MSK PROTOCOL COVER SHEET

Phase II Study of IL-5-receptor-alpha-chain (IL-5Ra) Inhibition With Benralizumab for Eosinophil-Related Cutaneous Adverse Events in Cancer Patients

Principal Investigator/Department: Alina Markova/Medicine

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-center, single-arm phase II study to evaluate the efficacy and safety of the anti-IL-5Rα chimeric monoclonal antibody benralizumab for the treatment of eosinophil-related cutaneous adverse events (ercAEs) resulting from immunotherapies or targeted therapies. Forty eight (48) patients will be enrolled and the estimated time to completion is 2 years. The primary endpoint for the study is the percent reduction in CTCAE grade 2/3 eosinophil-related cutaneous adverse events to grade ≤1. Eosinophil-related cutaneous adverse events are defined as maculopapular rash, pruritus/urticaria, bullous pemphigoid, or DRESS syndrome that are associated with blood eosinophil counts of at least .3 K/mcl. Secondary endpoints are safety and tolerability of benralizumab, calculated rash body surface area (BSA), relative dose intensity (RDI) of anticancer therapy, measurement of patient-reported quality of life, the ability to continue anticancer agents, effects on corticosteroid naïve and dependent/refractory ercAEs, the need for additional supportive care interventions (i.e. corticosteroids, antihistamines), and reduction in blood and skin eosinophils. An exploratory endpoint is analyzing eosinophils and Th2 immune pathway blood biomarkers (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, tryptase) that correlate with benralizumab efficacy. Patients with a diagnosis of solid or hematologic cancers undergoing treatment with checkpoint inhibitors (CPIs) or targeted therapies with a grade 2/3 cutaneous adverse associated with blood eosinophil counts of at least .3 K/mcl will be treated with benralizumab 30mg once every 4 weeks for the first 3 doses (Week 0/Day 1, Week 4/Day 28, and Week 8/Day 56), followed by once every 8 weeks for 3 additional doses (Week 16/Day 112, Week 24/Day 168, and Week 32/Day 224). CTCAE v5.0 ercAE assessments will be done at baseline and then at Week 2/Day14, Week 4/Day 28, and Week 8/Day 56, Week 16/Day 112, Week 24/Day 168, Week 32/Day 224 and 4 weeks post-last dose. Patients may remain on study until ercAE progression or unacceptable toxicity from benralizumab for up to 32 weeks.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives

- To evaluate the percent reduction in CTCAE grade 2/3 eosinophil-related cutaneous adverse events to grade ≤1 resulting from checkpoint inhibitors (CPIs) or targeted therapies with absolute blood eosinophil counts of at least .3 K/mcl.

Secondary objectives

- To investigate changes in adverse event-related quality of life using patient-reported questionnaires (PRO-CTCAE, Skindex 16).
- To investigate the safety/tolerability of benralizumab in patients with eosinophil-related cutaneous adverse events.
- To investigate the need for supportive medications (corticosteroids, antihistamines, immunosuppressants) in patients treated with benralizumab.
- To investigate the effect of benralizumab on subsequent planned cycles of checkpoint inhibitors (CPIs), or targeted therapies.
- To compare the effect of benralizumab on corticosteroid naïve and corticosteroid dependent/refractory ercAEs.

- To correlate the percent reduction in blood absolute eosinophil numbers and skin histology with clinical response to benralizumab.
- To investigate change in body surface area (BSA) of ercAE to quantify change in affected area in response to benralizumab over time.
- To investigate relative dose intensity (RDI) and compliance of patients' culprit anticancer therapy for the duration of the trial.

Exploratory objectives

- To discover changes in blood biomarkers (IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, tryptase) that correlate with response to benralizumab.

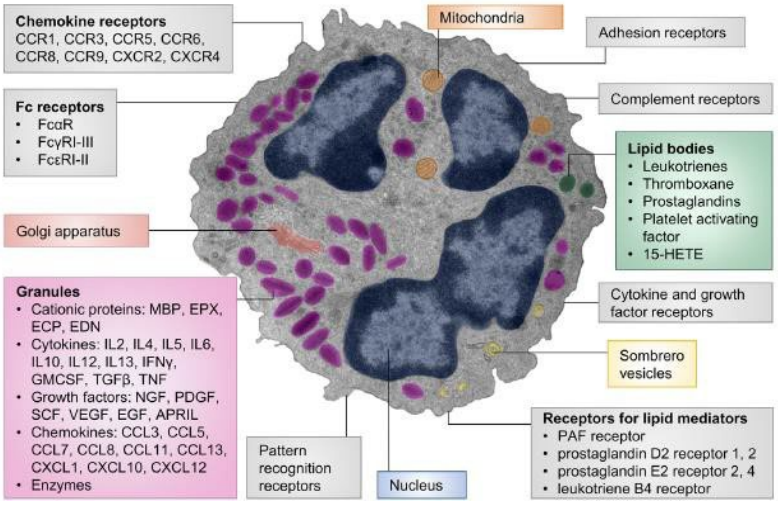
3.0 BACKGROUND AND RATIONALE

Background on eosinophil related cutaneous adverse events

In areas where helminth exposure is uncommon, medication-related drug reactions are a common cause of peripheral and blood eosinophilia (Ramirez and Frias, British Pharmacol Soc 2017). In the absence of systemic involvement, this condition generally constitutes a drug effect that can be caused by a myriad of medication classes, such as penicillin and sulphonamide drugs, and resolves upon drug discontinuation (Khoury and Bochner, JACIP 2018). In the oncology setting, eosinophil-related cutaneous adverse events (ercAEs) are also frequent (10-20%) (Fischer et al, Am J Dermatopathol 2015; Lucas-Truyols et al, Acta Dermosiligrof 2017; Fujisawa et al, J Dermatol Sci 2017), but their impact is greater: they result in interruption or discontinuation of life-prolonging antineoplastic agents, negatively affect a patient's quality of life, may affect other organs (i.e. liver and kidneys as part of the Drug Rash with Eosinophilia and Systemic Symptoms (Cho et al, Int J Mol Sci 2017)), and usually require treatment with corticosteroids which carry their own set of toxicities in an already vulnerable patient population. Indeed, in oncology drug development trials, dermatologic toxicities are a dose-limiting toxicity in 2.4% of cases (Drilon et al, Cancer 2016). There are no FDA approved therapies for ercAEs, and whereas off-label use of corticosteroids and interruption of the offending agent may be effective in most patients, there are no additional therapeutic options for patients with corticosteroid dependent/refractory ercAEs.

Possible eosinophil effects in cutaneous adverse events.

- **Damage of tissues by cytotoxic granule proteins**
- **Antibody-dependent cellular cytotoxicity**
- **Activation of tissue remodeling and fibrosis**
- **Antigen presentation**
- **Modulation of the adaptive immune response**
- **Promotion of B cell**



responses

- **Induction of tissue repair processes**

Abundant clinical data suggests that eosinophils play a pivotal role in cancer and cutaneous reactions to anticancer therapies (Davis and Rothemberg, Cancer Immunol Res 2014; Tracey et al, Am J Dermatopathol 2017; Sakkal and Miller, Curr Med Chem 2016; Roufousse 2015; Blank et al, Eur J Pharmacol 2016)). Indeed, between 1/1/2015 and 3/11/2019 there were 2652 patients evaluated by the dermatology service at MSKCC with skin conditions and associated eosinophilia (MEL, unpublished data). Of these, 584 patients were receiving immunotherapies, and the remaining were receiving other drugs including cytotoxic chemotherapy, targeted therapies, or supportive care drugs. Therefore, eosinophils represent an attractive target for the treatment of immune—related adverse events (irAEs), as they have been reported in biopsy samples from skin, gut, and lungs in patients treated with immune checkpoint inhibitors (CPIs) developing rash, colitis, and pneumonitisin the majority of patients with drug reactions (Kizawa et al, J Clin Oncol 2019; Occhipinti et al, Drug Saf Case 2018; Furubayashi et al, Mol Clin Oncol. 2019; Georgianos et al, Case Rep Nephrol 2019). In an analysis of 267 inpatients with ercAEs by any type of drug, 16.5% resulted in oncology patients, with 8.6% harboring an active cancer diagnosis, and the culprit being an antineoplastic agent in 11 of 154 drugs (7.1%) (Ramirez et al, Br J Clin Pharmacol 2017). In addition, high eosinophil and eosinophil-related cytokines (eotaxin-1, IL-9, TARC, IL-4) in blood have been associated with irAEs in melanoma patients treated with immune checkpoint inhibitors (ICIs) (Fujisawa et al, J Dermatol Sci 2017). Eosinophils are also well-known mediators of severe drug reactions in the non-cancer population, most notably maculopapular rashes (Kardaun et al, Br J Dermatol 2007). These are classified as Type 4 (Gell and Coombs) reactions and the immune mediators are Th2 cells and IL-4/13 and IL-5, with eosinophils playing a major role (Ramirez et al, Biomed Res Int 2018).

