Advances in the treatment of R/R diffuse large B-cell lymphoma

Abraham Avigdor M.D.
Sheba Medical Center
Relapse and refractory DLBCL

• Clinical and molecular heterogeneity of R/R DLBCL
• Current standards of care
  - 2\textsuperscript{nd} line therapy for transplant eligible patients
  - 2\textsuperscript{nd} line therapies for transplant ineligible patients
  - 3\textsuperscript{rd} line options for R/R DLBCL: CAR T- cells and polatuzumab
• The future: novel antibodies under investigation
• Can we decrease the rate of resistance by improving 1\textsuperscript{st} line therapy?
Different molecular patterns of relapse in DLBCL

Formalin-fixed-paraffin-embedded tumor samples from first diagnosis, relapsed or refractory disease from 28 patients using next-generation sequencing of the exons of 104 coding genes.

Melchardt T. et al., Oncotarget, 2016
Diffuse large B-cell lymphoma with primary treatment failure

N = 331 with primary treatment failure:
- primary progression while on upfront chemoimmunotherapy
- residual disease at the end of upfront therapy
- relapse <6 months from end of therapy

Three variables predicted decreased OS in multivariate analysis:
- The presence of primary progression
- Intermediate-high/high NCCN-IPI at time of treatment failure
- MYC translocation

Costa L. et al., AJH 2017
In rituximab era ~10-20% of R/R DLBCL patients are eventually cured by ASCT, presenting a significant unmet need.

ASCT is the standard of care for R/R DLBCL but carries significant limitations:

- **A** Ineligibility due to age, frailty, comorbidities, cognitive and physical conditions
- **B** Success dependent on history of chemotherapy prior to transplantation due to effect on chemo-resistance
- **C** High relapse rate post-ASCT, with poor survival (9 month median survival post-ASCT relapse)
- **D** There is no SoC for ASCT-ineligible/relapsed patients
- **D** Allogeneic SCT carries a 20% risk of mortality and significant burden of graft-versus-host disease

3 groups of patients with ultra-high risk features in R/R DLBCL.
Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Median OS – 6.3 months
20% of patients alive at 2 years

Response rates to chemotherapy

<table>
<thead>
<tr>
<th>Pooled (n=523)</th>
<th>Response rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>7</td>
</tr>
<tr>
<td>PR</td>
<td>18</td>
</tr>
</tbody>
</table>

ORR (CR) by refractory category, %

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Primary refractory</td>
<td>20 (3)</td>
</tr>
<tr>
<td>Refractory to ≥2L therapy</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Relapse ≤12 months post-ASCT</td>
<td>34 (15)</td>
</tr>
</tbody>
</table>

Michael Crump et al., Blood 2017
Relapse and refractory DLBCL

- Clinical and molecular heterogeneity of R/R DLBCL
- Current standards of care
  - 2<sup>nd</sup> line therapy for transplant eligible patients
  - 2<sup>nd</sup> line therapies for transplant ineligible patients
  - 3<sup>rd</sup> line options for R/R DLBCL: CAR T – cells and polatuzumab
- The future: novel antibodies under investigation
- Can we decrease the rate of resistance by improving 1<sup>st</sup> line therapy?
NCCN guidelines for R/R DLBCL

DIFFUSE LARGE B-CELL LYMPHOMA

RELAPSE/REFRACTORY DISEASE

ADDITIONAL THERAPY

RESPONSE #2

CONSOLIDATION/ADDITIONAL THERAPY

Consider prophylaxis for tumor lysis syndrome (See NHOOG-B)
See monomodal antibody and viral reactivation (NHOOG-B)

For patients with intention to proceed to transplant

See Suggested Regimens (BCEL-C)

Second-line therapy

High-dose therapy with autologous stem cell rescue (category 1) ± ISRTP on
or Clinical trial or
Allogeneic hematopoietic cell transplant in selected cases

Axicabtagene ciloleucel or
Tisagenlecleucel or
High-dose therapy with autologous stem cell rescue ± ISRTP
or Clinical trial or
Allogeneic hematopoietic cell transplant in selected cases

See Follow-up (BCEL-8)

Complete response

No response or progressive disease

See Relapse #2 or greater (BCEL-8)

Partial response

Complete response

Partial response

No response or progressive disease

See Relapse #2 or greater (BCEL-8)

Non-candidates for transplant

Clinical trial or
Second-line therapy
See Suggested Regimens (BCEL-C) or
Palliative ISRT
or Best supportive care


See Principles of Radiation Therapy (NHOOG-D).
Some NCCN Member Institutions require a complete metabolic response in order to proceed to high-dose therapy with autologous stem cell rescue.
Additional RT can be given before or after transplant to sites of previous positive disease.

Selected cases include mobilization failures and persistent bone marrow involvement.
See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
Salvage chemotherapy followed by high-dose therapy and ASCT is the standard treatment for relapsed DLBCL

**CORAL Study (N=396)**

- **ITT 3-yr OS**: 49%
- **ITT 3-yr PFS**: 37%

- **Pts. underwent ASCT (N=201)**: 3-yr PFS 53%

Christian Gisselbrecht, JCO 2010
Platinum-based salvage therapy is standard of care, but there is no preferred combination.

