HHS Public Access

Author manuscript

Eur J Cancer. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Eur J Cancer. 2016 June ; 60: 12–25. doi:10.1016/j.ejca.2016.02.010.

Characterization and management of dermatologic adverse events to agents targeting the PD-1 receptor

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IRB Status: The clinical and histopathological data was collected utilizing an IRB-approved waiver.

Submission Declaration: The contents of this manuscript have not been presented earlier, and are not under consideration for publication elsewhere.

CONFLICT OF INTEREST STATEMENT

VRB, **BB**, **MDH**, **NHS**, **RJM**, and **KJB** have no conflicts of interest to declare.

MAP has had a consulting or advisory role with Amgen and Bristol-Myers Squibb, and receives research support from Bristol-Myers Squibb and Novartis (Inst).

AML has a consulting or advisory role with Bristol-Myers Squibb, Janssen, Aduro, Efranat, Jounce, and Novartis, and receives research funding from Bristol-Myers Squibb (Inst), Janssen (Inst.), and Genentech (Inst).

SW has a speaking arrangement with Novartis, Bayer-Onyx, Pfizer, and Mediavation.

JDW has a consulting or advisory role with Bristol-Myers Squibb, Merck, MedImmune, Ziopharm, Polynoma, Polaris, Jounce, GlaxoSmithKline; receives honoraria from EMD Serono, Janssen Oncology, and research funding from Bristol-Myers Squibb (Inst), MedImmune (Inst), GlaxoSmithKline (Inst), Merck (Inst).

MEL has consulted for BMS and Merck, and received research support from Bristol-Myers Squibb (Inst).

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Abstract

Background—Dermatologic adverse events (AEs) are some of the most frequently observed toxicities of immune-checkpoint inhibitor therapy, but have received little attention. The drugs, pembrolizumab and nivolumab are recently approved inhibitors of the PD-1 receptor that have overlapping AE profiles however, the incidence, relative risk (RR), and clinico-morphological pattern of the associated dermatologic AEs is not known.

Methods—We conducted a systematic review of the literature, and performed a meta-analysis of dermatologic AEs with the use of pembrolizumab and nivolumab in cancer patients. An electronic search was conducted using the PubMed, and Web of Science, and on the ASCO and ESMO meeting abstracts' library for potentially relevant oncology trials employing the drugs at FDA-approved doses and reporting dermatologic AEs. The incidence, relative risk and 95% CIs were calculated using either random- or fixed-effects models based on the heterogeneity of included studies. The clinical presentation, histology of affected areas, and management strategies based on institutional experience, are also presented.

Results—Rash, pruritus and vitiligo were the most frequently reported AEs. The calculated incidence of all-grade rash with pembrolizumab and nivolumab was 16.7% (RR=2.6) and 14.3% (RR=2.5), respectively. Other significant all-grade AEs included pruritus [pembrolizumab: incidence, 20.2% (RR=49.9); nivolumab: incidence, 13.2% (RR=34.5)] and vitiligo [pembrolizumab: incidence, 8.3% (RR=17.5); nivolumab: 7.5% (RR=14.6)]. Interestingly, all the vitiligo events were reported in trials investigating melanoma. The RR for developing dermatologic toxicities in general, was 2.95 with pembrolizumab, and 2.3 with nivolumab.

Conclusion—We found that pembrolizumab and nivolumab are both associated with dermatologic AEs, primarily low-grade rash, pruritus, and vitiligo, which are reminiscent of those seen with ipilimumab. Knowledge of these findings is critical for optimal care, maintaining dose intensity, and health-related quality of life, in cancer patients receiving PD-1 inhibitors.

Keywords

adverse events; immune-checkpoint; immunotherapy; incidence; nivolumab; PD-1; pembrolizumab; programmed death-1; pruritus; rash; risk; targeted therapies; vitiligo

INTRODUCTION

Recent developments in cancer immunology at the cellular and molecular level have generated a renewed interest in the immunotherapy of cancer. The cytotoxic T lymphocyte antigen-4 (CTLA-4) signalling pathway, and more recently, the programmed death receptor-1 (PD-1)/PD ligand-1 (PD-L1/PD-L2) signalling pathway are being increasingly recognized as critical mediators ("checkpoints") of tumor-induced immune suppression. While the former (CTLA-4, with its ligands CD80 and CD86) is crucial in attenuating the activation of naive and memory T cells (in the early phase) after binding with the T cell receptor, the latter is active against T cell activity in peripheral tissues (PD-1, with its ligands

PD-L1/-L2) in chronic inflammatory states, and infection or cancer, thus suppressing autoimmunity.[1] More specifically, interaction between the ligand and PD-1 receptor delimits the body's normal anti-tumor immune response by inhibiting T-cell proliferation, down-modulating cytokines and anti-apoptotic molecules, and promoting induced T-reg cell proliferation—ultimately conferring immune resistance in tumor cells.[2–5]

Preclinical and clinical data have shown that pharmacological inhibition of the PD-1 signaling pathway is more beneficial (viv-a-vis CTLA-4 blockade), in terms of antitumor effects and adverse event (AE) rates.[6–9] This led to the eventual approval of two novel anti-PD-1 receptor IgG4-κ monoclonal antibodies (mAbs)—pembrolizumab (humanized; *Keytruda®*, Merck & Co., Inc., Whitehouse Station, NJ), and nivolumab (fully human; *Opdivo®*, Bristol-Myers Squibb Company, Princeton, NJ). At the time of this writing, both drugs were indicated for the treatment of unresectable or metastatic melanoma and metastatic non-small cell lung cancer (NSCLC), with nivolumab being additionally approved for renal cell carcinoma; the precise treatment regimen with either agent however varies, and is subject to certain underlying criteria (e.g. $BRAF^{V600}$ mutational status, prior treatment with ipilimumab/platinum-based chemotherapy/antiangiogenic therapy, or PD-L1 expression).[10,11] In general, these drugs inhibit the key immune-compromising interaction between the tumor cell PD-L1 (B7-H1)/PD-L2 (B7-DC) and T cell PD-1 receptors.[12]

In terms of AEs, their overall safety profiles appear impressive. However, the potential for developing dermatologic AEs remains significant—moreover, the pattern is understood to be different in frequency and character from most other chemotherapy and targeted therapy-induced AEs.[13] Some of these AEs manifest with signs of autoimmunity ("immune-related adverse events", irAEs), and are thought to be due to treatment-related nonspecific hyperfunctioning of the immune system. Our current understanding mostly stems from the ipilimumab experience, wherein the development of rash, pruritus, alopecia, and vitiligo (in 20–30% of patients)[14] may lead to anticancer therapy dose modifications and/or termination, besides impairing patients' health-related quality of life (HRQoL). Since very little is known about PD-1 inhibitor-induced dermatologic AEs, we sought to determine the incidence and risk, and describe the clinical characteristics in patients evaluated at our oncodermatology program.

PATIENTS AND METHODS

Data sources and search strategy

We conducted a systematic search of the literature to identify clinical trials of pembrolizumab and nivolumab, that reported dermatologic AEs. The Medline (via PubMed) and Thomson-Reuters' Web of Science databases were searched for studies published between January, 1960, and July, 2015. The following generic drug names and synonyms were used as search terms: pembrolizumab (MK-3475/lambrolizumab/Keytruda) and nivolumab (BMS-963558/ONO-4538/MDX-1106/Opdivo). In addition, pertinent abstracts from the American Society of Clinical Oncology's (ASCO) and the European Society for Medical Oncology's (ESMO) annual meetings/congresses were reviewed. The latest manufacturer's package inserts were also retrieved.

