INTRODUCTION

Psoriasis is a chronic immune-mediated disease that affects 3.2% of the adult US population [1] and is characterized by scaly red plaques [2] associated with a diminished quality of life [2,3]. Psoriasis is associated with multiple comorbidities, including arthritis, diabetes, cardiovascular disease and depression [4,5], as well as decreased life expectancy in patients with severe disease [6]. An increased risk of cancer has been observed among patients with psoriasis compared with the general population [7]. Cohort studies have shown that patients with psoriasis have an increased risk of specific cancers regardless of their treatment, including non-melanoma skin cancers (NMSCs), lymphohematopoietic cancers and cancers of the respiratory and digestive tracts [7-9]. The interleukin-12 (IL-12)/23 inhibitor ustekinumab is an established treatment for psoriasis, and IL-23-specific inhibitors are among the newest therapies, with promising efficacy and safety profiles (Table 1; Figure 1) [10,11]. IL-12 and IL-23 play a central role in T-cell-mediated immunity and the proinflammatory responses associated with autoimmune conditions [12-18]. However, in vitro and animal studies have suggested that IL-12 and IL-23 may have distinct roles in contributing to protective immune responses to tumors [19-21] and bacterial infections [12,22]. Thus, therapies targeted to IL-12 and IL-23 carry a theoretical risk of decreased defenses against pathogens and tumor surveillance. A concern for an increased risk of malignancy has been raised with other immunosuppressive therapies used for the treatment of psoriasis, such as anti-tumor necrosis factor (TNF) inhibitors, owing to the role of TNF in tumor growth inhibition [23]. This is a review of the currently available information on the role of IL-12 and IL-23 in tumor growth and is written for clinicians who want to understand the potential risk...
of malignancy associated with blocking IL-12 and/or IL-23 in the treatment of psoriasis.

2 | STRUCTURE AND BIOLOGICAL EFFECTS OF IL-12 AND IL-23 IN PSORIASIS

IL-12 and IL-23 are heterodimers, sharing a common p40 (beta chain) subunit that is combined with either a p35 alpha chain (IL-12) or p19 alpha chain (IL-23; Figure 1).[13,18] IL-12 and IL-23 signal through heterodimeric receptors, both of which contain IL-12 receptor β1 (IL-12Rβ1), which is coupled with IL-12Rβ2 to form the IL-12 receptor and with IL-23R to form the IL-23 receptor.[17,18]

Signalling, mediated through the Janus kinase–signal transducers and activators of transcription (Jak-STAT) pathway, ultimately results in IL-12 and IL-23 promoting the development of cell-mediated responses driven by different subsets of T helper (T\textsubscript{H}) cells.[17,18]

IL-12 plays a key role in differentiation, maintenance, and activity of immune cell subsets, including T\textsubscript{H}1 cells (which produce interferon-γ) and natural killer cells (Figure 2).[12,16,24] IL-23 has a key role in maintenance and activity of IL-17–producing T\textsubscript{H}17 cells and IL-22–producing T\textsubscript{H}22 cells.[25] In turn, IL-17 induces activation and proliferation of keratinocytes, which produce inflammatory cytokines, including IL-23, leading to a self-amplificatory loop.[26,27] Consequently, antibodies targeted to IL-12 and IL-23 (p40 inhibitors) affect T\textsubscript{H}1, T\textsubscript{H}17 and T\textsubscript{H}22 responses, whereas those targeted to IL-23 alone (p19 inhibitors) primarily affect T\textsubscript{H}17 and T\textsubscript{H}22 responses.[26,27]

3 | INHIBITORS OF IL-12/23 OR IL-23 FOR THE TREATMENT OF PSORIASIS

The development of anti–IL-12/23 antibodies was originally initiated based on the observation that mice deficient in the IL-12p40 subunit (the subunit shared by IL-12 and IL-23) and those treated with neutralizing anti–IL-12p40 antibodies showed resistance to autoimmune disease.[15] The discovery of IL-23[18] followed by the molecular characterization of IL-23[17] and other murine and genetic studies helped identify the key pathogenic role of IL-23 in psoriasis, as summarized by Gaffen et al.[25] It is now understood that IL-12 and IL-23 act on different components of the chronic inflammatory loop associated with the formation of psoriatic plaques.[28] An association between IL-12 and psoriasis is supported by the presence of T\textsubscript{H}1 cells and interferon-γ in psoriatic lesions.[29] However, recent data from a mouse model of psoriasis suggest that IL-12 may dampen skin inflammation in psoriasis by modulating IL-23–mediated inflammatory events, decreasing skin invasion by T\textsubscript{H}17 cells and promoting an anti-inflammatory genetic programme in keratinocytes.[30]

Two antibodies targeting IL-12/23p40—ustekinumab and briakinumab—have been evaluated as treatments for psoriasis and other immune-mediated diseases.[31–35] Ustekinumab is the only IL-12/23p40 inhibitor for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis approved by the Food and Drug Administration (FDA).[36] Clinical development of briakinumab was discontinued, thought to be because of safety concerns reported in the clinical trials, including cardiac events and malignancies.[31,37] Gusekumab was the first antibody specifically targeting

