Immunotherapy

Latest immune therapy approaches: BITE, CAR-T and checkpoint inhibitors

PD Dr. med. Ulf Petrausch
Medizinische Onkologie, FMH
Klinische Immunologie & Allergologie, FMH
Allgemeine Innere Medizin, FMH
T-cell-Receptors
1,000,000,000,000,000 (10^{15})

Stars in our galaxy
100,000,000,000 (10^{11})
Tolerance

10^{15}

Elimination of self-reactive T cells

2.5 \times 10^7

Nikolich-Zugich et al., Nature Reviews Immunology 4, 123-132 (February 2004)
The use of T cells to fight cancer

NO T cells to fight cancer

>50%

**T cells**

Immunomodulation:

- Checkpoint-Inhibitors
- IDO Inhibitors
- Agonistic antibodies
- TIL transfer
- Cytokines

**No T cells**

T cell generation/recruitment

- BITE
- Genetically modified T cells
- Oncolytic viruses
T cells

Immunomodulation:
- Checkpoint-Inhibitors
- IDO Inhibitors
- Agonistic antibodies
- TIL transfer
- Cytokines

No T cells

T cell generation/recruitment
- BITE
- Genetically modified T cells
- Oncolytic viruses
114 Studies found for:

adoptive | Recruiting, Not yet recruiting Studies | Cancer

Also searched for Neoplasm, Tumor, and Malignancy. See Search Details
History of Checkpoint Inhibitors: Key Milestones

<table>
<thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nivolumab⁴</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>Nivolumab⁵</td>
</tr>
<tr>
<td>RCC</td>
<td></td>
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<tr>
<td>Bladder cancer</td>
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<tr>
<td>R/M SCCHN</td>
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<td>Nivolumab (NSQ)²</td>
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<tr>
<td>Classical Hodgkin’s lymphoma</td>
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<td></td>
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<td>Nivolumab + ipilimumab²</td>
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<tr>
<td>Pembrolizumab²</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Pembrolizumab (PD-L1+)²,⁵</td>
</tr>
<tr>
<td>Nivolumab (SQ)¹</td>
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<tr>
<td>Nivolumab (NSQ)¹</td>
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<td>Nivolumab¹</td>
</tr>
</tbody>
</table>

Melanoma: THE example

B Overall Survival

A Overall Survival

No. at Risk
Nivolumab plus ipilimumab
Nivolumab
Ipilimumab

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>403</td>
</tr>
<tr>
<td>4</td>
<td>297</td>
</tr>
<tr>
<td>8</td>
<td>223</td>
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<td>12</td>
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<td>16</td>
<td>115</td>
</tr>
<tr>
<td>20</td>
<td>81</td>
</tr>
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<td>24</td>
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<td>28</td>
<td>33</td>
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<td>32</td>
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<td>7</td>
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<td>6</td>
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<td>48</td>
<td>4</td>
</tr>
<tr>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>56</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at Risk
Ipilimumab
gp100

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>137</td>
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<tr>
<td>4</td>
<td>106</td>
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<tr>
<td>8</td>
<td>79</td>
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<td>12</td>
<td>56</td>
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<td>16</td>
<td>38</td>
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<td>20</td>
<td>30</td>
</tr>
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<td>24</td>
<td>24</td>
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<td>28</td>
<td>13</td>
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<td>32</td>
<td>8</td>
</tr>
<tr>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>44</td>
<td>1</td>
</tr>
</tbody>
</table>

N Engl J Med 2017; 377:1345-1356 
Melanoma

- Langzeitdaten Ipilimumab von 1.861 Melanompatienten (8 Ph. II-, 2 Ph. III-, 2 Ph. IV-Studien)

Medianes OS, Monate (95% KI): 11,4 (10,7–12,1)
3-Jahres OS-Rate, % (95% KI): 22 (20–24)
Lung Cancer: THE most frequent one

**KEYNOTE-024 Study Design** (NCT02142738)

**Key Eligibility Criteria**
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

![Diagram](diagram.png)

- **Pembrolizumab** 200 mg IV Q3W (2 years)
- **Platinum-Doublet Chemotherapy** (4-6 cycles)

