Immunoterapia w hematologii. CAR T i BITE

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Uniwersyteckie Centrum Kliniczne WUM

Warszawa, 2019
Immune System
T Cells
Michał: 19-letni chory na ostrą białaczkę limfoblastyczną B-komórkową
Michał: 19-letni chory na ostrą białoćkę limfoblastyczną B-komórkową

1. Skuteczne leczenie chemioterapią

2. Przeszczepienie szpiku od dawcy

3. Nawrót
Wyniki leczenia po nawrocie ostrej białaczki limfoblastycznej u dorosłych

Przeżycie po nawrocie (po chemioterapii, transplantacji auto- i allogenicznych komórek krwiotwórczych)

1. Blinatumomab

2. Inotuzumab ozogamycyny

3. Limfocyty CAR T
Inactive Virus
Chimeric Antigen Receptors
Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19

Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19

James N. Kochenderfer,¹ Wyndham H. Wilson,² John E. Janik,² Mark E. Dudley,¹ Maryalice Stetler-Stevenson,³ Steven A. Feldman,¹ Irina Maric,⁴ Mark Raffeld,³ Debbie-Ann N. Nathan,¹ Brock J. Lanier,¹ Richard A. Morgan,¹ and Steven A. Rosenberg¹
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Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19


A

CD79a

B

CD79a

B cells/

T cells/

Transgene copy per 100 ng

Weeks after T cell infusion

Weeks after T cell infusion

Weeks after T cell infusion

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C

![Graphs showing B cells/L, T cells/L, and transgene copies per 100 ng DNA over weeks after T cell infusion.](https://example.com/graphs)
Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19


[Images of CT scans, T cell counts, and CD79a expression]

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Skuteczność CAR T w leczeniu opornej i nawrotowej ostrej białaczki limfoblástycznej B-komórkowej (B-ALL)
## Pierwsze badania

<table>
<thead>
<tr>
<th>Ref</th>
<th>Program/CAR</th>
<th>Population</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Lymphoblastic Leukemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maude et al. NEJM 2014</td>
<td>PENN 4-1BB</td>
<td>N=30 (ALL) Peds&amp;Adults</td>
<td>CR=90%</td>
</tr>
<tr>
<td>Davila et al. SciTrMed 2014</td>
<td>MSK CD28</td>
<td>N=16 (ALL) Adults</td>
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<td>Lee et al. Lancet 2015</td>
<td>NCI CD28</td>
<td>N=21 (ALL) Peds&amp;AYA</td>
<td>CR=67% Intent to Treat</td>
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<td>Turtle et al. JCI 2016</td>
<td>Seattle 4-1BB</td>
<td>N=30 Adults</td>
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<td>Kochenderfer JCO 2015</td>
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<td>N=15 (NHL/CLL)</td>
<td>CR=53% PR=27%</td>
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<td>Porter et al. SciTrMed 2014</td>
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</tr>
</tbody>
</table>
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia


Badanie 2 fazy, jednoramienne, przeprowadzone w 25 ośrodkach na świecie

Event-free and overall survival

- Event-free survival
- Overall survival

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Median Survival</th>
<th>Rate at 6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>75</td>
<td>19</td>
<td>90 (81–95)</td>
</tr>
<tr>
<td>Event-free</td>
<td>75</td>
<td>27</td>
<td>73 (60–82)</td>
</tr>
</tbody>
</table>

No. at Risk

Overall survival: 75 72 64 58 55 40 30 20 12 8 2 0
Event-free survival: 75 64 51 37 33 19 13 8 3 3 1 0

Months since Tisagenlecleucel Infusion

Probability
Wyniki leczenia po nawrocie ostrej białaczki limfoblastycznej u dorosłych

Przeżycie po nawrocie (po chemioterapii, transplantacji auto- i allogenicznych komórek krwiotwórczych)