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**TABLE 1** Inhibitors of IL-12/23 or IL-23 licensed or in clinical development for the treatment of psoriasis

| Generic name [compound] (brand name) | Antibody type | Mechanism of action | Manufacturer | References |
|-------------------------------------|---------------|---------------------|--------------|------------|
| Ustekinumab (CTNTO-1275) (Stelara™) | Fully human IgG1κ monoclonal antibody | Binds with high affinity to IL-12/23p40 subunit | Janssen Biotech Inc. | Kauffman et al[85] |
| Briakinumab (ABT-874, J-695) (Ozespa) | Fully human IgG1λ monoclonal antibody | Binds to IL-12/23p40 subunit | Abbott Laboratories Ltd | Fragoulis et al[86] Panaccione et al[87] |
| Gusekumab (CTNTO 1959) (Tremfya™) | Fully human IgG1λ monoclonal antibody | Binds to IL-23p19 subunit | Janssen Biotech Inc. | Reich et al[91] Gordon et al[96] |
| Tildrakizumab (MK-3222, SCH 900222) (Ilumya™) | Humanized mouse IgG1κ monoclonal antibody | Binds with high affinity to IL-23p19 subunit (297 pmol/L) | Merck & Co., Inc., and Sun Pharmaceutical Industries, Inc. | Reich et al[91] Papp et al[89] |
| Risankizumab (ABBV-066, BI 655066) | Humanized IgG1κ monoclonal antibody | Binds with high affinity to IL-23p19 subunit (dissociation constant <10 pmol/L) | Boehringer Ingelheim and AbbVie Inc. | Krueger et al[90] Papp et al[39] Singh et al[91] |
| Mirikizumab (LY3074828) | Humanized monoclonal antibody | Blocks IL-23 | Eli Lilly and Company | Eli Lilly and Company[92] |

Ig, immunoglobulin; IL, interleukin.

*US and European license applications withdrawn by manufacturer in 2011.[37]
IL-23p19 to be approved for the treatment of moderate-to-severe psoriasis\(^{[38]}\), and 3 further IL-23p19 inhibitors are currently in active development for the same indication. Efficacy and safety data have been published for tildrakizumab (phase 3\(^{[11]}\)) and risankizumab (phase 2\(^{[39]}\)); mirikizumab (LY3074828) is currently entering phase 2 development.\(^{[40]}\)

### 4 | MALIGNANCIES REPORTED IN CLINICAL TRIALS

A variety of cancer types have been reported in clinical trials of IL-12/23 and IL-23 inhibitors (Table 2). NMSCs were the most frequently reported malignancies. These are the most common malignancies in humans (albeit not routinely reported to cancer registries), with basal cell carcinomas (BCCs) more common than squamous cell carcinomas (SCCs).\(^{[41]}\) A meta-analysis of observational studies found that the risk of SCCs was increased in patients with psoriasis compared with the general population (standardized incidence ratio [SIR] = 5.31, 95% confidence interval [CI] = 2.63–10.71) and correlated with patient exposure to 8-methoxypsoralen–ultraviolet (UV) A therapy for treatment of psoriasis.\(^{[9]}\) Risk of BCCs was also increased in patients with psoriasis, but to a lesser extent than SCCs (SIR = 2.00, 95% CI = 1.83–2.20).\(^{[9]}\) In trials of ustekinumab for psoriasis, as in the general population,\(^{[41]}\) the proportion of BCCs was higher than that of SCCs.\(^{[32,42–44]}\) However, a pooled analysis of safety data from all briakinumab phase 2 and phase 3 trials and interim data from an open-label extension trial suggested that the risk of SCC was similar to the risk of BCC in patients treated with briakinumab, which may suggest a relative or absolute increase in the risk of SCC.\(^{[45]}\) Concern about the effect of briakinumab on NMSCs was thought to be one of the reasons for discontinuing its development.\(^{[31,37]}\)

The clinical evaluation of IL-23p19 inhibitors is ongoing, and data available thus far are limited. NMSCs have been reported in some clinical trials.\(^{[10,11,39,46]}\) Publications about tildrakizumab reported low numbers (7 cases total) of NMSCs but did not differentiate BCCs and SCCs.\(^{[11]}\) Two cases of BCCs were reported in the phase 2 trial of risankizumab.\(^{[39]}\)
TABLE 2  Reported malignancies in clinical trials of IL-12/23 and IL-23 inhibitors in patients with moderate-to-severe psoriasis receiving active treatment with an IL-12/23 or IL-23 inhibitor

