Case 1:
Patient with R/R DLBCL – European perspective

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# CAR T-cell treatment in R/R DLBCL: Pivotal phase II trials

<table>
<thead>
<tr>
<th>Study/Sponsor</th>
<th>Product</th>
<th>N</th>
<th>Best ORR</th>
<th>Best CR rate</th>
<th>Median FU, months</th>
<th>Median DOR, months</th>
<th>Progression-free at median FU</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1</td>
<td>CD19/CD28</td>
<td>101</td>
<td>83%</td>
<td>58%</td>
<td>27</td>
<td>11.1</td>
<td>39%</td>
<td>Locke, Lancet Oncol. 2018; Neelapu, NEJM. 2017</td>
</tr>
<tr>
<td>JULIET</td>
<td>CD19/4-1BB</td>
<td>111</td>
<td>52%</td>
<td>40%</td>
<td>19</td>
<td>NR</td>
<td>32%</td>
<td>Schuster, NEJM. 2018</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>CD19/4-1BB</td>
<td>256</td>
<td>73%</td>
<td>53%</td>
<td>12</td>
<td>NR</td>
<td>44%</td>
<td>Abramson, Lancet. 2020</td>
</tr>
</tbody>
</table>

**Note:**

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**Diagram:**
- **Apheresis:** Large B cell lymphoma 19.28z or 19.BBz
- **a. Manufacturing failure:** T cell infusion
- **b. Primary resistance:** Complete response
- **c. Relapse:** Antigen+ or Antigen-
- **Sustained complete response:**

Mechanisms of resistance to CD19 CAR T-cell therapy

- Lack of persistence
- Exhaustion of T cells
- Loss of target antigen
- Defects in death receptor signaling pathways
- Upregulation of checkpoints
- Hostile microenvironment

Relapse after CD19 CAR T-cell therapy

- Confirm relapse by biopsy
- Exclude pseudoprogression
  CD19/CD20 expression
  Biomarkers, e.g. PD-L1 expression
- Determine cell of origin
  Genetics (targetable mutations?)
  
- Patient preference
  
- Therapy
  - Circulating CAR T cells?
    - YES
      - Avoid T-cell toxic therapy
      - RT
      - Clinical trial (bispecific)
        - Non-GCB: Len, Ibr
        - GCB+non-GCB: Polatuzumab, checkpoint inhibitors, etc.
    - NO or unknown
      - Clinical trial
      - Immunochemotherapy
        - Non-GCB: Len, Ibr
        - GCB+non-GCB: Polatuzumab, (checkpoint inhibitors), etc.

- Best supportive care
Second infusion of CAR T cells

Study design
• 14 patients treated in ZUMA-1 (axi-cel) received a second infusion
• Eligibility: progressive disease after remission; no loss of CD19
• Retreatment source:
  • second bag (n = 4), manufactured from cryopreserved PBMC (n = 9), new apheresis (n = 1)

Results
• Median interval to retreatment, 9 months
• ORR, 57% (5 CR, 3 PR)
• Response to retreatment more often after CR at 1st treatment (86% vs 33%)
• Median duration of response after retreatment was 9.4 months (range, 0.03–18.2+)
• 2 patients still in remission at 11+ and 18+ months
• Comparable rates of CRS and fewer Grade ≥ 3 NT were observed
• Peak CAR T-cell expansion was lower upon retreatment vs 1st treatment

Conclusions
• Retreatment is feasible but responses are often not durable → use as bridge to allogeneic transplant?
• Currently not registered and not reimbursed

axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; NT, neurotoxicity; ORR, objective response rate; PBMC, peripheral blood mononuclear cell; PR, partial response.
New CAR T-cell indications and constructs

**Coming indications**
- Multiple myeloma
- CLL
- Hodgkin lymphoma
- Acute myeloid leukemia
- Solid tumors

**Combination with other agents**
- Ibrutinib
- Immune checkpoint inhibitors

**4th generation (TRUCKs)**

**Combined/multiple targets**

<table>
<thead>
<tr>
<th>Target</th>
<th>Number of studies</th>
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<tbody>
<tr>
<td>CD19/CD20</td>
<td>13</td>
</tr>
<tr>
<td>CD19/CD30</td>
<td>3</td>
</tr>
<tr>
<td>CD19/CD70</td>
<td>2</td>
</tr>
<tr>
<td>CD19/CD23</td>
<td>1</td>
</tr>
<tr>
<td>CD19/CD8</td>
<td>1</td>
</tr>
<tr>
<td>CD30/CD4</td>
<td>1</td>
</tr>
</tbody>
</table>


CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; NK, natural killer; TRUCK, T cells redirected for antigen-unrestricted cytokine-initiated killing.

