

# Post ASH Seminar

Antibody Innovation Generating World Class Products

December 17, 2012





### Forward Looking Statement

This presentation contains forward looking statements. The words "believe", "expect", "anticipate", "intend" and "plan" and similar expressions identify forward looking statements. All statements other than statements of historical facts included in this presentation, including, without limitation, those regarding our financial position, business strategy, plans and objectives of management for future operations (including development plans and objectives relating to our products), are forward looking statements. Such forward looking statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by such forward looking statements. Such forward looking statements are based on numerous assumptions regarding our present and future business strategies and the environment in which we will operate in the future. The important factors that could cause our actual results, performance or achievements to differ materially from those in the forward looking statements include, among others, risks associated with product discovery and development, uncertainties related to the outcome of clinical trials, slower than expected rates of patient recruitment, unforeseen safety issues resulting from the administration of our products in patients, uncertainties related to product manufacturing, the lack of market acceptance of our products, our inability to manage growth, the competitive environment in relation to our business area and markets, our inability to attract and retain suitably qualified personnel, the unenforceability or lack of protection of our patents and proprietary rights, our relationships with affiliated entities, changes and developments in technology which may render our products obsolete, and other factors. Further, certain forward looking statements are based upon assumptions of future events which may not prove to be accurate. The forward looking statements in this document speak only as at the date of this presentation.

.....



Jan van de Winkel, PhD

Dana Farber Cancer Institute

President & CEO

## Agenda

#### **News from the Clinic**

2:20 PM Daratumumab
2:45 PM Ofatumumab highlights from ASH
3:00 PM Clinical Pipeline Q&A
Clinical Pipeline Q&A
Jan van de Winkel Nikolai Brun Torben Plesner Prof. Paul Richardson, MD

#### **Pre-clinical Pipeline and Technology**

3:20 PM	Innovation fueling our pipeline	Jan van de Winkel	
3:25 PM	Pipeline progress: HuMax-TF-ADC aimed at the clinic	Jan van de Winkel	
3:30 PM	Trend-setting next generation antibody technologies	Paul Parren, PhD SVP & Scientific Director	
3:50 PM	Key takeaways & looking ahead	Jan van de Winkel	
3:55 PM	Q&A	Jan van de Winkel David Eatwell <i>EVP</i> & <i>CFO</i>	
4:30 PM	Close	Jan van de Winkel	
4:35 PM	Refreshments		3



# Impressive 2012 Achievements

Priority	Milestone	Current Progress
Maximize value of of atumumab	<ul> <li>» Report Ph II F&amp;A CLL refract. data</li> <li>» Ph III CLL mainten. safety interim data</li> <li>» Ph III DLBCL O vs R interim analysis for futility</li> <li>» Report data multiple ISS studies</li> </ul>	<ul> <li>Data presented at ASCO</li> <li>IDMC analysis expected H1 2013</li> <li>IDMC recommends continuing study</li> <li>Data from 11 ISS prest at ASCO, EHA,&amp; ASH</li> </ul>
Expansion Arzerra®	<ul> <li>» Launch &amp; reimbursement new countries</li> <li>» Filing in new territory</li> </ul>	<ul> <li>✓ 1<sup>st</sup> launch in S. America; now in 24 countries</li> <li>✓ GSK submitted NDA in Japan</li> </ul>
Daratumumab	<ul> <li>» Report efficacy data Ph I/II MM study</li> <li>» Initiate Ph I/II combination studies</li> <li>» Complete partnering</li> </ul>	<ul> <li>✓ Prelim. data ASCO, EHA, and ASH</li> <li>✓ 1<sup>st</sup> patient dosed Ph I/II study dara + Revlimid</li> <li>✓ Janssen agreement</li> </ul>
Expand pipeline	» Report proof-of-concepts ADC and DuoBody product candidates	<ul> <li>✓ DuoBody POCs presented at 14 conferences</li> <li>✓ Presented HuMax<sup>®</sup>-TF-ADC POC at Ann. ADC Series, and HuMax-TF-ADC &amp; HuMax- CD74 at 8<sup>th</sup> European Antibody Congress</li> </ul>
DuoBody <sup>®</sup> platform	<ul><li>» Enter new collaboration</li><li>» Advance platform</li></ul>	<ul> <li>✓ 3 collaborations: Novartis, Janssen &amp; KHK</li> <li>✓ 3 bispecific antibody programs activated by Janssen; \$2M POC milestone achieved</li> </ul>
Partnered programs	<ul> <li>» Report progress pre-clinical programs</li> <li>» Report progress clinical programs</li> <li>» Enter new collaboration</li> </ul>	<ul> <li>✓ 2nd &amp; 3rd Lundbeck milestones</li> <li>✓ Outlicense HuMax-IL8</li> </ul>
Manage and control cash burn	<ul> <li>» Reduce cash burn &amp; lengthen cash runway</li> <li>» Execute sale manufacturing facility</li> </ul>	<ul> <li>✓ Continuing operations improved 3 times</li> <li>✓ Cash runway now &gt; 4 years</li> <li>✓ Facility written down, sale projected Q1 2013</li> </ul>



