B-Cell NHL and Hodgkin’s Disease: Biologicals, Checkpoint Inhibitors, CAR-T cells

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Relevant financial relationships in the past twelve months by presenter or spouse/partner.

**Consultant:** Seattle Genetics, Genentech, Celgene, Pharmacyclics, Jansen, Teva, Bayer

**Speakers Bureau:** Seattle Genetics, Pharmacyclics

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Lymphoma Treatment: The Changing Landscape…

Targeted Therapy

- Biologicals
  - Immunotherapy
Immunotherapy: “The Cure is Inside Us…”

- “Releasing the brakes” in endogenous T-cells
  - Anti PD1/PDL1 antibodies

- Ex vivo manipulation of endogenous T-cells (“engineering”) to unleash their full potential:
  - Chimeric antigen receptor (CAR T-cells)

- “Engaging and activating” endogenous T-cells to destroy tumor cells:
  - Bispecific Antibodies
“Releasing the brakes” in T-cells by blocking PD1/PD-L1 interaction with antibodies

PD-1/PD-L1 Receptor Blocking Antibodies
### Releasing the “brakes” in T-cells induced clinically effective antitumor responses

**Checkpoint blockade with anti-PD1/PDL1 antibodies**
Approved by the FDA for treatment of patients with:
- metastatic melanoma
- non-small cell lung cancer
- renal carcinoma,
- bladder cancer,
- head and neck cancer,
- gastric cancer
- **Relapsed/refractory Hodgkin’s lymphoma**
- tumors displaying microsatellite instability (MSI)-high and mismatch repair deficiency (MRD)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target</th>
<th>Approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, NSCLC, RCC, HL</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, NSCLC, Head and Neck</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>Bladder Ca, NSCLC</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Merkel cell</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td></td>
</tr>
</tbody>
</table>
ASH 2017: Anti-PD1/PDL1 in NHL

- Initial studies demonstrated activity across multiple NHL subtypes:
  - ORRs of 40% in FL and 36% in DLBCL
  - ORRs of 15% in MF and 40% in PTCL

- Unlike the dramatic responses observed in Hodgkin’s lymphomas, the efficacy of anti PD1/PL1 antibodies as single agents in follicular and large cell lymphoma has been disappointed so far.

- Likely to find a “niche” in selected subtypes of NHL (ie, viral-related lymphomas) or in combination with other agents
CD19 CAR T-cells
Chimeric Antigen Receptor (CAR) T-cells

- Emerged from the groundwork set by the clinical successes of monoclonal antibody technology…

Figure 16.6 Janeway’s Immunobiology, 8ed. (© Garland Science 2012)

- Antibodies against CD19 have been generated and are highly specific…. Can this specificity be “introduced” into T-cells? How?

- CD19-CARs are antibody-derived receptors (anti-CD19) genetically “introduced” into T cells to allowed them to better recognize and destroy tumor cells expressing CD19……
Chimeric Antigen Receptor (CAR) T-cells
Redirecting the Specificity of T Cells

Courtesy of David Porter - U Penn
CD19 CARS in clinical trials

NCI

CHOP/U. Penn

FHCC

Baylor
ASH 2017: Results from three anti-CD19 CAR T-cell Platforms

Long-Term Follow-up ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (Axi-Cel; KTE-C19) in Patients with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)
*Sattva S. Neelapu, MD; Frederick L. Locke, MD at al*

Primary Analysis of JULIET: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma
*Stephen J. Schuster, MD, Michael R. Bishop, MD et al*

High Durable CR Rates in R/R Aggressive B-NHL Treated with the CD19-Directed CAR T Cell Product JCAR017 *(TRANSCEND NHL 001)*: Defined Composition Allows for Dose-Finding and Definition of Pivotal Cohort
*Jeremy S. Abramson et al.*
Anti-CD19 CAR T-cell Platforms
Patient Flow Diagrams