**Key End Points**
- **Primary**: PFS (RECIST v1.1 per blinded, independent central review)
- **Secondary**: OS, ORR, safety
- **Exploratory**: DOR

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.*
Lung Cancer

KEYNOTE-024 Overall Survival and Objective Response

Overall Survival

- Events, n | Median, mo | HR (95% CI) | P
- Pembrolizumab | 44 | NR | 0.60 (0.41-0.89) | 0.005
- Chemotherapy | 64 | NR | 1.00

40% risk reduction of death

Objective Response

- ORR, % (95% CI)
- CR
- PR

50% crossover in ITT population
54% crossover excluding ongoing pts

TTR, mo
- Pembrolizumab (n=69): median (range) = 2.2 mo (1.4-8.2)
- Chemotherapy (n=42): median (range) = 2.2 mo (1.8-12.4)

DOR, mo
- Pembrolizumab (n=69): median (range) = NR
- Chemotherapy (n=42): median (range) = 6.3 mo (2.1-12.6)
Liver Cancer: The Challenge for the Future

Hepatitis B:
• WHO Western Pacific Region: 6.2% of population (115 million people)
• WHO African Region: 6.1% of population (60 million people)
• WHO Eastern Mediterranean Region: 3.3% of population (21 million people)
• WHO South-East Asia Region: 2% of population (39 million people)
• WHO European Region: 1.6% of population (15 million people)
• WHO Region of the Americas: 0.7% of population (7 million people)

Hepatitis C:
• WHO Eastern Mediterranean Region: 2.3% of population (15 million people)
• WHO European Region: 1.5% of population (14 million people)
• WHO African Region: 1% of population (11 million people)
• WHO Region of the Americas: 1% of population (7 million people)
• WHO Western Pacific Region: 1% of population (14 million people)
• WHO South-East Asia Region: 0.5% of population (10 million people)
Liver Cancer

CheckMate 040 Study Design

- **Dose Escalation**
  - 0.1–10 mg/kg
  - All Patients (N = 262)
  - N = 48
  - Uninfected (n = 23)
  - HCV infected (n = 10)
  - HBV infected (n = 15)

- **Dose Expansion**
  - 3 mg/kg
  - N = 214
  - Uninfected (n = 113)
  - HCV infected (n = 50)
  - HBV infected (n = 51)

- **Sorafenib**
  - Experienced (2L) (n = 37)
  - Naive (1L) (n = 11)

**Study Endpoints**

**Primary**
- Safety and tolerability (escalation)
- Objective response rate<sup>a</sup> (expansion)

**Secondary**
- Objective response rate<sup>a</sup> (escalation)
- Disease control rate
- Time to response
- Duration of response
- Overall survival

**Other**
- Biomarker assessments
- Patient-reported outcomes<sup>b</sup>

- Disease assessment imaging (CT or MRI) every 6 weeks
- Interim analysis data cutoff date: August 8, 2016
  - Median follow-up was 13.3 months in the dose-escalation phase and 10.5 months in the dose-expansion phase

<sup>a</sup> RECIST v1.1; <sup>b</sup> Baseline and every 6 weeks through week 25 using the EQ-5D utility index and visual analog scale (VAS).

Presented at: 2017 Gastrointestinal Cancers Symposium | #GI17 Presented by: Dr Ignacio Melero

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Liver Cancer

**PD1-PDL-1 Axis in HCC**

<table>
<thead>
<tr>
<th>Expression Level</th>
<th>45-100%</th>
</tr>
</thead>
</table>
| **Expression Location** | HCC  
                        | Microenvironment  
                        | - Kupffer Cells  
                        | - Tumor Associated Monocytes |
| **Time** | ↑ Advanced Staged  
            | ↑ Viral Infection (HBV)  
            | ↑ Inflammation (TAE) |
| **Clinical Outcome** | ↓ DFS, ↓ OS |
| **PDL-1 Blockade** | HCC cell death in murine models |


Presented by: Ghassan Abou-Alfa, MD, MBA
Liver Cancer

Nivolumab Response Kinetics (CheckMate-040)

Tumor Burden

Solid shape = first occurrence of new lesion

Liver Cancer

Nivolumab OS by Prior Sorafenib (CheckMate-040)

