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ORIGINAL RESEARCH

Integrated Safety Analysis on Skin Cancers among Patients with Psoriasis Receiving Ixekizumab in Clinical Trials

Saxon D. Smith · Alexandros Stratigos · Matthias Augustin · Jose Manuel Carrascosa · Susanne Grond · Elisabeth Riedl · Wen Xu · Himanshu Patel · Mark Lebwohl

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ABSTRACT

Introduction: Limited data exist on skin cancer risk in patients with psoriasis using biologics. Here, we report treatment-emergent adverse events (TEAEs) of skin cancer in patients treated with ixekizumab from psoriasis clinical trials.

Methods: Integrated safety databases from 17 clinical trials of adults with moderate-to-severe psoriasis treated with ≥ 1 dose of ixekizumab for ≤ 5 years were used to analyze exposure-adjusted incidence rates (IRs) per 100 patient-years of exposure (PYE) and clinically characterize dermatologist-adjudicated skin cancer TEAEs.

Results: Of 6892 patients, 58 presented with ≥ 1 skin cancer TEAE (IR 0.3) with IRs remaining stable with longer ixekizumab exposure. Non-melanoma skin cancer (NMSC) was the most common event (IR 0.3) affecting 55 patients; of those, 44 had basal cell carcinoma (IR 0.2) and 16 had squamous cell carcinoma (IR 0.1). Two treatment-emergent melanoma events were identified; neither were classified as serious AEs.

Conclusions: Incidence of skin neoplasms in patients with psoriasis treated with ixekizumab for ≤ 5 years was low, and among those events, NMSC was most common. Limitations included that longer exposure may be required to confirm risk of skin cancer and that the study exclusion criteria of several studies, which excluded patients with skin cancer events

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S. D. Smith (✉)
ANU Medical School, ANU College of Health and Medicine, The Australian National University, Canberra, Australian Capital Territory, Australia
e-mail: dr.saxon.smith@gmail.com

A. Stratigos
Department of Dermatology, University of Athens, School of Medicine, Andreas Sygros Hospital, Athens, Greece

M. Augustin
Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

J. M. Carrascosa
Department of Dermatology, Hospital Universitari Germans Trias I Pujol, Badalona, Universidad Autónoma de Barcelona, IGTP, Badalona, Spain

S. Grond · W. Xu · H. Patel
Eli Lilly and Company, Indianapolis, IN, USA

E. Riedl
Department of Dermatology, Medical University of Vienna, Vienna, Austria

M. Lebwohl
Department of Dermatology, Mount Sinai Hospital, New York, NY, USA

within 5 years prior to baseline, might limit interpretation of skin cancer risk in this cohort. These findings support the safety profile of ixekizumab for patients requiring long-term psoriasis control.

Keywords: Ixekizumab; Long-term; Malignancy; Melanoma; Non-melanoma skin cancer; Psoriasis; Safety; Skin cancer; Skin neoplasm

Key Summary Points
Limited evidence of skin cancer risk for newer biologic therapies are available.
This study reports treatment-emergent adverse events of skin cancer in patients with moderate-to-severe psoriasis treated with ixekizumab for up to 5 years from 17 clinical trials.
Longer-term ixekizumab exposure is not associated with an increased risk of cutaneous malignancies, although longer-term data are needed.
Most patients had NMSCs, with a squamous cell carcinoma:basal cell carcinoma (BCC:SCC) ratio consistent with the general population.
These findings support the safety profile of ixekizumab for patients requiring long-term psoriasis control.

INTRODUCTION

Patients with psoriasis, a chronic immune-mediated disease, have increased risk to develop NMSC, especially squamous cell carcinoma (SCC), which increases with disease severity. This seems mainly related to UV exposure, specifically to phototherapy with psoralen and ultraviolet A (PUVA), with increased risk related to cumulative dose and increased in patients also treated with cyclosporine [1–7]. Similarly, reports investigating the contribution of TNF-inhibitors (TNFi) to skin cancer risk report increased rates of NMSC, largely driven by SCC and linked to prior phototherapy [8–10]. Conflicting evidence exists for TNFi regarding the risk of melanoma in patients with psoriasis [8, 9]. Indeed, PUVA has been associated with development of melanomas years after treatment [11]. A recent long-term safety analysis of adalimumab in patients with psoriasis reported increased standardized incidence rates (IRs) for SCC and melanoma [12].

