall survival would have been highly statistically significant if only the non–North American study sites were analyzed as these patients had a more restricted access to ipilimumab [13].

Regardless, immunotherapy has now moved forward into combination regimens to improve the numbers of patients who benefit from these treatments, including CTLA-4 antibodies combined with other checkpoint inhibitors or immune agonists. Ipilimumab has shown response rate of 58% together with the anti-PD-1 antibody nivolumab in patients with advanced melanoma [29], with a survival rate of 75% at two years [31]. Phase 1 clinical trials are ongoing for combination of tremelimumab with anti-PD-L1 antibody MEDI4736 in unresectable melanoma [32], advanced non-small cell lung cancers, head and neck cancers, and other solid tumors [33–35], and have moved to a phase 3 trial in previously treated advanced non-small cell lung cancers [36]. There are also trials of tremelimumab in combination with immune agonists; in a phase 1 study of tremelimumab with the agonistic CD40 antibody CP-870,893 in patients with metastatic melanoma, a response rate of 27.3% and a median OS of 26 months was observed in 24 patients [17]. Clinical trials have also examined the combination of CTLA-4 antibodies with targeted therapies such as BRAF and MEK inhibitors; the BRAF/MEK-inhibitor regimens offer much higher response rates at 65% although duration of responses is only about a year [37]. While preclinical data have suggested synergy with anti-CTLA-4 therapy [38], toxicity has been a significant concern with the targeted therapy combination studies, making further development challenging [39–41].

In conclusion, CTLA-4 blockade with tremelimumab can lead to long-lasting, sustained anti-tumor responses lasting well beyond a decade in a small proportion of patients with metastatic melanoma, and will likely continue to play a role in combination with other immunotherapeutics in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Few treatments for metastatic melanoma provide long term tumor regressions
- Response rate of 15.6% observed in 143 patients treated with tremelimumab
- Patients with tumor response to tremelimumab very likely to have durable responses
- Ten and 12.5 year estimated survival rates of 16% observed in these patients
- Anti-CTLA-4 memory immune responses against tumors can last beyond a decade