Many of these reactions involve only the skin but some patients manifest systemic features including fever, eosinophilia, lymphadenopathy and organ dysfunction which may principally affect the liver, bone marrow and/or kidneys (Cho et al, Int J Mol Sci 2017). The combination of a widespread eruption with systemic dysfunction is termed DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) or DIHS (Drug-Induced Hypersensitivity Syndrome). Eosinophilia is part of the RegiSCAR diagnostic criteria for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS/DIHS). There is now the realization that patients with DRESS often develop a worsening of the clinical picture after the initial reaction starts resolving. There may be recurrence of fever, either a leukocytosis or lymphopenia and deterioration of organ function. This is due to reactivation of members of the herpes virus family, HHV6 and HHV7 in particular, but EBV and/or CMV as well. Higher eosinophil counts correlated with poor liver function, extended hospitalization, and prolonged corticosteroid use in patients with EM–type, urticaria-like, and morbilliform drug eruptions. In addition, CPI lead to eosinophil-mediated cutaneous irAE that impact QoL and ability of patients to receive life prolonging or saving therapies (Phillips et al, J Clin Oncol 2019).
In a broad evaluation of non-cancer inpatient adverse cutaneous drug reactions, only 18% had peripheral eosinophilia (>300 × 10^6 cells l^{-1}). Eosinophil related cutaneous adverse events (ercAEs) have been described as a type IVb reaction, which involves a Th2-mediated immune response with secretion of IL-4, IL-13, and IL-5. IL-5 is known to be the key factor in regulating the growth, differentiation, and activation of eosinophils. Eosinophil activity is also

augmented by Th1 cytokines, including IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). There are numerous types of ercAE, ranging from benign, asymptomatic eosinophilia to potentially fatal reactions resulting in organ damage, such as drug reaction with eosinophilia and systemic symptoms (DRESS). The extent of clinical involvement is also heterogeneous, ranging from isolated peripheral eosinophilia or single organ involvement (lung, kidney, liver) with skin being the most common, to systemic disease affecting multiple organs, classically exemplified by drug reaction with eosinophilia and systemic symptoms (DRESS). Previous *in vivo* and *in vitro* data indicate that eosinophils are particularly involved in patients with DRESS syndrome. DRESS is a distinctive reaction, first described during treatment with anticonvulsant drugs (most commonly carbamazepine), and subsequently with a multitude of medication classes. However, antiepileptic medications remain the predominant cause of DRESS, with an incidence of 1 per 5000 to 10,000 exposures.

The actual definition of DRESS was proposed by Bocquet *et al.* in 1996 and updated in 2007 by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) Study Group. DRESS syndrome diagnosis is complex due to the wide variety of signs and symptoms not all present at the same time in the patient. The phenotype of the skin is imprecise; the most common presentation is polymorphous maculopapular (85%); however, monomorphic (15%), pustules (30%), and purpura (26%) also occur. Hypereosinophilia was present in 95% of cases. Other haematological manifestations were atypical lymphocytes (67%) and lymphadenopathy (54%). Internal organ involvement has been reported in 91% of cases, primarily due to hepatic injury (elevation of liver function tests or hepatomegaly). Other frequent symptoms were high fever (90%) and mild mucosal involvement (56%). The pathogenesis is unclear, but is most likely to involve several aspects, including a network of drug metabolites, specific HLA alleles, herpes viruses (EBV, HHV-6, HHV-7, or CMV), and immune system activation. Patients with high peripheral blood eosinophilia had poorer liver function, prolongation of hospitalization, and higher cumulative doses of corticosteroids. Eosinophil count in patients with an erythema multiforme-type drug eruption was associated with severe disease. In the RegiSCAR scoring system for the diagnosis of DRESS, the score increases with the degree of eosinophilia from one point if eosinophilia is between 700 and 1499 × 10^6 cells l^{-1}, to two points if eosinophilia is $\geq$1500 × 10^6 cells l^{-1}. The spectrum of eosinophilic drug reactions and the classes of medication associated with peripheral eosinophilia are expanding. Half (53.3%, 64/120 cases) of symptomatic eosinophilic drug reactions are potential DRESS cases, with higher numbers of cases during hospitalization than in the community. Higher eosinophil counts in patients with DRESS are significantly associated with greater impairment of liver function, prolonged hospitalization, and higher cumulative doses of corticosteroids.

In absence of other systemic involvement, isolated peripheral blood eosinophilia is a benign drug effect that can be caused by a myriad of medication classes. It might be a direct physiologic effect of certain cytokine or immune therapies (PD 1/L1 inhibitors, IL2, GM-CSF) secondary to expansion of IL-5-producing T cells; however, the mechanisms underlying most instances of drug-related eosinophilia have not been elucidated. Asymptomatic eosinophilia by drugs is more frequently observed than symptomatic eosinophilia. Among symptomatic eosinophilia cases, the most frequent cause was DRESS (64 cases, 53%), followed by eosinophilia with only dermatological symptoms (36 cases, 30%), and then with visceral involvement (19 cases, 16%). Substantial tissue damage is unlikely to occur with a low

eosinophil count, and expert opinion supports that isolated eosinophilia must be monitored; withdrawal of any drug that is not crucial for the patient is recommended, which is problematic in the oncology setting. Drug-induced eosinophilia, however, frequently prompts clinical concern regarding impending organ involvement. Data have shown that the development of symptoms after eosinophilia onset was more likely with earlier onset of eosinophilia, higher eosinophil count, and a delayed onset of corticosteroids. In a prospective cohort study of 824 patients receiving prolonged intravenous antibiotic therapy as outpatients, patients with eosinophilia had a significantly higher likelihood of rash (adjusted HR, 4.16; 95% CI: 2.54–6.83) or renal injury (HR, 2.13; 95% CI: 1.36–3.33), compared with the patients without eosinophilia. However, DRESS syndrome only occurred in seven patients (Blumenthal et al, JACI 2015). Data support that DRESS syndrome can occur at a higher frequency than previously reported in the drug-induced eosinophilia literature.

Targeting ercAEs with benralizumab would represent a paradigm shift, as adverse events would be amenable to prophylactic (if very frequent or in populations at risk) and effective reactive therapies, precluding the need for immunotherapy dose interruptions or discontinuations, while maintaining quality of life and efficacy. There is precedent for this concept, as the tumor necrosis α (TNF) inhibitor infliximab is recommended for the treatment of ICI-related colitis and the IL-6 inhibitor tocilizumab has been approved for the treatment of cytokine release syndrome related to chimeric antigen receptor T (CAR-T) therapies in cancer (Buder-Bakhaya et al, Front Immunol 2018). At MSKCC we have reported the efficacy of agents targeting IL12/23, IL4/13, CD20, and IgE in patients treated with cutaneous AEs related to immunotherapies, which has allowed continued administration of the culprit medication (Phillips et al, J Clin Oncol 2019).

Benralizumab

Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa) indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Besides linking IL-5R*α* through its Fab regions, benralizumab also binds via the constant Fc fragment to the Fc*γ*RIIIa receptor, located on cell membrane of natural killer (NK) cells. In this regard, it is worth noting that benralizumab was developed in Chinese hamster ovary cells not expressing the *α*-1,6-fucosyltransferase enzyme. As a consequence, lack of the fucose molecule in the sugar component of the CH2 domain of the constant segment of the monoclonal antibody is responsible for a remarkable enhancement (5 to 50 times) of benralizumab affinity for the Fc*γ*RIIIa receptor of NK cells. In particular, with regard to the original fucosylated antibody, afucosylation makes benralizumab capable of inducing a ≥1000-fold amplification of the apoptotic mechanism named antibody-dependent cell-mediated cytotoxicity (ADCC). Indeed, benralizumab is a potent inducer of eosinophil apoptosis operated by NK cells

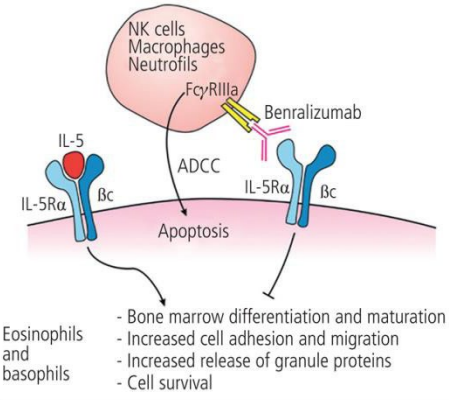


Figure. Mechanism of action of benralizumab

through the release of the proapoptotic proteins perforin and granzyme B. Afucosylation-dependent ADCC has also been demonstrated by benralizumab-induced increase in eosinophil staining with annexin V, a well-known biomarker of apoptosis.