| Inhibitor | Phase | Name | NCT # | Study length | N  | Treatment arms | Cases of reported malignancies | Reference |
|-----------|-------|------|-------|--------------|----|----------------|-----------------------------|-----------|
| Ustekinumab | 1 | Single dose | - | 16 wk | 18 | 0.1–5 mg/kg | None | Kauffman et al[85] |
| 2 | - | 00320216 | 36 wk | 120 | 45 or 90 mg | 2 | 1 | Krueger et al[44] |
| 3 | PHOENIX 1 | 00267969 | 76 wk | 766 | 45 or 90 mg | 4 | 1 | Leonardi et al[32] |
| Ext | PHOENIX 1 OLE | - | >5 y (264 wk) | 753 | 45 or 90 mg | 13 | 1 | Kimball et al[43] |
| 3 | PHOENIX 2 | 00307437 | 52 wk | 1230 | 45 or 90 mg | 7 | None | Papp et al[33] |
| 3 | ACCEPT | 00454584 | 64 wk | 903 | 45 or 90 mg | 6 + 2 | 1 | Griffiths et al[42] |
| 2 | Dose ranging | 02054481 | 48 wk | 166 | 45 or 90 mg | None | Papp et al[39] |
| 3 | NAVIGATE | 02203032 | 60 wk | 871 | 45 or 90 mg | 3 | None | Langley et al[93] |
| Briakinumab | 2 | M05-736 | 00292396 | 12 wk | 180 | 100 or 200 mg | 1 | None | Kimball et al[94] |
| 3 | M10-114 | 00691964 | 12 wk | 347 | 200–100 mg | 1 | 1 | Gottlieb et al[95] |
| 3 | M10-315 | 00710580 | 12 wk | 350 | 200–100 mg | 1 | 1 | Strober et al[96] |
| 3 | M10-255 | 00679731 | 52 wk | 317 | 200–100 mg | 1 | 1 | Reich et al[97] |
| 3 | M06-890 | 00570986 | 52 wk | 1465 | 200–100 mg | 4 | 6 | Gordon et al[91] |
| Guselkumab | 1 | Single, ascending dose | 00925574 | 24 wk | 24 | 10–300 mg | None | Sofen et al[88] |
| 2 | X-PLORE | 01483599 | 52 wk | 293 | 5–200 mg | 1 | 1 | Gordon et al[88] |
| 3 | VOYAGE 1 | 02207231 | 48 wk | 837 | 100 mg | 2 | 1 | Blauvelt et al[46] |
| 3 | VOYAGE 2 | 02207244 | 72 wk | 992 | 100 mg | 2 | 2 | Reich et al[10] |
| 3 | NAVIGATE | 02203032 | 60 wk | 871 | 100 mg | 1 | None | Langley et al[93] |

(Continues)
Prostate and breast cancers are the most common internal malignancies in men and women, respectively. Patients with psoriasis have not been found to have a significantly increased risk of prostate cancer compared with the general population, but the relative risk of breast cancer in patients with psoriasis is less clear. Two analyses showed no significant increased risk, and one showed a slightly increased risk compared with the general population. Several cases of prostate and breast cancers occurred in trials of ustekinumab, briakinumab and guselkumab. These malignancy events reported in clinical trials do not prove causation but do suggest a possible biological relationship that may trigger further investigation.

### TABLE 2 (Continued)

| Inhibitor  | Phase  | Name                  | NCT #       | Study length | N  | Treatment arms | Cases of reported malignancies | Reference |
|------------|--------|-----------------------|-------------|--------------|----|----------------|--------------------------------|-----------|
|            |        |                       |             |              |    |                | BCC | SCC | Prostate | Breast | Others |                      |           |
| Tildrakizumab | 1      | Sequential, rising, multiple dose | -  | 16 wk | 77 | 0.05–10 mg/kg | None |     | None |       |       |                      | Kopp et al[99] |
| 2b         | Dose finding | 01225731 | 52 wk | 353 | 5–200 mg | 1 malignant melanoma | Papp et al[89] |
| 3          | reSURFACE 1 | 01722331 | 64 wk | 772 | 100 mg or 200 mg | 4: unspecified | Reich et al[10] |
| 3          | reSURFACE 2 | 01729754 | 52 wk | 1090 | 100 mg or 200 mg | 4: unspecified | Reich et al[10] |
| Risankizumab | 1      | Single, rising dose | 01577550 | 24 wk | 39 | 0.01-5 mg | None reported | Krueger et al[90] |
| 2          | Dose ranging | 02054481 | 48 wk | 166 | 18, 90, or 180 mg | 2 | 1 salivary gland neoplasm | Papp et al[39] |

BCC, basal cell carcinoma; IL, interleukin; NCT, national clinical trial; NMSC, non-melanoma skin cancer; OLE, open-label extension; SCC, squamous cell carcinoma.

Blank cells indicate no cases were reported in the publication.

*vs placebo.
*BCC + SCC combined.
*vs etanercept.
*2 cases had both BCC and SCC.
*Active control vs risankizumab.
*Active control vs guselkumab.
*vs methotrexate.
*vs placebo or adalimumab.
*Data are reported up to week 28.
*vs ustekinumab.

