State of the art: CAR-T cell therapy in lymphoma

14th annual California Cancer Consortium conference

Tanya Siddiqi, MD
City of Hope Medical Center
8/11/18
Financial disclosures

- Consultant for Juno therapeutics
- Speaker for ibrutinib (Pharmacyclics/Janssen)
- Speaker for brentuximab vedotin (Seattle Genetics)
- Off label products I will discuss: JCAR017 (Juno CAR-T cells); COH CAR-T cells; KTE-C19 (Kite pharma CAR-T cells in mantle cell lymphoma)
B-cell non-Hodgkin lymphomas

- Small B-cell lymphoid neoplasms
  - CLL/SLL/B-PLL/MBL
  - Follicular lymphoma
  - Marginal zone lymphoma
  - Hairy cell lymphoma
  - Waldenstrom’s macroglobulinemia/LPL
  - Mantle cell lymphoma
- Diffuse large B-cell lymphoma
  - and all it’s subtypes like EBV+, PCNSL
- High grade B-cell lymphomas
  - NOS
  - Double/triple hit
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CD19 CAR T products in pivotal trials in B-NHL

NCI

U Penn

FHCRC / SCH

CD19 Ab

Hinge

Transmembrane

Signal 2

Signal 1

Gene transfer

Retrovirus

Lentivirus

Lentivirus

Kite Pharma

KTE-C19

Axicabtagene ciloleucel

Axi-cel

Novartis

CTL-019

Tisagenlecleucel

Juno Therapeutics

JCAR017 (CD4:CD8 = 1:1)

Lisocabtagene maraleucel

Liso-cel

Adapted from van der Steegen et al. Nat Rev Drug Discov 2015
CAR-T cell manufacturing

(i) Collection of PBMCs and transfer to GMP manufacturing facility
(ii) Viral gene transfer of TCR or CAR into PBMCs
(iii) Propagate genetically modified tumour-reactive T cells
(iv) Transfer cells from manufacturing centre to patient
(v) Precondition patient (e.g. chemotherapy) and transfuse T-cell therapy
ZUMA1: 1st multicenter trial of CD19 CAR T cell therapy in refractory aggressive B-cell NHL

**Phase 1 (N = 7)**

- **Refractory DLBCL/PMBCL/TFL (n = 7)**

**Phase 2 (N = 101)**

- **Cohort 1**
  - Refractory DLBCL (n = 77)

- **Cohort 2**
  - Refractory PMBCL/TFL (n = 24)

**Key eligibility criteria**

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline
- No bridging therapy allowed

**Conditioning regimen**

- Cyclophosphamide 500 mg/m² + fludarabine 30 mg/m² for 3 days
- **Axi-cell**: 2 × 10⁶ CAR+ cells/kg

- 99% enrolled were successfully manufactured
- 91% enrolled were dosed
- 17-day average turnaround time from apheresis to delivery to clinical site

**N = 108**

- Data cutoff: August 11, 2017
- Median follow-up: 15.4 months

**ZUMA1: Efficacy**

<table>
<thead>
<tr>
<th>Median follow-up, mo</th>
<th>Phase 2 Primary Analysis N = 101</th>
<th>Phase 1 and 2 Updated Analysis N = 108</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ORR</td>
<td>CR</td>
</tr>
<tr>
<td>Best objective response, %</td>
<td>82</td>
<td>54</td>
</tr>
<tr>
<td>Ongoing, %</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>58</td>
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<tr>
<td></td>
<td>42</td>
<td>40</td>
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</table>

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
- Median (range) time to conversion from PR to CR = 64 (49 – 424) days
- Study met primary endpoint for ORR (p < 0.0001) at primary analysis

ZUMA-1: Duration of Response by Best Objective Response

- Median duration of CR has not been reached
- 3 of 7 (43%) Phase 1 patients have ongoing CR at 24 months

NR, not reached.

