Mosunetuzumab, a Full-Length Bispecific CD20/CD3 Antibody, Displays Clinical Activity in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma (NHL): Interim Safety and Efficacy Results from a Phase I Study

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Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drug formats
  - PK properties enable once weekly to q3w dosing
  - Does not require ex-vivo T-cell manipulation
  - Off the shelf, readily available treatment

- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells

ADCC, antibody-dependent cell-mediated cytotoxicity

Sun et al. Sci Transl Med 2015
GO29781: study design

Open-label, multicenter Phase I/Ib study in R/R B-cell NHL patients (NCT02500407)

• **Patient population**
  – dose escalation: R/R NHL
  – dose expansion: R/R FL, MCL, DLBCL/trFL

• **Administration**
  – intravenous, administered in out-patient setting except with first maximal dose in dose escalation
  – initial treatment: eight cycles, up to 17 cycles allowed

• **Primary outcome measures**
  – MTD
  – tolerability
  – pharmacokinetics
  – best objective response, as per revised International Working Group response criteria (Cheson BD, et al. 2007)

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**Group A (n=33)**
Fixed dosing on D1 of each 21-day cycle

- 2.8mg
- 0.05mg

**Group B (n=98)**
Step-up dosing during Cycle 1
Fixed dosing on D1 of each 21-day cycle thereafter

- 1/2/20mg
- 0.4/1/2.8mg

D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; R/R, relapsed/refractory; tr, transformed
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DLBCL/trFL (n=75)</th>
<th>FL (n=38)</th>
<th>All safety-evaluable* (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>62 (19–84)</td>
<td>60.5 (37–85)</td>
<td>63 (19–85)</td>
</tr>
<tr>
<td><strong>Sex (male), n (%)</strong></td>
<td>49 (65.3)</td>
<td>24 (63.2)</td>
<td>84 (64.1)</td>
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<tr>
<td><strong>Prior systemic therapies, median (range)</strong></td>
<td>3 (1–9)</td>
<td>3 (1–14)</td>
<td>3 (1–14)</td>
</tr>
<tr>
<td><strong>Prior stem cell transplant, n (%)</strong></td>
<td>25 (33.3)</td>
<td>5 (13.2)</td>
<td>34 (26.0)</td>
</tr>
<tr>
<td><strong>Refractory to last prior therapy, n (%)†</strong></td>
<td>56 (74.7)</td>
<td>22 (57.9)</td>
<td>89 (67.9)</td>
</tr>
<tr>
<td><strong>Prior anti-CD20, n (%)</strong></td>
<td>75 (100)</td>
<td>38 (100)</td>
<td>131 (100)</td>
</tr>
<tr>
<td><strong>Refractory to any prior anti-CD20, n (%)†</strong></td>
<td>53 (70.7)</td>
<td>25 (65.8)</td>
<td>89 (67.9)</td>
</tr>
<tr>
<td><strong>Prior CAR-T, n (%)</strong></td>
<td>5 (6.7)</td>
<td>3 (7.9)</td>
<td>8 (6.1)</td>
</tr>
</tbody>
</table>

Data cut-off date: 17 August 2018

*Including additional 18 patients with other NHL histologies; †Definition of refractory: not achieving a response (PR or CR) or progressing within ≤6 months of the applicable treatment.

CR, complete response; CAR-T, chimeric antigen receptor T-cell; PR, partial response; trFL, transformed follicular lymphoma.
<table>
<thead>
<tr>
<th>Patient disposition</th>
<th>DLBCL/trFL (n=75)</th>
<th>FL (n=38)</th>
<th>All safety-evaluable* (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active on initial treatment,</strong> † n (%)</td>
<td>15 (20.0)</td>
<td>15 (39.5)</td>
<td>34 (26.0)</td>
</tr>
<tr>
<td><strong>Completed initial treatment,</strong> † n (%)</td>
<td>10 (13.3)</td>
<td>13 (34.2)</td>
<td>26 (19.8)</td>
</tr>
<tr>
<td><strong>Discontinued from initial treatment,</strong> † n (%)</td>
<td>50 (66.7)</td>
<td>10 (26.3)</td>
<td>71 (54.2)</td>
</tr>
<tr>
<td>Due to progressive disease, n (%)</td>
<td>44 (58.7)</td>
<td>8 (21.1)</td>
<td>60 (45.8)</td>
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<tr>
<td>Due to AE, n (%)</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
<td>1 (0.8)‡</td>
</tr>
<tr>
<td>Due to use of another cancer therapy, n (%)</td>
<td>2 (2.7)</td>
<td>1 (2.6)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Due to physician decision, n (%)</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Due to withdrawal by subject, n (%)</td>
<td>2 (2.7)</td>
<td>1 (2.6)</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Due to death, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.8)§¶</td>
</tr>
</tbody>
</table>

Data cut-off date: 17 August 2018

*Including additional 18 patients with other NHL histologies; †Patients initially receive eight cycles. If PR or SD at the end of eight cycles, treatment may continue for up to 17 cycles. Patients with relapsed disease may be re-treated; ‡Of four patients with AEs leading to withdrawal from treatment, only one had ‘AE’ entered as reason for initial treatment discontinuation; §Grade 5 HLH; ¶Of three patients with AEs leading to fatal outcomes, only one had ‘death’ entered as reason for discontinuation.

