Roche-sponsored satellite symposium at EULAR 2021

Mission: Possible – novel anti-CD20 promise for lupus nephritis?

Friday 4 June 2021
08:15–09:45 CET

Faculty
Prof. Richard Furie
Hofstra Northwell School of Medicine, New York, USA (Chair)

Prof. Thomas Dörner
Charité University Hospitals, Berlin, Germany

Dr Jay Garg
Genentech, South San Francisco, California, USA
Welcome and introduction

Professor Richard Furie
Division of Rheumatology
Hofstra Northwell School of Medicine,
Great Neck, New York, USA
## Agenda

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Presenter</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome and introduction</td>
<td>Richard Furie</td>
<td>5 min</td>
</tr>
<tr>
<td>Deciphering the complexities of LN</td>
<td>Thomas Dörner</td>
<td>15 min</td>
</tr>
<tr>
<td>How anti-CD20 therapies are advancing the treatment of LN</td>
<td>Richard Furie</td>
<td>15 min</td>
</tr>
<tr>
<td>Panel discussion and Q&amp;A: Optimising anti-CD20 therapy for LN</td>
<td>All Faculty</td>
<td>20 min</td>
</tr>
<tr>
<td>Summary and close</td>
<td>Richard Furie</td>
<td>5 min</td>
</tr>
</tbody>
</table>
Deciphering the complexities of LN

Professor Thomas Dörner
Innovative Therapies for Autoimmune Diseases
Department Medicine/Rheumatology and Clinical Immunology
Charité University Hospitals, Berlin, Germany
Disclosures

Support for clinical trials and scientific projects:
AbbVie, BMS/Celgene, Charite Research Organization, Roche, Sanofi, Novartis, UCB,
Deutsche Forschungsgemeinschaft, BMBF, Leibnitz Society/DRFZ

Honoraria for lectures and consulting:
AbbVie, BMS, Biogen, BMS/Celgene, Janssen, Eli Lilly, Pfizer, Novartis, Roche, UCB,
Rheumaakademie, DGRh

Reviewing and consulting for public institutions, charities:
Deutsche Forschungsgemeinschaft, BMBF, EULAR, Dutch Rheumafonds,
Medical Research Council (MRC) and Arthritis Research/UK, Wallenberg Foundation/Sweden,
Research Council of Norway
SLE can affect virtually every organ system

Cumulative frequencies of manifestations

- Neurological disease (18%)
  - Strokes (5%)
  - Cranial neuropathies (2%)
  - Seizures (4%)
  - Cognitive dysfunction (2%)

- Leucopenia (35%)

- Serositis (19%)

- Thrombocytopenia (16%)

- Antiphospholipid syndrome (10%)

- Lymphadenopathy (9%)

- Autoimmune haemolytic anaemia (3%)

- Fever (31%)

- Non-criteria major organ involvement (19%)

- Non-scarring alopecia (31%)

- Acute chronic lupus (71%)

- Chronic cutaneous lupus (11%)

- Malar rash (45%)

- Oral ulcers (26%)

- Renal disease (21%)

- Raynaud (37%)

- Livedo reticularis (10%)

- Arthritis (85%)

Childhood SLE
- Fever (46%)
- Neurological disease (17%)
- Renal disease (42%)

SLE, systemic lupus erythematosus
Lupus nephritis is a common manifestation of SLE

At diagnosis, approximately 25–50% of patients with SLE have clinical evidence of LN\textsuperscript{1}

50–60% of patients with SLE develop LN within the first 10 years of disease\textsuperscript{2}

LN, lupus nephritis; SLE, systemic lupus erythematosus

Outcome of LN remains poor: high unmet needs

| • 20–25% of patients with LN do not have sustained, complete or partial remission after 6–12 months¹ |
| • ESRD: overall 10-year incidence of ESRD was 4.3%, and with nephritis was 10.1% (inception cohort SLICC)² and 10% at 20 years (Italian cohort evaluated from 1986–2001)³ |
| • ~60% of patients with SLE have continuous active disease or flares in a year of observation¹,⁴ |
| • Even among responders, flares and overall deterioration are not unusual as medications are tapered – long-term GC/immunosuppressive therapy is common⁴–⁶ |

