T-Cell & NK-Cell Engaging Bispecific Antibodies 2019:

a business, stakeholder, technology and pipeline analysis

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Molecules from six different Ig-based T-cell redirecting bispecific antibody technologies and one T-cell engaging bispecific antibody technology have reached the clinic (Table 12). The collaboration of Genmab with Janssen has been very productive, already five T-cell redirecting DuoBodies are in clinical evaluation. A sixth T-cell redirecting DuoBody from Genmab is in clinical development. Three Veloci-Bi antibodies from Regeneron and two BEAT bispecifics from Glenmark have entered clinical development. Table 12 lists the tumor-associated targets of the Ig-based T-cell redirecting or engaging bispecific antibodies, most of the targets are well known and have already been or are being addressed by various treatment modalities (naked antibody, ADCC-enhanced antibody, antibody-drug conjugate, radio-labeled antibody, CAR-transduced T-cells).

Table 12: Overview of Partnering Deals of Technology Companies with Ig-Based T-Cell and NK Cell Engaging Bispecific Antibody Technologies

Company	Technology	Licensee	Terms
Abpro	MultiMabs in TetraBi Format	NJCTTQ	$ 60 mln R&D funding, up to $ 4 bln milestones, royalties
CytomX Therapeutics	Probody: IgG + peptide mask + protease-cleavable linker	Amgen	$ 40 mln upfront + $20 mln stock + up to $ 455 mln milestones + royalties
Genmab	DuoBody	Janssen	$ 5.5 mln up-front + ca. $ 191 mln/project + royalties
Glenmark Pharmaceuticals	BEAT: GBR1302 (Her2xCD3)	Harbour Biomed	Up to $ 120 mln + tiered royalties
Regeneron Pharmaceuticals	Veloci-Bi Antibody Technology	Sanofi	Umbrella collaboration
TeneoBio (TeneoOne)	BCMAxCD3 UniDab	AbbVie	$ 90 mln upfront + right to aquire product

Sd, single digit; dd, double digit;

The economic terms of Genmab's long-lasting collaboration with Janssen which only recently concluded with fourteen bispecific Duobodies selected, are relativly modest compared with those of more recent collaboration agreements, e.g. CytomX (Table iota1). Sanofi is in the phase of concluding its broad antibody discovery and development collaboration with Regeneron in favor of in house discovery (goal: two thirds). The collaboration included bispecific T-cell engaging antibodies for which Sanofi holds opt-in rights.

Thus, among the five clinical stage CD20-targeted T-cell redirecting antibodies are two different constructs from Roche (Table 27). All five CD20xCD3 bispecifics are molecules with a long half-life. IgM Biosciences pursues the develompent of a CD20 targeted 10-valent pentameric IgM with additional specificity for CD3. IGM-2323 binds CD20 antigen more potently (1000x) with greater CDC (100x) compared to IgG.

Table 27: Pipeline of CD20-Targeted Bispecific T-Cell and NK Cell Engaging Antibodies

Drug Code	Targets	Technology	Company	Indication	R&D Phase
GEN3013	CD20 x CD3	DuoBody	Genmab	B-cell lymphoma	I/II
IGM2323	CD20 x CD3	IgM-scFv	IGM Biosciences	B-cell lymphoma	0
REGN1979	CD20 x CD3	Veloci-Bi	Regeneron	Follicular lymphoma	II
RG6026	CD20 x CD3	2+1 IgG	Roche	B-cell lymphoma	I
RG7828	CD20 x CD3	KiH IgG	Roche	B-cell lymphoma	I/II
XmAb13676	CD20 x CD3	XmAb	Xencor	B-cell lymphoma	I

First clinical experience for CD20xCD3 bispecifics have been reported for Regeneron's RG1979 and for one of Roche's CD20 bispecific (RG6026).

REGN1979 is a hinge-stabilized CD20xCD3 bispecific full-length Veloci-Bi antibody based on an IgG4 isotype modified to reduce Fc binding. In Q3/2014, Regeneron initiated a phase I FiH cancer study of REGN1979. Based on initial PK data, the REGN1979 regimen was revised to 12 weekly doses followed by maintenance q2w dosing for 12 doses administered as intravenous infusions. As of June 1, 2018, 54 pts with B-NHL were at doses ranging from 0.03 to 27.0 mg REGN1979.

There were no dose-limiting toxicities (DLTs) so far. In patients with B-NHL, the most common treatment-related treatment-emergent adverse events (TR-TEAEs) included infusion-related reactions (IRR) or cytokine release syndrome (CRS); 26 pts experienced CRS (Grade 1–2, n=23; Grade 3, n=3) with a median duration of CRS of 2 (range 1–15) days. Six pts received tocilizumab. The severity of CRS symptoms declined through optimized pre-medication even with REGN1979 dose escalation. Other common Grade ≥3 TR-TEAEs were lymphocytopenia/ decreased lymphocyte count (n=8); neutropenia/ decreased neutrophil count (n=7); and thrombocytopenia/ decreased platelet count, hypotension, hypophosphatemia, and anemia (each n=3). Seventeen pts experienced a nervous system event including headache, dizziness,

mechanisms to destroy a cancer cell. Similarly, DART molecules targeting CD3 and a viral antigen can be used to recruit T cells to eliminate cells infected by a virus, such as HIV-infected cells.

Financial situation

As of December 31, 2018, MacroGenics' cash, cash equivalents and marketable securities were US$ 232.9 million, which did not include the $25 million upfront payment from Zai Lab or the $118.5 million net proceeds from the follow-on offering completed in February 2019 (Press Release Feb 26, 2019). Since the 2013 initial public offering (IPO), the company booked revenues of more than US$ 450 mln from collaborative and government agreements (Presentation Feb 26, 2019).