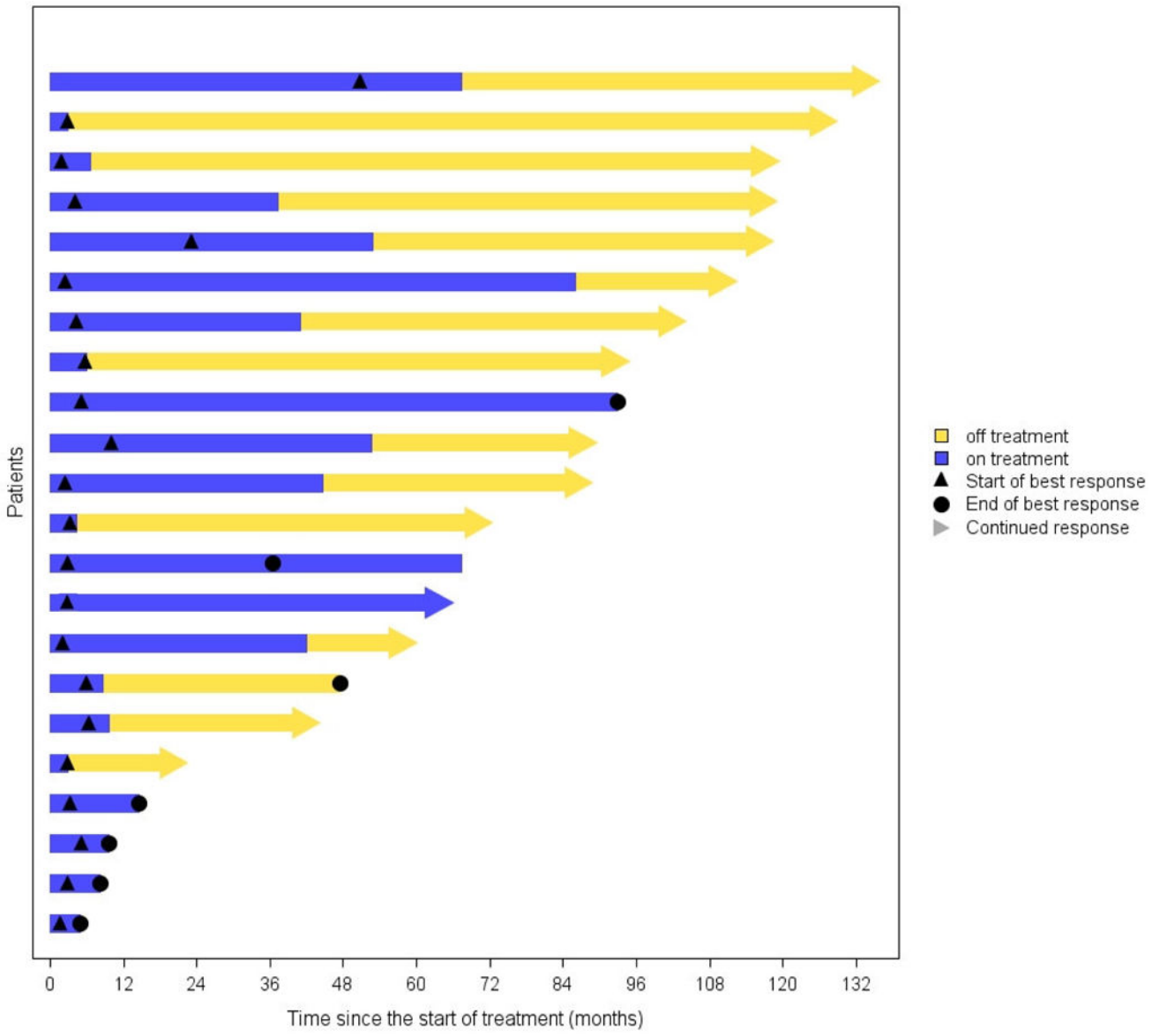

Figure 1.

Swimmer Plot. Each bar represents one subject. Blue bars indicate the time to and duration of response while on treatment; yellow bars indicate response duration after treatment discontinuation. Triangles indicate start of best response; circles indicate end of best response. Right arrows indicate ongoing response at time of last follow-up.