ESRD, end stage renal disease; GC, glucocorticoid; LN, lupus nephritis; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics

# 2019 EULAR/ACR Classification Criteria for SLE\(^1,2\)

**Entry criterion**

ANA at a titer of \(\geq 1:80\) or titer above local cut off

<table>
<thead>
<tr>
<th>Clinical domains</th>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Haematological</td>
<td>Leukopenia</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Autoimmune haemolysis</td>
<td>4</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Delirium</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Psychosis</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>5</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Non-scarring alopecia</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Oral ulcers</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Subacute cutaneous OR discoid lupus</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Acute cutaneous lupus</td>
<td>6</td>
</tr>
<tr>
<td>Serosal</td>
<td>Pleural or pericardial effusion</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Acute pericarditis</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Joint involvement</td>
<td>6</td>
</tr>
<tr>
<td>Renal</td>
<td>Proteinuria &gt;0.5g/24h</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Renal biopsy class 2 or 5 lupus nephritis</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Renal biopsy class 3 or 4 lupus nephritis</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunology domains</th>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid</td>
<td>Anti-cardiolipin antibodies OR Anti-(\beta)2GP1 antibodies OR Lupus anticoagulant</td>
<td>2</td>
</tr>
<tr>
<td>antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement proteins</td>
<td>Low C3 OR low C4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Low C3 AND low C4</td>
<td>4</td>
</tr>
<tr>
<td>SLE-specific</td>
<td>Anti-dsDNA antibody OR Anti-Smith antibody</td>
<td>6</td>
</tr>
<tr>
<td>antibodies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10 distinct domains

SLE classification: \(\geq 10\) points

ACR, American College of Rheumatology; ANA, antinuclear antibody; Anti-\(\beta\)2GP1, anti-\(\beta\)-2-glycoprotein I; anti-dsDNA, anti–double-stranded DNA; EULAR, The European Alliance of Associations for Rheumatology; SLE, systemic lupus erythematosus

Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total score

The pathogenesis of LN involves a variety of mechanisms

1. Genes and environmental factors
2. Abnormal immune response and loss of tolerance
3. Production of autoantibodies
4. Formation and deposition of immune complexes
5. Inflammation
6. Organ and tissue damage

**FC**, fragment crystallizable region; **FCR**, fragment crystallizable receptor; **IC**, immune complex; **IL-4**, interleukin-4; **IFN**, interferon; **LN**, lupus nephritis; **MHCII**, major histocompatibility complex class II; **ROS**, reactive oxygen species; **TGF-β**, transforming growth factor β; **TLR**, toll-like receptor; **TNFα**, tumor necrosis factor α; **UV**, ultraviolet

Pinheiro S et al. *J Bras Nefrol* 2019;41:252-265
B cells play a large role in the pathogenesis of LN

- B cells have diverse roles in the pathogenesis of lupus nephritis, including:
  1. B cells infiltrate the kidneys of patients with LN, and leukocyte-rich tubulointerstitial infiltrates are associated with greater risk for progression to renal failure.

- Production of pathogenic autoantibodies
- Production of immunomodulatory cytokines
- Processing and presenting antigen to T cells

LN. lupus nephritis
B-cell abnormalities in active SLE are consistent with abnormal disturbed memory\textsuperscript{1,2}

Identified CD27- B cell subsets in patients with SLE

Abnormal memory-like CD27- B cell subsets in SLE

- CD27-IgD- (DN)\(^1\)
- CD27-IgD-CD95\(^+\)\(^2\)
- CD27+/−CD19++\(^3\)
- CD27+/−CD21\(^{low}\)\(^4\)
- CD27-IgD- Syk++\(^5\)
- CD27-IgD- CXCR5- CD11c+ cells (DN2)\(^6\)

Other distinct CD27- B cell populations present in normals

- CD27-CD24++CD38++ transitional type 1 B cells\(^7\)
- CD5+ pre-naive B cells\(^8\)
- CD24++CD38++ Breg\(^9\)

Breg, regulatory B cells; IgD, Immunoglobulin D; SLE, systemic lupus erythematosus; Syk, tyrosine-protein kinase SYK / spleen tyrosine kinase

Phenotypic and functional characteristics of anergic, post-activated (APA) B cells

Disturbances of naive and memory B cells are characteristic of SLE, including reduced cytokine production and BCR responses by anergic post-activated B cells.

