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Dupilumab, A Monoclonal Antibody for Atopic Dermatitis: A Review of Current Literature

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ABSTRACT

Atopic dermatitis results when aberrant barrier function and immune activation occur within the skin. Standard therapies for atopic dermatitis have fallen short, prompting efforts to discover novel therapeutics for this disease. Of these, dupilumab, a fully human monoclonal antibody that inhibits the actions of both IL-4 and IL-13, has shown the greatest promise. Clinical trials of systemic dupilumab in moderate-to-severe atopic dermatitis have demonstrated marked improvement in patient symptoms, including pruritus and clinically visible disease. Importantly, dupilumab treatment has been correlated with changes in the molecular signature of diseased skin, with reduction of both inflammatory and proliferative markers. Dupilumab recently received US FDA breakthrough therapy designation for atopic dermatitis, with ongoing trials in both adult and pediatric populations. Altogether, dupilumab has shed new light on the pathomechanisms driving atopic dermatitis and is making unprecedented advances towards highly effective control of this debilitating disease.

Key words: atopic dermatitis, dupilumab, eczema, IL-4Rα, IL-4, IL-13, monoclonal antibody, EASI-50, EASI-75, SCORAD

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, resulting from defects in skin barrier function and innate and adaptive immune responses.[1,2] In its acute stages, AD presents with highly pruritic, inflamed lesions. Histologically, the epidermis of acute lesions is characterized by intracellular edema (spongiosis), and a sparse infiltrate consisting primarily of T lymphocytes. Marked perivascular inflammatory cell infiltrates with large numbers of T lymphocytes and macrophages are seen in the dermis. In its chronic stages, lesions are lichenified and plaque-like. Histologically, chronic lesions are distinguished by epidermal hyperplasia with prominent hyperkeratosis and minimal spongiosis.[3-7]

It is estimated that up to 30% of children and 10% of adults are affected by AD, with approximately 85% of all cases beginning within the first 5 years of life (early-onset AD).[3,4,8] Although many children experience remission of their disease by adolescence, a portion will continue to be affected into adulthood.[9] As well, a number of patients will have their first episode of AD diagnosed in adult life (late-onset AD), a presentation that often results in a more treatment-refractory form of the disease.[4] Of those affected by AD, up to 20% have a moderate-to-severe presentation, which often manifests as a recurrent disease with remitting and relapsing phases.[10] Importantly, AD impacts all aspects of patients' lives, from their physical wellbeing to their psychological and economical quality of life by disrupting sleep, daily functioning, and requiring patients to attend frequent medical appointments.[11-14]

Genetics play a large role in the development of AD. Affected individuals often have a strong family history of atopy, including AD, asthma and allergic rhinitis: the atopic triad.[15] Genome-wide association studies have implicated a number of genetic loci in the development of AD, including the 1q21, 3p26, 3q21, 5q31-33, 16q, 17q25, and 20p regions. These genetic loci are primarily involved in skin barrier and immune function.[16-21] Importantly, interventions aimed at repairing these defects in skin barrier function and immune dysregulation hold promise for treatment, prevention and, potentially, a cure for AD.

Recent advances in our understanding of the underlying pathogenesis and risk factors for AD has resulted in two opposing theories that attempt to explain the onset and natural history of the disease: the outside-in and the inside-out hypotheses.[22,23] The outside-in hypothesis proposes that genetic variations within the population result in a subpopulation of individuals that harbor defects in skin barrier function. A disrupted barrier permits allergens and microbes to cross the epithelium, which in turn

triggers an inflammatory reaction. Alternatively, the inside-out hypothesis proposes that the underlying defects occur at the level of the immune system. A polarized immune response in AD patients results in immunoglobulin E (IgE) sensitization to skin pathogens and contaminants. The resultant immune response induces local inflammation and skin barrier breakdown.[22,23] While debate around these theories remains, it is evident that a number of genetic and environmental factors contribute to skin barrier dysfunction and immune dysregulation in AD. The polyfactorial nature of AD accounts for the heterogeneity in severity and natural history of this disease. It is nonetheless apparent that optimal treatment of AD requires a comprehensive approach aimed at repairing defects in skin barrier function and addressing the characteristic immune abnormalities.

No currently available therapy provides complete remission or cure for affected patients. Management of AD includes patient education, optimal skin care practices, antihistamines (preferably first generation - sedating antihistamines), topical corticosteroids or topical calcineurin inhibitors (TCIs), systemic corticosteroids, systemic calcineurin inhibitors, phototherapy, and other oral immune-suppressants.[7,24] These treatments work to restore skin barrier function and suppress the inflammatory response.

The availability of safe and effective treatment for moderate-to-severe AD remains a significant unmet need. Research focused on the pathophysiology of AD has identified promising targets for the treatment of this disease. One targeted therapy that has shown promise in early clinical development and is the focus of this review is dupilumab, an interleukin (IL)-4 receptor alpha (IL-4Rα) antagonist.

