Role of Immunotherapy in Patients with Aggressive Lymphomas

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Disclosures

- Honoraria: Takeda, BMS, MSD, Sanofi, Roche, Novartis, Janssen
- Consultancy: Takeda, BMS, Novartis, Celgene, Janssen, Gilead, Sanofi
- Speaker’s bureau: Takeda
Long Term Outcome of Patients with Aggressive Lymphomas

Auto-HCT in patients with RR DLBCL: The Coral Trial (Gisselbrecht C et al, JCO 2010)

Long-term outcome for patients with HL relapsing after auto-HCT (Martínez C et al, Ann Oncol 2013)
Treatment Strategies in Hematological Neoplasias

Houot R et al, Cancer Immunol Res 2015
cHL frequently harbors alterations at 9p24.1 (including amplification), leading to overexpression of PD-L1 and PD-L2, on malignant Reed–Sternberg cells and on inflammatory cells in the tumor microenvironment → HL may have a genetically driven vulnerability to PD-1 blockade
Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death receptor-1 (PD-1) immune checkpoint pathway.

Long-Term Results of CheckMate 205

FDA approved – May 2016
EMA approved – November 2016

Armand P et al, J Clin Oncol 2018
Pembrolizumab (MK-3475)

- High-Affinity, IgG4, Humanized Monoclonal Antibody Against PD-1
- Exerts dual ligand blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics
- Demonstrated antitumor activity in multiple tumor types\(^1\)\(^-\)\(^7\)

KEYNOTE 087. Two Years Follow Up

- FDA approved – March 2017
- EMA approved – May 2017

Chen R et al, Blood 2019
Checkpoint Inhibition is Associated to a Wide Range of Autoimmune Side Effects

Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

MA Postow. NEJM 378 (2): 158-68, 2018
**Immune-related AEs Cohort B**

- Drug-related pneumonitis reported in 2 patients (grade 2 and grade 3) between first dose and 35 days after last dose
- Majority of events were manageable, with resolution occurring when immune-modulating medications were administered

Engert A; EHA 2016; Armand P, JCO 2018
Treatment Strategies in Hematological Neoplasias

Houot R et al, Cancer Immunol Res 2015
CD20-TCB (RG6026; RO7082859)

- Humanised 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

Dickinson M et al, ICML 2019 (unpublished results)
Study design

- CD20+ B-cell R/R NHL
- ≥1 prior therapy
- Age ≥18 years
- ≥1 measurable lesion
- Adequate hematologic and liver function
- ECOG PS ≤1

**PART I**: Single patient cohorts (N=3; 0.005mg, 0.015mg, 0.045mg)

Switch to **PART II** triggered by Gr 2 treatment-related AE (neutropenia)

**PART II**: Multiple patient cohorts (N=121 as of CCOD 3 May 2019)
CD20-TCB IV q2w for up to 12 14-day cycles OR q3w (from 10mg) for up to 8 21-day cycles

**Obinutuzumab pre-treatment**
- 1000mg IV on C1 D −7
- Mitigates CRS-associated toxicity
- Allows administration of full doses of CD20-TCB on C1D1

**Primary objectives**
- Safety/tolerability, PK, MTD/OBD and RP2D of CD20-TCB

MDT, maximum tolerated dose; OBD, optimal biological dose; RP2D, recommended Phase II dose

_Bacac et al. Clin Canc Res 2018
Dickinson M et al, ICML 2019 (unpublished results)_
Treatment-emergent AEs*

*Gr 1–4 AEs with ≥10% incidence and all Gr 5 AEs in ≥0.6mg cohorts only (N=88 patients)

CCOD: 3 May 2019

Dickinson M et al, ICML 2019 (unpublished results)
Cytokine Release Syndrome (CRS)

Incidence (%) of CRS events in ≥0.6mg cohorts only*

Distribution of onset of CRS events in ≥0.6mg cohorts only*

*N=88 patients
CCOD: 3 May 2019

Dickinson M et al, ICML 2019 (unpublished results)
Anti-tumor activity*

*≥0.6mg cohorts only (N=78 patients); †assessed by PET-CT and x criteria

CCOD: 3 May 2019

Dickinson M et al, ICML 2019 (unpublished results)
Duration of overall response by histology*

Median follow-up for patients with overall response*: 192 days

<table>
<thead>
<tr>
<th>Histology type</th>
<th>Probability (%)</th>
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<tbody>
<tr>
<td>aNHL (N=37)</td>
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<tr>
<td>NHL (N=6)</td>
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</tr>
</tbody>
</table>