Study selection and screening process

Our selection criteria included all prospective clinical trials (and/or cohorts) that: 1) investigated the utility of pembrolizumab or nivolumab at the FDA-approved dose in the treatment of cancer; 2) clearly reported a dermatologic AE in their safety data, with or without the clinical severity grading; and 3) were published in the English language (Fig. 1). We excluded any trials that: 1) involved combination regimens with other therapies/modalities (e.g. targeted therapy, chemotherapy, radiation therapy, other immunotherapies); and 2) did not list a dermatologic AE exclusively in any arm/cohort (Fig 1). Within the trials included for analysis, for skin eruptions, data was recorded only for instances of “rash”; others e.g. “rash maculopapular”, “macular/erythematous rash”, “pruritic rash”, “eczema”, “dermatitis”, “drug eruption” were excluded because of possible duplication in reporting within the same trial (the excluded data was not significant). In the event of duplicates, ambiguity or publications reporting on the same study population, only the most recent, relevant and/or comprehensive publication (abstract/manuscript) was retained. Any discrepancy in selection was resolved by consensus.

Data extraction and Clinical Endpoints

The data abstraction was conducted by two authors (V.R.B. and B.B.) independently and then reviewed. The variables extracted included the name of the first author, year of publication, clinical trial identifier (e.g. NCT#), study design, overall enrollment numbers, number of treatment arms/cohorts (experimental/control) and dosing details, all-grade and high-grade AEs among those evaluated for safety, the underlying cancer indication, AE reporting threshold, and the clinical severity grading system used. When AEs were reported as percentages, we manually calculated the numbers and rounded down to the nearest whole number, or excluded the publication if this was not possible.

The safety data in each clinical trial was examined for the clinical endpoints. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0,[15] issued by the National Cancer Institute (NCI), was predominantly used by all trials included in the analysis. We included the data from all trials reporting grade ≥ 1 rash, pruritus, or hypopigmentation/vitiligo. For dermatologic AEs where the available data did not lend itself to a statistical analysis, we employed descriptive methods.

Meta-analytic Strategy

All statistical analyses were performed using version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, N.J., USA).[16] The total number of patients with all-grade and high-grade rash, pruritus, and vitiligo were extracted from the clinical trials as delineated above (Fig 1). For each clinical trial, the incidence of rash, pruritus, and vitiligo were calculated, and the 95% confidence intervals (CI) were derived. The relative risk (RR) of AEs among patients assigned to the respective PD-1 receptor inhibitor was calculated and compared with those assigned to chemotherapy. To graphically represent the meta-analysis, forest plots were constructed.

For the meta-analysis, both the fixed-effects model (weighted with inverse variance) and the random-effects model were considered.[17] For each meta-analysis, Cochran’s Q statistic was

first calculated to assess the heterogeneity of the included trials. For *P* value <0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was used.[18] Otherwise, results from both the fixed-effects model and the random-effects model were evaluated, and if they were similar, only fixed-effects model results were reported. A two-tailed *P* value <0.05 was considered as statistically significant.

Case series

We obtained a waiver of research authorization from the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board (IRB) for this portion of the study. The electronic medical records of patients who were evaluated by a dermatologist (M.E.L.) for an AE that developed during treatment with pembrolizumab or nivolumab were identified using an institutional data mining service—the Information Systems' data delivery group, DataLine. Subsequently, the corresponding clinical notes, pathology slides/reports of available skin biopsy specimens, and clinical photographs were examined and relevant data was recorded.

RESULTS

Our search strategy yielded a total of 427 potentially relevant records related to nivolumab and 102 records for pembrolizumab. Of these, 8 studies [phase I (n=2),[19,20] phase II (n=2),[21,22] phase III randomized controlled (n=4)[8,23–25]] investigating nivolumab, and 5 studies [phase I (n=4),[26–29] expanded access program (n=1)[30]] of pembrolizumab were included in the final statistical analysis (Table 1).

Incidence of all-grade and high-grade (grades 3/4) rash and relative risk

The calculated incidence of all-grade rash with nivolumab was 14.3% (95% CI: 8.7–22.7%) in 178/1136 patients analyzed using the random-effects model, and ranged from 3.8% (5/131)[23] to 41.5% (17/41)[20] (Fig. 2A). The RR of developing all-grade rash to nivolumab as compared to the chemotherapy controls was 2.5 (95% CI: 1.3–5.0; *P*=0.008). For pembrolizumab, the incidence was 16.7% (95% CI: 11.9–23.0%) in 29/177 patients as per the fixed-effects model, and ranged from 0% (0/6)[28] to 18% (16/89)[27] (Fig. 2B). The RR of developing all-grade rash as compared to the chemotherapy controls was 2.6 (95% CI: 1.2–5.6; *P*=0.011).

The incidence of high-grade rash was low with both drugs [nivolumab – 1.2% (95% CI: 0.5–2.9%) in 8/1136 patients analyzed using the random-effects model, and ranged from 0% (0/131)[23] to 10% (1/10)[22]; pembrolizumab – 1.7% (95% CI: 0.4–6.7%) in 1/171 patients analyzed using the fixed-effects model, and ranged from 0% (0/89)[27] to 4.5% (1/22)[26]]. The RR for developing high-grade rash during treatment with nivolumab and pembrolizumab (as compared to the chemotherapy controls) was 0.7 (95% CI: 0.15–3.0; *P*=0.613) and 0.4 (95% CI: 0.04–4.1; *P*=0.424), respectively.

Incidence of all-grade and high-grade (grade 3) pruritus and relative risk

The calculated incidence of all-grade pruritus with nivolumab was 13.2% (95% CI: 8.9–19.2%) in 164/1126 patients analyzed using the random-effects model, and ranged from

2.3% (3/131)[23] to 31.7% (13/41)[20] (Fig. 2C). The RR of developing all-grade pruritus during treatment with nivolumab as compared to the chemotherapy controls was 34.5 (95% CI: 2.1–550.6; *P*=0.012). For pembrolizumab, it was 20.2% (95% CI: 14.8–26.9%) in 35/184 patients as per the fixed-effects model, and ranged from 10% (6/60)[30] to 25.8% (23/89)[27] (Fig. 2D). The RR of developing all-grade pruritus during treatment with pembrolizumab as compared to the chemotherapy controls was 49.9 (95% CI: 3.0–806.0; *P*=0.006).

The incidence of high-grade pruritus was low with both drugs [nivolumab – 0.5% (95% CI: 0.2–1.3%) in 2/1126 patients analyzed using the fixed-effects model; pembrolizumab – 2.3% (95% CI: 0.7–7.6%) in 1/177 patients analyzed using the fixed-effects model]. The RR of developing high-grade pruritus during treatment with nivolumab and pembrolizumab (as compared to the chemotherapy controls) was 1.5 (95% CI: 0.08–26.4; *P*=0.782) and 2.2 (95% CI: 0.09–53.3; *P*=0.63), respectively.

Incidence of all-grade and high-grade (grade 2) hypopigmentation/vitiligo and relative risk

All the vitiligo events were noted in trials of melanoma.[8,19,20,24–27] The calculated incidence of all-grade vitiligo with nivolumab was 7.5% (95% CI: 5.9–9.5%) in 62/878 patients analyzed using the fixed-effects model, and ranged from 2.4% (1/41)[20] to 10.7% (22/206)[25] (Fig. 2E). The RR of developing all-grade vitiligo during treatment with nivolumab was 14.6 (95% CI: 0.9–235.0; *P*=0.058) as compared to the chemotherapy controls. For pembrolizumab, the incidence was 8.3% (95% CI: 4.4–15.2%) in 9/111 patients as per the fixed-effects model, and ranged from 4.5% (1/22)[26] to 9% (8/89)[27] (Fig. 2F). The RR of developing all-grade vitiligo during treatment with pembrolizumab was 17.5 (95% CI: 1.03–296.44; *P*=0.048) as compared to the chemotherapy controls.

The incidence of high-grade vitiligo was low with both drugs [nivolumab – 0.4% (95% CI: 0.1–1.3%); pembrolizumab – 1.1% (95% CI: 0.2–7.4%)] as per the fixed-effects model. The RR of developing high-grade vitiligo during treatment with nivolumab was 0.35 (95% CI: 0.01–8.6; *P*=0.521) as compared to the chemotherapy controls; the RR for pembrolizumab could not be calculated due to lack of data.

In general, as compared to the chemotherapy controls, the overall RR for developing dermatologic AEs (rash, pruritus, vitiligo) with pembrolizumab was 2.95 (95% CI: 1.5–5.7%; *P*=0.001), and with nivolumab it was 2.3 (95% CI: 1.3–4.1%; *P*=0.004).