**ZUMA-1**

- 111 Enrolled
- Conditioning
- 101 Infused
  - 92 Primary Analysis
  - 101 Modified Intent-to-Treat (mITT)
- Patients not treated:
  - 4 AE
  - 2 No measurable disease
  - 1 Death due to PD
  - 1 Manufacture failure
- SAE (n = 2)

**JULIET**

- 147 Enrolled
- Patients not treated:
  - 5 Pending Infusion
  - 43 Discontinued Before Infusion
  - 9 Manufacture failure
  - 34 Patient-status related
    - 16 Deaths
    - 12 Physician decision
    - 3 Patient decision
    - 2 AEs
    - 1 Protocol deviation
- 99 Infused
- 99 Safety Evaluable
- 81 Response Evaluable
  (≥3 months follow-up or earlier disease progression)

**TRANSCEND**

- Enrolled Unknown
- Patients not treated:
- 91 Infused
- Safety Evaluable:
  - 91 FULL
  - 67 CORE
- Efficacy Evaluable:
  - 88 FULL
  - 65 CORE

**ZUMA-1 JULIET TRANSCEND**
## CAR T-cell studies in B-cell NHL

<table>
<thead>
<tr>
<th>Source</th>
<th>ZUMA-1</th>
<th>JULIET</th>
<th>TRANSCEND JCAR017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 2 Primary Analysis</strong></td>
<td>NEJM 2017 (DCO 11Aug17)</td>
<td>NEJM 2017 (DC0 8Mar17)</td>
<td>Phase 1/2 Interim Analysis Dose Finding ASH 2017</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>17 days; 99% successful</td>
<td>22 days</td>
<td>&lt; 21 days</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td>111 enrolled; 101 dosed and evaluable No bridging chemotherapy</td>
<td>147 enrolled; 99 dosed, 81 evaluable 90% Bridging chemotherapy</td>
<td>Enrollment not reported, 91 dosed (FULL); 67 in CORE</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>2.0 x10⁶ CAR T cells/kg &gt;100 kg 2.0 x 10⁸ fixed</td>
<td>Median, 3.1 x 10⁸ Range, 0.1-6.0 x 10⁸ cells</td>
<td>DL1 5.0 x 10⁷ CAR T cells (N=34) DL2 1.0 x10⁸ CAR T cells (N=29)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>76% DLBCL; 16% TFL; 8% PMBCL 79% refractory 21% relapsed post-ASCT ECOG 0 / 1: 42% / 58%</td>
<td>80% DLBCL; 19% FL 48% relapsed; 52% refractory 47% post ASCT ECOG 0/1: 55% / 45%</td>
<td>(CORE; N = 67) 76% de novo DLBCL; 24% TFL 66% chemorefractory 100% ECOG 0-1</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>mITT = 108 Median follow-up 15.4 mo ORR: 82%; 58% CR Ongoing response: 42%, 40% CR Median DOR: 11.1 mo</td>
<td>ITT = 111 Median follow-up 8.7 mo ORR: 77%; 51% CR Minimum efficacy f/u: 3 mo ORR: 53%; 40% CR 6-mo Rate: 37%; 30% CR Median DOR and OR NR 74% relapse-free at 6-mo Median follow-up: 5.6 mo</td>
<td>(CORE; N = 65) ORR: 80%; 55% CR Median OS NR; 6-mo: 86% Median DOR: 9.2 mo (NR for CR) Median follow-up: 6.3 mo</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Gr ≥ 3 CRS 13% Gr ≥ 3 NE 28% Gr 5 AE 3%</td>
<td>Gr ≥ 3 CRS 23% Gr ≥ 3 NE 12% Gr 5 AE 3%</td>
<td>Gr ≥ 3 CRS 1% Gr ≥ 3 NE 15% Gr 5 AE 2%</td>
</tr>
</tbody>
</table>
Patient Case: Ongoing 9+ mo Durable CR in Refractory DLBCL

- 62-yo M with DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-Lenalidomide
- No response to last 3 lines of therapy

Baseline

3 months

Neelapu & Locke et al ASH 2016, #LBA-6
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 month 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
### ZUMA-1

