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Identification of germline mutations affecting the incidence and prognosis of high-risk cutaneous squamous cell carcinoma: A pilot study

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Introduction: Cutaneous squamous cell carcinoma (SCC) is responsible for 1 million cases in the United States each year. The genomic landscape of SCC, particularly of high-risk SCC, remains to be elucidated.

Objective: To identify predictive biomarkers in cancer-associated genes in high-risk SCC patients compared with the American population (AP).

Methods: We performed next-generation sequencing (NGS) using a targeted mutation panel with 76 cancer-associated genes. We analyzed the presence of single nucleotide polymorphisms (SNPs) in a cohort of 20 high-risk SCCs compared with the AP (ExAC database).

Results: Seven SNPs showed significant differences in the AP versus high-risk SCC patients, respectively: EGFR rs1050171 (54.92%, 80%, $P = .0243$), HRAS rs12628 (36.8%, 60%, $P = .0316$), FAT1 rs35753072 (25.54%, 5%, $P = .035$), KIT rs3822214 4.23%, 20%, $P = .0005$), KIT rs3733542 (5.45%, 20%, $P = .004$), SF3B1 rs788018 (47%, 95%, $P < .0001$), and SMO rs2228617 (71.36%, 100%, $P = .0046$). Discussion/Conclusions: Missense rs1050171 and rs3822214 were present in significantly more SCC cases versus the general population (AP). Both of these SNPs have been associated with other malignancies. While the remainder are synonymous SNPs, there is growing evidence suggesting such variants play a role in disease. For example, rs12628 has been associated with an increased risk of melanoma. This pilot study identified SNPs significant in high-risk SCC compared with the AP. A larger follow-up study will help determine if these SNPs can be further explored as predictive biomarkers of high-risk SCC.

Commercial disclosure: None identified.

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Population pharmacokinetic modeling and simulations for GBR 830, a first-in-class humanized monoclonal antibody inhibiting OX40, to support clinical development in patients with moderate to severe atopic dermatitis

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GBR 830 is a monoclonal antibody against OX40, a costimulatory receptor present on activated T cells that are responsible for effector and memory immune responses. The safety and tolerability of single and repeated administration of GBR 830 has been demonstrated in phase 1 studies with healthy subjects and a phase 2a proof-of-concept study with patients who had moderate to severe atopic dermatitis (AD). To support pharmacokinetic (PK)-based dose selection for clinical development, a population PK model was developed using data from these completed studies (phase 1, PoC), with a total of 120 subjects contributing 1960 observations. Data were modeled employing NONMEM 7.3 using a first-order conditional estimation with interaction method. Intravenous (IV) and subcutaneous (SC) serum profiles were integrated into a 2-compartment model with linear clearance. Covariates (body weight, anti-drug antibody [ADA] status, disease [AD], age, sex, and race) were evaluated graphically before selecting for formal testing. Model parameters included systemic clearance (CL), intercompartmental clearance (Q), central (Vc) and peripheral (Vp) volumes, first order absorption from SC injection compartment (KA) and associated between-subject variability (BSV). Body weight was found to be the most important covariate influencing PK, followed by ADA. Final population parameter estimates were derived and model goodness-of-fit was assessed. The predictability was confirmed by prospective simulations of repeat IV infusions. Due to lack of rodent cross-reactivity for GBR 830, or any available surrogate antibody, dose regimen selection for an ongoing phase 2b study (NCT03568162) relied upon PK simulations to achieve a Ctrough that matched human whole-blood receptor occupancy.

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Clinical responses by self-reported PsA status at baseline among patients with moderate to severe psoriasis treated with guselkumab versus secukinumab: Week 48 results from the ECLIPSE study

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Introduction: ECLIPSE, a phase 3 trial, compared guselkumab (GUS), an anti−interleukin-23 monoclonal antibody, to secukinumab (SEC), an anti−interleukin-17A monoclonal antibody for moderate to severe plaque psoriasis. Here, we evaluated consistency of responses of GUS vs SEC in subgroups of psoriasis patients with and without self-reported PsA.

Methods: Adult patients were randomized to: GUS 100 mg at wks 0, 4, 12, then every 8 wks (n = 534) or SEC 300 mg (given as 150 mg × 2) at wks 0, 1, 2, 3, 4, then every 4 wks (n = 514) through wk 44. Proportions of patients at wk 48 achieving Psoriasis Area and Severity Index (PASI) 90, PASI100, Investigator's Global Assessment (IGA) score 0/1, and IGA score 0 responses were analyzed by self-reported PsA status at baseline. Missing data were imputed as non-response.

Results: Proportions of patients with and without self-reported PsA, respectively, were: 18.2% (97/534) and 81.8% (437/534) for GUS, and 15.4% (79/514) and 84.6% (435/514) for SEC. At wk 48, PASI90 response rates in GUS vs SEC patients with PsA, respectively, were 82.5% vs 63.3% (95% CI 5.0-33.4) and 84.9% vs 71.3% (95% CI 8.0-19.3) in patients without PsA. PASI100 response rates in GUS vs SEC patients with PsA, respectively, were 56.7% vs 44.3% (95% CI −3.5 to 28.3) and 58.6% vs 49.2% (95% CI 2.6-16.2) in patients without PsA. Similar results were observed for IGA 0/1 and IGA 0 responses, which were numerically higher in GUS patients in both PsA and non-PsA subgroups.

Discussion: At wk 48, GUS had numerically higher response rates compared with SEC for moderate to severe psoriasis patients with and without self-reported PsA.

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Whole blood transcriptomic profiling in a phase 3 study of the efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp

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Background: STYLE (NCT03123471), a phase 3, double-blind, placebo-controlled study, evaluated efficacy and safety of apremilast 30 mg bid (APR) in patients with moderate to severe plaque psoriasis of the scalp and moderate to severe plaque psoriasis. We report pharmacodynamic effects and association between gene expression and APR clinical response in STYLE.

Methods: Patients were randomized to APR or placebo through week 16 and continued or switched to APR through week 32. Whole blood samples were collected from patients (APR, n = 195; placebo, n = 102) at baseline, week 4, and week16. Response was defined as achieving ScPGA score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline. RNA sequencing at 30m read-depth yielded 786 unique RNAseq profiles.

Results: Nineteen genes showed differential pharmacodynamic profiles between APR and placebo. PDE4D, a direct APR target, was significantly increased in APR-treated males and more pronounced in non-responders. No baseline individual gene-expression biomarkers predicted APR response. Modularized gene-expression patterns of responders showed enrichment of 973 immunology-related pathways; the most enriched gene-set showed a pattern of T-cell activation. There were 2509 differentially expressed genes between sexes (sDEGs); a subset were hypothesized as disease-related (vs 566 sDEGs in healthy subjects). Females expressed elevated immunoglobulin genes; males expressed elevated neutrophil, natural killer cells, and eicosanoid genes.

Conclusions: We identified sex differences in gene expression in scalp psoriasis patients. PDE4D was increased in male non-responders. Baseline gene expression showed enrichment of T-cell gene sets among APR responders. Immune cell activation in untreated patients may modulate and inform APR response.

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