Immune and Targeted Therapies, Including CAR T Cells, for Blood Cancers

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Colorado Blood Cancer Institute
Targeted Therapy

• Therapy that takes advantage of molecular and genetic information to cause tumor cell kill by blocking key malignant cell function or by enhancing immunologic function.
• Specific (against tumor cell)
• Reduces global toxicity to patient
• More tolerable
• ? More effective
• More expensive!
Targeted Therapy

1. Drug therapy
   - Tyrosine Kinase Inhibitors
     • ABL – Imatinib, dasatinib, nilotinib
     • FLT-3 – Sorafenib, Midostaurin
     • BTK – Ibrutinib
     • PI3K – Idelsilibr, IPI-145
   - Small Molecules
     • BCL-2 inhibitor - ABT 199
     • Inhibition of transcription – BET inhibitor
Targeted Therapy

2. Immunologic/Immunotoxins Therapies
   - Antibody
     - CD 20 – rituxamab, obinotuzumab
     - CD 30 – brentuximab
     - CD 33 – SGN CD33a
   - Bifunctional
     • CD 19/CD3 – Blinotumamab
Targeted Therapy

2. Cellular Therapies
   - Chimeric Antigen Receptor (CAR) T Cells
     - CD 19 – Kite/Juno/Novartis
     - CD 20 – ?
     - CD 33 – ?
     - CD 138
The Mechanism of Action for ABT-199/GDC-0199
Evasion of Apoptosis is a Hallmark of Cancer

1. **Evasion of apoptosis**
2. Sustained angiogenesis for growth and survival (primarily solid tumors)
3. Self-sufficiency in growth signals
4. Insensitivity to anti-growth signals
5. Tissue invasion and metastasis
6. Limitless replication potential

Others: Evasion of immune system

The BCL-2 Family of Proteins Are Key Regulators of Apoptosis

- The BCL-2 family of proteins serve as key regulators of apoptosis, or programmed cell death\(^1\)
  - The family contains both pro- and anti-apoptotic family members
  - BCL-2 functions as an anti-apoptotic protein, promoting resistance to apoptosis
  - The dynamic balance occurring between pro- and anti-apoptotic members determines whether a cell will live or die

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Inhibition of BCL-2 Can Tip the Balance in Favor of Cell Death\textsuperscript{1,2,3}

In response to metabolic stress, normal cells and malignant cells increase expression of pro-apoptotic proteins.

As a means of resistance, BCL-2 expression is increased in malignant cells, to bind and sequester the surplus of pro-apoptotic proteins.

Agents that inhibit BCL-2 can release the store of pro-apoptotic proteins, tipping the balance in favor of cell death.

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ABT-199/GDC-0199: A Selective Inhibitor of BCL-2

**ABT-199/GDC-0199**

- An orally available small molecule inhibitor designed to selectively bind and inhibit BCL-2

- Structurally designed to bind to BCL-2 analogous to native pro-apoptotic proteins

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Cancer Cells Are “Primed” for Cell Death

- Malignant cells increase expression of BCL-2, allowing the cell to survive under continual metabolic stress\(^1\)
- The reserve of pro-apoptotic family members sequestered by BCL-2 can leave those cells vulnerable to apoptosis\(^1\)

ABT-199/GDC-0199 Selectively Binds and Inhibits BCL-2

- Upon entering the cell, ABT-199/GDC-0199 selectively binds to BCL-2 displacing the store of pro-apoptotic proteins\(^1\)

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Pro-apoptotic Proteins Initiate Destruction of the Cancer Cell

- With BCL-2 inhibited by ABT-199/GDC-0199, pro-apoptotic proteins are free to initiate apoptosis

- Activated pro-apoptotic proteins initiate a sequence of cellular events resulting in the ordered destruction of the cell

Inhibition of BCL-2 restores the ability of the cancer cell to undergo apoptosis

## Phase I Study ABT-199 in CLL

### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>Median [range]</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td>Male</td>
</tr>
<tr>
<td><strong>Diagnosis, n</strong></td>
<td>CLL / SLL</td>
</tr>
<tr>
<td><strong>Lymphocyte count (x 10⁹/L)</strong></td>
<td>Median [range]</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 x 10⁹</td>
</tr>
<tr>
<td><strong>Bulky nodes, n (%)</strong></td>
<td>≥5 cm</td>
</tr>
<tr>
<td></td>
<td>≥10 cm</td>
</tr>
<tr>
<td><strong>Number of prior therapies</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Median [range]</td>
</tr>
<tr>
<td><strong>17p Status, n (%)</strong></td>
<td>Deleted</td>
</tr>
<tr>
<td><strong>Rituximab, n (%)</strong></td>
<td>Prior Treatment</td>
</tr>
<tr>
<td></td>
<td>Refractory&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Fludarabine, n (%)</strong></td>
<td>Prior treatment</td>
</tr>
<tr>
<td></td>
<td>Refractory&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Myelosuppressive and other therapies