Other Dermatologic Adverse Events

The findings for other AEs were pooled, since the available data from the included studies was insufficient for a meta-analysis. In patients treated with nivolumab (at any dose), these included xerosis (5.3%, 20/373),[25,31] alopecia (2%, 10/502),[19,25] stomatitis (1.5%, 2/131),[23] urticaria (1.4%, 6/427),[19,23] photosensitivity reaction (1.4%, 3/206),[25] hyperhidrosis (0.9%, 2/206),[25] and skin exfoliation (0.7%, 1/131).[23] In patients treated with pembrolizumab (at any dose), these included xerosis (2.4%, 31/1264),[7,27,28,32] hair color changes (1.1%, 8/690),[7,26] alopecia (0.9%, 5/555),[7] and impaired healing (14%, 1/7).[29]

Case Series: Clinical characteristics and histopathology

Our institutional data yielded 9 patients with nivolumab-induced rash, and 5 patients with pembrolizumab-induced rash—the clinical and histopathological characteristics are summarized in Table 2, and depicted in Fig. 4. Majority of the patients (12/14) had grade 1/2 rash, and of those, treatment had been interrupted in 3 patients (nivolumab, n=2; pembrolizumab, n=1). The onset of rash after initiation of treatment, ranged from 3 weeks to 2 years in the case of nivolumab-treated patients, and 6 weeks to 20 weeks in pembrolizumab-treated patients. Clinically, it consisted of erythematous macules/papules/plaques (sometimes associated with a scale), with or without pruritus (Fig. 3A–C). The lesions were predominantly localized to the trunk and extremities (upper>lower). At the time of eruption, the peripheral blood eosinophil counts in all patients were within normal limits (WNL) however, autoantibody tests were not clinically indicated. On histopathology, a lichenoid reaction pattern/interface dermatitis, with mild superficial and perivascular lymphohistiocytic infiltrates and scattered eosinophils, was frequently noted (Fig. 4). In the management, medium-to-high potency topical corticosteroids generally sufficed, although oral antihistamines and corticosteroids were occasionally needed (Table 2).

DISCUSSION

Our study is the first to estimate the burden of dermatologic AEs with the use of PD-1 receptor inhibitors in cancer immunotherapy. The most commonly reported AEs were rash, pruritus, and vitiligo—the incidence and risk of developing all-grade and high grade events however, appears to be low with both the drugs, pembrolizumab (P) and nivolimumab (N). Pembrolizumab is a humanized mAb, which may have a slightly greater immunogenic potential than nivolumab (fully human mAb). Nevertheless, the AEs were mostly mild in severity (grades 1/2). The other AEs reported include xerosis (P, N), alopecia (P, N), stomatitis (N), urticaria (N), photosensitivity reactions (N), hyperhidrosis (N), skin exfoliation (N), and hair color changes (P), occurring at various doses.

Our findings suggest that the dermatologic AEs with these drugs appear to mirror the onset and pattern of irAEs seen with CTLA-4 blockade (ipilimumab),[14,33] and occur irrespective of the underlying cancer type being treated.[33] Ipilimumab acts by inhibiting an immune-checkpoint (CTLA-4) that allows tumor cells to evade immune responses, and it also has the potential to trigger autoimmune damage in previously protected normal cells. The skin is a major organ affected by this ‘enhanced’ autoimmunity.[34] Given that pembrolizumab and nivolumab target another immune-checkpoint (PD-1 receptor), it could be possible that a similar mechanism may be responsible for the resulting AEs. While the underlying mechanisms are not clear, the spectrum of dermatologic AEs from both classes of immune-checkpoint inhibitors appear to be strikingly similar (rash, pruritus, vitiligo). In the studies included in our meta-analysis, a majority of patients had been treated for melanoma, but it is not clear whether this could have influenced the development and/or pattern of AEs.

As can be inferred from our case series (Table 2), the rashes generally manifest with erythematous macules, papules, and plaques, predominantly localized to the trunk and extremities, and may be associated with pruritus. Maculopapular eruptions, responsive to low-potency topical corticosteroids, were recently reported in 29% (24/83) of patients in a

retrospective analysis of 2 pembrolizumab trials (in 33% after the 1st treatment cycle).[35] The onset in our patients however, ranged widely (3 weeks to 2 years), which may be indicative of both an acute and delayed immunological reaction to these drugs, as seen with many other drug-induced skin eruptions. The peripheral blood eosinophil counts were normal, which is in contrast to the experience with CTLA-4 blockade (ipilimumab).[34,36]

On histology, a lichenoid tissue reaction/interface dermatitis was frequently observed (Fig. 4A–D), similar to a case-series of 3 patients who developed lichenoid dermatitis during treatment with pembrolizumab.[37] This reaction pattern may be due to the nonspecific activation of T-cells (as a result of PD-1 receptor blockade), which may be targeting antigen (drug)-presenting keratinocytes in susceptible individuals.[38] An instance of psoriasiform eruption has also been documented.[39] In our patients, mostly medium-to-high potency topical (and sometimes oral) corticosteroids sufficed for the treatment of rashes due to either drug, although this could vary depending upon the clinical severity. In this regard, we have proposed an algorithm for the management of these AEs occurring due to nonspecific immunologic enhancement (Fig. 5).

In general, the dermatologic AEs from targeted therapies (erlotinib, sunitinib, sorafenib) have frequently been associated with efficacy, higher response rates and survival,[40,41] as is the case with IL-2,[42] but with ipilimumab-induced irAEs it is unclear whether they are associated with prognostically favorable outcomes.[43–45] Despite the anti-PD-1 receptor inhibitors being relatively new, early studies do in fact show associations with some dermatologic AEs and positive outcomes. With pembrolizumab, patients who developed dermatologic AEs had more favorable outcomes i.e. longer progression-free intervals as compared to those who did not.[35] Thus, it was suggested that the development of these AEs (especially hypopigmentation in melanoma patients) could serve as a surrogate marker for treatment response. Similarly, with nivolumab, both rash and vitiligo were associated with prolonged PFS and overall survival.[46] Interestingly, a previous meta-analysis found that the development of vitiligo-like depigmentation in immunotherapy-treated advanced melanoma patients was associated with a lower risk (two-fold) of disease progression, along with a lower risk (four-fold) of death, contrary to those not developing it.[47]

Our study has some limitations. First, the AE reporting can vary in clinical trials,[48,49] and moreover, the safety data is representative of summary results (not subject-level data). Second, the use of accurate terms for skin eruptions in oncology reports varies and/or overlaps (e.g. macular, maculopapular, rash, dermatitis, eczema), and it may be subject to investigator expertise—therefore, we only included instances of “rash” for consistency (although the excluded data was negligible). Third, clinical trials only report AEs above a certain threshold (e.g. >5% or 10%). Fourth, the relative risk calculations cannot be used to compare/contrast results between the drugs since the control arms varied across the studies. Lastly, the impact of dose modification/termination could not be ascertained. Therefore, our findings may be an under-estimation of the true incidence and severity of these AEs.

In summary, the safety profiles and clinicomorphological features of immune-checkpoint inhibitor (anti-CTLA-4, anti-PD-1)-induced AEs appear to be similar and manageable, however, direct head-to-head trials are needed for precise characterization. With newer anti-

PD-1 agents in the pipeline, and the likelihood of combination regimens (with chemotherapy, radiotherapy, targeted therapy, immunotherapy) increasing, it is imperative that oncologists and dermatologists be cognizant of the emerging pattern of dermatologic AEs with these agents and their management. This is critical for optimal care, maintaining dose intensity, and satisfactory health-related quality of life in cancer patients and survivors.

Acknowledgments

Funding Support: This work was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

This work was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

We thank the Information Systems' data delivery group (DataLine) at the Memorial Sloan-Kettering Cancer Center, especially Galina Yusim (Data Administrator) and Stuart Gardos (Project Manager), for their swift assistance with the complex task of medical data acquisition and electronic medical record search. We also thank Bernadette Murphy (Medical Photographer) for the clinical photographs.