Ustekinumab, which has been approved since 2009, is currently the only IL-12/23 or IL-12 inhibitor with postmarketing safety data. The prescribing information (PI) for ustekinumab contains a general warning that it "may increase risk of malignancy," based on the observations that (i) NMSCs were reported in 1.5% of patients and malignancies excluding NMSCs (non-NMSCs) were reported in 1.7% of patients among patients treated with ustekinumab (3.2 years’ median follow-up); (ii) the most frequently observed non-NMSCs were prostate, melanoma, colorectal and breast cancers, but they were similar in type and number to those expected in the general US population when adjusted for age, gender and race; and (iii) rapid appearance of multiple cutaneous SCCs was found in postmarketing reports among patients receiving ustekinumab who had pre-existing risk factors for developing NMSC. The concerns raised in the ustekinumab PI are in line with an analysis of postmarketing safety data reported to the FDA, which found that patients treated with ustekinumab were 15 times more likely to report a case of cancer than were patients treated with apremilast, a phosphodiesterase 4 (PDE-4) inhibitor. Furthermore, a safety signal was detected in a study of data from the FDA Adverse Event Reporting System database, which indicated that ustekinumab may be associated with several malignancies, including B-cell lymphoma; epithelioid sarcoma; and lung, oesophageal, ovarian, renal, testis and thyroid cancers.

In contrast, an analysis of data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) showed that patients with psoriasis treated with ustekinumab had numerically fewer non-NMSCs (0.48/100 patient-years [PYs]) than did patients treated with infliximab, a monoclonal antibody directed at TNF (0.79/100 PYs) or any other biologics (0.73/100 PYs) or non-biologics (0.84/100 PYs). Results from an analysis of the German Psoriasis Registry (PsoBest) showed similar
TABLE 3  IL-12/23 and IL-23 genetic deficiencies associated with increased risk of cancer

| Gene mutation or polymorphism | Effect on IL-12 and/or IL-23 | Effect on malignancy | Potential implications for therapy with IL-12/23 or IL-23 inhibitors |
|--------------------------------|-------------------------------|---------------------|-------------------------------------------------------------------|
| **IL-12Rβ1** homozygous deficiency case report | Loss of IL-12 and IL-23 functions | Oesophageal squamous cell carcinoma at age 25 y, relapse and death at age 29 y<sup>57</sup> | IL-12/23 inhibitors may increase risk of oesophageal cancer |
| **IL-12Rβ1** polymorphism: 378 GG/GC vs CC | Decreased IL-12 levels | Increased risk of oesophageal cancer<sup>60</sup> | IL-12/23 inhibitors may increase risk of oesophageal cancer |
| **IL-28B (IL-12p40)** polymorphisms: rs321227 AC/CC or CC vs AA, or C vs A | Decreased IL-12 levels | Increased risk of osteosarcoma<sup>61</sup> and osteosarcoma<sup>62</sup> and prostate cancers | IL-12/23 inhibitors may increase risk of osteosarcomas and bladder, cervical, oesophageal and prostate cancers |
| 1188 AC vs AA | | Increased risk of bladder cancer<sup>62</sup> | |
| rs2569254 GG vs AA | | Increased risk of cervical cancer<sup>64</sup> | |
| **IL-12A (IL-12p35)** polymorphisms: rs568408 GA/AA or GA vs GG | Decreased IL-12 levels | Increased risk of oesophageal cancer<sup>60</sup> and osteosarcoma<sup>61</sup> | IL-12/23 inhibitors may increase risk of osteosarcomas and oesophageal cancer in specific patient populations |
| **IL-23R** polymorphisms: rs6682925 TC/CC or TG/GG or T>C | Loss of IL-23 function | Increased risk of oesophageal cancer<sup>64</sup> hepatocellular carcinoma<sup>67</sup> and acute myeloid leukaemia<sup>68</sup> | IL-23 inhibitors may affect cancer risk of some cancers in specific patient populations |
| rs1884444n T>G | No association with risk of gastric cancer<sup>65</sup> | Decreased risk of gastric cancer<sup>65</sup> | IL-23 inhibitors may decrease risk of gastric cancer |

IL, interleukin; R, receptor.

rates of malignancies excluding NMSCs in patients receiving systemic therapies (0.46/100 PYs) or biologics (0.49/100 PYs), with no relevant differences between therapies.<sup>52</sup> Evidence from controlled clinical trials and registries indicates that ustekinumab is well tolerated, with rates of overall mortality and malignancy comparable with those expected in the general population.<sup>32,33,53,54</sup> Although the postmarketing pharmacovigilance studies mentioned previously were not designed to study causality or to quantify increased cancer risk associated with specific therapies,<sup>49,50</sup> they can be helpful to identify safety signals that may be relevant to the advancement of overall patient safety.<sup>53</sup> Postmarketing safety data are not yet available for tildrakizumab, guselkumab, tildrakizumab and risankizumab all excluded patients with a pre-existing malignancy in the preceding 5 years (except fully treated BCCs or SCCs of the skin and/or fully treated cervical carcinoma in situ).<sup>50,11,31,32,39,46</sup>