<sup>b</sup>Progressed on therapy or within 6 months of therapy

As of October 7, 2014

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
Phase I Study ABT-199 in CLL

Dosing Schedule of Venetoclax and Rituximab

Final Escalation Strategy:

Venetoclax
- Week 1 D1: 20 mg Test
- Week 1 D2–7: 50 mg
- Week 2: 100 mg
- Week 3: 200 mg
- Week 4: DCD
- Month 1: DCD
- Month 2–6: DCD

Rituximab
- N/A
- N/A
- N/A
- N/A
- N/A
- N/A
- N/A

OR: if one or more electrolytes meet Cairo-Bishop criteria and/or if there is ≥ 30% decrease in ALC with first dose

Venetoclax
- Week 1 D1: 20 mg Test
- Week 1 D2–7: 20 mg
- Week 2: 50 mg
- Week 3: 100 mg
- Week 4: 200 mg
- Week 5: DCD
- Week 6: DCD
- Month 2–6: DCD

Rituximab
- N/A
- N/A
- N/A
- N/A
- N/A
- N/A
- N/A

D, day; DCD, designated cohort dose
Protocol amendment permits 20 mg for first week, as needed

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
# Phase I Study ABT-199 in CLL
## Adverse Events (AEs)

<table>
<thead>
<tr>
<th>All Grade AEs (in ≥ 20% patients), n (%)</th>
<th>N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>49 (100)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (45)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Anemia(^{a})</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Thrombocytopenia(^{b})</td>
<td>11 (22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3/4 AEs (in ≥ 3 patients), n (%)</th>
<th>N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 3/4 AE</td>
<td>35 (71)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Thrombocytopenia(^{b})</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Anemia(^{a})</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious Adverse Events(^{c}) (in ≥2 patients), n (%)</th>
<th>N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Tumor Lysis Syndrome(^{d})</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

\(^{a}\) hemolytic (n=2 grade 3)

\(^{b}\) immune (n=2 all grade; n=1 grade 3)

\(^{c}\) More than 1 SAE may have occurred in the same person

\(^{d}\) Events occurred after the 1\(^{st}\) dose at 50 mg, prior to schedule modifications; 1 TLS event was fatal

As of October 7, 2014.

Adapted from the Roberts presentation at the 56\(^{th}\) American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
Phase I Study ABT-199 in CLL

Current Status

- 200 mg: 100% Active, 2 PD
- 300 mg: 100% Active, 2 PD
  - * Stopped venetoclax after CR/CRI
- 400 mg: 100% Active, 1 PD
  - * Stopped venetoclax after CR/CRI
- 500 mg: 100% Active, 1 PD
- 600 mg: 100% Active, 1 PD
- SE - 400 mg: 100% Active, 1 PD

Discontinuations:
- 10 out of 49 patients
- Progressive disease, PD (n=6)
- Adverse Event (n=2)
  - Tumor lysis (n=1)
  - Neuropathy (n=1)
- Withdrew consent (n=2)

As of October 7, 2014

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
## Preliminary Efficacy Results

<table>
<thead>
<tr>
<th>Best Response, n (%)</th>
<th>All Patients n=49</th>
<th>Evaluable Patients&lt;sup&gt;a&lt;/sup&gt; n=44</th>
<th>17p del Patients n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>43 (88)</td>
<td>39 (89)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Complete Response (CR)/CRi</td>
<td>15 (31)</td>
<td>15 (34)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>22 (45)</td>
<td>22 (50)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>PR unconfirmed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (12)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>2 (4)</td>
<td>2 (5)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>3 (6)</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Death (TLS)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (2)</td>
<td></td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Evaluable patients reached full bone marrow assessment at 7 months or discontinued

<sup>b</sup>PR unconfirmed = follow-up assessment not available at time of analysis (4 pending, 2 withdrew)

<sup>c</sup>No other fatal TLS events occurred after modification of the protocol

As of October 7, 2014

Adapted from the Roberts presentation at the 56<sup>th</sup> American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
Phase I Study ABT-199 in CLL

Other Preliminary Efficacy Results

- 30/32 (94%) patients with baseline lymphocyte counts > 5 x 10^9/L had a reduction to < 4 x 10^9 within 5 weeks of starting venetoclax.