ZUMA-1: Summary of Adverse Events

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Primary Analysis (N = 101)</th>
<th>Updated Analysis (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 AE</td>
<td>96 (95)</td>
<td>105 (97)</td>
</tr>
<tr>
<td>Grade ≥ 3 SAE</td>
<td>43 (43)</td>
<td>50 (46)</td>
</tr>
<tr>
<td>Grade ≥ 3 CRS</td>
<td>13 (13)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Grade ≥ 3 NE</td>
<td>28 (28)</td>
<td>33 (31)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>3 (3)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 (4)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- Since the primary analysis with ≥ 6 months of follow-up, there have been no new axi-cel–related CRS, NE, or Grade 5 AEs
- Most patients experienced hypogammaglobulinemia and B cell aplasia; 8% had IVIG support at any point on study
- 43% use of tocilizumab and 27% use of corticosteroids

<sup>a</sup>Grade 5 AEs occurred in 3 patients. Axi-cel–related, 2 (2%; HLH and cardiac arrest); axi-cel–unrelated, 1 (1%; pulmonary embolism). <sup>b</sup>The additional Grade 5 AE presented here is the previously reported<sup>1</sup> Phase 1 event of intracranial hemorrhage unrelated to axi-cel. 1.Locke FL, et al. *Mol Ther.* 2016. 25:285.
FDA approvals

• Axicabtagene ciloleucel/axi-cel (Kite Pharma) was FDA-approved in 10/2017 for patients with rel/ref DLBCL after 2 or more lines of therapy

• Tisagenlecleucel (Novartis) was also FDA-approved in 5/2018 for rel/ref DLBCL after 2 or more lines of therapy
JULIET trial: Ph2 study of tisagenlecleucel in DLBCL

- single-arm, open-label phase II trial, global study
- Autologous T cells that express a CD19-directed CAR (CTL019)
- Rel/ref DLBCL or FL pts
- N = 28, ages 22 to 76 years
- ORR 64% (18/28), CR in 6/14 with DLBCL (43%) and 10/14 with FL (71%)
- At a median follow-up of 28.6 months, 86% of DLBCL pts who had a response and 89% of FL pts who had a response maintained their response
- Severe CRS occurred in 5 patients (18%); serious encephalopathy occurred in 3 (11%)
- All patients in CR by 6 months remained in remission at 7.7-37.9 months (median 29.3 months)

The therapy was done on an outpatient basis for many patients (26%) and the manufacturing process allowed investigators to generate CAR T cells from previously collected and frozen blood cells, permitting successful shipment around the world.
TRANSCEND-NHL001: multicenter Ph1 trial of CD19-CAR for rel/ref aggressive B-NHL

Lisocabtagene Maraleucel (Liso-cel; JCAR017)
CD19-Directed Defined Cell Product

Abramson J, et al. ASCO and EHA 2018

Patient's PBMCs
- Immunomagnetic selection
- Lentivirus transduction
- Expansion
- Formulated at specified composition of CD4+ and CD8+ CAR+ T cells
- Administered at precise doses of CD4+ and CD8+ CAR+ T cells

CD8+ (targets tumor)
CD4+ (targets tumor, supports persistence)
Other PBMC Cell Types

City of Hope

Abramson J, et al. ASCO and EHA 2018
Multicenter, Seamless Design Pivotal Trial
(TRANSCEND NHL 001; NCT02631044)

Dose Finding (DF) Cohorts
- $5 \times 10^7$ cells (DL1), single dose ($S^b$)
- $5 \times 10^7$ cells (DL1), double dose ($D^c$)
- $1 \times 10^8$ cells (DL2), single dose ($S^b$)

Dose Expansion (DE) Cohorts
- DL1S
- DL2S

Pivotal DLBCL Cohort
- DL2S

Data will be presented from DF and DE DLBCL cohorts
- 102 patients treated (FULL)$^d$
- 73 patients treated in analysis set matching pivotal patient population (CORE)$^e$

$^a$ Disease-specific Dose Finding and Dose Expansion cohorts enrolled [DLBCL and MCL].
$^b$ Administered on Day 1.
$^c$ Administered on Day 1 and Day 14.
$^d$ DLBCL FULL cohort: DLBCL, NOS de novo and transformed from any indolent lymphoma; ECOG 0-2.
$^e$ DLBCL CORE cohort: DLBCL, NOS de novo and transformed from FL, ECOG 0-1, high grade B-cell lymphoma.

