Supplementary Material

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

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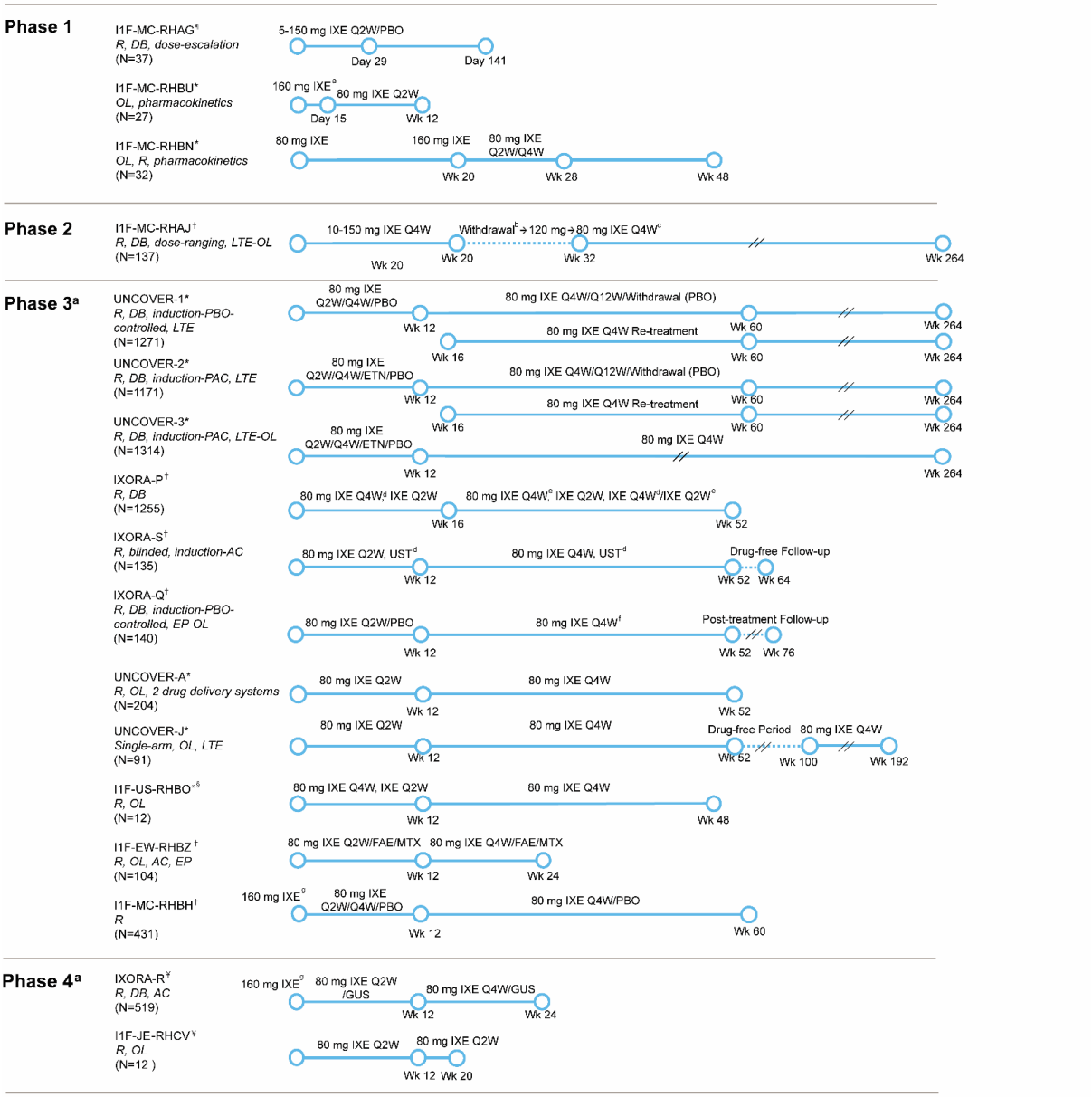
Supplemental Figure 1. Designs and numbers of patients for all studies included in the analysis.



