Targeted Therapy for B- and T-cell Non-Hodgkin’s Lymphomas

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

Consultant: Seattle Genetics, Genentech, Celgene, Pharmacyclics, Johnson, Teva

Speaker’s Bureau: Seattle Genetics, Celgene

The speaker will directly disclose the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.
Targeted Therapy

Surface Targets

Intracellular Targets
Targeted Therapy for Lymphomas

- **Antigenic (surface) targets**
  - **CD19**: CAR T-cells
  - **CD30**: Brentuximab Vedotin

- **Intracellular targets**
  - BTK
  - PI3K
  - \( bcl2 \)
  - Epigenetic Targets
Targeted Therapy

CD19

CAR T-cells
Chimeric Antigen Receptor (CAR) T-cells

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

- 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
Designing a Chimeric Antigen Receptor

SCFv hinge co-stim ζ chain

5’LTR ψ 3’LTR

SIGNAL 2
co-stimulatory molecule

SIGNAL 1
TCR ζ chain

antibody
Redirecting the Specificity of T Cells

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

NCI

CHOP/U. Penn

FHCC

Baylor
CAR T-cell Therapy

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 et 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
- Patients not treated:
  - 4 AE
  - 2 No measurable disease
  - 1 Death due to PD
  - 1 Manufacture failure
- 101 Infused
- 92 Primary Analysis
- 101 Modified Intent-to-Treat (mITT)
- 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
## CAR T-cell studies in B-cell NHL

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1</th>
<th>JULIET</th>
<th>TRANSCEND JCAR017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td>Phase 2 Primary Analysis</td>
<td>Phase 2 Primary Analysis</td>
<td>Phase 1/2 Interim Analysis Dose Finding</td>
</tr>
<tr>
<td></td>
<td>NEJM 2017 (DCO 11Aug17)</td>
<td>ASH 2017 (DC0 8Mar17)</td>
<td>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</td>
<td>147 enrolled; 99 dosed, 81 evaluable</td>
<td>Enrollment not reported, 91 dosed (FULL); 67 in CORE</td>
</tr>
<tr>
<td></td>
<td>No bridging chemotherapy</td>
<td>90% Bridging chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>2.0 x10^6 CAR T cells/kg</td>
<td>Median, 3.1 x10^8</td>
<td>DL1 5.0 x 10^7 CAR T cells (N=34)</td>
</tr>
<tr>
<td></td>
<td>&gt;100 kg 2.0 x 10^8 fixed</td>
<td>Range, 0.1-6.0 x 10^8 cells</td>
<td>DL2 1.0 x10^8 CAR T cells (N=29)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>• 76% DLBCL; 16% TFL; 8% PMBCL</td>
<td>• 80% DLBCL; 19% FL</td>
<td>(CORE; N = 67)</td>
</tr>
<tr>
<td></td>
<td>• 79% refractory</td>
<td>• 48% relapsed; 52% refractory</td>
<td>• 76% de novo DLBCL; 24% TFL</td>
</tr>
<tr>
<td></td>
<td>• 21% relapsed post-ASCT</td>
<td>• 47% post ASCT</td>
<td>• 66% chemorefractory</td>
</tr>
<tr>
<td></td>
<td>• ECOG 0 / 1: 42% / 58%</td>
<td>• ECOG 0/1: 55% / 45%</td>
<td>• 100% ECOG 0-1</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>mITT = 108</td>
<td>ITT = 111</td>
<td>(CORE; N = 65)</td>
</tr>
<tr>
<td></td>
<td>• Median follow-up 15.4 mo</td>
<td>• Minimum efficacy f/u: 3 mo</td>
<td>ORR: 80%; 55% CR</td>
</tr>
<tr>
<td></td>
<td>• ORR: 82%; 58% CR</td>
<td>• Median follow-up 8.7 mo</td>
<td>• Median OS NR; 6-mo: 86%</td>
</tr>
<tr>
<td></td>
<td>• Ongoing response: 42%, 40% CR</td>
<td>• ORR: 77%; 51% CR</td>
<td>• Median DOR: 9.2 mo (NR for CR)</td>
</tr>
<tr>
<td></td>
<td>• Median DOR: 11.1 mo</td>
<td></td>
<td>• Median follow-up: 6.3 mo</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>• Gr ≥ 3 CRS 13%</td>
<td>• Gr ≥ 3 CRS 23%</td>
<td>• Gr ≥ 3 CRS 1%</td>
</tr>
<tr>
<td></td>
<td>• Gr ≥ 3 NE 28%</td>
<td>• Gr ≥ 3 NE 12%</td>
<td>• Gr ≥ 3 NE 15%</td>
</tr>
<tr>
<td></td>
<td>• Gr 5 AE 3%</td>
<td>• Gr 5 AE 3%</td>
<td>• Gr 5 AE 2%</td>
</tr>
</tbody>
</table>
Adverse Events