**Ongoing Responses (> 1 year) Across Key Covariates**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>n(^2)</th>
<th>ORR</th>
<th>LCI(^a)</th>
<th>UCI(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N=108)</td>
<td>45</td>
<td>0.42</td>
<td>0.32</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Refractory Subgroup</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to ≥ 2nd line therapy (N=80)</td>
<td>31</td>
<td>0.39</td>
<td>0.28</td>
<td>0.50</td>
</tr>
<tr>
<td>Relapse post ASCT (N=25)</td>
<td>14</td>
<td>0.56</td>
<td>0.35</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 Years (N=81)</td>
<td>32</td>
<td>0.40</td>
<td>0.29</td>
<td>0.51</td>
</tr>
<tr>
<td>≥ 65 Years (N=27)</td>
<td>13</td>
<td>0.48</td>
<td>0.29</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Disease Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II (N=18)</td>
<td>11</td>
<td>0.61</td>
<td>0.36</td>
<td>0.83</td>
</tr>
<tr>
<td>III-IV (N=90)</td>
<td>34</td>
<td>0.38</td>
<td>0.28</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>IPI Risk Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 (N=60)</td>
<td>30</td>
<td>0.50</td>
<td>0.37</td>
<td>0.63</td>
</tr>
<tr>
<td>3-4 (N=48)</td>
<td>15</td>
<td>0.31</td>
<td>0.19</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Treatment History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Refractory Disease (N=27)</td>
<td>11</td>
<td>0.41</td>
<td>0.22</td>
<td>0.61</td>
</tr>
<tr>
<td>Refractory to 2 Consecutive Lines (N=55)</td>
<td>19</td>
<td>0.35</td>
<td>0.22</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>CD19 Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (N=77)</td>
<td>33</td>
<td>0.43</td>
<td>0.32</td>
<td>0.55</td>
</tr>
<tr>
<td>Negative (N=10)</td>
<td>5</td>
<td>0.50</td>
<td>0.19</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Cell of Origin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germinal Center B Cell-like (GCB) (N=52)</td>
<td>23</td>
<td>0.44</td>
<td>0.30</td>
<td>0.59</td>
</tr>
<tr>
<td>Activated B-Cell like (ABC) (N=18)</td>
<td>6</td>
<td>0.33</td>
<td>0.13</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>CD4/CD8 Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 (N=51)</td>
<td>21</td>
<td>0.41</td>
<td>0.28</td>
<td>0.56</td>
</tr>
<tr>
<td>≤1 (N=57)</td>
<td>24</td>
<td>0.42</td>
<td>0.29</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Tocilizumab Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N=49)</td>
<td>17</td>
<td>0.35</td>
<td>0.22</td>
<td>0.50</td>
</tr>
<tr>
<td>No (N=59)</td>
<td>28</td>
<td>0.47</td>
<td>0.34</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Corticosteroid Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N=30)</td>
<td>10</td>
<td>0.33</td>
<td>0.17</td>
<td>0.53</td>
</tr>
<tr>
<td>No (N=78)</td>
<td>35</td>
<td>0.45</td>
<td>0.34</td>
<td>0.57</td>
</tr>
</tbody>
</table>
ZUMA-1: Duration of Response by Best Objective Response

- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients having ongoing CR at 24 months
CAR T-cells: Efficacy

**August 30, 2017:** FDA Approves tisagenlecleucel (formerly CTL019) for the treatment of children and young adults (up to 25 years of age) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

**October 19, 2017:** FDA Approves axicabtagene ciloleucel (formerly KTE-C19) for the treatment of adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment.

