MSK PROTOCOL COVER SHEET

RETENTION: An Open-Label Phase 2 Trial of InteRIEukin (5) InhibiTion for the prEveNTION of Alpelisib Rash in Metastatic *PIK3CA*-mutant Hormone-Receptor Positive Breast Cancer

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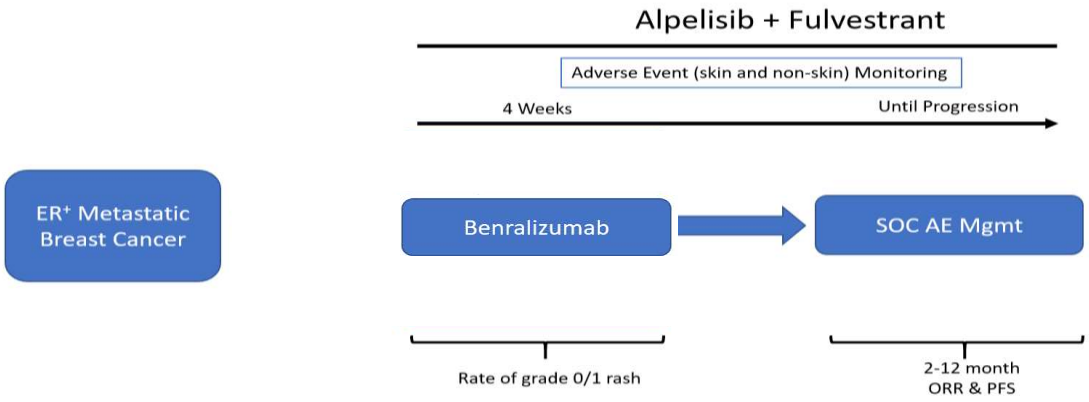
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a multi-center, open-label, phase 2 trial testing the efficacy and safety of 2 interventions that target rash during PI3K inhibitor therapy in postmenopausal women and men with histologically-confirmed, hormone receptor (HR)-positive, HER2-negative, PIK3CA mutant metastatic breast cancer (MBC). A total of 63 patients will be enrolled into one arm: benralizumab 30mg in combination with standard of care (SOC) endocrine therapy (fulvestrant or AIs or aromatase inhibitors (AIs)) and PI3K inhibition (alpelisib). A total of 43 patients will be enrolled at MSKCC and a total of 20 patients will be enrolled at the participating external institutions (10 patients at Stanford University and 10 patients at Dana Farber Cancer Institute). The primary endpoint is the proportion of patients with grade ≤1 rash rate at 4 weeks.



Patient Population: The primary study population will be postmenopausal women and men with histologically-confirmed, HR-positive, HER2-negative, *PIK3CA* mutant MBC who have received no more than 2 lines of endocrine-based therapy in the metastatic setting.

Design: A multi-center, open-label, phase 2 trial testing the efficacy and safety of one interventions (one anti IL-5 receptor antibody and one antihistamine) that target the maculopapular rash during PI3K inhibitor therapy in patients with HR-positive, HER2-negative, *PIK3CA* mutant MBC receiving first or second line therapy. Study participants (n=112) will enrolled to one arm: benralizumab (anti-IL5rα) in combination with SOC endocrine therapy (fulvestrant or AIs) and PI3K inhibition (alpelisib). The primary endpoint is the grade ≤1 rash rate at 4 weeks. The study size is determined to compare the grade ≤1 rash rate at four weeks with historical controls. It has been reported that approximately 34% of patients receiving alpelisib will develop ≥ grade 2 rash within the first 30 days. The corollary is that 66% of historical controls will have grade ≤1 rash within the first 30 days. An increase in rash control to approximately 88% is deemed to be clinically meaningful with the investigational agent under investigation (IL5r antibody). A sample size of 57 patients per group will achieve an 80% power to detect an odds ratio of 4.0 with respect to the primary endpoint. The proportion in the experimental group is assumed to be 0.66 under the null

hypothesis and 0.88 under the alternative hypothesis. The proportion is 0.66. If it is assumed that 10% of patients will withdraw consent or be lost to follow up, then 63 patients will need to be enrolled into this trial.

Treatment Plan: All participants will receive SOC endocrine therapy (fulvestrant or AIs) and PI3K inhibition (alpelisib). Participants will receive benralizumab 30mg subcutaneously on day -1. All participants will be monitored at regular visits for the duration of the trial. After 4 weeks, patients will be followed for safety at 90 days and disease progression for 1 year.

Estimated Time to Completion: 1 years.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: To determine if prophylactic IL-5 receptor inhibition results in a lower incidence of alpelisib rash when compared to historical controls.

Secondary Objectives

1. To determine the effect of prophylactic anti-IL-5 receptor inhibition on alpelisib dose interruption or modification when compared to historical controls as determined by relative dose intensity (RDI) during the initial 4 weeks of therapy (4W-RDI).
2. To determine the effect of prophylactic anti-IL-5 receptor inhibition on quality of life when compared to historical controls using the Functional Assessment of Cancer Therapy–Breast (FACT-B) and the PRO-CTCAE.
3. To determine the effect of prophylactic anti-IL-5 receptor inhibition on cumulative steroid dose when compared to historical controls.
4. To determine the effect of prophylactic anti-IL-5 receptor inhibition on time to development of alpelisib grade ≥2 rash when compared to historical controls.
5. To determine the safety of anti-IL-5 receptor inhibition and historical controls in patients receiving alpelisib, defined as adverse events definitely, possibly or probably related to anti-IL-5 receptor inhibition or historical controls.
6. To determine the effect of anti-IL-5 receptor and historical controls on non-skin alpelisib-related adverse events (eg. nausea, diarrhea, vomiting, anorexia, fatigue, weight loss).
7. To determine the overall response rate (ORR) and progression free survival (PFS) at 6 and 12 months post treatment initiation.

Exploratory Objectives

1. Explore the change in serum and skin inflammatory markers from baseline to 4 weeks (using non-invasive skin tape for skin).
2. Explore the change in histologic markers from skin biopsies in patients with rash, including eosinophil counts, CD4/8 count, IL-5, PI3 kinase pathway activation; at rash onset and at 28 days.

3.0 BACKGROUND AND RATIONALE

3.1 Poor outcomes in HR-positive MBC

Breast cancer mortality has decreased over the past decade, however survival for HR-positive MBC has remained suboptimal with a 5-year overall survival rate of only 26%.[1,2] While newer molecularly targeted therapies (e.g., PI3K inhibition) improve progression-free survival, treatment resistance and disease progression are inevitable. In addition, all MBC treatments cause a broad range of toxicities that negatively impact quality of life and physical functioning.[3-5]

3.2 PI3K/AKT/MTOR Pathway in Cancer

Cancer cells mutate and amplify their metabolic pathways to meet the energetic and synthetic demands of their hyperproliferative state. For example, enhancement of the phosphatidylinositol 3-kinase (PI3K) pathway is a hallmark of human cancer and other overgrowth disorders. PI3K mediates all of the intracellular effects of insulin including nutrient uptake, macromolecule synthesis, and cellular proliferation.

Insulin (via PI3K) is a known mitogen of breast tumor cells *in vitro*, and hyperinsulinemia increases rates of mammary tumors in mice. In humans, a greater consumption of foods that stimulate insulin release has been associated with an increased risk of breast cancer development. Increased PI3K activation in breast tumors may also enhance intra-tumoral insulin signaling. For example, *PIK3CA*, the gene encoding the catalytic subunit of PI3Kα, is the most frequently mutated oncogene in human cancer including HR-positive, HER2-negative, MBC. *PIK3CA* mutation has been reported in 20%-40% of breast cancers, but the incidence differs across multiple molecular breast cancer subtypes. It has been reported in 28%-47%, 23%-33% and 8%-25% of ER^+, $HER2^+$, and triple-negative breast cancers, respectively.