### Phase III trials evaluating salvage regimens in R/R DLBCL

<table>
<thead>
<tr>
<th>Study</th>
<th>Salvage regimens</th>
<th>ORR, %</th>
<th>Patients who received ASCT, %</th>
<th>p-value</th>
<th>OS rate, %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORAL&lt;sup&gt;2&lt;/sup&gt; n=396</td>
<td>R-DHAP vs R-ICE</td>
<td>63</td>
<td>54</td>
<td>-</td>
<td>3-year: 51</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64</td>
<td>50</td>
<td></td>
<td>3-year: 47</td>
<td></td>
</tr>
<tr>
<td>NCIC-CTG&lt;sup&gt;3&lt;/sup&gt; n=819</td>
<td>R-DHAP vs R-GDP</td>
<td>44</td>
<td>49</td>
<td>0.44</td>
<td>4-year: 39</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>52</td>
<td></td>
<td>4-year: 39</td>
<td></td>
</tr>
<tr>
<td>ORCHARRD&lt;sup&gt;4&lt;/sup&gt; n=445</td>
<td>R-DHAP vs O-DHAP</td>
<td>94</td>
<td>37</td>
<td>0.45</td>
<td>2-year: 38</td>
<td>0.38</td>
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<tr>
<td></td>
<td></td>
<td>84</td>
<td>33</td>
<td></td>
<td>2-year: 41</td>
<td></td>
</tr>
</tbody>
</table>

*<sup>n</sup> NCT00137985; †NCT00078949, included transformed and T-cell lymphoma

ASCT: autologous stem cell transplantation; CORAL: Collaborative Trial in Relapsed Aggressive Lymphoma; DHAP: dexamethasone, cisplatin and cytarabine; GDP: gemcitabine, dexamethasone and cisplatin; ICE: ifosfamide, etoposide and carboplatin; NCIC-CTG: National Cancer Institute of Canada Clinical Trials Group; O, ofatumumab; ORR, overall response rate; R, rituximab; R/R, relapsed/refractory

Outcomes for patients who relapse after receipt of a rituximab-containing induction regimen are particularly poor, even with ASCT.

CORAL Study (N=396)

Table 3: Response Rate and Survival According to Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total No. of Patients</th>
<th>Response CR/CRIu/PR No. of Patients</th>
<th>%</th>
<th>P</th>
<th>3-Year Event-Free Survival %</th>
<th>P</th>
<th>3-Year Overall Survival %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>396</td>
<td>246</td>
<td>63</td>
<td>31</td>
<td>50</td>
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<td></td>
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<tr>
<td>CR/CRIu</td>
<td>148</td>
<td>122</td>
<td>83</td>
<td>&lt;.001</td>
<td>47</td>
<td>&lt;.001</td>
<td>66</td>
<td>&lt;.01</td>
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<tr>
<td>Prior rituximab</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>147</td>
<td>122</td>
<td>83</td>
<td>&lt;.001</td>
<td>47</td>
<td>&lt;.001</td>
<td>66</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Yes</td>
<td>244</td>
<td>124</td>
<td>51</td>
<td>21</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse, &gt; 12 months</td>
<td>160</td>
<td>140</td>
<td>88</td>
<td>&lt;.001</td>
<td>45</td>
<td>&lt;.001</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Refractory, &lt; 12 months</td>
<td>228</td>
<td>106</td>
<td>45</td>
<td>20</td>
<td>35</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sasaPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>224</td>
<td>160</td>
<td>71</td>
<td>&lt;.001</td>
<td>40</td>
<td>&lt;.001</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>&gt; 1</td>
<td>146</td>
<td>76</td>
<td>52</td>
<td>18</td>
<td>32</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; CRIu, unconfirmed complete response; PR, partial response; sasaPI, secondary age-adjusted International Prognostic Index.

Christian Gisselbrecht, JCO 2010
NCCN guidelines for R/R DLBCL

DIFFUSE LARGE B-CELL LYMPHOMA

**RELAPSE/REFRACTORY DISEASE**

- Consider prophylaxis for tumor lysis syndrome (See NHODG-D).
- See monoclonal antibody and viral reactivation (NHODG-B).

**ADDITIONAL THERAPY**

- For patients with intention to proceed to transplant
  - Consider high-dose therapy with autologous stem cell rescue (category 1) ± ISRT\(^p\) or clinical trial.
  - See suggested regimens (BCEL-C).
- For patients with relapsed/refractory disease
  - Non-candidates for transplant

**RESPONSE #2**

- Complete response\(^v\)
  - High-dose therapy with autologous stem cell rescue (category 1) ± ISRT\(^p\), or clinical trial.
- Partial response\(^v, b, c\)
  - Axicabtagene ciloleucel or tisagenlecleucel\(^i, j\)
    - or High-dose therapy with autologous stem cell rescue ± ISRT\(^p, c\), or clinical trial.
    - or Allogeneic hematopoietic cell transplant in selected cases\(^d\) ± ISRT\(^p, c\).

**CONSOLIDATION/ADDITIONAL THERAPY**

- No response or progressive disease\(^v\)
  - See follow-up (BCEL-8).
- Clinical trial or second-line therapy
  - See suggested regimens (BCEL-C) or palliative ISRT\(^p\) or best supportive care.

- Complete response\(^v\)
  - Partial response\(^v, b, c\)
    - See follow-up (BCEL-8).

