Lymphoma - What to Watch

Laurie H. Sehn, MD, MPH

BC Cancer, Vancouver, BC
Abstract # 6 Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant to or Relapsing After Chimeric Antigen Receptor T-Cell (CAR-T) Therapies, and Is Active in Treatment through Multiple Lines

Session: Plenary Scientific Session
Sunday, December 8, 2019, 2:00 PM-4:00 PM
*Stephen J Schuster, MD*¹, *et al*
Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- Full-length humanized IgG1 antibody
  - Longer half-life than fragment-based drugs
  - PK properties enable once weekly to q3w dosing

- 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
Cycle 1 step-up dosing cohort overview

Mosunetuzumab regimen

- Single agent
- IV administration in outpatient setting*
- Cycle 1 step-up dosing then fixed dosing in subsequent cycles

Key inclusion criteria

- Relapsed disease or failure to respond after ≥1 prior regimen(s), ECOG PS 0–1

Key exclusion criteria

- Eligible for autologous SCT, prior CAR-T therapy within 30 days, prior allogenic SCT

Objectives

- Safety and tolerability, MTD, best objective response (per Cheson 2007 criteria¹)

Analysis

- Safety: C1D1/D8/D15 dose level: 0.4/1/2.8mg to 1/2/60mg
- Efficacy: C1D1/D8/D15 dose level: 0.4/1/2.8mg to 1/2/40.5mg‡

*except first maximal dose in dose-escalation cohorts

†enrolment ongoing; efficacy data at 60mg are immature

Patient population
Consistent with late-line relapsed, difficult-to-treat NHL

<table>
<thead>
<tr>
<th>n (% of safety evaluable pts)</th>
<th>All safety evaluable (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62.0 (19–96)</td>
</tr>
<tr>
<td>Male</td>
<td>172 (63.7%)</td>
</tr>
<tr>
<td>ECOG PS 1 at baseline</td>
<td>164 (61.2%)*</td>
</tr>
<tr>
<td>Aggressive NHL</td>
<td></td>
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<tr>
<td>DLBCL</td>
<td>117 (43.3%)</td>
</tr>
<tr>
<td>trFL</td>
<td>32 (11.9%)</td>
</tr>
<tr>
<td>MCL</td>
<td>23 (8.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3.0%)</td>
</tr>
<tr>
<td>Indolent NHL</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>82 (30.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Median prior systemic therapies, n (range)</td>
<td>3.0 (0–14)</td>
</tr>
<tr>
<td>Prior CAR-T therapy</td>
<td>30 (11.1%)</td>
</tr>
<tr>
<td>Prior autologous stem cell transplant</td>
<td>77 (28.5%)</td>
</tr>
<tr>
<td>Refractory† to last prior therapy</td>
<td>194 (71.9%)</td>
</tr>
<tr>
<td>Refractory† to prior anti-CD20 therapy</td>
<td>233 (86.7%)</td>
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</tbody>
</table>

30 pts with prior CAR-T therapy
- 17 DLBCL, 8 trFL, 5 FL
- Median 5 lines of prior systemic therapies (range 3–14)
- 29 pts (96.7%) refractory to prior anti-CD20 therapy
- 25 pts (83.3%) refractory to last prior therapy
- 22 pts (73.3%) refractory to prior CAR-T therapy

* n=268; † no response (PR or CR) or PD within ≤6 months of treatment
Pts, patients; trFL, transformed FL; NHL, B-cell non Hodgkin lymphoma; CCOD: Aug 9, 2019
## Cytokine release syndrome and neurological adverse events

<table>
<thead>
<tr>
<th>n (% of safety evaluable or prior CAR-T therapy pts) with ≥1 AE</th>
<th>All safety evaluable (n = 270)</th>
<th>Patients with prior CAR-T therapy (n = 30)</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Cytokine release syndrome (CRS) (Lee criteria(^1))</strong></td>
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<tr>
<td>Gr 1</td>
<td>54 (20.0%)</td>
<td>6 (20.0%)</td>
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<tr>
<td>Gr 2</td>
<td>21 (7.8%)</td>
<td>1 (3.3%)</td>
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<tr>
<td>Gr 3</td>
<td>3 (1.1%)</td>
<td>1 (3.3%)</td>
<td></td>
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<tr>
<td><strong>Neurological adverse events</strong></td>
<td>118 (43.7%)</td>
<td>13 (43.3%)</td>
<td></td>
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<tr>
<td>Gr 1</td>
<td>74 (27.4%)</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Gr 2</td>
<td>34 (12.6%)</td>
<td>3 (10.0%)</td>
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<tr>
<td>Gr 3</td>
<td>10 (3.7%)</td>
<td>3 (10.0%)</td>
<td></td>
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<tr>
<td>Related Gr 3</td>
<td>3 (1.1%)</td>
<td>1 (3.3%)</td>
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</table>

