

Tumor mutational burden and response to programmed cell death protein 1 inhibitors in a case series of patients with metastatic desmoplastic melanoma



To the Editor: Desmoplastic melanomas (4% of melanomas) are characterized by spindled melanocytes, collagenous or desmoplastic stroma, and an intense inflammatory response.¹ Desmoplastic melanomas carry a high mutation burden compared generally with other cancers.² Programmed cell death 1 protein (PD-1) inhibitors have been granted Food and Drug Administration approval for advanced melanoma as first-line therapy.³ In addition, a high mutation burden has been demonstrated as an effective predictor of response to checkpoint inhibitors, likely due to the increased neoepitope generation and cytotoxic T-cell activation. In this study, we examined 12 desmoplastic melanomas by using comprehensive genomic profiling and assessed tumor mutational burden (TMB) and response to PD-1 inhibitors during clinical care.

DNA was extracted from 40- μ m-thick paraffin-embedded sections, and comprehensive genomic

profiling was performed on hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of >650x for 236 or 315 genes plus the introns from 19 or 28 genes frequently involved in cancer. TMB was determined on up to 1.14 Mb of sequenced DNA by using an estimation algorithm that extrapolates to the genome as a whole.⁴

Comprehensive genomic profiling was performed on 1240 melanoma cases, including 12 desmoplastic melanomas. A mean of 54 (range 8-128) variants/sample, which were likely somatic on the basis of allele frequency, were detected in desmoplastic samples, and a mean of 22 variants/sample were predicted to be somatic in nondesmoplastic melanomas (Mann-Whitney-Wilcoxon, P value = .001). The average TMB in desmoplastic melanomas was 77 mutations/Mb, compared with 35 mutations/Mb across the remaining 1228 melanomas (Fig 1). In 10 of 12 samples, C>T and G>A mutations made up >80% of the base substitutions, indicating a ultraviolet light-related mutational signature. *TP53* was the most frequently mutated gene (9/12 cases). Alterations in neurofibromin (NF) genes were frequent, with *NF1* altered in 6 of 12 cases and *NF2* altered in 2 of 12 cases, consistent with previous studies.² Two cases lacking *NF1* or *NF2* mutations had *NRAS*-activating mutations. Other frequently mutated genes included cyclin-dependent kinase inhibitor 2A (6/12) and AT-rich interactive domain-containing

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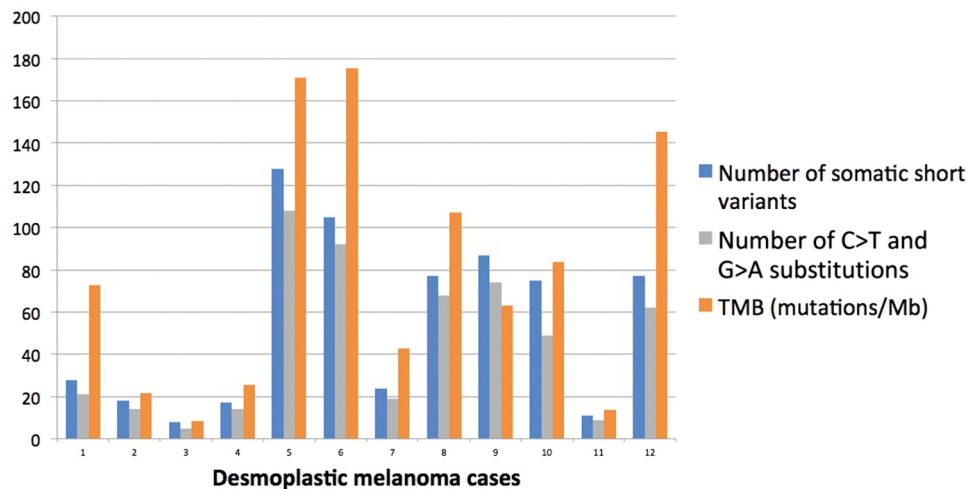


Fig 1. Mutation profile of 12 cases of desmoplastic melanoma. TMB, Tumor mutation burden.

Table I. Available demographic information, treatment history, and response to immunotherapy in cases of desmoplastic melanoma analyzed using CGP

Case no.	Age, y	Sex	Tissue of origin for CGP testing	Previous immunotherapy	Best response to immunotherapy
1	74	M	Skin	None	Pembrolizumab, PR, 6 mon, ongoing
2	80	M	Soft tissue	None	None
3	51	M	Skin	4 doses ipilimumab, PD	Pembrolizumab, PR, 11 mon
4	70	M	Skin	4 doses ipilimumab, PD	Pembrolizumab, SD, 11 mon, ongoing
5	56	M	Lung	8 doses of high-dose IL-2, PR	Pembrolizumab (no data available)
6	54	M	Skin	None	None
7	81	M	Skin	2 doses ipilimumab, PD	Pembrolizumab, SD, 2 mon, ongoing
8	29	M	Unknown	Interferon and ipilimumab, PD	Nivolumab, PR, ongoing
9	58	M	Skin	None	None
10	78	M	Skin	Unknown	Unknown
11	67	F	Soft tissue	Unknown	Unknown
12	62	M	Skin	Unknown	Unknown

CGP, Comprehensive genomic profiling; IL, interleukin; PD, progressive disease; PR, partial response; SD, stable disease.

protein 2 (5/12). All desmoplastic cases were *BRAF* wildtype.