. [a] For patients receiving IXE, the starting dose was 160 mg at Wk 0 prior to receiving 80 mg IXE (Q4W or Q2W); [b] Withdrawal period (Wks 20-32); patients were eligible for treatment with 80 mg IXE Q4W when improvement in Psoriasis Area and Severity Index score from baseline was ≤75%); [c] Protocol amendment–mandated dose regimen; [d] PBO administered to maintain study blind; [e] Step-up criteria determined if dosing increased from 80 mg IXE Q4W to 80 mg IXE Q2W for a patient who achieved static Physician's Global Assessment ≥2 at 2 consecutive visits during Wk 12 through Wk 40; [f] Based on investigator opinion, dosing increased from IXE Q4W to IXE Q2W between Wk 24 through Wk 40; [g] Subcutaneous injection of 160 mg starting dose (two 80 mg injections).

Exclusion criteria related to malignancies:

* Patients with active or a history of or signs or symptoms of malignant disease were excluded. Patients with successfully treated BCC (no more than 3), SCC of the skin § , cervical carcinoma in

situ, with no evidence of recurrence within 5 years of baseline (Week 0; Visit 2) were allowed to participate.
§ SCC of the skin (no more than 2).

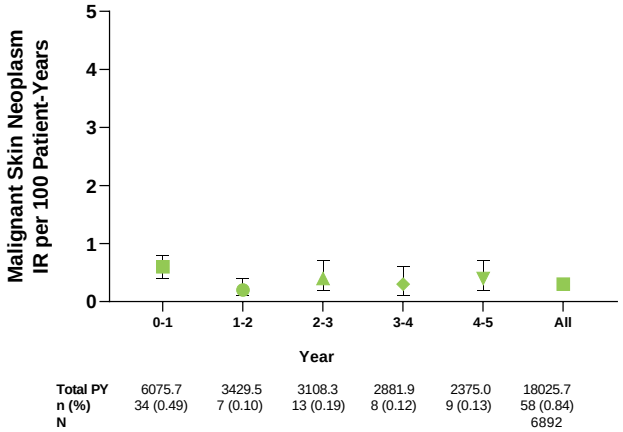
† Patients with active or a history of or signs or symptoms of malignant disease within 5 years prior to baseline (Week 0; Visit 2) were excluded. Patients with history of malignancy with no evidence of recurrence or active disease within 5 years prior to baseline were allowed to participate.

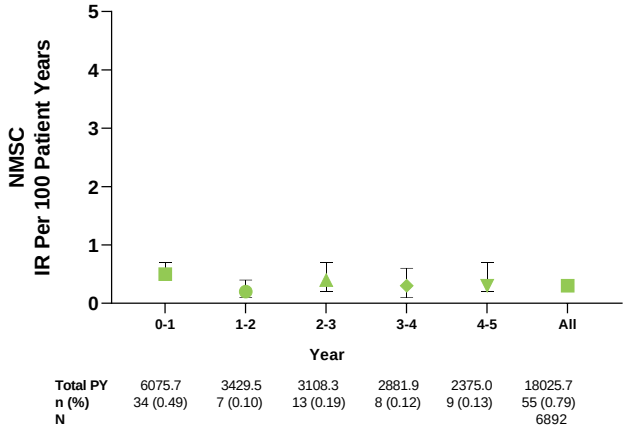
¥ Patients with active or a history of or signs or symptoms of malignant disease within 5 years prior to baseline (Week 0; Visit 2) except for BCC, SCC, skin Bowen's disease or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed. Patients with history of malignancy with no evidence of recurrence or active disease within 5 years of baseline may participate in the study.

