Bispecific antibody development in Immuno-Oncology: redirecting immune effector cells towards tumors

Thierry WURCH
Sr. Director – Global External Innovation

Joint Meeting of NC-IUPHAR and the British Pharmacological Society
Nov. 19-20, 2020
Agenda

- Introduction – General concepts
- T cell engagers
  - Prototypical TCE: blinatumomab
- NK cell engagers
  - Case study: AFM13 in T cell lymphoma
- Immune checkpoint modulators
  - Case study: MGD013, a PD1xLAG3 DART®
- Other bispecific Ab-based molecules
- Take home messages
Bispecifics: Year of FiH study entry

Reichert, J, 2018, The Antibody Society website
Bispecifics in Oncology

- Most (80%) are for cancer; 51 at Ph1 and 9 at Ph2
  - T-cell redirection (38/60, 63%) most common mechanism of action
  - Most frequent TAAs are CD20 and B-cell maturation antigen (5 bsAbs each), followed by CD33 and CD123 (4 bsAb each)

- EGFR family, Immune checkpoints targets also popular
  - VEGF, EGFR, HER2 (5, 4, 2 bsAbs, respectively), with DLL3/VEGF most frequent (3 bsAbs)
  - PD-1, PD-L1 (4, 2 bsAbs, respectively) with PD-1/CTLA4 most frequent (3 bsAbs)

Reichert, J, 2018, The Antibody Society website
Bispecifics in non-cancer indications

- Only 15 (20%) bsAbs currently in clinical studies are for non-cancer indications
  - 10 at Phase 1, 5 at Phase 2

- Disorders include immune-mediated/inflammatory (9 bsAb), metabolic, neurological, ophthalmic, respiratory disorders and infectious disease
  - Diverse array of targets, with IL-17 (3 bsAb) and TNF (2 bsAb) most frequent

- RO6867461 VEGF-A/Ang-2 CrossMab ready to enter Phase 3 in diabetic macular edema

Reichert, J, 2018, The Antibody Society website
A zoo of formats exists

Generally associated with extensive engineering

Brinkmann & Kontermann, MABS 2017
A zoo of formats exists

Unable to have differential valencies

Brinkmann & Kontermann, MABS 2017
Examples of bispecific diabody-based scaffolds

- **BiTE** (Bi-specific T-cell engager)
  - 1 single polypeptide chain
  - Flexible linker
  - No chain dimerization

- **DART** (Dual affinity retargeting)
  - 2 polypeptide chains
  - No linker – interchain disulfide bridge
  - Fusion to Ckappa and IgG1 upper hinge

- **TandAb** (Tetravalent tANDem antibody)
  - 1 single polypeptide chain
  - Highly flexible linkers
  - Chain dimerization

TCEs

NKCEs
BISPECIFIC T CELL ENGAGERS OR BITE®
T cell engagers create an immunological synapse

Regular T cell activation

- Specific T Cell Receptor
- Peptide Antigen Presentation and Processing
- MHC I/β2 Microglobulin
- Co-stimulatory Molecules

CD3-engaging scaffold

- Any Cytotoxic T Cell (= Polyclonal)
- No Peptide Antigen
- No Antigen Processing
- No APCs needed
- No MHC I/β2 Microglobulin
- No Co-stimulatory Molecules
Cytolytic Immune Synapse

