Strategy

Networking antibodies

By Stephen Hansen
Staff Writer

Even before Jan van de Winkel was promoted to president and CEO of **Genmab A/S** in June, the company had realized it was living beyond its means and started paring back. He has accelerated the process, putting forward what he believes is a more realistic strategy: the company will delay its transition into a commercial organization and, in the near to mid-term, hopes to turn its antibody R&D engine into a profit center.

With a valuation one-fourth what it was two and a half years ago, and half the cash it had then, cash preservation is now a key focus.

As a result, Genmab no longer plans to take all its internal programs into late-stage development. Instead it will look to generate non-dilutive capital through increased partnering. The company also will seek to monetize its antibody platform through multi-target deals, such as last month's partnering with **H. Lundbeck A/S** to discover and develop mAbs for CNS indications.

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Additionally, van de Winkel said Genmab will look to in-license new technologies, a strategy it had not pursued before. The first such deal was completed in September, which gave the company access to antibody-drug conjugate (ADC) technology from **Seattle Genetics Inc.**

van de Winkel said the plan is to turn Genmab into a "networked antibody company" with access to new technologies and a variety of partnerships that reduce Genmab's capital risk while advancing its pipeline. By 2020, he hopes Genmab will have 10 key strategic partners, and possibly five antibodies on the market.

van de Winkel said most of these five products will be partnered. Still, he added, "when our cash position would allow, I would love to push at least one of them to the finish line ourselves."

Seeds from Arzerra

Genmab's ambitions to become a commercial company were planted in December 2006 by a deal with **GlaxoSmithKline plc** to co-develop Arzerra ofatumumab. The human mAb against CD20 was then in Phase III trials to treat chronic lymphocytic leukemia (CLL) that is refractory to Rituxan rituximab, and to treat non-Hodgkin's lymphoma. The mAb was also in Phase II testing to treat rheumatoid arthritis (RA) and for first-line CLL.

Genmab received $102 million in license fees and $357 million in an equity investment and an option to co-promote Arzerra, along with an option to co-promote two GSK cancer drugs. The equity investment gave GSK a 10% stake in Genmab.

Then in 2007, Genmab got back one late-stage product and a preclinical mAb when Merck Serono S.A., a unit of **Merck KGaA**, returned rights to HuMax-CD4 zanolimumab and HuMax-TAC following a portfolio review.

Zanolimumab, which targets the CD4 receptor on T cells, was in Phase III testing for cutaneous T cell lymphoma (CTCL), with a Phase III trial expected to start in 2008 for non-cutaneous T cell lymphoma (NCTCL).

HuMax-TAC, a human mAb against interleukin-2 (IL-2) receptor, was in preclinical testing to treat autoimmune, inflammatory and hyperproliferative skin disorders and acute transplant rejection.

With a growing number of antibodies in the pipeline and $746 million in cash, then-President and CEO Lisa Drakeman set her sights on completing the Phase III trials for zanolimumab and another antibody, zalutumumab, and establishing commercial operations *(see BioCentury, Sept. 24, 2007)*.

In 2008, to provide manufacturing capacity, the company purchased a Minnesota antibody manufacturing facility from **PDL BioPharma Inc.** for $240 million.

Genmab also greatly expanded its clinical development organization to include one research and preclinical development facility in the Netherlands, and three clinical development sites in Denmark, New Jersey and London.

Unfortunately, the vision may have been too grand, as it required everything to work perfectly for all three mAbs.

Under Drakeman's leadership, the company closed the New Jersey and U.K. sites in 2009 and outsourced non-core R&D activities to CROs and CMOs.

The company also began to cut its R&D spend to match projected revenue for the expected launch of its first drug, Arzerra. Genmab dropped programs that had small markets or were outside its core area of cancer *(see BioCentury, Oct. 20, 2008)*.

"I think at the old Genmab, there was some expectation that everything we dreamed up would work," van de Winkel said.

Not surprisingly, not everything went to plan. In the case of zalutumumab, Genmab had to wind down a Phase I/II trial in colorectal cancer and a Phase II trial in non-small cell lung cancer (NSCLC) in order to redesign the trials to account for the new understanding of the role of K-Ras in those indications.

Then in March, the human mAb against EGFR1 (HER1; ErbB1) missed the primary endpoint of significantly increasing median overall survival (OS) in combination with best supportive care vs. best supportive care alone (6.7 vs. 5.2 months, p=0.0648) in a Phase III trial to treat refractory head and neck cancer.

Zalutumumab did significantly increase progression-free survival (PFS) by 61% vs. best supportive care alone (p=0.001).