ABBREVIATIONS/ACRONYMS USED

AE	adverse event
ASCO	American Society of Clinical Oncology
BRAF	B-rapidly accelerated fibrosarcoma proto-oncogene serine–threonine-protein kinase
CD	cluster of differentiation
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen-4
ESMO	European Society for Medical Oncology
HRQoL	health-related quality of life
mAb	monoclonal antibody
MSKCC	Memorial Sloan Kettering Cancer Center
NCI	National Cancer Institute
NRCT	non-randomized controlled trial
NSCLC	non-small-cell lung cancer
PFS	progression-free survival
ORR	overall response rate
RR	relative risk
USFDA	United States Food and Drug Administration

WNL within normal limits

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HIGHLIGHTS

- This is the first meta-analysis to ascertain the incidence and risk of developing dermatologic adverse events (AEs) during treatment with the recently approved PD-1 inhibitors, pembrolizumab and nivolumab.
- Skin rash, pruritus, and vitiligo are the most commonly reported AEs, although they appear to be primarily low-grade and manageable.
- Among the PD-1 inhibitor-induced skin rashes, the macular-papular morphology is most frequent, often portraying a lichenoid reaction/interface dermatitis pattern on histology.

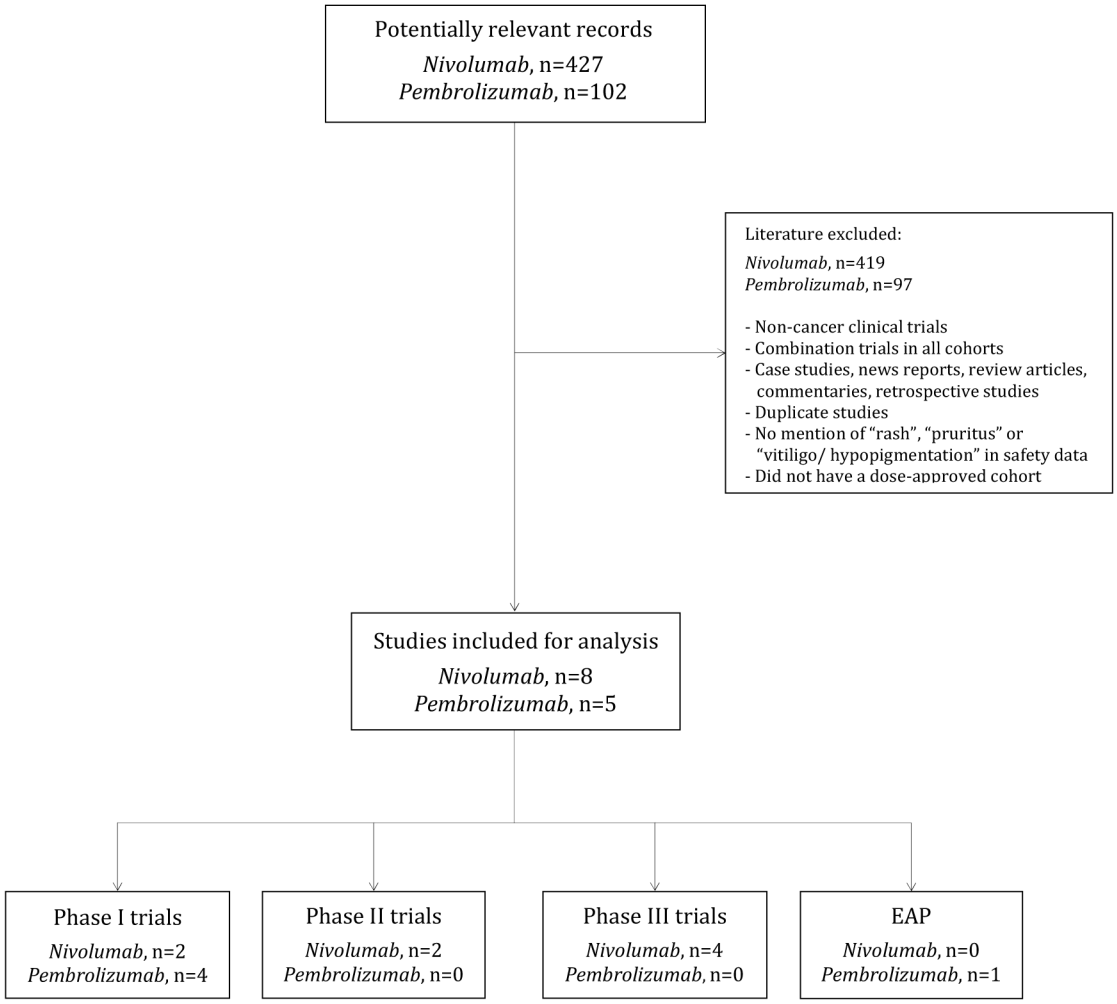
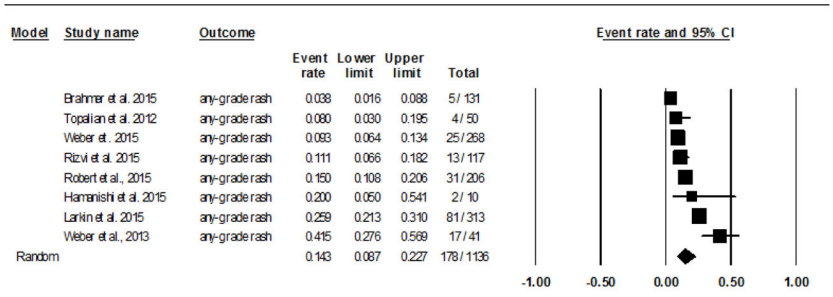
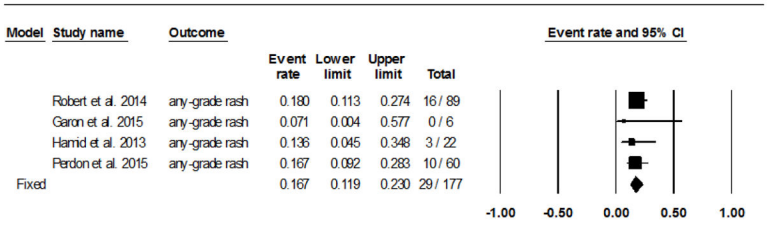


Fig 1.

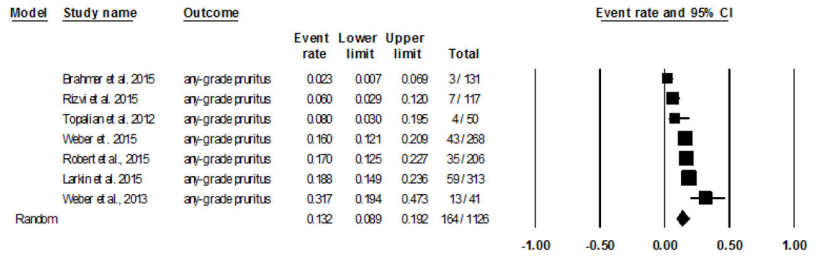
Flow diagram showing the selection process for clinical trials included in the final analysis.



