new drugs for lymphoma: Immune system and implementation

Prof. Dr. Martin Dreyling
Department of Medicine III
LMU Munich
Immunotherapy in hematology (lymphoma)

- Targeting the immune system:
  - car-T
  - bispecific antibodies
  - checkpoint modifier
Immunotherapies in lymphoma
Redirecting the T Cells

- transduction systems to get CARs into T cells:
  - Retroviral transduction
  - Lentiviral transduction
  - non viral transduction (sleeping beauty)

*Courtesy of C. Bollard*
Adoptive Immunotherapy in the clinics

1. **Leukapheresis:**
   Patient’s T cells are harvested\(^1\)\(^-\)\(^3\)

2. **T cells are activated**
   on antibody-coated beads, and genetically transduced *ex vivo* with a construct encoding for the anti-CD19 CAR\(^1\)-\(^3\)

3. **CTL019 cells undergo *ex vivo* expansion** on antibody-coated beads\(^1\)-\(^3\)

4. **Chemotherapy:**
   Patient receives a preparative lymphodepleting regimen before T-cell infusion\(^1\)-\(^3\)

5. **CTL019 cells are reinfused** into the patient\(^1\)-\(^3\)

---

\(^a\) Cellular reprogramming and *ex vivo* expansion are conducted at a cell processing facility.

Incomplete activation of 1\textsuperscript{st} generation CAR-T cells

- Incomplete activation of T cells

- Killing of tumor cells

Improved T cell activation and proliferation

- 2\textsuperscript{nd} gen CAR

- Improved T cell activation and proliferation

- CD28

- B7
CD19 CARs in clinical trials

MSKCC-28ζ CAR

Juno
MSKCC

Kite
NCI

Bluebird bio
Baylor

SJRH-4-1BBζ CAR
Imai et al. Leukemia 2004

CHOP/UP

FHCRC

Novartis

Juno
Patient 2 → Chemotherapy-refractory triple-hit DLBCL
Resolution of a large malignant pleural effusion and lymphoma masses – Duration of PR = 9 months
Impressive response of DLBCL two weeks after infusion of $10^7$ CAR T-cells/kg in a patient with lymphoma that persisted after allogeneic stem cell transplant.

Courtesy of Kochenderfer
**ZUMA-1: Phase 2 CONSORT Diagram**

- **Enrolled & Leukapheresed (n=111)**
- **Conditioning Cy 500 mg/m² Flu 30mg/m² × 3 days**
- **KTE-C19 2 × 10⁶/kg (n=101)**

- **Not treated:**
  - n=5 SAE
  - n=1 Product unavailable
  - n=2 Non-measurable disease

- **22 sites enrolled; 99% manufacturing success rate**
- **91% of enrolled patients dosed**
- **17 day average turnaround time from apheresis to delivery to clinical site**

- **1 month follow-up (n=93 DLBCL, TFL, PMBCL)**
- **≥3 month follow-up (n=51 DLBCL*, n=11 TFL/PMBCL)**

*Pre-specified interim analysis; data cutoff: Aug 24, 2016

- Neelapu, ASH 2016: LBA#6
## ZUMA-1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DLBCL (n=73)</th>
<th>TFL/PMBCL (n=20)</th>
<th>All Patients (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>59 (25-76)</td>
<td>58 (28-76)</td>
<td>59 (25-76)</td>
</tr>
<tr>
<td>Age ≥60 years, n (%)</td>
<td>36 (49)</td>
<td>9 (45)</td>
<td>45 (48)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>47 (64)</td>
<td>15 (75)</td>
<td>62 (67)</td>
</tr>
<tr>
<td><strong>ECOG performance status 1, n (%)</strong></td>
<td>48 (66)</td>
<td>8 (40)</td>
<td>56 (60)</td>
</tr>
<tr>
<td><strong>Median number of prior therapies (#)</strong></td>
<td>3 (1-7)</td>
<td>4 (2-12)</td>
<td>3 (1-12)</td>
</tr>
<tr>
<td><strong>IPI 3-4, n (%)</strong></td>
<td>32 (44)</td>
<td>9 (45)</td>
<td>41 (44)</td>
</tr>
<tr>
<td><strong>Disease stage III/IV, n (%)</strong></td>
<td>64 (88)</td>
<td>15 (75)</td>
<td>79 (85)</td>
</tr>
<tr>
<td><strong>Refractory subgroup, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory to 2(^{nd}) or later-line therapy</td>
<td>56 (77)</td>
<td>16 (80)</td>
<td>72 (77)</td>
</tr>
<tr>
<td>Relapse post-ASCT</td>
<td>15 (21)</td>
<td>4 (20)</td>
<td>19 (20)</td>
</tr>
</tbody>
</table>