*PR/CR, N=43
CCOD: 3 May 2019

Dickinson M et al, ICML 2019 (unpublished results)
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

Budde LE, ASH 2018 (unpublished results)
Treatment-emergent AEs
Group A and B; N=131; maximum single dose: 20 mg

AEs with ≥10% incidence or Grade 5 AE

- 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
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

Budde LE, ASH 2018 (unpublished results)
Efficacy of mosunetuzumab in R/R DLBCL/trFL

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

**Group B R/R DLBCL/trFL**

- B1 0.4/1.0/2.8 mg
- B2 0.8/2.0/4.2 mg
- B3 1.0/1.0/3.0 mg
- B4 1.0/2.0/6.0 mg
- B5 0.8/2.0/6.0 mg
- B6 1.0/2.0/9.0 mg
- B7 1.0/2.0/13.5 mg
- B8 1.0/2.0/20.0 mg

**ORR 16/47 (34.0%)**

**CR 9/47 (19.1%)**

- Complete responder

**Change in SPD from baseline (%)**

**Study day**

- 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

Budde LE, ASH 2018 (unpublished results)
Treatment Strategies in Hematological Neoplasias

Houot R et al, Cancer Immunol Res 2015
What are CART Cells?

CAR T cells are autologous T lymphocytes that are genetically engineered to express the binding site of specific antibodies, thereby directing the autologous polyclonal T cells to bind specific tumor–associated antigens. The construct is composed of a single chain variable fragment (scFv) fused to the activating intracellular domain of the T-cell receptor (TCR).
CAR T Cells Production IS a Complex Procedure
CAR-T cell trials worldwide

N= 492 (ClinicalTrials.gov accessed May 2019)

CAR-T cell trials worldwide

Number of studies

Year of registration

Phase 1
Phase 1/2
Phase 2
Phase 2/3
Phase 3
Phase 4
N/A

T-cell: 4
Lymphoid NOS: 8
Hodgkin: 8
CLL: 28
ALL: 109
B-cell lymphoma: 130

Relapsed / Refractory DLBCL have an Extremely Poor Outcome. The Scholar Study

Outcomes in patients with refractory/early relapse DLBCL were poor: 1-year and 2-year survival rates were 28% and 20%, respectively

Crump M et al. Blood 2017
## CAR T Cells in RR DLBCL

<table>
<thead>
<tr>
<th></th>
<th>Tisagenlecleucel¹</th>
<th>Axicabtagene ciloleucel²</th>
<th>Lisocabtagene maraleucel</th>
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<tbody>
<tr>
<td><strong>Company</strong></td>
<td>Novartis Pharmaceuticals</td>
<td>Kite Pharma</td>
<td>Juno Therapeutics</td>
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<tr>
<td><strong>Target</strong></td>
<td>CD19</td>
<td>CD19</td>
<td>CD19</td>
</tr>
<tr>
<td><strong>Costimulatory domain</strong></td>
<td>4-1BB</td>
<td>CD28</td>
<td>4-1BB</td>
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<td><strong>Key lymphoma trial</strong></td>
<td>JULIET</td>
<td>ZUMA-1</td>
<td>TRANSCEND</td>
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<tr>
<td><strong>Primary analysis</strong></td>
<td>Published 2019</td>
<td>Published 2017</td>
<td>Primary completion date in 2020</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>2018</td>
<td>2017</td>
<td>–</td>
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<tr>
<td><strong>EMA approval</strong></td>
<td>2018</td>
<td>2018</td>
<td>–</td>
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¹: CAR T cell therapy developed by Novartis Pharmaceuticals
²: CAR T cell therapy developed by Kite Pharma