### Patients ineligible for or who have failed SCT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>ORR, % (95% CI)</th>
<th>mPFS, months (95% CI)</th>
</tr>
</thead>
</table>
| **R-InO vs. investigator’s choice (IC) of R-B or R-G**¹  
  • R/R CD20+/CD22+ aggressive B-NHL  
  • Ineligible for HDC, with or without transplant  
 | R-InO | 166 | 41 (33–49) | 3.7 (2.9–5.0) |
|         | IC | 172 | 44 (36–51) | 3.5 (2.8–4.9) |
| **R-GemOx**²  
  • R/R CD20+ DLBCL  
  • Ineligible for HDC  
 | R-GemOx | 48 | 61 (45–74) | 4 vs 11 (by prior R treatment) 3 vs 10 (by early relapse) |
| **Pix-R vs Gem-R**³  
  • Relapsed aggressive B-cell NHL  
  • Ineligible for SCT  
 | Pix-R | 155 | 61.9 | 7.3 (5.2–8.4) |
|         | Gem-R | 157 | 43.9 | 6.3 (4.4–8.1) |

B, bendamustine; G, gemcitabine; IC, investigator’s choice; Pix, pixantrone; Pola, polatuzumab vedotin; R-GemOx, Rituximab + gemcitabine and oxaliplatin; R-InO, rituximab–Inotuzumab ozogamicin.

Targeted therapies in R/R DLBCL: lenalidomide

Phase II/III study of lenalidomide versus investigator’s choice* in R/R DLBCL

1° ORR 27.5% vs 11.8%; CR rate 9.8% vs 2.0%

*Gemcitabine, rituximab, etoposide, or oxaliplatin. †Weeks to months conversion rate: 4.345
CR, complete response; ORR, overall response rate; R/R, relapsed/refractory

Targeted therapies in R/R DLBCL: ibrutinib

N = 70,
ORR: ABC - 40%, GCB – 5%

Wyndham H W. et al., nature medicine 2017
Primary objective: To evaluate the overall response rate (ORR) of the combination of ibrutinib, bendamustine and rituximab (IBR).

A phase II study of ibrutinib in combination with bendamustine and rituximab (BR) for patients with R/R aggressive B cell lymphomas — an investigator initiated study at Sheba.

N = 72 Pts

with relapsed/ refractory aB-NHL (DLBCL, PMBCL, transformed indolent lymphoma, double or triple hit DLBCL and unclassifiable aggressive B cell lymphoma)

Screening Period (up to 30 days)

IRB CYCLE 1-6 (28 d)

Ibrutinib (560 mg, P.O)- C7...

PD

OR

Referral to allo-SCT

OR

Unacceptable toxicity

EOT (30 days after last dose)

FU Prior to PD every 12 Wks

After 3 years every 24 wks

FU after PD

Every 24 Wks

The final assessment of the last patient recruited will be done 2 years maximum from the end of chemotherapy.

52 patients were recruited until now

Kedmi M. et al., ASH 2018, 132: 4186
IBR - investigator initiated phase-2 study at Sheba interim analysis (N=32): response and survival

Median follow-up: 14 months

ORR – 45% (CR-30%, PR-15%)

Median OS: CR- not reached, no CR – 5.9 months

Figure 1

![Graphs showing PFS and OS](image)

Figure 1A: P=0.008  
Figure 1B: P=0.032

Kedmi M. et al., ASH 2018, 132: #4186
Relapse and refractory DLBCL

• Clinical and molecular heterogeneity of R/R DLBCL
• Current standards of care
  - 2nd line therapy for transplant eligible patients
  - 2nd line therapies for transplant ineligible patients
  - 3rd line options for R/R DLBCL: CAR T – cells and polatuzumab
• The future: novel antibodies under investigation
• Can we decrease the rate of resistance by improving 1st line therapy?
The results that have been reported to date for anti-CD19 CAR T-cell therapy in R/R DLBCL are the most encouraging.
Two CAR-Ts are approved for third-line treatment of R/R DLBCL

<table>
<thead>
<tr>
<th>KTE-C19</th>
<th>CTL019</th>
<th>JCAR017</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{axicabtagene ciloleucel} (axi-cell) Yescarta</td>
<td>\textit{tisagenlecleucel} (CTL019) Kymriah</td>
<td>\textit{lisocabtagene maraleucel} (liso-cell)</td>
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</table>

<table>
<thead>
<tr>
<th>Feature</th>
<th>Kite Pharma</th>
<th>Novartis</th>
<th>Juno Therapeutics</th>
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<tbody>
<tr>
<td>scFv (anti-CD19)</td>
<td>scFv (anti-CD19)</td>
<td>scFv (anti-CD19)</td>
<td></td>
</tr>
<tr>
<td>CD28-CD3ζ</td>
<td>4-1BB-CD3ζ</td>
<td>4-1BB-CD3ζ</td>
<td></td>
</tr>
<tr>
<td>FDA approved</td>
<td>FDA approved</td>
<td></td>
<td>investigational</td>
</tr>
</tbody>
</table>
Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicenter, phase 1–2 trial