- Cytokine release syndrome (CRS)
- CAR-related encephalopathy syndrome (CRES)
- Hemophagocytic lymphohistiocytosis (HLH)
- B-cell aplasia
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
KTE-C19 Induces Ongoing Complete Remission in TFL to Refractory DLBCL

Baseline

3 months (CR)

66 y/o female

Prior therapies:
- R-CHOP
- R-ICE

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

<table>
<thead>
<tr>
<th></th>
<th>Phase 2 Primary Analysis (n = 101)</th>
<th>Phase 1 and 2 Updated Analysis (N = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, mo</td>
<td>8.7</td>
<td>15.4</td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best response, %</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Ongoing, %</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ZUMA-1

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>n&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ORR</th>
<th>LCI&lt;sub&gt;l&lt;/sub&gt;</th>
<th>UCI&lt;sub&gt;l&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N=108)</td>
<td></td>
<td>45</td>
<td>0.42</td>
<td>0.32</td>
<td>0.52</td>
</tr>
<tr>
<td>Refractory Subgroup</td>
<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></td>
<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>Age</td>
<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></td>
<td>≥ 65 Years (N=27)</td>
<td>13</td>
<td>0.48</td>
<td>0.29</td>
<td>0.68</td>
</tr>
<tr>
<td>Disease Stage</td>
<td>I-II (N=18)</td>
<td>11</td>
<td>0.61</td>
<td>0.36</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>III-IV (N=90)</td>
<td>34</td>
<td>0.38</td>
<td>0.28</td>
<td>0.49</td>
</tr>
<tr>
<td>IPI Risk Score</td>
<td>0-2 (N=60)</td>
<td>30</td>
<td>0.50</td>
<td>0.37</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>3-4 (N=48)</td>
<td>15</td>
<td>0.31</td>
<td>0.19</td>
<td>0.46</td>
</tr>
<tr>
<td>Treatment History</td>
<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></td>
<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>CD19 Status</td>
<td>Positive (N=77)</td>
<td>33</td>
<td>0.43</td>
<td>0.32</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Negative (N=10)</td>
<td>5</td>
<td>0.50</td>
<td>0.19</td>
<td>0.81</td>
</tr>
<tr>
<td>Cell of Origin</td>
<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></td>
<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>CD4/CD8 Ratio</td>
<td>&gt;1 (N=51)</td>
<td>21</td>
<td>0.41</td>
<td>0.28</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>≤1 (N=57)</td>
<td>24</td>
<td>0.42</td>
<td>0.29</td>
<td>0.56</td>
</tr>
<tr>
<td>Tocilizumab Use</td>
<td>Yes (N=49)</td>
<td>17</td>
<td>0.35</td>
<td>0.22</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>No (N=59)</td>
<td>28</td>
<td>0.47</td>
<td>0.34</td>
<td>0.61</td>
</tr>
<tr>
<td>Corticosteroid Use</td>
<td>Yes (N=30)</td>
<td>10</td>
<td>0.33</td>
<td>0.17</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>No (N=78)</td>
<td>35</td>
<td>0.45</td>
<td>0.34</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Median duration of CR has not been reached

3/7 (43%) phase 1 patients having ongoing CR at 24 months
ASH 2017: Combinations of CAR T cell and checkpoint blockade

Phase 1 Results from ZUMA-6: Axicabtagene Ciloleucel (axi-cel; KTE-C19) in Combination with Atezolizumab for the Treatment of Patients with Refractory Diffuse Large B Cell Lymphoma (DLBCL)
Frederick L. Locke, MD at al.

Marked Re-Expansion of Chimeric Antigen Receptor (CAR) T Cells and Tumor Regression Following Nivolumab Treatment in a Patient Treated with Axicabtagene Ciloleucel (axi-cel; KTE-C19) for Refractory Diffuse Large B Cell Lymphoma (DLBCL)
Brian T. Hill, MD, PhD; Zachary J. Roberts, MD, PhD; John M. Rossi, MS; Mitchell R. Smith, MD, PhD

Phase I/II Study of Pembrolizumab for Progressive Diffuse Large B Cell Lymphoma after Anti-CD19 Directed Chimeric Antigen Receptor Modified T Cell Therapy
Elise A. Chong, Stephen J. Schuster et al.
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 Eventa, n (%)</th>
<th>Any Grade</th>
<th>Worst Grade 3</th>
<th>Worst Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>9 (100)</td>
<td>1 (11)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Axi-cel–related AE</td>
<td>9 (100)</td>
<td>3 (33)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Atezo-related AE</td>
<td>4 (44)</td>
<td>0</td>
<td>1 (11)</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
CAR T-cells: Efficacy