Abramson J, et al. ASCO and EHA 2018
TRANSCEND NHL 001 (NCT02631044)

Screen → Liso-cel Manufacturing* → PET-positive disease reconfirmed → Lymphodepletion (FLU 30 mg/m² and CY 300 mg/m² x 3d) → Liso-cel (2-7 days after FLU/CY) → FOLLOW-UP

Initial: 12 months
On-study: 24 months
Long-term: up to 15 years after last liso-cel treatment

ENROLLMENT COHORTS
- DLBCL after 2 lines of therapy:
  - DLBCL, NOS (de novo or transformed FL)
  - High grade B-cell lymphoma (double/triple hit)
  - DLBCL transformed from CLL or MZL
  - PMBCL
  - FL3B
- MCL after 1 line of therapy

PATIENT ELIGIBILITY
- Prior SCT allowed
- Secondary CNS involvement allowed
- ECOG 0-2
- No minimum absolute lymphocyte count requirement for apheresis

FLU, fludarabine; CY, cyclophosphamide
* Therapy for disease control allowed
* ECOG 2 and prior allogeneic HSCT excluded from pivotal cohort.

Abramson J, et al. ASCO and EHA 2018
CONSORT Diagram: DLBCL Cohort

Leukapheresed (n = 134)

Product unavailable (n=2)

Product available (n = 18)
  • Withdrew (n = 5)
  • PD or died (n = 13)

Liso-cel-Treated (n=114)

Received nonconforming liso-cel (n = 12)\(^a\)

Safety-Evaluable (n=102)

DL1S (n = 45)  DL1D (n = 6)  DL2S (n = 51)

- Product available for 99% (132/134) of patients apherased in DLBCL cohort
- Seven MCL subjects treated thus far with liso-cel at DL1S
- Eight patients treated in outpatient setting as of April 3

Abramson J, et al. ASCO and EHA 2018
Results – TRANSCEND NHL 001

- No increase in CRS or neurotoxicity (NT) at DL2 in the CORE set of patients
- No deaths from CRS or NT
- In the FULL set of pts, time to onset of CRS was 5 days and to NT was 10 days
- In the FULL set of pts, 5% received tocilizumab for CRS and 8% received steroids
- High responses seen: best overall response in the FULL subset was 75% with 54% CR (n=102); 40 and 34% respectively at 6 month followup [best for tFL subset]

Abramson J, et al. ASCO and EHA 2018
# High Response Rates in R/R DLBCL
Dose Response Relationship Observed in CORE Patient Population; DL2 Chosen for Pivotal Cohort

<table>
<thead>
<tr>
<th></th>
<th>All Dose Levels&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DL1S</th>
<th>DL2S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BOR, n&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>73</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>80 (68, 88)</td>
<td>79 (61, 91)</td>
<td>78 (62, 90)</td>
</tr>
<tr>
<td><strong>CR, % (95% CI)</strong></td>
<td>59 (47, 70)</td>
<td>55 (36, 72)</td>
<td>62 (45, 78)</td>
</tr>
<tr>
<td><strong>≥ 3-mo f/u, n&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>73</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td><strong>3-mo ORR, % (95% CI)</strong></td>
<td>59 (47, 70)</td>
<td>52 (34, 69)</td>
<td>65 (48, 80)</td>
</tr>
<tr>
<td><strong>3-mo CR, % (95% CI)</strong></td>
<td>45 (34, 57)</td>
<td>36 (20, 55)</td>
<td>51 (34, 68)</td>
</tr>
<tr>
<td><strong>≥ 6-mo f/u, n&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td>73</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td><strong>6-mo ORR, % (95% CI)</strong></td>
<td>47 (35, 59)</td>
<td>42 (26, 61)</td>
<td>49 (32, 66)</td>
</tr>
<tr>
<td><strong>6-mo CR, % (95% CI)</strong></td>
<td>41 (30, 53)</td>
<td>33 (18, 52)</td>
<td>46 (30, 63)</td>
</tr>
</tbody>
</table>

BOR, best overall response.