Meanwhile, zanolimumab was dropped because recruitment for the Phase III trial was very slow, owing to competing trials and approval of **Merck & Co. Inc.**'s Zolinza vorinostat for the same indication. The pharma already markets Zolinza to treat CTCL.

Additionally, the manufacturing process for zanolimumab was the oldest and most expensive in use at Genmab.

In February, Genmab granted **TenX Biopharma Inc.** ex-

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clusive, worldwide rights to the mAb in exchange for $4.5 million up front and undisclosed milestones, plus royalties.

On the plus side, Arzerra was approved to treat CLL in 2009 in the U.S. and earlier this year in the EU. But last year it missed the primary endpoint of overall response rate (ORR) at six months in a Phase III trial to treat NHL *(see BioCentury, Aug. 24, 2009)*.

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Too much too soon

"The previous Genmab I think was expanding too quickly. It was getting ahead of itself basically with aspirations of being a fully integrated commercial company with clinical development in three countries. With the benefit of hindsight, that was far too quick," van de Winkel told BioCentury.

According to van de Winkel, the expansion became problematic when the company found it could no longer depend on the markets for large capital infusions. Its last public offering was a private placement in 2006 in which Genmab raised DKK735 million ($119.5 million).

At the end of 1H10, Genmab had DKK931 million ($153.6 million) in cash and a six-month operating loss of DKK240.3 million ($39.6 million). Its 2009 operating loss was DKK498 million ($95.9 million).

van de Winkel, who was previously president of R&D and CSO, has set a goal of reducing operating expenses by 20% in 2011 *(see BioCentury, June 21)*.

EVP and CFO David Eatwell said the first step toward getting Genmab's cash burn under control was restructuring the deal with GSK and consolidating R&D into one facility.

In July, the biotech announced GSK would assume full responsibility for development of Arzerra for autoimmune indications. In exchange, Genmab received a £90 million ($135.5 million) payment.

The partners also capped Genmab's total contribution in cancer indications at £145 million ($218.3 million), with an annual spending cap of £17 million ($25.6 million) for the next six years.

Genmab relinquished rights to an undisclosed amount of development milestones and the first two sales milestones in autoimmune indications, while retaining double-digit royalties on autoimmune sales. In cancer, Genmab's potential milestones, which haven't been disclosed, will be reduced by 50%. Royalties in cancer remain unchanged at about 20%.

The company hopes to out-license zalutumumab, which would reduce R&D expenditures by DKK100 million ($17.6 million) in 2011, taking care of the planned 20% reduction in operating expenses.

For 2010, the estimated R&D expenditure for the company's three lead products — Arzerra, zalutumumab and daratumumab — is DKK400 million ($70.4 million). Before the paring down, Genmab had spent DKK413.3 million ($68.2 million) in 1H10; the company has not given full-year R&D guidance.

Arzerra is in Phase III testing for non-Hodgkin's lymphoma (NHL) and diffuse large B cell lymphoma (DLBCL). Next year, GSK plans to start a Phase IIb trial of a subcutaneous formulation to treat multiple sclerosis (MS). The pharma is reviewing its plans for further development of the subcutaneous formulation in RA.

According to van de Winkel, Genmab and regulatory authorities discussed the best path forward for zalutumumab following the Phase III failure in head and neck cancer, and the company now believes an MAA could be submitted in the EU for second-line use based on existing data. However, it believes additional clinical trials for the indication will be necessary before a BLA could be submitted to FDA.

The company is ramping up partnering discussions for the mAb, with the expectation the future U.S. or EU partners would be responsible for additional trials and regulatory filings.

van de Winkel also hopes to partner other candidates in the pipeline, such as HuMax-TAC, and to grant licenses to its antibody platform technology.

The deal with Lundbeck is an example. Genmab will generate and develop mAbs using its UltiMab and UniBody technologies against three undisclosed targets selected by Lundbeck. Genmab will receive DKK56 million ($10.5 million) up front.

Lundbeck has an option to take selected mAbs into clinical development for CNS indications at its own cost, which would result in Genmab being eligible for up to DKK227 million ($42.5 million) in milestones, plus single-digit royalties.

Genmab has a similar option to take selected mAbs into clinical development for cancer indications at its own cost, for which Lundbeck would be eligible for undisclosed milestones, plus single-digit royalties.

The company's next unpartnered program is daratumumab, a human mAb against CD38 that is in Phase I/II testing for multiple myeloma (MM), with data expected next year.

The company expects to file an IND for HuMax-cMet for cancer by the end of 2011. The human IgG1 antibody targets the c-Met proto-oncogene (MET; HGFR).

van de Winkel said some candidates could be partnered at the preclinical stage, while others could be taken into Phase III before finding a partner, as was done with ofatumumab. The timing will depend on the size of the potential market, differentiating characteristics of the mAb vs. competitors and Genmab's cash.