AE, adverse event; SD, standard deviation; HLH, hemophagocytic lymphohistiocytosis.
Step-up dosing during Cycle 1 enabled continued dose escalation with no worsening of toxicity profile

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Group A (n=33) [Max dose: 2.8 mg; Range: 0.05–2.8 mg]</th>
<th>Group B (n=98) [Max dose: 20.0 mg; Range: 0.4–20.0 mg]</th>
<th>All patients (n=131) [Max dose: 20.0 mg; Range: 0.05–20.0 mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>32 (97.0%)</td>
<td>92 (93.9%)</td>
<td>124 (94.7%)</td>
</tr>
<tr>
<td>Treatment-related AE*</td>
<td>24 (72.7%)</td>
<td>58 (59.2%)</td>
<td>82 (62.6%)</td>
</tr>
<tr>
<td>Grade ≥3 AE†</td>
<td>16 (48.5%)</td>
<td>56 (57.1%)</td>
<td>72 (55.0%)</td>
</tr>
<tr>
<td>Grade ≥3 treatment-related AE</td>
<td>7 (21.2%)</td>
<td>27 (27.6%)</td>
<td>34 (26.0%)</td>
</tr>
<tr>
<td>Neutropenia^</td>
<td>2 (6.1%)</td>
<td>13 (13.3%)</td>
<td>15 (11.5%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2 (6.1%)</td>
<td>5 (5.1%)</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3.0%)</td>
<td>3 (3.1%)</td>
<td>4 (3.1%)</td>
</tr>
<tr>
<td>Serious AE, excluding lymphoma progression‡</td>
<td>7 (21.2%)</td>
<td>26 (26.5%)</td>
<td>33 (25.2%)</td>
</tr>
<tr>
<td>AE leading to withdrawal from treatment</td>
<td>1 (3.0%)</td>
<td>3 (3.1%)</td>
<td>4 (3.1%)</td>
</tr>
<tr>
<td>Grade 5 AE, excluding lymphoma progression‡</td>
<td>1 (3.0%)</td>
<td>2 (2.0%)</td>
<td>3 (2.3%)‡</td>
</tr>
</tbody>
</table>

Data cut-off date: 17 August 2018. No MTD established for either Group A or B.

*Relationship between each AE and study treatment determined by investigator assessment; †Occurring in ≥10% of patients in any group; ^Includes AE terms ‘neutropenia’ and ‘neutrophil count decreased’; ‡Deaths due to macrophage activation syndrome/HLH (n=1), Candida sepsis (n=1), and disease-related large intestine perforation (n=1). 9 deaths occurred within 90 days of last mosunetuzumab administration due to malignant disease progression.
Treatment-emergent AEs
Group A and B; N=131; maximum single dose: 20 mg

- Majority of AEs were Grade 1 or 2
- Most treatment-related AEs were transient and reversible
  - 19% of events resolved within 24h; median duration 4 days (range 1–144 days)
- Median time to onset for all AEs: 18 days (i.e. during cycle 1)
- No evidence of cumulative or chronic toxicity

Data cut-off date: 17 August 2018
*Related AEs per investigator assessment
**AEs of special interest**

<table>
<thead>
<tr>
<th>n, (%)</th>
<th>All safety-evaluable (N=131)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRS (Lee criteria¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>30 (22.9%)</td>
<td>• Majority during cycle 1; median duration 2 days (range 0–19)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>0</td>
<td>• Two patients treated with tocilizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 40/41 (98%) events resolved</td>
</tr>
<tr>
<td><strong>Neurologic AEs†</strong></td>
<td>64 (48.9%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>61 (46.6%)</td>
<td>• Most common: headache (15.3%), dizziness (9.9%), insomnia (9.2%)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>3 (2.3%)</td>
<td>• Grade 3: seizure (HLH); confusion and hepatic encephalopathy; post-herpetic neuralgia (n=1 each)</td>
</tr>
<tr>
<td>Treatment-related (any grade)*</td>
<td>27 (20.6%)</td>
<td></td>
</tr>
<tr>
<td>Treatment-related (Grade ≥3)†</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>*<em>Neutropenia</em></td>
<td>25 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>3 (2.3%)</td>
<td>• Responsive to G-CSF; 37/41 (90%) events resolved</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>22 (16.8%)</td>
<td>• No concurrent Grade ≥3 infections reported</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4 (3.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes AE terms ‘neutropenia’ and ‘neutrophil count decreased’. Febrile neutropenia events were deemed unrelated to mosunetuzumab by investigator; †Defined as all AEs occurring in either the SOC nervous system disorders or SOC psychiatric disorders. *Per investigator assessment; Data cut-off date: 17 August 2018