- 43/43 (100%) patients who had post-baseline CT scan achieved at least 50% reduction in nodal mass by CT scan.

- 23/35 (66%) patients who had bone marrow assessment achieved complete marrow clearance by morphology.

*a* For patients with lymphocyte count ≥ 5 x 10^9/L at baseline (n=32); *b* For patients with post-baseline CT scan (n=43); *c* For patients who have bone marrow infiltrate data (n=35); as of October 7, 2014.

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
Bone Marrow Minimal Residual Disease (MRD) at 7 Months

MRD was assessed in 15 patients with CR/CRi and 22 patients with a PR using local institutional methods and sensitivity $\leq 10^{-4}$.

<table>
<thead>
<tr>
<th>Response Classification</th>
<th>Evaluated Patients</th>
<th>MRD Negative</th>
<th>MRD Positive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15</td>
<td>9</td>
<td>6 (range: 0.003% – 2.3%)</td>
<td>2/6 became MRD-negative at 9 months and 14 months</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
<td>8$^a$</td>
<td>14 (range: 0.05 – 0.44%)</td>
<td>4/8 with MRD-negative disease have one remaining lymph node &gt;1.5 cm as the only remaining evidence of disease</td>
</tr>
</tbody>
</table>

$^a$ Remaining lymph node sizes for the 8 patients with MRD negative PR:  
4 patients with a single lymph node (1.7, 2.2, 2.3 and 2.7 cm)  
4 patients with multiple (2-4) lymph nodes (largest of which is 2.2, 2.3, 2.3, and 2.4 cm)  
the last patient also has splenic involvement

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
Complete Remission: Discontinuation of Venetoclax

- 5 patients have discontinued venetoclax after achieving CR/CRI
  - Patients are continuing follow-up on study
  - No patient had progression

* A subsequent CT scan showed lymph node size (previously 1.5 cm) now 1.7 cm, thus now PR.
  As of October 7, 2014

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
Determination of Recommended Phase 2 Dose

- Early data indicated substantial efficacy at all doses in evaluated patients
- The MTD was not identified
- Selection of 400 mg for assessment in the safety expansion dose was based on trends of higher toxicities at doses greater than 400 mg and informed by data from other studies

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>All Grade 3/4 AEs</th>
<th>Related Grade 3/4 AEs</th>
<th>All Grade 3/4 Neutropenia</th>
<th>All GI AEs*</th>
<th>All Related SAEs</th>
<th>Dose interruptions/reductions*</th>
<th>ORR (CR+PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>6</td>
<td>4 (67)</td>
<td>3 (50)</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>1 (17)</td>
<td>4 (67)</td>
<td>6/6 (100)</td>
</tr>
<tr>
<td>300</td>
<td>10</td>
<td>9 (90)</td>
<td>7 (70)</td>
<td>7 (70)</td>
<td>6 (60)</td>
<td>2 (20)</td>
<td>9 (90)</td>
<td>8/10 (80)</td>
</tr>
<tr>
<td>400</td>
<td>8</td>
<td>5 (63)</td>
<td>2 (25)</td>
<td>1 (13)</td>
<td>3 (43)</td>
<td>2 (25)</td>
<td>3 (38)</td>
<td>7/8 (87)</td>
</tr>
<tr>
<td>500</td>
<td>7</td>
<td>5 (71)</td>
<td>3 (43)</td>
<td>3 (43)</td>
<td>6 (86)</td>
<td>0 (0)</td>
<td>4 (57)</td>
<td>5/7 (71)</td>
</tr>
<tr>
<td>600</td>
<td>10</td>
<td>8 (80)</td>
<td>7 (70)</td>
<td>6 (60)</td>
<td>6 (60)</td>
<td>3 (30)</td>
<td>8 (80)</td>
<td>10/10 (100)</td>
</tr>
</tbody>
</table>

AEs during Days 1-210
*There was 1 grade 3/4 GI AE (400 mg)

Adapted from the Roberts presentation at the 56th American Society of Hematology Annual Meeting and Exposition on December 8, 2014.
The combination of rituximab and venetoclax at a dose of 400 mg is well tolerated, with no new toxicities identified, as compared to monotherapy.

