Antibody-Based Therapeutics in Cancer

Helen Chen, M.D.
Investigational Drug Branch
Cancer Therapy Evaluation Program (CTEP)
DCTD
OUTLINE

• Basic concepts
  – Immunology of Ab
  – Types of Ab-based therapies

• Naked monoclonal antibody (mAb)
  – Mechanisms of action through Fv and Fc
  – Approaches to optimization

• Novel Ab constructs to expand the “effectors”
  – Redirecting T-cells to cancer cells
  – Redirect drug payloads to cancer (Ab-drug conjugates)
Basic structure of IgG

- **Bivalent monomer:**
  - 2 Heavy Chains:
    - Variable \((V_H)\) + constant \((C_H)\) regions
  - 2 Light chains: \(V_L + C_L\)
  - 4 subclasses:
    - IgG1, 2, 3 and 4

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**Figure 1. Potential anti-CD20 mAb effector mechanisms.**

- **(A) Fc-Fc**
  - R–dependent mechanisms. The Fc arm of anti-CD20 mAb recruits and activates Fc
  - RI/RIIIa (CD16) with a high affinity for IgG
  - Fc-polymorphisms of Fc
  - RI/RIIIa (CD16) with a high affinity for IgG

- **(B) CDC**
  - Complement fixation occurs when C1q, the globular head of C1, binds the Fc portion of 2 IgG molecules, which triggers a series
  - of enzymatic reactions that generate pores in the cell membrane (membrane attack complex) leading to cell lysis.

- **(C) Direct PCD**
  - Induced primarily by type II anti-CD20 mAbs
  - Direct phagocytosis (macrophages).

- **(D) Adaptive cellular immunity.**
  - Anti-CD20 mAbs promote the uptake of tumor antigens by dendritic
  - immune effector cells, including macrophages and NK cells, which in turn eliminate the target cell by release of cytotoxic mediators in ADCC (NK cells and macrophages) or

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**From bloodjournal.hematologylibrary.org**

- Evidence has emerged to suggest a potential role for passive
- Immune effector cells, including macrophages and NK cells, which in turn eliminate the target cell by release of cytotoxic mediators in ADCC (NK cells and macrophages) or

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**Adaptive immunity?**

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**Clinical responses.**

- Complement-dependent cytotoxicity (CDC), and the direct
- Antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis. These include mAb Fc-Fc
- appear to eliminate their targets by engaging in a range of effector
- mAbs work?

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**Antibody induced immunization**

- The relative contribution of each of these mechanisms appears
- to be at least partially dependent on the mouse model and type of
- anti-CD20 mAb used.

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**VH:**

- C1q
- Complement dependent cytotoxicity
- CDC

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**Fc:**

- Binding to host effector cells
- Fc-Fc
- Fv binding site

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**VH:**

- Fv-mediated target binding
- Complement dependent cytotoxicity
- CDC

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**Fc:**

- Fc-Fc dependence on activatory Fc
- Activatory Fc
- R-expressing immune effector cells
- ADCC
Key features of antibodies

• Through Fv, diverse and exquisite specificities against target antigens, or epitopes (Immunoglobulin variable gene rearrangement in B cells and hypermutation)

• Through Fc, ability to engage host immune components to targets (complement, NK cells, macrophages, neutrophils, DC)

• Distinct MOA from cellular immunity
  – Unlike TCR, Abs recognize unprocessed antigens independent of MHC

• Potential as a therapeutic platform:
  – Cell-free protein product
  – Long half-lives (150 KD MW), unlikely to have PK interactions with small molecules
  – Vast repertoire of B-cells with unique Fv regions for targets of interest
  – Modifiable for variable sizes and novel constructs: full IgG, Fab, scFv ….bispecific Ab, drug conjugates
History of monoclonal antibodies (mAb) for therapy

• 1975: First murine MAb from hybridoma (Kohler and Milstein, Nature)

• 1982: Anti-idiotypic mAb against lymphoma (Millar and Maloney)