Institut Català d’Oncologia
# Pivotal Trials. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>JULIET</th>
<th>ZUMA-1</th>
<th>TRANSCEND</th>
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<tbody>
<tr>
<td><strong>ECOG PS</strong></td>
<td>0 or 1</td>
<td>0 or 1</td>
<td>0 or 1</td>
</tr>
<tr>
<td><strong>Tumor type</strong></td>
<td>DLBCL, tFL</td>
<td>DLBCL, HGBCL, PMBCL, tFL</td>
<td>DLBCL, HGBCL, FL3B, tDLBCL, and MCL cohort</td>
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<tr>
<td><strong>Prior anti-CD19 therapy</strong></td>
<td>Not permitted</td>
<td>Not permitted</td>
<td>Permitted, if CD19+ status maintained</td>
</tr>
<tr>
<td><strong>Prior CAR-T</strong></td>
<td>Not permitted</td>
<td>Not permitted</td>
<td>Not permitted</td>
</tr>
<tr>
<td><strong>Prior autoSCT</strong></td>
<td>Permitted</td>
<td>Permitted</td>
<td>Permitted</td>
</tr>
<tr>
<td><strong>Prior alloSCT</strong></td>
<td>Not permitted</td>
<td>Not permitted</td>
<td>Not permitted if within 90 days of leukapheresis</td>
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<tr>
<td><strong>Prior/active CNS disease</strong></td>
<td>Yes/No</td>
<td>No/No</td>
<td>No/No</td>
</tr>
<tr>
<td><strong>Bridging therapy</strong></td>
<td>Permitted</td>
<td>Not permitted</td>
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## Pivotal Trials. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>JULIET&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ZUMA-1&lt;sup&gt;2&lt;/sup&gt;</th>
<th>TRANSCEND&lt;sup&gt;3&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>N apheresed (infused)</strong></td>
<td>167 (115)</td>
<td>119 (108)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(69) in DLBCL cohort</td>
</tr>
<tr>
<td><strong>Age, years (range)</strong></td>
<td>56 (22-76)</td>
<td>58 (51-64)</td>
<td>61 (26-82)</td>
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<tr>
<td><strong>Age ≥ 65 years, %</strong></td>
<td>23</td>
<td>24</td>
<td>-</td>
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<tr>
<td><strong>DLBCL, %</strong></td>
<td>80</td>
<td>76</td>
<td>-</td>
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<tr>
<td><strong>Double/triple hit rearrangement, n/N</strong></td>
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<td>16</td>
<td>-</td>
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<tr>
<td><strong>tFL, %</strong></td>
<td>19/70&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5/47</td>
<td>At least 16/69</td>
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<td><strong># of prior therapies, %</strong></td>
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<td>5</td>
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<td>69</td>
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<tr>
<td><strong>Prior autoSCT, %</strong></td>
<td>49 Not permitted</td>
<td>21 Not permitted</td>
<td>46 (any prior transplant)</td>
</tr>
<tr>
<td><strong>Refractory, %</strong></td>
<td>54</td>
<td>76</td>
<td>67 (chemorefractory)</td>
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<tr>
<td><strong>Bridging therapy, %</strong></td>
<td>90</td>
<td>Not permitted</td>
<td>Permitted</td>
</tr>
</tbody>
</table>
Pivotal Trials. Progression Free Survival

**JULIET:** 35% of patients still in PFS at median f/u of 14 months\(^1\)

**ZUMA-1:** 36% of patients still in PFS at median f/u of 27 months\(^2\)

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Median overall survival among infused patients was 12 months (95% CI, 7 months–NR) and not reached among patients who achieved CR (95% CI, 18 months–NR)
CART Cell Infusion is Associated with Significant and Characteristic Side Effects

Mini Mental State Examination: Difficulty in writing a sentence

Day 3

Day 4

2 hours post tocilizumab
8mg/kg

Day 5

I love my family

MMSE
29/30

27/30

27/30

29/30
CD19 CAR-T cell therapy: Safety

Incidence of CRS by Lee Scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Any grade</th>
<th>Grade 3-4</th>
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<tbody>
<tr>
<td>JULIET (N=111)</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>ZUMA-1 (N=108)</td>
<td>93</td>
<td>12</td>
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<tr>
<td>TRANSCEEND (N=69)</td>
<td>30</td>
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Incidence of NE by CTCAE v4.03

<table>
<thead>
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<td>JULIET (N=111)</td>
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<td>64</td>
<td>28</td>
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<td>TRANSCEEND (N=69)</td>
<td>20</td>
<td>14</td>
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</tbody>
</table>

Head-to-head studies have not been performed and no comparisons can be made.

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NE, neurological events.


CD19 CAR-T cell therapy: Tocilizumab use in JULIET and ZUMA-1

Head-to-head studies have not been performed and no comparisons can be made.

**JULIET (N = 63)**

- CRS grade
  - Grade 1: 30 patients with CRS
  - Grade 2: 20 patients with CRS
  - Grade 3: 10 patients with CRS
  - Grade 4: 5 patients with CRS

**ZUMA-1 (N = 100)**

- CRS grade
  - Grade 1: 40 patients with CRS
  - Grade 2: 30 patients with CRS
  - Grade 3: 20 patients with CRS
  - Grade 4: 5 patients with CRS

- CRS was regraded retrospectively by the Lee scale in the JULIET trial and prospectively per protocol in the ZUMA-1 trial.