Activation markers
- CD69
- CD25
- Granzymes
- Perforin
- Cytokines

Proliferation

Apoptosis
- Caspase activation
- DNA fragmentation
- PARP cleavage
- Morphological changes
<table>
<thead>
<tr>
<th>Specificities (Target × Effector Cell)</th>
<th>Drug</th>
<th>Stage</th>
<th>Comments</th>
<th>Trial Identifier</th>
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<tbody>
<tr>
<td>CD19 × CD3</td>
<td>Blinatumomab*</td>
<td>Market and multiple phase II/III ongoing studies</td>
<td>Treatment of refractory/relapsed ALL and phase II for t/r NHL</td>
<td>NCT02811679</td>
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<tr>
<td>CD19 × CD3</td>
<td>AFM11</td>
<td>Phase I</td>
<td>NHL and ALL</td>
<td>NCT02106091; NCT02848911</td>
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<tr>
<td>CD20 × CD3</td>
<td>RG6026* and REGN1979*</td>
<td>Phase I</td>
<td>NHL and CLL</td>
<td>NCT02290951; NCT02290951</td>
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<tr>
<td>CD20 × CD3</td>
<td>Mosunetuzumab*</td>
<td>Phase I</td>
<td>AML, CLL, and DLBCL</td>
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<td>CLEC12A × CD3</td>
<td>MCLA-117*</td>
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<td>CD33 × CD3</td>
<td>AMSG 330, GEM333, and AMV564</td>
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<td>MGD006, JNJ-63709178*, and APVO436*</td>
<td>Phase I</td>
<td>Multiple myeloma</td>
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<td>BCMA × CD3</td>
<td>BI 836909, JNJ64007957*, PF-06863135*, and REGN5458</td>
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<td>CD38 × CD3</td>
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<td>HER2-positive solid tumors</td>
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<tr>
<td>HER2 × CD3</td>
<td>GBR 1302*</td>
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<td>PSMA × CD3</td>
<td>AMG 160 and ES414*</td>
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<td>AMG 757</td>
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<td>Small-cell lung cancer</td>
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<td>NYESO1/LAGE-1A × CD3</td>
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<td>NYESO1 or LAGE-1A solid tumors</td>
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<td>GPC3 × CD3</td>
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<td>Gp100 × CD3</td>
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<td>Uveal melanoma</td>
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<td>GD2 × CD3</td>
<td>Hu3F8-BsAb* (GD2/CD3)</td>
<td>Phase I/II</td>
<td>Neuroblastoma, osteosarcoma, and other GD2-expressing solid tumors</td>
<td>NCT02570308; NCT03860207</td>
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</table>

Mostly Pre-PoC assets

Strohl & Naso, Antibodies 2019
Prototypical TCE: blinatumomab – BLINCYTO®

- **Engineering:**
  - 1 single polypeptide chain
  - Flexible linker
  - No chain dimerization

- **Dosing**
  - Continuous IV infusion
  - Dose weight-adapted
  - Lead-in dose (1/3 of target) to diminish CRS risk

### FDA approval history

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<th>Approval</th>
<th>Description</th>
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<td>Mar 29, 2018</td>
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<td>FDA Expands Approval of Blincyto (blinatumomab) to Treat Minimal Residual Disease-Positive B-Cell Precursor Acute Lymphoblastic Leukemia</td>
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<td>Jul 11, 2017</td>
<td>✅️</td>
<td>FDA Grants Full Approval for Blincyto (blinatumomab) to Treat Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia in Adults and Children</td>
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<td>Sep 1, 2016</td>
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<td>FDA Approves Blincyto (blinatumomab) For Use In Pediatric Patients With Philadelphia Chromosome-Negative Relapsed Or Refractory B-cell Precursor Acute Lymphoblastic Leukemia</td>
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<td>Dec 3, 2014</td>
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<td>FDA Approves Blincyto (blinatumomab) for Precursor B-Cell Acute Lymphoblastic Leukemia</td>
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BLINCYTO® TOWER
Ph.3 study: SAFETY

Two black boxed warnings issued by FDA:
- CRS
- Neurological toxicities
BLINCYTO® TOWER Ph.3 study: EFFICACY

Primary endpoint: Overall survival (intent-to-treat population)\(^4\)

Median OS
7.7 months
(95% CI: 5.6–11.8)

4.0 months
(95% CI: 1.2–16.0)

Survival Probability

BLINCYTO\(^{®}\) n=271
SOC Chemotherapy n=134
Censored

HRL 0.71 (95% CI: 0.55–0.93)
P = 0.03

Overall response

BLINCYTO\(^{®}\) significantly increased complete remission rates compared with SOC chemotherapy\(^4\)

CR/CRh*, §§

SOC n=271/134
(95% CI: 14–28)

BLINCYTO\(^{®}\) n=115/271
(95% CI: 37–49)