• 1980’s-90’s: Humanization of murine Abs
  – Recombinant chimeric Ab (’84)
  – CDR grafting → humanized Ab (’86)

• 1998: Fully human Mab:
  – XenoMouse
  – Phage scFv library

• Novel construct: Bispecific; Ab-drug-conjugate …

• 1997 - 2012: > 20 mAbs approved for cancer therapy
## Approved agents and New progress

<table>
<thead>
<tr>
<th>Targets</th>
<th>Approved</th>
<th>New/emerging (a partial list)</th>
</tr>
</thead>
</table>
| • **Tumor or stromal cell growth/survival factors** | *Cetuximab, Panitumumab  
*Trastuzumab, Pertuzumab  
* Bevacizumab, VEGF-TRAP | • Erb3, c-MET, HGF  
• FGF, Angiopoietin |
| • **Tumor Ag** (action through effectors)          | *Rituximab, *Ofatumumab;  
*Alemtuzumab                                                            | • Ch14.18 (anti-GD2) |
| • **Host immunity** (immunemodulator)              | *Ipilimumab                                                             | • PD1/PD-L1; CD40; OX40, 4-1BB  
• CD137, CD25                                                          |
| • **Ab-cytotoxic conjugate**                       | *Ibritumomab (zevalin)  
*Toxitumomab (baxxar);  
*SGN-35                                                                      | • Trastuzumab-DM1  
• CD19, CD22, CD56  
• PSMA, EphA2, Integrin, |
| • **Bispecific mAb**                               | *Catumaxomab (EPCAM xCD3 x FcR)                                         | • Blinatumomab (CD19xCD3 BiTE)  
• EpCAM xCD3 BiTE |

* * indicates experimental use only.
Unlabeled Full IgG Antibody Therapies

» Mechanism of action
» Strategies of optimization
Mechanism of Action of mAbs

Mediated by Fv binding to targets
- **Block target signaling**
  *EGFR, HER2
  *CTLA4
- **Induce program cell death**
  *Rituximab
- **Stimulate target signaling**
  *CD40, OX40 on T cell
  *TRAIL-DR5 on tumor cells

Mediated by Fc binding with innate host immune system
- **ADCC** (Fc-FcR mediated)
  *Rituximab
  *Others (IgG1 mAb against HER2, EGFR)
- **CDC** (Fc-complement)
  *Campath-1H

Adaptive Immunity through FcR on APC?
- *Reported with rituximab and trastuzumab

Not all MOA apply to all mAbs. Relevance to efficacy may differ by the target, the clinical setting and the agent

**Attempts to improve the efficacy of full IgG mAbs**
- **Optimize the Ag-binding site**
- **Enhance the Fc mediated effector functions**
  - Fc modulation
  - Combination with immune cytokines
Optimize the Ag-binding site (Fv) ... for the right epitopes and affinities (1)

Hundreds of unique mAbs can be created against a single target molecule, that recognize different epitopes, with variable affinities ... not all Ab drugs for a target are created equal

The antigen-bindings sites may be selected or optimized for desired features:

- Different mechanisms of antitumor effect:
  * Rituximab → GA101;
  * Trastuzumab → pertuzumab

- Agonist vs. Antagonist
  * CD40 agonist (CP-870,893) - as immunotherapy *
  * CD40 antagonist (CHIR-12.12) - as tumor - targeting agent (e.g. CLL)

- Different affinity or avidity ...
Is higher affinity better?

- Higher affinity has better target engagement and ADCC
- However, too high an affinity is not always desirable
  - Lower penetration in tumor
  - Excessive activation of effector cells (some anti-CD3 mAbs)

Affinity should be optimized for different settings

- solid vs. “liquid” tumors
- Tumor vs. host immune cell targets

Tumor update of anti-HER2 Fv with different affinities in mice

(10^{-7}-10^{-9} were optimal)

Adams et al, Ca Res, 2001
Enhance the host effector cell function (including ADCC)

Is ADCC a MOA of antitumor effects in patients?