Frederick L Locke et al., Lancet Oncol 2018

- Single-arm, multicenter, registrational trial at 22 sites in the USA and Israel
- N = 119 enrolled, 109 received cells, 101 assessable for activity
- Age ≥ 18
- R/R DLBCL NOS, PMBCL, TFL
- Bridging therapy – not allowed
- Lymphodepletion with Flu + Cy
- Target dose of $2 \times 10^6$/Kg CAR T-cells
- Median FU – 27.1 months
- ORR – 83%: CR – 58%, PR – 25%
- Ongoing responses in > 2 years: 39%

Median duration of response: 11.1 months
Median PFS: 5.9 months
Median OS: not reached
Long-term safety and activity of axicabtagene ciloleucel in refractory B-cell lymphoma (ZUMA-1): a single-arm, multicenter, phase 1–2 trial

PFS by response status at 3 months after axicabtagene ciloleucel

- N = 60 with response or SD
- Four of eight patients with partial responses and four of nine patients with stable disease at 3 months subsequently converted to complete responses.

Frederick L Locke et al., Lancet Oncol 2018
Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma (Juliet study)

A single-group, open-label, multicenter, international phase 2 study
- Age ≥ 18 yrs
- R/R DLBCL NOS, TFL, excluding PMBCL
- Median time from enrollment to infusion of CAR T-cells was 54 days
- 92% of pts. received bridging therapy
- median CAR T-cell dose: total $3.0 \times 10^8$ (range, $0.1 \times 10^8 - 6 \times 10^8$)
- 93% received lymphodepleting therapy:
  - 73% - Flu-Cy
  - 20% - bendamustine

Stephen J. Schuster et al., NEJM 2019
Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma (Juliet study)

Stephen J. Schuster et al., NEJM 2019

N = 93
Median FU – 14 months
Best ORR – 52% (CR – 40%, PR – 12%)
1 yr. OS – 49% (entire cohort), 90% (CR patients)
CAR-Ts are approved for third-line treatment of R/R DLBCL

<table>
<thead>
<tr>
<th></th>
<th>¹ZUMA-1</th>
<th>²JULIET</th>
</tr>
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<tbody>
<tr>
<td><strong>CAR T product</strong></td>
<td>KTE –C19, Axi-cel</td>
<td>CTL019, Tisa -cel</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease entity</td>
<td>DLBCL, tFL, PMBCL</td>
<td>DLBCL, tFL</td>
</tr>
<tr>
<td>Enrolled/infused, n</td>
<td>111/101</td>
<td>165/111</td>
</tr>
<tr>
<td>Prior lines of chemo, median, range</td>
<td>3 (1-7)</td>
<td>3 (1-8)</td>
</tr>
<tr>
<td><strong>Bridging therapy</strong></td>
<td>not allowed</td>
<td>allowed</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td></td>
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</tr>
<tr>
<td>CRS all/ ≥ grade 3, %</td>
<td>93/13</td>
<td>58/22</td>
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<tr>
<td>Neurotoxicity all/ ≥ grade 3, %</td>
<td>64/28</td>
<td>21/12</td>
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<td>Tocilizumab, %</td>
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<tr>
<td><strong>response</strong></td>
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<tr>
<td>ORR%</td>
<td>82</td>
<td>52</td>
</tr>
<tr>
<td>CR%</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td><strong>12 months PFS%</strong></td>
<td>44</td>
<td>~32</td>
</tr>
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<td><strong>24 months PFS%</strong></td>
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<td>-</td>
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<td><strong>12 months OS%</strong></td>
<td>59</td>
<td>49</td>
</tr>
<tr>
<td><strong>24 months OS%</strong></td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

1. Frederick L Locke et al., *Lancet Oncol* 2018
2. Stephen J. Schuster et al., *NEJM* 2019
Locally produced autologous CAR T-cells in Sheba Medical Center for CD19+ lymphoid malignancies

<table>
<thead>
<tr>
<th>Car T-cell product</th>
<th>Commercial partner</th>
<th>Academic partner</th>
<th>scFv</th>
<th>Gene transfer method</th>
<th>Costimulatory domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>KTE-C19 (axi-cel)</td>
<td>Kite/Gilead</td>
<td>NCI</td>
<td>Anti–CD19</td>
<td>Gamma-retrovirus</td>
<td>CD28–CD3ζ</td>
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<tr>
<td>CTL019 (tisa-cel)</td>
<td>Novartis</td>
<td>Upenn/CHOP</td>
<td>Anti–CD19</td>
<td>Lentivirus</td>
<td>4-1BB–CD3ζ</td>
</tr>
<tr>
<td>JCAR017 (liso-cel)</td>
<td>Juno Therapeutics</td>
<td>MSKCC, Fred Hutchinson, Seattle Children’s Hospital</td>
<td>Anti-CD19</td>
<td>Lentivirus</td>
<td>4-1BB–CD3ζ</td>
</tr>
</tbody>
</table>

The CAR used in Sheba is composed of an anti-CD19 single-chain Fv FMC63, CD28 co-stimulatory and CD3-zeta intracellular domains.
Locally produced autologous CAR T-cells in Sheba Medical Center for R/R CD19+ lymphoid malignancies

- **The program at Sheba (since June 2016):**
  - Single center, phase 1b/2 study of anti CD19 CAR T-cell therapy in children and adults with B-cell malignancies (NCT02772198)
  - Utilizes in-house production of anti-CD19 CAR T-cells (Laboratories at Ella Lemelbaum Institute for Immuno Oncology)
  - Enables treatment locally