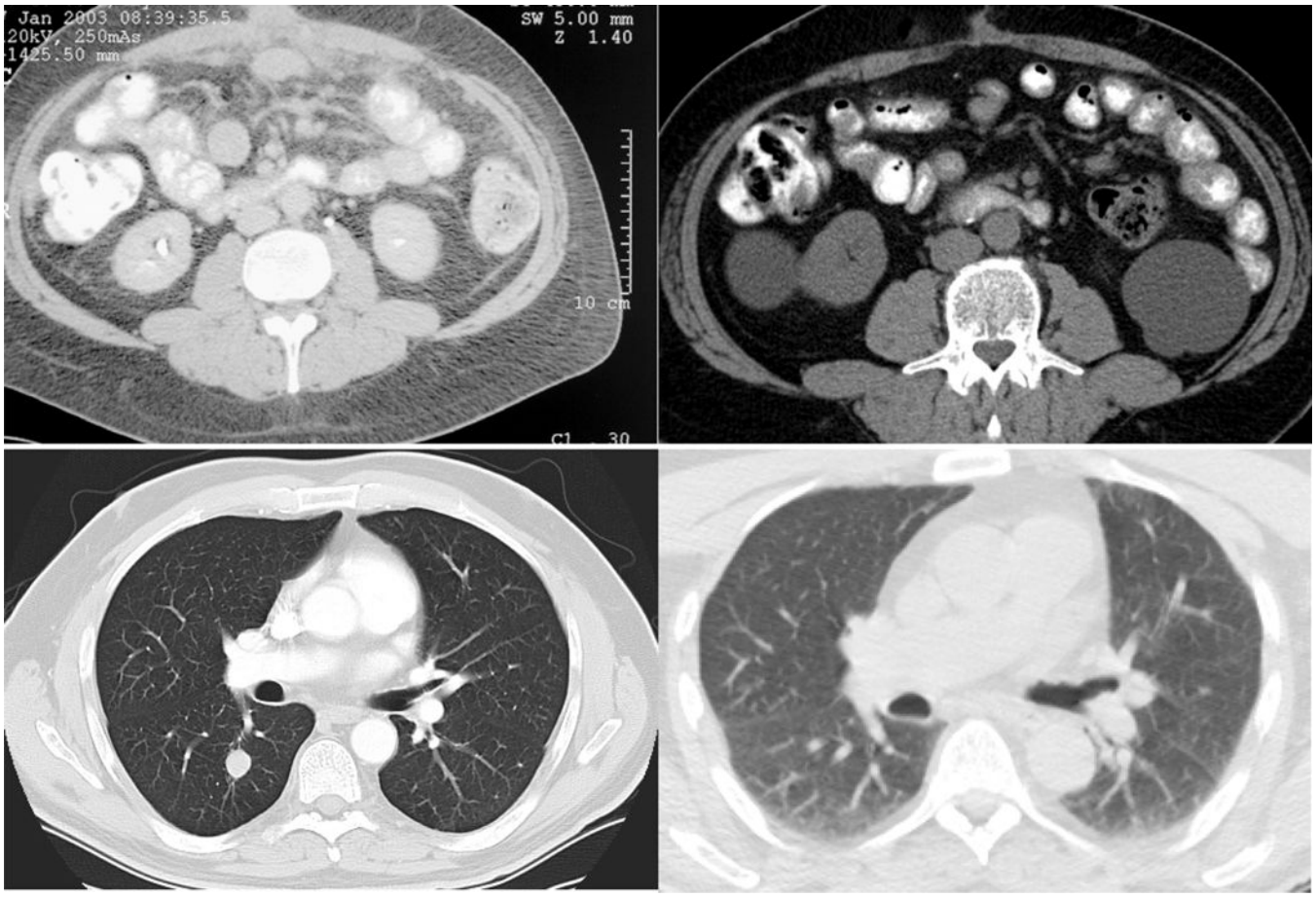

Figure 2.

Two patients with long lasting complete responses with tremelimumab therapy.

A) Patient A367-1001-125 - Baseline study from 1.7.2003 with arrows depicting peritoneal carcinomatosis.

B) Maintained complete response in 12.26.2012 in the same regions of previously visualized omental thickening and nodularity

C) Patient NRA9: Arrow pointing to right lower lobe pulmonary nodule on 11.28.2005