**6 | RISK OF MALIGNANCY IN HUMANS WITH GENETIC TRAITS SIMULATING NEUTRALIZATION OF IL-12 AND/OR IL-23**

In the first report of cancer in a patient with IL-12Rβ1 deficiency (the receptor subunit required to bind the p40 subunit shared by IL-12 and IL-23), the patient developed oesophageal SCC at age 25 years and died at age 29 years, an age at which this cancer is exceedingly rare (Table 3).<sup>57</sup> Additional studies of IL-12 genetic deficiencies have investigated whether such deficiencies are associated with increased likelihood of infections and cancer.<sup>58,59</sup> Genomewide association studies have shown that polymorphisms in genes encoding the IL-12p40 subunit or the IL-12p35 subunit, which result in a decreased biological effect of IL-12, are linked to increased susceptibility to oesophageal cancer,<sup>60</sup> osteosarcoma,<sup>61</sup> bladder cancer<sup>62</sup> and prostate cancer,<sup>63</sup> as well as susceptibility to and/or severity of cervical cancer.<sup>64</sup> Reports of genetic deficiencies simulating a deficiency in the IL-23–signalling pathway are limited. Several genomewide association studies have been conducted in Chinese populations; they show that variants of IL-23R, the subunit specific for the IL-23 receptor, are
TABLE 4  Malignancies in murine models of IL-23 deficiency

| Model | Effect on IL-23 | Tumor-promotion strategy | Effect on malignancy vs controls | Potential therapeutic implications for IL-23 inhibitors |
|-------|----------------|--------------------------|---------------------------------|-----------------------------------------------------|
| Treatment with anti–IL-23p19 antibody[20] | Loss of IL-23 function | Intradermal injection of skin tumor cells | Faster rejection of tumor cells and decreased tumor formation | May prevent tumor growth and enhance tumor rejection |
| Treatment with anti–IL-23p19 antibody[71] | Loss of IL-23 function | Experimental and spontaneous models of lung metastases SC injection of thymoma cells | Early suppression of lung metastases and modest inhibition of primary tumors with subcutaneous growth | May prevent tumor growth and metastasis |
| IL-23p19−/−[20] | Loss of IL-23 function | Chemical carcinogenesis Intradermal injection of skin tumor cells | Resistance to developing skin papillomas Resistance to developing tumors | May reduce risk of skin cancer May prevent tumor growth and enhance tumor rejection |
| IL-23p19−/−[70] | Loss of IL-23 function | Experimental model of lung metastases | Increased resistance to formation of lung metastases | May prevent tumor growth and enhance tumor rejection |
| IL-23p19−/−[72] | Loss of IL-23 function | Colorectal tumorigenesis in genetically predisposed mice | Decreased tumor number and growth | May prevent tumor growth and enhance tumor rejection |
| IL-23p19−/−[19] | Loss of IL-23 function | Skin UV radiation | Increased probability of skin tumor development | May increase risk of UV radiation–induced skin cancer |
| IL-23p19−/−[80] | Loss of IL-23 function | Chemically induced melanoma Chemically induced epithelial tumor | Increased number and size of melanomas Resistance to tumor development | May increase risk of melanoma May decrease risk of epithelial tumors |
| IL-23R−/−[20] | Loss of IL-23 receptor function | Intradermal injection of tumor cells | Resistance to tumor development | May prevent tumor growth and enhance tumor rejection |
| IL-23R−/−[72] | Loss of IL-23 receptor function | Colorectal tumorigenesis in genetically predisposed mice | Decreased tumor number and growth | May prevent tumor growth and enhance tumor rejection |

IL, interleukin; SC, subcutaneous; UV, ultraviolet.

associated with a significantly reduced risk of gastric cancer,[65] but with a significantly increased risk of oesophageal cancer,[66] hepato-cellular carcinoma[67] and acute myeloid leukaemia.[68] However, the effect of these IL-23R variants on the function of IL-23 (eg, gain, loss or no effect) was not specifically described in the studies. Taken together, these findings might lead to the hypothesis that IL-12/23 inhibitors have the potential to increase the risk of these cancers. However, a limitation of genomewide association studies is that they are not designed to investigate the causal relationship between a specific polymorphism and an increased cancer risk. For example, although several studies had shown that the TNF-238 polymorphism increased cancer risk, a meta-analysis of 34 studies did not find a significant association between this polymorphism and increased cancer risk.[69]

