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IPH4102 (an anti-KIR3DL2 antibody) in refractory cutaneous T cell lymphoma

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The aim of this first-in-human phase 1 trial was to evaluate the tolerance and efficacy of IPH4102, a monoclonal antibody targeting KIR3DL2, expressed on cutaneous T cell lymphoma. IPH4102 selectively depletes tumor cells through antibody-dependent cell-cytotoxicity and -phagocytosis. 35 Sezary Syndrome (SS) patients having failed at least 2 prior systemic therapies were included. IPH4102 was administered IV 4 times QW, then 10 times Q2W and Q4W thereafter. KIR3DL2-expressing cells were monitored in skin and blood by immunohistochemistry and flow cytometry. KIR3DL2 occupancy was evaluated semi-quantitatively by flow cytometry. Molecular Residual Disease (MRD) was measured by deep sequencing of the clonal TCR. No dose limiting toxicity was identified and the maximum tolerated dose was not reached. 42.9% patients experienced confirmed global response. Median duration of response and progression free survival were 13.8 (95% CI: 7.2 – NR) and 11.7 (95% CI: 8.1 – NR) months. IPH4102 induced drastic elimination of KIR3DL2-positive aberrant cells in skin and blood. In contrast, neither significant nor dose-related depletion of normal blood NK cells was observed. Decrease of KIR3DL2-expressing tumor cells in IHC after 4 weeks of treatment predicted clinical response 9 weeks later. MRD results confirmed the significant disappearance of the tumor clones in skin and blood. In conclusion, this study shows a favourable safety profile and clinical activity of IPH4102 in relapsed/refractory SS. Based on these results, the FDA granted Fast Track designation for IPH4101 in relapsed/refractory SS. A phase 2 study is currently underway to confirm the clinical activity in SS and to evaluate the potential of IPH4102 in other T-cell malignancies that express KIR3DL2.

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Novel biallelic RIPK4 mutations cause ectodermal dysplasia with cutaneous syndactyly

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A fine regulation of adhesive contacts between cells underlies many crucial processes during ectodermal tissues morphogenesis, renewal and maintenance. Ectodermal Dysplasias (EDs) are genetically heterogeneous genodermatoses affecting the development and/or homeostasis of two or more ectodermal derivatives, including hair, teeth, nails, and sweat glands. Clinically overlapping EDs occur as the result of defects in cell adhesion molecules (CAMs) or in their regulatory transcription factors (TFs). Here we report a family with two sibs from healthy parents affected by hair defects with alopecia, nail dysplasia, cutaneous syndactyly variably affecting fingers and toes and palmoplantar hypercheratosis. Such combination of features is diagnostic of nectinopathies caused by mutation in either *PVRL1* (nectin-1) or *PVRL4* (nectin-4) genes, but molecular analysis of these genes was negative in this family. By Whole Exome Sequencing, we identified two variants in *RIPK4* gene predicted to be pathogenic and not previously reported in the literature. The RIPK4 serine/threonine kinase is a major modulator of epidermal differentiation and is altered in two distinct genetic disorders with multiple pterigia, cleft lip/palate and other ectodermal defects known as Bartsocas-Papas and CHAND (Curly Hair-Ankyloblepharon-Nail Dysplasia) syndromes. Given the strong overlap between phenotypes resulting from nectins and RIPK4 alterations, we propose the existence of a functional link between RIPK4-mediated phosphorylation and CAMs playing a role during ectodermal morphogenesis and epidermal differentiation. Our results consolidate and expand the role of RIPK4 in epidermal development, differentiation and renewal, pinpointing the complex basis of EDs pathogenesis.

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Early major adverse cardiovascular events following the initiation of the anti-interleukin 12/23 antibody ustekinumab. A population-based case-time-control study

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Ustekinumab, a monoclonal antibody that targets interleukin (IL)-12/23, is used to treat psoriasis, psoriatic arthritis and Crohn disease. In 2011, a meta-analysis of randomized trials alerted on a potential risk of major adverse cardiovascular events (MACE) within the first months after the initiation of anti-IL-12/23 antibodies. Our objective was to assess if ustekinumab initiation may trigger MACE. Using the French National Health Insurance database, covering 66 million subjects, we included all patients exposed to ustekinumab between 2010 and 2016, classified according to their cardiovascular risk level (high vs. low risk). We conducted a case-time-control study. We defined the 'risk' period as the 6 months before MACE, defined as myocardial infarctions and strokes, and the 'reference' period as the 6 months before the risk period. The initiation of ustekinumab was screened in both periods, enabling to assess the odds-ratio (OR) between the initiation of ustekinumab and MACE. Among the 9290 patients exposed to ustekinumab, 179 displayed MACE: 65 myocardial infarctions, 68 unstable anginas and 46 strokes. Among patients at high-level cardiovascular risk, a significant association between ustekinumab initiation and MACE occurrence was identified (OR, 4.17; 95% CI, 1.19-14.59). Conversely, no association was found in patients at low-level cardiovascular risk (OR, 0.30; 95% CI, 0.03-3.13). From real-world data, we suggest that ustekinumab initiation could trigger MACE in patients at high cardiovascular risk, in line with current immunologic models of atherosclerotic disease. These results should call for caution regarding the prescription of ustekinumab in patients at high cardiovascular risk.