D) Right lower lobe nodule is no longer visualized on PET-CT 8.13.2013

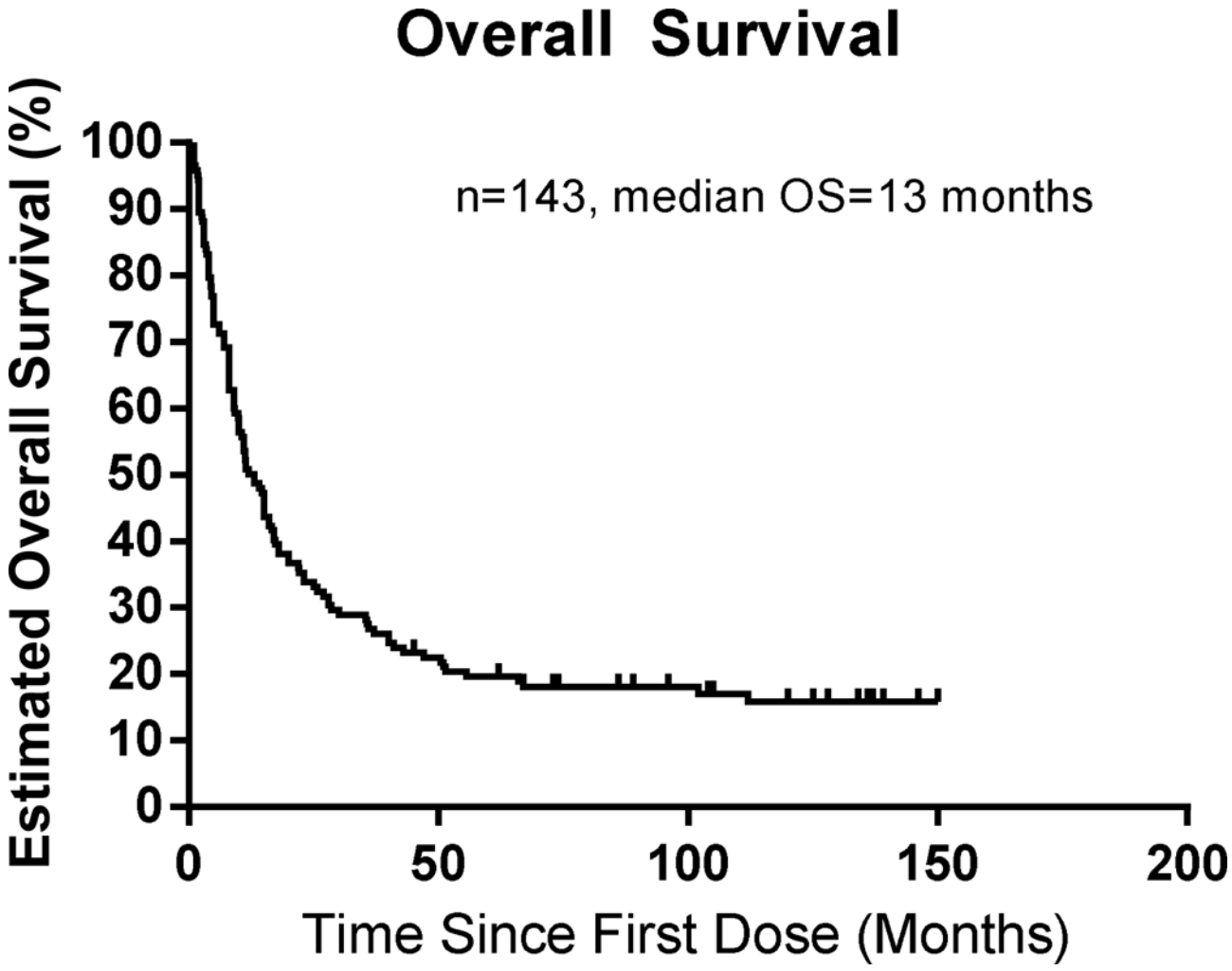

Figure 3.
Overall survival for all patients

Table 1

Patient Demographics

Age	Median = 55 (range 20–91)
Gender	100 male (70%), 43 female (30%)
Race/ethnicity	129 white, 12 Hispanic, 1 Asian, 1 unknown
Stage	
IIIc	18 (12.6%)
M1a	17 (11.9%)
M1b	28 (19.6%)
M1c	80 (55.9%)
Dose (mg/kg)	
0.01	2 (1.4%)
0.1	1 (0.7%)
1	1 (0.7%)
3	12 (8.4%)
6	12 (8.4%)
10	51 (35.7%)
15	56 (39.2%)
Unknown (either 10 or 15 mg/kg)	8 (5.6%)
Received post-tremelimumab systemic therapy	68 (47.9%)

Table 2

Clinical characteristics of patients who received an objective response with tremelimumab

Patient code	Age	Sex	Stage	Disease sites	Prior systemic Therapy	Tremelimumab highest dose/ number of doses	Grade 3/4 Treatment related toxicity/time of onset	P attern of progression/ post tremelimumab therapy	Best Response/PFS/OS
NRA 3	53	F	M1b	lung	none	3 mg/kg q month, 12 doses	none	Prog of residual single lung mass, resected by surgery	PR, 10 months, 102 months
A367-1001-113	49	F	M1b	lung, LN	ipilimumab, MART-1/dendritic cell vaccine, IL2+histamine	3 mg/kg, redosed	none	none	CR, 67+ months, 67+ months
A367-1002-12	58	F	M1c	bone, adrenal gland	adjuvant cancer vaccine	10 mg/kg q month, 3 doses	none	New liver mets, prog of adrenal mets/ temozolomide + thalidomide	PR, 4.7 months, 11.3 months
A367-1002-21	50	M	M1c	lung, skin, LN	adjuvant interferon	10 mg/kg, q month 7 doses	none	Tx stopped for complete surgical resection, developed brain mets, got SRS	PR, 48.2 months, 66.1 months
A367-1002-1111	90	M	IIIC	skin	BCG, AMG 706	10 mg/kg q month, 8 doses	none	Surgery (residual forearm skin lesion)	PR, 96 months, 96 months
A367-1002-15	65	M	M1c	lung, skin, LN	cisplatin+adriamycin	10 mg/kg q month, 45 doses	diarrhea (3) dyspnea (3), 8 years	Prog of skin mets/ Ipilimumab, then ADI + cisplatin	PR, 94.5 months, 125+ months
NRA14	57	M	IIIC	SC	MART-1 + gp100 peptide vaccines with IL-12	10 mg/kg q3 months, × 4 doses	none	None	CR, 89+ months, 89+ months
NRA9	51	M	M1b	lung	Dartmouth regimen	10 mg/kg q month	none	none	CR, 105+ months, 105+ months
A367-1002-1108	55	F	IIIC	SC	GM-CSF	10 mg/kg q month, 5 doses	hepatitis (3), 6 months, adrenal insufficiency (3), 7 months	none	CR, 120+months, 120+months
GA5	65	M	M1c	skin, LN, adrenal gland	none	15 mg/kg q3 month, 4 doses	none	Progressing lymph nodes/no further therapy	PR, 7 months, 20 months

