had not sufficiently responded to standard treatment and hence, were offered treatment with bortezomib. The disease activity score SLEDAI and anti-dsDNA antibody titers decreased upon treatment. In all patients with active lupus nephritis proteinuria declined within 6 weeks after start of bortezomib. Total IgG concentrations decreased in most patients by approximately 25%, however, they usually remained within normal limits. All adverse events were mild or moderate. A proteasome inhibitor that targets preferentially immunoproteasomes is currently under investigation in clinical trials for the treatment of autoimmune diseases.

c. TACI-Ig (atacicept) is a soluble fusion protein of the extracellular domain of TACI and the Fc part of human IgG. Atacicept binds and neutralises the TACI ligands BAFF and, even more importantly, APRIL, which is a key survival factor for plasma cells. Atacicept eliminates quite specifically plasma cells and – as a consequence – causes often hypogammaglobulinemia with increased risk of infections. There is some evidence from placebo-controlled multi-centre clinical trials that atacicept may ameliorate SLE disease activity.

d. Anti-CD38 antibodies: CD38 is an ectoenzyme on the plasma membrane of different cell types such as many B and T cell subsets including plasma blasts and plasma cells. The anti-CD38 antibody daratumumab is approved for the treatment of multiple myeloma. Case reports indicate that daratumumab may be also beneficial in antibody-mediated autoimmune diseases such as severe autoimmune thrombocytopenia, autoimmune haemolytic anaemia and SLE.

In summary, plasma cell-targeted treatments may represent a new and highly effective treatment approach in SLE as well as other antibody-mediated diseases. Placebo controlled clinical trials are required to prove the efficacy and safety of plasma-cell depleting treatments in refractory SLE.

Learning Objectives
- Explain why plasma cells represent an attractive target for the treatment of SLE and other antibody-mediated diseases
- Discuss existing treatments, in clinical trials, which eliminate plasma cells and describe their potential for treating patients with SLE

REFERENCES
Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral immunity. Here disturbances in cytokine production and B lineage cell disturbances became very evident in recent years. Identification of increased interleukin (IL)-6, IL-17, IL-12 and IL-23, BAFF, and especially type I interferon (IFN) production by different cell types, provided the rationale for targeting these cytokines or their corresponding cytokine receptors using biologics. Since these cytokines activate various intracellular pathways, such as Jak/Stat signalling, activation of the NfkB or using spleen tyrosine kinase (Syk), Bruton’s tyrosine kinase (BTK), small molecules inhibiting these pathways are being investigated in various clinical studies.

It should be emphasised that most of the above-mentioned intracellular pathways may vary between different immune cells and tissues and can have interactions which have not been fully described. However, certain strategies target multiple key pathways along with inhibiting various cytokines (multiple targeting therapy),1 which holds the promise to cover broadly heterogeneous SLE, a therapeutic principle that has already been introduced in other disciplines, such as antihypertensive and anti-infectious treatment algorithms.

As a first example in patients with SLE, treatment with the Jak1/Jak2 blocking agent (Jakinib) baricitinib showed improvements of skin and joint manifestations among patients with a daily dose of 4 mg/d but less pronounced under 2 mg/d in a principle that has already been introduced in other disciplines.

...and was originally applied to ancient philosophers who were not committed to any single system of philosophy; instead, these philosophers selected whichever doctrines pleased them from every school of thought.1 Much like the ancient Greek philosophers, drug target selection in SLE has spanned many pathways. Although belimumab has been the sole drug approved to date via the traditional route of a randomised controlled trial, it’s just a matter of time before drugs targeting other molecules and pathways are granted approval for SLE and lupus nephritis.

The potential drug targets in SLE appear limitless, making decisions regarding resource allocation incredibly challenging. Should components of the innate or the adaptive immune system be targeted? Perhaps both? This presentation will review various strategies being pursued in order to inhibit key pathways in SLE. The emphasis will be on investigational agents in Phase I and Phase II programmes.2,7

Learning Objectives
- Discuss strategies for inhibiting the type I interferon pathway
- Discuss methods to target B and T cells
- Review approaches to down-regulate pro-inflammatory cytokines

REFERENCES