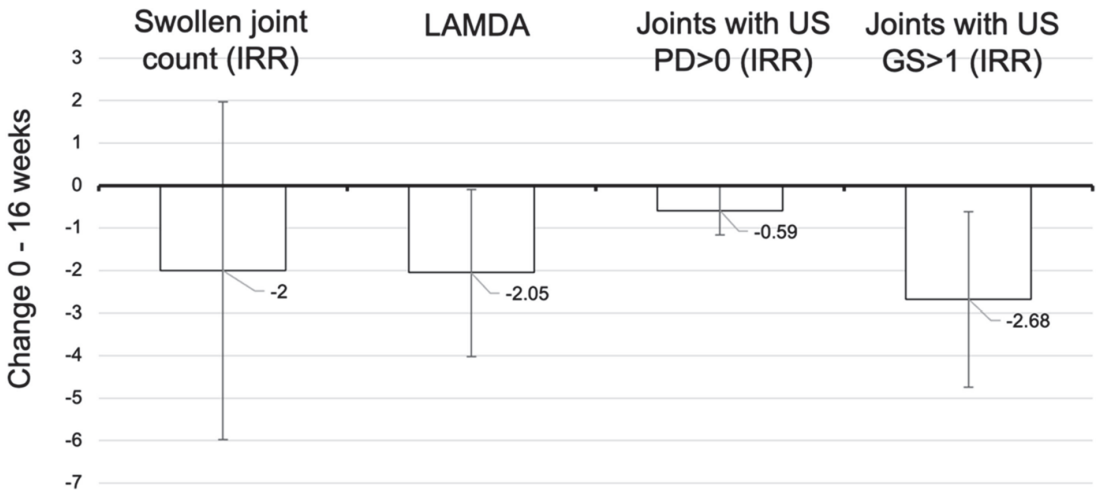

Abstract O14 Figure 2 16-week objective outcome measures across all rituximab cycles administered (n=22)

MSK ultrasound; (ii) preliminary evidence for efficacy of Rituximab.

Methods Enrolment required clinical synovitis and/or ultrasound tenosynovitis/joint power Doppler with ≤10mg prednisolone. Patients were randomized to 1000mg Rixathon or placebo, on days 1 and 15, each preceded by 100mg methylprednisolone. BILAG-2004, SLEDAI-2K, LAMDA, tender and swollen joint counts, physician global, patient MSK pain and global VAS, PROs, BICLA, SRI-4 were evaluated monthly. US of both hands and wrists was performed at 0 and 16 weeks. The primary endpoint was feasibility. The key efficacy timepoint was 16-weeks. After 16-weeks placebo patients with active disease were eligible for rescue rituximab with repeat follow-up assessments. US and LAMDA were validated against BILAG-MSK improvement using baseline-adjusted regression.

Results Of 27 patients randomised, 12 received placebo, of whom 9 received rescue. BILAG-MSK domain at baseline was scored A in 7/27 (26%), B in 16/27 (59%) and C in 2/27 (7.4%). At 16 weeks, BILAG-MSK response was significantly associated with improvement in LAMDA (OR 0.48, 95% CI 0.18, 0.84); US joints grey-scale (OR 0.56, 95% CI 0.28, 0.85) and US tendons PD (OR 0.33, 95% CI 0.04, 1.01).

Unexpectedly, some outcome measures showed greater improvement in patients who received methylprednisolone and placebo than with methylprednisolone and rituximab. These measures then converged by 16 weeks (figure 1). However, pooling all rituximab cycles administered (as initial therapy or as rescue) showed significant improvement in LAMDA (coefficient(95% CI) -2.68 (–4.02, -0.09)), number of joints with US-PD>0 (-0.59(-1.16, -0.02)), and number of joints with GS>1 (-2.68(-4.74, -0.62) at 16 weeks (figure 2).

Conclusions SLE arthritis trials offer a homogenous trial population, low GCs, and validated objective outcome measures. Initial worsening before benefit with rituximab may be explained by increased antigenic load and removal of B cell regulatory functions before beneficial effects on plasma cells and B cell antigen presentation are manifest. Detecting such nuances may reflect the greater sensitivity of this trial design.

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O15 B CELL, T CELL, CYTOTOXIC/NK CELL, AND MITOCHONDRIAL GENE DYSREGULATION PATTERNS SEPARATE NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS INTO TWO DISTINCT SUBGROUPS WITH DIFFERENTIAL ANTICIPATED RESPONSE TO TARGETED THERAPIES

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Objective The management of neuropsychiatric (NP) systemic lupus erythematosus (SLE) is poorly optimised and specific treatment is lacking. The aim of this study was to perform an in-depth investigation of the transcriptome of SLE patients with active central nervous system (CNS) involvement to gain insights into underlying molecular mechanisms and identify new potential drug targets for CNS lupus.

Methods We analysed differentially expressed genes in peripheral blood from patients with active CNS lupus (n=26) and active non-NP SLE (n=43) versus healthy controls (n=497) from the European PRECISESADS project (NTC02890121), as well as dysregulated gene modules. Gene modules were subjected to correlation analyses with serological markers, and regulatory network and druggability analysis.