Preliminary PK suggest no apparent effect of rituximab on venetoclax exposure.

The combination is highly active in patients with relapsed/refractory CLL.

- The overall response rate is 88% to date, including 31% CR/CRi.
- MRD negativity in the bone marrow is observed in 17 of 44 (38%) patients who reached full assessment at 7 months (including 7 patients who were not tested for MRD).
  - 9/15 patients in CR/CRi.
  - 8/22 patients in PR.

A phase 3 trial comparing venetoclax and rituximab versus bendamustine and rituximab in patients with previously treated CLL is underway.
Targeted Therapy

1. Drug therapy
   - Tyrosine Kinase Inhibitors
     • PI3K – IPI-145
PI3K-δ and PI3K-γ Support the Growth and Survival of B-cell and T-cell Malignancies

Cell differentiation, proliferation, activation and migration
Lymph Node Reduction in iNHL Patients with CT Scans

- 76% (13/17) of patients at 25 mg BID had ≥ 50% reduction in adenopathy
Progression-Free Survival (PFS)

**Median PFS not reached**

- 69% progression-free at 24 months (25 mg BID)
• Median OS not reached
  – 89% survival at 24 months (25 mg BID)
## IPI 145 Toxicity

### SAEs > 1 Patient (All Doses)

<table>
<thead>
<tr>
<th>SAE</th>
<th>25 mg BID n=19</th>
<th>All Doses N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia (combined)</td>
<td>4 (21)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (5)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (5)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (5)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 (5)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

### AEs Leading to Discontinuation

<table>
<thead>
<tr>
<th>AE</th>
<th>25 mg BID n=19</th>
<th>All Doses N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST increase</td>
<td>2 (11)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Pneumonia (combined)</td>
<td>1 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Rash (combined)</td>
<td>1 (5)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Herpes zoster (disseminated)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*Pneumonia (combined) = all preferred terms of pulmonary inflammation due to infectious or noninfectious etiologies

*Rash (combined) = all preferred terms associated with rash within Skin & Subcutaneous Tissue Disorders SOC*
Targeted Therapy (AML)

1. Immunconjugate
   – SGN CD33a
SGN-CD33A Proposed Mechanism of Action

Engineered cysteine anti-CD33 antibody, enables uniform site-specific conjugation
Cleavable dipeptide linker, highly stable in circulation
Pyrrolobenzodiazepine (PBD) dimer, binds DNA with high intrinsic affinity

1. SGN-CD33A binds to CD33
2. Complex is internalized and transported to lysosomes
3. PBD dimer released via proteolytic cleavage of linker & diffuses inside cell
4. PBD dimer crosslinks DNA, overwhelms DNA repair mechanisms & triggers a cascade of events leading to cell death
Emerging Dose-Response Relationship

Figure represents patients with paired baseline and post-baseline assessments.

- 17/22 (77%) at doses 40 mcg/kg or higher had ≥50% blast reduction.
Targeted Therapy (ALL)

1. Bifunctional Immunconjugate
   – Blinatumamab
Blinatumomab Engages Malignant Cells with Endogenous T cells

**Figure 4** Generation and structure of blinatumomab.

**Notes:** Variable domains (variable heavy chain [V\_h] and variable light chain [V\_l]) of a CD19-specific monoclonal antibody and a CD3-specific mAb were converted into single-chain antibodies (circle) recombinantly joined by nonimmunogenic linker sequences. Reprinted from *Pharmacology and Therapeutics*, Vol 136, Nagorsen D, Kufer P, Baeuerle PA, Bargou R. Blinatumomab: a historical perspective, Pages 334–342. Copyright © 2012, with permission from Elsevier.