*Neelapu, ASH 2016: LBA#6*
### ZUMA-1 Primary Endpoint ORR

*(Interim Analysis; p<0.0001)*

Best Overall Response in Patients with ≥3 Month Follow-up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>51</td>
<td>76%*</td>
<td>47%</td>
</tr>
<tr>
<td>TFL / PMBCL</td>
<td>11</td>
<td>91%</td>
<td>73%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>62</td>
<td>79%</td>
<td>52%</td>
</tr>
</tbody>
</table>

*P<0.0001 (exact binomial test comparing observed ORR to a historical control of 20%)

- At month 3 assessment the CR rate was 39%
- 7 patients with SD/PR at 1 mo converted to CR at 3 mo
- Complete Response in key subgroups:
  - 75% (n=9/12) CR relapsed post-ASCT
  - 47% (n=23/49) CR refractory to ≥2nd line

*Neelapu, ASH 2016: LBA#6*
# ZUMA-1 Pivotal Results

## Earlier KTE-C19 Outcomes in Aggressive NHL

<table>
<thead>
<tr>
<th></th>
<th>NCI Dose Finding (n=9)</th>
<th>NCI Kite Regimen (n=19)</th>
<th>ZUMA-1 Phase 1 ≥12 mo f/u (n= 7)</th>
<th>ZUMA-1 Phase 2 ≥3 mo f/u (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best CR, %</strong></td>
<td>56</td>
<td>47</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td><strong>3-Month CR, %</strong></td>
<td>56</td>
<td>47</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td><strong>6-Month CR, %</strong></td>
<td>56</td>
<td>47</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td><strong>9-Month CR, %</strong></td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>12-Month CR, %</strong></td>
<td>44% ongoing (31+ to 47+ mo)</td>
<td>47% ongoing (at 7+ to 24+ mo)</td>
<td>43% ongoing at 12+ months</td>
<td>Follow-up Ongoing</td>
</tr>
</tbody>
</table>

*Neelapu, ASH 2016: LBA#6*
CD19 CAR T-cells: Toxicities
No Pain No Gain??

- Toxicities resolve within 3 weeks
- included fever, hypotension, elevated creatinine, and neurological toxicity.
- Patients can require vasopressors and mechanical ventilation.
- Neurotoxicities include: aphasia, confusion, cranial nerve paresis, tremor, generalized myoclonus, seizures, death
- Cardiac events – not always in patients with pre existing cardiac history

Courtesy of C. Bollard
Immunotherapy in hematology (lymphoma)

- Targeting the immune system:
  - car-T
  - bispecific antibodies
  - checkpoint modifier
Blinatumomab (MT103), a Bispecific T Cell Engaging Single-chain BiTE® Antibody

Löffler, Blood, 2000
Mack, PNAS, 1995
Administration of blinatumomab

cIV administration via pump
• Inpatient & ambulatory; 24/7 for 4 weeks, 2 weeks off

Administration in inpatient and ambulatory home settings

Minimum of:
• Days 1–9, cycle 1
• Days 1–2, cycle 2

• cIV bag changes every 2 days* by home healthcare service or ambulatory setting*

*Based on US prescribing information
Safety profile – cytokine release

Incidence of cytokine release syndrome (Grade 3/4)

- MRD+ ALL
- r/r ALL
- B-NHL
- CAR-T-Cells in ALL

* Grading not indicated in publication,

Study Nr. 202 203 206 211 205 104 208 MSKCC UPenn NCI
MRD+ ALL 6% 13% 22% 23% 27%* 30%*
r/r ALL 202 203 206 211 205 104 208 MSKCC UPenn NCI
B-NHL 22% 23% 27%* 30%*
CAR-T-Cells in ALL