**Gene editing**
- Allogeneic CARs
- Third-party CARs
- NK-CARs

**Novel CAR T-cell constructs**

- Pooled CAR T-cell product
- Multi-CAR T-cell
- Tandem CAR T-cell
- Conditional CAR T-cell
- Split CARs
- iCARs
- Suicide switch
So what’s new in aggressive lymphoma other than CAR T?

**Immunotherapy**
- Novel ‘naked’ CD20 antibodies: not (more) effective
- Tafasitamab (+ lenalidomide)
- Antibody–drug conjugates: brentuximab vedotin, polatuzumab vedotin
- Immunomodulatory drugs: lenalidomide, avadomide, iberdomide
- Antibody-based – T cell activating:
  - ‘Immune checkpoint inhibitors’
  - Bispecific antibodies/BiTE
  - CAR T cells

**Precision medicine**
- Targeting intracellular kinases
- Proteasome inhibitors

**Induction of apoptosis**
- BCL2 antagonists

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BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor.
We should be capitalising on biological insights.... but it’s complicated....

- ‘Integrative genetic and clinical analysis through whole exome sequencing in 1001 diffuse large B cell lymphoma (DLBCL) patients reveals novel disease drivers and risk groups.’
- 158 significantly mutated genes/CNAs/SVs identified by whole exome sequencing of 304 newly diagnosed DLBCL patients, several of which are targetable.

Slide courtesy of Andrew Davies.

CNA, copy number alteration; SV, structural variant.
Access to novel drugs in Europe

• Approval by EMA → registration in Europe
• Reimbursement and access differ per country
• Some countries: direct access (e.g. Germany) or temporary access program (e.g. France)

Netherlands:
• Healthcare institute performs health technology assessment
  - Therapeutic value
  - Cost-effectiveness analysis/cost-utility analysis (societal perspective) → challenging if there is no SoC arm
  - Budget impact analysis
• New treatment can be placed in a ‘lock’ pending (secret) price negotiations MoH with company

→ For our patient: clinical trial is the best option

EMA, European Medicines Agency; MoH, Ministry of Health; SoC, standard of care.
Clinical trial options for this patient: Bispecific antibodies

**Epcoritamab (GEN 3013)**
- An anti-CD3 + anti-CD20 bispecific antibody
  
  **GCT3013-01**

- Phase I/II open-label study of GEN3013, single agent
- Single SC injection in 28-day cycles until PD or toxicity

**Response rates**
- N = 15
- ORR, 60%
- 20 CR
- 40 PR

**Blinatumomab**
- An anti-CD19 + anti-CD3 BiTE
- ORR rates of 37% as single agent in R/R B-cell NHL

**KEYNOTE-348**
- Phase Ib open-label study of blinatumomab combined with pembrolizumab
- Up to 2 cycles blinatumomab IV (Cycle 1, 8 weeks; Cycle 2, 28 days)

**Plus**
- 1 cycle pembrolizumab IV every 3 weeks until PD

**Primary outcome:**
- Incidence of dose-limiting toxicities

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BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CR, complete response; IV, intravenous; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SC, subcutaneous; TEAE, treatment-emergent adverse event.
Clinical trial options for this patient: CDK9 inhibition

AZD4573
- A potent and highly selective CDK9 inhibitor that suppresses MCL-1 and induces apoptosis

NCT03263637
- A first-in-human, phase I, open-label, dose-escalation study of AZD4573 in R/R haematological malignancies
- IV infusion, 3 dose levels (for 8 weeks maximum)

Primary outcomes:
- Incidence of AEs
- Dose-limiting toxicities
- Maximum tolerated dose


AE, adverse event; IV, intravenous; R/R, relapsed/refractory.
Thank you