**Target in SLE**
- **CD22**: Failed with epratuzumab
- **BTK**: Failed with fenebrutinib

**Target in RA**
- **BTK**: Failed with fenebrutinib in bDMARD-naive patients
- **Syk-i**: Failed with fostamatinib

**Target in CLL**
- **BTK**: Substantially lower responses in subgroups with mutations in the BCR signalling pathway

---

bDMARD, biological disease-modifying antirheumatic drugs; BCR, B cell receptor; BTK, Bruton’s tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCγ2, phosphodiesterase gamma-2; PSP, protein serine/threonine phosphatase; pSyk, phosphorylated spleen tyrosine kinase; PTP, protein tyrosine phosphatase; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

B cell-targeting, GC-dependent and -independent activation

APRIL, a proliferation inducing ligand; BAFF, B-cell activating factor; BLyS, B lymphocyte stimulator; CART, chimeric antigen receptor T cells; GC, glucocorticoid; mAb, monoclonal antibody; MPA=mycophenolic acid

Modified acc. Dörner T & Lipsky PE. Curr Opin Rheumatol 2014;26:228–236

Germinal Center

TFH Cell

Short-lived low avidity IgM secreting plasmablast

Short-lived avidity IgM/IgG secreting plasmablast

Long-lived high avidity IgG secreting plasma cell

Blood

Bone marrow/MALT

Secondary lymphoid tissue

CD40 : CD154

IL-21

ICOS : ICOSL

Bortezomib

Anti-CD38
Daratumumab

Anti-CD38
Anti-CD19/CART

Anti-CD20 mAb

Anti-CD40

Anti-BAFF
Belimumab

Atacicept

Non-proliferating, long-lived, high affinity plasma cell

B cell

CD40-L

Tfh cell

CD40

T cell-dependent response

T cell-independent response

All anti-BAFF effects

Modified acc. Dörner T & Lipsky PE. Curr Opin Rheumatol 2014;26:228–236
Proposed treatment algorithm for established and suggested pathological subtypes of LN

The preservation of quality of life through achievement of clinical improvement during a 6–12-month induction phase, followed by a maintenance phase that prevents further organ damage is the goal of LN treatment.

ISN–RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis

*According to the 2019 update of EULAR recommendations.
†Dose of six pulses every 2 weeks at a fixed dose of 500 mg as recommended by the Euro Lupus Nephritis Trial.
‡Still at trial stage; efficacy unknown

The treatment algorithm for established pathological subtypes (ISN–RPS classes I–VI) is based on recommendations from the Joint EULAR and European Renal Association–European Dialysis and Transplant Association, ACR, the 2019 update of EULAR recommendations, and the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.

Dörner T & Furie R. Lancet 2010;393:2344–2358
Mechanisms of B cell depletion by anti-CD20 mAbs

- Anti-CD20 mAbs deplete B cells via several mechanisms\(^1\)–\(^4\)

**Mechanisms of B cell depletion by anti-CD20 mAbs**

1. Anti-CD20 mAbs bind to CD20 on B cells.
2. CD20 binds to CD40, activating B cells.
3. Antibody-dependent cellular cytotoxicity (ADCC) kills B cells.
4. Complement-dependent cytotoxicity (CDC) leads to B cell death.
5. Direct cell death occurs.

ADCC, antibody-dependent cellular cytotoxicity; FCγR, Fc-gamma receptor; mAbs, monoclonal antibodies; NK, natural killer

Accumulating clinical trial evidence supports B cells as therapeutic targets in LN

- Rituximab and ocrelizumab studies in LN (LUNAR and BELONG) missed primary endpoints, but showed evidence of partial benefits over control\(^1,2\)

- Achievement of complete B-cell depletion is associated with improved responses, and failure to achieve complete B-cell depletion with increased risk of progression\(^3\) – 5

Strong clinical and scientific rationale to evaluate hypothesis that deeper and more sustained B cell depletion will improve responses in LN