Partnering

MacroGenics has entered into collaborations with other companies, including collaboration and license agreements with, for example, Les Laboratoires Servier and Institut de Recherches Servier (collectively, Servier), Green Cross Corporation (GC Pharma), Incyte Corporation, Zai Lab Limited and F. Hoffman La Roche.

With respect to T-cell redirecting bispecific antibodies, MacroGenics has agreements with Pfizer and Servier:

In October 2010, MacroGenics entered into a global research collaboration and license agreement with **Pfizer** to discover, develop and commercialize Dual-Affinity Re-Targeting (DART) products directed at two undisclosed cancer targets at that time. MacroGenics received an upfront cash payment and research funding. In addition, MacroGenics is eligible to receive escalating preclinical, clinical, regulatory and commercial milestone payments as well as tiered royalties on sales of products resulting from the collaboration (Press Release Oct 26, 2010). In early 2016, Pfizer advanced PF-06671008, a DART molecule that targets P-cadherin and CD3, by submitting an IND application that has been cleared by the FDA (Press Release Feb 29, 2016). This molecules still is in Pfizer's pipeline (Pfizer Pipeline Jan 29, 2019). As of April 2019, the phase I study of PF-06671008 was still ongoing, but no longer recruiting (ClinicalTrials.gov NCT02659631).

discovered that a single point mutation in the CH3 domain and two mutations at cysteine residues within the IgG hinge region was sufficient to generate Half DVD-Ig similar to the ones generated with multiple mutations at the CH3 domain.

8.1.9 Human Heavy Chain Antibody (UniAb) Platform for Bispecifics

Teneobio has developed technologies, including a transgenic rat platform, UniRat, expressing human heavy chain antibodies (**UniAbs**) and a state-of-the-art sequence-based discovery engine (**TeneoSeek**) to create novel multispecific antibodies for various therapeutic indications. Using this technology, Teneobio has identified an unprecedented number of novel anti-CD3s, which in the context of bi- or multispecifics, enable maximal T-cell redirection for tumor cytotoxicity and minimal cytokine release. Teneobio has created a T-cell engaging bispecific antibody platform with tuned T-cell agonism that can be used to optimize the therapeutic index for a variety of tumor antigens (Vafa, 2018).

Teneobio's human Ig transgenic platform, the UniRat, is based on a triple knockout rat wherein the expressions of the native variable coding sequences and the heavy and light chain constant regions have been inactivated. The UniRat has been genetically modified to exclusively express the full human VDJ repertoire (all VH families), with transgenes of human heavy chain variable domains linked to a conserved rat Fc. Immunization of the Uni-Rat elicits a normal antibody response that results in the expression of UniAbs, human heavy-chain-only antibodies of approximately 80 kDa, contrasting with the standard ~150-kDa human IgG. Importantly, heavy chain variable domains from the UniRat, **UniDabs**, are the smallest antigen-binding units of a human IgG at approximately 12.5 kDa (~100 amino acids) and can be assembled as modular domains of multispecifics.

The following Figure illustrates a subset of such multispecific formats, enabling the generation of a plenitude of specificities against different epitopes on the same antigen or different specificities for different antigens. Heterodimerization of such heavy-chain-only multispecifics or their combination with standard heavy light-chain formats is feasible, given that UniDabs (VH domains) do not interact with either kappa or lambda light chains *in vitro* or when co-expressed in cell lines.

objectives include assessment of biomarkers, immunogenicity and additional measures of anti-tumor activity.

In Part 1 of the ongoing study, intravenous GBR 1342 is administered on Days 1 and 15 in 28-day treatment cycles at escalating doses (1 – 1,000 ng/kg). The first 4 cohorts consist of a single subject. Subsequent cohorts use a 3+3 enrollment design. In Part 2, 65 evaluable subjects will be treated at the MTD identified in Part 1 until disease progression or unacceptable toxicity occurs. Primary endpoints include AEs (frequency, severity), number of dose-limiting toxicities during Cycle 1 (Part 1), and objective response to GBR 1342 (Part 2). Secondary endpoints include pharmacokinetics and anti-tumor activity of GBR 1342 (progression-free and overall survival).

In November 2018, Glenmark announced the decision to launch a Phase 1 trial in solid tumors for its CD38xCD3 bispecific antibody GBR 1342 (Press Release Nov 7, 2018). The company intends to file an IND application for GBR 1342 in solid tumors and initiate a clinical trial in 2019. The decision to expand clinical development of GBR 1342 was based on a recently completed *ex vivo* translational study in multiple solid tumors utilizing the clinically validated CANscript™ platform, where treatment with GBR 1342 revealed predictive responses in various tumor types. CANscript is a completely human, autologous human tumor platform that integrates an algorithm–driven strategy to predict clinical responses.

9.1.34 GBR1372

GBR 1372 is an EGFRxCD3 bispecific antibody based on Glenmark's proprietary BEAT platform. It targets epidermal growth factor receptor (EGFR), a proven target in several cancers including squamous cell carcinoma of the head and neck and colorectal cancer. GBR1372 includes a single chain, variable fragment arm with anti-EGFR specificity and a fragment antigen binding (Fab) arm with anti-CD3ε specificity. The scFv x Fab BEAT format sprevent light chain mispairing and facilitates direct conversion of any antibody pair into one bispecific antibody. Glenmark has substituted the protein-protein interface between the CH3 domains of the antibody Fc region with the protein-protein interface found in the T-cell receptor constant region so that the engineered bispecific antibody preferentially forms heterodimers over homodimers (Back, 2014).

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