CAR, chimeric antigen receptor; CRS, cytokine release syndrome.
## Treatment with CART Cells for RR DLBCL. Real World Evidence

<table>
<thead>
<tr>
<th></th>
<th>JULIET(^1,2)</th>
<th>ZUMA-1(^3)</th>
<th>TRANSCEND(^4)</th>
<th>RWE (axi-cel)(^5)</th>
<th>RWE (axi-cel)(^6)</th>
<th>Elderly (≥65) (axi-cel)(^7)</th>
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</thead>
<tbody>
<tr>
<td>N apheresed (infused)</td>
<td>167 (115)</td>
<td>119 (108)</td>
<td>(69) in DLBCL cohort</td>
<td>295 (274)</td>
<td>104 (91)</td>
<td>17</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>56 (22-76)</td>
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<td>61 (26-82)</td>
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<td>63.8 (21-80)</td>
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<td>Age ≥ 65 years, %</td>
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<td>-</td>
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<td>43</td>
<td>76</td>
</tr>
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<td>tFL, %</td>
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<td>-</td>
<td>26</td>
<td>-</td>
<td>24</td>
</tr>
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<td>Double/triple hit, n/N</td>
<td>19/70(^1)</td>
<td>5/47</td>
<td>At least 16/69</td>
<td>-</td>
<td>21/104 and 4/104</td>
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<td># of prior therapies, %</td>
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<tr>
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<td>Median: 3</td>
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<tr>
<td>3+</td>
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<td>75</td>
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<tr>
<td>Prior autoSCT, %</td>
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<td>21 Not permitted</td>
<td>46 (any prior transplant)</td>
<td>33</td>
<td>2</td>
<td>27</td>
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<tr>
<td>Prior alloSCT, %</td>
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<td>-</td>
<td>75</td>
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<tr>
<td>Refractory, %</td>
<td>54</td>
<td>76</td>
<td>67 (chemorefractory)</td>
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<tr>
<td>Bridging therapy, %</td>
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<td>55</td>
<td>40</td>
<td>Not permitted</td>
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</table>

# Treatment with CART Cells for RR DLBCL. Real World Evidence

<table>
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<tr>
<th></th>
<th>JULIET&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>ZUMA-1&lt;sup&gt;3&lt;/sup&gt;</th>
<th>TRANSCEND&lt;sup&gt;4,5&lt;/sup&gt;</th>
<th>RWE (axi-cel)&lt;sup&gt;6&lt;/sup&gt;</th>
<th>RWE (axi-cel)&lt;sup&gt;7&lt;/sup&gt;</th>
<th>Elderly (≥65) (axi-cel)&lt;sup&gt;8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N evaluable for efficacy/safety</td>
<td>99/111</td>
<td>101/108</td>
<td>68 in DLBCL cohort/102</td>
<td>274</td>
<td>95</td>
<td>17/17</td>
</tr>
<tr>
<td>ORR, %</td>
<td>54 (43-64)</td>
<td>74</td>
<td>75</td>
<td>81 at 90 days</td>
<td>71</td>
<td>–</td>
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<tr>
<td>CR rate, %</td>
<td>40</td>
<td>54</td>
<td>56</td>
<td>57 at 90 days</td>
<td>44</td>
<td>47 at 30 days</td>
</tr>
<tr>
<td>DOR, %</td>
<td>6-mo: 66% 12-18-mo: 64%</td>
<td>Median: 11.1 months (4.2-NE)</td>
<td>–</td>
<td>–</td>
<td>Median: 4.9 months</td>
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<tr>
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<td>11</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Tocilizumab received, %</td>
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<td>45</td>
<td>29</td>
<td>63</td>
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<tr>
<td>Grade 3/4 NE, %</td>
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<td>32</td>
<td>14</td>
<td>33</td>
<td>39</td>
<td>29</td>
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<tr>
<td>Steroids received, %</td>
<td>11</td>
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<td>48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55</td>
<td>64</td>
<td>–</td>
</tr>
</tbody>
</table>

CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; NE, neurological events; ORR, overall response rate; RWE, real-world evidence.

*According to the 2019 ASCO presentation, 2144 patients with CRS and/or NE received dexamethasone treatment.

What About the Future in the CART Arena?