Obinutuzumab is a glycoengineered, humanised type 2 anti-CD20 mAb

- Obinutuzumab results in superior B cell depletion vs rituximab in lymphoid tissue of non-human primates\(^1\) and patient with SLE whole blood samples\(^2\)
- Enhanced depletion of tissue resident B cells by obinutuzumab is expected to result in clinical benefit\(^2\)

Obinutuzumab is under investigation to treat LN
- Phase II NOBILITY trial (completed)\(^3\)
- Phase III REGENCY trial (recruiting)\(^4\)

Obinutuzumab is glycoengineered for increased binding affinity, resulting in increased ability to deplete CD20-positive B cells\(^5\)

FCR, fragment crystallizable receptor; LN, lupus nephritis; mAb, monoclonal antibody; SLE, systemic lupus erythematosus
LN is a common manifestation of SLE; it is associated with high morbidity and mortality

The main goal in treating LN is to stop the inflammation in the kidneys and prevent permanent damage

B cells are central to LN pathogenesis and so represent a potential therapeutic target

Variability in B cell depletion with type 1 anti-CD20 mAbs in SLE may be responsible for inconsistent clinical responses

Greater B cell depletion with the type 2 anti-CD20 mAb obinutuzumab may lead to improved clinical responses in LN and is being investigated in clinical trials
How anti-CD20 therapies are advancing the treatment of LN

Professor Richard Furie
Division of Rheumatology
Hofstra Northwell School of Medicine, Great Neck, New York, United States
Disclosures

• Genentech/Roche
• AstraZeneca
• GlaxoSmithKline
• Aurinia Pharmaceuticals
## LN: how are we performing?

<table>
<thead>
<tr>
<th>Drug/Study</th>
<th>Year</th>
<th>Endpoint</th>
<th>Placebo response (standard of care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF¹</td>
<td>2009</td>
<td>CR</td>
<td>9%</td>
</tr>
<tr>
<td>Rituximab²</td>
<td>2012</td>
<td>CR</td>
<td>31%</td>
</tr>
<tr>
<td>Abatacept³</td>
<td>2014</td>
<td>CR</td>
<td>3%; 12% (CRrev)</td>
</tr>
<tr>
<td>Abatacept⁴</td>
<td>2014</td>
<td>CR</td>
<td>30%</td>
</tr>
<tr>
<td>Sirukumab⁵</td>
<td>2016</td>
<td>CR</td>
<td>0%</td>
</tr>
<tr>
<td>BIIB023⁶</td>
<td>2016</td>
<td>CR + &gt;50% ↓ proteinuria</td>
<td>6% (+ 14% CR 3m run-in)</td>
</tr>
<tr>
<td>Voclosporin⁷</td>
<td>2016</td>
<td>CR (+ pred &lt;10 mg/d)</td>
<td>19% (6 m); 24% (12 m)</td>
</tr>
<tr>
<td>Abatacept⁸</td>
<td>2018</td>
<td>CR</td>
<td>34%</td>
</tr>
<tr>
<td>R, CYC, B⁹</td>
<td>2018</td>
<td>CR</td>
<td>38%</td>
</tr>
<tr>
<td>Voclosporin¹⁰</td>
<td>2019</td>
<td>RR</td>
<td>23%</td>
</tr>
<tr>
<td>Obinutuzumab¹¹</td>
<td>2019</td>
<td>CR</td>
<td>23%</td>
</tr>
<tr>
<td>Belimumumab¹²</td>
<td>2020</td>
<td>PERR</td>
<td>32%</td>
</tr>
</tbody>
</table>

B, belimumab; CR, complete response; CRrev, efficacy endpoint defined post-hoc to account for renal function misclassifications; CYC, cyclophosphamide; LN, lupus nephritis; MMF, mycophenolate mofetil; PERR, primary efficacy renal response; Pred, prednisone; R, rituximab; RR, renal response.