- Direct in vivo evidence of ADCC is not available. However, there are indirect evidences:

  - Preclinical:
    • Knockout of FcγR gene in mice or mutation of Ab Fc can reduce antitumor effects of anti-CD20 and anti-HER2 antibodies

  - Clinical:
    • In patients, polymorphism of the host FcR receptor affected activity of rituximab in follicular lymphoma ...
Host Fc Receptor polymorphism and mAb Activity

**FcγRIIIA polymorphism** (4985G>T) with phenylalanine (F) to valine (V) substitution at aa position 158

- **158 V/V** has greater affinity Fc compared to **158 F/F** → greater ADCC in vitro

- **Rituximab in FL:** 158 V/V Predicted better response than F/F
  - 92-100% VS. 53-64%

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**Study 1:** Follicular Lymphoma Patients Receiving Rituximab Monotherapy

- **V/V**: 100% Response, 0% Non-Response
- **F/F**: 67% Response, 33% Non-Response

**Study 2:** Follicular Lymphoma Patients Receiving Rituximab Monotherapy

- **V/V**: 92% Response, 8% Non-Response
- **F/F**: 59% Response, 41% Non-Response


Impact of in FcγRIIIa in mAb Activity

- Conflicting results from other studies:
  - FcγRIIIA 158 V/V not predictive for rituximab in
    - CLL, or
    - rituximab + chemo in NHL
  - In solid tumors: results inconsistent


C225 + CPT-11 (n=69):
FcγRIIa-131H/H and FcγIIIa-158V/V: better PFS than 131R and 158F carriers

C225 alone (n=39):
FcγRIIa-131H and FcγIIIa-158F better than 131R and 158 V

Trastuzumab + taxol (n= 54):
FcγRIIa-131H and FcγIIIa-158V/V better
Factors that may impact the Fc-mediated innate host immunity

**Host factors:**
- FcR polymorphism
- Type of effector cells (PMN, NK, macrophages) and FcRs involved in the interaction

**mAb factors:**
- **Fv:** affinity and epitopes
- **IgG1** vs. **IgG2** … *IgG1 if ADCC is desirable. IgG2 to avoid ADCC (e.g. for host-cell targeting mAbs)*

**Fc chemistry**
- A.A. sequence
- Glycosylation (fucose content)

**Tumor factors:**
- Tumor microenvironment may be suppressive of NK and CTL
- **Access to effector cells**
  - Solid vs. liquid tumors
  - Bulky vs. minimal residual diseases
Improving the features of mAb - Example of anti-CD20 mAbs

Rituximab: a prototype anti-CD20 mAb (chimeric IgG1)

- Fc-FcγR
- ADCC
- CDC
- Ab-induced programmed cell death (PCD)
  - Fv interacts with lipid raft (type I epitope)
- Adaptive immunity?
Evolution of anti-CD20 mAbs

• 2nd generation … humanized mAb
  – Ofatumumab – c/w rituximab:
    • Type I epitope (closer to membrane, slower off rate) → ↑ CDC (10x)
    • Clinical activity:
      – CLL: ORR in refractory CLL (58%, 47%) – FDA approved;
      – FL: 11% in rituximab-refractory tumors

• 3rd generation …Fc modification
  – AME-133v
    • Type I epitope, higher affinity
    • Fc modified (a.a. substitution) → ↑ affinity for 158 F/F; ↑ ADCC (5-7X)
    • Phase I – ORR 5/23 in FL in pts with low-affinity FcR (158 F/F or F/V)

  – GA101
    • Type II epitope → more Programmed Cell Death
    • Fc modified (non-fucosylated)

GA101 Demonstrated Increased Direct Cell Death (DCD) and ADCC

- More direct cell death with GA101 vs rituximab
- ~100-fold higher ADCC than rituximab and ofatumumab

Randomized Phase 2 Trial in Relapsed iNHL
(GAUSS Trial)
- GA101 vs. rituximab in patients had prior rituximab more than 6 months before study (N = 175)