- **Advantages:**
  - Uses fresh cells
  - Abrogates the need for cryopreservation and shipment of cells
  - Reduces costs involved
  - Any R/R CD19+ lymphoid malignancies
  - Very short production time
Locally produced autologous CAR T-cells in Sheba Medical Center for R/R CD19+ lymphoid malignancies

**Duration:** 9-10 days

**Treatment:** lymphodepletion with:
- Flu 25 mg/m² X 3d &
- CTX 900 mg/m² x 1d

**Target cell Dosing:**
- 1- 1.5 X 10⁶/Kg fresh transduced T-cells

**Procedure:**
1. Leukapheresis PBMCs
2. T-cell activation/transduction³ using anti CD3 (OKT-3) and IL-2/retrovirus
3. Modified T-cell expansion⁴ using IL-2
4. Chemotherapy
5. Modified T-cell infusion
Locally produced autologous CAR T-cells in Sheba Medical Center for CD19+ lymphoid malignancies

Total enrollment from June 2016 - 100 patients
62 adult cohort (started in June 2017)
38 pediatric cohort

<table>
<thead>
<tr>
<th>Adult cohort</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Enrolled/infused, n</td>
<td>62/60*</td>
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<tr>
<td>Disease entity, n</td>
<td></td>
</tr>
<tr>
<td>Aggressive B cell lymphoma</td>
<td>53</td>
</tr>
<tr>
<td>B-ALL</td>
<td>7</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Death within 30 days of infusion, n</td>
<td>2**</td>
</tr>
</tbody>
</table>

*2 deaths from progressive Richter transformation
**one patient with ALL – due to sepsis
one patient with DLBCL- due to progressive disease
Interim analysis of the adult Sheba cohort with only aggressive B cell lymphoma: overall response rate

<table>
<thead>
<tr>
<th>Overall response rate 28 days post infusion, n (%)</th>
<th>N = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18 (60)</td>
</tr>
<tr>
<td>CR</td>
<td>9 (30)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (30)</td>
</tr>
<tr>
<td>NR/PD</td>
<td>12 (40)</td>
</tr>
</tbody>
</table>

Data cutoff on January 22, 2019
Sheba cohort - Survival

median FU - 5.1 month.
19 patients - alive, 11 - died (9 - disease progression, 2 - transplant related toxicity)

Overall survival
- Median OS 20.7 months
- Estimated OS 18 months – 52%

Progression free survival
- Median PFS 3.7 months
- Estimated PFS 18 months – 25%
Among the 18 pts with an objective response: estimated PFS at 18 months - 44%
ZUMA-7 Axi-cel vs. SOC Second-Line Therapy in Adult R/R DLBCL: Study Schema and Endpoints

Clinicaltrials.gov: NCT03391466

All agents or uses are investigational. Efficacy and safety have not been established. Visit clinicaltrials.gov for more information on trial inclusion and exclusion criteria.

AEs=adverse events; ASCT=autologous stem cell transplantation; axi-cel=axicabtagene ciloleucel; CR=complete response; DOR=duration of response; DLBCL=diffuse large B cell lymphoma; EFS=event-free survival; HDT=high-dose therapy; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient reported outcome; R-ICE=rituximab + ifosfamide + carboplatin + etoposide; R/R=relapsed/refractory.

*Patients will receive a 3-day lymphodepleting regimen consisting of fludarabine 30 mg/m²/d + cyclophosphamide 500 mg/m²/d (days −5 to −3) followed by 2 rest days (day −2 and day −1). On Day 0, patients will receive a single infusion of axi-cel administered intravenously at 2 × 10⁶ anti-CD19 CAR T cells/kg.

**Patients will receive 2-3 cycles of investigator’s choice of a platinum-based combination chemotherapy regimen (eg, R-ICE) administered every 2-3 weeks.

Defined as death, disease progression, or new lymphoma therapy.
Polatuzumab vedotin: an ADC targeted to CD79b approved for 3\textsuperscript{rd} line in DLBCL

ADC, antibody–drug conjugate; Fc, fragment crystallisable; MMAE, monomethyl auristatin E; MoA, mechanism of action

Randomised Phase II study of pola-BR versus BR (GO29365): study design

Patients
- R/R DLBCL
- R/R FL

Safety run-in phase
- Pola 1.8mg/kg + BR (n=6/histology)
- Pola 1.8mg/kg + BG (n=6/histology)

Phase II expansion
- Pola 1.8mg/kg + BG (n=20/histology)

Phase II randomisation
- Pola 1.8mg/kg + BR (n=40/histology)
- BR (n=40/histology)

Primary endpoint (Phase II): PET-CR rate according to modified Lugano criteria

BG, bendamustine and obinutuzumab; BR, bendamustine and rituximab; FL, follicular lymphoma; PET-CR, positron electron tomography–complete response; pola, polatuzumab vedotin; R, randomisation; R/R, relapsed/refractory

Sehn L, et al. Abstract #1683, ASH 2018
## GO29365: Baseline characteristics generally balanced between arms