• 81% chorych uzyskało całkowitą remisję (CR) w ciągu 3 miesiący

60% z tych, którzy uzyskali całkowitą remisję ma szansę na wyleczenie

**Kymriah:** (tisagenlecleucel)

Pierwszy produkt zarejestrowany w FDA do leczenia nawrotowej i opornej B-ALL u dzieci i młodych dorosłych (do 25 roku życia) 30 sierpień 2017
Skuteczność limfocytów CAR T w leczeniu opornych i nawrotowych chłoniaków B-komórkowych
SCHOLAR-1: The First and Largest Patient-Level Meta-Analysis of Chemorefractory DLBCL

SCHOLAR-1: is a retrospective analysis of 636 patients with refractory DLBCL. Integrated data from:

- Two large phase 3 studies
  - LYSARC-CORAL
  - Canadian Cancer Trials Group-LY.12

- Two observational cohorts
  - MD Anderson Cancer Center
  - Mayo Clinic/University of Iowa

Median OS was 6.3 months (95% CI, 5.9-7.0)

The pooled CR was 7%

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Wieloośrodkowe badanie 2 fazy (111 pacjentów) u chorych na chłoniaki rozlane z dużej komórki B (DLBCL), pierwotne chłoniaki śródpiersia i transformowane chłoniaki grudkowe, oporne na chemioterapię

18 października 2017

Yescarta™ (Axicabtagene Ciloleucel) zatwierdzona przez FDA do leczenia dorosłych chorych na opornego chłoniaka DLBCL, po min 2 liniach leczenia
Emily Whitehead First Child Treated in Trial of T Cell Therapy for Acute Lymphoblastic Leukemia
Emily Whitehead First Child Treated in Trial of T Cell Therapy for Acute Lymphoblastic Leukemia
BiTE® antibody constructs: linking anti-CD3 to anti-TAA capability

α-TAA antibody  BiTE®  α-CD3 antibody

Very short distance between arms allows T cells and tumour cells to come into close proximity

BiTE®, bispecific T-cell engager; $V_H$, heavy chain variable region; $V_L$, light chain variable region

Baeuerle PA, Reinhardt C. Cancer Res 2009;69:4941–4
BiTE® antibody constructs: designed to bridge ANY cytotoxic T cell to target cancer cells

- Genetically linked minimal binding domains of mAbs for CD3 on T cells and for TAAs on target cancer cells\(^1\)\(^–\)\(^3\)
- Immunological synapse formation is forced
  - Bypasses MHC/antigen-dependent activation of T cells\(^3\)\(^–\)\(^5\)
- Activation achieved independently of\(^1\)
  - TCR specificity
  - Co-stimulation
  - Peptide antigen presentation

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\(^1\) Baeuerle PA, Reinhardt C. Cancer Res 2009;69:4941–4;
\(^3\) Frankel SR, Baeuerle PA. Curr Opin Chem Biol 2013;17:385–92;
**Blinatumomab**: BiTE® antibody construct designed to bridge T cells to CD19-expressing cancer cells

95–100% of B-precursor ALL tumours are CD19+.

▼This medicinal product is subject to additional monitoring. All suspected adverse reactions should be reported

Blinatumomab: BiTE<sup>®</sup> antibody construct designed to bridge T cells to CD19-expressing cancer cells, inducing cancer cell death<sup>1</sup>

Blinatumomab enables single T cells to eliminate multiple target cells by serial lysis

This video represents activity over an approximate 9-hour period.

Implications of MRD Status


ALL, acute lymphoblastic leukemia; CR, complete remission; HSCT, hematopoetic stem cell transplant; MRD, minimal residual disease.