P < 0.001**

20%
42%

Primary endpoint: Overall survival\(^4\)

BLINCYTO\(^{®}\) single-agent immunotherapy\(^4\) n=271

- Continuous IV infusion for 1 to 2 induction cycles (4 weeks on, 2 weeks off)
- 9 mcg/day on days 1–7 of cycle 1 and 28 mcg/day on subsequent days

Consolidation, maintenance,\(^{1}\) and follow-up, depending on response to induction

Standard-of-care chemotherapy\(^4\) (investigator’s choice of one of the regimens below) n=134

- FLAG + anthracycline-based regimen
- HIDAC-based regimen
- High-dose methotrexate–based regimen
- Clofarabine-based regimens

Median duration of remission (DOR)

BLINCYTO\(^{®}\) produced a more durable remission compared with SOC chemotherapy among patients who had CR/CRh\(^*\)

5.4 months
(95% CI: 1.8–19.0)

7.6 months
(95% CI: 5.8–10.2)
BISPECIFIC NK CELL ENGAGERS
NK cell engagers: mimicking the TCE concept

- Mimicking Mab Fc properties: ADCC/ADCP
- Selective binding to CD16a/FcγRIIIa
- No binding to inhibitory FcγRIIa
- Independent of CD16a polymorphism (V/F158)

Major NK cell activators: CD16 and/or NKp46
### Reminder: human FcγRs

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<tr>
<th>Name</th>
<th>FcγRI</th>
<th>FcγRIIa</th>
<th>FcγRIIb</th>
<th>FcγRIIc</th>
<th>FcγRIIIa</th>
<th>FcγRIIIb</th>
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<td>CD64</td>
<td>CD32a</td>
<td>C32b</td>
<td>CD32c</td>
<td>CD16a</td>
<td>CD16b</td>
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</tbody>
</table>

#### Structure

- **FcγRI**: Common y-chain, ITAM
- **FcγRIIa**: ITTIM
- **FcγRIIb**: ITIM
- **FcγRIIc**: ITIM
- **FcγRIIIa**: GPI
- **FcγRIIIb**: GPI

#### Function

- **Activating**
- **Inhibitory**

#### Affinity

- **High**
- **Low**

#### SNP

- **131H/R**: Reduced affinity to IgG2
- **232I/T**: Decreased inhibitory activity
- **57Q/X**: Stop codon (non-functional protein)
- **158F/V**: Increased affinity to IgG1/3/4
- **NA1/2**: Reduced affinity to IgG1/3

Activated by hIgG1
## Examples of NK cell engagers

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Format</th>
<th>Targets</th>
<th>Molecules/Biotech</th>
<th>Development stage</th>
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<tbody>
<tr>
<td>NK cell redirection</td>
<td>Tandab</td>
<td>CD30xCD16</td>
<td>AFM13</td>
<td>Ph.2</td>
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<tr>
<td></td>
<td>Tandab</td>
<td>BCMAxCD16</td>
<td>AFM26</td>
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<td>triKE</td>
<td>CD133xCD16</td>
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<td>PC</td>
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<td>BiKE</td>
<td>CS1xNKG2D</td>
<td>N.A.</td>
<td>PC</td>
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<tr>
<td></td>
<td>IgG like</td>
<td>CD20xNKp46</td>
<td>Innate Pharma</td>
<td>PC</td>
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</tbody>
</table>

Wurch & Chames, Médecines&Sciences 2019
AFM13 induces CD30-specific NK cell activation & proliferation

**Activation markers**
- CD25
- CD137
- Granzymes
- Perforin
- Cytokines (IL15, IFNγ)

**Apoptosis**
- Caspase activation
- DNA fragmentation
- PARP cleavage
AFM13 Is the Most Advanced Bispecific NK-Cell Engaging Antibody in Clinical Development Substantially Enhancing NK-Cell Effector Function and Proliferation

AFM13-mediated NK cell activation

AFM13-mediated tumor cell killing

CD25/IL-2Rα

CD132/IL-2Rγ

CD69

CD137

DNAM-1

CD16

L428

Karpas-299

NK cells only

+ soluble AFM13

+ Karpas-299+AFM13

+ Karpas-299+AFM12

AFM12: CD19xCD16a

Pahl J et al, ASH2016
AFM13-induced ADCP is:
- tumor antigen-specific
- depends on binding to both CD16a on macrophages AND TA on tumor cells

Wingert et al, ASH2018
Clinical and Biological Evaluation of the Novel CD30/CD16A Tetravalent Bispecific Antibody (AFM13) in Relapsed or Refractory CD30-Positive Lymphoma with Cutaneous Presentation: A Biomarker Phase Ib/Ila Study (NCT03192202).