<table>
<thead>
<tr>
<th>% unless otherwise stated</th>
<th>BR (n=40)</th>
<th>Pola + BR (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>71 (30–84)</td>
<td>67 (33–86)</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>77.5</td>
<td>82.5</td>
</tr>
<tr>
<td>≥2</td>
<td>22.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>IPI ≥3</td>
<td>73</td>
<td>55</td>
</tr>
<tr>
<td>Bulky disease (≥7.5 cm)</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>DoR to last treatment ≤12 months</td>
<td>83</td>
<td>80</td>
</tr>
</tbody>
</table>

Data cut-off: 3 May 2017
BR, bendamustine and rituximab; DoR; duration of response; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; pola, polatuzumab vedotin; PS, performance status

Sehn L, et al. Abstract #1683, ASH 2018
Sehn L, et al. Abstract #7507. ASCO 2018
GO29365: Baseline characteristics generally balanced between arms

<table>
<thead>
<tr>
<th>% unless otherwise stated</th>
<th>BR (n=40)</th>
<th>Pola + BR (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lines of prior treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>27.5</td>
</tr>
<tr>
<td>≥2</td>
<td>70</td>
<td>72.5</td>
</tr>
<tr>
<td>Prior treatment lines, median (range)</td>
<td>2 (1–5)</td>
<td>2 (1–7)</td>
</tr>
<tr>
<td>Prior bone marrow transplant</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>Prior bendamustine</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Prior anti-CD20 agent</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Refractory to last prior therapy*</td>
<td>83</td>
<td>75</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>70</td>
<td>50</td>
</tr>
</tbody>
</table>

Data cut-off: 3 May 2017
*No response or progressive disease within 6 months of last dose of treatment
BR, bendamustine and rituximab; pola, polatuzumab vedotin

Sehn L, et al. Abstract #1683, ASH 2018
Sehn L, et al. Abstract #7507. ASCO 2018
GO29365: Addition of pola to BR improved response rates

Response at EOT (IRC)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>BR</th>
<th>Pola + BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>OR</td>
<td>18</td>
<td>40</td>
</tr>
</tbody>
</table>

\(p=0.008\) \(p=0.026\)

Seven patients have ongoing response durations of ≥20 months at data cut-off

Best overall response and CR (INV)\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>BOR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Pola + BR</td>
<td>70</td>
<td>58</td>
</tr>
</tbody>
</table>

Data cut-off: 1. 30 April 2018, 2. May 2017

*Primary endpoint; PET-CR is assessed by modified Lugano criteria

BOR, best overall response; BR, bendamustine and rituximab; CR, complete response; EOT, end of treatment; INV, investigator; IRC, independent review committee; OR, objective response; pola, polatuzumab vedotin

1. Sehn L, et al. Abstract #1683, ASH 2018
GO29365: DoR and PFS were significantly longer with pola + BR versus BR

<table>
<thead>
<tr>
<th>Investigator assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Median DoR, months</strong></td>
</tr>
<tr>
<td>(range)</td>
</tr>
<tr>
<td><strong>HR (95% CI), p-value</strong></td>
</tr>
<tr>
<td>(0.20–0.95), p=0.0321</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
</tr>
<tr>
<td>(range)</td>
</tr>
<tr>
<td><strong>HR (95% CI), p-value</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

HR and p-values based on stratified analysis
BR, bendamustine and rituximab; DoR, duration of response; pola, polatuzumab vedotin

Sehn L, et al. Abstract #1683, ASH 2018
GO29365: OS was significantly longer with pola + BR versus BR

Efficacy benefit with pola + BR was seen regardless of cell of origin or double expressor status

Sehn L, et al. Abstract #1683, ASH 2018
GO29365: Are we seeing long-term survival benefit with Pola + BR?

n=46; long-term follow-up data from pooled safety run-in and randomised patients

2-year PFS of 31.4% indicates long-term disease control

22% of pola + BR patients remain in complete remission at last follow-up (ongoing DoR of >20 months)

Maximum follow-up: 45.9 months; median follow-up: 27.6 months

BR, bendamustine and rituximab; pola, polatuzumab vedotin

Sehn L, et al. Abstract #202, ICML 2019
GO29365: all-grade AEs in ≥20% patients*

Median number of completed cycles: 3 (range, 1–6) with BR; 5 (range, 1–6) with pola + BR

AE, adverse event; BR, bendamustine and rituximab; pola, polatuzumab vedotin; *Combined DLBCL and FL cohorts

Sehn L, et al. Abstract #7507. ASCO 2018
Pola in combination with R-GemOx will be investigated in R/R DLBCL in the Phase III POLARGO study

**Rationale**
- Pola + BR had an acceptable safety profile and demonstrated benefit vs BR in the GO29365 study
- R-GemOx is another widely used combination in DLBCL

**Patients**
- Ages ≥18 years
- Histologically confirmed R/R DLBCL
- ≥1 bi-dimensionally measurable lesion
- ECOG PS 0−2
- Adequate haematological function

**Endpoints**
- **Primary:** OS
- **Secondary:** Other efficacy and safety

BR, bendamustine + R; CHP, cyclophosphamide, doxorubicin and prednisone; CR, complete response; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GemOx, gemcitabine and oxaliplatin; PET-CT, positron emission tomography–computed tomography; PK, pharmacokinetics; pola, polatuzumab vedotin; PS, performance status; R, rituximab; RCT, randomised controlled trial; R/R, relapsed refractory
Pola will be investigated in R/R DLBCL in combination with R-ICE in a Phase III bridge-to-transplant study.