**Abbreviations:** CD, cluster of differentiation; mAb, monoclonal antibody.
Blinatumomab Study Design.

- Dose-finding stage
  - Cohort 1: 15 μg/m²/d
    - Safety evaluation → stop
  - Cohort 2a: 5-15 μg/m²/d
    - Safety evaluation
  - Cohort 2b: 5-15-30 μg/m²/d
    - Safety evaluation → stop

- Stage 2 of Simon 2-stage design
  - Cohort 3: 5-15 μg/m²/d

Max S. Topp et al. JCO 2014;32:4134-4140
# Blinatumamab Treatment in Relapsed and Refractory ALL

## Table 1. Patient Demographic and Clinical Characteristics (N = 36)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>18-77</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>61</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td><strong>Prior therapy/disease status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior HSCT</td>
<td>21</td>
<td>58</td>
</tr>
<tr>
<td>Primary refractory</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>First salvage after first CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 12 months after initial diagnosis</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>&gt; 12 months after initial diagnosis</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>≥ Second salvage</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Prior HSCT</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td><strong>Cytogenetic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph positive</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>t(4;11)</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td><strong>Bone marrow blasts at screening, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>6-97</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; HSCT, hematopoietic stem-cell transplantation; Ph, Philadelphia chromosome.

*Based on central laboratory screening results unless unavailable (data from two patients based on local laboratory screening).*
Blinatumamab for Relapsed and Refractory ALL

**Figure A**
- **Relapse-Free Survival**
- **Time (months)**
- **N**
  - No censoring of aHSCT: 25, Median: 7.6 (4.5 to 9.5)
  - Censoring of aHSCT: 25, Median: 7.9 (2.8 to NE)

**Table A**
- **No. at risk**
  - No censoring of aHSCT: 25, 16, 3, 1, 0, 0
  - Censoring of aHSCT: 25, 7, 2, 1, 0, 0

**Figure B**
- **Overall Survival**
- **Time (months)**
- **N**
  - No censoring of aHSCT: 36, 9.8 (8.5 to 14.9)
  - Censoring of aHSCT: 36, 14.9 (8.2 to 21.9)

**Table B**
- **No. at risk**
  - No censoring of aHSCT: 36, 29, 11, 4, 1, 0
  - Censoring of aHSCT: 36, 13, 7, 3, 1, 0

**Figure C**
- **Overall Survival**
- **Time (months)**
- **N**
  - No prior aHSCT: 21, 14.1 (6.0 to 23.9)
  - Prior aHSCT: 15, 8.8 (1.3 to 14.9)

**Table C**
- **No. at risk**
  - No prior aHSCT: 21, 18, 9, 3, 1, 0
  - Prior aHSCT: 15, 11, 2, 1, 0, 0
<table>
<thead>
<tr>
<th>AE</th>
<th>Dose-Finding Stage</th>
<th>Extension Stage</th>
<th>Optimal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1 (15 µg/m² per day; n = 7)</td>
<td>Cohort 2a (5 to 15 µg/m² per day; n = 5)</td>
<td>Cohort 2b (5 to 15 to 30 µg/m² per day; n = 6)</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Worst grade 1 or 2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Worst grade ≥ 3</td>
<td>7</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>5</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>Grade 5†</td>
<td>1</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Permanently discontinued treatment because of AEs</td>
<td>4</td>
<td>57</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Blood IgA decrease</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Blood IgG decrease</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Blood IgM decrease</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Fibrin D dimer increase</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>3</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood potassium decrease</td>
<td>2</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein increase</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Catheter site infection</td>
<td>1</td>
<td>14</td>
<td>1</td>
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<tr>
<td>Cytokine release syndrome</td>
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<td>14</td>
<td>0</td>
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<tr>
<td>Febrile neutropenia</td>
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<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increase</td>
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<td>0</td>
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<tr>
<td>Hypertension</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>1</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; Ig, immunoglobulin.

*Includes AEs both unrelated and considered to be possibly related to blinatumomab treatment.
†Fatal (grade 5) AEs reported during core study: cohort 1: infection (n = 1); cohort 2a: fungal pneumonia (n = 1); cohort 2b: *Candida* sepsis (n = 1); cohort 3: pulmonary sepsis and pneumonia (n = 1), sepsis (n = 1), and fungal infection of brain (n = 1).
Targeted Therapy (ALL and NHL)

1. CAR T cells
   – anti CD19
Why Consider CAR T Cell therapy

- Remarkable responses demonstrated in refractory B cell malignances
- Potential ability to target other malignancies with suitable antigenic targets
- Specialized activity: need for cell processing and BMT like capabilities to perform this therapy
- Could replace the use of BMT for some indications
- Patients will seek heme malignancy programs that can offer this therapy
RIC Principle

Shift burden of tumor cell kill from cytotoxic Chemoradiotherapy to Donor T cells
Graft vs Tumor Effect

Approaches to Overcome Immune Tolerance to Tumors.