<table>
<thead>
<tr>
<th>Group</th>
<th>Died/Treated</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib naive</td>
<td>7/11</td>
<td>14.1 (3.2-28.6)</td>
</tr>
<tr>
<td>Sorafenib treated</td>
<td>22/37</td>
<td>15.0 (5.0-18.9)</td>
</tr>
</tbody>
</table>


Presented at 2017 Gastrointestinal Cancers Symposium | #GI17

Presented by: Ghassan Abou-Alfa, MD, MBA
### Safety: Dose-Expansion Phase

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Uninfected (n = 113)</th>
<th>HCV Infected (n = 50)</th>
<th>HBV Infected (n = 51)</th>
<th>All Dose Expansion (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any treatment-related AE (TRAEs)</td>
<td>84 (74)</td>
<td>22 (19)</td>
<td>40 (80)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>TRAEs (≥ 5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34 (30)</td>
<td>2 (2)</td>
<td>8 (16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18 (16)</td>
<td>0</td>
<td>14 (28)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>16 (14)</td>
<td>2 (2)</td>
<td>9 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (17)</td>
<td>2 (2)</td>
<td>5 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (9)</td>
<td>0</td>
<td>6 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>9 (8)</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (5)</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Laboratory TRAEs (≥ 5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increase</td>
<td>9 (8)</td>
<td>4 (4)</td>
<td>6 (12)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>7 (6)</td>
<td>2 (2)</td>
<td>7 (14)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
Liver Cancer

Local strategies to engage the immune system
T cells

Immunomodulation:
- Checkpoint-Inhibitors
- IDO Inhibitors
- Agonistic antibodies
- TIL transfer
- Cytokines

No T cells

T cell generation/recruitment
- BITE
- Genetically modified T cells
- Oncolytic viruses
1,000,000,000,000,000 + 1 = 25,000,000
Adoptive T-cell transfer

1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion

+/- Lymphodepleting conditioning

modifiziert von Jacobson and Ritz J, Blood 2011
Leukemia: CD19-specific T cells

# Klinische Anwendungen:

## Table 1. Selected summary of the reported clinical trials of chimeric antigen receptor-T-cell therapy in B-acute lymphoblastic leukemia.