**Endpoints**

**Primary:** 2-year EFS rate

**Secondary:** Other efficacy and safety

ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HDT, high-dose therapy; ICE, ifosfamide, etoposide and carboplatin; PET, positron emission tomography; PS, performance status; R, rituximab; R/R, relapsed/refractory; SCT, stem cell transplant.
Relapse and refractory DLBCL

• Clinical and molecular heterogeneity of R/R DLBCL
• **Current standards of care**
  - 2\textsuperscript{nd} line therapy for transplant eligible patients
  - 2\textsuperscript{nd} line therapies for transplant ineligible patients
  - 3\textsuperscript{rd} line options for R/R DLBCL: CAR T – cells and polatuzumab
• **The future: novel antibodies under investigation**
• **Can we decrease the rate of resistance by improving 1\textsuperscript{st} line therapy?**
Novel antibody therapies are under investigation in DLBCL

- Alemtuzumab
- CD20, T-cell bispecifics
- ADC (polatuzumab vedotin)
- ADC (caltuximab ravtansine)
- MOR208 (tafasitamab)
- Anti-PD1 has mild efficacy as a single agent in R/R DLBCL (ORR - 10%) except in PMBCL (ORR -45%, CR –13%)

Potential B-cell targets

Potential T-cell targets

ADC, antibody–drug conjugate; TCB, T-cell bispecific antibodies
Blinatumomab had moderate efficacy in a Phase II study in aggressive B-cell lymphoma

Coyle L, et al. Blood 2018

**AEs, %**

<table>
<thead>
<tr>
<th>Cohort III (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment-emergent AEs</strong></td>
</tr>
<tr>
<td><strong>Grade ≥3</strong></td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Bone marrow toxicity</td>
</tr>
<tr>
<td>Thromboembolic events</td>
</tr>
<tr>
<td><strong>Grade ≥4</strong></td>
</tr>
<tr>
<td>AEs leading to treatment</td>
</tr>
<tr>
<td>discontinuation,</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>ORR*, %</td>
</tr>
<tr>
<td><strong>Median OS, months (95% CI)</strong></td>
</tr>
</tbody>
</table>

*Complete metabolic response + partial metabolic response AE, adverse event; CIV, continuous intravenous infusion NE, not estimable; ORR, objective response rate
Mosunetuzumab shows encouraging efficacy and acceptable tolerability in a Phase I study

Phase I/Ib study of mosunetuzumab in R/R B-cell NHL

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>All patients (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AEs</td>
<td>63</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>55</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>25</td>
</tr>
<tr>
<td>Leading to treatment withdrawal</td>
<td>3</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>3</td>
</tr>
</tbody>
</table>

Outcomes, %

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=19)</th>
<th>Group B (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response*</td>
<td>10.5</td>
<td>34.0</td>
</tr>
<tr>
<td>CR</td>
<td>10.5</td>
<td>19.1</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>14.9</td>
</tr>
<tr>
<td>SD</td>
<td>15.8</td>
<td>4.3</td>
</tr>
<tr>
<td>PD</td>
<td>63.2</td>
<td>55.3</td>
</tr>
<tr>
<td>Missing/not done</td>
<td>10.5</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Data cut-off date: 17 August 2018

*Initial treatment: eight cycles, up to 17 cycles allowed depending on response status
†Defined as the best response across all visits with or without PET scan as determined by investigator; AE, adverse event; C, cycle; CR, complete response; D, Day; PD, progressive disease; PR, partial response, R/R, relapsed/refractory; SD, stable disease

Budde E, et al., Abstract 399, ASH 2018; Oral presentation
CD20-TCB a novel ‘2:1’ format T-cell-engaging bispecific antibody shows promising efficacy at highest dose

- Humanized bispecific mAb targeting CD20 and CD3
- Induces rapid T-cell activation, proliferation and cytokine release, leading to target cell lysis
- 2:1 (CD20:CD3) format offers
  - strong activity in presence of residual aCD20 from previous lines of therapy
  - ability to combine with other aCD20s, including obinutuzumab pre-treatment to control/mitigate CRS
- NP30179 (NCT03075696)
  - open-label Phase I dose-escalation study of single-agent CD20-TCB in R/R NHL patients
  - data from 3 May 2019 CCOD are presented

ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CCOD, clinical cut-off date; CDC, complement-dependent cytotoxicity; CRS, cytokine release syndrome

Bacac et al.; Clin Canc Res 2018
CD20-TCB a novel ‘2:1’ format T-cell-engaging bispecific antibody shows promising efficacy at highest dose

Phase I dose-escalation study of CD20-TCB

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>NHL cohorts ≥600 µg (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AE</td>
<td>72</td>
</tr>
<tr>
<td>Treatment-related SAE</td>
<td>34</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>56</td>
</tr>
<tr>
<td>Grade 5 AEs</td>
<td>0</td>
</tr>
<tr>
<td>CRS (Grade 1–2/≥3)</td>
<td>39/0</td>
</tr>
<tr>
<td>CNS toxicity (Grade 1–2/≥3)</td>
<td>25/5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes, %</th>
<th>DLBCL 600 µg–1mg (n=14)</th>
<th>DLBCL 1.8–4mg (n=7)</th>
<th>DLBCL 10–16mg (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>21</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>CR</td>
<td>14</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>14</td>
<td>27</td>
</tr>
</tbody>
</table>

