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Activity of ipilimumab at 10 mg/kg in patients with advanced melanoma is independent of baseline prognostic factors

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Background: Several factors predict a poor prognosis in patients (pts) with advanced melanoma, including advanced stage of disease, age 60+, elevated serum levels of lactate dehydrogenase (LDH), and lack of a prior response to therapy. Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen-4, yet the impact of prognostic factors on ipilimumab activity in these pts is unknown.
Methods: In this pooled analysis of two completed Phase II studies, prognostic factors in previously treated advanced melanoma pts administered/randomized to ipilimumab at 10 mg/kg were explored (CA184−008, N = 155 and CA184−022, N = 72). Ipilimumab was given every 3 weeks (Q3W) ×4 (induction); eligible pts could receive ipilimumab Q12W starting at W24 (maintenance). Response was based on modified World Health Organization criteria. Each variable was analyzed separately; LDH levels were not capped for study entry, and pts were stratified by normal and elevated (>1× upper limit of normal [UNL]) levels.
Results: No statistically significant association between disease control rate (DCR; complete or partial response plus stable disease) or median overall survival (OS) and several baseline prognostic factors was obtained (Table).

Prognostic factor	Endpoint	
	DCR (%)* [95% CI]	Median OS, months [95% CI]
Age		
<65 yrs	25.2 [18.5−32.9]	11.6 [9.5−16.3]
⩾65 yrs	32.9 [22.5−44.6]	7.6 [5.1−16.3]
M stage		
M0	33.3 [9.9−65.1]	21.9 [10.2−NR]
M1a	41.0 [25.6−57.9]	15.7 [10.2−NR]
M1b	26.4 [15.3−40.3]	15.4 [9.3−17.9]
M1c	23.6 [16.4−32.1]	6.6 [5.1−12.2]
Response to prior therapy		
Yes	32.5 [18.6−49.1]	11.6 [5.7−18.4]
No	26.7 [20.5−33.7]	10.7 [7.7−15.4]
LDH, all M stages		
Normal	29.7 [21.4−39.1]	15.7 [10.2−18.4]
Elevated	25.9 [18.2−34.8]	7.0 [4.4−12.2]
LDH, M1c stage only†		
Normal	28.6 [15.7−44.6]	15.0 [6.31−NR]
Elevated	21.0 [12.7−31.5]	4.8 [3.4−8.57

NR, not reached; *In study 022, pts treated with ipilimumab 0.3 mg/kg (control arm) had a DCR of 13.7% [6.8−23.8] (all M stages); †Of the total 227 pts, 123 (54%) had M1c stage disease, with 42 having normal LDH and 81 having elevated LDH (of which 32 had LDH 2× UNL).

Conclusions: Despite their previously identified prognostic value in the general advanced melanoma population, no factor had a statistically significant effect on ipilimumab activity.

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Changes in peripheral blood absolute lymphocyte count (ALC) may guide patient selection for continued treatment with ipilimumab

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Background: The anti-CTLA-4 monoclonal antibody, ipilimumab, induces durable antitumor responses in patients (pts) with advanced melanoma. However, a reliable marker of ipilimumab activity has not been identified. We evaluated whether changes in peripheral blood ALC are associated with ipilimumab disease control.
Methods: Peripheral ALC from routine safety labs were collected from 533 pts with unresectable stage III or IV melanoma treated with ipilimumab in four Phase II studies. Ipilimumab was given every 3 weeks (Q3W) ×4; eligible pts could continue to receive ipilimumab Q12W at Week 24. ALC was first analyzed in studies CA184007, 008, and 022 combined (ipilimumab at 0.3, 3, or 10 mg/kg), and then analyzed for confirmation in the separate study, CA184004 (ipilimumab at 3 or 10 mg/kg). Using modified World Health Organization criteria, response-evaluable pts (n = 444) were classified as those who achieved disease control (DC; defined here as complete or partial response, or stable disease through Week 24) and those who did not achieve DC.
Results: In combined analyses from studies CA184007, 008, and 022 (n = 379), pts who achieved DC had a greater mean rate of ALC change (slope) than pts who did not achieve DC ($P = 0.0013$); in these 3 studies, no pt with a negative ALC slope over the induction period achieved DC (Table). These associations were confirmed in study CA184004 (n = 65): pts who achieved DC had a greater mean slope ($P = 0.00042$), and only 1 pt with a (slightly) negative ALC slope achieved DC (Table). Further analyses will determine if there is a potential association between changes in ALC and overall survival.

Dose (mg/kg)	Group	N	Mean slope (1000 cells/μL/week)	Standard deviation of slope	Fraction negative slope
Studies 007, 008, 022 pooled					
0.3	DC achieved	0	NA	NA	NA
	DC not achieved	47	−0.005	0.024	0.60
	Unknown	7	0.019	0.029	0.43
3	DC achieved	6	0.043	0.039	0
	DC not achieved	39	0.023	0.057	0.21
	Unknown	9	0.022	0.048	0.22
10	DC achieved	49	0.086	0.051	0
	DC not achieved	197	0.054	0.077	0.18
	Unknown	25	0.077	0.091	0.20
Study 004					
3	DC achieved	6	0.030	0.030	0.17
	DC not achieved	21	−0.019	0.068	0.52
	Unknown	5	0.028	0.026	0
10	DC achieved	6	0.153	0.124	0
	DC not achieved	23	0.030	0.063	0.30
	Unknown	4	−0.036	0.172	0.50

Conclusions: The positive association of a greater average rate of increase in ALC with DC at 10 mg/kg supports this dose for ipilimumab studies. A negative ALC slope could possibly be used to identify those pts in which ipilimumab therapy should be discontinued as they are unlikely to achieve DC.

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The cytotoxic activity of the phage E protein suppress the growth of murine B16 melanomas in vitro and in vivo

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Background: Melanoma represents only 4% of all skin cancers but nearly 80% of total skin cancer deaths, predominantly because of metastatic spread. Apart from surgery, the treatment options for melanoma, particularly metastatic melanoma, are relatively limited and emphasize the