* Grading not indicated in publication,

# Safety profile – CNS Toxicity

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Any Grade\n(n=23)</th>
<th>Grade 3\n(n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All neurological AEs</td>
<td>16 (70)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Tremor</td>
<td>11 (48)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>4 (17)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (13)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>3 (13)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>2 (9)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>2 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Grade 2 CNS toxicity**

- Tremor
- Speech disorder
- Dizziness
- Encephalopathy
- Aphasia
- Paresthesia
- Somnolence
- Disorientation

**Grade 3 CNS toxicity**

- All neurological AEs
- Tremor
- Speech disorder
- Encephalopathy
- Disorientation
Clinical activity of blinatumomab in patients with relapsed/refractory B-Non-Hodgkin Lymphoma

Baseline

Bone marrow biopsy
Small lymphocytic lymphoma

After Treatment

MT103 15 µg/m²/24 h
Treatment

Liver biopsy
Mantle cell lymphoma

MT103 60 µg/m²/24 h
Treatment

CD20 post therapy

Bargou, Science, 2008
Response in Bulky Disease: MCL

- Patient with MCL stage IVA; 42y, male
- Blinatumomab treatment: 5 → 60 µg/m²/d
Efficacy (RR) in Indolent and Aggressive NHL at 60 μg/m²/d

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>CR + CRu n (%)</th>
<th>PR n (%)</th>
<th>ORR n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>13/35</td>
<td>11/35</td>
<td>24/35 (69)</td>
</tr>
<tr>
<td>FL</td>
<td>6/15</td>
<td>6/15</td>
<td>12/15 (80)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>4/11</td>
<td>2/11</td>
<td>6/11 (55)</td>
</tr>
<tr>
<td>MCL</td>
<td>3/7</td>
<td>2/7</td>
<td>5/7 (71)</td>
</tr>
<tr>
<td>Other (MZL, LPL)</td>
<td>0/2</td>
<td>1/2</td>
<td>1/2 (50)</td>
</tr>
</tbody>
</table>

Actually Exposed to 60 μg/m²/d – N = 35

Göbeler, JCO 2016
Phase I Trial: long term remission in patients with relapsed non-Hodgkin lymphoma

Duration of Response (Days)

highest dose level
60 μg/m²/day
# Comparison CARs versus BiTEs

<table>
<thead>
<tr>
<th></th>
<th>CD19-CAR T-cells</th>
<th>Blinatumomab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy in lymphoma</strong></td>
<td>Response rate &gt; 50% (DLBCL)</td>
<td>Response rate 35–55% (DLBCL)</td>
</tr>
<tr>
<td><strong>Duration of effects</strong></td>
<td>Stable transfection over months</td>
<td>Short half-life (~2 hours)</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Needs preparation Feasible in 90% (^1)</td>
<td>Immediately available</td>
</tr>
<tr>
<td><strong>Lymphodepleting chemotherapy</strong></td>
<td>Necessary (Fludarabine +/- Cyclophosphamide)</td>
<td>Not necessary</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Neurotoxicity Grade 3 &gt;20% (?) Cytokine release syndrome</td>
<td>Neurotoxicity Grade 3 &gt;20% Discontinuation and restart!</td>
</tr>
</tbody>
</table>

\(^1\) Lee, Lancet 2015
Precious materials

Ranking list of „Business insider“, September 2014

1. Antimatter
   1g = 60 Trillions $

2. Californium 252
   1g = 30.000.000€

3. Rhino horn
   1g = 110€

4. Diamonds
   1g = 50.000€

5. Gold
   1g = 34 €

6. Plutonium
   1g = 4000€

7. Eculizumab
   1g = 20.000€

(sufficient for >500 patients)
**Follicular lymphoma: Clinical characteristics**

- about 25% of lymphoma
- Median age 60-65 years
- 85% advanced stage III/IV
- Indolent clinical course (median survival 15-20 years)
- In relapse still sensitive to therapy
Early progression of disease (POD)

Overall survival (OS) [months]