Immune Dysfunction in AD

Recent research has demonstrated that immune system dysfunction plays a central role in the development and persistence of AD. These cellular and cytokine targets provide potential therapeutic opportunities. AD skin has been shown to harbor increased levels of the TH2 cytokines IL-4, IL-5, IL-10, and IL-13, with a corresponding decrease in the TH1 cytokines interferon-γ and IL-2.[25-30] IL-4 and IL-13 have established roles in B-cell differentiation and class switching, thus providing a plausible link to characteristic elevations of serum IgE levels in AD patients.[4,31] Importantly, these TH2 cytokines have been shown to contribute to AD pathogenesis, as mice genetically engineered to over-express these cytokines develop skin barrier defects and an AD-like disease.[32-35] High levels of the TH2 cytokines IL-4 and IL-13 in AD skin have been shown to act as inhibitors of both epidermal differentiation and production of antimicrobial peptides.[36-38] IL-4 and IL-13 signal through a common receptor, IL-4Rα, to activate the Signal Transducer and Activator of Transcription 6 (STAT6)/Janus kinase 1 (JAK1) signalling cascade, and genetic polymorphisms in IL-4, IL-13 and IL-4Rα have all been associated with the development of AD in specific populations.[39-44] Mice that have been genetically engineered to over-express a constitutively active STAT6 display decreased expression of epidermal differentiation complex genes, including filaggrin, loricrin, and involucrin, and develop an AD-like disease by allowing for enhanced penetration of allergens and pathogens across the skin barrier.[45] Importantly, IL-4 deficiency was shown to be protective against the development of allergic skin inflammation in these mice, as was treatment with immune-modulators targeting either IL-4 or IL-13.[45] Additionally, IL-4 and IL-13 have also been demonstrated to regulate expression of genes, such as β-defensins and cathelicidin, involved in susceptibility to skin pathogens including *Staphylococcus aureus* and herpes simplex virus, potentially accounting for the fact that AD patients have an increased propensity for infection by these pathogens.[36-38] Together, this evidence suggests that targeting TH2 polarization in AD, including antagonism of IL-4 and IL-13, could be efficacious in the treatment of AD.

Dupilumab Clinical Trials in AD

Given the importance of the TH2 inflammatory pathway in AD, it is not surprising that researchers have explored if the inhibition of IL-4 and IL-13 could provide a potential new treatment approach for this chronic, difficult-to-manage disease. Dupilumab is a fully human monoclonal antibody that binds the IL-4α receptor subunit, effectively blocking signalling from both IL-4 and IL-13. First tested for therapeutic value in asthma,[46] dupilumab has shown impressive results in trials for AD, and looks to change the management landscape for this debilitating disease. To date, several phase I and II trials have been completed, with other phase II and III trials currently underway in both adult and pediatric populations (Table 1).

Recently, a collection of phase I/II trials were published, which looked at the effects of dupilumab on moderate-to-severe AD refractory to topical glucocorticoids and calcineurin inhibitors.[47] Four trials in this publication include two phase I, 4 week monotherapy trials looking at safety as a primary endpoint (NCT01259323/study M4A and NCT01385657/study M4B) and two phase II trials, one 12 week monotherapy trial (NCT01548404/study M12) and one trial of dupilumab plus mid-high potency topical glucocorticoids with 4 weeks active treatment and 8 weeks follow-up period (NCT01639040/study C4). In the program, patients aged 18 years or older with moderate-to-severe AD and an Investigator Global Assessment (IGA) of ≥3 and a Scoring Atopic Dermatitis (SCORAD) score of ≥20 (study C4), or an Eczema Area and Severity Index (EASI) score ≥12 (studies M4A and M4B) or ≥16 (study M12), were included. Remarkably, in these phase I/II trials, patients treated with dupilumab experienced rapid improvement in AD disease activity. In study M12, the 12 week monotherapy trial, significantly more patients in the dupilumab arm experienced a ≥50% reduction in EASI score (EASI-50) as compared to the placebo arm (85% vs. 35%, respectively; $p<0.001$), near-to-complete clearance of skin lesions with an IGA of 0 or 1 (40% vs. 7%, respectively; $p<0.001$), and decreased pruritus with improvement on the pruritus Numerical Rating Scale (NRS) (56% vs. 15%, respectively; $p<0.05$).[47] When combined with topical glucocorticoids in the C4 study, all patients treated with dupilumab reached EASI-50, compared with only half of those receiving topical glucocorticoids plus placebo ($p=0.002$). Importantly, patients receiving dual therapy with dupilumab used less than half the glucocorticoid therapy required by those patients receiving glucocorticoid plus placebo ($p=0.16$).[47]

The adverse event (AE) profiles were similar between the groups receiving either dupilumab or placebo in all of the studies. Most AEs were considered mild-to-moderate in severity, transient, and more likely to result in study discontinuation in the placebo group.

Trial ID	Phase	Status	N	Title of Study	Primary Outcome Measure
NCT01015027	I	Completed	48	A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Phase 1 Study of the Safety and Tolerability of Intravenously Administered REGN668 in Healthy Volunteers	TEAE at 85 days (11 visits)
NCT01259323 (Study M4A)	I	Completed	30	A Randomized, Double-Blind, Placebo-Controlled, Sequential Ascending, Repeated-Dose Study of the Safety and Pharmacokinetics of Subcutaneous REGN668 in Patients With Moderate-to-Severe Extrinsic Atopic Dermatitis	TEAE at 12 weeks
NCT01385657 (Study M4B)	I/II	Completed	37	A Randomized, Double-Blind, Placebo-Controlled, Sequential Ascending, Repeated-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Subcutaneous REGN668 in Patients With Moderate-to-Severe Atopic Dermatitis	TEAE at 12 weeks
NCT01859988	II	Completed	380	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Investigating the Efficacy, Safety, Pharmacokinetic and Biomarker Profiles of REGN668 Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis	Percent change in EASI score at 16 weeks
NCT01548404 (Study M12)	II	Completed	109	A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose Study of the Efficacy, Safety, Tolerability, and Pharmacodynamics of Subcutaneously-Administered REGN668 in Adult Patients With Extrinsic Moderate-to-Severe Atopic Dermatitis	Percent change in EASI score at 12 weeks
NCT01639040 (Study C4)	II	Completed	31	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Safety of REGN668 Administered Concomitantly With Topical Corticosteroids to Patients With Moderate-to-Severe Atopic Dermatitis	TEAE at 78 days
NCT01979016	II	Completed	54	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Investigating the Efficacy, Safety, Serum Concentration and Biomarker Profile of Dupilumab Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis	Percent change in EASI score at 16 weeks
NCT02407756	II	Active	80	A Phase 2a Study Investigating the Safety, Pharmacokinetics, Immunogenicity, and Exploratory Efficacy of Dupilumab in Patients Aged ≥6 to <18 Years With Atopic Dermatitis	Pharmacokinetic parameters in pediatric patients at 12 weeks
NCT02277743	III	Active	600	A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis (SOLO-1)	Proportion of patients with both IGA 0 to 1 and a reduction from baseline of ≥2 points at 16 weeks
NCT02277769	III	Active	600	A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis (SOLO-2)	Proportion of patients with both IGA 0 to 1 and a reduction from baseline of ≥2 points at 16 weeks
NCT02260986	III	Active	700	A Randomized, Double-Blind, Placebo-Controlled Study to Demonstrate the Efficacy and Long-Term Safety of Dupilumab in Adult Patients With Moderate-to-Severe Atopic Dermatitis	Proportion of patients with both IGA 0 to 1 and a reduction from baseline of ≥2 points at 16 weeks (Additional measures assessed up to 52 weeks)
NCT02395133	III	Active	440	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Investigating the Efficacy and Safety of Multiple Dupilumab Dose Regimens Administered as Monotherapy for Maintaining Treatment Response in Patients With Atopic Dermatitis	Proportion of patients with IGA scores of 0 or 1 at 36 weeks
NCT01949311	III	Active	800	An Open-label Study of Dupilumab in Patients With Atopic Dermatitis Who Participated in Previous Dupilumab Clinical Trials	TEAE at 52 and 116 weeks