Response at End of Induction (Primary Endpoint)

<table>
<thead>
<tr>
<th>Patients with follicular lymphoma</th>
<th>Rituximab (n = 75)</th>
<th>GA101 (n = 74)</th>
</tr>
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<tbody>
<tr>
<td>Overall response rate (ORR)</td>
<td>20 (26.7%)</td>
<td>33 (44.6%)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>3 (4.0%)</td>
<td>4 (5.4%)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (22.7%)</td>
<td>29 (39.2%)</td>
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- Clinical data with Fc-modified anti-CD20 mAbs were interesting but,
  - Contribution of ADCC effects uncertain
    - both Fv vs. Fc were modified from rituximab
  - No Head to head comparison to rituximab in rituximab naïve patient
- Other Fc-modulated mAbs in development: CD19, HER2 …
Combination of mAbs with cytokines
- Example of chimeric anti-GD2 mAbs (Ch 14.18) in neuroblastoma

**Background:**
- **GD2:** overexpressed in neuroblastoma, melanoma
- **Chimeric anti-GD2 (ch14.18)** produced at NCI in 1989
- **In vitro findings:** ADCC by anti-GD2 mAb was by GM-CSF or IL-2

**Early clinical experience with ch14.18**
- Single agent in advanced disease → modest activity (<10%)
- Combination with GM-CSF → encouraging activity (20-30%)
- Pilot study of ch14.18 +GM-CSF/IL2 in MRD (CCG0935) → feasible

**Hypothesis:** Ch14.18 plus cytokines may be active in NB MRD
- 2001: Phase III trial ANBL0032
  - PI: Alice Yu
  - Children’s Oncology Group
  - Sponsor: CTEP
ANBL0032 – a phase III trial with immunotherapy + Ch14.18 in high risk neuroblastoma

Dx → Induction chemotherapy → ASCT

- No ImmunoRx 13-cis-RA
- 13-cis-RA

Experimental arm: immunotherapy

<table>
<thead>
<tr>
<th>Course 1</th>
<th>Course 2</th>
<th>Course 3</th>
<th>Course 4</th>
<th>Course 5</th>
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<tr>
<td>Ch14.18</td>
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<tr>
<td>GM-CSF</td>
<td>Aldesleukin (IL-2)</td>
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<td>GM-CSF</td>
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<tr>
<td>RA</td>
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PI: Alice Yu
Children’s Oncology Group
Sponsor: CTEP
Ch14.18 + Cytokines Improves Event-free Survival and Overall Survival For High Risk Neuroblastoma

Yu et al, NEJM 2010

Additional development of anti-GD2 mAbs:
• Combination with lenalidomide to enhance effector function
• Ch14.18-IL-2 fusion protein
• Humanized version
Can passive immunotherapy (e.g. Tumor-targeting IgG mAb) induce active immunity?
Can passive immunotherapy induce active immunity?

- **Preclinical data**: anti-CD20 mAb protected mice from tumor challenges *(Abes et al, Blood 20010)*

  - Protection not transferrable via sera. Required CD4 /CD8 cells
  - Protection was specific to CD20+ tumors
  - Protection cannot be achieved by other cytotoxic agents (indicating possible requirement of Fc/FcR interaction rather than just Ag release from cell kill)
Can passive immunotherapy induce active immunity?