7  RISK OF MALIGNANCY IN ANIMAL MODELS SIMULATING NEUTRALIZATION OF IL-12 AND/OR IL-23

The malignancy data from animal models of IL-23 deficiency are conflicting. Mice that had lost IL-23 function via deficiencies in either IL-23p19 or IL-23R or by treatment with antibodies to IL-23p19 showed resistance to skin tumor growth/development (Table 4).[20] IL-23-deficient mice[70] and mice treated with anti–IL-23p19[71] have also been shown to have an increased resistance to melanoma-induced lung metastases. Furthermore, in this model of melanoma-induced metastases, anti–IL-23 antibody used in combination with IL-2 or anti-erbB2 antibody significantly inhibited subcutaneous growth of established mammary carcinomas and suppressed established and spontaneous lung metastases.[71] Deficiencies in IL-23p19 or IL-23R also resulted in decreased tumor multiplicity and growth in a mouse model of colorectal tumors.[72] These findings suggest that IL-23p19 inhibitors might prevent the growth and/or enhance the rejection of some tumors, possibly via effects on IL-22, which has been implicated in the development of epithelial tumors.[73,74] A number of studies have found that increased levels of IL-23 are associated with unfavourable outcomes in various malignancies in humans.[75–79] In contrast, other studies suggest that IL-23p19 deficiency might enhance the risk of certain cancers. For example, IL-23-deficient mice demonstrated an increased risk of development of chemically induced melanoma.[80] However, in a model of UV radiation, IL-23-deficient mice demonstrated both an increased risk of developing sarcoma and
a decreased risk of developing epithelial tumors compared with wild-type mice. Further studies are needed to confirm this finding.

Similarly, the studies on IL-12 also show conflicting data. Several studies of mice with IL-12-specific loss of function via deficiency in IL-12p35\textsuperscript{[20]} or IL-12Rβ\textsubscript{2}\textsuperscript{[81]} showed an increased risk of tumor development (Table 5), but, in models of UV radiation\textsuperscript{[19]} or chemically induced melanomas,\textsuperscript{[80]} IL-12p35-deficient mice had the same risk of induced skin tumors as did their wild-type counterparts.
8 | CONCLUSIONS

Patients with psoriasis and/or receiving treatment for psoriasis have an increased risk of cancer. Inhibitors of IL-12/23 and IL-23 are effective treatment approaches for psoriasis. Existing data provide evidence to support an association between impaired IL-12 and/or IL-23 signalling and both tumor growth and resistance to tumor growth, although the nature of these relationships is not fully understood. Long-term postmarketing safety evaluations of agents targeting IL-12/23 and IL-23 are needed to fully appreciate the associated malignancy risk. The implications for therapeutic inhibition of IL-12/23 or IL-23 remain uncertain, although monitoring of patients for NMSC and malignancy seems warranted.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