Table 1: Clinical trials of dupilumab in AD

TEAE = treatment-emergent adverse events; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment (on a 5-point scale)

The most common treatment-emergent adverse events (TEAEs) were nasopharyngitis and headache, which were more frequently reported in those subjects receiving dupilumab. Serious AEs were more frequently reported in the placebo groups (9/80) compared with the dupilumab groups (2/127). Interestingly, there were four times as many skin infections reported in the placebo groups (17/80) compared to the dupilumab groups (6/127), suggesting that dupilumab might improve skin barrier function. There were more injection site reactions in the dupilumab group but these were generally mild. There were no opportunistic infections or deaths in any of these studies.[47]

When evaluating the molecular signature of genes expressed in non-lesional and lesional skin from the patients included in these trials, dupilumab-treated skin showed marked improvements with downregulation of markers of both epidermal proliferation and upregulation of genes involved in skin barrier function.[26] Dupilumab treatment also suppressed the expression of genes related to the activation of T cells and related inflammatory pathways, a major driver in AD clinical disease. After only 4 weeks of dupilumab treatment, the transcriptome of skin harvested from AD patients resembled that of non-lesional skin.[26]

Another phase II international 16 week dose-ranging study (NCT01859988) including 380 patients has been completed and recently published.[48] Patients were 18 years or older and had an EASI score of ≥12 at screening (≥16 at baseline) with an inadequate response to topical therapy. This was a dose ranging study and patients were randomized to receive dupilumab 300 mg once a week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks or placebo once a week for 16 weeks. When compared to placebo, all dupilumab dosing regimens showed a significant improvement in EASI score from baseline. The least-square means improvement of EASI score was -73.7% (300 mg every week), -68.2% (300 mg every 2 weeks), -65.4% (200 mg every 2 weeks), -63.5% (300 mg every 4 weeks), -44.8% (100 mg every 4 weeks) compared to -18.1% (placebo) ($p<0.0001$ for all comparisons).[48] The AE profile was similar to previously published studies with the most commonly reported AEs of nasopharyngitis, exacerbation of AD, headache and upper respiratory tract infection. There were more reports of herpes infections in the dupilumab group (8%) when compared to placebo (2%) as well as conjunctival inflammation (7% vs. 3%, respectively). The rate of injection site reactions was 7% in the dupilumab group vs. 3% in the placebo group.[48]

A summary of the burden of disease in this patient group has also been published, which showed a significant burden of disease including that on quality of life as based on a number of patient reported measures: Dermatology Life Quality Index (DLQI), EuroQoL (EQ-5D) Health Status Questionnaire, Hospital and Anxiety Depression Scale (HADS), 5-D Pruritus and Patient Oriented Eczema Measure (POEM).[49]

The pooled results of the 300 mg dupilumab group from this 16 week phase II study and the 300 mg group of the M12 study compared to placebo were presented recently.[50] Dupilumab was administered weekly as monotherapy and no additional topical steroids were allowed; the analysis included a total population of patients given placebo (n=115) or dupilumab 300 mg (n=118) with a loading dose at week 1. The improvement in SCORAD from baseline was 37 points for dupilumab (baseline score 66) and 11 for placebo (baseline score 68), respectively ($p<0.0001$ vs. placebo at week 12). At 12 weeks, dupilumab resulted in an EASI percent improvement of 74% vs. 23% for placebo ($p<0.0001$) and the absolute change (mean±SD) was -21.1±12.0 for dupilumab and -6.9±14.0 for placebo. Significantly higher proportions of dupilumab-treated patients achieved EASI-50 compared with placebo (85.6% vs. 32.2%; $p<0.0001$) and EASI-75 compared with placebo (61.0% vs. 13.9%; $p<0.0001$) at week 12. Additionally, significant improvement in pruritus was noted as dupilumab resulted in pruritus NRS mean percent improvement of 53% vs. 8% for placebo ($p<0.0001$) at week 12.[50] The safety profile was similar to previous studies and between the two groups. The TEAEs occurring in ≥5% of trial participants during the 12 week placebo-controlled period for placebo vs. 300 mg dupilumab included upper respiratory tract infection (33.9% vs. 42.4%), skin infections (29.7% vs. 16.4%), conjunctival inflammation/infection (3.5% vs. 15.3%), headache (7.8% vs. 14.4%), and dermatitis (14.8% vs. 11.0%), respectively. There were more injection site reactions in the dupilumab group (13.6%) vs. placebo (6.1%). There were no deaths in either study.[48,50]

Results from these studies have been extremely encouraging and prompted the quick expansion to clinical trials to evaluate the efficacy of dupilumab in pediatric patients, as well as the long-term safety of the drug. Currently, a phase II pharmacokinetic study in pediatric patients ≥6 and <18 years is ongoing (NCT02407756) as well as a long-term extension study for patients who participated in any trial from the phase I-III program (NCT01949311). Both members of the dermatologic community and patients affected by AD eagerly await the final results of these clinical trials.