Of 9 patients with clinical treatment history available, 6 received a PD-1 inhibitor, and 5 of 5 with available response data had stable disease or better, including 2 with ongoing partial responses (Table I). Four of these patients also received prior treatment with ipilimumab, but none of them responded.

Our study is limited by our small number of desmoplastic melanomas and even fewer with clinical information, but a multi-institutional study in 60 patients with advanced desmoplastic melanoma treated with varied PD-1 ligand pathway inhibitors showed a 6-month progression-free survival rate of 77% and 1-year overall survival rate of 80%.⁵ The correlation between TMB and response to PD-1 blockade has been reasonably established in the context of many cancer types, including conventional melanoma, nonsmall cell lung cancer, and others, while ultraviolet radiation has been shown to increase the somatic mutation rate in melanomas. The cases we have highlighted confirm that desmoplastic melanomas might respond well to PD-1 inhibitors.

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REFERENCES

1. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. *Cancer*. 1998;83:1128-1135.
2. Shain AH, Garrido M, Botton T, et al. Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. *Nat Genet*. 2015;47:1194-1199.
3. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521-2532.
4. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9(1):34.
5. Eroglu Z, Zaretsky JM, Hu-Lieskova S, et al. High response rate to PD-1 blockade in desmoplastic melanomas. *Nature*. 2018;553(7688):347-350.

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Optimal concentration range of ustekinumab in patients with plaque-type psoriasis



To the Editor: Ustekinumab has a better efficacy and safety profile than earlier anti-tumor necrosis factor biologics. Some biologics elicit an unwanted immune response in the patient by the production of antidrug antibodies, leading to reduced drug levels, loss of clinical response, and adverse events.¹ Monitoring of ustekinumab levels and antibodies to ustekinumab (ATUs) may be useful for future clinical practice to complement clinical assessment and optimize patient treatment.

The aims of this study were to analyze the association between serum trough levels of ustekinumab and treatment response in patients with psoriasis at 52 weeks and to establish an optimal concentration range of ustekinumab levels. Patients were treated with 45 mg of ustekinumab initially and 4 weeks later, followed by 45 mg every 12 weeks.

We recruited 37 patients with moderate-to-severe psoriasis treated with ustekinumab in an observational, cross-sectional, prospective, single-center study (Table D). Blood samples collected within 72 hours before administration of ustekinumab were analyzed for levels of ustekinumab and ATUs by enzyme-linked immunosorbent assays with Promonitor-UTK and Promonitor-ANTI-UTK tests, respectively (Progenika, Spain).²

Table 1. Baseline demographics and clinical characteristics for the total population of patients with psoriasis (N = 37)

Variable	Value
Demographics	
Median age, y (IQR)	48.0 (39.0-57.5)
Age at diagnosis, y	23.0 (14.0-39.0)
Age at initial treatment, y	48.0 (38.0-45.5)
Women, (%)	17 (46)
Men, (%)	20 (54)
Disease status	
Mean duration of disease, y (IQR)	19.0 (11.0-35.5)
Mean baseline PASI (IQR)	13.0 (9.4-16.4)
Medication, n (%)	
Ustekinumab-naïve group	15 (40.5)
Maintenance group	22 (59.5)
Prior biologic use, n (%)	25 (67.6)
1 biologic	8 (21.6)
2 biologics	10 (27.0)
3 biologics	7 (18.9)
Adalimumab	16 (43.2)
Etanercept	29 (51.3)
Efalizumab	13 (35.1)
Concomitant medications, n (%)	5 (13.5)
Methotrexate	2 (5.4)
Leflunomide	1 (2.7)
Cyclosporine A	2 (5.4)

The mean duration of exposure ustekinumab in the maintenance group before recruitment was 30.6 months.

IQR, Interquartile range; PASI, Psoriasis Area and Severity Index.

Disease activity was assessed according to the Psoriasis Area and Severity Index (PASI) and clinical improvement (Δ PASI), as indicated by the proportion of patients achieving a 75% reduction in PASI score or the proportion of patients achieving a 90% in PASI score relative to baseline. The Spearman correlation and Mann-Whitney U test were used to determine the association between ustekinumab and PASI score and that between ustekinumab and clinical response, respectively. Significance was set at P less than .05.

A significant inverse correlation between ustekinumab levels and PASI score at week 52 ($r = -0.39$; $P < .05$) was found. The median concentration of ustekinumab was significantly higher ($P < .05$) in good responders (Δ PASI > 90%) (median concentration 0.47 μ g/mL [interquartile range (IQR), 0.31-0.70]) and moderate responders (75% < Δ PASI < 90%) (median concentration, 0.32 μ g/mL [IQR, 0.15-0.53]) than in nonresponders (Δ PASI < 75%) (median concentration, <0.131 μ g/mL [IQR, <0.13 to 0.32]).

Two patients (5.4%) were positive for ATUs, which is in agreement with other cohort studies and clinical trials (5.2%-7.0%)³⁻⁵ and had no