• **August 30, 2017:** FDA Approves *tisagenlecleucel* (Kymriah, 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* (Yescarta), 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

**November 16, 2017:** FDA gives “breakthrough” designation to anti-BCMA CAR T-Cell therapy for patients with Multiple Myeloma
Targeted Therapy

CD30
Brentuximab
Phase 3 ALCANZA Trial: Brentuximab vs investigator’s choice

- 131 patients with CD30+ CTCL who received prior systemic or radiation therapy
  - Primary cutaneous ALCL: At least one prior systemic or radiation therapy
  - Mycosis Fungoides: At least one prior systemic therapy

**Inclusion Diagnosis of CD30+ MF or pcALCL**
- ≥10% CD30+ on either neoplastic cells or lymphoid infiltrate by central review of ≥1 biopsy (2 required for MF)
- MF patients with ≥1 prior systemic therapy
- pcALCL patients with prior radiotherapy or ≥1 prior systemic therapy

**Exclusion:**
- Progression on both prior methotrexate and bexarotene

* within 28 days of randomization

Screening*

**Randomization**

- Up to 48 weeks (16x 21-day cycles)

- Brentuximab vedotin: 1.8 mg/kg IV, every 3 weeks

- MTX: 5–50 mg PO, weekly or Bexarotene: 300 mg/m² PO qd

**End of treatment visit**

- 30 days after last dose of study drug

**Post-treatment follow-up**

- Every 12 weeks for 2 years and then every 6 months thereafter

**Within 28 days of randomization**

- MTX or bexarotene was managed as standard of care, targeting maximum tolerated effective dose

- Patients were recruited from 52 centers across 13 countries

Kim, Y.H. et al, ASH 2016
Progression-free survival (ITT population)

Assessed by independent review

Lost-rank test p-value: <0.001
Hazard ratio (95% CI): 0.270 (0.169, 0.430)
Median (months): BV: 16.7; MTX or Bex: 3.5
Number of events: BV: 36 MTX or Bex: 50

Brentuximab vedotin
Methotrexate or bexarotene

Number of patients at risk:
Brentuximab vedotin
64 59 58 54 51 50 48 47 46 43 38 38 29 27 27 19 17 13 12 11 8 7 7 6 3 3 1 1
Methotrexate or bexarotene
64 54 42 34 24 17 13 12 11 8 8 7 6 5 5 4 4 3 1 1

Assessed by independent review
Bex, bexarotene; MTX, methotrexate

Kim, Y.H. et al, ASH 2016
Brentuximab Vedotin in Frontline Hodgkins (ASH 2017-Plenary presentation)

Brentuximab Vedotin Plus Doxorubicin, Vinblastine, Dacarbazine (A+AVD) as Frontline Therapy Demonstrates Significantly Improved Modified Progression-Free Survival versus ABVD in Patients with Previously Untreated Stage III or IV Hodgkin Lymphoma: The Phase 3 ECHELON-1 Study


JM Connors et al. NEJM . December 2017
Brentuximab Vedotin in Frontline Hodgkin's (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
- ABVD x 6 cycles (n=670)
- A+AVD x 6 cycles (n=664)
  - Brentuximab vedotin: 1.2 mg/kg IV infusion Days 1 & 15

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)

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

cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival

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>PET6 Event</th>
<th>Follow-up</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>PET6 = D1, 2</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>PET6 = D1, 2</td>
<td>Tx</td>
</tr>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>PET6 = D3, 4, 5</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Dx</td>
<td>Tx</td>
<td>PET6 = 1–5</td>
<td>Follow-up</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 Hodgkins (ASH 2017-Plenary presentation)

Modified PFS per independent review

Number of events

<table>
<thead>
<tr>
<th>Category</th>
<th>A+AVD</th>
<th>ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>90</td>
<td>102</td>
</tr>
<tr>
<td>Death</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Modified progression</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

Probability of modified PFS

Log-rank test p-value: 0.035

HR 0.77 (95% CI: 0.60–0.98)

Median follow-up (range): 24.9 months (0.0–49.3)

Modified PFS per investigator

Number of events

<table>
<thead>
<tr>
<th>Category</th>
<th>A+AVD</th>
<th>ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>73</td>
<td>103</td>
</tr>
<tr>
<td>Death</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Modified progression</td>
<td>35</td>
<td>39</td>
</tr>
</tbody>
</table>

Probability of modified PFS

Log-rank test p-value: 0.007

HR 0.73 (95% CI: 0.57–0.92)