It can thus be argued that benralizumab is capable of killing eosinophils via a dual mechanism: the blockade of IL-5-mediated survival of these cells and the enhancement of eosinophil apoptosis induced by activation of the FcγRIIIa receptor of NK cells. By acting via such very powerful modalities, benralizumab rapidly and effectively depletes eosinophils in patients with asthma, thereby drastically reducing cell counts in both airways and peripheral blood. Benralizumab was recently approved by US FDA for the add-on biological therapy of severe eosinophilic asthma. A meta-analysis referring to 1951 subjects with eosinophilic asthma, enrolled in several different phase 1, 2, and 3 randomized controlled trials, demonstrated that, when compared to placebo, benralizumab induced significant score improvements of asthma control questionnaire-6 (ACQ-6) and asthma quality of life questionnaire (AQLQ) and enhanced Forced expiratory volume (FEV_1)and also decreased the annual rate of disease exacerbations.

In the 52-week Phase 2 dose-ranging trial, asthma patients received 1 of 3 doses of benralizumab [2 mg (n=81), 20 mg (n=81), or 100 mg (n=222)] or placebo (n=222). All doses were administered every 4 weeks for the first 3 doses, followed by every 8 weeks thereafter. Median blood eosinophil levels at baseline were 310, 280, 190 cells/μL in the 2, 20, and 100 mg benralizumab and placebo groups, respectively. Dose-dependent reductions in blood eosinophils were observed. At the time of the last dose (Week 40), median blood eosinophil counts were 100, 50, 40, 170 cells/μL in the 2, 20, and 100 mg benralizumab and placebo groups, respectively.

A reduction in blood eosinophil counts was observed 24 hours post dosing in a Phase 2 trial. In Trials 1 and 2, following subcutaneous (SC) administration of benralizumab at the recommended dose blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/μL. This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period.

Treatment with benralizumab was also associated with reductions in blood basophils, which was consistently observed across all clinical studies. In the Phase 2 dose-ranging trial, blood basophil counts were measured by flow cytometry. Median blood basophil counts were 45, 52, 46, and 40 cells/μL in the 2 mg, 20 mg and 100 mg benralizumab and placebo groups, respectively. At 52 weeks (12 weeks after the last dose), median blood basophil counts were 42, 18, 17, and 46 cells/μL in the 2 mg, 20 mg and 100 mg benralizumab and placebo groups, respectively.

Benralizumab and placebo induced similar patterns of adverse effects. Benralizumab was characterized by a good safety profile. In fact, only mild-to-moderate and self-limiting adverse reactions occurred, such as cough, bronchitis, fever, headache, muscle spasms, dizziness, hyperhidrosis, and anxiety. After 12 weeks of treatment, anti-benralizumab antibodies were found in 6 patients, but no clinical consequence was reported. In 18 patients with severe eosinophilic and corticosteroid-dependent asthma showed that 30 mg of benralizumab,

administered subcutaneously every 4 or 8 weeks, when compared to placebo, significantly decreased the counts of mature eosinophils in both blood and induced sputum. In blood, benralizumab also significantly reduced the number of eosinophil progenitors. A similar result was also detected in induced sputum, where, however, this effect of benralizumab did not reach the threshold of statistical significance, probably because of the small number of matched data sets. Moreover, in blood, benralizumab significantly lowered the number of ILC2 cells expressing IL-5R*α*, and a similar effect was also observed in induced sputum, where, however, only a trend, and not a significant difference, was found. Serum eosinophil derived neurotoxins (EDN) concentrations were also significantly diminished by benralizumab. In addition, benralizumab significantly increased the levels of granzyme B and interferon-*γ* in cell-free sputum supernatants. Therefore, the latter findings suggest that benralizumab was able to stimulate the activity of NK cells. All these biological effects of benralizumab were paralleled by relevant clinical and functional improvements, including a decrease in the maintenance dosage of oral corticosteroids, a better asthma control, and an increased ratio of prebronchodilator FEV_1 to FVC (forced vital capacity). In particular, because of its very effective action as IL-5R*α* antagonist, benralizumab has been shown to be capable of significantly inhibiting eosinophil differentiation in the bone marrow, as well as eosinophilic infiltration of airways. These eosinopenic effects are further potentiated by ADCC-mediated eosinophil apoptosis, operated by NK cells, and stimulated by benralizumab. At clinical and functional levels, such a dual mechanism of action of benralizumab translates into relevant improvements, including a significant decrease of asthma exacerbations, a better symptom control, a marked sparing effect on the intake of oral corticosteroids, and an important attenuation of airflow limitation. All these features, associated with a very good safety and tolerability profile, make benralizumab a valuable therapeutic option for add-on biological treatment of severe eosinophilic asthma. These effects were associated with drastic reductions in blood eosinophil counts and also in serum concentrations of the eosinophilic cytotoxic proteins ECP and EDN. Benralizumab is currently being investigated for other indications in which eosinophils play a major role, such as atopic dermatitis, eosinophilic gastritis, esophagitis, polyposis, rhinosinusitis, granulomatosis with polyangiitis, and hypereosinophilic syndrome. Based on the implication of eosinophils in cancer therapy-related cutaneous events, there is a strong rationale for its use in this setting. Interestingly, a 71 year old patient treated with the PD-L1 inhibitor pembrolizumab and worsening asthma associated with eosinophilia was treated with benralizumab. In 2 days there was resolution of asthma attacks and cough, and peak flow increased, along with a marked reduction in eosinophils, and tumor response to pembrolizumab was maintained (Izumo et al, 2019)

PIK3CA-Related Overgrowth Spectrum disorder

On April 5, 2022, the Food and Drug Administration granted accelerated approval to alpelisib for adult and pediatric patients two years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy.

In a retrospective study, approximately 50% of metastatic breast cancer patients receiving alpelisib develop dermatologic adverse events with associated peripheral eosinophilia (Wang et al, 2020).

Based on this new FDA-approved indication for alpelisib and the high incidence rate of alpelisib dermatologic adverse events with associated peripheral eosinophilia, benralizumab may provide benefit for this non-cancer patient population.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm phase II study of patients with grade 2/3 eosinophil-related cutaneous adverse events treated with benralizumab. The primary objective is to determine the reduction of 2/3 ercAEs to grade ≤1. Secondary endpoints are reduction in blood and skin eosinophils and its association with response, safety/tolerability of benralizumab, impact on quality of life, concomitant supportive medications, calculated rash body surface area (BSA), relative dose intensity (RDI) of anticancer therapy, and ability to continue anticancer therapy. An exploratory endpoint is analyzing blood biomarkers that correlate with benralizumab efficacy.

4.2 Intervention

All eligible patients will receive a benralizumab dose of 30 mg SC administered by a healthcare provider once every 4 weeks for the first 3 doses, followed by once every 8 weeks for 3 additional doses. This is the approved dose and schedule for eosinophilic asthma. Eosinophil-related cutaneous AE assessments will be conducted at baseline, Week 0/Day 1 (+/-3), Week 2/Day 14 (+/-3), Week 4/Day 28 (+/-3), and Week 8/Day 56 (+/-3) using CTCAE v5.0. Patients may remain on study until progression of ercAE or unacceptable toxicity from benralizumab. Patients will continue receiving the investigational agent for up to 32 weeks (6 doses).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

Benralizumab is a humanized recombinant monoclonal antibody of the isotype IgG1k immunoglobulin that specifically binds to the alpha chain of the interleukin 5 receptor (IL-5R) with a dissociation constant of 11 pM. The IL-5 receptor is expressed on the surface of eosinophils and basophils. Benralizumab inhibits the binding of IL-5 as well as the hetero-oligomerization of the alpha and beta subunits of the IL-5R, thus blocking, signal transduction. In an in vitro setting, the absence of fucose in the Fc domain of benralizumab facilitates binding (45.5 nM) to FcγRIII receptors on immune effectors cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC).

Benralizumab is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection. Since benralizumab is a protein, a few translucent or white to off-white particles may be present in the solution. The protein chemical formula is $C_{6492}H_{10060}N_{1724}O_{2028}S_{42;}$ with a protein average weight of 146054.0 Da. Benralizumab should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended.