- Majority of CRS events (96.2%) Gr 1–2
- Mostly in Cycle 1; median duration: 2 days (range 1–59)
- 8/270 pts (3.0%) treated with tocilizumab
- 112 (96.6%) events resolved by the CCOD

- Definitions from Nervous System Disorders and Psychiatric Disorders System Organ Classes\(^2\)
- Most common neurological events included headache (15.6%), insomnia (9.3%), and dizziness (9.3%)
- Low rate of Gr 3 events
- Low rate of ICANS-like events (1.1%)
Efficacy: Responses Observed Across Multiple Dose Levels and NHL Subtypes

Change in tumor burden by NHL type and dose cohort in Group B

R/R aggressive NHL

Change in SPD (%)

ORR 34/98 (35.1%)
CR 20/98 (20.6%)

R/R indolent NHL

Change in SPD (%)

ORR 37/55 (67.3%)
CR 20/55 (36.4%)

Most patients in CR remain in remission;
15/20 pts with aggressive NHL and 19/20 pts with iNHL,
median follow-up 4 months (range: 0–19) and 6 months (range: 0–24)

Bartlett, et al. ASCO 2019
Abstract 343 Two Years Rituximab Maintenance Vs. Observation after First Line Treatment with Bendamustine Plus Rituximab (B-R) in Patients with Waldenström's Macroglobulinemia (MW): Results of a Prospective, Randomized, Multicenter Phase 3 Study (the StiL NHL7-2008 MAINTAIN trial)

Sunday, December 8, 2019: 7:30 AM
Tangerine 3 (WF3-4), Level 2 (Orange County Convention Center)
Mathias J Rummel, MD, PhD¹*, et al
StiL NHL 7-2008 MAINTAIN trial: previous results

**Follicular Lymphoma: B-R + 2 years R vs. B-R + 4 years R**

![Graph showing PFS events and hazard ratio for Follicular Lymphoma.](image)

**Follicular Lymphoma: B-R (NHL1) vs B-R + R (NHL7)**

![Graph showing PFS events and hazard ratio for Follicular Lymphoma.](image)

**Mantel Cell Lymphoma: B-R vs. B-R + 2 years R**

![Graph showing PFS events and hazard ratio for Mantel Cell Lymphoma.](image)

**Marginal Zone Lymphoma: B-R vs. B-R + 2 years R**

![Graph showing PFS events and hazard ratio for Marginal Zone Lymphoma.](image)
B-R + Watch & Wait vs. B-R + 2 years Rituximab

StiL NHL 7-2008 - MAINTAIN

- WM $\rightarrow \geq$ PR $\rightarrow$ R
- n = 296
- SD, PD $\downarrow$
- off study

Bendamustine-Rituximab + Watch & Wait
(n = 109)

Bendamustine-Rituximab + 2 years Rituximab q 2 months
(n = 109)
Progression free survival (80 months median follow-up)

Hazard ratio, 1.21 (95% CI 0.78 – 1.89)  
p = 0.3982

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<thead>
<tr>
<th>Time (months)</th>
<th>Observation</th>
<th>R maint.</th>
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<tr>
<td>106.3</td>
<td>118.4</td>
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<tr>
<td>events (n)</td>
<td>42</td>
<td>36</td>
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<table>
<thead>
<tr>
<th>Pts at risk</th>
<th>Observ</th>
<th>R maint.</th>
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<td>102</td>
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349 PET-Directed Therapy for Patients with Limited-Stage Diffuse Large B-Cell Lymphoma - Results of Intergroup Nctn Study S1001

Sunday, December 8, 2019: 7:30 AM
Hall E2, Level 2 (Orange County Convention Center)
Daniel O. Persky, et al.
Background

- ~30% of de novo DLBCL presents as limited stage
- Favorable outcome, but delayed relapses observed
- Combined modality treatment has been standard of care
  - Improved local control
  - Lower toxicity
  - Better PFS/OS (with initial follow-up pre-rituximab)
- In rituximab era, treatment options include:
  - R-CHOPx3 + XRT, R-CHOPx4, R-CHOPx6
Clinical Trials in Limited Stage DLBCL in the Rituximab Era