Limited evidence of skin cancer risk is available for newer biologic therapies including interleukin (IL)-17 inhibitors. However, given the chronicity of psoriasis, information on skin cancer risk with long-term treatments are essential to informing long-term disease management.

The safety and tolerability of ixekizumab, a high-affinity monoclonal antibody that specifically neutralizes IL-17A, has been established for the treatment of patients with psoriasis for up to 5 years [13–16]. We report the rates and clinical characteristics of malignant skin neoplasms, including but not limited to NMSC and melanoma, in a large safety cohort of patients with psoriasis treated with ixekizumab from 17 clinical trials.

OBJECTIVE

This post hoc analysis aimed to evaluate skin-cancer-treatment-emergent adverse events (SC-TEAE) in adult patients with psoriasis treated with ixekizumab for up to 5 years, from 17 clinical studies.

METHODS

Patients and Study Design

This analysis pooled cumulative safety data from 17 clinical studies in adult patients with psoriasis (Figure S1). The study designs have been published elsewhere (references [16–28], NCT02993471, NCT03073213, NCT03364309). The trial registration numbers for the studies discussed are the following: UNCOVER-1, UNCOVER-2, UNCOVER-3, UNCOVER-A and UNCOVER-J, and NCT0147 4512, NCT01597245, NCT01646177, NCT0177

7191 and NCT01624233, respectively; IXORA-P, IXORA-S, IXORA-Q, and IXORA-R, and NCT025 13550, NCT02561806, NCT02718898 and NCT 03573323, respectively; RHBN, NCT03073213, RHBO, NCT02387801; RHBZ, NCT02634801; RHAJ, NCT01107457; RHBU, NCT02993471; RHBH, NCT03364309; and RHCV, NCT03942042.

Patients who developed a malignancy during the trials were required to discontinue from study treatment, however, patients were allowed to continue treatment if they developed ≤ 2 NMSCs over any 12-month study period. Exclusion criteria related to patient history of skin neoplasms are depicted in Figure S1. Skin cancer events encoded within the Medical Dictionary for Regulatory Activities (MedDRA) High-Level Group Term "Skin neoplasms malignant and unspecified" were extracted, evaluated on the basis of dermatologist adjudication, and frequencies were reported for: NMSC, SCC, and basal cell carcinoma (BCC), melanoma, and other skin neoplasms. Baseline patient characteristics, descriptive analyses of treatment-emergent skin cancers, therapies of treatment-emergent skin cancers, and implications on study continuation were presented.

Compliance with Ethics Guidelines

Protocols for all studies included in this analysis were approved by the Institutional Review Board or Ethics Committee at each participating site. All studies included in this analysis were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all eligible patients before undergoing study-related procedures.

Statistical Analyses

All randomized patients who received ≥ 1 dose of the study drug in 17 clinical trials were included in the safety analysis population. Frequencies or exposure-adjusted IRs of adverse events (AEs) were summarized. IRs were expressed as number of unique patients with a particular category of event per 100 patient-years of ixekizumab exposure (PYE). Multiple AEs that occurred in different intervals were counted multiple times. As long-term control data were not available, previously published data for placebo and ixekizumab groups from the large Phase 3 UNCOVER studies were reported as time-adjusted IRs.

RESULTS

Overall, 58 patients with ≥ 1 skin cancer TEAEs (88 events total) in 6892 ixekizumab-treated patients (18,025.7 PYE) were identified, corresponding to an IR/100 PYE of 0.3. Of those, most patients reported ≥ 1 NMSC event (n = 55 patients with 85 events, IR 0.3). Among those, 44 patients had a BCC (IR 0.2) and 16 patients had a SCC (IR 0.1), and 5 of these patients had both SCC and BCC events (Table 1). Two patients were identified with a melanoma (IR 0.03) and one patient with a dermatofibrosarcoma protuberans (DFSP; IR 0.01; details below). When analyzed in yearly intervals, most skin cancer events were identified within the first year of exposure to ixekizumab (n = 34, IR 0.6). IRs remained stable with longer ixekizumab exposure (Table 2; Figure S2).

