CD19 ADCs Effectively Targeting B Cell Malignancies – a clinical perspective.

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• **Research Funding**
  ONO Pharmaceuticals, Gilead

• **Consultancy**
  Roche
  MorphoSys
  Servier
  ADC Biotech
its closer to space than it is to the sea*

*according to facebook user Daniel Lettin

How can we use antibodies rationally for tumour-specific therapy?

Mabs with improved effector functions

Antibody drug conjugates / Bispecific Abs / Monovalent Abs / Ab fragments etc etc
Antibody Therapy for Diphtheria 1900’s.

The Nobel Prize in Physiology or Medicine 1901 "for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths"
The many different shades of B-cell malignancy.
A very “busy therapeutic area”. (Not “real cancers”)

Nearly all B-cell malignancies express CD19 and CD20

Cure 85% of childhood ALL
Adult disease problematic

BTKi

B-ALL
* BCR-ABL1 translocation
  Mutations in RUNX1, PBX1, MLL, PTPN11 and/or RAS
Efficacy of R-CHOP in DLBCL OS: Transformed vs. 10

How do we identify prospectively those patients destined to relapse early? How can we treat them more effectively?

Usually highly aggressive malignancies with short doubling times. Genetically very heterogeneous. ANY role of chemotherapy for some of these malignancies??

Single agent unlikely to have marked efficacy in most patients. Cf marked efficacy of Brentuximab in classical Hodgkin lymphoma.

KEY POINTS
- Since rituximab-based chemotherapy, DLBCL patients without relapse after 2 years from diagnosis have an outcome comparable to healthy individuals. A total of 20% of the patients at diagnosis will, however, present a primary refractory disease (i.e., relapsing within a year or not responding to first-line strategy). These patients represent an unmet medical need.
- The bad prognostic value of ABC subtype is conserved at relapse. Indeed, nongerminal center patients (according to Hans algorithm) respond poorly to salvage and notably to R-DHAP regimen. As well, MYC rearrangement observed in FISH analysis also impacts PFS and OS of these relapse and refractory patients.
- Disease status and a low number of salvage regimens at the time of transplant are important prognostic markers and nonresponding patients to second-line strategy have a very poor OS (4 months in retrospective analysis). Nevertheless, late-responding patients (i.e., after more than two salvages) might still benefit from an intensification followed by ASCT. Therefore, ASCT remains recommended for primary refractory patients, only if they reach a good response assessed by PET-CT scan before transplant.
- If ASCT is an option for chemo-sensitive patients, the majority of primary refractory patients will not respond to salvage and new therapeutic options are warranted. Recent progress allowed the development of targeted therapies and associations with immuno-chemotherapy are now evaluated. Ibrutinib, a BTK inhibitor, has shown to improve the efficacy of R-CHOP with an acceptable tolerability profile.
Chronic lymphocytic leukaemia as a good therapeutic “model”.

Relatively indolent disease. High white cell count in peripheral blood allows rapid assessment of efficacy.
$^{111}$Indium-Zevalin imaging demonstrates tumour penetration but only after 48h.
CD20 – a good therapeutic target for B-cell malignancies?

Function?

Not mutated or deregulated as a consequence of malignancy

Low level expression in some diseases (CD20negative CLL)

Modulates/internalises/exosomes

?type 2 CD20 Mabs better – induce direct cell death

Little efficacy of rituximab or obinutuzumab as single agent

Would CD20 be developed as a therapeutic in 2016?
The role of gender and weight on rituximab clearance and serum elimination half life in elderly patients with DLBCL

Carsten Müller, Niels Murawski, Martin H. J. Wiesen, Gerhard Held, Viola Poeschel, Samira Zeynalova, Michael Wenger, Christina Nickenig, Norma Peter, Eva Lengfelder, Bernd Metzner, Tanja Rixecker, Carsten Zwick, Michael Pfreundschuh and Marcel Reiser
MDACC Phase II FC-R – why don’t we add rituximab to our best chemotherapy?

NO effect of adding in CD23 Mab to FC-R
Possible mechanisms of action of CD20 Mabs in B-cell malignancies.