Survival probability

Early POD
19% of patients

No early POD

Casulo, JCO 2015
Prognosis of FL patients is depending on

- Clinical features (FLIPI, FLIPI-2)
- Gene mutations (m7-FLIPI)
- Cells of the microenvironment
- Time of first relapse (< or > two years)
- Radiological criteria (PET)

In contrast, treatment decision is currently based on

- Histological grading
- Clinical staging
- Tumor burden

→ Subgroups of patients may need different treatment approaches
Chemotherapy-free treatment for follicular lymphoma: „The debate of the decade“

• Cheson BD: CLL and NHL: the end of chemotherapy? *Blood* 2014

• Bachy E: Are we nearing an era of chemotherapy-free management of indolent lymphoma? *Clin Cancer Res* 2014


• Cheah CY: Chemotherapy-free treatment of follicular lymphoma: we have the ingredients, now for some recipes. *Oncology* 2015


• ........

....not yet, but soon....
Aim of targeted therapies

• they should be more effective especially in patients with poor prognosis

• they should be less toxic in patients with favorable outcome
**S1608: Randomized phase II trial in early progressing or refractory FL**

**FL progressing within 2 years or refractory to bendamustine based therapy; mandatory tissue**

- **TGR-1202** + Obinutuzumab
  - N = 45

- **Lenalidomide** + Obinutuzumab
  - N = 45

- **CHOP** + Obinutuzumab
  - N = 45

ASCT allowed as consolidation per investigator choice

Primary clinical objective: CR by PET/CT

Primary translational objective: Validation of m7-FLIPI
Double refractory FL
PI3Kδ inhibition

Gopal, NEJM 2014
## Class I PI3K isoforms

<table>
<thead>
<tr>
<th>Class I PI3K isoform</th>
<th>Cellular expression</th>
<th>Primary physiological role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha (α)</td>
<td>Broad</td>
<td>• Insulin signaling and angiogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resistance mechanism in lymphoma</td>
</tr>
<tr>
<td>Beta (β)</td>
<td>Broad</td>
<td>• Platelet function</td>
</tr>
<tr>
<td>Gamma (γ)</td>
<td>Leukocytes</td>
<td>• Neutrophil and T-cell function</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Leukocytes</td>
<td>• B-cell signaling, development, and survival</td>
</tr>
</tbody>
</table>

Okkenhaug, Nat Rev Immunol 2003; Seiler, Drugs 2016; Iyengar Blood 2013

Dreyling, ICML 2017
Copanlisib
Safety profile

<table>
<thead>
<tr>
<th>Common treatment-related AEs, n (%)</th>
<th>Total (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Any treatment-related AE</td>
<td>126 (88.7%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>69 (48.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (28.9%)</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>35 (24.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (18.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (15.5%)</td>
</tr>
<tr>
<td>Lung infection</td>
<td>20 (14.1%)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>19 (13.4%)</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>17 (12.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12.0%)</td>
</tr>
<tr>
<td>Laboratory toxicities</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>39 (27.7%)</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>32 (22.7%)</td>
</tr>
<tr>
<td>Treatment-related AEs of special interest</td>
<td>10 (7.0%)</td>
</tr>
<tr>
<td>Pneumonitis (non-infectious)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Colitis</td>
<td></td>
</tr>
</tbody>
</table>

- 2 patients (1.4%) had grade 3 pneumonitis and 1 patient (0.7%) had grade 4 colitis
- 3 deaths (2.1%) were drug-related: lung infection, respiratory failure, and a thromboembolic event (0.7%)
Copanlisib
Best response (target lesions)

Best change in target lesion size from baseline (%)

Individual patients (n=125)

Dreyling, ICML 2017
Copanlisib
Survival rates

Progression-free survival

- Median PFS: 11.2 months (95% CI 8.1-24.2)
- FL: 11.2 months (95% CI 7.8-24.2)

Overall survival

- Median OS not yet reached

Dreyling, ICML 2017
Copanlisib
Gene expression profiling

**PI3K / BCR pathway gene expression**: low

**PI3K / BCR pathway gene expression**: high

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Best response:</th>
<th>PI3K pathway gene expression</th>
<th>BCR pathway gene expression</th>
<th>Macrophage gene expression signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR(*) / PR</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>SD / PD / NE</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