Patient Characteristics

Patients with ≥ 1 skin cancer TEAE tended to be older (median age 58.5) and to have a longer duration of psoriasis (median 27.0 years) compared with all ixekizumab-treated patients (median age 46.0 years with 16.7 years duration). All those patients were of white ethnicity and from North America, Europe, or Australia. A total of 69.0% had received prior systemic therapy, and 37.9% had received another biologic before receiving ixekizumab. Rates of prior phototherapy (37.9% versus 38.7%) and specifically PUVA therapy, as well as any systemic therapy (69.0% versus 64.1%) were similar between those with versus without skin cancer TEAE, although more patients with ≥ 1 skin cancer TEAE were pretreated with biologics, compared with those without skin cancer TEAEs (37.9% versus 28.9%; Table 3).

Table 1 Overview of treatment-emergent skin cancer events

	Primary psoriasis placebo-controlled integrated analysis set (RHAZ, RHBA, RHBC)			All psoriasis IXE exposure integrated analysis set
	PBO **PY = 180.0** ***N* = 791** ***n* (IR)**	**IXE Q4W** **PY = 265.9** ***N* = 1161** ***n* (IR)**	**IXE Q2W** **PY = 268.6** ***N* = 1167** ***n* (IR)**	**Total IXE** **PY = 18,025.7** ***N* = 6892** ***n* (IR) [95% CI]**
Patients with ≥ 1 TE skin cancer	1 (0.6)	1 (0.4)	2 (0.7)	58 (0.3) [0.2, 0.4]
Non-melanoma skin cancer	1 (0.6)	1 (0.4)	2 (0.7)	55 (0.3) [0.2, 0.4]
BCC	0 (0.0)	1 (0.4)	2 (0.7)	44 (0.2) [0.2, 0.3]
SCC	1 (0.6)	0 (0.0)	0 (0.0)	16 (0.1) [0.1, 0.1]
Other skin neoplasms	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.01) [0.0, 0.0]
Melanoma	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.01) [0.0, 0.0]
Skin cancer SAE	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.03) [0.0, 0.1]
BCC	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.02) [0.0, 0.1]
SCC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.01) [0.0, 0.0]
Other skin neoplasms[a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.01) [0.0, 0.0]
Discontinuation due to skin cancer	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.01) [0.0, 0.0]

BCC basal cell carcinoma, *IR* incidence rate, *IXE* ixekizumab, *n* number of patients with at least one treatment-emergent skin cancer event, *PBO* placebo, *PY* patient-years, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SAE* serious adverse event, *SCC* squamous cell carcinoma, *TEAE* treatment-emergent adverse event

[a]1 case of dermatofibrosarcoma protuberans

Of the 58 ixekizumab-treated patients who developed treatment-emergent skin cancer events, 12.1% (7/58) had a reported history of skin cancer (4 with history of SCC, 2 with history of BCC, 1 with melanoma history). Neither of the two patients who developed a treatment-emergent melanoma reported skin cancer history. Conversely, of all patients treated with ixekizumab in the clinical trial program, 0.7% (50/6892) had skin cancer history prior to 5 years before baseline, as set out by the exclusion criteria. Of those, most (86%, 43/50) did not develop skin cancer while on ixekizumab treatment.

Nonmelanoma Skin Cancers—BCC events

There were 56 BCC events in 44 patients, most commonly on sun-exposed body areas. In total, 24 (42.9%) events occurred on the head/neck region, 10 (17.9%) on the back or chest, 5 (8.9%) on the extremities and in 17 (30.4%) cases no location was reported. Most BCC events were of mild (41.1%) or moderate (53.6%) severity as reported by the investigator and no patients discontinued treatment due to BCC (Table 4). Median (IQR) time to onset for BCC events was 412.5 (123.5–1007.5) days (Table S1). A total of four events (9.1%) were classified as serious adverse events (SAE; three patients required hospitalization and one was considered medically significant, requiring intervention; Table 5) and most patients (92.9%) had recovered by time of data abstraction. Of the 44 patients who developed BCC, 4 (9.1%) had previous history of skin cancer (2 with history of SCC, 1 each with BCC or melanoma history),20 (45.5%) received prior phototherapy (11 UVB, 4 PUVA, 3 both UVB & PUVA, 2 not specified), and 16 (36.4%) patients