Conclusion

Over the last several years, a number of important scientific and clinical discoveries have been made regarding the pathogenesis of AD. We now understand better than ever that AD results from defects in skin barrier function and innate and adaptive immune responses, both of which have important therapeutic implications. These discoveries not only explain the limitations of currently used treatments for AD, but also provide a map forward in our discovery of novel therapeutics for this difficult-to-treat skin disorder. Dupilumab is helping to shed new light on the pathomechanisms driving atopic dermatitis, and leading the way towards highly effective control of this debilitating disease.

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Nivolumab for Metastatic Melanoma

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Conflicts of interest: None Reported.

ABSTRACT

Melanoma is an aggressive skin cancer with a generally poor prognosis at Stage III-IV disease. Traditionally, metastatic melanoma was treated by surgical resection, when possible, and with systemic chemotherapy. New developments in molecular biology have led to the identification of immune checkpoints which are exploited by malignant cells, allowing them to go undetected by the immune system. Nivolumab (Opdivo®) is a human monoclonal antibody which prevents immune inhibition by interacting with PD-1 on tumor cells; thus, increasing tumor-specific T cell proliferation. Nivolumab has demonstrated efficacy superior to that of standard chemotherapy and relative safety in clinical trials. Indeed, the outcomes for patients with advanced melanoma are being improved by novel biologic agents such as nivolumab.

Key words: antineoplastic agent, melanoma, Opdivo®, PD-1 inhibitor, programmed cell death 1 receptor, signal transduction, skin neoplasms

Introduction

A melanoma is an aggressive tumor often occurring on the skin that is caused by the transformation of melanocytes into malignant cells.[1] Many cases are classified as melanoma *in situ*, with tumors localized only to the epidermis (Stage 0); however, some melanomas are invasive and infiltrate the dermis (Stage I-II), and still others spread to nearby lymph node(s) (Stage III), or to distant lymph nodes and/or organ systems (Stage IV).[2] Stage III-IV disease is termed 'metastatic melanoma' and occurs in roughly 30% of patients after excision of the primary tumor.[2,3] The 5-year survival rate is 23% when metastatic melanoma presents in the skin.[4] In order to evade immune recognition, certain tumors may exploit immune-regulatory checkpoints which suppress excessive T lymphocyte function in normal physiologic conditions; thereby permitting unregulated proliferation of malignant cells.[5]

Preclinical cancer studies suggest that interrupting co-receptor interactions responsible for inhibitory signaling on tumor-specific T cells would activate the anti-tumor immune response.[5] One such co-receptor is programmed death receptor-1 (PD-1). PD-1 inhibits T cell activation, leading to reduced proliferation, cytokine production, and cytolysis via interactions with its ligands PD-L1 and PD-L2.[6] On December 22, 2014, nivolumab (Opdivo®), a human monoclonal antibody against PD-1 receptor, was approved by the US FDA for the treatment of unresectable or metastatic melanoma that is unresponsive to other drugs.[7] Nivolumab binds PD-1 with high affinity and impedes both PD-L1 and PD-L2 interaction; thus, increasing tumor-specific T cell proliferation.

Phase I and II

Two phase I dose-escalation trials were performed to assess the preliminary efficacy, safety and pharmacokinetics of nivolumab.[6,8] Both trials enrolled participants with advanced metastatic non-small cell lung cancer (NSCLC), melanoma, castrate-resistant prostate cancer, renal cell carcinoma, and colorectal cancer. Doses ranging from 0.1-10 mg/kg of nivolumab were administered by intravenous (IV) infusion every 2 weeks. Pharmacokinetic data from these studies showed that the median time to peak serum concentration of nivolumab is 1 to 4 hours after dosing.[8] Nivolumab yields an approximate serum half-life (t1/2) of 12 days for 0.3, 1, and 3 mg/kg doses and up to 20 days for the 10 mg/kg dose.[6] Maximum concentration (C_{max}) and area under the curve (AUC) are directly related to dose.[6,8] PD-1-receptor occupancy on the surface of circulating CD3+ cells was also assessed.[6,8] After one infusion at a dose of 0.1 to 10 mg/kg, surface occupancy was dose-independent with a mean peak occupancy of 85% (70% to 97%) observed at 4 to 24 hours and a mean plateau occupancy of 72% observed at ≥57 days;[6] however, another study of cell surface occupancy in participants with melanoma showed that the median occupancy was 64% to 70% and varied according to dose.[8] Tumor biopsies from phase I suggested a potentially significant association between PD-L1 cell surface expression and clinical response to nivolumab (P=0.048)[6] which was further investigated in subsequent studies.

One-hundred and seven advanced melanoma participants from the phase I trial were followed for up to 4 years after treatment initiation to monitor survival, tumor remission and the long-term safety of nivolumab.[8] Sixty-two percent of these participants had received at least two prior systemic treatments.[9] The objective response rate (ORR), defined as the proportion of participants who had a complete or partial response was 25%, 18/26 participants were treated for a year or more.[8] The ORR increased to 33% at 4 years' follow-up, with a median response duration of 2 years.[8,9] Stable disease lasting ≥24 weeks was originally observed in 6% of participants and increased by another 1% at 4 years' follow-up.[8,9] Median overall survival was 16.8 months (95% confidence interval [CI] = 12.5-31.6), and 1 and 2 year survival rates were 62% (95% CI = 53%-72%) and 44% (95% CI = 32%-53%), respectively.[9]

The most common treatment emergent adverse events (TEAEs) in participants treated with nivolumab were fatigue (32%), rash (23%), and diarrhea (18%).[9] TEAEs of immunologic significance included skin disorders (35%), gastrointestinal disorders (18%), and endocrinopathies (13%). Five participants experienced

Grade 3 or 4 TEAEs.[9] The majority of AEs occurred within the first 6 months of treatment and the frequency of AEs did not increase with prolonged use.[9]

Yamazaki and colleagues reported preliminary results from their phase II study of 35 participants with advanced melanoma.[10] Nivolumab was administered at a dose of 2 mg/kg every 3 weeks until unacceptable toxicity, disease progression, or complete response. The ORR was 23% (8/35) with median progression-free survival of 6.14 months. TEAEs occurred in 45.7% of participants and consisted mainly of elevated gamma-glutamyl transpeptidase, anemia, decreased hematocrit, hemoglobin and red blood cell counts, and loss of appetite. No drug-related deaths were reported.