Cytokine Therapy
- IL-2, IFN
- IL-7, IL-15, IL-21

Therapeutic Vaccines
- Dendritic cell vaccines
- DNA, RNA, Engineered tumor cells

Checkpoint blockade
- anti-CLTA4
- anti-PD1

Tumor-specific T cell
- MHC+peptide antigen

Treg MDSC

Chemotherapy

Antibody-drug conjugates
- Gentuzumab ozogamicin

T cell clones

CAR T cells

TCR engineered T cells


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CAR T cells

• Key element is production of T cells transfected with a fusion protein with two main components
  – Antigen recognition domain e.g. CD19
  – T cell activation domain/costimulatory domains e.g. CD28 costimulatory domain and T-cell receptor (TCR)
    – T cell activation domains
• Achieved through transduction into autologous T cells of vectors with coding DNA
Schematic of CAR T cell Patient Treatment.

1) T Cell Collection

2) T Cell Transfection
   1. Binding
   2. Fusion

3) T Cell Adoptive Transfer
   3. Integration
   4. Transcription and protein expression
   5. CAR cell membrane insertion
   +/- Lymphodepleting conditioning

4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate

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Jacobson CA, and Ritz J Blood 2011;118:4761-4762
CAR T cells in NHL

15 patients with advanced B-cell malignancies
  9 diffuse large B-cell lymphoma (DLBCL),
  2 indolent lymphomas,
  4 chronic lymphocytic leukemia.
• Patients received cyclophosphamide and fludarabine followed by a single infusion of anti-CD19 CAR T cells.

RESULTS:
• eight achieved complete remissions (CRs),
• four achieved partial remissions, one had stable lymphoma, and
• two were not evaluable for response.
• CRs were obtained by four of seven evaluable patients with chemotherapy-refractory DLBCL;
  three of these four CRs with durations ranging from 9 to 22 months.

Acute toxicities
• fever, hypotension, delirium, and other neurologic toxicities resolved within 3 weeks after cell infusion.
• One patient died suddenly as a result of an unknown cause 16 days after cell infusion.

Kochenderfer JN et, JCO AUGUST 2014
CAR T in NHL

Responses in Chemotherapy-Refractory DLBCL in Patients Given anti-CD19 CAR T cells.
Results in ALL

- Autologous T cells transduced with a CD19-directed chimeric antigen receptor (CTL019) lentiviral vector in patients with relapsed or refractory ALL

- Doses of $0.76 \times 10^6$ to $20.6 \times 10^6$ CTL019 cells per kilogram

Results

- 30 children and adults received CTL019.
- Complete remission in 27 patients (90%), 15 after prior stem-cell transplantation.
- CTL019 cells proliferated in vivo and were detectable in the blood, bone marrow, and cerebrospinal fluid
- 6-month event-free survival rate of 67% and overall survival rate of 78%
- At 6 months, the probability of persistence of CTL019 was 68% (95% CI, 50 to 92)
- Probability of relapse-free B-cell aplasia was 73% (95% CI, 57 to 94)

RESULTS IN ALL Cytokine-release syndrome

- All the patients had the cytokine-release syndrome

- Severe cytokine-release syndrome, which developed in 27% of the patients
  - was associated with a higher disease burden before infusion

- Effectively treated with the anti–interleukin-6 receptor antibody tocilizumab

- 30% treated in ICU

- Not directly correlated with neurological toxicity
Toxicities of CAR T therapy

- Fever
- Hypotension
- Pulmonary leak
- Coagulopathy
- Cytopenias
- Renal changes
- Neurological
- B cell aplasia with hypogammaglobulinemia
- Tumor lysis syndrome

Cytokine Release Syndrome

Generally reversible
Occur in the first few weeks
Some respond to anti-IL6 monoclonal antibody
Inpatient monitoring required after infusions

“On target, off organ” toxicities limits choice of targets
Toxicities may vary by disease, disease burden, antigenic target, vector design, etc
Conclusion

- Targeted therapy takes advantage of molecular and genetic information to cause tumor cell kill.
- There is an explosion of novel therapies that may help change the natural history of many aggressive blood cancers.
- Therapies include:
  1. Small molecules (TKI, anti BCL2, BCR inhibitors...)
  2. Immunconjugates, bifunctional agent
  3. CAR T cells.
- Agents have unique toxicities
- Are likely to be very expensive