In model systems of cancer, targeting PI3K using small molecules (i.e. PI3K inhibitors) improves markers of cell proliferation, and in some circumstances, promotes cell death. Unfortunately, the strong preclinical evidence supporting PI3K inhibition as a therapeutic strategy in solid tumors has not been broadly realized in human clinical trials. Two promising PI3K inhibitors, buparlisib and taselisib, stalled in their quest for FDA approval after demonstrating only modest effects in *PIK3CA* mutant breast cancer. Interestingly, when one more carefully interrogates the existing clinical data, it is clear that certain patients dramatically respond to PI3K inhibition. For example, over 50% of patients undergoing [^{18}F]-FDG-PET/CT scanning in a phase Ib study of buparlisib in $ER^+/HER2^-$ MBC exhibited a reduction in FDG tumor uptake at 2 and 8 weeks post-treatment initiation. This reduction

correlated with the duration of treatment, suggesting the decrease in tumor metabolism enhanced the response to therapy.

3.3 Alpelisib for the Treatment of HR-positive MBC

Alpelisib is an oral, α-specific PI3K inhibitor that has been recently approved in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR^+, $HER2^-$, *PIK3CA*-mutated, MBC following progression on or after an endocrine-based regimen. In the phase 3 SOLAR-1 trial, an improvement in progression-free survival (PFS) was observed in *PIK3CA*-mutated patients treated with alpelisib plus fulvestrant (n=169) compared with placebo plus fulvestrant (n=172) (11 mo vs 5.7 mo; hazard ratio [HR] 0.65, $P<0.001$).[23] Overall response rate (ORR) and clinical benefit rate (CBR) in the *PIK3CA*-mutated cohort were greater in the alpelisib-fulvestrant or AIs group compared with the placebo-fulvestrant or group (ORR 26.6% vs 12.8%; CBR 61.5% vs 45.3%). The most common AEs reported in the safety population for alpelisib (n=284) and placebo groups (n=287) were hyperglycemia (63.7% vs 9.8%), diarrhea (57.7% vs 15.7%), nausea (44.7% vs 22.3%), decreased appetite (35.6% vs 10.5%), rash (35.6% vs 5.9%), or maculopapular rash (14.1% vs 1.7%). Serious AEs (SAEs) were reported by 99 (34.9%) alpelisib-treated patients and 48 (16.7%) placebo-treated patients. Permanent discontinuation due to AEs occurred in 71 alpelisib-treated patients (25%) and 12 (4.2%) placebo-treated patients. The most common AEs leading to discontinuation of alpelisib were hyperglycemia (18 patients, 6.3%) and rash (9 patients, 3.2%).[23] The combination of fulvestrant or AIs and alpelisib is now a new standard of care therapy in the treatment of ER^+ *PIK3CA*-mutant MBC.

3.4. Dermatologic adverse events to PI3K inhibition with alpelisib

Second to hyperglycemia, rash has been reported as a common cause of discontinuation of alpelisib (3.2%), signifying an obstacle to achieving therapeutic benefit. Maculopapular rashes related to alpelisib are likely an on- target effect of PI3K inhibition, occurring in 57% of patients. While alpelisib has high selectivity to inhibit the p110α subunit of PI3Kα, small molecule inhibitors with selectivity against various combinations of PI3K isoforms, such as buparlisib, have also demonstrated frequent dAEs with similar maculopapular morphology. Our most extensive in-human experi- ence is with the pan-PI3K inhibitor buparlisib (BKM120, Novartis). Despite the neurologic adverse events that preempted FDA-approval, trials with buparlisib illustrated many safety issues and was a preview for adverse events of other candidate inhibitors of the PI3K pathway. In a phaseI study for buparlisib, a primarily pruritic maculopapular rash concentrated on the torso was observed. For grade 3/4 rash occurring in two or more patients, the incidence was 11%; and for all-grade rash, the incidence was 43%. Inthe BELLE-2 phase III study, there was a 32% incidence ofrash, with 8% grade 3/4 rash. Experience with idelalisib, copanlisib, and duvelisib continues to report significant dAEs. Idelalisib, a PI3Kδ specific inhibitor, reported a 13% incidence of any grade rash, with 2–3.6% incidence of grade3 rash. With copanlisib, which selectively inhib- its PI3Kα/δ, maculopapular rash of any grade was notedin 13- 16% of all patients with grade

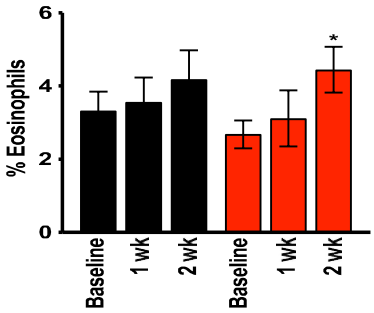
3 rashes occurring in 7–13% of patients. In patients receiving duvelisib, which targets p110γ/δ, maculopapular rash was observed in 16.2–18.6% or patients, and grade 3 rash was seen in < 5% of patients. It is unlikely that the diverse chemical structures represented in these PI3K inhibitors have similar non-specific activities that cause maculopapular rash.

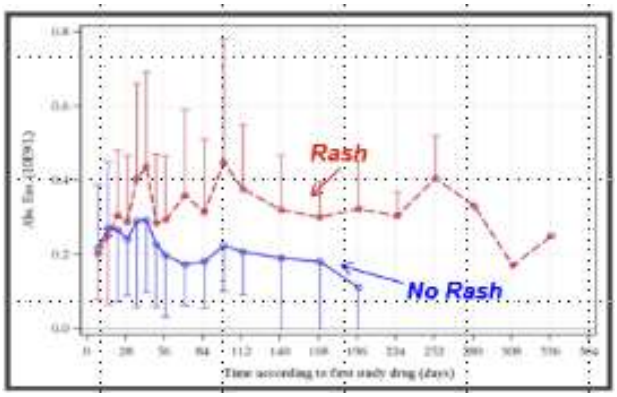
It is unclear how inhibition of PI3K signaling causes maculopapular rash, since the PI3Kα isoform is expressed at low levels in immune cells, it is unlikely that direct inhibition of PI3Kα signaling in this environment is the primary event. In addition, it is unlikely that off-target inhibition of PI3Kδ by alpelisib is the primary event, as there are com-parably fewer maculopapular rashes associated with use of δ-targeting molecules—idelalisib, copanlisib, and duvelisib. Alpelisib may shift recruitment and maturation of different immune cell types as a direct result of disrupted PI3Kα signaling in the skin or an indirect result of disrupted PI3Kα signaling in other tissues, causing systemic exposure to compensatory molecules (i.e. hyperinsulinemia). Upon inhibition of PI3Kα, metabolic tissues have impaired uptake of serum glucose, leading to hyperglycemia and a compensatory increase in insulin. However, we found that hyperglycemia is not correlated with alpelisib-related dAEs. Insulin resistance at baseline, as reflected by HbA1C and C-peptide levels, was also not correlated with alpelisib-related dAEs. It is possible that patients that are euglycemic have appropriate hyperinsulinemia which activates certain immune cells.

Inhibition of PI3Kα signaling may cause intrinsic structural changes to the epidermis and dermis. Activation of PI3K in epithelium does not simply cause tumorigenesis. Rather, the PI3K pathway coordinates keratinocyte fate. PI3Kα activation has been shown to suppress epidermal progenitor cell self-renewal, with activation of Akt, the immediate downstream effector, resulting in increased keratinocyte differentiation, while inhibition of PI3Kα induces apoptosis. Also, since estrogen has been demonstrated to have anti-aging and anti-inflammatory effects in skin, there is consideration for the effects of estrogen signal-ing and crosstalk with the PI3K pathway, which may explain the emergence of the maculopapular rash phenotype observed in patients with alpelisib-related dAEs.

Previous analyses suggests that histamine producing cells and eosinophils have some role in alpelisib-related rash. All patients receiving alpelisib have a trend towards increased eosinophils, with a more pronounced effect in patients with rash. Interestingly, pre- treatment absolute eosinophil count may be lower in patients who develop rash. We also found that patients developing rash had a statistically significant increase in eosinophils after 2 weeks of

receiving alpelisib ($p < 0.05$) (below, lefty). This has also been demonstrated in phase 1





study of alpelisib in combination with fulvestrant or AIs (below, right). Prospective analyses and anecdotal experience at MSK with over 100 patients has revealed that 90% of rash develops within the first 4 weeks, Indeed, the median time to onset of grade 3-4 rash was 13 days in the pivotal SOLAR-1 trial.

3.5. Eosinophils and Drug Reactions

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%) (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 (i.e hyperglycemia). There are no FDA approved therapies for drug reactions associated with eosinophils, and drug interruption/discontinuation and systemic steroids are current reactive management strategies.

