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Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study

To the Editor: Case reports[1] and the high tumor mutational burden[2] of basal cell carcinomas (BCCs) compared with other tumor types suggest that programmed death-ligand 1 (PD-L1) inhibitors may be active against advanced BCCs. Many advanced BCCs are refractory to[3] or are recurrent[4] after hedgehog pathway inhibitors, and therefore PD-L1 inhibitors could be a useful therapeutic option. We present a proof-of-principle, nonrandomized, open-label study of pembrolizumab (200 mg intravenously every 3 weeks), with or without vismodegib (150 mg orally daily), for eligible subjects with advanced BCCs. The primary outcome was the overall response rate (ORR) for all evaluable subjects at 18 weeks.

Sixteen participants, 9 receiving pembrolizumab monotherapy and 7 receiving pembrolizumab plus vismodegib, were evaluable by the revised Response Evaluation Criteria In Solid Tumors[5] (version 1.1) at data cutoff. The ORR for all evaluable subjects was 38% (6/16 patients; 95% confidence interval 15-65%; $P = .003$) at 18 weeks (Table I, Fig 1). The ORR at 18 weeks for pembrolizumab monotherapy group was 44% (4/9 patients; 95% confidence interval 14-79%; $P = .008$), and for the dual therapy group was 29% (2/7 patients; 95% confidence interval 4-71%; $P = .15$).

The median time to response for all responders ($n = 6$) was 10.4 weeks (range 8.4-17.4 weeks). The median duration of response for all responders ($n = 6$) was 67.3 weeks (range 28.0-82.0 weeks; Table I).

One-year progression-free survival probability was 70%, and the 1-year overall survival probability was 94% for all evaluable subjects ($n = 16$; Table I).

Before pembrolizumab, 29% (2/7 patients) expressed PD-L1 at ≥1% of tumor cells. There was no significant correlation between prepembrolizumab PD-L1 expression and best percentage change in BCC diameter.

There were no life-threatening adverse events (AEs) or deaths during the study. Three severe (grade 3) AEs occurred out of 98 AEs from 16 participants. Only 1 of the severe AEs, hyponatremia, was attributed to pembrolizumab. There were 23 immune-related AEs, with dermatitis and fatigue as the most common (all grade 1 or 2), and only 1 severe immune-related AE (the aforementioned hyponatremia).

As a proof-of-principle study, we conclude that pembrolizumab is active against BCCs. Although the 2 groups were not directly compared, the response rate of the pembrolizumab plus vismodegib group was not superior to the monotherapy group. The lack of life-threatening AEs or death suggests that pembrolizumab has a reasonable safety profile in patients with BCC.

This study is limited by its sample size, because advanced BCCs are an uncommon disease. Nevertheless, the efficacy and safety data presented here could be used in future meta-analyses and compared with forthcoming multi-institutional studies on PD-L1 inhibitors against advanced BCCs.

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Anne Lynn S. Chang, MD,[a] Duy C. Tran, BS,[a] John G. D. Cannon, BS,[a] Shufeng Li, MS,[a] Mark Jeng, PhD,[a] Roma Patel, PA-C,[b] Lindsay Van der Bokke, RN,[b] Alana Pague, BS,[b] Richard Brotherton, RN,[b] Kerri E. Rieger, MD PhD,[c] Ansuman T. Satpathy, MD, PhD,[d] Kathryn E. Yost, BS,[d] Sunil Reddy, MD,[e] Kavita Sarin, MD, PhD,[a] and A. Dimitrios Colevas, MD[e]

From the Department of Dermatology,[a] Stanford University School of Medicine; Stanford Cancer Institute,[b] Cancer Clinical Trials Office; Stanford Dermatopathology Service,[c] Department of Pathology; Department of Epithelial Biology,[d] and the Department of Medicine/Medical Oncology,[e] Stanford University School of Medicine and Stanford Cancer Institute, Stanford.

