The use of baseline tumor size to prognosticate overall survival in stage IV melanoma patients treated with the PD-1 inhibitor pembrolizumab

Philip Friedlander

Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA
Correspondence to: Philip Friedlander, MD, PhD. Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA. Email: philip.friedlander@mssm.edu.
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Historically patients who developed stage IV melanoma were expected to live less than one year. Clinical outcome was heterogeneous as evidenced by a tail end to the overall survival (OS) curve which identifies a small subset of patients, encompassing less than 10% of the total population, who are long term survivors (1). Prognostic factors incorporated into the current American Joint Committee on Cancer (AJCC) version 8 melanoma staging system include sites of metastases and the presence or absence of elevated serum lactate dehydrogenase (LDH) (2). The staging system uses these parameters to subdivide stage IV melanoma patients into four prognostic groups. In the best prognostic group (M1a) metastases are restricted to soft tissue and lymph nodes while in the intermediate prognostic M1b group metastases are present in the lung. When metastases develop in other non-central nervous system organs (M1c) or the central nervous system (M1d) prognosis worsens. Within each subgroup the presence of elevated serum LDH predicts for worsened survival.

The poor survival outcomes for stage IV melanoma patients reflect limitations in the efficacy of available therapy. Until 2011 the only Food and Drug Administration (FDA) approved treatments were dacarbazine, a cytotoxic chemotherapy, and the cytokine interleukin-2 administered at high doses (3,4). Neither therapy has demonstrated in randomized studies an OS benefit although 5% of patients treated with HD-IL-2 develop durable benefit.

Recent advances using immune checkpoint modulators and therapies targeting specific melanoma associated mutations have led to the approval of therapies that confer survival benefit.

The immune system contains multiple positive and negative regulators of T-cell activity. Modulation of the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and the programmed death-1 (PD-1) checkpoints leads to anti-melanoma activity. Ipilimumab, an inhibitor of CTLA-4 enhances T-cell priming and decreases suppressor T-cell activity (5). Nivolumab and pembrolizumab are anti-PD-1 antibodies which prevent PD-1 present on the T-cell from binding its ligand PD-L1 present on tumor cells leading to increased T-cell activity in the tumor microenvironment (6,7). The CheckMate 067 study randomized 945 untreated metastatic melanoma patients to treatment with nivolumab monotherapy, ipilimumab monotherapy or combined ipilimumab plus nivolumab (6). At 48 months follow-up, median OS was not reached in the combined therapy group, 36.9% in the nivolumab group, and 19.9 months in the ipilimumab group. While efficacy is important when considering a treatment option, the benefits need to be weighed against toxicity risks. The respective rates of grade 3 or higher toxicity were 59%, 22%, and 28% in the combination therapy, nivolumab, and ipilimumab treated patients.

In a recent issue of *Clinical Cancer Research*, Joseph *et al.*

Table 1 Factors associated with ORR and OS

ORR		OS	
Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Normal LDH	Normal LDH	Normal LDH	Normal LDH
Stage M0, M1a, M1b		Stage M0, M1a, M1b	
BTS below the median		BTS below the median	BTS below the median
Site of metastases	Site of metastases	Site of metastases	Site of metastases
PD-L1-positive tumors		PD-L1-positive tumors	
No prior therapy	No prior therapy	No prior therapy	
No prior ipilimumab treatment		ECOG performance status 0	ECOG performance status 0
Wild-type BRAF			

ORR, overall rate of response; OS, overall survival; LDH, lactate dehydrogenase; BTS, baseline tumor size.

investigate the relationship between baseline tumor size (BTS) and efficacy of pembrolizumab in 583 metastatic melanoma patients treated as part of the KEYNOTE-001 study (8). In the study, patients with advanced melanoma were treated with one of three pembrolizumab regimens which have been shown in randomized comparisons to be equally efficacious (2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks). Because all patients in the study were treated with pembrolizumab the authors cannot conclude if a baseline characteristic is prognostic or predictive for an improved clinical outcome.

BTS is meant to reflect the overall tumor burden. However the degree to which calculated BTS reflects overall tumor burden depends on how BTS is calculated. Joesph *et al.* use RECIST v1.1 to measure by central review the BTS (9). A limitation is that not all metastases are measured or included in the calculation. Rather, the sum of the greatest dimension of up to 10 measurable target lesions as selected by investigators are used to calculate BTS. Patients whose sum is greater than the population median are considered to have a high BTS and those below the median to have a low BTS. This definition does not completely characterize the biologic behavior of a given patient's tumor. Melanoma presenting on imaging as numerous small metastases, the presence of many non-target lesions, or presence of metastases defined as not measurable by RECIST v1.1 criteria such as bone metastases are not included in the BTS measurement. The biologic behavior of a melanoma presenting in an oligometastatic fashion with one large metastasis is likely very different from melanomas presenting as innumerable very tiny metastases. To more

completely capture tumor burden and biologic behavior it would be of interest to assess the association of the total number of lesions and organs involved and the baseline tumor proliferation rate to treatment response and survival.

Despite the limitations inherent in the BTS calculation, Joseph *et al.* can still assess the association of high or low BTS defined by their method of calculation with other baseline clinical factors and efficacy outcomes. The authors use logistic regression analysis to evaluate the association of BTS and other baseline factors on response rate. Cox regression analysis is used to associate these factors with OS.