- PI3K and BCR pathway gene expression levels were associated with response ($p = 0.009-0.035$; $n=71$)

Dreyling, ICML 2017
Conclusions

- The favorable risk–benefit profile supports the use of copanlisib in relapsed or refractory indolent lymphoma

- The safety profile for copanlisib was manageable and distinct compared oral PI3K inhibitors, possibly due to the intermittent schedule and i.v. route of administration

- Current Phase III studies investigate copanlisib in combination with rituximab (NCT02367040) and R-CHOP / rituximab + bendamustine (NCT02626455)
TAZEMETOSTAT FOR THE TREATMENT OF B-CELL NHL

- EZH2 is an epigenetic regulator of gene expression and plays a critical role in multiple forms of cancer
  - Activating mutations of EZH2 can act as an oncogenic driver for cancers, especially in FL and GCB-DLBCL, present in ~20% of patients

- Tazemetostat
  - First-in-class, potent and selective oral inhibitor of mutated and wild-type EZH2
  - Preclinical activity in DLBCL cells lines, with greater activity in EZH2 mutant models
  - Monotherapy activity and favorable safety in phase 1 studies in patients with relapsed or refractory (R/R) NHL, as well as certain genetically defined solid tumors

Morschhauser, ICML 2017
### Toxicity of Tazemetostat

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event</th>
<th>All TEAEs</th>
<th>Patients (n=210) with:</th>
<th>Treatment-Related TEAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
<td>All Grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (20%)</td>
<td>1 (&lt;1%)</td>
<td>29 (14%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39 (19%)</td>
<td>19 (9%)</td>
<td>28 (13%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>33 (16%)</td>
<td>16 (8%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Cough</td>
<td>30 (14%)</td>
<td>1 (&lt;1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26 (12%)</td>
<td>5 (2%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>24 (11%)</td>
<td>1 (&lt;1%)</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22 (10%)</td>
<td>3 (1%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21 (10%)</td>
<td>15 (7%)</td>
<td>19 (9%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 (10%)</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (10%)</td>
<td>2 (1%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>14 (7%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>13 (6%)</td>
<td>1 (&lt;1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (6%)</td>
<td>0</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 (6%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (6%)</td>
<td>3 (1%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (6%)</td>
<td>0</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (6%)</td>
<td>0</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (5%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>11 (5%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10 (5%)</td>
<td>0</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>10 (5%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>
TUMOR REDUCTION IN FOLLICULAR LYMPHOMA

75% of patients experienced reduction of tumor burden

Percent Change from Baseline

FL EZH2 Mutant
FL EZH2 Wild-type
Remains On Study
**EZH2-blockade: Tazemetostat in relapsed DLBCL/FL**

**Response rates**

Phase II, n=165 (FL: 29), median of three previous therapies

<table>
<thead>
<tr>
<th></th>
<th>DLBCL</th>
<th></th>
<th>FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZH2 mut</td>
<td>40%</td>
<td>EZH2 wt</td>
<td>18%</td>
</tr>
<tr>
<td>n=10</td>
<td></td>
<td>n=85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EZH2 mut</td>
<td>EZH2 wt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>63%</td>
<td>n=8</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=46</td>
<td></td>
</tr>
</tbody>
</table>

Grade 3 AE: 18%
AE >10%, all grade: nausea, thrombocytopenia, cough, diarrhea, fatigue, asthenia
A novel clinicogenetic risk algorithm

(\url{http://www.glsg.de/m7-flipi/})

Pastore, Lancet Oncology 2015
What could be the next step in first-line therapy?

Follicular lymphoma

„Aggressive FL“ (20%)  
need to be identified

„Indolent FL“ (80%)

Imunochemotherapy alone not sufficient  
Greatest need for novel approaches

Patients benefit from immunochemotherapy  
Some patients are overtreated?

new therapies have to
• identify biomarkers
• define targets
• enable tailored therapy (+/- chemotherapy)

new therapies have to
• reduce toxicity (early – late)
• maintain/increase efficacy
• be economically acceptable
Acknowledgements