Benralizumab, FDA approved on November 14, 2017, was developed by MedImmune, AstraZeneca's global biologic research and development arm. Benralizumab is provided as a 30 mg/mL solution in a single-dose prefilled syringe, provided by AstraZeneca Pharmaceuticals LP (NDC Code(s): 0310-1730-30, 0310-1730-85). Each single-dose prefilled syringe delivers 1 mL containing 30 mg benralizumab, L-histidine (1.4 mg); L-histidine hydrochloride monohydrate (2.3 mg); polysorbate 20 (0.06 mg); α,α-trehalose dihydrate (95 mg); and Water for Injection, USP. The single-dose prefilled syringe contains a 1 mL glass syringe with a staked 29 gauge ½ inch stainless steel needle. It needs to be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

- Patients must have pathologically or cytologically confirmed solid or hematologic cancers.
  OR
- Patient is receiving alpelisib for PIK3CA-Related Overgrowth Spectrum disorder.
- Female and male aged 18 to 85 years, inclusively, at the time of Week 0/Day 1 of treatment.
- Patients must have a therapy-related CTCAE grade 2/3 (See Appendix A) cutaneous adverse event defined as any cutaneous reaction listed below and blood eosinophil counts of at least .3 K/mcl.
  - Rash maculo-papular
  - Bullous dermatitis
  - Pruritus
  - Urticaria
  - Eczema
- Patients must plan to continue on culprit drugs (cancer patients).
- Patients planning to receive alpelisib indicated for PIK3CA-Related Overgrowth Spectrum disorder OR patients receiving immunotherapy and/or targeted therapy, including but not limited to the following agents, will be eligible for inclusion:
  - Immunotherapies: ipilimumab, nivolumab, pembrolizumab, avelumab, durvalumab, atezolizumab tremelimumab.
  - Targeted therapies: trastuzumab, pertuzumab, alpelisib, osimertinib, everolimus, temsirolimus, sorafenib, regorafenib.
- Patients using topicals/orals for indication of skin rash/pruritus for at least 7 days should continue using these drugs for the study duration.
- Adequate bone marrow, liver and renal function:
  - Total bilirubin ≤ 1.5 x the upper limit of normal (ULN)
  - Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
  - Alkaline phosphatase ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
  - Serum creatinine ≤ 1.8 xULN or calculated creatinine clearance >45 ml/min

  - Platelet count > 50 K/mcL , hemoglobin (Hb) > 8 g/dL, absolute neutrophil count (ANC) >1.0 K/mcL. Blood transfusion to meet the inclusion criteria will not be allowed.
- ECOG performance status 0-1 (see Appendix C).
- Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
- Female patients are authorized to participate if they meet the following criteria:
  - Women of child bearing potential must meet both of the following conditions:
    - Have a negative serum pregnancy test prior to enrollment and within 14 days prior to administration of the investigational product (IP).
    - Patient must use an effective form of birth control (confirmed by the Investigator) throughout the study duration and within 16 weeks after last dose of IP.
  - Female subjects who cannot bear children as evidenced by one or more of the following:
    - Bilateral Oophorectomy
    - Bilateral Salpingectomy
    - Bilateral Salpingectomy-Oophorectomy
    - Hysterectomy
    - Menopause (no menses ≥ 1 year prior to treatment)
    - Surgical Sterilization (i.e., tubal ligation or blockage)

    Note: If criteria not met, patient should be regarded as having child bearing potential

- Subject must be able to receive a subcutaneous injection.
- New/worsening ercAE within 90 days prior to study enrollment. Note: This assessment will be performed by the treating investigator.

6.2 Participant Exclusion Criteria

- Concurrent use of another investigational drug or device for the ercAE (i.e., outside of study treatment) during, or within 4 weeks of treatment.
- Patients receiving prednisone ≥20mg a day.
- Known use of anti-IL-5 agents or biologics for the treatment of asthma which are known to decrease blood eosinophil levels.
- Patients cannot use new topicals or medications for indication of pruritus or skin rash
- Known history of anaphylaxis to biologic therapy
- A helminthic parasitic infection diagnosed within 24 weeks prior to the first treatment, that had not been treated with, or has failed to respond to, standard of care therapy.
- Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
- Active infection that would impair the ability of the patient to receive study treatment.
- Women who are pregnant or breast-feeding.

- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Receipt of live attenuated vaccines 30 days prior to the date of randomization
    - Receipt of inactive/killed vaccinations (e.g., inactive influenza) is allowed provided they were not administered within 1 week before/after any investigational product administration.
- Known history of allergy or reaction to the investigational product formulation

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. Patient recruitment most likely will occur in the medical oncology and dermatology clinics. If the investigator is a member of the treatment team, s/he will screen their patients' medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Investigators will discuss the study and review/sign the informed consent documents with the patient.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent

Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

Not applicable

8.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

The following assessments need to be preformed within the below timelines:

<u>Within 45 days of treatment start:</u>

- Signed Informed Consent Form

<u>Within 30 days of treatment start:</u>

- Skin biopsy per SOC

Prior to registration and within 14 days of treatment start:

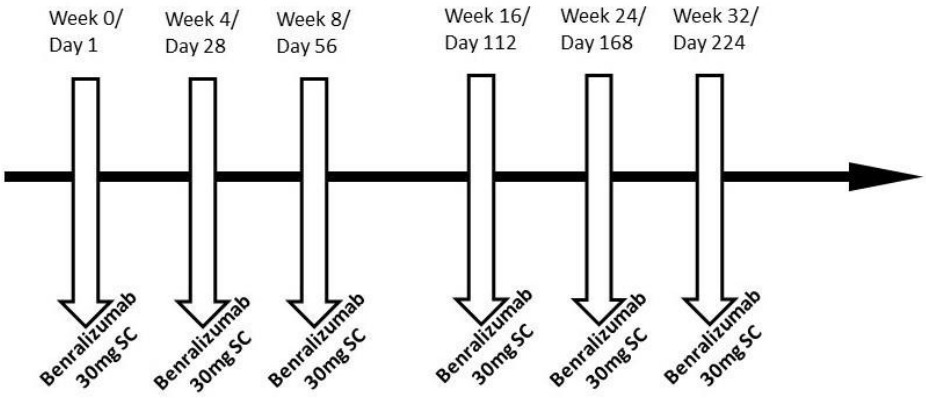
- Serum pregnancy test for women of child-bearing potential

On day -7 to -1:

- Medical history
- Demographics
- Physical Examination and vital signs, including heart rate, blood pressure, weight, and temperature
- Skin exam
- Concomitant medication review
- ECOG performance status
- CBC with differential
- Comprehensive Metabolic Panel, including Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium
- Phosphorus

10.0 TREATMENT/INTERVENTION PLAN

- Benralizumab 30mg as a subcutaneous injection will be administered by a healthcare professional at once every 4 weeks for the first 3 doses (Week 0/Day 1, Week 4/Day 28, and Week 8/Day 56), followed by once every 8 weeks for 3 additional doses (Week 16/Day 112, Week 24/Day 168, and Week 32/Day 224), per the labeling instructions.



- Patients will also have a comprehensive physical examination at Week 0/Day 1
- Skin examination prior to benralizumab administration will be completed at Week 0/Day 1, Week 4/Day 28, Week 8/Day 56).

- Phlebotomy for CBC w differential at every visit (Screening, Week 0/Day 1, Week 2/Day 14, Week 4/Day 28, Week 8/Day 56, Week 16/Day 112, Week 24/Day 168, Week 32/Day 224, and 4 Weeks post-last dose).
- Total body photography at Screening, Week 0/Day 1, Week 4/Day 28, Week 8/Day 56,.
- Research blood collection for biomarker analysis (MSD Panel and IL-5) on Week 0/Day 1, Week 4/Day 28 and Week 8/Day 56:
    - Approximately 10 mL of blood will be collected in a green top sodium heparin Vacutainer tube. This sample will be sent to the Immune Monitoring Facility (IMF).
    - Approximately 4 mL of blood will be collected in a lavender top tube (with EDTA). This sample will be sent to Mayo Clinic.