Phase III

A randomized, double-blind, phase III trial assessed the efficacy and safety of nivolumab versus standard chemotherapy (dacarbazine) in melanoma without BRAF mutation.[11] Four-hundred and eighteen participants were randomized to nivolumab 3 mg/kg every 2 weeks (N=210) or dacarbazine 1000 mg/m^2 every 3 weeks (N=208). ORRs and median progression-free survival are presented in Table 1. The ORR was significantly higher in the nivolumab group compared to the dacarbazine group and the proportion of participants with a complete response was higher with nivolumab than with dacarbazine (7.6% vs. 1.0%). The duration of progression-free survival was also longer in participants treated with nivolumab compared to those treated with dacarbazine.

The trial was stopped early due to nivolumab's clear benefit over standard chemotherapy in improving overall survival.[12] The median overall survival was not reached in the nivolumab group and was 10.8 months (95% CI = 9.3%-12.1%) in the dacarbazine group.[11] Overall survival rates at 1 year were 72.9% (95% CI = 65.5%-78.9%) and 42.1% (95% CI = 33%-50.9%) in the nivolumab and dacarbazine groups, respectively. Nivolumab significantly increased overall survival compared to dacarbazine (hazard ratio for death = 0.42; 99.79% CI = 0.25-0.73; P<0.001).

The incidence of AEs was similar between treatments (74.3% vs. 75.6% in the nivolumab and dacarbazine groups, respectively); yet the frequency of AEs of grade 3 or 4 was lower for participants treated with nivolumab than with dacarbazine (11.7% vs. 17.6%).[11] The most common TEAEs with nivolumab were fatigue (19.9%), pruritus (17.0%), and nausea (16.5%). The proportion of participants who discontinued the study due to TEAEs was 6.8% and 11.7% in the nivolumab and dacarbazine groups, respectively. No drug-related deaths occurred in either group.

Nivolumab's efficacy in treating ipilimumab- or ipilimumab/BRAF inhibitor-refractory melanoma was investigated in 405 participants.[13] Participants were randomized to receive an IV infusion of nivolumab at a dose of 3 mg/kg, or investigator's choice of chemotherapy (ICC), either dacarbazine 1000 mg/m^2 every 3 weeks or carboplatin AUC 6 plus paclitaxel 175 mg/m^2 every 3 weeks by IV infusion, until disease progression or unacceptable toxicity. Tumors were assessed at baseline, 9 weeks, and every 6 weeks for the first year, then every 12 weeks until disease progression, death or study withdrawal. Safety was assessed in all participants who received at least one dose of study drug. The primary endpoint was the proportion of participants who had an OR. Secondary endpoints included progression-free survival rates, and PD-L1 tumor expression.

ORRs and median progression-free survival are displayed in Table 1. ORRs were higher with nivolumab than with ICC, although no statistical comparison was made. Median time to response was 2.1 months and 3.5 months in the nivolumab and ICC groups, respectively. Median progression-free survival was not significantly different between nivolumab and ICC. The ORR with nivolumab was higher for PD-L1 positive tumors (43.6%) than PD-L1 negative tumors (20.3%), while ORRs were similar with ICC in both types of tumors (9.0% vs. 13.0%).

Rates of TEAEs were 68% in the nivolumab group and 79% in the ICC group. Fatigue, pruritus and diarrhea were the most common AEs with nivolumab, while nausea, alopecia and fatigue were the most common AEs with ICC. Grade 3 to 4 AEs occurred in 9% of participants treated with nivolumab and in 31% of participants treated with ICC. Drug toxicity led to the discontinuation of treatment in 3% and 7% of the participants in the nivolumab and ICC groups, respectively.

Clinical trials have also assessed the safety and efficacy of nivolumab in combination with ipilimumab for the treatment of advanced melanoma.[14,15] Eighty-six participants in a phase I trial were treated either concurrently with escalating doses of nivolumab (cohort 1: 0.3 mg/kg nivolumab + 3 mg/kg ipilimumab, cohort 2: 1 mg/kg nivolumab + 3 mg/kg ipilimumab, cohort 3: 3 mg/kg nivolumab + 1 mg/kg ipilimumab, cohort 4: 3 mg/kg nivolumab + 3 mg/kg ipilimumab, cohort 5: 10 mg/kg nivolumab + 3 mg/kg ipilimumab, 10 mg/kg nivolumab + 10 mg/kg ipilimumab), or sequentially with nivolumab 1 mg/kg and 3 mg/kg every 2 weeks for up to 48 doses.[14] Participants were followed for 2.5 years after the start of treatment. Clinical activity was assessed at weeks 12, 18, 24, 30 and 36, and every 12 weeks thereafter in the concurrent therapy cohorts, while the sequentially treated cohorts were assessed at week 8 and every 8 weeks thereafter. PD-L1 tumor-cell expression was also characterized.

The ORR in the concurrent regimen cohorts was 40% (95% CI = 27-55) across all doses.[14] Sixteen participants experienced a ≥80% reduction in tumor size. Five complete responses were included among those with a ≥80% reduction. Nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg were the maximum doses associated with an acceptable safety profile in the sequential treatment cohort. The ORR in participants who received the sequential regimen was 53% (95% CI = 28%-77%), including three complete responses; all participants who attained OR had a ≥80% tumor reduction at the first scheduled assessment. Twenty percent of participants (95% CI = 8%-39%) in the sequenced regimen cohorts had an OR, including one complete response. Four participants in the sequenced regimen cohorts had a tumor reduction of ≥80%. ORs were noted in 6/13 and 9/22 participants with PD-L1 positive and PD-L1 negative tumors, respectively. Ninety-three percent of participants experienced TEAEs, the most common being rash (55%), pruritus (47%), fatigue (38%), and diarrhea (34%). Eleven participants (11%) in the concurrent regimen group and three (9%) in the sequenced regimen discontinued treatment due to TEAEs.