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REFERENCES

[1] T. D. Rachakonda, C. W. Schupp, A. W. Armstrong, J. Am. Acad. Dermatol. 2014, 70, 512.
[2] A. Menter, A. Gottlieb, S. R. Feldman, A. S. Van Voorhees, C. L. Leonardi, K. B. Gordon, M. Lebwohl, J. Y. Koo, C. A. Elmets, N. J. Korman, K. R. Beutner, R. Bhushan, J. Am. Acad. Dermatol. 2008, 58, 826.
[3] J. de Korte, M. A. Sprangers, F. M. Membrers, J. D. Bos, J. Investig. Dermatol. Symp. Proc. 2004, 9, 140.
[4] A. B. Kimball, A. Gueiran, M. Tsaneva, A. P. Yu, E. Q. Wu, S. R. Gupta, Y. Bao, P. M. Mulani, J. Eur. Acad. Dermatol. Venereol. 2011, 25, 157.
[5] H. Yeung, J. Takeshita, N. N. Mehta, S. E. Kimmel, A. Ogdie, D. J. Margolis, D. B. Shin, R. Attor, A. B. Troxel, J. M. Gelfand, JAMA Dermatol. 2013, 149, 1173.
[6] J. M. Gelfand, A. B. Troxel, J. D. Lewis, S. K. Kudr, D. B. Shin, X. Wang, D. J. Margolis, B. L. Strom, Arch. Dermatol. 2007, 143, 1493.
[7] Y. B. Brauchli, S. S. Jick, M. Miret, C. R. Meier, J. Invest. Dermatol. 2009, 129, 2604.
[8] Z. C. Chiesa Fuxench, D. B. Shin, A. Ogdie Beatty, J. M. Gelfand, JAMA Dermatol. 2016, 152, 282.
[9] C. Poupard, E. Benaunt, C. Horreau, T. Barnetche, L. Misery, M. A. Richard, S. Aractingi, F. Aubin, B. Cribier, P. Joly, D. Jullien, M. Le Maitre, J. P. Ortonne, C. Pau, J. Eur. Acad. Dermatol. Venereol. 2013, 27(Suppl 3), 36.
[10] K. Reich, A. W. Armstrong, P. Foley, M. Song, Y. Wasfi, B. Randazzo, S. Li, Y. K. Shen, K. B. Gordon, J. Am. Acad. Dermatol. 2017, 76, 418.
[11] K. Reich, K. A. Papp, A. Blauvelt, S. K. Tyring, R. Sinclair, D. Thaci, K. Nograles, A. Mehta, N. Cichanowitz, Q. Li, K. Liu, C. La Rosa, S. Green, A. B. Kimbal, Lancet 2017, 390, 276.
[12] C. S. Hsieh, S. E. Macatonia, C. S. Tripp, S. F. Wolf, A. O’Garra, K. M. Murphy, Science 1993, 260, 547.
[13] M. Kobayashi, L. Fitz, M. Ryan, R. M. Hewick, S. C. Clark, S. Chan, R. Loudon, F. Sherman, B. Perussia, J. Exp. Med. 1989, 170, 827.
[14] C. L. Langrish, Y. Chen, W. M. Blumenschein, J. Mattson, B. Basham, J. D. Sedgwick, T. McClanahan, R. A. Kastelein, D. C. Jia, J. Exp. Med. 2005, 201, 233.
[15] J. P. Leonard, K. E. Waldburger, S. J. Goldman, J. Exp. Med. 1995, 181, 381.
[16] R. Manetti, P. Parronchi, M. G. Giudizi, M. P. Piccinni, E. Maggi, G. Trinchieri, S. Romagnani, J. Exp. Med. 1993, 177, 1199.
[17] C. Parham, M. Chirica, J. Timans, E. Vaisberg, M. Travis, J. Cheung, S. Pflanz, R. Zhang, K. P. Singh, F. Vega, W. To, J. Wagner, A. M. O’Farrell, T. McClanahan, S. Zurawski, C. Hannum, D. Gorman, D. M. Rennick, R. A. Kastelein, R. de Waal Malefyt, K. W. Moore, K. W. Moore. J. Immunol. 2002, 168, 5699.
[18] B. Oppmann, R. Lesley, B. Blom, J. C. Timans, Y. Xu, B. Hunte, F. Vega, N. Yu, J. Wang, K. Singh, F. Zonin, E. Vaisberg, T. Churakova, M. Liu, D. Gorman, J. Wagner, S. Zurawski, Y. Liu, J. S. Abrams, K. W. Moore, D. Rennick, R. de Waal Malefyt, C. Hannum, J. F. Bazan, R. A. Kastelein, Immunity 2000, 13, 715.
[19] C. Jantschitsch, M. Weichenthal, E. Proksch, T. Schwarz, A. Schwarz, J. Invest. Dermatol. 2012, 132, 1479.
[20] J. L. Langowski, X. Zhang, L. Wu, J. D. Mattson, T. Chen, K. Smith, B. Basham, T. McClanahan, R. A. Kastelein, M. O. Nature 2006, 442, 461.
[21] A. Maeda, S. W. Schneider, M. Kojima, S. Beissert, T. Schwarz, A. Schwarz, Cancer Res. 2006, 66, 2962.
[22] K. I. Happel, P. J. Dubin, M. Zheng, N. Ghilardi, C. Lockhart, L. J. Quinton, A. R. Oden, J. E. Shellito, G. J. Bagby, S. Nelson, J. K. Kolls, J. Exp. Med. 2005, 202, 761.
[23] T. Bongartz, A. J. Sutton, M. J. Sweeting, I. Buchan, E. L. Matteson, V. Montori, JAMA 2006, 295, 2275.
[24] W. E. Thierfelder, J. M. van Deursen, K. Yamamoto, R. A. Tripp, S. R. Sarawar, R. T. Carson, M. Y. Sangster, D. A. Vignali, P. C. Doherty, G. C. Grosvedl, J. N. Ihle, Nature 1996, 382, 171.
[25] S. L. Gaffen, R. Jain, A. V. Garg, D. J. Cua, Nat. Rev. Immunol. 2014, 14, 585.
[26] G. Girolomoni, R. Strohal, L. Puig, H. Bachelez, J. Barker, W. H. Boehncke, J. C. Prinz. J. Eur. Acad. Dermatol. Venereol. 2017, 31, 1616.
[27] C. W. Lynde, Y. Poulin, R. Vender, M. Bourcier, S. Khalil, J. Am. Acad. Dermatol. 2014, 71, 141.
[28] F. O. Nestle, D. H. Kaplan, J. Barker, N. Engl. J. Med. 2009, 361, 496.
[29] S. K. Szabo, C. Hammerberg, Y. Yoshida, Z. Bata-Csorgo, K. D. Cooper, J. Invest. Dermatol. 1998, 111, 1072.
[30] P. Kulig, S. Musiol, S. N. Freiherber, B. Schreiner, G. Gyuveszi, G. Russo, S. Pantelyushin, K. Kishihara, A. Alessandri, T. Kundig, F. Sallusto, G. F. Hofbauer, S. Haak, B. Becker, Nat. Commun. 2016, 7, 13466.
[80] T. H. Nasti, J. B. Cochran, R. V. Vachhani, K. McKay, Y. Tsuruta, M. Athar, L. Timares, C. A. Elmets, J. Immunol. 2017, 198, 950.