Q=61.723, I2=88.659, P<0.001



Q=0.678, I2<0.001, P=0.878



Q=32.040, I2=81.273, P<0.001

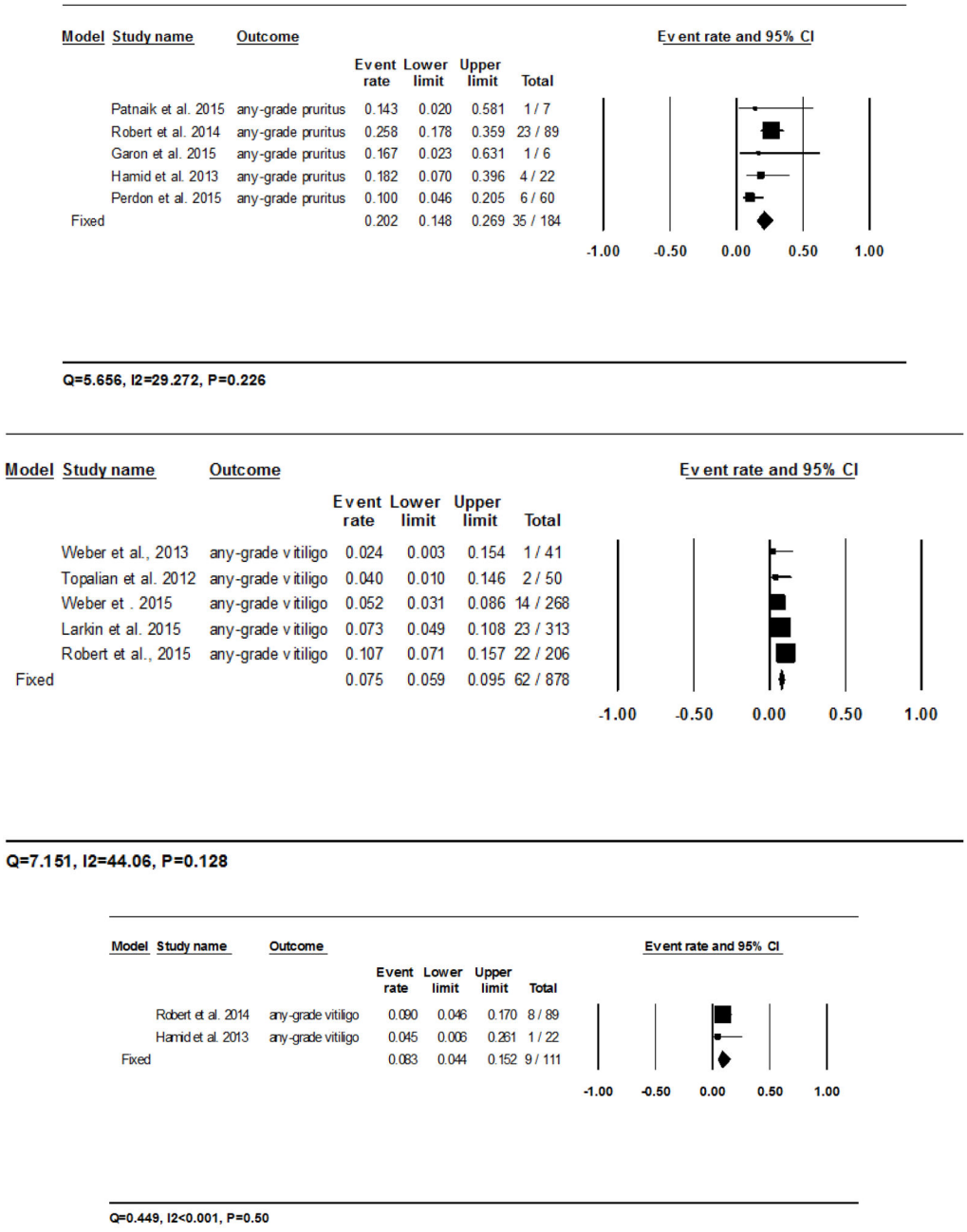
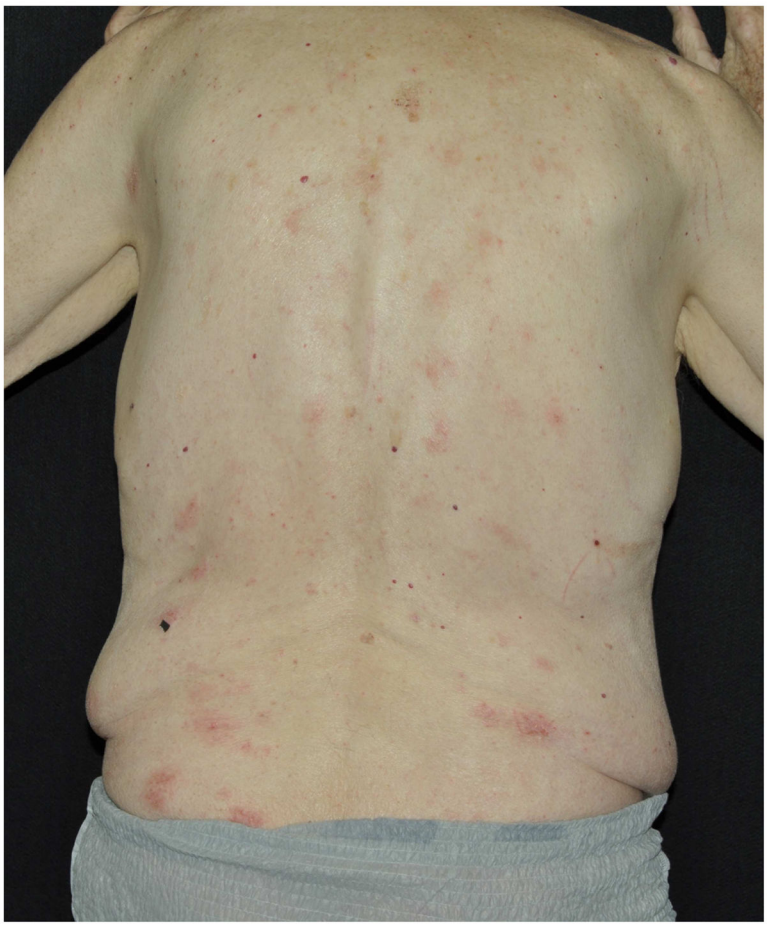


Fig 2.

Forest plot corresponding to the main random-effects meta-analysis, including risk estimates quantifying the relationship between treatment with the PD-1 inhibitors, nivolumab and pembrolizumab, and the development of: all-grade rash to nivolumab (Fig 2A) and pembrolizumab (Fig 2B), all-grade pruritus to nivolumab (Fig 2C) and pembrolizumab (Fig 2D), all-grade vitiligo to nivolumab (Fig 2E) and pembrolizumab (Fig 2F). The size of the square box represents each risk estimate, and is proportional to the weight that the risk estimate contributed to the summary risk estimate (diamond symbol). ■ = risk estimate in each trial; horizontal lines "—" = 95% CI; ◆ = summary risk estimate



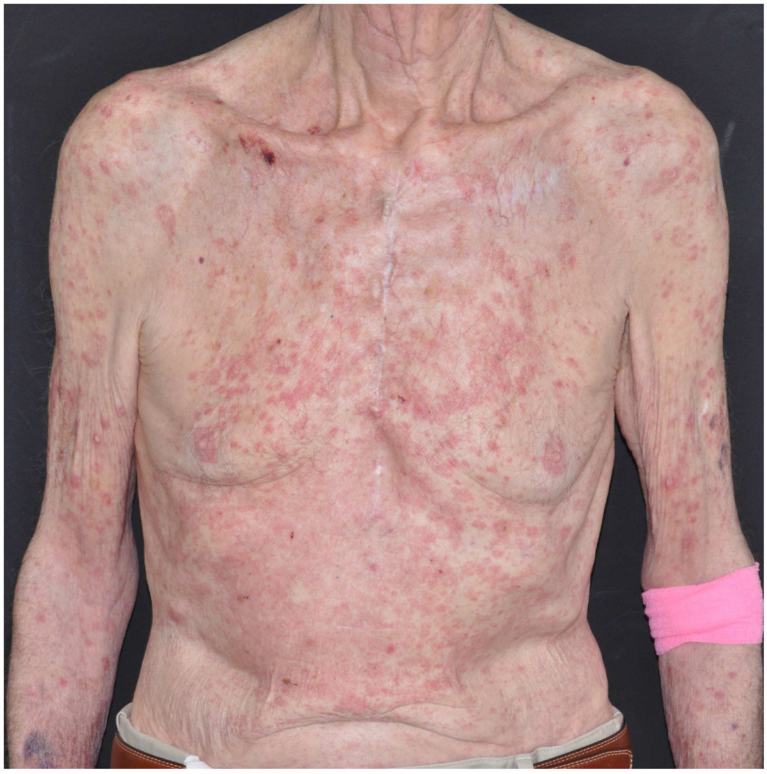
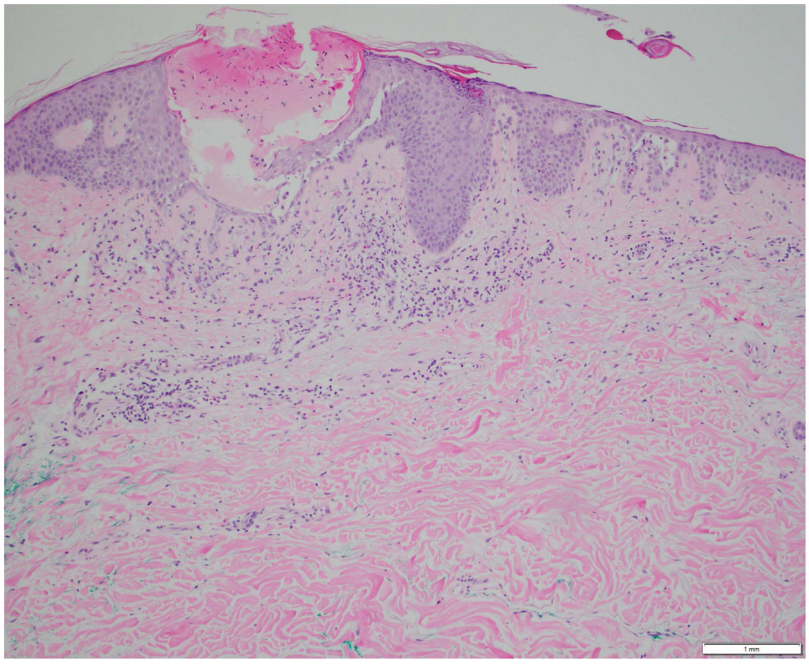