- **In patients**, Rituximab induced lymphoma idiotype-specific T cell response (*Hichey et al, Blood 2009*)

ELISpot assay for IFNγ-producing T-cells:
- Id-specific T cells significantly increased after rituximab therapy

- Rituximab capable of inducing active immune responses
- No evidence that this mechanism is necessary or sufficient for efficacy
- However, such a potential mode of action is attractive and should be explored for optimization
OUTLINE

• Basic concepts
  – Immunology of Ab
  – Types of Ab-based therapies

• Unmodified full IgG mAb
  – Mechanisms of action through Fv and Fc;
  – Approaches to optimization

• Novel constructs to expand the “effectors”
  – Redirecting T- cells to cancer cells
  – Redirect drug payloads to cancer (Ab-drug conjugates)
  – … others
Ab-Drug Conjugates (ADCs)

» Many ADCs
» Few successes
» Lessons learned
**Ab-drug Conjugate (ADC) and Critical elements**

**Antigen targets:**
- **Solid tumor:**
  - PSMA
  - MUC1
  - Mesothelin
  - CanAg
  - GPNMB
  - CEA
  - Integrin
  - Cripto-1
  - EphA2
  - Her-2
- **Hem:** CD19, 56, 70, **22, CD30, 33**

**Cytotoxic payload:**
- Calicheamicin
- Maytansine (DM1/4)
- Auristatin (MMAE)
- Toxins

**Linkers:**
- **Hydrazone** – relatively unstable in plasma → premature release of chemo
- **Disulfide**
- **Thioether**
- **Peptide**
- ...

**Elements critical to success:**
- Target Ag expression in tumors vs. normal tissues
- Linker selection
- Intrinsic sensitivity of tumor cells to the chemotherapy
## Activities of ADC

<table>
<thead>
<tr>
<th>Target</th>
<th>Activity</th>
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</table>
| SGN-35 (Brentuximab vedotin) | • **ALCL**: 86% (57% CR)  
• **HD**: 75% (34% CR)  
*ORR was 10-20% with unmodified anti-CD30 mAb |
| Trastuzumab-DM1 (T-DM1) | • **Pts with** HER2+ *(IHC 3+ or FISH+)* breast ca  
• **ORR 37.5%** *(Burris et al, JCO 2011)*  
Phase III for T-DM1 vs. lapatinib + capcitabine  
• Significant improvement in PFS and OS |

*Many ADCs had been in development ....*

- Similar linkers and payload
- Similar to Her2 and CD30, targets are shared by normal tissues … *Unlike CD30, normal tissues with solid tumor targets may be more prone to toxicities* *(Skin, GI)*
- Target expression variable among patients …. *Unlike T-DM1, reliable assays not always available to select tumors with overexpression*

*Proper target and/or patient selection are essential to success with ADC*
Re-directing T cells through mAb engineering

Examples:

» T-body (Chimeric Ag Receptor, or CAR)

» Bispecific Mab - Tumor Ag binding + CD3 binding
Chimeric Ag Receptor (CAR) – Replacing the TCR variable region with scFv

Engineered TCR for CAR → T-cell transduction

- scFv (to tumor Ag)
- T-cell costimulatory molecule (CD28, CD3ζ or CD137)

Adoptive transfer of CAR modified T cells

- Transduction
- Expansion
- Enrich transgene-expressing T cells
- PBMC collection
- Infusion
- Lymphodepletion conditioning therapy

Clinical trials to date
- FBP (folic acid R); CEA (GI); CAIX (RCC)...
- EGFRvIII
- CD19; CD20
- HER2
- others

Gene transcription

Combing the diversity of mAb with potency of T cells

Turtle et al, Cur Opinion in Immunol 2012

1st generation: scFv + TCR signaling domain
2nd generation: scFV + CD28
3rd generation: scFv + CD3ζ + CD28 or CD137 (4-1BB)
Clinical Experience: CD19 CAR

(Porter et al, NEJM 2011)

- **Construct**: Anti-CD19 scFv + CD3-CD137 modified T cells
- **Rx**: nonablative myelosuppression → adoptive T cell transfer (1 x 10^5 CD19 CAR cells)
- **Patient**: w/ refractory CLL, received low dose

**Outcome**: Significant CD19-CAR T cell expansion around D10; Persistent after 6 months

- Cytokine release (IFN-γ, CXCL9/10, IL6)
- Tumor lysis syndrome
- Complete remission by D28

(Kochenderfer et al, Blood 2011)