Incomplete efficacy in LN with type 1 anti-CD20 mAbs

B cells are central to LN

In lupus, autoreactive B cells:¹
- Secrete pathogenic autoantibodies and proinflammatory cytokines
- Present self-antigens
- Activate T cells

Prior experience with type 1 anti-CD20 therapy

Two RCTs failed to confirm clinical benefit of type 1 anti-CD20 therapies in LN
- LUNAR (n=144): no Complete Renal Response benefit when rituximab added to SOC²
- BELONG (n=223): no Complete Renal Response benefit when ocrelizumab added to SOC³

B cell depletion associated with response

LUNAR: Achievement of Complete peripheral depletion⁴

<table>
<thead>
<tr>
<th>Percent of participants</th>
<th>Week 52</th>
<th>Week 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete peripheral depletion</td>
<td>40%</td>
<td>47%</td>
</tr>
<tr>
<td>Incomplete peripheral depletion</td>
<td>27%</td>
<td>13%</td>
</tr>
</tbody>
</table>

CD19 count measured with conventional flow cytometry

- Rituximab failed to achieve complete depletion in many lupus patients when assessed with conventional flow cytometry⁴
- Murine models have demonstrated B cells that are resistant to depletion with rituximab⁴
- Enhanced depletion of tissue-resident B cells by obinutuzumab might result in increased clinical benefit in patients with LN⁵
- This was investigated in the NOBILITY trial⁵

LN, lupus nephritis; RCT, randomized controlled trial; SOC, standard of care

Key inclusion criteria:
- ISN/RPS Class 3 or 4 LN within six months; concomitant class 5 permitted
- UPCR ≥1 on 24-hour collection

Key exclusion criteria:
- Rapidly progressive glomerulonephritis
- eGFR <30 mL/min/1.73 m²
- >50% of glomeruli with sclerosis

Primary endpoint:
- CRR at week 52

Key secondary endpoints:
- Overall renal response (CRR or PRR)
- Change in levels of dsDNA, C3, C4

Pre-specified alpha level = 0.2
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab + MMF (n = 63)</th>
<th>Placebo + MMF (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>55 (87%)</td>
<td>51 (82%)</td>
</tr>
<tr>
<td>Age</td>
<td>33.1 ± 9.8</td>
<td>31.9 ± 10.1</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>42 (67%)</td>
<td>49 (79%)</td>
</tr>
<tr>
<td>White</td>
<td>28 (44%)</td>
<td>26 (42%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (10%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Prior history of LN</td>
<td>40 (64%)</td>
<td>35 (57%)</td>
</tr>
<tr>
<td>Class 4 LN</td>
<td>49 (78%)</td>
<td>44 (71%)</td>
</tr>
<tr>
<td>Concomitant class 5 LN</td>
<td>20 (32%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Serum creatinine – mg/dL</td>
<td>0.87 ± 0.34</td>
<td>0.80 ± 0.33</td>
</tr>
<tr>
<td>Serum creatinine ≤ULN</td>
<td>51 (81%)</td>
<td>55 (89%)</td>
</tr>
<tr>
<td>UPCR</td>
<td>3.3 ± 2.7</td>
<td>2.9 ± 2.5</td>
</tr>
<tr>
<td>Anti-dsDNA positive</td>
<td>31 (49%)</td>
<td>36 (58%)</td>
</tr>
<tr>
<td>C3 &lt;90 mg/dL</td>
<td>43 (68%)</td>
<td>37 (60%)</td>
</tr>
<tr>
<td>C4 &lt;16 mg/dL</td>
<td>37 (59%)</td>
<td>44 (71%)</td>
</tr>
</tbody>
</table>

dsDNA, double stranded DNA; LN, lupus nephritis; MMF, mycophenolate mofetil; ULN, upper limit of normal; UPCR, urine protein/creatinine ratio
Furie R et al. ACR. 2020; Oral presentation, abstract 0988
# Exposure and disposition

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab + MMF (n = 63)</th>
<th>Placebo + MMF (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received four study drug infusions</td>
<td>57 (90%)</td>
<td>54 (87%)</td>
</tr>
<tr>
<td>Completed follow-up through:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>59 (94%)</td>
<td>56 (90%)</td>
</tr>
<tr>
<td>Week 104</td>
<td>56 (89%)</td>
<td>46 (74%)</td>
</tr>
<tr>
<td>Corticosteroid exposure – median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through week 52</td>
<td>4,008 mg</td>
<td>4,009 mg</td>
</tr>
<tr>
<td>Through week 104</td>
<td>6,561 mg</td>
<td>6,672 mg</td>
</tr>
<tr>
<td>Required rescue therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through week 52</td>
<td>6 (10%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Through week 104</td>
<td>14 (22%)</td>
<td>25 (40%)</td>
</tr>
<tr>
<td>Died</td>
<td>1 (2%)</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

MMF, mycophenolate mofetil; ULN, upper limit of normal
All categorical variables are reported as n (%). Continuous variables are reported as mean ± SD
Furie R et al. ACR. 2020; Oral presentation, abstract 0988
Renal response endpoints

The primary endpoint was complete renal response (CRR) at week 52.