Table 2 Treatment-emergent skin cancer events by yearly interval

	Year [0,1] PY = 6075.7	Year [1, 2] PY = 3429.5	Year [2, 3] PY = 3108.3	Year [3, 4] PY = 2881.9	Year [4, 5] PY = 2375.0	Year ≥ 5 PY = 155.4	Total IXE PY = 18,025.7, *N* = 6892
Patients with ≥ 1 TEAE skin cancer	34 (0.6) [0.4–0.8]	7 (0.2) [0.1–0.4]	13 (0.4) [0.2–0.7]	8 (0.3) [0.1–0.6]	9 (0.4) [0.2–0.7]	0 (0.0) [0.0–5.1]	58[¤] (0.3) [0.2–0.4]
NMSC	32 (0.5) [0.4–0.7]	7 (0.2) [0.1–0.4]	13 (0.4) [0.2–0.7]	8 (0.3) [0.1–0.6]	8 (0.3) [0.2–0.7]	0 (0.0) [0.0–5.1]	55[¢] (0.3) [0.2–0.4]
BCC[†]	23 (0.4) [0.3–0.6]	5 (0.1) [0.1–0.4]	11 (0.4) [0.2–0.6]	5 (0.2) [0.1–0.4]	4 (0.2) [0.1–0.4]	0 (0.0) [0.0–5.1]	44 (0.2) [0.2–0.3]
SCC[†],*	10 (0.2) [0.1–0.3]	2 (0.1) [0.0–0.2]	5 (0.2) [0.1–0.4]	3 (0.1) [0.0–0.3]	4 (0.2) [0.1–0.4]	0 (0.0) [0.0–5.1]	16 (0.1) [0.1–0.1]
Melanoma	1 (0.02) [0.0–0.1]	0 (0.0) [0.0–0.2]	0 (0.0) [0.0–0.3]	0 (0.0) [0.0–0.3]	1 (0.04) [0.0–0.3]	0 (0.0) [0.0–5.1]	2 (0.01) [0.0–0.04]
Other skin neoplasm[‡]	1 (0.0) [0.0–0.1]	0 (0.0) [0.0–0.2]	0 (0.0) [0.0–0.3]	0 (0.0) [0.0–0.3]	0 (0.0) [0.0–0.3]	0 (0.0) [0.0–5.1]	1 (0.01) [0.0–0.04]

Data presented as: *n* (IR) [95% CI]

BCC basal cell carcinoma, *IR* incidence rate, *IXE* ixekizumab, *n* number of patients with at least one treatment-emergent skin cancer event, *NMSC* non-melanoma skin cancer, *PBO* placebo, *PY* patient-years, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SAE* serious adverse event, *SCC* squamous cell carcinoma, *TEAE* treatment-emergent adverse event

[¤]88 events, [¢]85 events. [†]Five patients had both SCC and BCC events. *SCC subtypes included SCC of the skin (*n* = 13; 20 events), Bowen's disease (*n* = 4; 4 events), lip SCC (*n* = 2; 3 events), and keratoacanthoma type SCC (*n* = 1; 1 event). [‡] 1 case of dermatofibrosarcoma protuberans