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 dermatologic adverse events (dAEs), 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).

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.

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 rashes with alpelisib, ranging from benign, asymptomatic eosinophilia to grade 4 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.

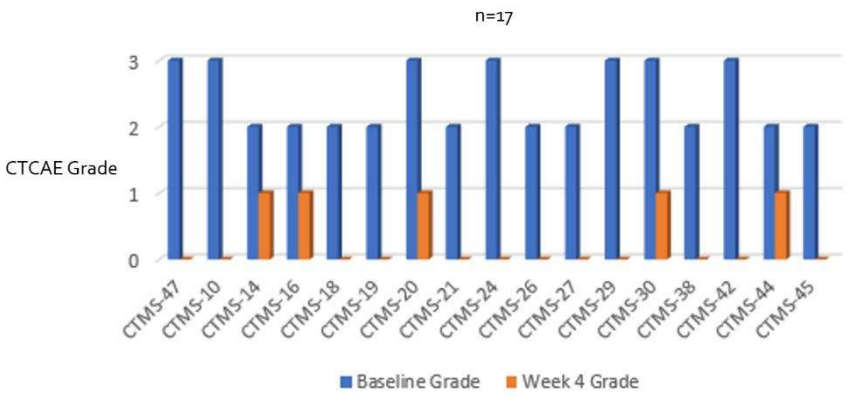
The actual definition of DRESS was proposed by Bocquet *et al.* in 1996 and updated in 2007 by the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) Study Group. DRESS syndrome diagnosis is complex due to the wide variety of signs and symptoms not all present at the same time in the patient. 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 mucosal involvement (56%). 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%). 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 alpelisib rash with an IL-5 receptor antibody represents a paradigm shift, as it would be amenable to prophylactic (if very frequent or in populations at risk) and effective reactive therapies, precluding the need for alpelisib dose interruptions or discontinuations, while maintaining quality of life and dosing. 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).

Our current single-arm trial investigating the treatment of grade 2/3 eosinophil related AEs includes 17 patients with grade 2/3 alpelisib rashes who were treated with benralizumab in a reactive fashion (#20-344 IIT, PI Lacouture). Patients continued on alpelisib while on the trial. All 17 patients showed therapeutic response, defined as a reduction in eosinophil related AE grade ≤ 1 at week 4 post treatment initiation. Clinical response correlated with reduction in blood eosinophils to 0K/mcl at week 4 in all patients. Rash did not recur after corticosteroids were discontinued and alpelisib was rechallenged to the initial dose. No adverse events were attributed to benralizumab in this study.



3.6. 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

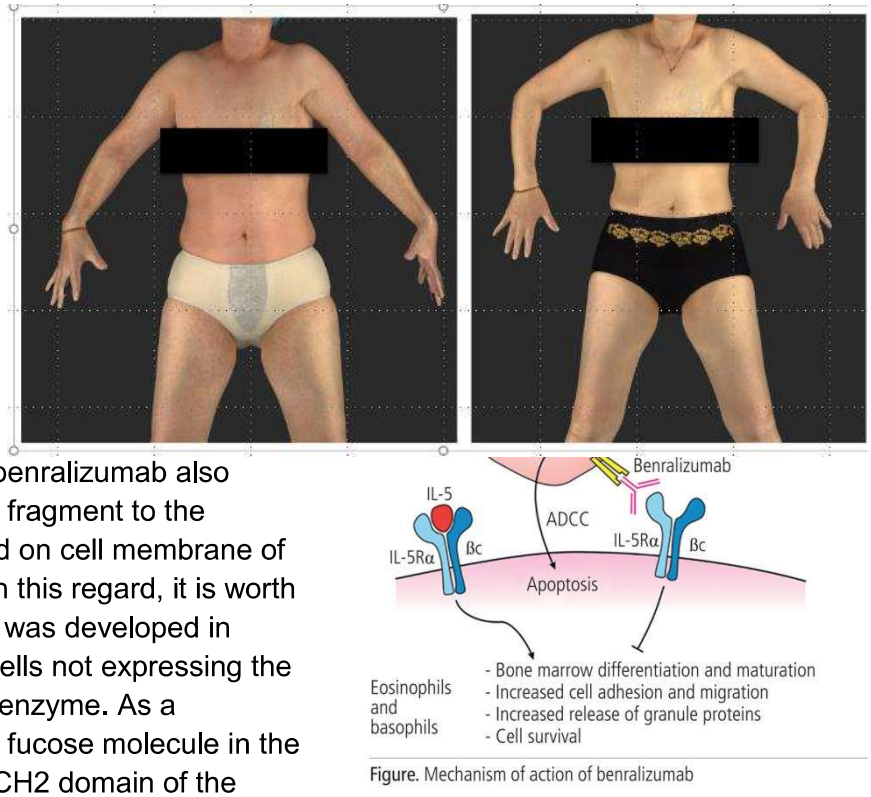


Figure. Mechanism of action of benralizumab

responsible for a remarkable enhancement (5 to 50 times) of benralizumab affinity for the FcγRIIIa 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 through the release of the proapoptotic proteins perforin and granzyme B. A fucosylation-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 favorable 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-5Rα, 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-5Rα 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).

3.7. Overall Study Rationale and Objectives

A maculopapular rash with eosinophilia is an expected effect of alpelisib that limits medication adherence and efficacy, and patient quality of life. We have identified one strategy that treated the alpelisib-induced rash with eosinophilia: an inhibitor of the IL-5rα. There is extensive pre-clinical and anecdotal clinical data supporting the presence of eosinophilia in alpelisib rash and the role of eosinophils in drug reactions, hence inhibition of these cells may prevent alpelisib rash. In this trial, we will formally test the efficacy and safety of eosinophil depletion with the IL-5 receptor inhibitor benralizumab in postmenopausal women and men with histologically-confirmed, HR-positive, HER2-negative, *PIK3CA*-mutant MBC. The objectives are as follows:

Primary Objective: To determine if prophylactic IL-5 receptor inhibition results in a lower incidence of alpelisib rash when compared to historical controls.

Secondary Objectives

1. To determine the effect of prophylactic anti-IL-5 receptor inhibition on alpelisib dose interruption or modification when compared to historical controls as determined by relative dose intensity (RDI) during the initial 4 weeks of therapy (4W-RDI).
2. To determine the effect of prophylactic anti-IL-5 receptor inhibition on quality of life when compared to historical controls using the Functional Assessment of Cancer Therapy–Breast (FACT-B) and the PRO-CTCAE.
3. To determine the effect of prophylactic anti-IL-5 receptor inhibition on cumulative steroid dose when compared to historical controls.
4. To determine the effect of prophylactic anti-IL-5 receptor inhibition on time to development of alpelisib grade ≥2 rash when compared to historical controls.
5. To determine the safety of anti-IL-5 receptor inhibition and historical controls in patients receiving alpelisib, defined as adverse events definitely, possibly or probably related to anti-IL-5 receptor inhibition or historical controls
6. To determine the effect of anti-IL-5 receptor and historical controls on non-skin alpelisib-related adverse events (eg. nausea, diarrhea, vomiting, anorexia, fatigue, weight loss).
7. To determine the overall response rate (ORR) and progression free survival (PFS) at 6 and 12 months post treatment initiation.

Exploratory Objectives

1. Explore the change in serum and skin inflammatory markers from baseline to 4 weeks (using non-invasive skin tape for skin).
2. Explore the change in histologic markers from skin biopsies in patients with rash, including eosinophil counts, CD4/8 count, IL-5, PI3 kinase pathway activation; at rash onset and at 28 days.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a prospective, MSK investigator-initiated, multi-center, open-label, phase 2 trial testing the efficacy and safety of one interventions that targets interleukin 5 receptors during PI3K inhibitor therapy in patients with HR-positive, HER2-negative, *PIK3CA* mutant MBC receiving first or second line therapy. Study participants (n=63) will be treated with benralizumab in combination with SOC endocrine therapy (fulvestrant or AIs) and PI3K inhibition (alpelisib). Crossover will not be allowed. The primary endpoint is the grade ≤1 rash rate at 4 weeks.

Postmenopausal women and men with histologically-confirmed, HR-positive, HER2-negative, *PIK3CA* mutant MBC who have received no more than 1 line of endocrine-based therapy in the metastatic setting will be eligible. Study recruitment will be done by MSK and the participating institutions. Patients will be screened by members of the institution's breast oncology service. Those deemed eligible will complete baseline skin exam, skin tape stripping, blood work and urinalysis (See section 9.0).