In univariate analysis, a BTS below the median associated with a higher overall rate of response (ORR) and with a greater chance of the response being complete when compared to patients with an above median BTS (ORR 44% versus 23%, $P<0.001$ and complete response rate 18% versus 2%, $P<0.001$). However, in multivariate analysis BTS did not independently associate with response rate and therefore was not an independent predictor of response. Rather three baseline clinical factors (normal serum LDH level, no prior systemic therapy to treat the melanoma, and sites of metastases) remained independently associated with increased rate of response. Factors associated with response rate in univariate and multivariate analyses are listed in *Table 1*. The loss of BTS as an independent response predictor in multivariate analysis is likely due to the strong association of BTS with the other baseline clinical factors.

The data presented in Joseph *et al.* does not support the use of BTS to predict for response to pembrolizumab, however when assessing OS in the context of pembrolizumab treatment, BTS associates with OS in

univariate analysis and remains independently associated in multivariate analysis. At one year, the survival rates were 80% and 48% respectively for patients with below and above median BTS. Baseline features that independently associate with longer OS following multivariate analysis are normal LDH level, BTS below the median, ECOG performance status of 0, and site of metastasis. Factors associated with OS in univariate and multivariate analyses are listed in *Table 1*. Therefore BTS appears to be a prognostic marker for the OS of advanced melanoma patients treated with pembrolizumab. The prognostic value of BTS still needs to be validated prospectively. As all the patients treated on the KEYNOTE-001 study received pembrolizumab, the authors cannot conclude if below median BTS is prognostic for survival in the context of treatment with other anti-PD-1 regimens or CTLA-4 blockade.

Elevation of serum LDH is associated with a poor survival outcome. The worsened prognosis is possibly related to an increased tumor proliferation rate and metabolic factors. In Joseph *et al.* 11% of patients with low BTS had elevation of LDH and serum LDH level remained an independent predictor for survival. The metastatic and proliferative potential of melanoma likely reflects genomic alterations in the tumor and the interplay of tumor antigens with immunomodulatory factors present in the tumor microenvironment and the periphery. Differences in immune surveillance and regulation and tumor specific genomic changes likely contribute to variations in the number, location, and size of metastases part of which is captured in the BTS measurement.

The location of metastases also contributes to prognosis. As discussed previously, stage IV melanoma patients are sub-staged based on the tissue and organs involved. Joseph *et al.* show a strikingly higher response rate to pembrolizumab in patients with lung only metastases when compared to those with liver metastases (62% versus 22% respectively). Similarly, patients with lung only metastases have a 1-year OS of 89% as compared to a 1-year OS rate of 53% in patients with liver metastases. This difference might in part be explained by the greater median BTS in patients with liver metastases when compared to those with lung only metastases (15.3 versus 3.9 cm, P<0.001). The data suggests that both BTS and tumor location predict for survival outcome as evidenced by the independent association of these two characteristics in multivariate survival analysis.

A challenge faced by medical oncologists is the choice of initial systemic therapy to treat a given patient with stage IV melanoma. If the melanoma expresses wild-type BRAF (no mutation at position V600) the primary consideration is anti-PD-1 monotherapy versus ipilimumab plus nivolumab. If the melanoma contains a V600 mutation in BRAF the decision further includes a BRAF targeted approach using BRAF plus MEK inhibitors. The FDA has approved three combinations of BRAF and MEK inhibitors which confer approximately 70% response rates although efficacy is limited by development of resistance with median duration of response 10.5 months (10). We lack randomized data comparing the sequencing of anti-PD-1 based and anti-BRAF based approaches. Ongoing clinical trials randomizing the order of immunotherapy and targeted therapy eventually may help guide optimal sequencing. The data presented in Joseph *et al.* does not help select the optimal sequence or choice of immunotherapy. While patients with below median BTS had a 1-year OS rate of 89%, patients with above median BTS still had a meaningful 1-year survival rate of 48% leaving anti-PD-1 monotherapy as a viable treatment option. A three year pooled analysis of two large trials treating V600 BRAF mutant melanoma patients with dabrafenib and trametinib, BRAF and MEK inhibitors respectively, showed that both the sum of metastasis diameters (analogous to BTS) and the number of organs involved independently predicted for duration of progression free survival (PFS) (11). Patients with fewer than three organs involved had better PFS than those with three or more involved. The ability of BTS to guide in the decision to use anti-PD-1 based immunotherapy or anti-BRAF targeted therapy in advanced melanoma patients whose melanoma contains a targetable BRAF mutation is not known. Assessing the relationship of BTS with progression free and OS in melanoma patients treated in clinical trials that randomize to different sequences of sequential immunotherapy and BRAF targeted therapy may help elucidate the role for BTS in guiding treatment sequence. Similarly the value of BTS in choosing between upfront treatment with anti-PD-1 monotherapy and combination ipilimumab plus nivolumab can be elucidated through prospective assessment in randomized clinical trials.

In summary Joseph *et al.* associate BTS with other baseline clinical factors and demonstrate an independent prognostic role for BTS in predicting the OS of advanced melanoma patients treated with pembrolizumab. The association between BTS and survival needs validation in prospective studies and can be incorporated into study designs. The ability of BTS to independently predict

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survival in the context of other immune and targeted therapies can be studied to determine prognostic value which possibly may then be considered in defining optimal treatment selection.

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Footnotes

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