Phase 3 BELINDA trial (NCT03570892)
- Adult patients with aggressive B-cell NHL after failure of rituximab-and anthracycline-containing first-line therapy
- Tisagenlecleucel after optional bridging and lymphodepleting chemotherapy
- Platinum-based immuno-chemotherapy followed in responding patients with high-dose chemotherapy and autoSCT
- Primary endpoint: EFS by BIRC per Lugano criteria
- Secondary endpoints: EFS by investigator OS ORR DOR HRQOL PRO Transgene concentration Immunogenicity Presence of RCL

Phase 3 TRANSFORM trial (NCT03575351)
- Patients (18 to 75 years of age) who relapsed within 12 months from are refractory to anti-CD20 antibody and anthracycline-containing first-line therapy for aggressive B-cell NHL and are eligible for autoSCT
- Lisocabtagene maraleucel (JCAR017)
- R-DHAP, R-ICE, or R-GDP, followed in responding patients with BEAM and autoSCT
- Primary endpoint: EFS
- Secondary endpoints:
  - CR rate
  - PFS
  - OS
  - ORR
  - DOR
  - PFS-2
  - Safety
  - HRQOL
  - Rate of transplant

Phase 3 ZUMA-7 trial (NCT03391466)
- Adult patients with relapsed/refractory DLBCL after first-line rituximab and anthracycline-based chemotherapy
- Axicabtagene ciloleucel following a conditioning chemotherapy regimen of fludarabine and cyclophosphamide
- Platinum-containing salvage chemotherapy followed by high-dose therapy and autoSCT in responders
- Primary endpoint: EFS by BIRC per Lugano criteria
- Secondary endpoints:
  - ORR
  - OS
And ....... Future Partners?

**Phase 1 PORTIA Trial**
- Patients with r/r B-cell NHL and ≥ 1 prior line of therapy
  - Day 0: JCAR014 infusion
  - Day 15-18: Begin pembrolizumab treatment, Q3W up to 6 doses
  - Day 0: Tisagenlecleucel infusion

**Primary endpoint:**
- Percentage of participants receiving pembrolizumab per protocol
- Dose-timing phase: Incidence of DLTs
- Expansion phase: 3-month ORR

**Secondary endpoints:**
- DOR
- PFS
- OS
- Cellular kinetics and impact of pembrolizumab immunogenicity

*Estimated enrollment: 32 patients*

**Phase 1/2 PLATFORM Trial**
- Patients with r/r B-cell NHL with ≥ 2 prior lines of therapy
  - JCAR017 will be administered at a single flat dose of 5 x 10^7 CAR+ T cells or 1 x 10^8 CAR+ T cells
  - Durvalumab will be administered at different doses and/or schedules

**Primary endpoint:**
- DLTs
- CR rate

**Secondary endpoints:**
- Safety
- PFS
- OS
- ORR
- DOR
- EFS
- PK
- HRQOL/QOL

*Estimated enrollment: 100 patients*
What About Other Cellular-Based Strategies in this Setting?

<table>
<thead>
<tr>
<th>Advantage over standard CT</th>
<th>PRO CARTS</th>
<th>PRO ALLOHCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy effect</td>
<td>Immunotherapy effect</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Response to salvage chemotherapy</th>
<th>PRO CARTS</th>
<th>PRO ALLOHCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not necessary</td>
<td>Required</td>
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<table>
<thead>
<tr>
<th>Overall survival</th>
<th>PRO CARTS</th>
<th>PRO ALLOHCT</th>
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</thead>
<tbody>
<tr>
<td>40-50% (limited follow-up)</td>
<td>30-50% (more evidence-based data)</td>
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<table>
<thead>
<tr>
<th>Toxicity</th>
<th>PRO CARTS</th>
<th>PRO ALLOHCT</th>
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</thead>
<tbody>
<tr>
<td>TRM &lt;5%</td>
<td>Chronic disabilities (cGVHD, long-term toxicities) in 30-50% patients</td>
<td></td>
</tr>
<tr>
<td>Long-term toxicity seems manageable</td>
<td>QoL affected by recurrent support therapies and long-term disabilities</td>
<td></td>
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<tr>
<td>QoL not severely affected</td>
<td></td>
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<table>
<thead>
<tr>
<th>Costs</th>
<th>PRO CARTS</th>
<th>PRO ALLOHCT</th>
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</thead>
<tbody>
<tr>
<td>€ 300,000-400,000 € depending on country</td>
<td>€ 80,000-150,000, not considering costs of complications (see GVHD and related drugs)</td>
<td></td>
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</tbody>
</table>
Conclusions

• Immunotherapy strategies have / will have a prominent role in the treatment of aggressive lymphomas

  – Checkpoint inhibitors highly effective in patients with RR HL; they are already being tested in earlier phases of the disease
  – Biespecific MoAb also show promising ORR / CR rates; long term results are eagerly awaited
  – CART cell constructs already approved in patients with DLBCL that have failed at least 2 prior lines of therapy

• Toxicity profile is quite unique in all these treatment strategies; multidisciplinary teams are needed