4.2 Intervention

Eligible patients will undergo screening and baseline procedures per the pretreatment study schedule (Section 8.0). Study inclusion and exclusion criteria will be applied per section 6.0. Patients will undergo SOC histologic assessment and genomic analysis, and research blood testing. Once eligibility is confirmed, patients will receive benralizumab.

Patients will receive fulvestrant or AIs and PI3K inhibition (alpelisib) per SOC (fulvestrant on days 1, 15, 29 and monthly thereafter; Ais on a daily continuous basis). Participants will receive one injection of benralizumab 30mg subcutaneously on day -1.

Adherence, tolerance, and adverse effects (AEs) of the therapeutic agents will be evaluated at weeks 2 and 4. Research staff and investigators will review adherence and tolerance medications, AEs or intolerance, and collectskin tape strips, urinalyses, and research bloods or biopsies per Section 11.0.

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v5.0).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

Alpelisib

a. Dosage and administration
   Alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor

receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. The recommended dose of Alpelisib is 300 mg (two 150 mg film-coated tablets) taken orally, once daily, with food. Patients should take their dose of Alpelisib at approximately the same time each day. Alpelisib tablets are swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact. If a dose of Alpelisib is missed, it can be taken with food within 9 hours after the time it is usually taken. After more than 9 hours, the dose is skipped for that day and resumed the next day.

b. Preparation
Alpelisib has been formulated as immediate-release tablets for oral administration. The tablet consists of a mixture of alpelisib drug substance with microcrystalline cellulose, low substituted hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide (anhydrous), and magnesium stearate. The clinical trial tablets will be supplied in 150-mg (caplet) dose strengths.

c. Storage
Alpelisib dosage forms and strengths include 50 mg, 150 mg, and 200 mg film-coated tablets.
300 mg daily dose: Each carton contains 2 blister packs. Each blister pack contains a 14-day supply of 28 tablets (28 tablets, 150 mg alpelisib per tablet).
250 mg daily dose: Each carton contains 2 blister packs. Each blister pack contains a 14-day supply of 28 tablets (14 tablets, 200 mg alpelisib per tablet and 14 tablets, 50 mg alpelisib per tablet).
200 mg daily dose: Each carton contains 1 blister pack. Each blister pack contains a 28-day supply of 28 tablets (28 tablets, 200 mg alpelisib per tablet).
Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F).

Benralizumab
Benralizumab is FDA approved as a maintenance treatment of patients 12 years or older with severe asthma and an eosinophilic phenotype and will be provided by AstraZeneca. Benralizumab use in this study will be IND exempt (request submitted) The pathology of severe asthma with eosinophilic phenotype is also denotated as TH2-high phenotype.

a. Dosage and administration

Benralizumab is an IL-5R inhibitor to be administered as a single dose of 30mg subcutaneously at least 1 day and no more than 7 days prior to alpelisib initiation.

b. Preparation

Check the expiration date (EXP). Do not use if the expiration date has passed. Let benralizumab warm up at room temperature between 68°F to 77°F (20°C to 25°C) for about 30 minutes before giving the injection. Do not warm the benralizumab PEN in any other way. For example, do not warm it in a microwave or hot water, or put it near other heat sources. Use benralizumab within 14 days of removing from the refrigerator. After 14 days, throw away the benralizumab PEN. Do not remove the cap until you have reached Step 6. Look at the liquid in the benralizumab PEN through the viewing window. The liquid should be clear and colorless to slightly yellow. It may contain small white particles. Do not inject benralizumab if the liquid is cloudy, discolored, or contains large particles. You may see small air bubbles in the liquid. This is normal. You do not need to do anything about it. the recommended injection site is the front of your thigh or the lower part of your stomach (abdomen). A caregiver may inject you in the upper-arm, thigh, or abdomen. Do not try to inject yourself in the arm. For each injection, choose a different site that is at least 1-inch (3-cm) away from where you last injected. Do not inject: into the 2-inch (5-cm) area around your belly-button, where the skin is tender, bruised, scaly or hard, into scars or damaged skin, through clothing. Wash your hands well with soap and water. Clean the injection site with an alcohol wipe in a circular motion. Let it air dry. Do not touch the cleaned area before injecting. Do not fan or blow on the cleaned area. Hold the benralizumab PEN with 1 hand. Carefully pull the cap straight off with your other hand. Put the cap aside to throw away later. The green needle guard is now exposed. It is there to prevent you from touching the needle. Do not try to touch the needle or push on the needle guard with your finger. Do not try to put the cap back on the benralizumab PEN. You could cause the injection to happen too soon or damage the needle. Complete the following steps right away after removing the cap. You can either gently pinch at the injection site or give the injection without pinching the skin. Inject benralizumab at a 90o angle. Hold the benralizumab PEN in place for the entire injection. Do not change the position of the benralizumab PEN after the injection has started. Check the viewing window to make sure all the liquid has been injected.

c. Storage

Store benralizumab in a refrigerator between 36°F to 46°F (2°C to 8°C) in its original carton until you are ready to use it. benralizumab may be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 14 days. • Once removed from the refrigerator and brought to room temperature, benralizumab must be used within 14 days or thrown away (disposed of). Do not use if• it has been frozen • it has been dropped or damaged • the security seal on the carton has been broken • the expiration date (EXP) has passed. Do not • shake your benralizumab PEN • share or reuse your benralizumab PEN • expose your benralizumab PEN to heat. Each benralizumab PEN contains a single dose of benralizumab and cannot be reused. • Put your used benralizumab PEN in a FDA-cleared sharps disposal container right away after use.

Drug Accountability

The site investigator or designee is responsible for maintaining accurate records (including dates and quantities) of study drug received, patients to whom study drug is dispensed (patient-by patient dose-specific accounting), and study drug lost or accidentally or deliberately destroyed. The Investigator or its designee must retain all unused or expired study supplies until the Sponsor or its designee has confirmed the accountability data.

Unused study drug must be kept in a secure location for accountability and reconciliation by the PI or its designee. The site investigator or its designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after the PI or its designee has granted approval for drug destruction. The PI or its designee must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to the PI or its designee and retained in the Investigator's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the PI or its designee upon request. The return of study drug or study drug materials must be accounted for on a Study Drug Return Form provided by the PI or its designee.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

The benralizumab will be provided by AstraZeneca. The alpelisib will be provided by Novartis.

Patient Compliance

Patients will be given study drug, dosing diaries, and detailed instructions on how to take medications at home. Patients will be instructed to return all used and unused study drug containers at each study visit. Patient compliance with the dosing schedule will be assessed by reconciliation of the used and unused study drug at each clinic visit and review of the dosing diaries. The quantity of dispensed and returned study drug must be recorded on a study drug accountability log. Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will determine the patient's adherence to the dosing schedule by reviewing the dosing diaries and questioning the patient about any discrepancies, recording the number of tablets and strengths returned, the date returned, and determining treatment compliance before dispensing new medication to the study patient.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

1. Histologically confirmed metastatic HR-positive, HER2-negative breast cancer. HR positive is defined by ER status >10% immunohistochemical (IHC) staining of any intensity.
2. Must be scheduled to receive SOC endocrine therapy (alpelisib plus fulvestrant or AIs)
3. Presence of one or more activating *PIK3CA* mutations in tumor tissue.
4. Measurable disease per RECIST v1.1 OR at least one predominantly lytic bone lesion must be present.
5. Written informed consent provided
6. Female or male ≥18 years of age
7. Eastern Cooperative Oncology Group performance status of 0 or 1.
8. Life expectancy ≥6 months.
9. Adequate organ and marrow function as defined below:
   - Hemoglobin ≥8.0 g/dL (without blood transfusion within 7 days of laboratory test used to determine eligibility)
   - Absolute neutrophil count ≥1.0 × 10^9/L (without granulocyte colony stimulating factor support within 2 weeks of laboratory test used to determine eligibility)
   - Platelet count ≥50 × 10^9/L (without transfusion within 2 weeks of laboratory test used to determine eligibility)
   - Total bilirubin (TB) ≤1.0 × institutional upper limit of normal (ULN; Patients with known Gilbert's disease who have TB ≤3 × ULN may be enrolled)
   - Aspartate transaminase/alanine transaminase ≤2.5 × ULN with normal alkaline phosphatase (≤5 × ULN for patients with liver metastases) OR ≤1.5 × ULN in conjunction with alkaline phosphatase >2.5 × ULN
   - Creatinine ≤1.5 mg/dL.
10. Able to swallow oral medication.
11. Willing to be treated in the study arm and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations
12. Women must be of postmenopausal status. Postmenopausal status is defined by any one of the following criteria:
    - Prior bilateral oophorectomy
    - Age ≥60 years
    - Age <60 years and amenorrheic for at least 12 months (spontaneous cessation of menses for 12 consecutive months or more in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle-stimulating hormone and estradiol levels in the postmenopausal range without an alternative cause.