This study is subject to Stanford Human Subjects Approval Protocol 34925 and is listed at clinicaltrials.gov (NCT02690948).

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Table I. Primary and secondary outcomes

Outcome	All evaluable participants (N = 16)	Pembrolizumab monotherapy (n = 9)	Pembrolizumab plus vismodegib (n = 7)
Overall response rate (range), n	38% (15-65%), 6	44% (14-79%), 4	29% (4-71%), 2
One-year PFS probability, %	70	62	83
One-year OS probability, %	94	89	100
Median treatment duration, weeks (range)	18.5 (5.9-73.0)	19.0 (10-73.0)	18.0 (5.9-38.6)
Median time to response, weeks (range), n	10.4 (8.4-17.4), 6	12.4 (8.4-17.4), 4	10.3 (8.7-11.9), 2
Median duration of response, weeks (range), n	67.3 (28.0-82.0), 6	67.6 (31.4-82.0), 4	52.8 (28.0-77.6), 2
Median time from pembrolizumab start date to next treatment start date, weeks (range), n	21.9 (6.1-43.3), 6	21.9 (15.4-43.3), 4	19.2 (6.1-32.3), 2

Overall response rates were calculated at the 18-week time point. One-year progression-free survival and overall survival probabilities were calculated using the Kaplan–Meier method.
OS, Overall survival; *PFS*, progression-free survival.

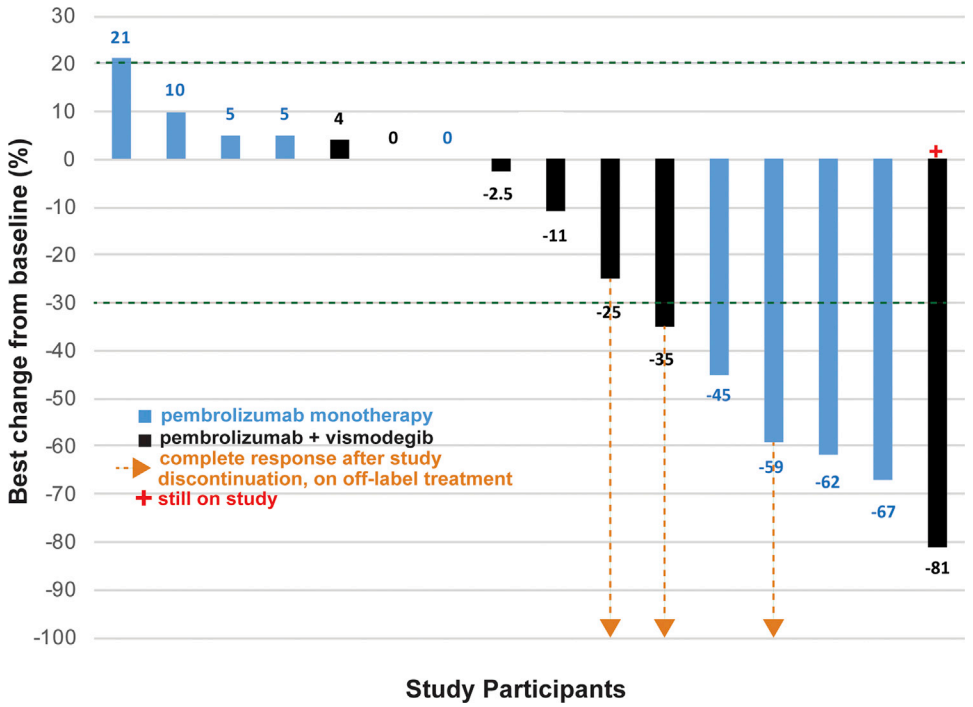

Fig 1. Waterfall plot showing best percent change in the diameter of targeted basal cell carcinoma lesions from baseline for all evaluable subjects. The dotted arrows indicate 3 subjects who achieved complete response after study discontinuation, based on imaging and clinical documentation.