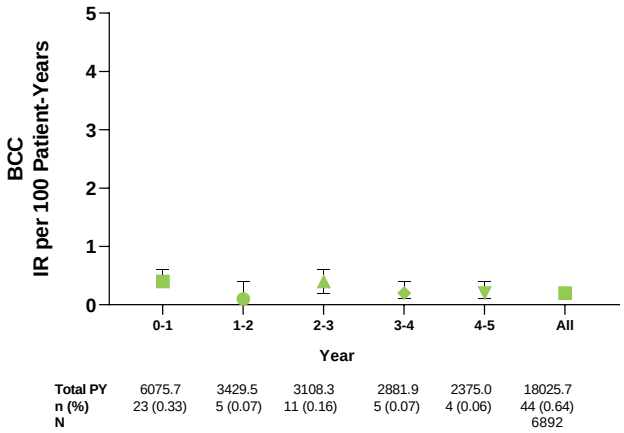
¶ Patients with current or a history of lymphoproliferative disease or a primary or recurrent malignant disease.
Abbreviations: AC, active comparator; DB, double-blind; EP, optional extension period after Wk 24 during which patients received 80 mg IXE Q4W up to Wk 60; ETN, 50 mg etanercept twice weekly; FAE, fumaric acid esters 105-mg starting dose followed by 215 mg given orally 1–3 times per day; GUS, guselkumab 100 mg at Wk 0, Wk 4, then Q8W; IXE, ixekizumab; IXE Q2W, ixekizumab every 2 weeks; IXE Q4W, ixekizumab every 4 weeks; IXE Q12W, ixekizumab every 12 weeks; LTE, long-term extension; MTX, methotrexate 7.5-mg starting dose up to 30 mg given orally once a week; N, number of patients; OL, open-label; PAC, placebo-controlled and active comparator; PASI, Psoriasis Area Severity Index; PBO, placebo; Q2W Every 2 weeks, Q4W Every 4 weeks; R, randomized; sPGA, Static Physician's Global Assessment; UST, 45 mg ustekinumab given as subcutaneous injection for participants ≤ 100 kg and 90 mg subcutaneous injection for participants > 100 kg at weeks 0, 4, 16, 28 and 40, Wk week.
Information from Figure 1 of Armstrong et al, 2020 [20] are included in this figure.

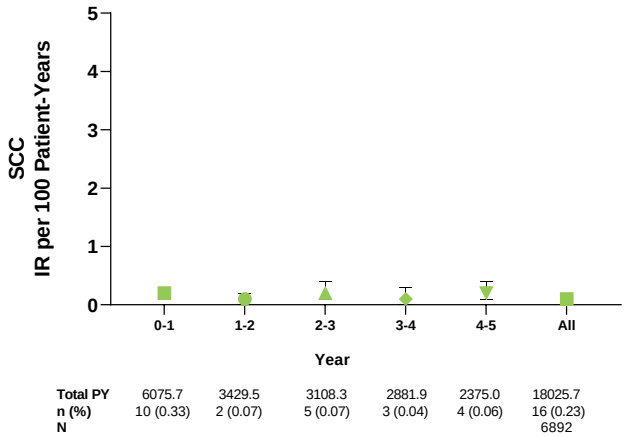
Supplemental figure 1 has been created by Lilly, including some of the information presented previously in Figure 1 of Armstrong et al, 2020. New information is also presented. Full reference: Armstrong, A., Paul, C., Puig, L. et al. Safety of Ixekizumab Treatment for up to 5 Years in Adult Patients with Moderate-to-Severe Psoriasis: Results from Greater Than 17,000 Patient-Years of Exposure. Dermatol Ther (Heidelb) 10, 133–150 (2020). https://doi.org/10.1007/s13555-019-00340-3

Supplemental Figure 2. Treatment-emergent skin cancer events by yearly interval from all IXE trials.