Table 3 Baseline demographics of patients with skin cancer events

	IXE-treated patients with ≥ 1 TE skin cancer event (*N* = 58)	All IXE-treated patients without skin cancer TEAE (*N* = 6834)
Age in years, mean (SD)	59.3 (10.8)	45.6 (13.2)
Gender, *n* (%)		
Male	42 (72.4)	4654 (68.1)
Female	16 (27.6)	2180 (31.9)
Race, *n* (%)		
American Indian or Alaska Native	0 (0.0)	76 (1.1)
Asian	0 (0.0)	914 (13.4)
Black or African American	0 (0.0)	206 (3.0)
Naïve Hawaiian or other Pacific Islander	0 (0.0)	15 (0.2)
White	58 (100.0)	5554 (81.3)
Multiple	0 (0.0)	62 (0.9)
Geographic region, *n* (%)		
Asia	0 (0.0)	244 (3.6)
North America	42 (72.4)	3553 (52.0)
Europe	10 (17.2)	2241 (32.8)
Central America/ South America	0 (0.0)	174 (2.5)
Australia	6 (10.3)	159 (2.3)
Other	0 (0.0)	463 (6.8)
BMI (kg/m^2), mean (SD)	30.3 (5.6)	30.4 (7.3)
Duration of Ps symptoms in years, mean (SD)	27.2 (14.0)	18.6 (12.1)
Skin cancer history, *n* (%)	7 (12.1)	43 (0.6)
BCC	4 (6.9)	
SCC	2 (3.4)	
Melanoma	1 (1.7)	
Prior systemic therapy, *n* (%)	40 (69.0)	4378 (64.1)
Non-biologic systemic only	18 (31.0)	2400 (35.1)
Biologic therapy only	8 (13.8)	818 (12.0)
Biologic and nonbiologic	14 (24.1)	1160 (17.0)
Phototherapy	22 (37.9)	2647 (38.7)
UVB	12 (20.7)	1509 (22.1)
PUVA	6 (10.3)	624 (9.1)
PUVA & UVB	3 (5.2)	329 (4.8)
Unspecified	2 (3.4)	185 (2.7)
Prior biologic therapy, *n* (%)		
Ever	22 (37.9)[a]	1978 (28.9)
TNF inhibitors		
Infliximab	6 (10.3)	615 (9.0)
Etanercept	4 (6.9)	216 (3.2)
Adalimumab	3 (5.2)	655 (9.6)
Certolizumab	0 (0.0)	14 (0.2)

Table 3 continued

	IXE-treated patients with ≥ 1 TE skin cancer event (*N* = 58)	All IXE-treated patients without skin cancer TEAE (*N* = 6834)
Golimumab	0 (0.0)	20 (0.3)
LFA1 inhibitor		
Efalizumab	4 (6.9)	110 (1.6)
LFA3 inhibitor		
Alefacept	3 (5.2)	51 (0.7)
IL12/23 inhibitor		
Ustekinumab	4 (6.9)	488 (7.1)
IL17 inhibitor		
Brodalumab	1 (1.7)	278 (4.1)
Secukinumab	0 (0.0)	37 (0.5)
Others		
Others (< 0.5%) or unspecified	3 (5.2)	655 (9.6)
Used 1 therapy	13 (22.4)	1272 (18.6)
Used 2 therapies	5 (8.6)	414 (6.1)
Used ≥ 3 therapies	4 (6.9)	292 (4.3)

BMI body mass index, *IR* incidence rate, *IXE* ixekizumab, *N* total number of patients, *n* number of patients with at least one treatment-emergent skin cancer event, *Ps* psoriasis, *SD* standard deviation, *TE* treatment-emergent

were biologic experienced (including 6 TNFi; Table 4). Of those with known Psoriasis Area and Severity Index (PASI) at the time of BCC event, 88.2% (30/34) had PASI ≤ 5 and 67.6% (23/34) had PASI ≤ 2, indicating that detection of BCC was linked in most cases to high skin clearance.

Nonmelanoma Skin Cancers—SCC events

There were 29 SCC events in 16 patients, most commonly on sun-exposed body areas: 13 (44.8%) events occurred on the extremities, 8 (27.6%) occurred on the head, lips, or neck, 3 (10.3%) occurred on the back or chest, and 5 (17.2%) were unspecified. Most SCC events were rated mild (51.7%) or moderate (44.8%) in severity as reported by the investigator and no patients discontinued due to SCC (Table 4). Median (IQR) time to onset for SCC events was 309.0 (84.5–1019.0) days (Table S1). SCC subtypes included 20 events of SCC of the skin in 13 patients, 4 events of Bowen's disease in 4 patients, 3 events of lip SCC in 2 patients, and 1 keratoacathoma type SCC in 1 patient. Only one SCC event was considered a SAE (Table 5). Of 16 patients who developed SCC, 4 (25%) had a history of skin neoplasm (3 with a history of SCC, 1 with a history of BCC), 2 (12.5%) patients had received prior PUVA phototherapy, 1 (6.3%) patient received UVB, and 9 (56.3%) were biologic experienced (including 4 TNFi; Table 4). At the time of the SCC event, PASI was ≤ 5 in 85.7% (12/14) and ≤ 2 in 57.1% (8/14) of patients with SCC, indicating low skin involvement in most patients with known PASI at time of SCC detection.