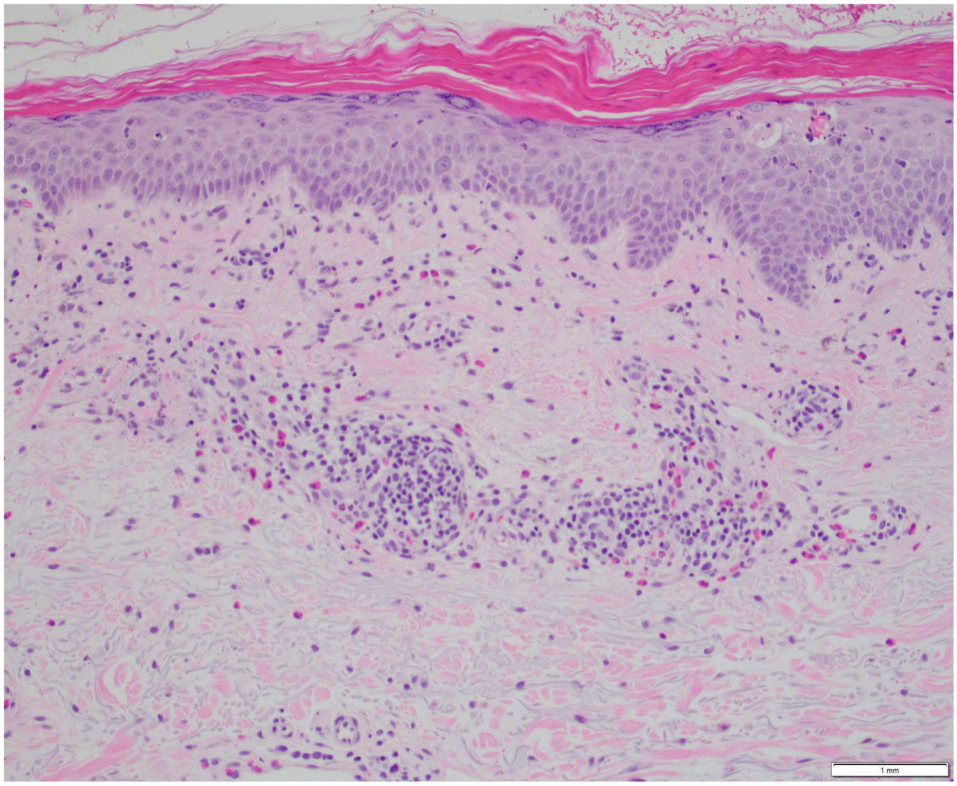
Fig 3.

(A, B) Clinical photographs of skin rash in patients being treated with PD-1 inhibitors (graded as per the NCI-CTCAE):

A. Grade 2 rash in a 79-year-old man, appearing after 6 weeks of therapy with pembrolizumab (10mg/kg q2wks.) for metastatic melanoma.

B. Grade 3 rash on the trunk and upper extremities of a 80-year-old man, appearing after 2 months of therapy with pembrolizumab (2mg/kg q2wks.) for stage IV melanoma.





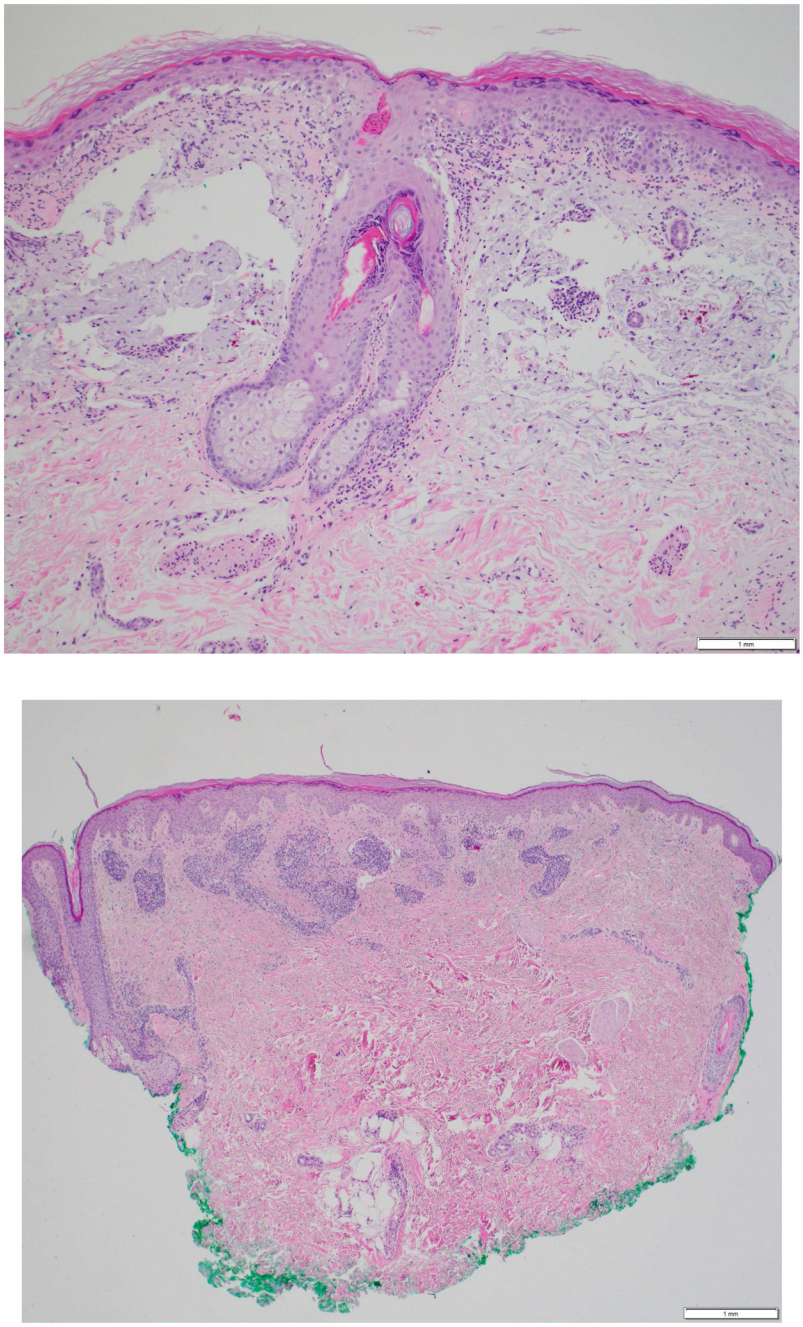


Fig 4.