Median follow-up (range): 25.0 months (0.0–49.3)

JM Connors et al. NEJM . December 2017
Brentuximab Vedotin in Frontline Hodgkin's (ASH 2017-Plenary presentation)

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
Intracellular Targets

- BCR signaling
  - BTK inhibitors
  - PI3K inhibitors

- Apoptotic pathways
  - bcl2 inhibitors

- Survival pathways
  - mTOR
  - NFKb

- Cell-cycle pathways
  - Cyclins
  - CDK4/6

- Epigenetic pathways
  - Hypomethylating agents
  - In T-cell lymphomas
ASH 2017: BTK inhibitors in relapsed MCL

- Ibrutinib, Acalabrutinib and Zanabrutinib (BGB311-BeiGene)

- **Ibrutinib: (Rule et al)**
  - 3.5 years f/u: Better outcomes for patients with relapsed/refractory MCL that received ibrutinib after one line of treatment versus >1
  - Median PFS: Approx. 3 years in patients with 1 prior therapy and 4 y for those in CR

- **Acalabrutinib Phase 2 ACE-LY-004 Study (Wang et al)**
  - ORR: 81%, CR: 40%, PR:41%
  - High risk MIPI: Only 17%
  - Less AF and bleeding episodes
  - Most common AE: Headaches

- **Zanabrutinib (Tam et al)**
  - High plasma concentration and longer exposure (160 mg bid: 100% BTK in LN)
  - 38 MCL patients. ORR: 88% CR: 25%
  - Responses in other subtypes (FL: ORR: 41%, CR: 18%; LCL: ORR:31%, CR: 15%)
  - Durable responses seen
PI3K inhibitors in B-cell malignancies

- **Idelalisib** ($\delta$) (FDA-approved)
  - Treatment of Relapsed CLL in combination with rituximab
  - Treatment of Relapsed Follicular or SLL who have received 2 prior treatments

- **Copanlisib** ($\alpha,\delta$) (FDA-approved)
  - As a third-line treatment for patients with relapsed follicular lymphoma

- **Umbralisib** ($\delta$) (TGR-1202)
  - ASH 2017 (David et al): Integrated Safety Analysis in Patients with Relapsed/Refractory Lymphoid Malignancies

- **INCB050465** (highly selective $\delta$)
  - ASH 2017 (Forero-Torres et al): Results from a Phase 1/2 Study in Patients with Relapsed or Refractory B-Cell Malignancies (CITADEL-101)
Venetoclax (ABT-199): A selective oral bcl2 inhibitor in B-cell Malignancies

- Venetoclax is FDA-approved for the treatment of patients with:
  - Chronic Lymphocytic Leukemia (CLL) with 17p deletion who have received at least one prior treatment

- As a single agent significant activity in relapsed/refractory MCL

- **ASH 2017**: Impressive results when used in combination with BTK inhibitor, Ibrutinib, in patients with relapsed/refractory B-cell malignancies
Venetoclax in combination with Ibrutinib: A promising combination for MCL

- 23 pts with relapsed/refractory MCL
  - 50% have p53 aberrations
  - 75% have high risk prognostic score
- CR at 16 weeks by CT scan: 42% (9% with ibrutinib- historical controls)
- CR rate by PET: 62% at 16 weeks
- MRD clearance: 67% by flow and 38% by ASO-PCR
- Time-to-event analysis: 78% of patients with ongoing response at 15 months.
- Well tolerated
Azacitidine in Patients With Relapsed/Refractory PTCL: Efficacy

- Median follow-up: 84 days (19 – 1236)

- ORR for the entire population was 53% (10/19), but was significantly higher in AITL patients than in patients with other PTCL entities
  - 9/12: 75% (AITL)
  - 1/7: 14% (other PTCL)

- TET2 was sequenced in 16 patients and was mutated in 11/12 (92%) AITL and 1/4 (25%) other PTCL
  - 9/9 (100%) AITL patients who experienced at least partial response after 5-AZA treatment were TET2 mutated

Delarue et al. ASH 2016; Abstract 4164
Where Are We Going Next?.....

Combinations
Combinations

• **Of targeted agents… ie, BTK inhibitor plus:**
  – Lenalidomide or next generation IMIDs
  – Next generation MTOR inhibitors
  – Bortezomib or novel proteasome inhibitors
  – Epigenetic modifiers

• **Targeted agents plus immunotherapy:**
  • Targeted agent (s) + Novel monoclonal antibodies
  • Targeted agents + checkpoint blockade antibodies
  • Targeted agents (Ibrutinib) + CAR T-cells

• **Targeted agents plus conventional chemotherapy:**
  – BTK inhibitor plus BR
  – PI3K inhibitor plus BR
THANKS

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