Missed doses will not be made up.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Study Procedures	Screening Visit (-7 days to Day 1)[5]	Week 0/ Day 1	Week 2/ Day 14 (+/- 3 days)	Week 4/ Day 28 (+/- 3 days)	Week 8/ Day 56 (+/- 3 days)	Week 16/ Day 112 (+/- 7 days)[4]	Week 24/ Day 168 (+/- 7 days)[4]	Week 32/ Day 224 (+/- 7 days)[4]	4 Weeks post-last dose (+/- 7 days)
Informed Consent	X[1]								
Demographics	X								
Medical history	X								
Concomitant medication review	X	X	X	X	X	X	X	X	X
Serum pregnancy test, per SOC and if applicable	X[2]								
Skin biopsy[3]	X			X					
CBC with differential	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel	X								
Physical exam and vital signs (HR, BP, weight, and temperature)	X								
Skin Exam (prior to Benralizumab administration)		X		X	X				
ECOG Performance Status (Appendix C)	X								
Total body photography	X	X		X	X				
Eosinophil-related Adverse Event Grading (CTCAE v5.0) (Appendix A)	X	X	X	X	X	X	X	X	X
Research blood collection for biomarker analysis (IL-5 & MSD Panel)		X		X	X				

Adverse event evaluation	X	X	X	X	X	X	X	X	X
Patient self-assessment (PRO-CTCAE (Appendix D) & Skindex 16 (Appendix B)	X	X	X	X	X	X	X	X	X
RegiSCAR Scoring System for Diagnosing DRESS Syndrome		X							
Benralizumab 30mg SC administration		X		X	X	X	X	X	

SOC, standard of care.

1. Informed consent within 45 days prior to treatment.
2. Serum pregnancy test for WOCBP within 14 days prior to treatment.
3. The baseline skin biopsy will be obtained within 30 days of treatment start, if applicable per standard of care. The biopsy at day 28 will be RNB if the patient's symptoms are improving.
4. Assessments will continue as long as the patient continues receiving benralizumab (up to 32 weeks). If a patient discontinues benralizumab, they will move to the 4 weeks post-last dose follow-up visit.
5. Screening and Week 0/Day 1 visits can be combined as long as comprehensive metabolic panel, CBC w/ differential, and pregnancy test (if applicable) are resulted to confirm eligibility prior to first benralizumab injection.

12.0 CRITERIA FOR REMOVAL FROM STUDY

- Patients may be removed from the study for protocol non-compliance with visits.
- If at any time the patient develops unacceptable toxicity he/she will be removed from study.
- Participants can be removed from the study at any time if the investigator considers that it is in their best interest to do so.
- Patients may withdraw consent from the study at any time.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

Please refer to Section 11.0 regarding the timing of ercAE assessments. Documentation (photographic) must be provided for patients removed from study for ercAE progression. Response and ercAE severity will be evaluated in this study using the Common Terminology Criteria for Adverse Events version 5.0. Changes in severity grade by specific skin/subcutaneous tissue AE term will be used.

13.1 Criteria for Therapeutic Response/Outcome Assessment

Evaluation of ercAE by CTCAE v5.0
Response (R): Grade 2 or 3 event reduction to grade 0 or 1.
Nonresponding AE (nrAE): Grade 2 or 3 event that does not reduce to grade 0 or 1.
Progressive AE (pAE): Grade 2 event that increases by ≥1 grade in severity.

13.2 Criteria for Study Endpoint Evaluability

Patients who are removed from the study prior to starting Benralizumab will be considered inevaluable and replaced. Patients who receive at least one dose of Benralizumab will be included in the evaluation of the primary objective if they have a post-therapy documented clinical response. Patients who progress and are placed on agents instead of or in addition to the culprit agents will be removed from the study. Patients who receive steroids at doses greater than prednisone 20mg a day or equivalent or other immunosuppressive agents to manage additional irAEs will be considered a failure for the primary endpoint.

14.0 BIOSTATISTICS

This is a single-center single-arm phase II study to evaluate the efficacy and safety of benralizumab for the treatment of eosinophil-related cutaneous adverse events (ercAE) in patients having grade 2/3 ercAE to various treatments (such as checkpoint inhibitors ortargeted therapies) with blood eosinophil counts of at least .3 K/mcL.

The primary endpoint of efficacy is defined as the proportion of patients who have a reduction from CTCAE grade 2/3 eosinophil-related cutaneous adverse events to grade ≤1 following treatment with benralizumab. The study will be declared positive if ≥70% of patients have a reduction of grade 2/3 eosinophil-related cutaneous adverse events to grade ≤1 (between Week 0/Day 1 and Week 4/Day 28).

Data from medical oncology and other MSK visits will be collected at the last study visit for each patient and immune related adverse events with grade and attribution will be included in the final analysis.

Data analysis will be conducted by externally funded biostatistician (consultant), George Dranitsaris of Augmentium Pharma Consulting Inc. The Consultant will serve to review, analyze, and assess data, documents and information provided from MSK, which shall be MSK's Confidential Information, and provide subsequent guidance in a format. The Consultant will also provide independent information to support MSK's clinical research activities. Additional projects that are beyond the scope of this WP with require a separate document executed in writing between the Parties. The Services shall be provided by Consultant at the direction and discretion of MSK and all deliverables or other materials produced by the Consultant shall be subject to Section 5 of the Agreement. The consultant will have access to participant PHI including name, demographics (DOB, age, gender, race, ethnicity), medical history (treatment start and end date and treatment information) and questionnaire responses. Details of this contract are available on the PIMS regulatory binder.

14.1 Populations for Analyses

A total of 48 evaluable patients will be accrued to this study. Patients having a solid tumor or hematologic malignancy, grade 2/3 ercAE to various treatments and blood eosinophil counts of at least .3 K/mcL will be recruited from the medical oncology and dermatology clinics (Section 7.0). Patients will receive benralizumab treatment on Week 0/Day 1 and Week 4/Day 28, and will be assessed for efficacy at baseline Week 0/Day 1 (+/- 3 days), Week 2/Day 14 (+/- 3 day), Week 4/Day 28 (+/- 3day) and Week 8/Day 56 (+/- 3 days) (Section 4.2). If the second dose is missed, it will not be made up (Section 10.0). Patients can remain on study until progression of ercAE or unacceptable toxicity related to benralizumab up to 32 weeks (Section 4.2).

Patients will be considered evaluable as long as they receive at least one dose of benralizumab. Patients who are enrolled and removed from study before they receive their first dose of benralizumab will be considered inevaluable and will be replaced. Data analyses for the primary, secondary and exploratory endpoints will be based on 28 evaluable patients. Summary statistics will also be reported separately for patients removed from the study, including a summary of reasons for removal, their median duration in the study and range, mean and standard deviation of their eosinophil counts, and proportion of in ercAE categories at baseline and at all follow-up times prior to their removal from the study.

Primary endpoint:
Efficacy: We will compare the decrease in patients with grade 2/3 ercAEs to grade ≤1 (between Week 0/Day 1 and Week 4/Day 28) in 28 evaluable patients using a one-sample test for proportions. Benralizumab will be declared to be efficacious if a response (reduction from grade 2/3 to grade ≤1) is achieved by ≥70% of patients. As noted in Section 3, high eosinophil levels refers to a count of > 300 eosinophils per microliter of blood (based on studies in eosinophilic asthma patients that resulted in the approval of benralizumab). With an expected response rate of >70% at Week 4/Day 28 and 28 evaluable patients and a historical reference value of 40% (response based on an improvement of ercAEs grades of

other treatment regimens from clinical experience of the PI) we have >80% power to detect a significant difference if we observe a decrease in grade 2/3 ercAEs to grade ≤1 in 17 or more of the 28 participants at Week 4/Day 28 based on a mixed model for repeated measures analysis with an alpha-level of 5%. An expansion cohort of 19 patients was added once the initial 28 patients were accrued.

On average, we expect to accrue 2 patients to this protocol per month. The overall accrual period for this study will be 15 months.

Secondary endpoints:
AE-related quality of life: Quality of life will be assessed for all patients at Week 0/ Day 1, Week 2/Day 14, Week 4/Day 28 and Week 8/Day 56, Week 16/Day 112, Week 24/Day 168, Week 32/Day 224 and 4 weeks post-last dose using PRO-CTCAE and Skindex 16 (Appendix D). Prior to conducting analyses, we will evaluate questionnaire compliance. The amount of missing data across the PRO instruments will be summarized. A questionnaire will be considered complete if enough questions were completed to be a valid score. Since these instruments are broken into sections, completion of any section for a given adverse event will be considered complete information for that adverse event. Baseline characteristics of study participants with completed and incomplete QOL data will be compared in a descriptive manner. Mouth/throat sores, dry skin and itchy skin are reported on a 5-point scale, while rash, hives and sensitivity of the skin to sunlight are reported on a 2-point scale. These symptoms will be summarized using descriptive statistics. The proportion of patients with different levels of these symptoms will be assessed at each study time point along with exact binomial confidence intervals. A summary score for the Skindex-16 will calculated for each participant at each time point. The total Skindex-16 score will with summarized for each study time point along with 95% confidence intervals.