Ahmed Sawas, MD1, Pei-Hsuan Chen2, George Viad, PhD3, Mikael Lipschitz2, Jennifer Lue, MD1, Changchun Deng, MD, PhD3, Jennifer E Amengual, MD1, Enrica Marchi, MD1, Francesca Montanari, MD1, Maher Abdul-Hay, MD1, Jonath Shulman, MD1, Hager Elgedawte2, Matthew Shong1, Karen Khan, RN1, Larisa Geskin, MD1, Scott J. Rodig, MD, PhD1, and Owen A. O’Connor, MD, PhD1

<table>
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<tr>
<th>Cohort</th>
<th>Dose regimen</th>
<th>Total exposure</th>
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<tr>
<td></td>
<td>Dose</td>
<td>Schedule</td>
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<tr>
<td>1</td>
<td>1.5 mg/kg</td>
<td>weekly</td>
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<tr>
<td>2</td>
<td>7.0 mg/kg</td>
<td>weekly</td>
</tr>
<tr>
<td>3</td>
<td>7.0 mg/kg CI4/1*</td>
<td>weekly</td>
</tr>
<tr>
<td>4</td>
<td>200 mg flat dose</td>
<td>weekly</td>
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</tbody>
</table>

*1 mg/kg loading 6 mg/kg as continuous infusion for 5 days per week

- **AFM13 well tolerated**
- **AFM13 high ORR 50% & active post-Adcetris**
- **Biomarkers indicated increased NKs in responders**

Sawas A et al, ICML2019

### Disease: forms of cutaneous T cell lymphoma:
- S-ALCL: systemic anaplastic large cell lymphoma
- T-MF: transformed mycosis fungoides

### Toxicity
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Disease</th>
<th>Toxicity</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S-ALCL, Alk (-)</td>
<td>No AE</td>
<td>PR</td>
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<tr>
<td></td>
<td>T-MF</td>
<td>No AE</td>
<td>POD</td>
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<tr>
<td></td>
<td>C- ALCL</td>
<td>Rash (G4) Skin infection (G3)</td>
<td>CR</td>
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<tr>
<td>2</td>
<td>MF</td>
<td>IRR (G1)</td>
<td>SD</td>
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<td>T-MF</td>
<td>IRR (G1)</td>
<td>SD</td>
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<td>T-MF</td>
<td>Skin infection (G3) IRR (G1)</td>
<td>Not assessed</td>
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<td>3</td>
<td>T-MF</td>
<td>No AE</td>
<td>PR</td>
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<tr>
<td>4</td>
<td>T-MF</td>
<td>No AE</td>
<td>PR</td>
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</table>

### Clinical response:
- CR: complete response
- PR: partial response
- PoD: progression of disease

Disease: forms of cutaneous T cell lymphoma:
S-ALCL: systemic anaplastic large cell lymphoma
T-MF: transformed mycosis fungoides

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BISPECIFIC IMMUNE CELLS MODULATORS
Major immune receptors controlling T cell activation

Bispecific MoAs engaging immune checkpoints:

- Dual Targeting of 2 inhibitory ICPs *i.e.*, **PD1xLAG3**
- Dual co-targeting of one inhibitory and one co-stimulatory ICP *i.e.*, **PD-L1x4-1BB**
- Tumor-restricted co-stim. ICP targeting *i.e.*, **Her2x4-1BB**
### Examples of Bispecific ICP modulators

