Objectives: To evaluate the impact of UPA and AbbV599 on immunologic pathways associated with SLE pathogenesis.

Methods: SLE patients (n = 205) were randomized to placebo (PBO): n = 75; UPA 30mg QD: n = 62; AbbV599 n = 68). At screening, patients were stratified by their SLE Disease Activity Index 2000 (SLEDAI-2K) score, corticosteroid dose (> 10-mg prednisone or not), immunosuppressant and IFN score. Proteomic analyses were performed on the plasma samples using a commercial proximity-extension immunoassay. A repeated mixed linear model was used to compare changes in biomarkers vs PBO and Pearson’s correlation was tested to compare protein biomarkers, IFN score, and SLEDAI-2K score. All analyses were corrected for multiple testing using the Benjamini–Hochberg method. Enrichment analyses were performed to elucidate the biological pathways associated with changes in protein biomarkers.

Results: As expected, elevated IFN gene expression at baseline was associated with higher SLEDAI-2K disease activity scores, increased auto-antibody directed immune parameters, and lower levels of complement components. Expression of serum proteins related to the IFN pathway, such as CXCL10, sialic acid binding immunoglobulin-like lectin 1, IFN gamma, and ZBP1, positively correlated with the IFN score. Treatment with UPA monotherapy or the combination AbbV-599 significantly reduced the IFN gene scores compared with PBO at weeks 4 and 24 (p ≤.0001). Proteomic analyses revealed 301 protein biomarkers differentially modulated at weeks 2, 12, and 24 compared with PBO, including significant down-regulation of Type I IFN pathway proteins. There were additional impacts of UPA and AbbV-599 on T-cell associated cytokines, B cells, macrophages, and innate response markers. These effects were similar in activity with UPA and AbbV-599, suggesting that the main effect was attributable to activity of UPA.

Conclusion: These results suggest that the clinical benefit demonstrated by UPA in patients with SLE includes the modulation of Type I IFN with impact on several core pathogenic pathways involved in SLE. The main biomarker effects of UPA and AbbV-599 were driven by UPA.


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**POS134 NOVEL APPROACH TO TREAT SYMPTOMATIC LUPUS ERYTHEMATOSUS, BY TARGETING THE “ROOT CAUSE”: B CELLS AND PLASMA CELLS, USING BCMA-CD19 COMPOUND CAR**

**Keywords:** Autoantibodies, Systemic lupus erythematosus, Clinical trials

Y. Yuan1, S. He2, W. Zhang3, H. Zhang3, V. Destefano4, M. Wada5, K. Pinz5, G. Deeren4, Y. MAT, M. Wang6, F. LI1, M. Hong1, L. Ting1, C. ZOU1, M. Wang1, L. Ding3, Y. Liang1, Y. MA1, W. Wang1, 2Zhongshan People’s Hospital; Department of Translational Medicine, Zhisuang, China; 2Zhongshan People’s Hospital, Department of Rheumatoid Immunology, Zhisuang, China; 3Peking University Shenzhen Hospital; Department of Hematology, Zhenzhen; China; 4iCell Gene Therapeutics Inc., Research & Development Division, Stony Brook, United States of America; 5CAR Bio Therapeutics Ltd, Research & Development Division, Zhongshan, China

**Background:** Systemic lupus erythematosus (SLE) is a heterogeneous multi-system autoimmune disease characterized by the presence of auto-antibodies produced by the “root cause” B and plasma cells. Autoantibody depletion has been attempted by targeting B cells, however no such treatment addresses both B and plasma cells.

**Objectives:** We assess the safety and efficacy of dual resetting B and plasma cell populations using our novel BCMA-CD19 cCAR T (cCAR) in an open label phase I clinical trial.