He also said Genmab is now open to doing multi-target discovery deals similar to a 2001 deal with **Roche** that was expanded in 2002. In that case, Genmab used its UltiMAb antibody technology to develop human antibodies against undisclosed disease targets identified by the pharma.

The two lead candidates to come out of that deal are RG4930, a human antibody that inhibits OX40 ligand (OX40L; CD134L) that is in Phase II development for asthma; and RG1512, a human mAb against P selectin (SELP; CD62P) that is in Phase I for peripheral vascular disease.

"I want to create access to capital by doing a number of deals, rather than by going back to the market," van de Winkel said.

"We are well capitalized right now. We have a product on the market, so we actually have an income stream that should accelerate in the future, and between now and then we will form new partnerships that will bring in new capital which strengthens our product base," he added.

According to Eatwell, Genmab expects to have DKK1.4 billion ($250.7 million) in cash at year end, which would give the company at least a three-year runway based on a projected

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ANALYSIS

COVER STORY

LAMbasting brain cancer
U.S. and German researchers have developed a nanoconjugate that selectively targets brain cancer and thus could have fewer dose-limiting toxicities than current therapies. Arrogene Nanotechnology has added the findings to its portfolio of drug delivery technologies.

TARGETS & MECHANISMS

Stemming ovarian cancer
A Boston team has identified ovarian cancer stem cells that may be responsible for the disease's high relapse rate. The group also discovered that a naturally occurring hormone called anti-Mullerian hormone can wipe out the stem cells, but manufacturing it could prove challenging.

Depression paths of least resistance
In two separate reports, U.S. and European researchers have identified new depression targets that could help identify or treat patients who fail to respond to or who develop resistance to marketed drugs. One of the targets, P11, is already in the preclinical pipelines of Neurologix and Intra-Cellular Therapies for therapeutic and diagnostic applications, respectively.

S1PR2's plaque attack
Inhibiting a receptor called S1PR2 could assault atherosclerotic plaques from multiple angles, according to findings by Japanese researchers. The receptor does have widespread expression, though, which could lead to safety issues in a chronic condition.

THE DISTILLERY

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annual burn rate of DKK450 million ($79.2 million).

If the company is able to get DKK800 million ($145 million) for the manufacturing facility it purchased from PDL, Eatwell said the YE10 cash position would increase to DKK2.2 billion ($391.4 million). That would give Genmab almost five years of cash, excluding any licensing deals or increased Arzerra royalties.

The desire to conserve cash isn't preventing Genmab from looking to step up its in-licensing of new technologies.

Under the first such deal, Genmab received rights last month to use Seattle Genetics' ADC technology with Genmab's preclinical cancer candidate HuMax-TF, a human mAb against tissue factor.

Genmab will be responsible for preclinical and Phase I testing, after which Seattle Genetics will have an option to co-develop the products. For co-developed products, the partners will share costs and profits 50/50. Seattle Genetics is eligible for milestones and royalties on products it does not co-develop.

In addition to bringing new technologies in-house, Genmab is developing new technologies internally, including a bispecific antibody technology that is in the early stages. van de Winkel said Genmab would seek to establish a business arrangement that would result in the financing of the industrial validation of the technology by a partner, while still retaining access to it for the biotech's internal programs.

Business decisions

van de Winkel's strategy will require the company to make more commercially and regulatory-minded decisions during preclinical and clinical development, so that the antibodies with the best market potential and regulatory pathway are prioritized.

To do this, van de Winkel set up a multi-disciplinary portfolio board earlier this year. The board includes representatives from research, clinical development, medical affairs, business development and finance.

Previously, R&D decisions were made in "more of a silo fashion," he said, such that research leaders decided which antibodies moved into preclinical development, while clinical development leaders would decide which moved into the clinic.

"We can't invest in everything, and we certainly can't invest in projects that are scientifically interesting but don't make good business sense. It takes great discipline to cap failures early," van de Winkel said.

Going forward, van de Winkel said Genmab has the capacity to start four new programs per year. "That should result in one IND candidate every year for the years going forward," he said.

"Over the years, we have set up a very efficient IND-generating engine, with 11 INDs over the last 11 years and still there are seven of those antibodies in development, so this is a pretty good track record," he noted.

COMPANIES AND INSTITUTIONS MENTIONED

Genmab A/S (CSE:GEN), Copenhagen, Denmark
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
PDL BioPharma Inc. (NASDAQ:PDLI), Incline Village, Nev.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Seattle Genetics Inc. (NASDAQ:SGEN), Bothell, Wash.
TenX Biopharma Inc. Philadelphia, Pa.