6.2 Participant Exclusion Criteria

1. Known hypersensitivity to alpelisib, fulvestrant or AIs, benralizumab, or to any of the excipients of alpelisib, fulvestrant or AIs, or benralizumab.
2. Concurrent malignancy (basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or cervical cancer in situ that have undergone curative intent therapy are allowed)
3. Individuals with impaired decision making capacity.
4. Concurrent use of another investigational drug or device for the rash (i.e., outside of study treatment) during, or within 4 weeks of treatment.
5. Known use of anti-IL-5 agents or other biologics for the treatment of asthma which are known to decrease blood eosinophil levels within the past 12 weeks.

6. Known history of anaphylaxis to benralizumab therapy.
7. A helminthic parasitic infection diagnosed within 24 weeks prior to the first treatment, and assent when applicable, was obtained that had not been treated with, or has failed to respond to, standard of care therapy.
8. Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
9. Active infection that would impair the ability of the patient to receive study treatment.
10. Women who are pregnant or breast-feeding.
11. Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
12. Oral corticosteroids at a dose of ≥20mg/day prednisone or equivalent within 14 days expected to continue during alpelisib therapy.
13. More than 2 lines of endocrine-based therapy in the metastatic setting.

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 at Memorial Sloan Kettering Cancer Center (MSK) and the participating institutions. If the investigator is a member of the treatment team, s/he will screen their patient's 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.

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 for 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.

Potential study participants who meet our basic inclusion/exclusion criteria will be approached by their physician to volunteer for this study. If the patient indicates a willingness to participate, a consenting professional (board-certified oncologist) will explain the study in detail. All study recruitment will be done by MSK, and the participating institutions. The total accrual goal is 63 evaluable patients. A total of 43 patients will be enrolled at MSKCC and a total of 20 patients will be enrolled at the participating external institutions (10 patients at Stanford University and 10 patients at Dana Farber Cancer Institute). We anticipate consenting approximately 4 patients per month.

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

No randomization will occur in this study. After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trials Management System (CTMS).

8.0 INFORMED CONSENT PROCEDURES

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.
6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants/LARs. The participant/LAR will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants/LARs must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant/LAR and consenting professional will sign and date the consent form. The participant/LAR must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

Patients who consent to the study will require the following tests within 14 days prior to treatment start:

1. History (including menstrual history) and dermatologic exam
2. Consent to Protocol
3. Review of concomitant medications
4. Vital signs (blood pressure, heart rate, temperature), height, weight
5. ECOG performance status
6. Toxicity (symptom) Assessment QOL will be assessed using the Functional Assessment of Cancer Therapy – Breast (FACT-B) scale developed for the assessment of patient symptoms and QOL in breast cancer patients and the PRO-CTAE. Allergy questionnaire will also be administered to identify history of atopic disease.
7. Baseline Data Form
8. Standardized total body photography
9. Skin tape stripping in 2 locations
10. Evidence of disease evaluation as per SOC, such as:
    1. Diagnostic CT chest/abdomen/pelvis scan OR MRI chest/abdomen/pelvis scan

10.0 TREATMENT/INTERVENTION PLAN

Patients will receive fulvestrant or AIs 500 mg IM on days 1, 15, 29 and once monthly thereafter. Alpelisib 300mg by mouth once daily will be initiated with the first fulvestrant or AIs dose (day 1). Patients will continue alpelisib and endocrine therapy until disease progression or unacceptable toxicity as determined by their treating clinician.

Patients will receive benralizumab on day -1 to -7 of alpelisib initiation. Skin tape strips and research blood will be collected prior to alpelisib initiation.

Dose reductions and modifications

This study will use the NCI Common Toxicity Criteria (CTC) AE version 5.0 for toxicity assessment.

Alpelisib

The recommended dose modifications for adverse reactions (ARs) are listed in Table 1.

Table 1. Alpelisib dose reduction guidelines

Alpelisib dose level	Dose and schedule	Number and strength of tablets
Starting dose	300 mg once daily	Two 150 mg tablets **OR ALTERNATIVELY** One 200mg and two 50mg tablets can be used to reach the 300 mg dose level
First dose-reduction	250 mg once daily	One 200 mg tablet and one 50 mg tablet
Second dose-reduction	200 mg once daily[1]	One 200 mg table

[1]If further dose reduction below 200 mg once daily is required, discontinue alpelisib

Rash

Table 2. Dose modification and management for rash.

Grade	**Recommendation**
Grade 1 Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	No dose adjustment required. OTC moisturizers and sun protection
Grade 2 Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	No dose adjustment required. OTC moisturizers and sun protection
Grade 3 Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	Interrupt alpelisib. Prednisone 50mg a day over 10 days (with pneumocystis prophylaxis and PPI). Restart alpelisib as per package insert.
Grade 4 (SJS/TEN) Life-threatening consequences; urgent intervention indicated	Permanently discontinue alpelisib, consult with dermatologist

Hyperglycemia

Table 3. Dose modification and management for hyperglycemia

Fasting Plasma Glucose (FPG)/Blood Glucose Values	**Recommendation**
Grade 1 FPG > ULN-160 mg/dL or > ULN-8.9 mmol/L	No dose adjustment required. Initiate metformin 500 mg AC QD (titrate up by 500 mg QD weekly as needed and tolerated to max 2000 mg per day)
Grade 2 FPG > 160-250 mg/dL or > 8.9-13.9 mmol/L	No dose adjustment required. Initiate/maximize metformin and add secondary non-insulin agent If persistent Grade 2 hyperglycemia, add another secondary non-insulin agent or a tertiary non-insulin agent If FPG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days under appropriate antidiabetic treatment, reduce dose by 1 dose level and follow FPG value specific recommendations.
Grade 3 > 250-500 mg/dL or > 13.9-27.8 mmol/L	Interrupt alpelisib. Administer intravenous hydration and consider appropriate treatment (e.g., intervention for electrolyte/ketoacidosis/hyperosmolar disturbances which may include short-term insulin). Initiate/maximize metformin, add secondary non-insulin agent plus additional secondary non-insulin agent or tertiary non-insulin agent. If FPG decreases to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days under appropriate anti-diabetic treatment, resume alpelisib without dose adjustment for first grade 3 occurence. If second or third occurrence, resume at 1 or 2 lower dose levels, respectively. If FPG improves to grade 2 (160-250 mg/dL or 8.9-13.9 mmol/L) after addition of secondary non-insulin agent (Table 3), follow dose modification and management for grade 2 hyperglycemia (see above). If FPG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 3 to 5 days days, initiate/maximize non-insulin antidiabetic treatment or, if needed, add insulin (Table 5). If FPG does not decrease to ≤ 160 mg/dL or 8.9 mmol/L within 21 days following antidiabetic treatment, permanently discontinue alpelisib treatment.
Grade 4	Interrupt alpelisib.

> 500 mg/dL or ≥ 27.8 mmol/L	Administer intravenous hydration and consider appropriate treatment (e.g., intervention for electrolyte/ketoacidosis/hyperosmolar disturbances which may include short-term insulin), re-check FPG within 24 hours and as clinically indicated. Initiate/maximize metformin, add secondary non-insulin agent (Table 3) plus additional secondary non-insulin agent (Table 3) or tertiary non-insulin agent (Table 4). Add insulin (Table 5). If FPG decreases to ≤ 500 mg/dL or 27.8 mmol/L, follow FPG value specific recommendations for Grade 3. If FPG is remains at > 500 mg/dL or 27.8 mmol/L after IV hydration and acute antidiabetic treatment, permanently discontinue alpelisib treatment.