Baseline high tumor burden<sup>e</sup> well balanced between DL1 and DL2 (~1/3)

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<sup>a</sup> Three patients treated on DL1D with similar outcomes.
<sup>b</sup> Includes patients with event of PD, death, or 28-day restaging scans. Two patients did not have restaging scans available.
<sup>c</sup> The denominator is number of patients who received JCAR017 ≥ 3 months ago, prior to data snapshot date, with an efficacy assessment at month 3 or prior assessment of PD or death.
<sup>d</sup> The denominator is number of patients who received JCAR017 ≥ 6 months ago, prior to data snapshot date, with an efficacy assessment at month 6 or prior assessment of PD or death.
<sup>e</sup> Defined as sum of the products of diameters (SPD) > 50 cm².

Data as of May 4, 2018

Abramson J, et al. ASCO and EHA 2018
Durability of Response (DOR)
DOR Encouraging in High-Risk DLBCL Patient Population

**FULL**

- CR: NR (9.2, NR)
- All: NR (3.9, NR)
- PR: 2.1 mos (1.1, 3.9)

**CORE**

- CR: NR (NR, NR)
- All: NR (5.0, NR)
- PR: 2.1 mos (1.0, 5.0)

In CORE population, 88% of patients with CR at 3 months stay in CR at 6 months; 97% of patients in response at 6 months stay in response for a longer-term

Median F/U=8 months (mos)

Abramson J, et al. ASCO and EHA 2018
Ongoing CAR-T cell trials for DLBCL at COH

• Phase I study to evaluate cellular immunotherapy using memory-enriched T cells lentivirally transduced to express a CD19-specific, hinge-optimized, CD28-costimulatory chimeric receptor and a truncated EGFR following lymphodepleting chemotherapy in adult patients with CD19+ B-cell lymphoproliferative neoplasms [NHL and CLL strata]

• Celgene PLATFORM trial
  – JCAR017 + [durvalumab]/[CC-122]/etc
  – Various dose levels
  – Rel/ref DLBCL
  – No CNS involvement allowed
B-cell non-Hodgkin lymphomas

- Small B-cell lymphoid neoplasms
  - **CLL/SLL/B-PLL/MBL**
  - Follicular lymphoma
  - Marginal zone lymphoma
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  - **Mantle cell lymphoma**

- Diffuse large B-cell lymphoma
  - and all it’s subtypes like EBV+, PCNSL,

- High grade B-cell lymphomas
  - NOS
  - Double/triple hit
CD19 specific CAR-T cells in CLL

- N = 14 (heavily pretreated); median cell dose = 1.6x10^8 CTL019 cells
- 4 CRs (29%), all MRD neg and with no relapses; 4 (29%) PRs; ORR 57%
- CAR-T cells detectable 3 yrs later in some
- Expected toxicities: B cell aplasia, delayed TLS and cytokine release syndrome in all responding patients

CD19 CAR-T cells in ibrutinib-refractory CLL

- N = 24, median age 60 yrs
- MTD 2x10^6 CAR-T cells/kg; CD8+:CD4+ CAR-T cells 1:1
- 19 ibrutinib ref, 3 ibrutinib intolerant, 2 had not progressed on ibrutinib; 6 were ref to venetoclax; 23 had complex karyotype and/or del17p
- 20 pts (83%) had CRS and 8 pts (33%) had neurotoxicity
- ORR at 1 month in 19 of 20 restaged pts who had received Flu/Cy and CAR-T cells at or below MTD was 74% (4/19 CR, 10/19 PR)
- 15/17 patients (88%) with marrow disease before CAR-T cells had no disease by flow cytometry after CAR-T cells; 12 underwent deep IGH sequencing and 7 had no malignant IGH sequences detected
- Absence of the malignant IGH clone in marrow of patients with CLL who responded by IWCLL criteria was associated with 100% progression-free survival and overall survival (median 6.6 months follow-up) after CAR-T cell immunotherapy

TRANSCEND-CLL (017004) - ongoing

- Main inclusion criteria:
  - CLL/SLL with indication to treat
  - Relapsed/refractory after 2 (if with high risk features) or 3 (if no high risk features) lines of therapy including ibrutinib (or intolerant to ibrutinib)
  - Monotherapy as well as combination (ibrutinib) cohorts

Zuma 2: Ph2 study of KTE-C19 in MCL (ongoing)
- Rel/ref MCL
- Upto 5 prior lines of therapy including ibrutinib