Melanoma Events

AEs of melanoma were recorded as preferred term "malignant melanoma." In total, two melanoma events were noted, and neither case was considered a SAE. One event was reported in a 62-year-old white male patient in the USA in study IXORA-P. The investigator rated the event as mild. Event onset was 43 days after ixekizumab initiation. Previous therapies for psoriasis included topical only. The patient was discontinued from the study. Detailed information about melanoma thickness and/or specific therapy were not provided. The second event was reported as melanoma in situ in a 43-year-old white male patient from Australia, enrolled in UNCOVER-2, who had a 25-year history of psoriasis. Previous therapies included UVB phototherapy and one non-biologic

Table 4 Characterization of BCC and SCC events

	Year [0,1] PY = 6075.7 *n* (IR)	Year [1, 2] PY = 3429.5 *n* (IR)	Year [2, 3] PY = 3108.3 *n* (IR)	Year [3, 4] PY = 2881.9 *n* (IR)	Year [4, 5] PY = 2375.0 *n* (IR)	Year ≥ 5 PY = 155.4 *n* (IR)	Total IXE PY = 18,025.7 *N* = 6892 *N* (IR)
Non-melanoma skin cancer	32 (0.5)	7 (0.2)	13 (0.4)	8 (0.3)	8 (0.3)	0 (0.0)	55 (0.3)
Basal cell carcinoma	23 (0.4)	5 (0.1)	11 (0.4)	5 (0.2)	4 (0.2)	0 (0.0)	44 (0.2)
Squamous cell carcinoma	10 (0.2)	2 (0.1)	5 (0.2)	3 (0.1)	4 (0.2)	0 (0.0)	16 (0.1)

	Basal cell carcinoma: 56 events in 44 patients	**Squamous cell carcinoma: 29 events in 16 patients**
Body locations by events, *n* (%)		
Head/neck	24 (42.9)	8 (27.6)
Corps (back/chest)	10 (17.9)	3 (10.3)
Extremities	5 (8.9)	13 (44.8)
Unspecified	17 (30.4)	5 (17.2)
Severity by event, *n* (%)		
Mild	23 (41.1)	15 (51.7)
Moderate	31 (53.6)	13 (44.8)
Severe	2 (3.5)	1 (3.4)
Unknown	1 (1.8)	0 (0.0)
Serious adverse events, *n* (IR) [95% CI]	4 (0.02) [0.0–0.1]	1 (0.01) [0.0–0.0]
Outcomes by events, *n* (%)		
Recovered/resolved	52 (92.9)	28 (96.6)
Recovering/resolving	2 (3.6)	1 (3.4)
Not recovered/not resolved	2 (3.6)	0 (0.0)
Skin cancer history by patients, *n* (%)	4 (9.1)	4 (25.0)
Prior therapy by patients, *n* (%)		

Table 4 continued

	Basal cell carcinoma:56 events in 44 patients	Squamous cell carcinoma:29 events in 16 patients
Phototherapy	20 (45.5)	3 (18.8)
UVB	11 (25.0)	1 (6.3)
PUVA	4 (9.1)	2 (12.5)
PUVA & UVB	3 (6.8)	0 (0.0)
Unspecified	2 (4.5)	0 (0.0)
Biologics	16 (36.4)	9 (56.3)
Median time to onset (IQR), days	412.5 (123.5–1007.5)	309.0 (84.5–1019.0)

IR incidence rate, *N* total number of patients, *n* number of patients per category, *PUVA* psoralen and ultraviolet A, *PY* patient years, *UVB* ultraviolet B

systemic therapy. The melanoma event was rated as moderate in severity and did not lead to discontinuation. Event onset relative to ixekizumab initiation was 1726 days and the patient had reached a PASI90 response at time of melanoma identification. Both patients were reported to have recovered.