Results Unsupervised co-expression network analysis revealed 23 dysregulated gene modules (figure 1A). Four showed differential dysregulation between two distinct subgroups of CNS lupus patients. The interferon module was upregulated in both subgroups. The 'B cell', 'T cell', 'cytotoxic/NK cell', and

'mitochondrial cluster' gene modules were all found to be more downregulated in one subgroup, while the other subgroup showed varied dysregulation patterns. Drugs annotated to the cytotoxic/NK cell network included pegaptanib, a selective vascular endothelial growth factor (VEGF) antagonist, while many anticonvulsants such as zonisamide, lamotrigine, and oxcarbazepine showed potential for counteracting the transcriptomic signature associated with the B cell module. Druggability analysis for the mitochondrial cluster module revealed potential for the centrally acting angiotensin-converting enzyme inhibitor captopril, the mammalian target of rapamycin (mTOR) inhibitor everolimus, the proteasome inhibitor bortezomib, the toll-like receptor 5 (TLR5) agonist entolimod, and the spleen tyrosine kinase (SYK) inhibitor fostamatinib. In silico prediction algorithms demonstrated a greater anticipated response to anifrolumab and calcineurin inhibitors for the active CNS subgroup with B cell, T cell, cytotoxic/NK cell, and mitochondrial gene downregulation compared with the patient subgroup of mixed dysregulation patterns (figure 1B).

Conclusion In this cohort of SLE patients of European origin, B cell, T cell, cytotoxic/NK cell, and mitochondrial gene dysregulation patterns separated active CNS lupus patients into two distinct subgroups with differential anticipated response to type I interferon and calcineurin inhibition. Our study provides a conceptual framework for precision medicine in CNS lupus.

Conflicts of interest IP has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia, Bristol Myers Squibb, Elli Lilly, Gilead, GlaxoSmithKline, Janssen, Novartis, Otsuka, and Roche. The other authors declare that they have no conflicts of interest related to this work.

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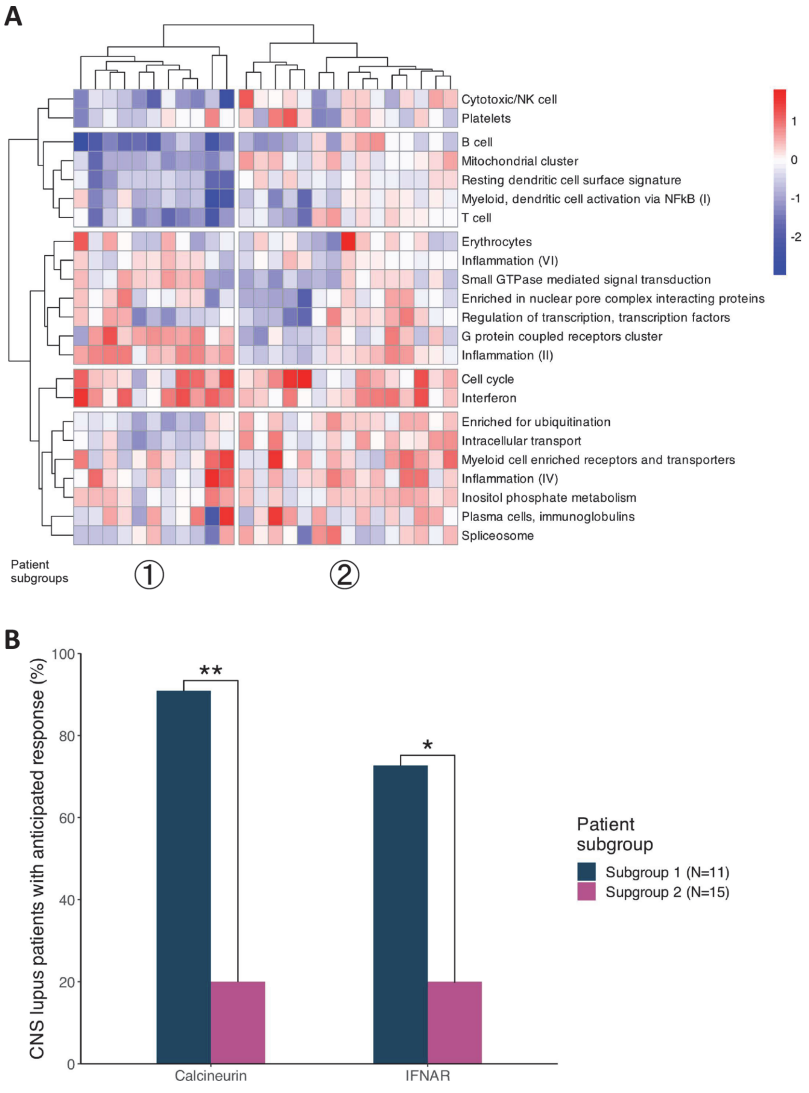

Abstract O15 Figure 1 B cell, T cell, cytotoxic/NK cell, and mitochondrial gene dysregulation patterns separate patients with active CNS lupus into two distinct subgroups with differential anticipated response to targeted therapies. (A) Heatmap displaying the 23 dysregulated gene modules, grouping the patients into two main subgroups Subgroup 1 was characterised by a more prominent downregulation of the B cell, T cell, cytotoxic/NK cell, and mitochondrial gene modules. Subgroup 2 showed mixed dysregulation patterns. Red colour denote upregulated gene modules and blue colour downregulated gene modules compared to healthy controls. (B) Bars depicting proportions of patients with an anticipated benefit from inhibition of selected drug targets between the two active CNS lupus patient subgroups.