The Skindex-16 has been shown to have good reproducibility (r = 0.88-0.90). Patients answer every question with a number ranging from 0 (never bothered) to 6 (always bothered). After the questionnaire is completed, the responses to each item are transformed to a linear scale of 100 that ranges from 0 (never bothered) to 100 (always bothered). Consequently, each item has a minimum score of 0 and a maximum score of 100. The Skindex-16 results are reported as an overall score and as 3 domain scores: symptoms, emotions, and functioning. For the overall score, the mean score of all items is calculated. Thus, the overall score has a minimum of 0 and a maximum of 100. Items 1 through 4 on the Skindex-16 pertain to the symptoms domain. The mean of these items is calculated, and a symptoms domain score is determined that also ranges from 0 to 100. Similarly, the emotions domain is based on items 5 through 11, and an emotions domain score is calculated on a scale from 0 to 100. The functioning domain is based on items 12 through 16, and a functioning domain score is calculated in the same manner. Skindex-16 items also are analyzed within each domain to assess the influence of specific items on the overall domain score. The means of the transformed scores for each item are compared statistically within each domain. When up to 25% of Skindex-16 items have missing responses, the items with non-missing responses will be scored. For the analysis of the Skindex-16 score change from baseline, patients with a missing score at week 4 will have the Skindex-16 score imputed by their baseline Skindex-16 score. This method is considered conservative under the

assumption that the majority of patients will withdraw prematurely from the study, resulting in missing the week 4 score.

For the PRO-CTCAE, each item is scored individually, as they are rated 0-4 by the patient. Interpretation of scores will be descriptive. If an individual item is not completed, it will be considered missing. There are otherwise no subscales or minimum thresholds for item completion to calculate a score on a given item.

Safety and tolerability of benralizumab: This endpoint will be measured in terms of CTCAE v5.0 ercAE. The proportion of patients with different grade categories (0, 1, 2 etc) will be assessed at each study time point along with exact binomial confidence intervals. Patients progressing to grade 4 ercAE will be removed from the study (Section 12.0). The proportion of such patients at each time point will be reported. The proportion of patients having a reduction and the proportion having an increase in ercAE grade category will be reported.

Need for supportive medication: The proportion of patients requiring supportive medications such as corticosteroids, antihistamines and immunosuppressants will be reported at each time point along with exact binomial confidence intervals.

Effect of benralizumab on subsequent planned cycles of checkpoint inhibitors (CPIs) or targeted therapies: We will measure changes in blood eosinophil levels between baseline and cycles of various planned treatments for these patients, and report the mean, standard deviation, range and number of patients scheduled to receive different therapies.

Effect of benralizumab on corticosteroid naïve and corticosteroid dependent/refractory ercAEs: Corticosteroid naïve patients are those not receiving corticosteroids for 14 days since Week 0/Day 1 of benralizumab treatment. Corticosteroid dependent/refractory ercAEs are patients that are on prednisone 10mg a day or greater at the initiation of study. We will report the number of corticosteroid naïve and dependent/refractory ercAE patients, measure change in blood eosinophil levels between Week 0/Day 1 and Week 8/Day 56, report descriptive statistics such as mean, standard deviation and range in these groups of patients.

Effect on eosinophil counts: Changes in eosinophil counts will be calculated and reported as percent reduction +/- standard deviation. In addition to comparing baseline and end-of-study percent change in eosinophils, we will also compare percent changes across baseline ercAE categories and end-of-study ercAE categories. We will use regression models to examine the association between longitudinal measurements of percent change in eosinophils at Week 0/Day 1, Week 2/Day 14, Week 4/Day 28, and Week 8/Day 56, Week 16/Day 112, Week 24/Day 168, Week 32/Day 224 and 4 weeks post-last dose and longitudinal measurements of ercAE categories.

Body Surface Area (BSA): Changes in BSA of ercAE will be calculated from total body photography images taken at Week 0/Day 1, Week 4/Day 28, and Week 8/Day 56. We will use regression models and descriptive statistics to quantify change in affected BSA in response to benralizumab.

Relative Dose Intensity (RDI): RDI of the culprit anticancer therapy will be calculated from Week 0/ Day 1 to end of study date of the trial for each patient. Relative dosage and standard dosage will be derived based on the investigators' and primary oncologists' notes and other documentation from the electronic medical records at Memorial Sloan Kettering Cancer Center. We will use regression models to assess differences in compliance to different culprit anticancer therapies in response to benralizumab.

Exploratory objective:
We will measure blood biomarkers – IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, tryptase – at Week 0/Day 1, Week 4/Day 28, and Week 8/Day 56. We will correlate baseline levels of each biomarker with response to benralizumab, where response will be coded as a binary value for each patient with response = 1 if a patient's ercAE reduced to grade 0 or 1, and response = 0 otherwise. We will report the difference in average value of biomarkers between the two response groups and the standard error of the difference. Next, we will correlate the response with biomarker measurements taken on Week 4/Day 28. We will also calculate the slope of each biomarker value over time for each patient and correlate the slope with the response. These are exploratory investigation, for which we will report differences in means and standard errors, but not p-values. Where relevant, we will also report these correlations separately based on the evaluable patients and those removed from the study.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

The dose of benralizumab is 30mg SC once every 4 weeks for the first 3 doses, followed by once every 8 weeks for 3 additional doses.. Doses will be delayed for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines described in sections below. Dose adjustments for hematologic toxicity are based on the blood counts obtained prior to the day of treatment.

Most common adverse reactions (incidence greater than or equal to 5%) include headache and pharyngitis. Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of benralizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, benralizumab should be discontinued.

Systemic or topical corticosteroids should not be abruptly interrupted or discontinued upon initiation of therapy with benralizumab. Reductions in corticosteroid dose, if appropriate, should be gradual. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if benralizumab will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with benralizumab. If patients become infected while receiving treatment with benralizumab and

do not respond to anti-helminth treatment, discontinue treatment with benralizumab until infection resolves.

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of benralizumab. The data described below reflect exposure to benralizumab in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for benralizumab is derived from two phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [benralizumab every 4 weeks (n = 841), every 4 weeks for 3 doses, then every 8 weeks (n = 822), and placebo (n = 847)]. While a dosing regimen of benralizumab every 4 weeks was included in clinical trials, benralizumab administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown below.

Adverse Reactions with BENRALIZUMAB with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	BENRALIZUMAB (N= 822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions†	3	3

Adverse reactions from Trial 3 with 28 weeks of treatment with benralizumab (n = 73) or placebo (n = 75) in which the incidence was more common in benralizumab than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively). The frequencies for the remaining adverse reactions with benralizumab were similar to placebo.

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with benralizumab compared with 1.9% in patients treated with placebo. As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with benralizumab at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with benralizumab developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody

titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed. The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of benralizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody that binds to IL-5Rα such as benralizumab is unknown.

Animal Data
In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Human Data
Of the total number of patients in clinical trials of benralizumab, 13% (n = 320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

CTCAE Version 5 will be utilized for toxicity evaluation.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

15.2 External AE Reporting

Adverse Event Reporting Period

All AEs/SAEs, irrespective of attribution of causality, must be reported.

AE reporting, irrespective of seriousness, ends 30 days after the last dose of the study drug.

SAEs considered related to study drug(s) or study procedures occurring after the end of the AE reporting period (as defined above) must be reported.

If an SAE is present at the last study visit, the SAE should be followed to resolution or until the Investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.
Each recorded AE or SAE will be described using CTCAE v5.0 , including , duration (eg, start and end dates), severity, grade, suspected relationship to the study drug, and any actions taken.
Adverse events related to disease under study (cancer in this case) including disease progression will not be reported as SAE for Benralizumab. Since Benralizumab can cause hypersensitivity reactions including anaphylaxis involving the skin, any worsening of cutaneous reactions should be reviewed by the investigator in the context of possible hypersensitivity reactions and assessed with other suspect concomitant medications before reporting.

Pregnancy

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

If the associated AE fulfills serious criteria, Investigators should report the event to the Sponsor within 5 days using the MSK SAE form.

In the event that the subject received more than the recommended benralizumab dosage, the subject should be treated with appropriate supportive management to mitigate adverse effects.

Expedited Reporting Requirements for SAEs

Investigators should report any SAEs to AstraZeneca within 5 calendar days using the MSK SAE form. The Sponsor will submit appropriate reports to applicable local regulatory agencies and to IRBs as required. MSK will notify AstraZeneca in parallel with submission to

the IRB and Regulatory Authorities for Suspected Unexpected Serious Adverse Reactions (SUSARs) and within fifteen (15) calendar days of awareness for other SAEs..

Follow-up information will be submitted to AstraZeneca within the same time frame as initial reports.

Whenever possible, SAEs should be reported by diagnosis term not as a constellation of symptoms.