**May 1st, 2018:** FDA Approves tisagenlecleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two lines of systemic therapy (DLBCL, high grade B-cell lymphoma and DLBCL arising from FL).
Adverse Events

- Cytokine release syndrome (CRS)
- CAR-related encephalopathy syndrome (CRES)
- B-cell aplasia
- Hemophagocytic lymphohistiocytosis (HLH)
**CD19 antigen-negative relapse in B cell malignancies after CD19 CAR-T cells**

Before CAR-T cells

Day 14 after CAR-T cells

Day 106 after CAR-T cells

**CD19-neg relapse in B-ALL, NHL and CLL**

in B-ALL:
- MSKCC: 2/14
- UPenn: 13/20
- FHCRC: 2/9

40%

Turtle, J Clin Invest, 2016
Lee, ASH, 2015
Park, ASCO, 2015
Maude, ASCO, 2016
Turtle, J Clin Oncol, 2017
Evans, Br J Haem, 2015
Future Directions in CD19 CAR T-cell Therapy…. 

…combination with checkpoint blockade antibodies
ZUMA-6: Axi-cel + Atezo in Refractory DLBCL
Results

Patients

- Median age: 57 y (range, 29 – 66)
- Disease stage: 33% stage II, 33% stage III, 44% stage IV
- Median 3 prior therapies (range, 2 – 4)
- 22% B symptoms
- 33% bulky disease
- All patients assessed (6/9) had baseline PD-L1 expression on tumor cells and/or immune cell infiltrate

Efficacy

- CR rate: 56%; ORR: 89%
- 2/9 patients experienced PR to CR conversions at 6 and 9 months after axi-cel treatment
- 3/9 patients had PD following response

Safety

<table>
<thead>
<tr>
<th>Patients With Adverse Event&lt;sup&gt;a&lt;/sup&gt;, n (%)</th>
<th>Overall (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
</tr>
<tr>
<td>Any AE</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Axi-cel–related AE</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Atezo-related AE</td>
<td>4 (44)</td>
</tr>
</tbody>
</table>

- There were no Grade 5 events
- Combination of atezo after axi-cel did not lead to increased use of tocilizumab or steroids
- One DLT of cytopenias (Grade 3 anemia, Grade 4 thrombocytopenia, and Grade 4 neutropenia)
- Generally, atezo-related AEs were infrequent and did not require specific intervention

Locke FL, et al. ASH 2017. Abstract #2826
# Beyond CD19: Extending the CAR antigen repertoire

<table>
<thead>
<tr>
<th>Specificity/Construct</th>
<th>Author(s)</th>
<th>Center</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD20- 3rd gen 28/41BB - limited lymphodepletion</strong></td>
<td>Till et al, Blood 2011</td>
<td>FHCRC</td>
<td>Indolent NHL/MCL 0/3 CR</td>
</tr>
<tr>
<td>Kappa</td>
<td>Ramos, JCI, 2016</td>
<td>Baylor</td>
<td>2/9 CR and 1/9 PR in NHL/CLL</td>
</tr>
<tr>
<td>CD30</td>
<td>Ramos et al, JCI 2017</td>
<td>Baylor</td>
<td>2/3 CR - ALCL / DLBCL</td>
</tr>
</tbody>
</table>

**Soon to be tested in NHL: CD7, ROR1, BAFF**

*Hudecek, Blood, 2010 (FHCRC)*
Monoclonal antibodies can be modified to increase their activity

<table>
<thead>
<tr>
<th>Fucosylated</th>
<th>Bispecific</th>
<th>Radiolabeled</th>
<th>ADCs</th>
</tr>
</thead>
</table>

The activity of mAbs can be enhanced by combining two antibodies in a single agent

The activity of mAbs can be enhanced by adding chemotherapeutic drugs

Antibody Drug Conjugates (ADC)

- Brentuximab vedotin (CD30) - HL
- Polatuzumab vedotin (CD79b) - NHL
- Loncastuximab Tesirine (CD19) - NHL
**Brentuximab Vedotin in Frontline Hodgkings**
(ASH 2017-Plenary presentation)

**ECHELON-1**: Open-label, global, randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL

- **218 study sites in 21 countries worldwide**

- **Screening CT/PET scan**
  - **Randomization (N=1334)**
  - **1:1 randomization**
  - **ABVD x 6 cycles (n=670)**