- Similar results from NCI using (scFv-CD3-CD28):
  - 5 PR, 1CR (7-15+m) in 8 pts
Clinical Experience: HER2 CAR

Case report: (Morgan et al, Mol Therapeutics 2010)

HER2-CAR (ERB2 scFv + CD3-CD28-137) – modified T cell transfer in a patient with HER2+ colon cancer with lung and liver metastases

- Respiratory distress, cytokine storm 15 minutes after infusion. Died from multi-organ failure in 5 days

- Autopsy:
  - Lung alveolar damage; microangiopathy
  - CAR cell infiltrates mainly in LN and lungs
    - No differential distribution to tumor metastases (HER2 3+)
    - Low level of normal tissue (including lung) expression of HER2

- The construct is highly specific and potent in activating T cells upon Ag recognition

- Low level of target expression in the lung appeared to make lungs the “first-pass” organ after HER2 CAR
Re-directing T cells by Ab specificity

» T-body (Chimeric Ag Receptor, or CAR)

» Bispecific Mab - *Tumor Ag binding + CD3 binding*
  - Many attempts
  - EPCAM x CD3 x (FcR) – *Trifunctional Catumaxomab* – approved for malignant ascites for patients with ovarian cancer
  - CD19 x CD3 (CD19 BiTE) - *Blinatumomab*
Blinatumomab (MT103), a **Bispecific T-Cell Engaging (BiTE®)** Antibody

(A) Anti-CD19 Antibody

![Diagram](image)

**Construct (Tandem scFv):**
- Linking the VH-VL of a murine anti-19 mAb with an anti-CD3 mAb
- MW (55kD) – short half-life (2-3 hrs)

**Kinetic Constants:**
- $K_d_{CD19} = 1.49 \times 10^{-9} \text{M}$
- $K_d_{CD3} = 2.60 \times 10^{-7} \text{M}$
Blinatumomab (AMG-103) - MOA

- **MOA**
  - **Signaling**
    - **B Lymphoma Cell**
    - **Cytotoxic T Cell**
    - **CD19**
    - **CD3**
    - **CD69**
    - **CD25**
  - **Apoptotic Cell Death**
- **T cell Proliferation**
  - **Formation of cytotoxic T-cell synapses with tumor cell**
  - **Tumor and B cell lysis**
  - **T-cell proliferation and activation in situ**

- **Synapses**
  - **Granzyme**
  - **Perforin**

- **Redirected Cell Lysis**

- **MHC independent, polyclonal activation of T cells, but only upon presence of target Ag**
- **Bypass typical T-cell immune suppressive mechanisms**
- **Does not require costimulatory molecules**
CD19 BiTE induced T-cell proliferation and maturation in patients

PBL from patients with ALL MRD treated with MT103

A

![Cell Count (10^3/µL) over Time (days) for CD4+ T cells, CD8+ T cells, and B cells](chart_A.png)

- **CD4+**
- **CD8+**
- **B cells**

B

![Cell Count (10^3/µL) over Time (days) for Naive CD8+ T cells, CD8+ TCM cells, CD8+ TEM cells, and CD8+ TEMRA cells](chart_B.png)

- **CD8+ TEM**

**Effector memory T cell (TEM)**

**Central memory T cells (TCM)**

Topp et al JCO 211
**CD19 BiTE activity in B-cell ALL**

- **MRD:** Phase 2 in adult with MRD after chemotherapy *(Topp et al JCO 2011; Topp et al, Blood 2012)*

  15 µg/m²/d continuous infusion - 4 wks on / 2 wk off (*3 cycles after CR*)

<table>
<thead>
<tr>
<th>Molecular CR</th>
<th>Relapse free survival</th>
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<tbody>
<tr>
<td>16/20 (80%)</td>
<td>61% at 33 m</td>
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</table>

- **Relapsed/refractory diseases:** Phase 2 in adult ALL *(Topp et al ASCO 2012)*