	Study Arms	Objective Response (%)	95% CI (%)	P-value	Median Progression-free Survival (months)	95% CI	P-value
Robert et al. 2015	Nivolumab 3 mg/kg [a]	40.0	33.3-47.0	<0.001	5.1	3.5-10.8	<0.001
	Dacarbazine 1000 mg/m^2	13.9	9.5-19.4		2.2	2.1-2.4	
Weber et al. 2015	Nivolumab 3 mg/kg	31.1	23.1-40.2	--	8.3	2.8-18.4	ns
	Investigator's choice of chemotherapy	4.7	2.3-6.5		4.2	2.1-6.3	
Larkin et al. 2015	Nivolumab 3 mg/kg	43.7	38.1-49.3	--	6.9	4.3-9.5	<0.001*
	Ipilimumab 3 mg/kg	19.0	14.9-23.8		2.9	2.8-3.4	
	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg + nivolumab 3 mg/kg	57.6	52.0-63.2		11.5	8.9-16.7	

Table 1. Objective response and median-progression-free survival[11,13,15]

[a] Objective response was 52.7% (95% CI = 40.8%-64.3%) in PD-L1 positive tumors and 33.1% (95% CI = 25.2%-41.7%) in PD-L1 negative tumors.

* Comparing nivolumab + ipilimumab to ipilimumab alone and comparing nivolumab alone to ipilimumab alone. ns = not significant

In a double-blind, phase III study, 945 participants were randomized to receive either: 1) nivolumab 3 mg/kg every 2 weeks (plus ipilimumab matched placebo) for 4 doses; 2) nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and thereafter; or 3) ipilimumab 3 mg/kg every 3 weeks (plus nivolumab-matched placebo) for 4 doses by IV infusion.[15] Treatment continued until disease progression, unacceptable toxicity or study withdrawal.

Median progression-free survival was significantly longer with nivolumab plus ipilimumab than with ipilimumab alone and with nivolumab than with ipilimumab (Table 1).[15] No significant difference in the hazard of death or disease progression between the combination treatment and nivolumab only groups was found. The ORRs were highest among participants treated with nivolumab plus ipilimumab, followed by those treated with nivolumab only, and ipilimumab only (Table 1). Median time to OR was similar in the three groups (2.76, 2.78, and 2.79 months in the nivolumab plus ipilimumab, nivolumab, and ipilimumab groups, respectively). Complete response rates were also highest with nivolumab plus ipilimumab (11.5%), than with nivolumab (8.9%) or ipilimumab (2.2%) alone. The highest ORRs were observed in participants with PD-L1-positive tumors treated with nivolumab plus ipilimumab (72.1%; 95% CI = 59.9%-82.3%) or nivolumab only (57.5%; 95% CI = 45.9%-68.5%).

TEAEs occurred in 95.5% of the nivolumab plus ipilimumab group, in 86.2% of the ipilimumab group, and in 82.1% of the nivolumab group.[15] The most common TEAEs in all groups were diarrhea, fatigue, pruritus and rash. The incidence of grade 3 or 4 AEs was highest in the combination group (55.0%), compared to the ipilimumab (27.3%) and nivolumab-only (16.3%) groups. TEAEs led to study discontinuation in 36.4%, 14.8% and 7.7% of the nivolumab plus ipilimumab, ipilimumab only and nivolumab only groups, respectively. One participant in the nivolumab group died of neutropenia and one participant in the ipilimumab group died of cardiac arrest. No deaths were reported with the combination treatment.

Discussion

Nivolumab has demonstrated greater efficacy when compared to standard chemotherapy in clinical trials.[11,13] Nivolumab produced higher objective response rates, longer median progression-free survival, and increased overall survival compared to standard chemotherapy.[11,13] Participants with ipilimumab- or ipilimumab/BRAF inhibitor-refractory melanoma treated with nivolumab also had higher response rates and a faster time to response than those treated with investigator's choice of chemotherapy.[13] Participants treated with nivolumab had significantly longer progression-free survival and higher OR and complete response rates compared to participants treated with ipilimumab monotherapy.[14] Furthermore, patients who did not respond to previous ipilimumab therapy did have a response to treatment with nivolumab.[14] Nivolumab/ipilimumab combination therapy is also encouraging.[15] Nivolumab treatment is associated with a risk of immune-mediated pneumonitis, colitis, hepatitis, renal dysfunction and endocrinopathy.[16] The most common TEAEs with nivolumab were fatigue, pruritus, rash, diarrhea and nausea; however, AE rates were similar or lower with nivolumab than with dacarbazine or carboplatin plus paclitaxel.[11,13] Furthermore, the incidence of grade 3 or 4 AEs was lower with nivolumab compared to standard chemotherapy or with ipilimumab monotherapy.[11,13,15]

Until recently, surgical resection, when possible, coupled with standard chemotherapy was the first-line treatment for Stage III melanoma and for palliation of Stage IV disease. However, the rates of recurrence and metastasis remained high, as the disease is often refractory to surgery and/or systemic treatment. Advances in genetics and tumor biomarker recognition have led to the synthesis of novel biological agents for the treatment of metastatic melanoma. Nivolumab is one such agent and with an improved safety and efficacy profile over traditional therapy, it proves a promising development in the treatment of advanced melanoma.