- **A+AVD x 6 cycles (n=664)**
  - Brentuximab vedotin: 1.2 mg/kg IV infusion
  - Days 1 & 15

- **Follow-up**
  - Every 3 months for 36 months, then every 6 months until study closure

- **Inclusion criteria**
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function

- **End-of-Cycle-2 PET scan**
  - Deauville 5; could receive alternate therapy per physician’s choice (not a modified PFS event)

---

*JM Connors et al. NEJM . December 2017*
ECHELON-1: Primary endpoint definition

- Primary endpoint: modified PFS per IRF
  - A modified PFS event was defined as the first of:
    - Progression
    - Death from any cause
  - PET6 = D3, 4, 5 after completion of frontline therapy followed by subsequent anticancer therapy

<table>
<thead>
<tr>
<th>Per IRF</th>
<th>Dx</th>
<th>Tx</th>
<th>PET6 = D1, 2</th>
<th>Follow-up</th>
<th>No event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>PET6 = D1, 2</td>
<td>Tx</td>
<td>Follow-up</td>
<td>No event</td>
</tr>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>PET6 = D3, 4, 5</td>
<td>Follow-up</td>
<td>No event</td>
<td></td>
</tr>
</tbody>
</table>

- PD/death at any time
- Tx w/o “Cheson” progression

D, Deauville score; Dx, diagnosis; IRF, independent review facility; PD, progressive disease; PET6, end-of-cycle-6 PET; Tx, treatment
Brentuximab Vedotin in Frontline Hodgkin's (ASH 2017-Plenary presentation)

**Modified PFS per independent review**

- **Number of events**
  - Progression: 90 (A+AVD), 102 (ABVD)
  - Death: 18 (A+AVD), 22 (ABVD)
  - Modified progression: 9 (A+AVD), 22 (ABVD)
  - Chemotherapy: 7 (A+AVD), 15 (ABVD)
  - Radiotherapy: 2 (A+AVD), 7 (ABVD)

**Modified PFS per investigator**

- **Number of events**
  - Progression: 73 (A+AVD), 103 (ABVD)
  - Death: 15 (A+AVD), 22 (ABVD)
  - Modified progression: 35 (A+AVD), 39 (ABVD)

**Modified PFS estimates**

- **A+AVD**
  - 2-year: 82.1 (95% CI: 70.7–85.0)
  - Median follow-up (range): 24.9 months (0.0–49.3)

- **ABVD**
  - 2-year: 77.2 (95% CI: 73.7–80.4)
  - Median follow-up (range): 25.0 months (0.0–49.3)

JM Connors et al. NEJM. December 2017
Summary and conclusions

• ECHELON-1 results
  – Significantly superior modified PFS with brentuximab vedotin in combination with AVD compared to ABVD
  – Independent review 23% reduction in risk of progression, death or need for additional anticancer therapy
    • 2-year modified PFS 82% vs 77%
  – Investigator review 27% reduction in risk of progression, death or need for additional anticancer therapy
    • 2-year modified PFS 81% vs 74%

• Brentuximab vedotin in combination with AVD
  – More effective than ABVD for the frontline treatment of advanced-stage cHL
  – Manageable toxicity profile
    • Bleomycin can be omitted
    • G-CSF primary prophylaxis is recommended for all patients
    • 67% of pts with PN had resolution or improvement by ≥1 grade at last follow-up

FDA Approval: March 2018
Encouraging Early Results from the First in-Human Clinical Trial of ADCT-402 (Loncastuximab Tesirine) in Relapsed/Refractory B-Cell NHL

Brad S. Kahl et al. Abstract # 187

Study Design
• Adct-402 (loncastuximab tesirine; Lonca-T) is an antibody-drug conjugate of a humanized anti-CD19 antibody conjugated to pyrrolobenzodiazepine (PBD) dimer toxin

  • Patients received doses of Lonca-T from 15 to 200 µg/kg

Patients
• 138 patients enrolled

  • Median age 63.5 years, median 3 prior therapies, with DLBCL (n=95), MCL (n=12), FL (n=12), MZL (n=5), CLL (n=4), or other (n=10)