pertinent to the study. The authors have not been paid to write this article by a pharmaceutical company or other agency. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

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Address correspondence to: Anne Lynn S. Chang, MD, Department of Dermatology, Stanford University School of Medicine, 450 Broadway St, Mail Code 5334, Redwood City, CA 94063

E-mail: alschang@stanford.edu

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Ruxolitinib for the treatment of severe alopecia areata

To the Editor: Recent advances in our understanding of the pathogenesis of alopecia areata (AA)[1] have led to the use of Janus kinase (JAK) inhibitors for the treatment of AA.[2,3] There are considerably more data regarding the JAK1/3 inhibitor tofacitinib for treatment of AA than the JAK1/2 inhibitor ruxolitinib.[4,5] In an open-label study of 12 patients with moderate-to-severe AA, high-dose ruxolitinib was efficacious.[4] We present a series of 8 patients with severe AA treated with ruxolitinib and show that hair regrowth may be achieved at a lower dose.

From May 2015 through April 2018, 8 patients with severe AA (≥50% scalp hair loss), including alopecia totalis (AT) and alopecia universalis (AU), were treated with ruxolitinib monotherapy, 10 to 25 mg twice daily, for 5 to 31 months (mean 13.9, standard deviation [SD] 8.5). Of the 8 patients, 6 had been treated previously with tofacitinib for at least 4 months (mean, 11.3 [SD, 7.0]); of these, patients 4 and 8 underwent a 4- to 8-week washout before starting to take ruxolitinib whereas the other 4 patients switched directly to ruxolitinib. The mean duration of the current episode of AT or AU was 2.9 years (SD, 2.3; range, 0.5-5). Patient characteristics and treatment courses are detailed in Table I. Before undergoing treatment with ruxolitinib (or tofacitinib), patients were screened for *Mycobacterium tuberculosis* with use of the QuantiFERON-TB Gold test (Qiagen, Hilden, Germany), for human immunodeficiency virus, and for hepatitis B and C viruses. Before and during treatment, laboratory evaluation included a complete blood count with differential, complete metabolic panel, and fasting lipid panel.

Of the 8 patients, 5 achieved complete or near-complete regrowth of hair with ruxolitinib, with a mean improvement in Severity of Alopecia Tool

Table I. Patient clinical characteristics and treatment course

Patient	M/F	Age at start of therapy with either tofacitinib or ruxolitinib	AA or AT/AU	Current episode of AT/AU, y	SALT score before therapy with either tofacitinib or ruxolitinib	Total duration of tofacitinib therapy before ruxolitinib therapy, mo	Dose and duration of the higher dose of tofacitinib	Change in SALT score with tofacitinib therapy, %	Duration of ruxolitinib therapy, mo	Dose of ruxolitinib	Change in SALT score with ruxolitinib therapy, %
1	M	44	AT/AU	1	100	NA	NA	NA	21	25 mg bid	99%
2	F	18	AT/AU	5	100	NA	NA	NA	31	10 mg bid	100%
3	F	57	AT/AU	0.5	100	12	10 mg bid for 10 wk	60%	7	10 mg bid	100%
4	M	20	AA	NA	50	23	10 mg bid for 12 mo	92%	16	10 mg bid	99%
5	F	14	AT/AU	1	100	4	10 mg bid for 2 mo	0%	10	10 mg bid	91%
6	M	20	AT/AU	5	100	13	15 mg daily for 4 mo	0%	5	25 mg bid	0%
7	M	24	AA	NA	94	4	10 mg bid for 2 mo	0%	9	25 mg bid	0%
8	F	18	AT/AU	5	100	12	NA	60%	5	10-20 mg bid	−150%*

AA, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis; *bid*, twice daily; *F*, female; *M*, male; *NA*, not applicable; *SALT*, Severity of Alopecia Tool.
*Negative percent change in SALT score indicates worsening of disease.