[81] I. Airoldi, E. Di Carlo, C. Cocco, C. Sorrentino, F. Fais, M. Cilli, T. D’Antuono, M. P. Colombo, V. Pistoia, Blood 2005, 106, 3846.

[82] S. D. Sharma, S. M. Meeran, N. Katiyar, G. B. Tisdale, N. Yusuf, H. Xu, C. A. Elmets, S. K. Katiyar, Carcinogenesis 2009, 30, 1970.

[83] S. E. Street, J. A. Trapani, D. MacGregor, M. J. Smyth, J. Exp. Med. 2002, 196, 129.

[84] A. B. Kimball, J. Shenfeld, N. A. Accortt, M. S. Anthony, K. J. Rothman, D. Pariser, Br. J. Dermatol. 2015, 173, 1183.

[85] C. L. Kauffman, N. Aria, E. Tolchi, T. S. McCormick, K. D. Cooper, A. B. Gottlieb, D. E. Everitt, B. Frederick, Y. Zhu, M. A. Graham, C. E. Pendlery, M. A. Mascelli, J. Invest. Dermatol. 2004, 123, 1037.

[86] G. E. Fragoulis, S. Siebert, I. B. McInnes, Annu. Rev. Med. 2016, 67, 337.

[87] R. Panaccione, W. J. Sandborn, G. L. Gordon, S. D. Lee, A. Safdi, S. Sedghi, B. G. Feagan, S. Hanauer, W. Reinisch, J. F. Valentine, B. Huang, R. Carcereri, Inflamm. Bowel Dis. 2015, 21, 1329.

[88] K. B. Gordon, K. C. Duffin, R. Bissonnette, J. C. Prinz, Y. Wasfi, S. Li, Y. K. Shen, P. Szapary, B. Randazzo, K. Reich, N. Engl. J. Med. 2015, 373, 136.

[89] K. Papp, D. Thaci, K. Reich, E. Riedl, R. G. Langley, J. G. Krueger, A. B. Gottlieb, H. Nakagawa, E. P. Bowman, A. Mehta, Q. Li, Y. Zhou, R. Shames, Br. J. Dermatol. 2015, 173, 930.

[90] J. G. Krueger, L. K. Ferris, A. Menter, F. Wagner, A. White, S. Visvanathan, B. Lalovic, S. Aslanyan, E. E. Wang, D. Hall, A. Solinger, S. Padula, P. Scholl, J. Allergy Clin. Immunol. 2015, 136, 116.

[91] S. Singh, R. R. Kroo-Barrett, K. A. Canada, X. Zhu, E. Sepulveda, H. Wu, Y. He, E. L. Raymond, J. Ahlberg, L. E. Frego, L. M. Amodeo, K. M. Catron, D. H. Presky, J. H. Hanke, Mabs. 2015, 7, 778.

[92] Eli Lilly and Company. Clinical development pipeline, https://www.lilly.com/discovery/pipeline (accessed: March 29, 2017).

[93] R. G. Langley, T. F. Tsai, S. Flavin, M. Song, B. Randazzo, Y. Wasfi, J. Jiang, S. Li, L. Puig, Br. J. Dermatol. 2018, 178, 114.

[94] A. B. Kimball, K. B. Gordon, R. G. Langley, A. Menter, E. K. Chartash, J. Valdes, Arch. Dermatol. 2008, 144, 200.

[95] A. B. Gottlieb, C. Leonardi, F. Kerdel, S. Mehlis, M. Olds, D. A. Williams, Br. J. Dermatol. 2011, 165, 652.

[96] B. E. Strober, J. J. Crowley, P. S. Yamauchi, M. Olds, D. A. Williams, Br. J. Dermatol. 2011, 165, 661.

[97] K. Reich, R. G. Langley, M. Lebwohl, P. Szapary, C. Guzzo, N. Yeilding, S. Li, M. C. Hsu, C. E. Griffiths, Br. J. Dermatol. 2011, 164, 862.

[98] H. Sofen, S. Smith, R. T. Matheson, C. L. Leonardi, C. Calderon, C. Brodmerkel, K. Li, K. Campbell, S. J. Marciniak Jr, Y. Wasfi, Y. Wang, P. Szapary, J. G. Krueger, J. Allergy Clin. Immunol. 2014, 133, 1032.

[99] T. Kopp, E. Riedl, C. Bangert, E. P. Bowman, E. Greisenegger, A. Horowitz, H. Kittler, W. M. Blumenschein, T. K. McClanahan, T. Marbury, C. Zachariae, D. Xu, X. S. Hou, A. Mehta, A. S. Zandvliet, D. Montgomery, F. van Aarle, S. Khalilieh, Nature 2015, 521, 222.

[100] S. M. Meeran, T. Punathil, S. K. Katiyar, J. Invest. Dermatol. 2008, 128, 2716.

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