**Wurch & Chames, Médecines & Sciences 2019**

<table>
<thead>
<tr>
<th>Mode of Action</th>
<th>Targets</th>
<th>Molecule</th>
<th>Development stage</th>
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<tr>
<td><strong>Co-inhibitory immune modulators</strong></td>
<td>Co-engagement of two inhibitory ICPs to enhance T cell activation</td>
<td>PD-1xLAG-3</td>
<td>MGD013</td>
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<td>PD-1xTIM-3</td>
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<td>PD-1xTIM-3</td>
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<td>PD-L1xLAG-3</td>
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<td>CTLA-4xLAG-3</td>
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<td>CTLA-4xCD1</td>
<td>MGD019</td>
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<td><strong>Dual immune modulators</strong></td>
<td>Co-engagement of both inhibitory &amp; co-stimulatory ICPs to maximize T cell activation</td>
<td>PD-1xICOS</td>
<td>XmAb23104</td>
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<td>PD-L1x4-1BB</td>
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<td>CTLA-4xGITR</td>
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<td><strong>Tumor-retargeted immune-modulators</strong></td>
<td>Selective tumor targeting of a co-stimulatory ICP by co-engagement of a tumor-associated antigen</td>
<td>HER2x4-1BB</td>
<td>PRS-343</td>
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<td>GPC3x4-1BB</td>
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<td><strong>Immune modulators &amp; cytokines</strong></td>
<td>ICP engagement coupled to a cytokine</td>
<td>PD-L1 xTGF-βtrap</td>
<td>M7624</td>
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<td>CTLA-4 xTGF-βtrap</td>
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A Phase 1 Dose Escalation Study of PRS-343, a HER2/4-1BB Bispecific Molecule, in Patients with HER2-positive Malignancies
HER2-targeting moiety of the drug localizes to the tumor microenvironment and facilitates 4-1BB cross-linking

4-1BB cross-linking ameliorates T-cell exhaustion and is critical for T-cell expansion

HER2 targeting Antibody

4-1BB targeting Anticalin® Proteins
### Summary of Responses of PRS-343 in Monotherapy

<table>
<thead>
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<th>Cohort</th>
<th>Best Response</th>
<th>13b</th>
<th>12b</th>
<th>11c</th>
<th>Obi</th>
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<th>11</th>
<th>10</th>
<th>9</th>
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<td>12 mg/kg, Q2W</td>
<td>8 mg/kg, QW</td>
<td>8 mg/Kg, Q2W</td>
<td>8 mg/kg, Q2W</td>
<td>8 mg/kg, Q3W</td>
<td>5 mg/kg, Q3W</td>
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**ACTIVE SCHEDULES**

- **Schedule 1**: Q3W dosing on day 1; 21-day cycle
- **Schedule 2 (b)**: Q2W dosing on days 1, 15; 28-day cycle
- **Schedule 3 (c)**: Q1W dosing on days 1, 8, 15; 21-day cycle
- **In combination with atezolizumab**: Q3W dosing on day 1; 21-day cycle
Increase in CD8+T Cells Support 4-1BB Engagement by PRS-343
Other examples of bispecific Ab-based molecules

TCR-based TCE
- Product: IMCgp100
- Biotech: Immunocore (UK)
- Engineered solTCR against gp100 fused to CD3 scFv
- Pivotal study in metastatic uveal melanoma on-going

Immunocytokines
- Product: bintrafusp alfa/M7824
- Pharma: Merck Serono/NCI
- PD-L1 Mab fused to TGF-β trap
- Pivotal study in 1st line NSCLC
Take-Home messages

- Novel immune cell activators have emerged in the last decades thanks to the increased knowledge in tumor immunology and the engineering and design of numerous novel antibody- & non-Ig-based formats
- Most of these novel therapeutics showed promising preclinical data & for the most advanced early signs of clinical efficacy
- Despite the approval of blinatumomab in 2014 & first ICP inhibitors in 2011 (ipi) and 2014 (nivo), next generation molecules with potential BiC profile show difficulties to gain approval
- Solid tumors remain a real challenge for these novel classes of immune cell modulators
- Combination treatments will certainly be needed to increase the clinical benefit for patients
THANK YOU FOR YOUR ATTENTION

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