Table 4. Secondary non-insulin agents for antihyperglycemia treatment

Class	Risk for weight loss	Drug and recommended dosage[A]	Other Considerations for Treatment[A,B]
DPP-4 inhibitors	No	• Alogliptin 25 mg • Saxagliptin 5 mg • Linagliptin 5 mg • Sitagliptin 100 mg	• Typically well tolerated • Theoretical risk of acute pancreatitis • Joint pain
Thiazolidinediones	No	• Pioglitazone 45 mg • Rosiglitazone 4 mg	• Exercise extreme caution when using in patients with or at risk for congestive heart failure and patients at risk falls/fractures
GLP-1 receptor agonists	Yes	• Exenatide (extended release) 2 mg powder for suspension or pen • Exenatide 10 µg pen • Dulaglutide 1.5/0.5 mL pen • Semaglutide 1 mg pen • Liraglutide 18 mg/3 mL pen	• GI AEs are common (nausea, vomiting, diarrhea) • Injection site reactions • Risk of pancreatitis • Risk of thyroid C-cell tumors
α-Glucosidase inhibitors	No	• Acarbose 100 mg	• GI AEs are common

A. American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care 2019;42:S1-S193;
B. Pfeiffer AF and Klein HH. The treatment of type 2 diabetes. Dtsch Arztebl Int 2014;111:69-82

Table 5. Tertiary non-insulin agents for antihyperglycemia treatment

Class	Risk for weight loss	Drug and recommended dosage[A]	Other Considerations for Treatment[A,B]
Meglitinides	No	• Nateglinide 60-120 mg AC • Repaglinide 0.5-4 mg AC	Potential AEs include: • Hypoglycemia • Weight Gain • Diarrhea • Nausea
Sulfonylureas	No	• Glimepiride 1-8 mg PO OD • Glipizide 5-40 mg PO (OD or split dose BID) • Glipizide XR 5-20 mg PO • Glyburide* 2.5-20 mg OD • Glyburide micronized* 3-12 mg OD	Potential AEs include: • Hypoglycemia • Weight Gain • Diarrhea • Nausea

A. American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care 2019;42:S1-S193;
B. Pfeiffer AF and Klein HH. The treatment of type 2 diabetes. Dtsch Arztebl Int 2014;111:69-82
*contraindicated with eGFR<30; OD, once daily; AC, before meals

Table 6. Insulin for antihyperglycemia treatment

Class	Risk for weight loss	Drug	Recommended starting dose	Other Considerations for Treatment[A,B]
Basal insulin	No	• Insulin glargine • Insulin detemir	0.2 units per kg SC OD Increase for goal fasting FSBG < 160 mg/dL	Potential AEs include: • Hypoglycemia • Weight Gain
Rapid acting insulin	No	• Insulin aspart • Insulin lispro • Insulin glulisine	Start sliding scale AC FPG Units 70-99 0 100-149 0 150-199 2 200-249 3 250-299 4 300-349 5 350-399 6 over 400 7	Potential AEs include: • Hypoglycemia • Weight Gain

A. American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care 2019;42:S1-S193;
B. Pfeiffer AF and Klein HH. The treatment of type 2 diabetes. Dtsch Arztebl Int 2014;111:69-82

Diarrhea

Table 7. Dose modification and management for diarrhea.

Grade	Recommendation
Grade 1	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt alpelisib dose until recovery to Grade ≤ 1, then resume at same dose level.
Grade 3 and 4	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt alpelisib dose until recovery to Grade ≤ 1, then resume at the next lower dose level.

Other toxicities

Table 8. Dose modification and management for other toxicities (excluding hyperglycemia, rash, and diarrhea).

Grade	Recommendation
Grade 1 or 2	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.[1,2]
Grade 3	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4	Permanently discontinue alpelisib.

[1]For Grade 2 and 3 pancreatitis, interrupt alpelisib dose until recovery to Grade < 2 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity reoccurs, permanently discontinue alpelisib treatment.
[2]For Grade 2 total bilirubin elevation, interrupt alpelisib dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.

Fulvestrant or AIs

There is no dose modification for fulvestrant or AIs

Benralizumab

The starting dose of benralizumab is 30 mg on the first week of administration as a single dose.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Patients will be seen on day -1 of treatment initiation, day 14, and day 28 with a +/- 7 day window. Each evaluation will consist of the following:

- History and dermatologic examination with standardized photography, ECOG performance status.
- Recording of the adverse events
- Labs, skin tape strips per Table 8

Patients will be assessed radiographically per standard of care.

The PRO-CTCAE, FACT, and allergy questionnaire (Block 2014 FFQ) will be administered at baseline and every 2 weeks (Appendices 2- 4). The allergy questionnaire will be administer at baseline.

All visits will be conducted within the Breast Medicine Service. Any patients with active rash at the time of their study visit should also be evaluated for the rash by the dermatology service for CTCAE grading, photography, and management. If a patient does not have a rash, baseline photography will not be performed; documentation will reflect the absence of a baseline rash.

Table 9 Study Procedures.

Study Procedures	Screening with 14 days of D -1	Day -1 to -7	Day 1 Alpelisib initiation	Day 14±7	Day 28±7	Day 90 **(Safety Visit)**	Day 365 **(Follow Up)**
Informed consent	X						
Demographics	X						
Medical history	X						
ECOG	X			X	X		
Skin exam	X			X	X	X	
Vital signs	X			X	X	X	
Conmeds	X			X	X	X	
Study Questionnaires[1]	X			X	X	X	
AE evaluation	X			X	X	X	
Skin tape strips[2]	X			X	X		
CBC with Differential/chemistry[3]	X			X	X		
IgE (serum total)	X			X	X		
Allergy Panel[4]	X						
Hyperglycemia panel[5]	X			X	X		
Skin biopsy				X[6]	X[6]		
Cytokine panel[7]	X			X	X		
Benralizumab injection		X					
Alpelisib			Once a day by mouth				
Chart Review							X

[1]Allergy questionnaire on Day 1 only; [2]Skin tape strips will be sent to National Jewish Health for analysis [3] CBC with differential and comprehensive metabolic panel. [4]Includes Allergy Aminal, Dust, food screening, grass profile, mold, tree and weed profile. [5]HbA1c, fructosamine, C-peptide (fasting) [6]For patients with rash, a SOC skin biopsy will be conducted and an additional sample sent to National Jewish Health for research analysis. [7] Cytokine panel is to be sent to the sent to immune monitor facility- Dr. Phil Wong's lab.

12.0 CRITERIA FOR REMOVAL FROM STUDY

1) > 2 consecutive weeks of a delay in treatment due to toxicities
2) Progressive disease (breast cancer)
3) Unacceptable toxicity
4) Intercurrent, non-cancer related illness that prevents continuation of protocol therapy or follow-up
5) Major protocol violation that would render the patient inevaluable for efficacy
6) Repeated non-compliance by the patient with protocol requirements
7) Changes in the patient's condition or study intervention related toxicity such that, in the opinion of the investigator, continued participation in the protocol would compromise patient well-being
8) Withdrawal of patient's consent for personal reasons
9) Death

We do not expect any of the above criteria to occur with high frequency as the 4 week PFS for this population is over 90%. All participants for whom we are able to obtain the 4 week primary endpoint (had rash event prior to 4 weeks) will be considered evaluable for the primary rash endpoint under the intention-to-treat (ITT) approach.

12.1 End of Study

The end of study will occur when all patients have been followed for 1 year or death, withdrawal of consent, or are lost to follow-up.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

To assess subjects in the Benralizumab achieving treatment success, defined as grade ≤1 rash rate at 4 weeks, as assessed by the NCI CTCAE v5.0.

13.2 Secondary Endpoints Criteria for Study Endpoint Evaluability

1. To determine the effect of prophylactic anti-IL-5 receptor inhibition on alpelisib dose interruption or modification when compared to historical controls as determined by relative dose intensity (RDI) during the initial 4 weeks of therapy (4W-RDI).
2. To determine the effect of prophylactic IL-5 receptor inhibition on quality of life when compared to historical controls by computing the total score of the Functional Assessment of Cancer Therapy–Breast (FACT-B) and the PRO-CTCAE.
3. To determine the effect of prophylactic IL-5 receptor inhibition on steroid use when compared to historical controls, defined by the total amount of systemic corticosteroids multiplied by the number of days for the total amount (in mgs).