Photomicrographs showing the histopathological features of skin rash with the PD-1 inhibitors, nivolumab (Figs. 4A, 4B) and pembrolizumab (Figs. 4C, 4D): Fig 4A. Spongiotic and focally intraepidermal acantholytic dermatitis with lymphocytes and eosinophils, Fig 4B. Psoriasiform and spongiotic dermatitis with lymphocytes and eosinophils, Fig 4C. Lichenoid interface dermatitis, Fig 4D. Interface and perivascular lymphocytic dermatitis. (Refer to Table 2 for the clinical descriptions).

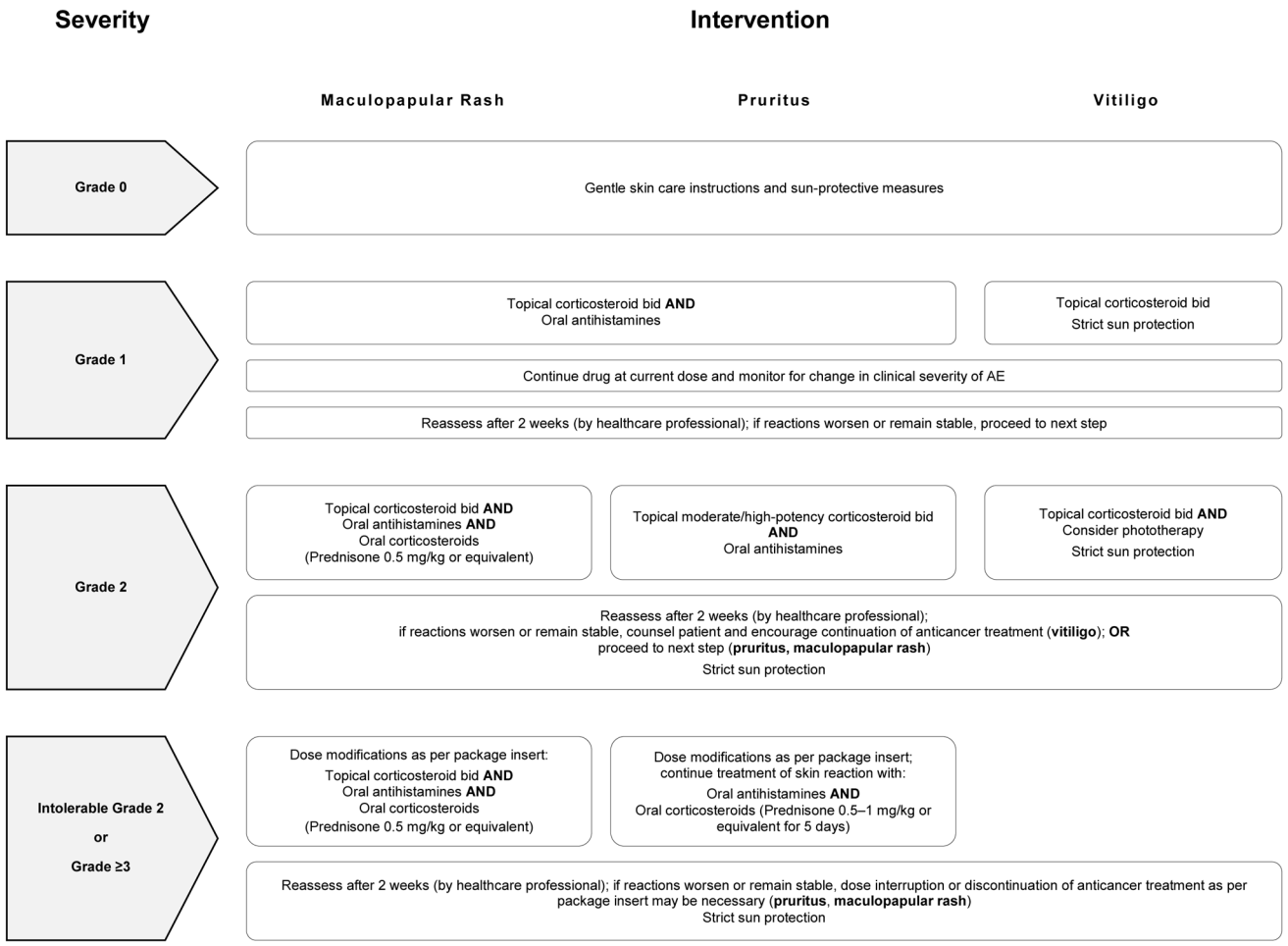


Fig 5.

Treatment algorithm for the management of anti-PD-1 inhibitor-induced dermatologic AEs.

Table 1

Characteristics of all oncology clinical trials included in the final analysis.[†]

Trial (first author, year)	Trial Design	Investigational arm	Control Arm(s)/Cohorts	Total Enrollment[*]	Treated patients[**] (assessed for AEs)	Underlying Malignancy	CTCAE version
Brahmer et al., 2015[23]	Phase III, randomized, open-label	Nivolumab 3mg/kg q2wks.	Docetaxel 75mg/m^2 of BSA q3wks.	352	131	Advanced squamous-cell NSCLC	4
Larkin et al., 2015[8]	Phase III, randomized, double-blind	Nivolumab 3mg/kg q2wks. + Ipilimumab-matched placebo	Ipilimumab 3mg/kg q3wks.+ Nivolumab-matched placebo *OR* Nivolumab 1mg/kg q3wks. + Ipilimumab 3mg/kg q3wks.	1296	313	Unresectable stage III/IV malignant melanoma	4
Weber et al., 2015[24]	Phase III, randomized controlled, open-label	Nivolumab 3mg/kg q2wks.	Investigator choice of chemotherapy	631	268	Unresectable stage III/IV malignant melanoma	4
Robert et al., 2015[25]	Phase III, randomized, double-blind	Nivolumab 3mg/kg q2wks. + Dacarbazine-matched placebo	Dacarbazine 1000mg/m^2 q3wks. + Nivolumab matched-placebo	518	206	Untreated stage III/IV melanoma (without a BRAF mutation)	4
Rizvi et al., 2015[21]	Phase II, single-arm	Nivolumab 3mg/kg q2wks.	X	140	117	Advanced refractory squamous NSCLC	4
Hamanishi et al., 2015[22]	Phase II, non-randomized, single-arm, open-label	Nivolumab 3mg/kg q2wks.	X	20	10	Advanced or relapsed, platinum-resistant ovarian cancer	X
Weber et al., 2013[20]	Phase I, open-label, multi-dose, dose-escalation study	Nivolumab 3mg/kg q2wks. (Cohort 6)[†]	Nivolumab 1mg/kg q2wks. + Peptide vaccine (Cohort 1) Nivolumab 3mg/kg q2wks. + Peptide vaccine (Cohort 2) Nivolumab 10mg/kg q2wks. + Peptide vaccine (Cohort 3) Nivolumab 3mg/kg q2wks. + Peptide vaccine (Cohort 4)[†] Nivolumab 3mg/kg q2wks. + Peptide vaccine (Cohort 5)[††]	90	41	Ipilimumab-refractory or Ipilimumab-naïve melanoma	4

Trial (first author, year)	Trial Design	Investigational arm	Control Arm(s)/Cohorts	Total Enrollment*	Treated patients** (assessed for AEs)	Underlying Malignancy	CTCAE version
Topalian et al., 2012[19]	Phase I	Nivolumab 3mg/kg q2wks.	X	296	50	Advanced melanoma, NSCLC, RCC, castration-resistant prostate cancer, or CRC	3
Robert et al., 2014[27]	Phase I, open-label	Pembrolizumab 2mg/kg q3wks.	X	178	89	Ipilimumab-refractory advanced melanoma	4
Garon et al., 2015[28]	Phase I	Pembrolizumab 2mg/kg q3wks.	X	495	6	Advanced NSCLC	4
Hamid et al., 2013[26]	Phase I	Pembrolizumab 2mg/kg q3wks.	X	135	22	Advanced Melanoma	4
Perdon et al., 2015[30]	EAP	Pembrolizumab 2mg/kg q3wks.	X	62	60	Advanced melanoma	NA
Patnaik et al., 2015[29]	Phase I	Pembrolizumab 2mg/kg q3wks.	X	31	7	Advanced solid tumors	4

Abbreviations: Adverse events, AEs; Colorectal cancer, CRC; Renal cell cancer, RCC; Non-small-cell lung cancer, NSCLC; NA, not available

†The relative risk was calculated and compared only in trials with chemotherapy (as controls);

*Represents the overall number of patients treated with the drug at all doses in the trial and/or cohort;

**Represents the number of patients who were treated with the drug at the FDA-approved dose in the trial and/or cohort, and were included in the analysis;

†For cohorts 4 and 6, only grade 1 and 2 dose-limiting toxicities for ipilimumab were allowed;

††Cohort 5 patients were required to have had grade 3 dose-limiting toxicity for ipilimumab.