Efficacy
• ORR in DLBCL: 55% (CR: 37%)
• Median PFS in DLBCL: 3.5 months
• Median DOR in DLBCL: 4.9months

Safety
• TEAEs reported in 98%; Grade ≥ 3 in 64%
• Most common Grade ≥ 3 TEAEs:
  – Nonhematologic: increased gamma-glutamyltransferase 14%, fatigue 5%, increased alkaline phosphatase 5%
  – Hematologic: neutropenia 15%, anemia 12%, thrombocytopenia 12%

  • 1 DLT reported (worsening of thrombocytopenia at 200 µg/kg) and MTD was not reached
Blinatumomab is a Bispecific T-Cell Engaging (BiTE) Antibody

\[ \alpha \text{-CD3 Antibody} \quad \rightarrow \quad \text{BiTE}^\text{®} \quad \text{Blinatumomab} \quad \rightarrow \quad \text{T Cell} \]

\[ \alpha \text{-CD19 Antibody} \quad \rightarrow \quad \text{Target Antigen CD19} \quad \rightarrow \quad \text{Tumor Cell} \]

Redirected Lysis

Topp et al. ASH 2010, abst # 174
Nine, 2 and 14 patients enrolled in cohorts I, II and III, respectively.

**Stage 1**: Stepwise dosing (cohort I: 9, 28 and 112 μg/d) compared to constant dosing of 112 μg/d (cohort II).

Based on the benefit/risk assessment from stage 1, stepwise dosing was chosen for cohort III in stage 2.

Patients achieving response after 8 weeks could receive a 4-week consolidation cycle after a 4-week treatment-free period. All patients received prophylactic dexamethasone.

**Primary endpoint**: ORR
Response to Blinatumomab

<table>
<thead>
<tr>
<th>Response</th>
<th>n = 21*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>43%</td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>5 (24%)</td>
</tr>
</tbody>
</table>

- All patients who responded did so within the first 8-week cycle.
- Among responders (n = 9), the median duration of response was 11.6 months.

- **Most common AEs:** Tremor (52%), pyrexia (44%), diarrhea (24%), fatigue (24%), edema (24%) and pneumonia (24%).
- Seven patients (cohort I, n = 3; cohort II, n = 2; cohort III, n = 2) had Grade 3 neurologic AEs: disorientation, encephalopathy, aphasia and epilepsy (n = 2 each)
- Serious AEs occurred in 92% of patients. Most common: pneumonia (24%), device-related infection (16%) and pyrexia (16%)

Viardot A et al. Proc ASH 2014;Abstract 4460
## Selected Bispecific Antibodies in Development for Lymphomas

<table>
<thead>
<tr>
<th>Developer</th>
<th>Molecule</th>
<th>Targets</th>
<th>Technology</th>
<th>Indications</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affimed</strong></td>
<td>AFM13</td>
<td>CD30xCD16</td>
<td>NK engaging bispecific tetravalent tandem diabody</td>
<td>HL</td>
<td>Phase 2</td>
</tr>
<tr>
<td><strong>Affimed</strong></td>
<td>AFM11</td>
<td>CD19xCD3</td>
<td>T-cell engaging bispecific TandAb</td>
<td>NHL</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Macrogenics, J&amp;J</td>
<td>MDG011</td>
<td>CD19xCD3</td>
<td>DART bispecific Ab</td>
<td>B-cell cancers</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Regeneron</td>
<td>REGN1979</td>
<td>CD20xCD3</td>
<td>Bispecific Ab</td>
<td>CD20+ B-cell cancers</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Roche/Genentech</td>
<td>RG7828</td>
<td>CD20xCD3</td>
<td>Full-length T-cell dependent bispecific Ab</td>
<td>B-cell tumors</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

*Modified from Sheridan, C. Nature Biotech. 34:12;1215-17 (2016)*
THANKS
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