- ADCC – but which are the crucial effector populations? Can these be enhanced/activated?
- NOT CDC – although complement activation is necessary.
- Direct induction of cell death? Lysosomal cell death/apoptosis (does this occur in vivo?)
- Down-regulation of key anti-apoptotic molecules (eg BCL2) resulting in chemosensitization?
- Non-specific immune stimulatory response as with IVIG?
- Induction of a specific anti-tumor immune response?
- Other considerations
  - Does CD20 modulate/internalize in some cases of DLBCL?
  - Role of FcRγ polymorphisms
  - Role of CD20 containing exosomes

REAL-TIME PK MONITORING OF SERUM LEVELS MANDATORY FOR THE RATIONAL USE OF RITUXIMAB??
CD19 as a therapeutic target

- CD19 molecule is a 95kDa cell-surface protein of human B lymphocytes with two extracellular Ig-like domains and a 240 amino acid cytoplasmic tail
- Very early use as a naked Mab and then as a B4 Mab Ricin toxin conjugate
- Fc optimised “naked” Mab now in clinical trials
- Several different ADCs
  - Target for CAR-T cells in CLL/DLBCL/BCP-ALL
  - Bispecific antibodies and antibody constructs
CD19-directed CAR-T cells have amazing efficacy in some instances.
**Potent In vitro and In vivo Activity of an Fc-Engineered Anti-CD19 Monoclonal Antibody against Lymphoma and Leukemia**

**Raji cell line**
- Doesn’t internalise

**SU-DHL-6 cell line**
- Directly induces apoptosis
- Induction of cell cycle arrest

**Activity in SCID mouse xenograft model**

The investigator-assessed ORR across all NHL subtypes was 22% (20/89) with clinical activity seen in:
- DLBCL (26% [9/35]; 2 CR, 7 PR; median duration of response [mDoR] 7.7 months),
- FL (23% [7/31]; 1 CR, 6 PR; mDoR 2.6 months),
- iNHL (36% [4/11]; 1 CR, 3 PR) cohorts (MCL, 0/12 responses).

**ICML meeting June 2015**

*A PHASE II A STUDY OF SINGLE-AGENT MOR208, AN FC-OPTIMIZED ANTI-CD19 ANTIBODY, IN PATIENTS WITH RELAPSED OR REFRACTORY B-CELL NON-HODGKIN’S LYMPHOMA*
Does CD19 internalise in presence of bivalent Mab?

High CD21 expression inhibits internalization of anti-CD19 antibodies and cytotoxicity of an anti-CD19-drug conjugate

VARIABLE internalisation of CD19 Mabs
Not limited to one specific Mab
Correlation with CD21 (complement receptor) expression
– cell lines with high level CD21 do not internalise rapidly whereas cells with no CD21 do

Table 1. Characteristics of cell lines used in this study (shown in order of increasing CD21 expression).

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Cell type</th>
<th>EBV</th>
<th>CD21</th>
<th>CD19</th>
<th>CD20</th>
<th>CD22</th>
<th>CD79</th>
<th>CD77</th>
<th>CD19 uptake</th>
<th>Naked effect</th>
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<tr>
<td>SuDHLL-4</td>
<td>Diffuse large B-cell lymphoma</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Ramos</td>
<td>American Burkitt lymphoma</td>
<td></td>
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<tr>
<td>DoHH1-2</td>
<td>Follicular lymphoma</td>
<td></td>
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<tr>
<td>Namalwa</td>
<td>African Burkitt lymphoma</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td></td>
<td>+</td>
<td>++</td>
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<tr>
<td>Daudi</td>
<td>African Burkitt lymphoma</td>
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<td>-</td>
<td>+</td>
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<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Ramos-CD21 clone 3</td>
<td>American Burkitt lymphoma +CD21&lt;sup&gt;mod&lt;/sup&gt;</td>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>++</td>
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<tr>
<td>ARH77</td>
<td>Plasma Cell leukemia</td>
<td></td>
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<tr>
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<td>African Burkitt lymphoma</td>
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<td>+</td>
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<td>+</td>
<td>++</td>
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<tr>
<td>Ramos-CD21 Clone 1</td>
<td>American Burkitt lymphoma +CD21&lt;sup&gt;hi&lt;/sup&gt;</td>
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CD19 ADCs SAR-3419 - Coltuximab ravtansine

Design of Coltuximab Ravtansine, a CD19-Targeting Antibody–Drug Conjugate (ADC) for the Treatment of B-Cell Malignancies: Structure–Activity Relationships and Preclinical Evaluation

E. Erica Hong, Hans Erickson, Robert J. Lutz, Kathleen R. Whiteman, Gregory Jones, Yelena Kovtun, Veronique Blanc, and John M. Lambert

1ImmunoGen, Inc., 830 Winter Street, Waltham, Massachusetts 02451, United States
2Sanofi, 13 quai Jules Guesde, Vitry sur Seine, 94403 France

<table>
<thead>
<tr>
<th>ADC</th>
<th>Dose (mg/kg)</th>
<th>T-C</th>
<th>Log10 Cell Kill</th>
<th>Complete Regression</th>
<th>Tumor-free Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAR3419</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>6/6</td>
<td>6/6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>82</td>
<td>6.8</td>
<td>6/6</td>
<td>5/6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>50</td>
<td>4.2</td>
<td>6/6</td>
<td>0/6</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>5</td>
<td>0.4</td>
<td>0/6</td>
<td>0/6</td>
</tr>
</tbody>
</table>
Clinical studies with Coltuximab ravtansine (Sanofi/Immunogen).