Other Malignant Neoplasms of the Skin

One other skin neoplasm was detected; a DFSP which occurred in a 47-year-old white female in the USA (study IXORA-P). Of note, the lesion, diagnosed as DFSP on the mons pubis 13 days after initiation of ixekizumab treatment, was reported to have been present for $\geq$ 1 year prior to enrollment and led to study drug discontinuation. Diagnosis was confirmed by immunohistochemical detection of CD34-positive spindle cells in the lesion, and surgery was planned at the most recent follow-up. The patient had received a previous therapy with brodalumab over 6 years.

DISCUSSION

We assessed skin neoplasm events in 6892 patients with psoriasis treated with ixekizumab for up to 5 years with 18,025.7 total PYE. Incidence of skin cancer TEAEs was low, with 88 events in 58 patients. IRs remained stable or decreased over time. Most patients who had a history of skin cancer (n = 50), in line with the exclusion criteria, did not develop skin cancer in the ixekizumab trials. Most TEAEs were mild or moderate as reported by the study investigator and were eventually resolved. Two events of melanoma were noted, and neither were reported as SAEs. One DFSP, reported as serious, was also noted. Only two skin cancer events led to study drug discontinuation, one event each of melanoma and DFSP. Both cases were identified shortly after ixekizumab treatment initiation; 13 and 43 days for the DFSP and melanoma cases, respectively. Given that > 80% of patients in this analysis had a PASI $\leq$ 5 at the time of skin cancer detection, perhaps the ability of ixekizumab to clear skin in the study and the study setting may have favored

Table 5 Summary of serious skin cancer events

Description	Severity	Disc	Outcome	Onset (Days)	M/F	Age	Study	Treatment
Basal cell carcinoma on right forehead	Moderate	No	Recovered/resolved	772	M	58	RHAZ	IXE Q4W extension
Basal cell carcinoma	Severe	No	Recovered/resolved	314	F	55	RHBC	IXE Q4W extension
Basal cell carcinoma on right cheek	Moderate	No	Recovered/resolved	312	F	56	RHBC	IXE Q4W extension
Basal cell carcinoma on the eyebrow	Mild	No	Recovered/resolved	356	M	54	RHBC	IXE Q4W extension
Squamous cell carcinoma of skin	Severe	No	Recovered/resolved	32	M	51	RHBL	IXE Q2W
Dermatofibrosarcoma protuberans on the right side of the mons pubis	Severe	Yes	Not recovered/not resolved	13	F	47	RHBP	IXE Q4W/Q2W

Disc. discontinued treatment, *F* female, *M* male

identification of potentially preexisting conditions. Most TEAEs were NMSCs, all in white patients and predominantly located on body areas potentially exposed to sunlight. Patients with skin cancer TEAEs tended to be older than those without, an observation which is consistent with previous reports of increased skin cancer risk with increased age [29]. Overall, prior phototherapy use, a well-known risk factor for skin cancer, was similar between patients with versus without TEAE skin cancer events; however, patients with TEAE skin cancer events seemed to have higher prior biologic therapy use (Table 3). While recent evidence suggests the use of biologics in patients with a history of cancer appears to be safe [30–32], further research is warranted. In the general population the BCC:SCC ratio is believed to be around 4:1, with considerable variations according to age and ranging in the literature from 1:1 to 10:1 depending on population, ethnic group, and sex [33–35]. However, it is well known that immunocompromised patients have an increased risk of developing SCC leading to a reversal of the BCC:SCC ratio [36, 37]. In this study, although a small number of skin cancer events were identified, the BCC:SCC ratio was 2.8:1, in line with observations in the immunocompetent general population. Overall, these results corroborate previous descriptions for the safety profile of ixekizumab and support that longer exposure to this IL-17 inhibitor was not associated with increased risk of treatment-emergent skin cancer. [13–16]

IL-17, primarily produced by Th17 cells, is prevalent in the tumor microenvironment and is commonly found in various tumors including melanoma and NMSCs (BCC and SCC) [38–40]. Significantly higher levels of IL-17 expression have been detected by immunohistochemistry in melanomas than in melanocytic nevi, suggesting involvement of IL-17 in cutaneous melanoma development or progression [41]. IL-17 and Th17 cells have been described as having both pro- and anti-tumoral effects [42]. This dichotomy depends on tumor stage, tumor microenvironment, and level of IL-17 or number of Th17 cells as described elsewhere. [38, 43, 44]