If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event AE term, as death is typically the outcome of the event, not the event itself.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

All SAEs are to be submitted to the AstraZeneca Product Safety mailbox:
AEMailboxClinicalTrialTCS@astrazeneca.com

Type and Duration of Follow-up of Subjects after Adverse Events
All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

Reporting Requirements at the End of the Study
MSK will Provide AstraZeneca, at latest within two weeks after Database Lock, a **final unblinded line listing of all SAEs notified to regulatory authority and AstraZeneca during the study for safety event reconciliation**.

i. The email subject line **MUST** contain: ESR-19-14427 the study acronym (if possible) and the text “End of study reconciliation”
ii. Studies with more than 50 SAEs should provide unblinding randomization data in xml-format

The final end of study line listings should be sent using a secure email, to the AstraZeneca Data Entry Site (DES):
AE-MailboxDCR-TCS@astrazeneca.com

Final end of study line listings may also be faxed using the same subject line as above for sending emails to:
- Preferred Fax Number: +1 302 886 4114
- Backup fax number: +46 31 776 37 34

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK’s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the

Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into Medidata. Source documentation will be available to support the computerized patient record. Research blood collection for biomarker analysis and photographic data will be deidentified; will be labelled with patient study IDs to preserve links to clinical data. Canfield imaging systems Inc will be used to store photographic data.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for

Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

1: Simon SCS, Utikal J, Umansky V. Opposing roles of eosinophils in cancer. Cancer Immunol Immunother. 2019 May; 68(5):823-33.

2: Khoury P, Bochner BS. Consultation for Elevated Blood Eosinophils: Clinical Presentations, High Value Diagnostic Tests, and Treatment Options. J Allergy Clin Immunol Pract. 2018 Sep - Oct;6(5):1446-53.

3: Buder-Bakhaya K, Hassel JC. Biomarkers for Clinical Benefit of Immune Checkpoint Inhibitor Treatment-A Review From the Melanoma Perspective and Beyond. Front Immunol. 2018 Jun 28;9:1474.

4: Ramirez GA, Yacoub MR, Ripa M, Mannina D, Cariddi A, Saporiti N, Ciceri F, Castagna A, Colombo G, Dagna L. Eosinophils from Physiology to Disease: A Comprehensive Review. Biomed Res Int. 2018 Jan 28;2018:9095275.

5: Rigoni A, Colombo MP, Pucillo C. Mast cells, basophils and eosinophils: From allergy to cancer. Semin Immunol. 2018 Feb;35:29-34.

6: Varricchi G, Galdiero MR, Loffredo S, Lucarini V, Marone G, Mattei F, Marone G, Schiavoni G. Eosinophils: The unsung heroes in cancer? Oncoimmunology. 2017 Nov 13;7(2):e1393134.

7: Reichman H, Karo-Atar D, Munitz A. Emerging Roles for Eosinophils in the Tumor Microenvironment. Trends Cancer. 2016 Nov;2(11):664-75.

8: Lucas-Truyols S, Rodrigo-Nicolás B, Lloret-Ruiz C, Quecedo-Estébanez E. Eosinophilic Dermatosis of Hematologic Malignancy. Actas Dermosifiliogr. 2017 Jul - Aug;108(6):e39-e44

9: Tracey EH, Modi B, Micheletti RG. Pemetrexed-Induced Pseudocellulitis Reaction With Eosinophilic Infiltrate on Skin Biopsy. Am J Dermatopathol. 2017 Jan;39(1):e1-e2.

10: Sakkal S, Miller S, Apostolopoulos V, Nurgali K. Eosinophils in Cancer: Favourable or Unfavourable? Curr Med Chem. 2016;23(7):650-66.

11: Klion AD. Eosinophilia: a pragmatic approach to diagnosis and treatment. Hematology Am Soc Hematol Educ Program. 2015;2015:92-7.

12: Gotlib J. Tyrosine Kinase Inhibitors and Therapeutic Antibodies in Advanced Eosinophilic Disorders and Systemic Mastocytosis. Curr Hematol Malig Rep. 2015 Dec;10(4):351-61.

13: Roufosse F. Management of Hypereosinophilic Syndromes. Immunol Allergy Clin North Am. 2015 Aug;35(3):561-75.

14: Blank U, Charles N, Benhamou M. The high-affinity immunoglobulin E receptor as pharmacological target. Eur J Pharmacol. 2016 May 5;778:24-32.

15: Davoine F, Lacy P. Eosinophil cytokines, chemokines, and growth factors: emerging roles in immunity. Front Immunol. 2014 Nov 10;5:570.

16: Davis BP, Rothenberg ME. Eosinophils and cancer. Cancer Immunol Res. 2014 Jan;2(1):1-8.

17: Lacouture ME, Wolchok JD, Yosipovitch G, Kähler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol. 2014 Jul;71(1):161-9.

18: Mao Y, Poschke I, Kiessling R. Tumour-induced immune suppression: role of inflammatory mediators released by myelomonocytic cells. J Intern Med. 2014 Aug;276(2):154-70.

19: Cao C, Gu Y, Zhu C, Palmai-Pallag T, Lan F, Chen Z, Li W, Shen H, Ying S. Potential roles of eosinophils in cancer therapy: epidemiological studies, experimental models, and clinical pathology. Recent Pat Anticancer Drug Discov. 2014 May;9(2):241-8.

20: Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. Allergy. 2013 Jul;68(7):829-35.

21: Amini-Vaughan ZJ, Martinez-Moczygemba M, Huston DP. Therapeutic strategies for harnessing human eosinophils in allergic inflammation, hypereosinophilic disorders, and cancer. Curr Allergy Asthma Rep. 2012 Oct;12(5):402-12.

22: Gatault S, Legrand F, Delbeke M, Loiseau S, Capron M. Involvement of osinophils in the anti-tumor response. Cancer Immunol Immunother. 2012 Sep;61(9):1527-34.

23: Daniels TR, Martínez-Maza O, Penichet ML. Animal models for IgE-meditated cancer immunotherapy. Cancer Immunol Immunother. 2012 Sep;61(9):1535-46.

24: Verstraeten AS, De Weerdt A, van Den Eynden G, Van Marck E, Snoeckx A, Jorens PG. Excessive eosinophilia as paraneoplastic syndrome in a patient with non-small-cell lung

carcinoma: a case report and review of the literature. Acta Clin Belg. 2011 Jul-Aug;66(4):293-7.

25: Pereira MC, Oliveira DT, Kowalski LP. The role of eosinophils and eosinophil cationic protein in oral cancer: a review. Arch Oral Biol. 2011 Apr;56(4):353-8.

26: Jensen-Jarolim E, Achatz G, Turner MC, Karagiannis S, Legrand F, Capron M, Penichet ML, Rodríguez JA, Siccardi AG, Vangelista L, Riemer AB, Gould H. AllergoOncology: the role of IgE-mediated allergy in cancer. Allergy. 2008 Oct;63(10):1255-66.

27: Menzella F, Biava M, Bagnasco D, Galeone C, Simonazzi A, Ruggiero P, Facciolongo N. Efficacy and steroid-sparing effect of benralizumab: has it an advantage over its competitors? Drugs Context. 2019 Apr 15;8:212580.

28: Brussino L, Heffler E, Bucca C, Nicola S, Rolla G. Eosinophils Target Therapy for Severe Asthma: Critical Points. Biomed Res Int. 2018 Oct 25;2018:7582057.

29: Roufosse F. Targeting the Interleukin-5 Pathway for Treatment of Eosinophilic Conditions Other than Asthma. Front Med (Lausanne). 2018 Apr 6;5:49.

30: Hassani M, Koenderman L. Immunological and hematological effects of IL-5(Rα)-targeted therapy: An overview. Allergy. 2018 Oct;73(10):1979-88.

31: Kupczyk M, Kuna P. Benralizumab: an anti-IL-5 receptor α monoclonal antibody in the treatment of asthma. Immunotherapy. 2018 Apr;10(5):349-59.

32: Legrand F, Klion AD. Biologic therapies targeting eosinophils: current status and future prospects. J Allergy Clin Immunol Pract. 2015 Mar-Apr;3(2):167-74.

34: Osawa T, Inoue S, Umeda M, Hasegawa T, Makino T, Hori A, Tanaka K, Yasuda M, Mizui T, Sawa T, Sugiyama Y, Goto C. [Predictors of Nivolumab-Induced Skin Reactions]. Gan To Kagaku Ryoho. 2018 Oct;45(10):1533-35.

35: Fucà G, Galli G, Poggi M, Lo Russo G, Proto C, Imbimbo M, Ferrara R, Zilembo N, Ganzinelli M, Sica A, Torri V, Colombo MP, Vernieri C, Balsari A, de Braud F, Garassino MC, Signorelli D. Modulation of peripheral blood immune cells by early use of steroids and its association with clinical outcomes in patients with metastatic non-small cell lung cancer treated with immune checkpoint inhibitors. ESMO Open. 2019 Feb 27;4(1):e000457.