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Patients</th>
<th>PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>SWOG S0014 Persky, JCO 2008</td>
<td>Ph II: R-CHOPx3 + IFRT</td>
<td>Stage-modified IPI≥1 (n=60)</td>
<td>4-y: 88%</td>
<td>4-y: 92%</td>
</tr>
<tr>
<td>SWOG S0313 Persky, Blood 2015</td>
<td>Ph II: CHOPx3 + IFRT + RIT</td>
<td>Stage-modified IPI≥1 (n=46)</td>
<td>5-y: 82%</td>
<td>5-y: 87%</td>
</tr>
<tr>
<td>MINT Trial, Pfreundschuh, Lancet Oncol 2011</td>
<td>Ph III: CHOPx6 v R-CHOPx6 (+IFRT for stage I bulky)</td>
<td>Subgroup: aAIPI=0, &lt;7.5cm (n=101)</td>
<td>6-y: 90%</td>
<td>6-y: 95%</td>
</tr>
<tr>
<td>Flyer Trial Poeschel, ASH 2018 #781</td>
<td>Ph III: R-CHOPx6 v R-CHOPx4+2R</td>
<td>16-60 y; aAIPI=0, &lt;7.5cm (N=588)</td>
<td>3-y: 94 v 96%</td>
<td>3-y: 98 v 99%</td>
</tr>
<tr>
<td>LYS/A/GOELMS Lamy, Blood 2018</td>
<td>Ph III: PET-guided (PET-pos if &gt;mediast) R-CHOPx4-6 v R-CHOPx4-6 + RT</td>
<td>18-75 y; stage I/II, &lt;7cm (n=319)</td>
<td>5-y EFS: 89 v 92%</td>
<td>5-y: 92 v 96%</td>
</tr>
<tr>
<td>NCTN S1001 Persky, ASH 2019 #349</td>
<td>PH II: PET-guided (PET-negative D1-3) R-CHOPx4 v R-CHOPx3 + IFRT/RIT</td>
<td>Stage I/II, &lt;10cm (n=132)</td>
<td>5-y: 87%</td>
<td>5-y: 90%</td>
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NCTN S1001 Schema:

- **PET+**
  - R-CHOP x 3
  - IFRT
  - Zevalin

- **PET-**
  - R-CHOP x 1

**Stage I/II DLBCL by CT and PET**

**Stage I/II DLBCL by CT but III/IV by PET**

R-CHOP x 6
NCTN S1001 Results:

Progression-free Survival

Overall Survival
Long-term Follow-up of a PET-Guided Approach to Treatment of Limited Stage DLBCL in BC

LH Sehn, DW Scott, D Villa, AS Gerrie, CL Freeman, C Parsons, T Pickles, A Lo, P Farinha, GW Slack, D Wilson, RP Tonseth, JM Connors, KJ Savage

BC Cancer Centre for Lymphoid Cancer

The University of British Columbia

Vancouver, Canada
Time-to-Progression According to PET Status (n=313)

PET NEG
5-y TTP: 92% (95% CI 88-96%)

PET-POS
5-y TTP: 80% (95% CI 70-91%)

P=0.01
Abstract 463 Efficacy and Survival in Newly Diagnosed Advanced Extranodal Natural Killer/T-Cell Lymphoma: A Randomized, Controlled, Multicenter and Open-Labeled Study with Ddgp Regimen Versus SMILE Regimen

Sunday, December 8, 2019: 12:00 PM
Valencia D (W415D), Level 4 (Orange County Convention Center)
Xinhua Wang, et al
N=80

Eligibility:
- Patients aged 14-70
- Newly diagnosed ENKTL in stages III/IV
- ECOG performance score of 0-2

Treatment:

**DDGP regimen** (cisplatin 20 mg/m² on day 1-4; dexamethasone 15mg/m2 on d1-5; gemcitabine 800mg/m2 on d1,8; pegasparagase 2500 IU/m2 on d1; 21 days per cycle) X6

or

**SMILE regimen** (methotrexate 2g/m2 on d1; dexamethasone 40mg/m2 on d2-4; ifosfamide 1500mg/m2 on d2-4; L-asparaginase 6000 U/m2 on d3-9; etoposide 100 mg/m2 on d2–4; 21 days per cycle) X6

**Primary endpoint:** PFS
Abstract 19 Whole Exome and Transcriptome Sequencing in 1042 Cases Reveals Distinct Clinically Relevant Genetic Subgroups of Follicular Lymphoma

Saturday, December 7, 2019: 7:30 AM
W230, Level 2 (Orange County Convention Center)
Xiang Li1*, et al.

Abstract 551 Towards Non-Invasive Classification of DLBCL Genetic Subtypes By Ctdna Profiling

Monday, December 9, 2019: 8:00 AM
W230, Level 2 (Orange County Convention Center)
Mohammad Shahrokh Esfahani, et al.
Abstract 655 An Atlas of Clinically-Distinct Tumor Cellular Ecosystems in Diffuse Large B Cell Lymphoma
Monday, December 9, 2019: 10:30 AM
Chloe B. Steen, et al.
Sessions

Aggressive Lymphoma (Diffuse Large B-Cell and Other Aggressive B-Cell Non-Hodgkin Lymphomas)—Results from Prospective Clinical Trials: Results from CAR T-Cell Trials
Saturday 2:00-3:30

Aggressive Lymphoma (Diffuse Large B-Cell and Other Aggressive B-Cell Non-Hodgkin Lymphomas)—Results from Retrospective/Observational Studies: Cellular Therapies
Monday 2:45-4:15