Data cut-off: 26 October 2018
AE, adverse event; CR, complete response; CRS, cytokine release syndrome; D, day; ORR, objective response rate; Q2W, every 2 weeks; Q3W, every 3 weeks; R/R, relapsed/refractory; SAE, serious AE

Hutchings M, et al.; Blood 2018
Novel antibody therapies are under investigation in DLBCL

Anti-PD1 has mild efficacy as a single agent in R/R DLBCL (ORR - 10%) except in PMBCL (ORR -45%, CR –13%)
Anti-CD47 Hu5F9-G4 + rituximab showed promising activity in a Phase Ib study in R/R B-cell NHL
Anti-CD47 Hu5F9-G4 + rituximab showed promising activity in a Phase Ib study in R/R B-cell NHL


<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All patients n=22</th>
<th>DLBCL n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of previous therapies (range)</td>
<td>4 (2–10)</td>
<td>4 (2–10)</td>
</tr>
<tr>
<td>Refractory to most recent regimen, %</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>Refractory to previous rituximab, %</td>
<td>95</td>
<td>93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AEs, %</th>
<th>All patients n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>41</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
</tr>
<tr>
<td>Anaemia</td>
<td>41</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most common SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy outcomes, %</th>
<th>All patients n=22</th>
<th>DLBCL n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>CR</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>PR</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Median DoR, months</td>
<td>–</td>
<td>NR</td>
</tr>
</tbody>
</table>

CR, complete response; DoR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SAE, serious adverse event
Relapse and refractory DLBCL

• Clinical and molecular heterogeneity of R/R DLBCL

• **Current standards of care**
  - 2\textsuperscript{nd} line therapy for transplant eligible patients
  - 2\textsuperscript{nd} line therapies for transplant ineligible patients
  - 3\textsuperscript{rd} line options for R/R DLBCL: CAR T – cells and polatuzumab

• **The future: novel antibodies under investigation**

• **Can we decrease the rate of resistance by improving 1\textsuperscript{st} line therapy?**
1st line DLBCL: can we improve OS on R-CHOP?

**↑ Intensity/density**
- R-CHOP-14
- DA-EPOCH-R
- HDC + ASCT
- R-ACVBP

**Maintenance**
- Lenalidomide
- Rituximab
- Everolimus
- Enzastaurin

**IMIDs/small molecules**
- Bortezomib
- Ibrutinib
- Lenalidomide

**Antibody therapies**
- G-CHOP

Small improvement only in aaIPI=1

ACVB, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; ASCT, autologous stem cell transplant; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHP, cyclophosphamide, doxorubicin and prednisone; DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; G, obinutuzumab; HDC, high-dose chemotherapy; IMID, immunomodulatory imide drug; pola, polatuzumab; R, rituximab
Pola + R-CHP is being compared with R-CHOP in the Phase III POLARIX study in previously untreated DLBCL

**Patients**
- Previously untreated DLBCL
- Ages 18–80 years
- IPI 2–5
- ECOG PS 0–2

**(n=875; 24 countries)**

**Endpoints**

**Primary:** PFS by INV

**Secondary:** PET-CT CR (by IRC) at EOT; EFS, 2-year PFS, OS

---

**ARM A**

- Pola 1.8mg/kg
- R-CHP + vincristine placebo

**Rituximab**
- Cycles 7 and 8
- 1 cycle = 21 days

**ARM B**

- R-CHOP + pola placebo
- 6 cycles
- 2 cycles

**Stratification factors:**
- IPI score (2 vs 3–5)
- Bulky disease (>7.5 cm)
- Geographic region

**CPH; cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EOT, end of treatment; IPI, International Prognostic Index; IRC, Independent Review Committee; INV, investigator; PET-CT, positron emission tomography–computed tomography; pola, polatuzumab vedotin; PS, performance status; R, rituximab**

*Tilly H. et al., Abstract #7571, ASCO 2019 (ClinicalTrials.gov identifier NCT03274492)*
Improving the outcome of high-risk aggressive B-cell lymphoma patients with nivolumab maintenance therapy – The NivoM Trial: an investigator initiated at Sheba

- This is a phase II prospective single arm study.
- Sample size is 50.

Treatment:
- All the participating patients will receive 240mg nivolumab every 2 weeks for 8 doses for 4 months, and later every 480 mg every 4 weeks for 2 years (cycle 9-30) for a maximum of 30 doses, starting 10±2 weeks after the last cycle of R-anthracycline based induction.

12 patients were recruited in the last 6 months

Kedmi M. & Avigdor A.
R/R DLBCL 2019: how I treat?

R/R DLBCL

Eligible for ASCT

CR
Follow-up
Best supportive care
Pola-BR for CAR T ineligible
Refractory/relapse
CAR T
Refractory/relapse
Pola-BR for CAR T ineligible
Pola-BR for CAR T ineligible
Best supportive care

Ineligible for ASCT

Immuno-Chemotherapy/clinical study
CR
Follow-up

AlloSCT if eligible
Good response
Pola – BR/clinical trial
no response
Clinical trial/best supportive care
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