36: Lou Y, Marin-Acevedo JA, Vishnu P, Manochakian R, Dholaria B, Soyano A, Luo Y, Zhang Y, Knutson KL. Hypereosinophilia in a patient with metastatic non-small-cell lung cancer treated with antiprogrammed cell death 1 (anti-PD-1) therapy. Immunotherapy. 2019 May;11(7):577-84.

37: Izumo T, Terada Y, Tone M, Inomata M, Kuse N, Awano N, Moriya A, Jo T, Yoshimura H, Furuhata Y. Rapid effects of benralizumab on severe asthma during surgery for residual tumor after advanced lung squamous cell carcinoma treatment with pembrolizumab. Respir Med Case Rep. 2019 Feb 19;26:292-5.

38: Hollande C, Boussier J, Ziai J, Nozawa T, Bondet V, Phung W, Lu B, Duffy D, Paradis V, Mallet V, Eberl G, Sandoval W, Schartner JM, Pol S, Barreira da Silva R, Albert ML. Inhibition of the dipeptidyl peptidase DPP4 (CD26) reveals IL-33-dependent eosinophil-mediated control of tumor growth. Nat Immunol. 2019 Mar;20(3):257-264.

39: Georgianos PI, Vaios V, Leontaridou E, Karayannopoulou G, Koletsa T, Sioulis A, Balaskas EV, Zebekakis PE. Acute Interstitial Nephritis in a Patient with Non-Small Cell Lung Cancer under Immunotherapy with Nivolumab. Case Rep Nephrol. 2019 Jan 15;2019:3614980.

40: Wolf MT, Ganguly S, Wang TL, Anderson CW, Sadtler K, Narain R, Cherry C, Parrillo AJ, Park BV, Wang G, Pan F, Sukumar S, Pardoll DM, Elisseeff JH. A biologic scaffold-associated type 2 immune microenvironment inhibits tumor formation and synergizes with checkpoint immunotherapy. Sci Transl Med. 2019 Jan 30;11(477). pii: eaat7973.

41: Furubayashi N, Negishi T, Uozumi T, Takamatsu D, Shiraishi K, Hirose D, Nakamura M. Isolated adrenocorticotropic hormone deficiency potentially induced by nivolumab following pseudo-progression in clear cell renal cell carcinoma: A case report. Mol Clin Oncol. 2019 Feb;10(2):304-8.

42: Fulkerson PC, Rothenberg ME. Eosinophil Development, Disease Involvement, and Therapeutic Suppression. Adv Immunol. 2018;138:1-34.

43: Occhipinti M, Falcone R, Onesti CE, Marchetti P. Hyperprogressive Disease and Early Hypereosinophilia After Anti-PD-1 Treatment: A Case Report. Drug Saf Case Rep. 2018 Mar 13;5(1):12.

44: Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, Hata H, Gosho M, Tanaka R, Yamaguchi K, Nonomura Y, Hirai I, Furudate S, Okuhira H, Imafuku K, Aoki M, Matsushita S. Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab.J Dermatol Sci. 2017 Nov;88(2):225-31.

45: Perret RE, Josselin N, Knol AC, Khammari A, Cassecuel J, Peuvrel L, Dreno B; Supported by GESTIM Nantes group of cutaneous adverse events induced by anticancer drugs. Histopathological aspects of cutaneous erythematous-papular eruptions induced by immune checkpoint inhibitors for the treatment of metastatic melanoma. Int J Dermatol. 2017 May;56(5):527-33.

46: Tetzlaff MT, Nagarajan P, Chon S, Huen A, Diab A, Omar P, Aung PP, Torres-Cabala CA, Mays SR, Prieto VG, Curry JL. Lichenoid Dermatologic Toxicity From Immune Checkpoint Blockade Therapy: A Detailed Examination of the Clinicopathologic Features. Am J Dermatopathol. 2017 Feb;39(2):121-9.

47: Kourie HR, Paesmans M, Klastersky J. Biomarkers for adverse events associated with immune checkpoint inhibitors. Biomark Med. 2016 Oct;10(10):1029-31.

48: Lacouture ME, Wolchok JD, Yosipovitch G, Kähler KC, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol. 2014 Jul;71(1):161-9.

49: Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, Shabafrouz K, Ribi C, Cairoli A, Guex-Crosier Y, Kuntzer T, Michielin O, Peters S, Coukos G, Spertini F, Thompson JA, Obeid M. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019 May 15.

50: Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, Michielin O, Peters S, Coukos G, Spertini F, Thompson JA, Obeid M. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol. 2019 Jan;20(1):e54-e64.

51: Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, Martínez-Bernal G, Ferrara R, Lai WV, Hendriks LEL, Sabari JK, Caramella C, Plodkowski AJ, Halpenny D, Chaft JE, Planchard D, Riely GJ, Besse B, Hellmann MD. Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. J Clin Oncol. 2018 Oct1; 36(28):2872-8.

52: Phillips GS, Wu J, Hellmann MD, Postow MA, Rizvi NA, Freites-Martinez A, Chan D, Dusza S, Motzer RJ, Rosenberg JE, Callahan MK, Chapman PB, Geskin L, Lopez AT, Reed VA, Fabbrocini G, Annunziata MC, Kukoyi O, Pabani A, Yang CH, Chung WH, Markova A, Lacouture ME. Treatment Outcomes of Immune-Related Cutaneous Adverse Events. J Clin Oncol. 2019

53: Izumo T, Terada Y, Tone M, Inomata M, Kuse N, Awano N, Moriya A, Jo T, Yoshimura H, Furuhata Y. Rapid effects of benralizumab on severe asthma during surgery for residual tumor after advanced lung squamous cell carcinoma treatment with pembrolizumab. Respir Med Case Rep. 2019 Feb 19;26:292-5.

54: Drilon A, Eaton AA, Schindler K, Gounder MM, Spriggs DR, Harris P, Ivy SP, Iasonos A, Lacouture ME, Hyman DM. Beyond the dose-limiting toxicity period: Dermatologic adverse events of patients on phase 1 trials of the Cancer Therapeutics Evaluation Program. Cancer. 2016 Apr 15;122(8):1228-37.

55: Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007 Mar;156(3):609-11.

56: Ramírez E, Medrano-Casique N, Tong HY, Bellón T, Cabañas R, Fiandor A, González-Ramos J, Herranz P, Trigo E, Muñoz M, Borobia AM, Carcas AJ, Frías J. Eosinophilic drug reactions detected by a prospective pharmacovigilance programme in a tertiary hospital. Br J Clin Pharmacol. 2017 Feb;83(2):400-15.

57: Izumo T, Terada Y, Tone M, Inomata M, Kuse N, Awano N, Moriya A, Jo T, Yoshimura H, Furuhata Y. Rapid effects of benralizumab on severe asthma during surgery for residual tumor after advanced lung squamous cell carcinoma treatment with pembrolizumab. Respir Med Case Rep. 2019 Feb 19;26:292-5.

58: Cho YT, Yang CW, Chu CY. Drug Reaction with Eosinophilia and Systemic Symptoms

(DRESS): An Interplay among Drugs, Viruses, and Immune System. Int J Mol Sci. 2017 Jun 9;18(6). pii: E1243.

59: Fischer A, Jakubowski AA, Lacouture ME, Hollmann TJ, Drucker AM, Maloy M, Prockop S, Querfeld C, Busam KJ, Pulitzer MP. Histopathologic Features of Cutaneous Acute Graft-Versus-Host Disease in T-Cell-Depleted Peripheral Blood Stem Cell Transplant Recipients. Am J Dermatopathol. 2015 Jul;37(7):523-9.

60. Wang DG, Barrios DM, Blinder VS, Bromberg JF, Drullinsky PR, Funt SA, Jhaveri KL, Lake DE, Lyons T, Modi S, Razavi P, Sidel M, Traina TA, Vahdat LT, Lacouture ME. Dermatologic adverse events related to the PI3Kα inhibitor alpelisib (BYL719) in patients with breast cancer. Breast Cancer Res Treat. 2020 Aug;183(1):227-237. doi: 10.1007/s10549-020-05726-y. Epub 2020 Jun 29. PMID: 32613539

18.0 APPENDICES

Appendix A: Eosinophil-related Adverse Event Grading (CTCAE v5.0)

Appendix B: Skindex-16

Appendix C: ECOG Performance Status

Appendix D: PRO-CTCAE for Skin Events

Appendix E: RegiSCAR Scoring System for Diagnosing DRESS Syndrome