4. To determine the effect of prophylactic IL-5 receptor inhibition on time to development of alpelisib rash when compared to best historical controls treatment as the number of days from day 1.
5. To determine the safety of IL-5 receptor inhibition and antihistamines in patients receiving alpelisib by CTCAE v5.0 grading.
6. To determine the effect of IL-5 historical controls inhibition and antihistamines on non-skin alpelisib related adverse events CTCAE v5.0 grading.
7. To determine the overall response rate (ORR) and progression free survival (PFS) at 6 and 12 months post treatment initiation.

Adherence to alpelisib: Adherence to alpelisib will be assessed by 4W-RDI. The 4W-RDI will be calculated as the cumulative dose within the initial 4 weeks of starting alpelisib treatment divided by the standard dose.

Changes in inflammatory biomarkers in skin and related to rash: Blood will be collected at baseline, 14 days, and 28 days. Circulating levels of cytokines, will be measured at the immune monitoring facilty at MSK. CBC w differential, CMP, allergy panel and IgE will be measured in clinical chemistry laboratories using established protocols at each participating site.

Quality of Life: QOL will be assessed by the Functional Assessment of Cancer Therapy–Breast (FACT-B) (version 4) scale Appendice 3. The FACT-B contains 37-items, divided into four primary subscales for physical well-being (7 items), functional well-being (7 items), emotional well-being (6 items), and social/family well-being (7 items) that comprise the FACT–General (FACT-G) scale, in addition to a breast cancer subscale (10 items). The five subscales will be summed to obtain the FACT-B score (for a total score of 148).[42] We will also compute the FACT-G score (27 items, excluding the breast cancer subscale; total score of 108). All items are rated on a 0 to 4 Likert scale, using the following response format: 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much. Respondents are asked to respond to each question as it applies to the past 7 days. Higher scores on the FACT-B indicate higher QOL. Internal consistency for the FACT-G and FACT-B is well established. The PRO-CTCAE for rash, and other alpelisib AEs (i.e mucositis, diarrhea) will be administered at every visit.

13.3 Exploratory Endpoints

1. Explore the change in serum and skin inflammatory markers from baseline to 4 weeks (using non-invasive skin tape for skin).
2. Explore the change in histologic markers from skin biopsies in patients with rash, including eosinophil counts, CD4/8 count, IL-5, PI3 kinase pathway activation; at rash onset and at 28 days.

Skin tape strips (STS) sample acquisition. In this study STS will be collected from each study

participant at the initiation of treatment, day 14 and day 28 of the study. At each time point twenty large D-Squame tape strips (CuDerm; Ø30mm) will be collected from the designated skin area with no lesions. If on day 14 or day 28 skin rash is present, STS sampling of the lesional area will be performed as well. D-Squame D500 pressure instrument will be used to apply equivalent pressure (225 g/cm^2) for STS collection. Collected STS will be stored adhered to storage cards (CuDerm) to minimize air exposure of the collected material and kept frozen at - 80°C prior to processing.

Protein extraction from STS. Due to the relatively small quantity of biomaterial collected from the skin with adhesive STS, our protocol was optimized to minimize the total volume of extraction buffer for each sample. Extraction chambers containing individual STS (in extraction buffer) will be placed in a Cole-Parmer 8891 bath sonicator for 30 minutes at 40kHz at 65W. After the sonication, STS will be removed from the buffer, protein extracts will be transferred into microtubes and centrifuged to clear cell debris and tape adhesive residue. Samples will be cryopreserved for future analysis. Total protein levels in STS extracts will be measured with NanoOrange Protein Quantitation Kit (Invitrogen).

MSD multiplex assay from plasma. Protein extracts will be analyzed using the MSD U-Plex human cytokine multiplex platform. We will aim to profile the expression of cytokines and chemokines in the skin prior and during rash development targeting Th1, Th2, Th17 and general inflammation (general inflammation: IL-1a, IL-1b, IL-18, IL-6, and IL-8; Th2 cytokines: CCL17, CCL22, TSLP, IL-33, IL-13, IL-4, IL-5, IL-22, IL-31, and eotaxin 3; Th1/Th17 cytokines: IL-12, IL-17a, IL-17c, IL-IL-23, and IP-10). For statistical analysis, cytokine concentrations below the fit curve range (signal below the bottom of the bottom-of-the-curve fit, no concentration given) will be assigned the value of the lowest sample concentration detected below the standard curve detection limit to maintain the ranking order. The MSD assay results will be normalized to the total protein in each sample.

Assessment of skin biopsies. Skin biopsies will be collected from the skin site with rash. Skin biopsy will be fixed in 10% buffered formalin. Preserved skin biopsies will be paraffin embedded and sectioned. Skin biopsy sections will be used to assess inflammatory cell infiltrates and inflammatory mediators in the skin through RNA transcripts profiling and immunostaining.

RNA preparation and real-time RT-PCR. RNA FFPE kit (Qiagen) will be used for RNA extraction from FFPE preserved skin biopsy samples according to the manufacturer's protocol. RNA will be reverse-transcribed into cDNA using SuperScript VILO MasterMix (Life Technologies, Thermo Fisher Scientific). cDNA will be analyzed by real-time RT-PCR using an ABI Prism 7300 sequence detector (Applied Biosystems, Thermo Fisher Scientific). Primers and probes for selected gene targets will be purchased from Applied Biosystems, Thermo Fisher Scientific.

Immunofluorescence staining. Skin biopsy sections will be stained with the specific antibodies to detect tissue eosinophils, lymphocytes, IL-5 and PI3 kinase pathway activation. Visualization of additional inflammatory cytokines/chemokines of interest will be considered based on the results of the inflammatory mediator assessment form the multiplex MSD assays of protein extracts prepared from STS samples. Nuclei will be visualized with DAPI, and wheat germ agglutinin-conjugated FITC will be used to stain the cytoskeleton. The slides will be visualized with fluorescence microscopy (Leica) Slidebook 6.0 (Intelligent Imaging Innovations) will be used for data analysis. Skin biopsy sections from healthy control subjects obtained through other studies will be used for comparison.

Novelty of proposed studies

Proposed exploratory studies will provide novel insights about the longitudinal production of inflammatory mediators and cytokines in the multiplex format in the skin of cancer patients with

targeted PI3 kinase inhibition with alpelisib and concomitant inhibition of IL-5 or histamine signaling during the course of therapy. The information about the production of these mediators in patients that do not develop skin rash, or in the skin with skin rash before and after skin rash onset will be acquired.

The study will allow visualization of inflammatory infiltrates and IL-5 production in skin biopsies from patients with rash despite treatment with anti-IL5 receptor blocking antibody or histamine H1 inhibitor, to determine what type of skin inflammatory response persists in patients with skin rash and whether skin tissue eosinophil and IL-5 elimination was efficient.

The study will explore evidence of PI3 kinase pathway inhibition in skin biopsies from cancer patients with rash.

14.0 BIOSTATISTICS

Sample Size

This will single arm trial. The target sample size is intended to test the hypothesis that benralizumab reduces the frequency of grade ≥ grade 2 rash at 4 weeks relative to the historical controls in patients receiving alpelisib. The primary endpoint in the current study will be the proportion of patients to achieve a rash grade of 1 or less. It has been reported that approximately 34% of patients receiving alpelisib will develop ≥ grade 2 rash within the first 30 days. An increase in rash control to approximately 88% is deemed to be clinically meaningful with the investigational agent. Sample sizes of 57 patients achieves an 80% power to detect a difference based on a two sample proportions test. Due to potential attrition during the course of the study, the sample size will be increased by 10%. The resultant sample size will be 63 patients.

General Statistical Plan

There will be one analysis population the current study. The modified intent to treat (ITT) population will be all patients regardless of treatment compliance for whom investigators were able to obtain a 4-week efficacy assessment. The safety population will be patients who received at least one dose of study drug or the standard of care, regardless of any efficacy assessments. All efficacy analyses will be based on the modified ITT population. Patient, clinical and safety data as well as primary, secondary and exploratory endpoints will initially be presented descriptively as means, medians, or proportions with appropriate measures of variance (i.e. range, SD, 95%CI). The primary endpoint, , ≥ grade 2 rash versus < grade 2 rash will be evaluated using generalized linear models (GLIM), with a logit link function and a Bernoulli distribution. A group*time interaction will be included to assess the difference in the outcome measure at the specific study time points. Differences in the frequency of grade 0/1 rash overall all study visits (days 14, 28 and 90) will be assessed using mixed models for repeated measures as a secondary analysis.