  Step-up dosing schedule 5 → 15 µg/m²/d

<table>
<thead>
<tr>
<th>CR</th>
<th>Duration of CR</th>
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<tbody>
<tr>
<td>17/23 (72%)</td>
<td>44% CR</td>
</tr>
<tr>
<td></td>
<td>28% CRh</td>
</tr>
<tr>
<td></td>
<td>8.9 m (median)</td>
</tr>
<tr>
<td>*15/17 with molecular CR</td>
<td></td>
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Pivotal trial in pediatric ALL MRD ongoing
### CD19 BiTE in B-cell lymphoma

#### Phase 1 dose-escalation trial in B-cell NHL

- **Activity (dose dependent):**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patients</th>
<th>CR</th>
<th>PR</th>
<th>Overall RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 – 5 µg/m²/24 h</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0/13</td>
</tr>
<tr>
<td>15 &amp; 30 µg/m²/24 h</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td>4/20</td>
</tr>
<tr>
<td>60 µg/m²/24 h</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>8/9*</td>
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<tr>
<td>90 µg/m²/24 h</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2/4#</td>
</tr>
</tbody>
</table>

*Durable PR/CR in MCL, CLL and FL

**AEs:**
- CNS events at 60 µg/m²/d: confusion, Seizure
- Patients with low peripheral B cells at higher risk

* **Mitigation strategy:** Stepwise increment to target dose (5 → 15 → 60 µg/m²/d)
Safety

• **Common toxicities with MT103**
  – Cytokine release syndrome – more serious in ALL with high tumor bulk
  – lymphopenia

• **Neurological /psychiatric AEs –**
  – G1-3: HA, dizziness, tremor, aphasia, encephalopathy, cerebellar syndrome, Seizure
    • Mostly occurring in cycle 1; reversible
  – Dose-related
    • *In ALL* (15 µg/m²/d): 2/20 discontinued therapy
    • *In NHL* (60 µg/m²/d or higher): 12 patients discontinued therapy
  – Possible risk factor: Low peripheral B cell count at baseline

*Step-up dosing schedule and steroids feasible and effective in ALL*
**EpCAM BiTE (MT110)**

**The target:**
- Epithelial adhesion molecule. Also present also on cancer stem cells.
- In tight junction in normal tissues

**Phase I dose escalation trial in advanced solid tumors**

**(Fiedler et al, ASCO 2012)**

- **Safety and Doses:**
  - Not tolerable at > 10 µg/m²/d with standard schedule
  - DLT: diarrhea, abdominal pain, LFT (*LFT associated with first dose*)
  - 5 different dosing schedules were explored
    - Step up dosing required

- **Activity** (n=43 evaluable, at different dose/schedules)
  - Reduction in circulating tumor cells. SD 35%
  - NO PRs

**BiTE antibodies in development**
- CD19
- CD33
- EpCAM
- CEA
- EGFR
- Eph2
- HER2
What have we learned about T-cell engaging Ab- approaches

*Bispecific antibodies, BiTE, CARs*

- Use of Ab to redirect T cells to target cells is a powerful strategy
  - Potent and specific
  - MHC independent
  - May bypass typical immune-suppressive mechanism

- Encouraging data in hematological malignancies

**Challenges:**

- T-cell activation can induce significant toxicities (target-triggered cytokine release or target-mediated tissue damage)
  - Challenging for many solid tumor targets

- Careful selection of target and development of mitigation strategy will be critical to achieving therapeutic window
Summary and future directions
Summary

- Exquisite specificity, and ability to carry “effector arms” (native or engineered) is unique among drug modalities
- Successes with: IgG mAbs targeting the tumor antigens, host immune cells and stromal factors; ADCs; Bispecific Abs
- New technology will continue to generate new designs and constructs

Considerations:

- Better understanding of MOA, especially in relationship to host immune system
- Identification / prioritization of targets
  - cancer genome project (surface molecule with somatic mutations?)
  - Phase display library screen
- ... chose the right construct (“effector arm”) appropriate for the target
- ... in the right patients using biomarkers for patient selections