CRR

<table>
<thead>
<tr>
<th>Week 52</th>
<th>35%</th>
<th>23%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBI + MMF (n = 63)</td>
<td>PBO + MMF (n = 62)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 76</th>
<th>38%</th>
<th>18%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBI + MMF (n = 63)</td>
<td>PBO + MMF (n = 62)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 104</th>
<th>41%</th>
<th>23%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBI + MMF (n = 63)</td>
<td>PBO + MMF (n = 62)</td>
<td></td>
</tr>
</tbody>
</table>

CRR required all of:
- UPCR < 0.5
- Serum creatinine ≤ upper limit of normal
- Serum creatinine ≤ 115% of baseline value
- < 10 RBC/hpf without RBC casts

CRR, completely renal response; MMF, mycophenolate mofetil; OBI, Obinutuzumab; PBO, placebo; RBC/hpf, red blood cells per high power field; UPCR, urine protein/creatinine ratio

Furie R et al. ACR. 2020; Oral presentation, abstract 0988
Renal responses over time

* P < 0.2; ** P < 0.05; *** P < 0.01 for comparison vs placebo
CRR, complete renal response; MMF, mycophenolate mofetil; PRR, partial renal response
Furie R et al. ACR. 2020; Oral presentation, abstract 0988
Mean changes in laboratory values

Last observation prior to treatment failure is applied for missing data. Comparisons were adjusted for stratification factors (region, race).

* P < 0.02; ** P < 0.05; *** P < 0.01; **** P < 0.001 for comparison vs. placebo.

dsDNA, double stranded DNA; MMF, mycophenolate mofetil; UPCR, urine protein/creatinine ratio

Furie R et al. ACR. 2020; Oral presentation, abstract 0988
Mean change in eGFR at week 104

<table>
<thead>
<tr>
<th>Week</th>
<th>Obinutuzumab + MMF (n = 63)</th>
<th>Placebo + MMF (n = 62)</th>
<th>Difference (80% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+6.5</td>
<td>–3.2</td>
<td>9.7 (4.5 to 14.9)</td>
<td>0.018</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil
Rovin B et al. ASN. 2020; Oral presentation, abstract 53A

* P < 0.02; ** P < 0.05 for comparison vs. placebo
Pharmacodynamics

Conventional flow cytometry (≤5 cells/μL)

Patients with depletion (%)

<table>
<thead>
<tr>
<th>Week</th>
<th>Obinutuzumab + MMF</th>
<th>Placebo + MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>98% 2%</td>
<td>96% 4%</td>
</tr>
<tr>
<td>4</td>
<td>96% 4%</td>
<td>96% 5%</td>
</tr>
<tr>
<td>12</td>
<td>96% 5%</td>
<td>93% 4%</td>
</tr>
<tr>
<td>24</td>
<td>93% 4%</td>
<td>94% 2%</td>
</tr>
<tr>
<td>52</td>
<td>94% 2%</td>
<td>16% 12%</td>
</tr>
<tr>
<td>104</td>
<td>16% 12%</td>
<td></td>
</tr>
</tbody>
</table>

Obinutuzumab + MMF
Placebo + MMF

Last obinutuzumab dose

MMF, mycophenolate mofetil
Furie R et al. ACR. 2020; Oral presentation, abstract 0988
Mean levels of B cells and plasmablasts over time by treatment group

**Total CD19+ B-cells (cells/µL)**

**Memory CD27+CD19+ B-cells (cells/µL)**

**Naïve CD27-CD19+B-cells (cells/µL)**

**CD19+CD27+CD38++ plasmablasts (cells/µL)**

Study Visit (weeks)