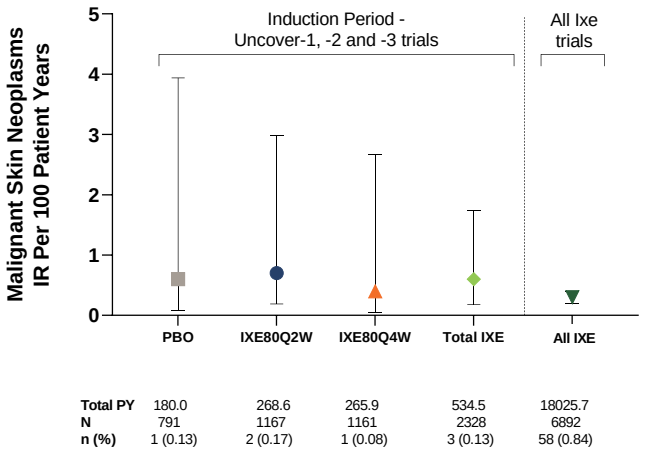


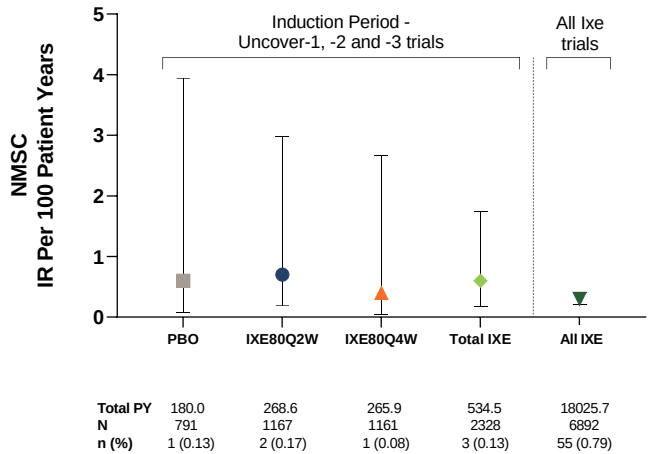


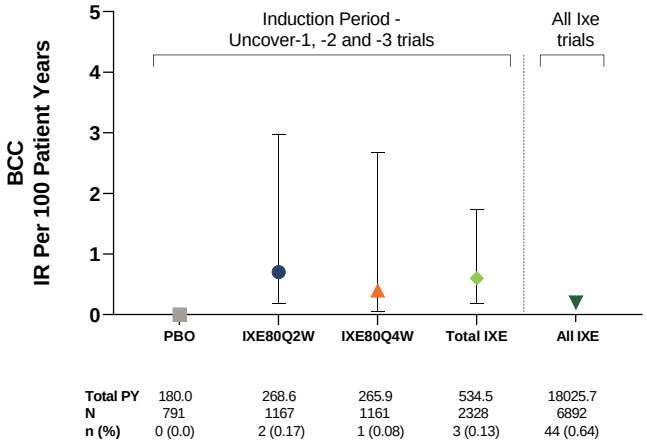


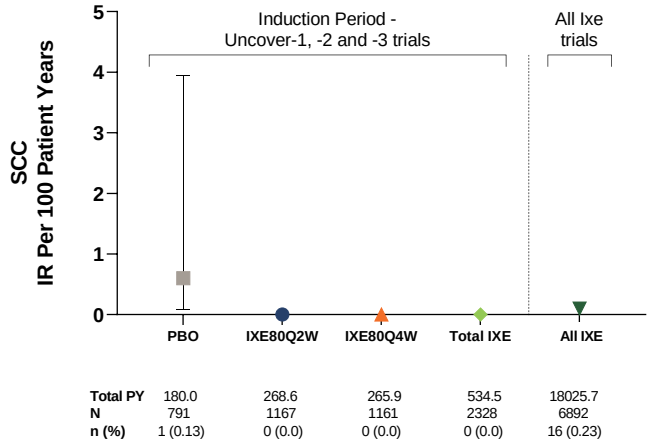
Incidence rate of malignant skin neoplasms (a), NMSC (b), SCC (c) and BCC (d). Abbreviations: BCC = basal cell carcinoma; Ixe = ixekizumab; N = Total number of patients; n = number of patients per category; NMSC = non-melanoma skin cancer; IR = incidence rate; PBO = placebo; SCC = squamous cell cancer.

Supplemental Figure 3. Treatment-emergent skin cancer events from the placebo-controlled induction period of UNCOVER-1, UNCOVER-2 and UNCOVER-3.









Incidence rate of malignant skin neoplasms (a), NMSC (b), SCC (c) and BCC (d). Treatment-emergent skin cancer events from all ixezumab trials included in this study are shown (right; A-D) Abbreviations: BCC = basal cell carcinoma; Ixe = ixekizumab; N = Total number of patients; n = number of patients per category; NMSC = non-melanoma skin cancer; IR = incidence rate; PBO = placebo; SCC = squamous cell cancer.

Supplemental table 1. Time to onset (days) of skin cancer TEAEs.

Category	N	Mean	SD
Patients with >=1 TEAE	58	676	585
Nonmelanoma skin cancer	55	682	573
Basal cell carcinoma	44	621	539
Squamous cell carcinoma	16	820	619
Bowen's disease	4	936	334
Keratoacanthoma	1	51	NA
Lip squamous cell carcinoma	2	715	462
Squamous cell carcinoma	7	977	670
Squamous cell carcinoma of skin	8	334	580
Melanoma	2	842	1130
Malignant Melanoma	1	43	NA
Malignant Melanoma in situ	1	1641	NA
Other skin neoplasms	1	13	NA
Dermatofibrosarcoma protuberans	1	13	NA

N = number of patients per category; SD = standard deviation; TEAE = treatment-emergent adverse events; BCC.