**Results:** Forty-four patients were treated on seven dose levels ranging from 5 to 70 mg/m². SAR3419 recommended dose was determined as 55 mg/m² qw. Twenty-five patients received the qw/q2w schedule at 55 mg/m², which showed an improved safety profile compared with the qw schedule. Antilymphoma activity was observed with both schedules in around 30% of patients with either indolent or aggressive diseases. SAR3419 displayed a long terminal half-life (approximately 7 days) and a low clearance (approximately 0.6 L/d), with no dose effect. The qw/q2w schedule allowed limiting accumulation with a decrease in SAR3419 plasma trough and average concentrations by around 1.4-fold compared with the qw schedule.

**Table 2. Related nonhematologic TEAE >10%**

<table>
<thead>
<tr>
<th></th>
<th>Weekly schedule</th>
<th>Optimized schedule</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MTD (N = 21)</td>
<td>All (N = 44)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>6 (28.5%)</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>5 (23.8%)</td>
<td>5 (11.3%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>7 (33.3%)</td>
<td>10 (22.7%)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>5 (23.8%)</td>
<td>6 (13.6%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>5 (23.8%)</td>
<td>12 (27.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (14.3%)</td>
<td>8 (18.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (14.3%)</td>
<td>7 (15.9%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site condition</td>
<td>5 (23.8%)</td>
<td>10 (22.7%)</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>5 (23.8%)</td>
<td>10 (22.7%)</td>
</tr>
</tbody>
</table>
Starlyte phase II study of coltuximab ravtansine (CoR, SAR3419) single agent: Clinical activity and safety in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL; NCT01472887).

- Pts with CD19+ relapsed DLBCL and not candidate for transplantation were eligible.

  **Biopsy was required at baseline.**

- CoR 55 mg/m² was administered weekly for 4 weeks then bi-weekly until disease progression or other study discontinuation criteria. Tumor assessments were done every 12 weeks.

- Results: 41 pts evaluable. Median age 71. 92.7% had ECOG performance status 0-1.

- **The ORR was 43.9% including 5 complete responses (12.2%).**

- Peripheral neuropathies were observed in 5 pts, all were gr 1-2. Hematological toxicity was moderate.

- **Conclusions:** CoR as single agent demonstrated significant activity in R/R DLBCL pts and reached its primary endpoint for ORR, with acceptable safety profile.

ImmunoGen is evaluating preclinically coltuximab ravtansine administered with marketed anticancer agents and expects to start clinical testing combination(s) in 2016.
Seattle Genetics CD19 ADCs

Denintuzumab mafodotin (SGN-CD19A) humanized CD19 monoclonal conjugated to (MMAF) via a maleimidocaproyl linker.

182 A Phase 1 Study of Denintuzumab Mafodotin (SGN-CD19A) in Relapsed/Refactory B- Lineage Non-Hodgkin Lymphoma

1328 A Phase 1 Study of Denintuzumab Mafodotin (SGN-CD19A) Plus RICE Versus RICE Alone for Diffuse Large B-Cell Lymphoma

Ocular superficial microcystic keratopathy were observed in 56-84% of pts. Keratopathy was managed with topical steroids and dose modifications, and improved/resolved within a median of ~3 wks.
Polatuzumab vedotin/CD79B ADC in B-NHL

Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study

Lancet Oncol 2015; 16: 704-15

2726 Polatuzumab Vedotin Combined with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) for Patients with Previously Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Preliminary Results of a Phase Ib Dose-Escalation

Significant grade 3 or 4 toxicities in 38% of patients including severe neutropenia and neuropathy.
Conclusions

• B-cell malignancy area is very “busy”.
• Several previously untreatable diseases (eg TP53 mutant CLL) now responding well to combinations of targeted therapies with minimal toxicities.
• Major unmet need is R/R DLBCL.
• Single agent ADC unlikely to have “Brentuximab” type efficacy.
• CD19 extremely well validated target.

**BETTER BIOLOGY! Expression does not equate with sensitivity!**

• Preclinical evaluation of ADCs cannot be on cell lines alone
• Xenograft models insufficient
• Necessity for primary cells and/or PDX models - better prediction of responses

• Target antigen epitopes important
Ernest and Helen Scott Haematological Research Institute

**Laboratory work**
- New targets
- MOA - in vitro and in vivo
- Synergistic combinations
- Reverse translation

**Clinical side**
- Phase I first in man studies
- *Investigator lead studies*
- *Clinical research fellows*

**BENCH**

**BEDSIDE**

THANK YOU FOR LISTENING!