multiple indications to date, to characterize the safety profile of atacicept.

Methods Analyses were based on 3 pooled datasets: double-blind placebo-controlled (DBPC) set (n=1568; key endpoint: treatment-emergent AEs [TEAEs]); SLE set (n=761; key end-point: IgG change and serious infection rates); and full analy-sis set (n=1845; key endpoint: exposure-adjusted mortality).

Results Of 1568 patients in the DBPC set, 30.8% received placebo, 8.2% atacicept 25 mg, 24.5% atacicept 75 mg and 36.5% atacicept 150 mg. Overall, baseline characteristics were balanced across treatment arms. Treatment exposure was simi-lar with placebo and atacicept 75 and 150 mg (278.3, 225.0 and 286.7 patient-years, respectively), but was lower with ata-cicept 25 mg (51.5 patient-years). Exposure-adjusted TEAE rates were generally higher with atacicept vs placebo, with no consistent association between atacicept dose and cardiac arrhythmias, serious and severe infections or injection site reactions (table 1). Serious infection and serious TEAE rates were similar between atacicept and placebo. TEAE-related dis-continuation rates were higher with atacicept vs placebo (16.1 vs 10.9 per 100 patient-years). In the SLE set, there was no association between reduced IgG levels and increased infection rates. Across all studies (full analysis set), 11 patients died during treatment (10 atacicept [0.5%], 1 placebo [0.1%]). Infection-related deaths in the DBPC set are shown in the table 1. Exposure-adjusted mortality rates per 100 patient-years were 3.60 (95% CI: 0.90–14.38) with atacicept 25 mg, 0.34 (95% CI: 0.05–2.43) with 75 mg, 1.18 (95% CI: 0.49–2.82) with 150 mg, and 0.44 (95% CI: 0.06–3.12) with placebo.

Conclusions Results from this pooled analysis clarify the bene-fit-risk relationship for atacicept, which is being further eval-uated in additional clinical studies in IgA nephropathy and SLE.

characteristics, biomarkers and clinical efficacy. In addition, the baseline expression and change in expression of putative APRIL-responder genes were compared among the clusters. APRIL-responder genes were identified by combining differen-tial expression results from the APRIL-SLE study (Week 52 vs. Day 1 randomization) and tabalumab Phase III studies (Week 52 vs. Baseline; GSE88887).

Results Patient gene expression data (N=105; Placebo: N=30; atacicept 75 mg: N=40; atacicept 150 mg N=35) was used to group patients into 5 main clusters (P1-P5) by predominant characteristic cells: P1, T helper cells; P2, plasma cells; P3, neutrophils and B cells; P4, B cells; P5, activated dendritic cells. Patients in P2 and P5 were more likely to have positive anti-dsDNA antibodies (≥30 IU/ml) and elevated BLyS (≥1.6 ng/ml), as well as high IFN gene signature in the blood. Patients in P2 were more likely to have low complement C3 and C4 levels. In P2, P4, and P5 clusters the flare rate in the placebo group was significantly higher than in P1 and P3. In P2 and P4, atacicept 150mg treatment group showed delayed time to flare and reduced flare rate as compared with the pla-cebo group. A comparison of differentially-expressed genes from clinical studies of SLE patients on atacicept (targets BLyS & APRIL) vs tabalumab (targets BLyS) revealed possible APRIL-responder genes: SDC1, PARM1 and MZB1. These genes have a higher baseline expression in the P2 and P4 compared to other clusters. SDC1 was reduced more in P2, P4, and P5 after atacicept treatment, while PARM1 and MZB1 decreased after atacicept treatment in P2 and P4.

Conclusions These post-hoc analyses revealed different subsets of SLE patients based on their molecular profiles, which iden-tified patient subsets that might have differential treatment effect of atacicept vs placebo, and provided insights into potential mechanisms of flare.

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211 IDENTIFYING LUPUS PATIENT SUBSETS AND SPECIFIC PHARMACODYNAMIC CHANGES THROUGH IMMUNE CELL DECONVOLUTION OF GENE EXPRESSION DATA IN ATACICEPT-TREATED PATIENTS IN THE APRIL-SLE STUDY

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Background The Phase II/III APRIL-SLE study evaluated the safety and efficacy of atacicept in systemic lupus erythemato-sus (SLE). The goal of this post-hoc analysis was to use cell-based gene signatures on the APRIL-SLE gene expression data to identify clusters of patients with potential to flare and to assess for difference in treatment effect of atacicept vs placebo.

Methods A published immune cell deconvolution algorithm was applied to whole-blood gene expression data from APRIL-SLE to identify relative proportions of 17 immune cell types. Patients were then grouped into clusters based on these immune cell profiles using a k-medoid clustering algorithm, and were compared to each other based on patient

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212 PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-FINDING STUDY, EVALUATING THE BRUTON'S TYROSINE KINASE INHIBITOR EVOBRUTINIB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: STUDY DESIGN

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Background Evobrutinib is a highly specific, oral inhibitor of Bruton's tyrosine kinase, a key regulator of B cell and macro-phage functions implicated in SLE. Evobrutinib was shown to be well tolerated in healthy volunteers in a phase 1b study and subsequently advanced to phase 2.

Methods In this double-blind, placebo-controlled, potentially pivotal, 52-week dose-finding study with an optional open-label extension (OLE) and a 4-week safety follow-up period (NCT02975336), patients are randomized 1:1:1:1 to receive low, mid or high dose evobrutinib, or placebo (figure 1). Eligible patients are aged 18–75 years, with an SLE diagno-sis (SLICC criteria or ≥4/11 ACR classification criteria) ≥6 months prior to screening, a SLEDAI-2K total score of ≥6 (including SLEDAI-2K clinical score ≥4) at screening, and