**Example diagram based on a clinical study.**

1. **Multi-agent chemotherapy**
2. **Response assessment**
3. **Morphologic Assessment**
   - CR: 85%–92%
   - CR: < 5% blasts in bone marrow
4. **Molecular Assessment**
   - MRD–
     - Decreased risk of relapse
     - Improved outcomes
   - MRD+
     - Increased risk of relapse
     - ALL salvage treatment
     - Generally poor outcomes: limited efficacy, high morbidity
5. **No CR**
MRD Status Is Associated With CR and Survival

Patients with continuous CR

5-year CCR rate

- MRD-: 35% (N=120)
- MRD+: 74% (N=384)

Probability of Survival

5-year survival rate

- MRD-: 42% (N=120)
- MRD+: 80% (N=384)

CR, complete remission; MRD, minimal residual disease.
Pre-transplant MRD Status Affects Outcome in CR1 and Beyond

CR1 = 90, CR2 = 58, >CR2 = 12
*MRD status not influenced by adjusting for CR status (P = 0.70)*

CR1, first complete remission; CR2, second complete remission; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival

BLAST: Blinatumomab\textsuperscript{▼} for Patients With Minimal Residual Disease (MRD) in B-cell Precursor Acute Lymphoblastic Leukemia (ALL)

Amgen Study IDs: MT103-202 (Phase II Pilot) and MT103-203 (Phase II BLAST)

ClinicalTrials.gov Identifier: NCT00560794 and NCT01207388

\textsuperscript{▼}This medicinal product is subject to additional monitoring. All suspected adverse reactions should be reported.

Blinatumomab is indicated as monotherapy for the treatment of adults with Ph-negative CD19-positive relapsed or refractory B-precursor ALL. Blinatumomab is indicated as monotherapy for the treatment of adults with Ph-negative CD19-positive B-precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%. Blinatumomab is indicated as monotherapy in paediatric patients aged 1 year or older with Ph-negative CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic HSCT. All other settings are investigational.

\textit{Pilot} = phase 2 study of the BiTE\textsuperscript{®} Blinatumomab (MT103-202) in patients with MRD of B-cell precursor ALL

\textit{BLAST} = confirmatory phase 2 study of blinatumomab (MT103-203) in patients with MRD of B-cell precursor ALL
**Study Design**

**Blast (MT103-203) Study**

**Key inclusion criteria**
- Age ≥ 18 years
- B-cell precursor ALL in complete hematologic remission
- MRD-positive, defined as a level of ≥ 10^-3 (molecular failure or molecular relapse) in an assay with a minimum sensitivity of 10^-4
- ANC ≥ 1,000/μL
- Platelets ≥ 50,000/μL
- Hemoglobin level ≥ 9 g/dL
- Blasts < 5%

**Key exclusion criteria**
- Circulating blasts or extramedullary ALL involvement
- History of relevant CNS pathology or current relevant CNS pathology
- Prior alloHSCT
- Prior chemotherapy (within 2 weeks) or radiotherapy (within 4 weeks)

ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; ANC, absolute neutrophil count; CNS, central nervous system; MRD, minimal residual disease.

Study Design

Blast (MT103-203) Study

Primary endpoint
Rate of complete MRD response after first cycle among patients in the primary endpoint full analysis set (i.e., MRD-negative [assay minimum sensitivity $10^{-4}$])

Secondary endpoints
• Hematologic RFS among Ph− patients at 18 months after initiation of blinatumomab in the key secondary endpoint full analysis set
• Duration of complete MRD response
• Overall survival
• Duration of hematologic remission
• Incidence and severity of AEs

AE, adverse event; MRD, minimal residual disease; Ph−, Philadelphia chromosome negative; RFS, relapse-free survival.
Study Design
Treatment Overview

**Cycle 1**,2,a
Blinatumomab cIV 15 µg/m²/day x 28 days per cycle
(4 weeks on/2 weeks off)

**Primary endpoint assessment**

**Patients ineligible for alloHSCT**1,2
- Up to three additional cycles

**Patients eligible for alloHSCT**1,2,b
- Up to three additional cycles
- AlloHSCT when donor is available

**100-day alloHSCT-related mortality assessment**3

**2-year follow-up for efficacy**2,c

**5-year survival follow-up (Q6M)**2

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Complete Minimal Residual Disease Response After Cycle 1 by Clinical Characteristics