**Methods:** We constructed a cCAR composed of a complete BCMA-CD19 CAR fused to a complete CD19-CAR, separated via self-cleaving P2A peptide. The cCAR functional activity was assessed in co-culture assays with multiple cell lines and mouse models. T cells from peripheral blood obtained via apheresis were transfected to create cCAR. Cessation of steroids and immunosuppressing medications was followed by conditioning. Patients received monthly IgG until B cells recovered. Patients were dosed from 1.5×10^9 cCAR cells/kg body weight and monitored. P1 and P2: 20-year history of managed SLE and received cCAR as compassionate use for B cell lymphoma. P1 and P2 achieved complete remission (CR). After 1-year follow up demonstrated CR of SLE, hospital approved additional SLE/Lupus Nephritis (LN) patients for treatment. Baseline Characteristics: 12 patients received CAR in total. Patents aged 32-58. Ten of 12 were female. P1 and P2: SLEDAI-2K score 4, and 8, respectively. Patient 3-12: SLEDAI-2K baseline score mean 11 range 6 to 16. All of patients (3-12) had LN on kidney biopsy between IV to V with failure of standard therapy.

**Results:** Safety: Overall cCAR has been well tolerated to date. There have been no severe adverse events (SAE) or infections attributed to cCAR, no CRES and no CRS above Grade 1. All patients with >3 weeks follow up had a mild fever (CRS grade 1) which resolved with supportive care. Onset of mild fever occurred between days 3 to 14 and resolved within a week of onset. Efficacy: B cells were entirely depleted in peripheral blood 3-14 days post cCAR. Three patients treated >6 months in CR (SLEDAI-2K = 0, all autoantibodies negative, and normal complement). P1 and P2 maintain drug free CR and with no autoantibodies post-cCAR approximately 40 and 20 months respectively. All B cells recovered within 2-6 months with no indications of relapse. At 1-4 months post-treatment 9 patients were negative for, anti-dsDNA autoantibody, anti-nuclear autoantibody, anti-Sa/Ro52 autoantibody, anti-SSA/Ro60 autoantibody, anti-ribosomal P, and anti-U1-snRNP. Among 9 patients rapid improvement within 1 month after cCAR, mean SLEDAI-2K dropped from 8.7 mean at baseline to 2 at 1 month (7 patients no symptoms), and mean drop to 0.88 within 6 months (9 patients no symptoms). All patients achieved 100% response and are maintaining medication free recovery. (no immunosuppressives or glucocorticoids). An immune “reset” was confirmed via flow cytometry showing that most of recuring cells are naïve B cells, and further observed in BCR deep sequencing (patients 3-4), whereby IgG and IgA clones are absent and non-class-switched BCR repertoires are present with >95% IgG heavy chain.

**Conclusion:** These data on the 12 patients treated with cCAR demonstrate that the intervention is well tolerated. Initial data suggests immune system “reset” with long-term remission is possible as cCAR treats the “root cause” of disease by depleting autoreactive antibodies produced by plasma cells and memory B cells. This approach can be extended to other B and/or plasma cell mediated autoimmune disorders. The full dataset will be updated at the meeting.

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**POS135 EFFECT OF IMMUNOMODULATORY THERAPIES ON ANTIPHOSPHOLIPID BLOOD CLOTS IN CHILDREN WITH ANTIPHOSPHOLIPID SYNDROME**

**Keywords:** Anti-phospholipid syndrome, Autoantibodies

P. Morán Álvarez1, E. Marasco1, V. Messia1, F. De Benedetti1, C. Bracaglia1, 1Ospedale Pediatrico Bambino Gesù, Pediatric Rheumatology, Rome, Italy

**Background:** Pediatric Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by vascular and/or arterial thrombotic events (TE) associated with 2 consecutive positive determinations at least 12 weeks apart of antiphospholipid antibodies (aPL), IgG/IgM anticardiolipin (aCL), IgG/IgM [IgG2]-glycoprotein I (a)2G2PI) and/or lupus anticoagulant (LA). Recent data suggests that aPL levels may decrease over time due to the natural history of the disease or to treatments. Therefore, monitoring of aPL levels may represent a strategy to evaluate disease activity and response to the therapy.

**Objectives:** To investigate the trend over time of aPL titers in children with APS comparing patients under immunomodulatory therapies and those without them.

**Methods:** A descriptive, observational, cross-sectional study was carried out in children with APS. aPLs testing was carried out in all patients from diagnosis every 3-4 months for 2 years. Interferon Gene Signature (IGS) was assessed as described by Crow[1]. Laboratory parameters, clinical and demographic data was retrieved and analyzed. Statistical analysis was performed with software R, v.4.0.3.