Table 2

Clinical characteristics of drug eruptions in adult cancer patients receiving nivolumab and pembrolizumab.

Age, sex	Underlying malignancy	Medication, Dose	Allergies	Onset of rash (post-1st dose)	CTCAE Grade v4.03	Clinical description*	Treatment (Outcome)	Histopathologic description	Dose reduction/ interruption due to rash
72, F	Urothelial cancer (Stage IV)	Nivolumab, 3mg/kg q2w	Benzonatate, Erythromycin, Loratadine, Penicillin, TMP/SMX	3 weeks	1	Multiple (>100), slightly raised, erythematous, mildly scaly papules, scattered diffusely on both upper extremities and trunk	Triamcinolone cream 0.1%, bid (Improved)	Lichenoid dermatitis	No
18, M	High-Grade astrocytoma	Nivolumab, 3mg/kg q2w	NKDA	4 weeks	3	Multiple (>100), discrete, slightly raised, pink to erythematous papules (coalescing at places) on all the extremities, trunk, buttocks; cheilitis	Prednisone 20mg tid, Clobetasol spray 0.05%, bid (Improved)	Mild vacuolar interface dermatitis with superficial perivascular lymphoeosinophilic infiltrate	No
73, M	NSCLC	Nivolumab, 3mg/kg q2w	NKDA	12 weeks	2	Few, light pink, monomorphic macules, follicular at places; some coalescing into patches on the chest, abdomen, back and arms	Medrol Dosepak 4mg (as directed)†, Triamcinolone cream 0.1%, bid (Improved)	Perivascular lymphocytic dermatitis with a few eosinophils	Yes (Interruption)
56, F	Breast cancer	Nivolumab, 3mg/kg q2w	Acetaminophen, Amoxicillin, Oxycodone	96 weeks	2	Few, well-demarcated, erythematous, mildly scaly papules and plaques, scattered haphazardly on the back, buttocks, posterior aspect of left arm, and bilateral lower extremities	Medrol Dosepak 4mg, (as directed)† Triamcinolone cream 0.1%, bid (Improved)	Pityriasiform, lichenoid and spongiotic dermatitis	No
85, M	SCLC (Stage IV)	Nivolumab, 3mg/kg q2w	NKDA	12 weeks	2	Few, non-scaly, erythematous papules and plaques on the chest/ upper abdomen and lower back	Clobetasol lotion 0.05%, bid (Improved)	Spongiotic, vesicular and superficial perivascular dermatitis with eosinophils (Fig. 4A)	Yes (Interruption upon progressing to Grade 3, months later)
64, F	Melanoma, metastatic (*BRAF* ^{V600E})	Nivolumab, 3mg/kg q2w	Penicillin, Statins	8 weeks	1	Few, discrete, erythematous papules on the upper trunk	Triamcinolone spray, bid (Improved)	Spongiotic, lichenoid and focal intra-epidermal acantholytic dermatitis with lymphocytes and eosinophils (Fig. 4B)	No
54, M	Melanoma, metastatic	Nivolumab, 3mg/kg q2w	NKDA	36 weeks	1	Multiple (>100), erythematous papules with ill-defined borders (few, coalescing at places) on the upper chest and extending down to the abdomen with excoriations), and back	Clobetasol cream 0.05%, bid, Fexofenadine 180mg, od, Diphenhydramine 25mg, qHS (Improved)	Interface, perivascular and periadnexal lymphocytic dermatitis, with a few plasma cells and minor vascular damage	No
70, F	MALT lymphoma	Nivolumab, 1mg/kg q2w	NKDA	14 weeks	1	Few, mildly scaly, erythematous macules, papules (some mildly scaly) and a plaque on bilateral lower extremities	Fluocinonide cream 0.05%, bid (Improved)	Lichenoid interface dermatitis	No
53, M	Multiple Myeloma	Nivolumab, 1mg/kg q2w	Penicillin	5 weeks	1	Erythematous macules and papules on the extremities, penis with a few excoriations	Hydrocortisone cream 2.5%,	NA	No

Age, sex	Underlying malignancy	Medication, Dose	Allergies	Onset of rash (post-1st dose)	CTCAE Grade v4.03	Clinical description*	Treatment (Outcome)	Histopathologic description	Dose reduction/ interruption due to rash
							Diphenhydramine 50mg, qHS (Improved)		
79, M	Melanoma, metastatic	Pembrolizumab, 10mg/kg q2w	Penicillin	6 weeks	2	Erythematous, discrete, eczematous patches on the abdomen, back, and bilateral lower extremities (some with impetiginized crust); yellow-crusted plaque with underlying erythema on the right shoulder (Fig. 3A)	Triamcinolone cream 0.1%, bid, Clobetasol cream 0.05%, bid, Hydroxyzine 10mg, q8h PRN (Improved)	Psoriasiform, spongiotic and superficial dermal lymphoeosinophilic dermatitis on the left back; sparse perivascular lymphocytic dermatitis on the left medial back	No
80, M	Melanoma, metastatic; CLL	Pembrolizumab, 2mg/kg q3w	NKDA	8 weeks	3	Oval red macules (some with eroded scale) on the chest, back, arms; erosions on the upper and lower lips (Fig. 3B)	Medrol Dosepak 4mg (as directed) †, Clobex spray 0.05%, bid, Triamcinolone cream 0.1%, bid (Improved)	Lichenoid and perivascular lymphocytic dermatitis with dysmaturation and apoptosis of keratinocytes (Fig. 4C)	Yes (Interruption)
62, M	Melanoma, metastatic	Pembrolizumab, 2mg/kg q3w	Penicillin	20 weeks	2	Few, pink to erythematous papules and psoriasiform plaques on the dorsal aspect of extremities; papules on the abdomen	Clobetasol foam 0.05%, bid, Diphenhydramine 25mg, qHS (Improved)	Lichenoid dermatitis	No
44, F	Primary mediastinal B-cell lymphoma	Pembrolizumab, 10mg/kg q3w	Oxycodone	12 weeks	1	Flat-topped, slightly scaly shiny (lichenoid) papules on the dorsal aspects of the hands, forearms, lateral neck and upper chest (sun-exposed areas)	Triamcinolone cream 0.1%, bid (Improved)	Superficial and deep perivascular, periadnexal and interface dermatitis with vasculopathic changes and keratinocyte dysmaturation (Fig. 4D)	No
80, M	NSCLC, metastatic	Pembrolizumab, 2mg/kg q3w	Cephalexin	~8.5 weeks	2	Multiple erythematous macules and papules on the upper extremities and trunk	Clobetasol foam/spray, bid, Hydroxyzine 25mg, bid (Lost to follow-up)	Lichenoid interface dermatitis with intraepidermal acantholysis and keratinocyte apoptosis	Unknown (Lost to follow-up)

*At the time of presentation.

†Day 1: 8 mg PO before breakfast, 4 mg after lunch and after dinner, and 8 mg at bedtime; Day 2: 4 mg PO before breakfast, after lunch, and after dinner and 8 mg at bedtime; Day 3: 4 mg PO before breakfast, after lunch, after dinner, and at bedtime; Day 4: 4 mg PO before breakfast, after lunch, and at bedtime; Day 5: 4 mg PO before breakfast and at bedtime; Day 6: 4 mg PO before breakfast; May be tapered over 12 days (to decrease chance of dermatitis flare-up).