**Primary Endpoint Efficacy Set**

<table>
<thead>
<tr>
<th>Category</th>
<th>n/N</th>
<th>% (95% exact CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>82/103</td>
<td>80 (71–87)</td>
</tr>
<tr>
<td>MRD Level at Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10(^{-3}) to &lt; 10(^{-2})</td>
<td>40/51</td>
<td>78 (65–89)</td>
</tr>
<tr>
<td>≥ 10(^{-2}) to &lt; 10(^{-1})</td>
<td>36/43</td>
<td>84 (69–93)</td>
</tr>
<tr>
<td>≥ 10(^{-1}) to &lt; 1</td>
<td>6/9</td>
<td>67 (30–93)</td>
</tr>
<tr>
<td>Relapse History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>55/66</td>
<td>83 (72–91)</td>
</tr>
<tr>
<td>CR2/3</td>
<td>27/37</td>
<td>73 (56–86)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35/43</td>
<td>81 (67–92)</td>
</tr>
<tr>
<td>Male</td>
<td>47/60</td>
<td>78 (66–88)</td>
</tr>
<tr>
<td>Age, Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>11/13</td>
<td>85 (55–98)</td>
</tr>
<tr>
<td>55–65</td>
<td>17/23</td>
<td>74 (52–90)</td>
</tr>
<tr>
<td>35–54</td>
<td>25/35</td>
<td>71 (54–85)</td>
</tr>
<tr>
<td>18–34</td>
<td>29/32</td>
<td>91 (75–98)</td>
</tr>
</tbody>
</table>

*MRD negative with sensitivity of 10\(^{-4}\) (1:10,000)

CI, confidence interval; CR, complete remission; FAS, full analysis set; MRD, minimal residual disease.

### Long-Term Outcomes by Minimal Residual Disease Complete Responders and Nonresponders in Cycle 1

#### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MRD Responders&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MRD Nonresponders&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median&lt;sup&gt;b&lt;/sup&gt; (95% CI)</td>
<td>48/110</td>
<td>31/85</td>
<td>14/22</td>
</tr>
<tr>
<td>Estimated probability at 18 months (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>36.5 (19.8–NR)</td>
<td>38.9 (33.7–NR)</td>
<td>12.5 (3.2–NR)</td>
</tr>
<tr>
<td>Estimated probability at 18 months (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.67 (0.58–0.75)</td>
<td>0.70 (0.59–0.79)</td>
<td>0.34 (0.15–0.54)</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>0.002</td>
</tr>
</tbody>
</table>

#### Hematologic RFS

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MRD Responders&lt;sup&gt;a&lt;/sup&gt;</th>
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</tr>
<tr>
<td>Median&lt;sup&gt;b&lt;/sup&gt; (95% CI)</td>
<td>62/110</td>
<td>40/85</td>
<td>12/15</td>
</tr>
<tr>
<td>Estimated probability at 18 months (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18.9 (12.3–35.2)</td>
<td>23.6 (17.4–NR)</td>
<td>5.7 (1.6–13.6)</td>
</tr>
<tr>
<td>Estimated probability at 18 months (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.53 (0.44–0.62)</td>
<td>0.58 (0.46–0.68)</td>
<td>0.20 (0.05–0.42)</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>0.002</td>
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#### Duration of hematologic remission<sup>d</sup>

<table>
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<tr>
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<td>7/15</td>
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<td>Estimated probability at 18 months (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NR (NR–NR)</td>
<td>NR (NR–NR)</td>
<td>NR (3.7–NR)</td>
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<tr>
<td>Estimated probability at 18 months (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.7 (0.61–0.78)</td>
<td>0.77 (0.67–0.85)</td>
<td>0.53 (0.30–0.80)</td>
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<tr>
<td><strong>P</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>0.14</td>
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<sup>a</sup>Landmark analysis includes patients in both, the Key Secondary Full Analysis Set and the Primary Endpoint Analysis Set, and excludes patients with an event (death or relapse) or censored before day 45. <sup>b</sup>Kaplan-Meier estimate. <sup>c</sup>Log-rank test P value. <sup>d</sup>Duration of hematologic remission is evaluated by 1 – cumulative incidence function of hematological relapse with death in hematologic CR as a competing event. <sup>e</sup>Gray's test P value.