In skin cancer specifically, IL-17 promotes tumor formation in mouse keratinocytes [45] and has a critical role in supporting cancer-associated inflammation in the tumor microenvironment of murine skin cancer [46]. In BCC

and SCC in vitro, IL-17 and IL-22 promote tumor cell proliferation and migration [40]. Additionally, IL-17 upregulates anti-apoptotic and angiogenic genes, promoting tumor cell growth in mouse models of melanoma and NMSCs [40, 47, 48]. In support of a critical role for IL-17 in tumor progression, locally targeting the IL-17/IL-17RA axis via shRNA in a melanoma model suppressed tumor development [49]. In 2015 Nardinocchi et al. reported that their data encourage the administration of anti-IL-17 and anti-IL-22 biological drugs in patients with psoriasis at risk for development of skin cancer [40].

In contrast, tumor-inhibitory effects have also been attributed to IL-17 and Th17 cells. While IL-17 was reported to inhibit growth of hematopoietic tumors by enhancing cytotoxic T lymphocyte activity, Th17-polarized cells were shown to eliminate advanced B16 melanoma [38, 50, 51]. However, tumor elimination was primarily linked to large established tumors and was mainly driven by IFNγ.

Recently, other studies examined the incidence of skin cancer TEAEs in patients with psoriasis. An integrated safety analysis of 18 clinical trials in 3727 patients with psoriasis (5429.7 PYs) treated with the TNFi and adalimumab reported an IR/100PY of 0.6 and 0.2 for NMSC and melanoma, respectively [12]. Analysis of 1965 patients with psoriasis from seven studies who received etanercept treatment observed an IR of 0.46 and 0.59 for SCC and BCC, respectively, and no melanoma cases were observed [52]. A long-term safety analysis of treatment of 3117 patients (8998 PYs) with psoriasis treated with ustekinumab observed an IR of 0.52/100PY for NMSC events [53], while safety analysis of 2725 total PY of treatment with secukinumab over 52 weeks observed a NMSC event rate of 0.48/100PY [54]. Overall, observations of IRs for NMSC and melanoma for patients treated with ixekizumab in our study are comparable, if not lower than, rates reported in the literature for patients with psoriasis in general [4], those treated with biologics in real-world settings [4], or those treated for psoriasis in clinical trials with other biologics such as secukinumab [54] or ustekinumab [55].

While more research is needed to better understand the role of IL-17 in tumor biology, the current literature seems to support our findings that ixekizumab-mediated IL-17A blockade in patients with psoriasis did not lead to an increased risk for skin malignancies within the observation period.

Limitations

There were limitations to this analysis. Several of the ixekizumab trials excluded patients with skin cancer events within 5 years prior to baseline, therefore, the risk of developing skin cancer for patients receiving ixekizumab treatment with a recent history of skin cancer could not be fully determined here. The lack of placebo-controlled data beyond week 12 impaired the ability to compare IRs with a control group at later periods. The small number of events may mean that larger populations are required to confirm the risk of skin cancer events. High rates of prior treatment in the patient population limit interpretation of ixekizumab treatment alone. It should be noted that not all potential risk factors that may influence risk of skin cancer development, such as Fitzpatrick skin type and actinic damage, could be considered in the present analysis, and information on the cumulative dose of phototherapy received by patients was not collected. Finally, the limited observation period precludes risk assessment beyond 5 years. Nevertheless, these data contribute to growing evidence supporting the safety of ixekizumab treatment regarding skin cancer risk.

CONCLUSIONS

In summary, the incidence of skin cancer TEAEs was low and did not increase with longer exposure to ixekizumab in patients with psoriasis. Most patients had NMSCs, with a BCC:SCC ratio consistent with the general population. Most events were resolved and did not lead to ixekizumab discontinuation.

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Compliance with Ethics Guidelines. Protocols for all studies included in this analysis were approved by the Institutional Review Board or Ethics Committee at each participating site. All studies included in this analysis were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all eligible patients before undergoing study-related procedures.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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