<table>
<thead>
<tr>
<th>Center</th>
<th>Target</th>
<th>No.</th>
<th>CAR</th>
<th>Vector</th>
<th>Disease</th>
<th>Results</th>
<th>Role of HSCT</th>
<th>Chemotherapy</th>
<th>Notes</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>NCI</td>
<td>CD19</td>
<td>20</td>
<td>28-ζ</td>
<td>RV</td>
<td>Children and young adult patient</td>
<td>CR 61%, OS 51% at 6 months, DFS 78.8% at 6 months</td>
<td>17/20 patients with MRD negative disease went to HSCT</td>
<td>Flu/Cy</td>
<td>No relapse after HSCT, 2/3 patients with no HSCT relapsed with CD19-negative disease</td>
<td>[25]</td>
</tr>
<tr>
<td>MSKCC</td>
<td>CD19</td>
<td>16</td>
<td>28-ζ</td>
<td>RV</td>
<td>Adults ALL</td>
<td>88% CR or CRi, 75% achieved an MRD-negative disease status</td>
<td>7 of the 16 (44%) patients eligible for an allo-SCT treated for an allo-SCT</td>
<td>N/A</td>
<td>No relapses for these patients underwent allo-HSCT after CAR-T therapy</td>
<td>[26]</td>
</tr>
<tr>
<td>UPenn/CHOP</td>
<td>CD19</td>
<td>30</td>
<td>CD28-4-1BB-ζ</td>
<td>LV</td>
<td>Children and adults</td>
<td>90% CR, 22/27 patients with MRD negative CR</td>
<td>3 patients underwent allo-HSCT</td>
<td>Variable</td>
<td>3 patients underwent allo-HSCT remained in remission 7 to 12 months after the CAR-T infusion</td>
<td>[28]</td>
</tr>
<tr>
<td>UPenn/CHOP</td>
<td>CD19</td>
<td>53</td>
<td>4-1BB-ζ</td>
<td>LV</td>
<td>Children and young adult patients</td>
<td>CR 50/53(94%), EFS: 70% at 6 months and 45% at 12 months; OS: 78% at 12 months.</td>
<td>6/29 patients in CR received HSCT. Of 20 relapsed patients, 3 has HSCT after CAR-T treatment</td>
<td>Flu/Cy</td>
<td>20 relapsed, 13/20 (65%) with CD19-negative disease. CAR-T cells persisted for 3-39 months. 4 patients with leukemic meningitis reached remission after CAR-T-cell treatment</td>
<td>[29]</td>
</tr>
<tr>
<td>FHCRC</td>
<td>CD19</td>
<td>30</td>
<td>CD28-4-1BB-ζ</td>
<td>LV</td>
<td>ALL</td>
<td>CR 30/30 (100%), 27/29(93%) at MRD negative CR</td>
<td>N/A</td>
<td>Flu/Cy or Cy/VP</td>
<td>First CAR with defined CD4+ and CD8+ T-cell subsets</td>
<td>[30]</td>
</tr>
<tr>
<td>BCM</td>
<td>CD19</td>
<td>6</td>
<td>28-ζ</td>
<td>RV</td>
<td>ALL</td>
<td>CR 100%</td>
<td>N/A</td>
<td>N/A</td>
<td>CR lasting from 2 months to 8 months</td>
<td>[32]</td>
</tr>
<tr>
<td>China (multicenter)</td>
<td>CD19</td>
<td>50</td>
<td>28-4-1BB-27-ζ</td>
<td>LV</td>
<td>ALL</td>
<td>CR 94.3% when blasts &lt;50%, 66.7% when blasts &gt;50%</td>
<td>N/A</td>
<td>Variable</td>
<td>First 4th-G CAR</td>
<td>[35]</td>
</tr>
<tr>
<td>MSKCC</td>
<td>CD19</td>
<td>46</td>
<td>28-ζ</td>
<td>RV</td>
<td>Adult ALL</td>
<td>83% CR rate</td>
<td>12 patients underwent HSCT</td>
<td>Cy</td>
<td>No differences in outcomes whether or not HSCT was done. The OS at 6 months was 76 and 14% in the MRD-CR cohort and in the MRD+ CR cohort, respectively</td>
<td>[39]</td>
</tr>
<tr>
<td>MDACC</td>
<td>CD19</td>
<td>42</td>
<td>28-ζ</td>
<td>SB</td>
<td>Adjuvant post-allo-HSCT(10), relapse (8)</td>
<td>Adjuvant trial: CR 3/10(30%); Relapse trial: CR 3/13(23%, for all disease)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>[70]</td>
</tr>
</tbody>
</table>

4th-G: Fourth-generation; 4-1BB is alternatively known as CD137 or TNFRSF9 (TNF receptor superfamily member 9); ALL: Acute lymphoblastic leukemia; Allo-HSCT: Allogeneic hematopoietic stem cell transplantation; BCM: Baylor College of Medicine; CAR: Chimeric antigen receptor; CAR-T cell: Chimeric antigen receptors redirected T cell; CHOP: Children’s Hospital of Philadelphia; CR: Complete remission; FHCRC: Fred Hutchinson Cancer Research Center; HSCT: Hematopoietic stem cell transplantation; LV: Lentiviral; MDACC: MD Anderson Cancer Center; MRD: Minimal residual leukemia; MSKCC: Memorial Sloan-Kettering Cancer Center; NCI: National Cancer Institute; RV: Retroviral; SB: Sleeping beauty; UPenn: University of Pennsylvania.
FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

For Immediate Release
August 30, 2017

With FDA Approval for Advanced Lymphoma, Second CAR T-Cell Therapy Moves to the Clinic

The U.S. Food and Drug Administration (FDA) today approved Kymria (axicabtagene ciloleucel) (Yescarta™) for patients with large B-cell lymphomas whose cancer has progressed after receiving at least two prior treatment regimens. Large B-cell lymphomas include diffuse large B-cell lymphoma (DLBCL), the most common type; primary mediastinal large B-cell lymphoma; high-grade B-cell lymphoma; and transformed follicular lymphoma.