CI, confidence interval; CR, complete remission; MRD, minimal residual disease; NR, not reached; n, patients with events (deaths for overall survival, death in CR, or relapse for RFS and relapse for duration of hematologic remission); N, patients at risk; RFS, relapse-free survival.

Overall Survival (Cont’d)

Overall Survivala by MRD Response1 During Cycle 1

Median (95% CI) overall survival was 38.9 (33.7–NR) vs 12.5 (3.2–NR) months (P = 0.002) in patients with and without a complete MRD response in cycle 1, respectively

aOverall survival not censoring at alloSCT and post-blinatumomab chemotherapy.
alloSCT, allogeneic stem cell transplantation; CI, confidence interval; MRD, minimal residual disease; NR, not reached.
Relapse-Free Survival

**RFS\(^a\) Among Patients in Secondary EP FAS\(^1\)**

Median (95% CI) RFS was 18.9 (12.3–35.2) months with a median follow-up of 29.9 months

**RFS\(^a\) Among Patients in Secondary EP FAS by Remission Status at Screening\(^2\)**

Median (95% CI) RFS was 24.6 (18.7–NR) vs 11.0 (6.8–15.4) months among patients treated within first CR vs later CR (unadjusted HR 2.09; 95% CI, 1.26–3.48; \(P = 0.004\))

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\(^a\)RFS without censoring at HSCT and post-blinatumomab chemotherapy. Estimates of RFS at 18 months were similar with or without censoring for post-blinatumomab HSCT and chemotherapy.

\(^1\)CI, confidence interval; CR, complete remission; EP, endpoint; FAS, full analysis set; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; NR, not reached; Ph−, Philadelphia chromosome negative; RFS, relapse-free survival.


2. Study MT103-203 Clinical Study Report (Amgen data on file).
Median (95% CI) RFS among MRD responders at cycle 1 in first CR, ≥ 2nd CR, and among MRD nonresponders at cycle 1 was NR (20.8–NR), 13.9 (7.8–NR), and 5.7 (1.6–13.6) months, respectively.

RFS\(^a\) Among Patients in Secondary EP FAS by Remission Status at Screening and Responder Status

**Median (95% CI) RFS among MRD responders at cycle 1 in first CR, ≥ 2nd CR, and among MRD nonresponders at cycle 1 was NR (20.8–NR), 13.9 (7.8–NR), and 5.7 (1.6–13.6) months, respectively.**

\(^a\)RFS without censoring at alloSCT and post-blinatumomab chemotherapy by complete MRD responder status in cycle 1 and salvage status among evaluable patients (landmark analysis, excluding patients who were censored, or had relapsed or died, within 45 days of beginning treatment).

Targeted immunotherapy with blinatumomab treatment resulted in a substantial molecular response rate and improved long-term outcomes among patients with chemotherapy-resistant MRD who responded to the treatment.

The proportion of evaluable patients who achieved complete MRD response after blinatumomab treatment in the BLAST study was 78% (88/113).

A landmark analysis of the BLAST study showed that complete MRD responders had a significantly longer RFS and overall survival than MRD nonresponders.

Blinatumomab was well tolerated in the BLAST study, with the most frequent AEs observed being pyrexia, headache, tremor, and neutropenia.

In the BLAST study, 12 (10%) and three (3%) patients had grade 3 and 4 neurologic events, respectively. Four (3%) patients had cytokine release syndrome (two grade 1 and two grade 3), all during cycle 1.