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Integration of multi-omic data identifies psoriasis endotypes correlating with clinical and immunological phenotypes

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We are performing omic analyses of psoriasis and psoriatic arthritis (PsA) patients to address the hypothesis that biomarker discovery will inform more individualized care of individuals (endotypes) with psoriasis and their comorbidities. We collected whole blood from psoriasis patients (n=59, 16 PsA; mean PASI=8.6 (range 0-33.5) with 9 healthy controls) and PBMCs (n=9 psoriasis, n=5 controls). RNASeq was performed using Illumina TruSeq Total RNA kits and a NextSeq 550 (15M+ paired reads/sample, 75 bp). Significant differentially expressed genes (DEGs; $p<0.05$) were identified between psoriasis/PsA patients and controls, and pathways were identified by gene set variation analysis. A general psoriasis signature was found vs. controls featuring upregulated interferons that trended toward an increase with age using linear regression. Other psoriatic endotypes were identified using proinflammatory biomarkers that clustered patients by increasing PASI score, gender and ethnicity. Network analysis identified interactions between the interferome and metabolic stimuli in psoriatic patients vs. controls. PSA patients uniquely expressed heat shock genes versus patients without joint involvement. Whole blood cytometric analysis revealed increased intermediate monocytes ($CD14^{+}CD16^{++}$) in psoriasis vs. controls ($p<0.05$). Regression analysis between the immunoflow and RNASeq data revealed that psoriasis patients with higher percentages of $CD14^{+}CD16^{++}$ monocytes also expressed unique inflammasome genes. Analysis of whole blood versus PBMCs from psoriasis patients revealed unique DEG perhaps reflective of each sample type's cellular composition. Our integrated omic and clinical approach is revealing classifiers of patients with the most severe forms of psoriasis and PSA that may be used to improve their standard of care.

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Daily practice of rituximab treatment for pemphigus: a retrospective study of 65 patients

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Pemphigus is a group of auto-immune mucocutaneous blistering diseases characterized by circulating autoantibodies against desmosomal proteins. The two major groups are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Long-term systemic corticosteroids are considered the mainstay treatment but are associated with significant adverse effects. Recent studies showed high effectiveness of rituximab in pemphigus, addressing the drug as first-line treatment. The aim of this study is to analyze retrospectively the effectiveness and safety of rituximab in pemphigus, and to compare different treatment regimens regarding additional infusions. The medical records of 65 pemphigus patients treated with different doses of rituximab were reviewed retrospectively. Effectiveness was measured by outcomes defined as disease control (DC), partial remission (PR), complete remission (CR) and relapses. Safety was measured by reported adverse events. All patients (65) achieved DC (100%), PR and CR were obtained by 10 and 49 patients (16% and 79%), respectively. PV patients with mucocutaneous lesions responded better than PV patients with only mucosal lesions (n=33, 100% versus n=14, 82%; p=0,035). Forty-five percent of the patients (n=17) who received the maintenance dose at month 6 developed a relapse, in contrast to 75% of the patients (n=18) without the maintenance infusion (p=0,019). The group with maintenance infusion at month 6 differed in mean cumulative corticosteroid dose (2157mg compared to 809mg respectively, p=0,013) and pemphigus subtype (PF 78% versus 22% respectively and PV 54% versus 45% respectively). Seven percent severe adverse events were reported, none life threatening. In conclusion, rituximab is a safe and effective treatment for pemphigus. Additional 500 mg rituximab at month 6 and 12 might prevent relapses, however further studies need to focus on predictive factors for relapses.

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Safety and efficacy of sirolimus gel therapy for patients with TSC involving facial skin lesions in a long-term clinical trial

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Tuberous sclerosis complex (TSC), an autosomal dominant genetic disorder caused by the constitutive activation of the mTORC1 signaling pathway, gives rise to hamartomas in various organs including the skin. Facial angiofibromas (AF)—the most predominant manifestations among skin lesions—are observed in about 75% of TSC patients. The progression of AF can cause severe disfigurement, thus adversely affecting their quality of life. We conducted a multicenter, long-term, open-label, uncontrolled clinical trial of the sirolimus gel in 94 patients with TSC involving facial skin lesions (angiofibromas, cephalic plaques, and hypomelanotic macules). The primary endpoint was the rate of adverse event (AE)-caused discontinuation. The main secondary endpoint was the efficacy of the gel. The independent review committee adjudicated the efficacy of the gel according to the 6-category criterion based on the photographs of skin lesions that were taken during the first 12 months of the trial. The rate of AE-caused discontinuation was 2.1% (2/94 patients). Furthermore, application site irritation and dry skin occurred relatively frequently. However, none of drug-related AEs was serious, and most AEs resolved rapidly. The response rates of angiofibromas, plaques, and hypomelanotic macules were 78.2% (95% CI: 68.0-86.3%), 66.7% (95% CI: 51.1-80.0%), and 72.2% (95% CI: 46.5-90.3%), respectively. We conclude that the gel had good long-term tolerability and was effective for TSC facial skin lesions.