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Increased PD-L1 Tumor Expression Correlates with High Rate of Response to PD-1 Inhibitors in Patients with Unresectable, Recurrent, and Metastatic Cutaneous Squamous Cell Carcinoma

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INTRODUCTION

PD-1 inhibitors were approved for locally advanced and metastatic cutaneous squamous cell carcinoma (CSCC) in 2019 with ORR of 47% and CR of 4%. The identification of tumor characteristics that predict potential responders to immune checkpoint inhibitors (ICI) is an area of ongoing research. Here we present a series of consecutive patients with locally advanced unresectable, recurrent, or metastatic CSCC treated with PD-1 inhibitors and analyze tumor and blood genomics as well as PD-L1 expression with the aim to correlate with treatment response.

METHODS

We analyzed all cases of CSCC treated with single agent PD-1 inhibitors in the last 2 years at Wake Forest Comprehensive Cancer Center. Demographic and outcome data was collected. Tumors tested for genomics and PD-L1 expression in all cases with available tissue. PD-L1 tumor expression was tested by IHC utilizing DAKO 22C3 pharmDx antibodies. Tumor genomic studies including TMB and MSI were performed by Foundation Medicine platform. Blood was tested for circulating tumor DNA by Guardant 360 platform, at the beginning of treatment and in follow up at the time of maximum response. Response was assessed by RECIST 1.1 Criteria.

RESULTS

Eleven patients with CSCC treated with PD-1 ICI were included in this study. Five patients had locally advanced disease, five patients had recurrent locally advanced disease, and three patients had metastatic disease. Three patients received treatment for at least 12 months and all have CR to date. Two patients have been on treatment for 6 months, and they have excellent PR with possible CR per imaging studies. Of the six patients who have been on treatment for less than 6 months, one patient has excellent PR with negative PET, three patients have very good clinical response with imaging studies pending, one patient has questionable response, and one patient only recently started treatment. Treatment is well tolerated with no treatment discontinuation. Immune-related complications are rare consisting of only one patient developing hypothyroidism during

Table 1.

G	A	S	L/R/M	IOD (mo)	IOR	D	Previous	PD-L1	TMB	Guardant before IO		Guardant after IO		F1		AE	OBS
										TP53	Other	TP53	Other	TP53	Other		
M	73	N	L	20	CR	On	Surg, Adj CRT	TPS 60%	61	0	0	Y163N	ARID1A ATM	G266E R248Q	BRIP1, CD22, FANCC, MEN1, NOTCH2		Other primary cSCC x5 RA-PDN 5 mg + MTX
F	97	N	L	14	CR	3 mo	-	TPS 60%	11	0	KIT CRCA1	0	KIT BRCA2	E286K	CDKN2A, NOTCH2, TERT	Hypothyroid	Other primary cSCC x3
M	76	N	L	14	CR	On	Surg, Adj RT	TPS 30%	19	0	JAK2	0	0	P278S	ASXL, CDKN2A, NOTCH1, PIK3CA, TERT	Fatigue	Mets to right parotid
F	81	N	L	9	PR	On	n/a	NET		S99F Q100 Q16 SS SNV	CDKN2A BRCA2 MAP2K1	ND	ND	NET	NET		Other primary cSCC x2
M	91	FS	M	6	PR	On	Adj RT	NET	NET	NET	NET	NET	NET	NET	NET	Fatigue	
M	75	N	R	4	PR	On	None	TPS 20%	21	H193L R342	0	ND	ND	G245N R342	CASP8, MLL2, NOTCH1, RB1	Fatigue	
F	64	N	R	4	PD	On	Surg, Adj RT	CPS 30	8	G266R	0	ND	ND	G262V	FGF12, MDM2, NOTCH1, PIK3CA, PRKCI, SOX2, TERT, TERC		
M	77	FS	R	5	PR	On	Surg, Adj RT	TPS 90%	163	V143M R248W Q136	CCND2 CDKN2A BRCA2 TERT	ND	ND	R248W	ALK, BRCA2, CCND1, BARD1, ATR, AXIN1, CDKN2A/B, FGF19, FGF3, FGF4, MYCN, NOTCH1, TERT		Lung Nodules
M	83	N	R	5	PR	On	Surg	TPS 20%	35	0	KRAS	ND	ND	R213Q P278F SS 75-1G>A	ASXL1, CDKN2A, DBMT3A, MLL2, NOTCH1, RB1, TERT, TET2		
M	80	N	M	4	PD	On	Surg	NET	NET	0	NRAS	ND	ND	ND	ND		
M	65	FS	L	8	PR	On	Surg, RT	TPS 10%	ND	T155P	PTEN	ND	ND	R342 R213	CDKN2A, HGF, KEAP1, MLL2, MRE11A, SMARCA4, TNFAIP3		

G = gender; A = age; L/R/M = loco-regional/recurrent/metastatic; IOD = duration of treatment with immunotherapy; IOR= response obtained with immunotherapy (CR = complete response, PR = partial response, PD = progression of disease); D = duration of response after immunotherapy was stopped; Previous = treatments received before starting immunotherapy; PD-L1 = PD-L1 status measured in all cases with DAKO223 antibodies; TMB = Tumor Mutation Burden measured by Foundation Medicine in tumor tissue; Guardant before/after IO = genomic mutations in blood tested by Guardant 360 platform;F1 = genomic mutation in tumor tested by Foundation; AE = adverse events; Obs = observations; NET = not enough tissue for testing.

treatment. Eight patients had sufficient tumor tissue for genomic and PD-L1 testing. Initial blood genomic testing was performed in 10 of 11 patients and in follow up in all three patients who achieved maximum response. Patients with CR had PD-L1 of at least 30%. The additional tested patients have PD-L1 above 10%. The most frequently mutated tDNA gene was TP53 and the second most frequently mutated gene was the NOTCH1/2. TMB was intermediate or high in all tested patients.

DISCUSSION

Treatment of locally advanced unresectable, recurrent, and metastatic CSCC with ICI has led to a dramatic change in the management and prognosis of CSCC. Our series of patients with CSCC has a higher than reported rate of response and especially complete response. This corresponds with high TP53 alterations (100% of patients), NOTCH 1/2 alterations (90% of patients) and high level of expression of PD-L1 (90% patients). Interestingly, PD-L1 rates were higher than previously published.

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