Patient code	Age	Sex	Stage	Disease sites	Prior systemic Therapy	Tremelimumab highest dose/ number of doses	Grade 3/4 Treatment related toxicity/time of onset	P attern of progression/ post tremelimumab therapy	Best Response/PFS/OS
A367-1002-14	63	M	M1b	lung	biochemotherapy	15 mg/kg q month, 15 doses	none	New brain and adrenal mets/SRS to brain, temozolomide + thalidomide	PR, 14.8 months, 28 months
NRA15	48	M	M1a	LN	none	15 mg/kg q3 months, 2 doses	none	none	PR, 89+ months, 89+ months
A367-1002-1222	79	M	IIIC	skin, LN	melphalan, dendritic cell vaccine	Unknown dose, 3 doses	arthritis (3), 3 months	Surgery (residual left calf lesion)	PR, 104+ months, 104+ months
A367-1001-14	76	F	M1b	lung	adjuvant GMCSF	15 mg/kg q month, 17 doses	rash (3), pancreatitis (3), 4 years	New SQ and small bowel mets/surgical resection & resumed tremelimumab	CR, 37.1 months, 134.5+ months
GA29	79	F	IIIC	skin, SC	none	15 mg/kg q3 months, 3 doses	colitis (3), 8 months	none	CR, 45+ months, 45+ months
GA18	49	F	M1a	skin	GM-CSF	15 mg/kg q3 months. 3 doses	none	none	CR, 62+months, 62+months
GA31	49	F	IIIC	skin	none	15 mg/kg q3 months, 2 doses	none	none	CR, 73+ months, 73+ months
A367-1002-31	66	M	M1b	lung, LN	biochemotherapy	15 mg/kg q month, 36 doses	pancreatitis (3), 6 years	none	CR, 120+ months, 120+ months
A367-1002-1202	67	M	IIIC	skin	temozolamide + Imiquimod	15 mg/kg q3 months, 4 doses	none	none	CR, 120+ months, 120+ months
A367-1002-1203	39	M	M1c	bone, adrenal gland, skin	adjuvant melanoma lysate vaccine	15 mg/kg q3 months, 15 doses	none	none	CR, 120+ months, 120+ months
A367-1001-125	42	M	M1c	lung, liver, peritoneal omental, SC	XRT, IL-2/Interferon-2b combination	15 mg/kg, 31 doses	lipase elevation (3), 1 month	Did not progress/ lenalidomide, then repeat tremelimumab	CR, 136+ months, 136+ months
A367-1001-13	53	M	M1b	lung	none	15 mg/kg, 1 dose	diarrhea (3), 6 weeks	none	CR, 139+ months, 139+ months

Abbreviations: ADI = Arginine deiminase; BCG = Bacillus Calmette-Guérin, Biochemotherapy = combination of chemotherapy with IL-2 and Interferon-α2; CR = Complete response; Dartmouth regimen = dacarbazine/cisplatin/carmustine/tamoxifen; F= female; GM-CSF = Granulocyte-macrophage colony-stimulating factor; gp100 = glycoprotein 100; IL = Interleukin; LN = Lymph node; M = Male; MART1 = Melanoma-associated antigen recognized by T cells; PR = Partial response; PFS = progression free survival; Prog = progression; SC =Subcutaneous; SRS = stereotactic radiosurgery