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Skin Treatments Introduced in 2015

Type/Class of Therapy	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
Adipolytic Agent	**Deoxycholic acid injection** *Belkyra*™ (Canada) *Kybella*™ (US) Kythera Biopharmaceuticals	This first-in-class adipolytic agent was approved for treating moderate to severe submental fat. Deoxycholic acid (ATX-101) is indicated for the reduction of submental fat, which commonly presents as a double chin.	Health Canada US FDA
Actinic Keratosis	**5-fluorouracil 0.5% + salicylic acid 10% solution** *Actikerall*™ Cipher Pharmaceuticals	This topical antineoplastic agent was approved for the treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (Grade I/II) of the face, forehead and balding scalp in immunocompetent adult patients.	Health Canada
Anti-acne Agents	**Adapalene 0.3% + benzoyl peroxide 2.5% gel** *Epiduo® Forte* (US) *Tactupump Forte*™ (Canada) Galderma	Fixed combination adapalene 0.3% and benzoyl peroxide 2.5% gel was approved for the once-daily, topical treatment of acne vulgaris. This preparation is the first combination of these strengths of adapalene and benzoyl peroxide.	Health Canada US FDA
Antibacterial Agents	**Dalbavancin IV injection** *Dalvance*™ Durata Therapeutics	Dalbavancin, a novel second generation lipoglycopeptide antibiotic, was approved for the treatment of adults with skin infections. Treatment is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms.	European Commission (EU)
	Tedizolid phosphate tablets and IV injection *Sivextro*™ Cubist Pharmaceuticals	Tedizolid, a novel oxazolidinone-class antibacterial agent, was approved for the treatment of adult ABSSSI caused by susceptible Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).	Health Canada
Anti-cancer Agents	**Cobimetinib + vemurafenib** *Cotellic*™ + *Zelboraf*® Daiichi Sankyo Group Exelixis Genetech (Roche Group)	Approval was granted to cobimetinib (MEK-inhibitor) for use in combination with vemurafenib (BRAF-inhibitor) as an oral treatment for patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma.	European Commission Swissmedic (Switzerland) US FDA

Anti-cancer Agents *continued*	**Dabrafenib + trametinib** *Tafinlar® + Mekinist®* Novartis AG	Combination therapy with dabrafenib (Tafinlar®) + trametinib (Mekinist®) was approved to treat patients with BRAF V600E/K mutation-positive unresectable or metastatic melanoma as detected by an FDA-approved test.	US FDA
	Ipilimumab IV injection *Yervoy®* Bristol-Myers Squibb	This immune checkpoint inhibitor was approved for the additional indication of adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of >1 mm (Stage III) who have undergone complete resection including total lymphadenectomy.	US FDA
	Nivolumab IV infusion *Opdivo®* Bristol-Myers Squibb	This human programmed death receptor-1 (PD-1) blocking monoclonal antibody was approved to treat previously untreated cases of BRAF V600 wild-type unresectable or metastatic melanoma in adults.	European Commission Health Canada
	Nivolumab + ipilimumab *Opdivo® + Yervoy®* Bristol-Myers Squibb Company	Nivolumab in combination with ipilimumab was approved for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.	US FDA
	Pembrolizumab IV injection *Keytruda®* Merck & Co., Inc.	Pembrolizumab was approved for the treatment of unresectable or metastatic melanoma as first-line therapy and/or for previously treated patients. In December 2015, the FDA approved an expanded indication for pembrolizumab to include the first-line treatment of patients with advanced melanoma.	European Commission Health Canada MHRA (UK) US FDA
	Sonidegib phosphate capsules *Odomzo®* Novartis Pharmaceuticals	Sonidegib received approval to treat patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or who are not candidates for surgery or radiation therapy.	US FDA
	Talimogene laherparepvec (T-Vec) oncolytic virus therapy *Imlygic™* BioVex Inc/Amgen Inc.	The first viral-based cancer therapeutic was approved for treating melanoma lesions in the skin and lymph nodes that cannot be removed completely by surgery. Derived from HSV type 1 (cold sore virus), Imlygic® has been modified to replicate within tumors and produce the immune stimulatory protein human GM-CSF, resulting in the death of tumor cells through an anti-tumor immune response.	European Commission US FDA
Antiviral Agent	**Human papillomavirus 9-valent vaccine, recombinant** *Gardasil®9* Merck	This vaccine was approved for use in females 9 to 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and genital warts caused by HPV types 6 and 11. GARDASIL®9 is also approved for use in boys 9 to 15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. GARDASIL®9 includes the greatest number of HPV types in any available HPV vaccine. It was FDA-approved in 2014 for use in boys 9 to 15 years of age for the prevention of these diseases. The FDA approved an expanded age indication for GARDASIL®9 in December 2015 to include use in males 16 through 26 years of age.	Health Canada US FDA
Dermal Fillers	**Dermal filler with calcium hydroxylapatite (CaHA) + integral 0.3% lidocaine** *Radiesse® (+)* Merz	Approval was granted to Radiesse® (+), an injectable implant dermal filler that contains a small quantity of the local anesthetic lidocaine. Radiesse® (+) is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.	Health Canada US FDA