PK/PD results

- Mosunetuzumab PK is generally dose-proportional; half-life of 6–11 days
- No anti-drug antibodies detected

Mosunetuzumab Cycle 1 PK
(Group B: step-up dosing in Cycle 1)

- Maximum levels of peripheral T-cell activation and IL-6 elevation occur after first dose of Cycle 1
  - Kinetics consistent with time of onset of CRS
  - Magnitude of IL-6 spike in line with the low grades of CRS

Data cut-off date: 17 August 2018
Mosunetuzumab exhibits anti-tumor activity in multiple histologies

Group A+B patients treated at ≥1.2 mg dose (primary response population)

- First responses observed in Group A at doses ≥1.2 mg
- Complete responses observed in DLBCL, trFL, FL, RS, MCL, MZL

Data cut-off date: 17 August 2018.

†Patients who have response data available at any time; ‡CR, assessed by the investigator with or without PET, marked for efficacy-evaluable patients (when SPD data available).

CR, complete response; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RS, Richter transformation; SLL, small lymphocytic lymphoma; SPD, sum of the product diameters; tr, transformed
Efficacy of mosunetuzumab in R/R DLBCL/trFL

Early evidence of durable CR; re-treatment following relapse re-induced CR

• Median duration of CR: not reached
• Median duration of follow-up for CR: 298 days (range 46–816 days)

Data cut-off date: 17 August 2018

†CR, assessed by the investigator with or without positron emission tomography, marked for efficacy-evaluable patients (when SPD data available). tr, transformed
Efficacy of mosunetuzumab in R/R FL

Early evidence of durable CR; no relapses observed to date

Data cut-off date: 17 August 2018

*Complete response, assessed by the investigator with or without positron emission tomography, marked for efficacy-evaluable patients (when SPD data available).
CR in a CAR-T-refractory patient with DLBCL

- Prior therapies included R-CHOP and R-ICE
- Patient subsequently received CD19 CAR-T in combination with PD-L1 blockade
  - CR achieved; disease relapsed within 4 months
  - Severe neurologic toxicity occurred (seizure)
- Mosunetuzumab administered as single-agent therapy (0.8/2.0/4.2 mg)
  - CR achieved after 3 cycles
  - No CRS or neurologic AEs except Gr 1 headache
  - Allogeneic stem cell transplant pursued after 4 cycles of mosunetuzumab
  - No evidence of disease relapse after 1 year in remission
Conclusions

- Mosunetuzumab induces durable CR in late-line R/R indolent and aggressive NHL
  - Pharmacodynamic activation of peripheral T-cells confirms MOA
  - Clinical activity observed with intermittent (q3W) dosing and limited treatment duration

- Favorable safety profile
  - Cycle 1 step-up dosing appears to mitigate toxicity
  - MTD not reached
  - Most AEs during Cycle 1; mild, transient and reversible; no evidence of cumulative or chronic toxicity
  - Low rate of treatment discontinuation due to AEs
  - No Grade 3 CRS
  - Low frequency (0.8%) of Grade 3 neurotoxicity related to mosunetuzumab

- Single-agent dose and schedule continues to be optimized
- Combinations with chemotherapy, atezolizumab and polatuzumab vedotin under investigation
Acknowledgements

- The patients, study investigators, coordinators and nurses
- The sponsor, F. Hoffmann-La Roche Ltd
- The contract research organization, Covance
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Study sites

<table>
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<tr>
<th>CANADA</th>
<th>USA (cont’d)</th>
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<tbody>
<tr>
<td>Laurie Sehn</td>
<td>Andre Goy</td>
</tr>
<tr>
<td>BC Cancer</td>
<td>Hackensack University Medical Center</td>
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<tr>
<td>Sarit Assouline</td>
<td>Stephen Schuster</td>
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<td>Jewish General</td>
<td>Hospital of the University of Pennsylvania</td>
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<td>Hospital</td>
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<td>Memorial Sloan-Kettering Cancer</td>
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<td>Nancy Bartlett</td>
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