Axicabtagene, a form of immunotherapy called CAR T-cell therapy, was initially developed at NCI by Steven Rosenberg, M.D., Ph.D., of the Surgery Branch in NCI’s Center for Cancer Research (CCR), and his colleagues. It was later licensed to a private company, Kite Pharma, for further development and commercialization.
# Lymphoma

## ZUMA-1: Met Primary Endpoint ORR (P < .0001)<sup>a</sup> in Combined Group

<table>
<thead>
<tr>
<th>Best Response</th>
<th>DLBCL</th>
<th>TFL/PMBCCL</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR (%)</td>
<td>CR (%)</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>mITT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n = 77</td>
<td>82</td>
<td>n = 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

92 axi-cel–dosed patients had 6 mo of follow-up. ORR 82%, P<0.0001. <sup>b</sup>mITT (modified intention-to-treat) set of all patients dosed with axi-cel. CR, complete response; DLBCL, diffuse large B-cell lymphoma; ORR, objective response rate; PMBCCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.

Locke & Neelapu et al, AACR 2017, #9986
BITE (Blinatumomab)

- Engineered T cell
- Native T cell
- MHC I/II
- Malignant cell
- CD19
- CD20
- CD22
- Naked mAb
- ADC
- Bistpecific T-cell engager (BiTE®)
- Dual affinity retargeting (DART)
- Tetravalent tandem diabody (TandAb®)

- CD19
- CD3

- Single polypeptide chain
- Interchain disulfide bridge

- CD19
- CD3
- CD3
- CD19

- Two polypeptide chains
- Chain dimerization
## ALL & Lymphoma

### Table 2

Clinical efficacy of blinatumomab

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th>Treatment schedule</th>
<th>Response rate</th>
<th>Relapse-free survival</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-positive ALL(^{105,106})</td>
<td>20 *</td>
<td>15 µg/m(^2) per day continuous i.v. x 4 weeks every 6-week cycle</td>
<td>NA</td>
<td>61% at 33 months</td>
<td>NA</td>
</tr>
<tr>
<td>ALL(^{107})</td>
<td>36 *</td>
<td>5 µg/m(^2) and 15 µg/m(^2) per day (week 1, and thereafter until 4 weeks, respectively)</td>
<td>NA</td>
<td>Median of 7.6 months</td>
<td>9.8 months</td>
</tr>
<tr>
<td>ALL(^{108})</td>
<td>189 *</td>
<td>9 µg and 28 µg per day (week 1, and thereafter, respectively) continuous i.v. x 4 weeks every 6-week cycle</td>
<td>NA</td>
<td>Median of 5.9 months</td>
<td>6.1 months</td>
</tr>
<tr>
<td>B-NHL (FL, MCL, DLBCL)(^{103})</td>
<td>35 ‡</td>
<td>60 µg/m(^2) per day continuous i.v.</td>
<td>69</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>DLBCL(^{109})</td>
<td>21 ‡</td>
<td>Cohort I and III: 9 µg, 28 µg, and 112 µg per day (week 1, week 2, and thereafter, respectively), cohort II: 112 µg per day x 8 weeks</td>
<td>43</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* In published report.
‡ In reported abstract. Abbreviations: ALL, acute lymphocytic leukaemia; B-NHL, B-cell non-Hodgkin lymphoma; CR, complete response; DLBCL, diffuse large-B-cell lymphoma; FL, follicular lymphoma; i.v., intravenous; MCL, mantle-cell lymphoma; MRD, minimal residual disease; NR, not applicable or available; ORR, overall response rate; PR, partial response; SD, stable disease.
Summary

- Checkpoint-Inhibitors are immune-modulators: pre-existing anti-tumor T cells are necessary
- The immune system as therapeutic partner opens new ways to fight cancer
- Checkpoint-Inhibitors become (are) mainstays of therapeutic approaches
- Checkpoint-Inhibitors so far have not lead to cure!
- Checkpoint-Inhibitors will be integrated into combination therapies
- Large proportion of patients have no immune system capable to recognize and destroy cancer
- CAR T cells are one option:
  - CAR T anti-CD19 low-hanging fruit, since we can life without B cells
  - CAR T anti-other surface proteins: dangerous! Will take long time to develop
- CAR T in ALL bridge to allo-transplant
- BITE another option
Swiss Tumor Immunology Institute

• Network for physicians and patients
• Focus on the use of immunotherapy and its challenges
• Registry for quality control
• Supported by industry and private donations
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