The total number of dose reductions and delays between study groups over the trial period will be compared using Poisson regression analysis. The absolute difference in the FACT-B and PRO-CTCAE scores from day 1 to 14 and 28 between groups will be also be evaluated using repeated measures mixed models. The cumulative dose of corticosteroid use between

the Benralizumab group over the study period will be compared using the Wilcoxan Rank Sum test. Time to the development of grade 1 or 2 rash will be evaluated using Kaplan-Meier time to event curves and assessed using the log rank test and Cox proportional hazards regression analysis. The Yates corrected chi square test will be used to compare the frequency of non-skin alpelisib related adverse events between groups, as well as 6 and 12 month ORR and PFS. Differences between the Benralizumab group on IL-5 inhibition and antihistamines and non-skin alpelisib related adverse events will be evaluated using linear mixed models. Changes in inflammatory biomarkers in skin and related to rash and all other exploratory endpoints will only be evaluated graphically with descriptive statistics. Given the exploratory nature of the current trial, there will be no adjustments for multiplicity. All the statistical analyses will be performed using SAS® Version 9.4 or higher. De-identified data will be shared via MSK secured e-mail quarterly to Augmentium Pharma Consulting for statistical analysis.

Patients may be removed from the study for various reasons as outlined in section 12.0 of the protocol. Descriptive statistics will be reported separately for patients removed from the study, including a summary of reasons for removal, their median duration in the study and range, median, range, and the distribution of rash grades at all follow-up times prior to their removal from the study.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

CTCAE Version 5 will be utilized for toxicity evaluation.

Alpelisib

The most common adverse reactions including laboratory abnormalities (all grades, incidence ≥ 20%) are glucose increased, creatinine increased, diarrhea, rash, lymphocyte count decreased, GGT increased, nausea, ALT increased, fatigue, hemoglobin decreased, lipase increased, decreased appetite, stomatitis, vomiting, weight decreased, calcium decreased, glucose decreased, aPTT prolonged, and alopecia.

Severe Hypersensitivity: Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, were reported in patients treated with Alpelisib. Severe hypersensitivity reactions were manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of Grade 3 and 4 hypersensitivity reactions was 0.7%.

Severe Cutaneous Reactions: Severe cutaneous reactions, including Stevens-Johnson Syndrome (SJS) and Erythema Multiforme (EM) were reported in patients treated with Alpelisib. SJS and EM were reported in 0.4% and 1.1% of patients, respectively.

Hyperglycemia: Severe hyperglycemia, including ketoacidosis, has been reported in patients treated with Alpelisib. Hyperglycemia was reported in 65% of patients treated with Alpelisib. Grade 3 (FPG > 250-500 mg/dL) and Grade 4 (FPG > 500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n = 2) treated with Alpelisib. Among the patients who experienced Grade ≥ 2 (FPG 160-250 mg/dL) hyperglycemia, the median time to first occurrence of hyperglycemia was 15

days (range: 5 to 517 days). In the 187 patients with hyperglycemia, 87% (163/187) were managed with anti-diabetic medication, and 76% (142/187) reported use of metformin as single agent or in combination with other anti-diabetic medication [i.e., insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas]. In patients with Grade ≥ 2 hyperglycemia with at least 1 grade improvement (n = 153), median time to improvement from the first event was 8 days (range: 2 to 65 days). In all patients with elevated FPG who continued fulvestrant or AIs treatment after discontinuing Alpelisib (n = 54), 96% (n = 52) of patients had FPG levels that returned to baseline. The safety of Alpelisib in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the SOLAR-1 trial. Patients with a medical history of Type 2 diabetes were included.

Pneumonitis: Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, has been reported in patients treated with Alpelisib. Pneumonitis was reported in 1.8% of patients treated with Alpelisib.

Diarrhea: Severe diarrhea, including dehydration and acute kidney injury, occurred in patients treated with Alpelisib. Most patients (58%) experienced diarrhea during treatment with Alpelisib. Grade 3 diarrhea occurred in 7% (n = 19) of patients. Among patients with Grade 2 or 3 diarrhea (n = 71), the median time to onset was 46 days (range: 1 to 442 days).

Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, Alpelisib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-fetal mortality (post implantation

loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures based on area under the curve (AUC) that were ≥ 0.8 times the exposure in humans at the recommended dose of 300 mg/day. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Alpelisib and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with Alpelisib and for 1 week after the last dose.

Benralizumab

Safety
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. 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 AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal

results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.
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 occurs 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 (e.g., 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 SAE Reporting

To ensure patient safety, every SAE, regardless of suspected causality, begins at time of intervention and until at least 30 days after the patient has stopped study treatment must be reported to Novartis and AstraZeneca within 24 hours of MSK learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form to:

- The Novartis Patient Safety department by email (clinicalsafetyop.phuseh@novartis.com) within 24 hours of MSK learning of its occurrence.
- The AstraZeneca Patient Safety department along with the AstraZenecas provided cover sheet by email (AEMailboxClinicalTrialTCS@astrazeneca.com), or by fax to AstraZeneca's designated fax line: +1 302 886 4114. If a secure email is not available, AE information must be sent by fax

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the MSK investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period (or 5 half-lives, if half-life is established, whichever is longer) should only be reported to Novartis and AstraZeneca if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis and AstraZeneca within 24 hours of MSK learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis and AstraZeneca Patient Safety department by email (clinicalsafetyop.phuseh@novartis.com) and (AEMailboxClinicalTrialTCS@astrazeneca.com) respectively. Pregnancy follow-up should include an assessment of the possible relationship to the [investigational/study treatment] (select as appropriate) any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

For multicenter trials where MSK is the data coordinating center, please refer to the MSK Multicenter Trial Addendum. All required SAE reporting to the funders and/or drug suppliers will be completed by MSK only.

16.0 PROTECTION OF HUMAN PARTICIPANTS

Prior to the enrollment of each participant, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the participant. It will be reviewed that participation in this clinical trial is voluntary and that the participant may withdraw consent at any time.

Consent process: All patients who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All participants will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 8.0.

Potential Risks: Our eligibility criteria and screening procedures are established to exclude individuals for whom this study treatment is not appropriate. Our screening procedures begin with medical chart review to identify any individuals with any condition or reasons that may prohibit study entry followed by oncologist approval to screen/identify patients who may not be eligible for any additional reasons. Finally, in-person assessments will be performed to screen/identify patients.

Risks of research participation: The greatest risk is release of information from health or research records in a way that violates privacy rights. MSKCC will protect records so that name, address, phone number, and any other information that identifies the participant will be kept private. It will be stated to the participant that the chance that this information will be given to an unauthorized individual without the participant's permission is very small.

Costs/compensation: Patients will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The patients will not be billed

for any study-related procedures. The participant is informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for the participant to receive money for any new products, tests, and discoveries that might come from this research.

Alternatives: The alternative to this trial would be not to participate in the study and receive routine standard of care.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (eg. qualified monitors from MSKCC) and external personnel, its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

Voluntariness of research participation: It is stated that taking part in this study is voluntary and patients have the right to withdraw at any time. Participation in the study will not impact on the clinical care patients receive.

Withdrawal: A note-to-file documenting the patient's withdraw must be filed in his/her EMR.

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 MSK Clinical Research Coordinator (CRC) will be assigned to the study. This CRC will be supervised by the Clinical Research Manager (CRM) and the Principal Investigator in the Breast Medicine Service. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. Case Report Forms (eCRFs) within an Electronic Data Capture (EDC), Medidata. Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

Data storage

Data will be stored in a Medidata database generated specifically for this study. MSK's Medidata application analyst will assist with building the database based on provided specifications.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

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. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently, as appropriate.

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting data and specimen analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

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 exist 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 of Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

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.

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18.0 APPENDICES

1.0 Alpelisib CTCAE AEs of interest.

2.0 Allergy Questionnaire

3.0 FACT-B Questionnaire

4.0 Pro-CTCAE Questionnaire

5.0 Alpelisib Pill diary

6.0 Laboratory Manual

19.0 MSK MULTICENTER TRIAL ADDENDUM