Error bars represent 95% confidence intervals of the mean

MMF: mycophenolate mofetil

Vital EM et al. ACR. 2020; Oral presentation, abstract 903295
Week 76 responses by B cell depletion status

- Obinutuzumab sustained depletion (n = 32)
- Obinutuzumab detectable B cells (n = 20)
- Placebo + MMF (n = 62)

** Complete renal response (CRR)**
- **50%**
- **35%**
- **18%**

** Modified completed renal response (mCRR)**
- **72%**
- **50%**
- **37%**

** Overall renal response (CRR or PRR)**
- **66%**
- **45%**
- **29%**

CRR required all of:
- UPCR <0.5
- Serum creatinine ≤ upper limit of normal
- Serum creatinine ≤115% of baseline value
- <10 RBC/hpf without RBC casts

Modified CRR required:
- UPCR <0.5
- Serum creatinine ≤ the upper limit of normal

PRR required all of:
- UPCR ≥50% reduction to <1 (to <3 if baseline ≥3)
- Serum creatinine ≤115% of baseline value
- RBC ≤50% above baseline or <10 RBC/hpf

* P < 0.2 vs placebo group; ** P < 0.05 vs placebo group; *** P < 0.001 vs placebo group

Eleven patients in the obinutuzumab group with insufficient data to determine depletion status are excluded.
Safety summary through week 104

<table>
<thead>
<tr>
<th>Event</th>
<th>Obinutuzumab + MMF (n = 64)</th>
<th>Placebo + MMF (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>58 (91%)</td>
<td>54 (89%)</td>
</tr>
<tr>
<td>Deaths (cause)</td>
<td>1 (2%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>GI perforation</td>
<td></td>
<td>GI bleed, SLE, PML, respiratory infection</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>16 (25%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Serious infection events</td>
<td>5 (8%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Infection adverse event</td>
<td>48 (75%)</td>
<td>38 (62%)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation from blinded infusions</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>10 (16%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Infusion-related reaction (7), headache, tachycardia, hypertension, nausea</td>
<td></td>
<td>Infusion-related reaction (6), insomnia</td>
</tr>
<tr>
<td>Serious infusion-related reaction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; MMF, mycophenolate mofetil; PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus
All categorical variables are reported as n (%)
One patient randomised to placebo inadvertently received active obinutuzumab during the first cycle. This patient is included in the obinutuzumab group for safety analyses
Furie R et al. ACR. 2020; Oral presentation, abstract 0988
Summary

- The phase 2 NOBILITY study met its primary and key secondary endpoints.
- Obinutuzumab resulted in clinically meaningful renal response benefits over SOC alone that were sustained through week 104.
- Significant improvements in serologies and proteinuria were also observed.
- Obinutuzumab resulted in rapid and complete depletion of peripheral B cells without an increase in SAEs, serious infections, or deaths over SOC alone.
- B cell depletion strategies are very much alive and well! The phase 3 REGENCY study is currently recruiting patients with proliferative LN.
Panel discussion and Q&A: Optimising anti-CD20 therapy for LN

Prof. Richard Furie
Hofstra Northwell School of Medicine, New York, USA (Chair)

Prof. Thomas Dörner
Charité University Hospitals, Berlin, Germany

Dr Jay Garg
Genentech, South San Francisco, California, USA
Summary and close

Professor Richard Furie
Division of Rheumatology
Hofstra Northwell School of Medicine,
Great Neck, New York, USA
Summary

• LN is associated with high morbidity and mortality and represent an area of high unmet needs

• B cells are central to LN pathogenesis and are being investigated as a potential therapeutic target using anti-CD20 mAbs

• Clinical responses to anti-CD20 mAbs appear to be better when complete depletion of B cells is achieved in LN

• In the phase II NOBILITY study of obinutuzumab, clinically meaningful renal response benefits over SOC alone that were sustained through Week 104

• Obinutuzumab will be further investigated in the Phase III REGENCY study, which is currently recruiting patients with proliferative LN
Ask your question!

- Put your questions to the panel by using the ‘Connect with us’ facility on the Roche EULAR portal homepage
- This facility will be available until the end of the day on 5th June