Dermal Fillers *continued*	**Dermal filler with calcium hydroxylapatite (CaHA)** *Radiesse®* Merz North America	This dermal filler was approved for hand augmentation to correct volume loss in the dorsum of the hands. Treatment provides an immediate volumizing effect and can help to reduce the prominence of tendons and veins.	US FDA
	Hyaluronic acid (HA) filler *Juvederm® Ultra XC* Allergan plc	Marketing approval was granted to this HA-based dermal filler for injection into the lips and perioral area for lip augmentation in adults >21 years of age.	US FDA
	HA gel injectable dermal filler *Restylane® Lyft with Lidocaine* Galderma	Market approval was granted to this injectable gel to increase volume and smooth wrinkles in the face of patients aged >21 years. Restylane® Lyft was formerly marketed as Perlane-L®.	US FDA
	Polymethylmethacrylate collagen dermal filler *Bellafill®* Suneva Medical, Inc.	Approval was granted to this dermal filler for the treatment of acne scars. Bellafill® is the only filler indicated for the correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients >21 years of age.	US FDA
Hidradenitis Suppurativa	**Adalimumab SC injection** *Humira®* AbbVie Inc.	Approval was granted to this tumor necrosis factor-alpha (TNF-α) inhibitor for the treatment of moderate to severe hidradenitis suppurativa (acne inversa).	European Commission US FDA
Psoriasis	**Betamethasone valerate 0.1% patch** *Beteflam™* Cipher Pharmaceuticals	The Beteflam™ Patch is a novel, self-adhesive medicated plaster, containing 0.1% betamethasone valerate, approved for the treatment of inflammatory skin conditions such as chronic plaque psoriasis.	Health Canada
	Calcipotriene 0.005% + betamethasone dipropionate 0.064% foam *Enstilar®* LEO Pharma Inc.	A foam containing a fixed combination of calcipotriene and betamethasone dipropionate was approved for the topical treatment of plaque psoriasis in adults 18 years of age and older. This once-daily, alcohol-free foam formulation in a pressurized spray allows application across large body areas of plaque psoriasis.	US FDA
	Secukinumab SC injection *Consentyx™* Novartis Pharmaceuticals	Approval was granted to secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy, or a combination of both. Secukinumab is a fully human monoclonal antibody that inhibits the proinflammatory cytokine interleukin 17A (IL-17A).	Health Canada European Commission US FDA
Psoriatic Arthritis	**Apremilast tablets** *Otezla®* Celgene Corporation	An expanded indication for psoriatic arthritis was granted to apremilast, an oral phosphodiesterase-4 inhibitor, which was initially approved in November 2014 for moderate to severe plaque psoriasis.	Health Canada
Rosacea	**Azelaic acid 15% foam** *Finacea® Foam* Bayer HealthCare	Azelaic acid 15% foam was approved for the topical treatment of the inflammatory papules and pustules of mild to moderate rosacea.	US FDA
	Ivermectin 1% cream *Rosiver®* Galderma Canada Inc.	Ivermectin 1% cream was approved for the once-daily topical treatment of inflammatory lesions, or bumps and pimples, of rosacea. Ivermectin has both anti-inflammatory and antiparasitic effects.	Health Canada
Varicose Veins	**Polidocanol 1% injectable foam** *Varithena®* BTG plc	Polidocanol injectable foam was approved for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein (GSV) system, above and below the knee.	Health Canada
	Varicose vein procedure with n-butyl-2-cyanoacrylate adhesive polymer *VenaSeal™ Closure System* Covidien LLC/Medtronic	Approval was granted to the first adhesive varicose vein treatment. VenaSeal™ closure system is the only non-tumescent, non-thermal, non-sclerosant procedure to permanently treat varicose veins of the legs by sealing the affected superficial veins using an adhesive agent.	US FDA

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Update on Drugs

Name/Company	Approval Dates/Comments
Betamethasone valerate topical patch *Beteflam™* Cipher Pharmaceuticals	In December 2015, Health Canada approved a betamethasone valerate topical patch for the treatment of mild to moderate plaque psoriasis of the elbows and knees for a maximum duration of 30 days in adult patients. This novel self-adhesive medicated plaster contains 0.1% betamethasone valerate. The patch is applied once-daily to the affected region.
Human papillomavirus (HPV) 9-valent vaccine, recombinant *Gardasil®9* Merck	The US FDA approved an expanded age indication for GARDASIL®9 in December 2015 to include use in males 16 to 26 years of age, for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. GARDASIL®9 is already approved for use in boys 9 to 15 years of age for the prevention of these diseases.
Talimogene laherparepvec (T-Vec) intralesional injection *Imlygic®* Amgen Inc.	The European Commission (EC) approved talimogene laherparepvec (the first viral-based cancer therapeutic) in December 2015 for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a), with no bone, brain, lung or other visceral disease.
Pembrolizumab IV injection *Keytruda®* Merck & Co., Inc.	The FDA approved an expanded indication for pembrolizumab (anti-PD-1 programmed death receptor-1) therapy in December 2015 to include the first-line treatment of patients with unresectable or metastatic melanoma. This approval marks the second FDA-approved indication in advanced melanoma for Keytruda®, which is now the first anti-PD-1 therapy approved for previously untreated advanced melanoma patients regardless of BRAF status.
Adalimumab SC injection *Humira®* AbbVie Inc.	Health Canada approved adalimumab in January 2016 for the treatment of adults with active moderate to severe hidradenitis suppurativa (acne inversa), who have not responded to conventional therapy, including systemic antibiotics.
Secukinumab SC injection *Cosentyx®* Novartis AG	In January 2016, the FDA expanded its approval of secukinumab to include two new indications – the treatment of adult patients with active psoriatic arthritis and active ankylosing spondylitis. Secukinumab is a monoclonal antibody that inhibits IL-17A – elevated levels of this cytokine are associated with inflammatory diseases.
Ustekinumab SC injection *Stelara®* Janssen Inc.	In January 2016, Health Canada approved ustekinumab, a fully human interleukin (IL)-12 and IL-23 antagonist, for the treatment of chronic moderate to severe plaque psoriasis in adolescent patients aged 12 to 17 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. This marks the first biologic to gain regulatory approval for the treatment of moderate to severe psoriasis in adolescents.
Nivolumab + ipilimumab *Opdivo® + Yervoy®* Bristol-Myers Squibb Company	In January 2016, expanded FDA approval was granted to nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma. This approval expands the original indication for the Opdivo® + Yervoy® regimen for treating patients with BRAF V600 wild-type unresectable or metastatic melanoma to include patients regardless of BRAF mutational status.

Erratum: Due to an editing error, the incorrect US FDA approval date of November 2016 for dabrafenib + trametinib (Tafinlar® + Mekinist®, Novartis AG) was inadvertently published in *Skin Therapy Letter* 2016 Jan-Feb;21(1):12. The correct approval date is November 2015. The publisher apologizes for any inconvenience.