# Antibody Innovation Generating World Class Products

- Focus on human antibodies to treat cancer
- Proven ability to bring product to market
  - One marketed product (Arzerra<sup>®</sup>) with growing sales
  - First-in-class daratumumab expected to be next marketed product
- Strong innovation focus
  - Proprietary bispecific technology DuoBody<sup>®</sup> Platform
  - Innovative pre-clinical pipeline including HuMax<sup>®</sup>-TF-ADC
  - World class antibody know-how
- Strategic collaborations with blue chip partners including GSK and Janssen
- Capital efficient model aimed at creating a sustainable business

# Delivering on Our Commitments

Strategy update 2010

- Focus on core competence
  - Extract value from validated technology
  - Lead in next-generation technologies
- Turn science into medicine
  - Arzerra<sup>®</sup> on market
  - Daratumumab moving towards market
- Build a profitable & successful biotech
  - Flexible, lean and efficient operating model
  - Maximize value through partnerships

Post ASH 2012



# **Genmab Product Innovation**





# Arzerra<sup>®</sup> (ofatumumab)

#### **About Arzerra**

- Fully human antibody
- Approved in US, EU & other territories for patients with CLL that does not respond to current treatments (fludarabine & alemtuzumab)
- Targets CD20 molecule on B-cells which can become cancerous
- Effectively engages immune system
- Slow release from disease target increases length of treatment effect
- Successful collabor. with GSK since 2006



#### **Arzerra Sales Growth**



#### **Future Growth Drivers**

- New Drug Application submitted Japan for CLL patients who received prior therapy
- Continued worldwide rollout
- Blockbuster potential in Cancer; broad potential in Autoimmune diseases
- Broad clinical program 7 cancer pivotal trials ongoing



## Ofatumumab: Driving Value Through Data Cancer Pivotal Study Readouts as of December 2012



#### **Relapsed DLBCL** (n=410)

Ofatuniumab + Chemo vs Rituximab + Chemo

= recruitment completed





# Daratumumab (HuMax<sup>®</sup>-CD38)

- First-in-class fully human antibody
- Targets CD38 molecule on multiple myeloma (MM) cells
- Potential in: MM, DLBCL, FL, Plasma Cell Leukemia, Mantle Cell lymphoma, ALL & AML
- Partnership with Janssen
- Potential MM market > \$3.9 billion
- Encouraging pre-clinical data
  - Broad-spectrum killing activity
  - Inhibits tumor growth; active at very low doses
  - Enhances cell killing in combination with current treatments (Revlimid, Velcade)





# Daratumumab Collaboration

#### **Deal Terms**

- Janssen Biotech, Inc.\* licenses worldwide rights: fully funds all development & commercialization
- \$55M upfront payment to Genmab
- \$80M equity investment by Johnson & Johnson Development Corporation (10.7% stake)
- > \$1.1 Bn total potential deal value
  - Incl. development, regulatory, and sales milestones
  - Plus double digit tiered royalties on global sales

#### **Development Plans**

- Genmab continues ongoing multiple myeloma (MM) studies
  - Phase I/II monotherapy
  - Phase I/II Revlimid combination
- Janssen to initiate >10 new studies
  - Several Phase III studies

#### **Potential Indications**

- Studies planned in 3 new indications
- Future potential indications
  - Acute myeloid leukemia (AML)
  - Diffuse large B-cell lymphoma (DLBCL)
  - Plasma cell leukemia (PCL)
  - Follicular lymphoma (FL)
  - Mantle cell lymphoma
  - Acute lymphoblastic leukemia (ALL)

## Hybrid Business Model Trend-Setting Technologies & Differentiated Products





# News from the Clinic

Daratumumab

Presented by Prof. Torben Plesner, MD Vejle Hospital, Denmark



# DARATUMUMAB, A CD38 MONOCLONAL ANTIBODY IN PATIENTS WITH MULTIPLE MYELOMA

# DATA FROM A DOSE-ESCALATION PHASE I/II STUDY

Torben Plesner, Henk Lokhorst, Peter Gimsing, Hareth Nahi, Steen Lisby, Paul Richardson

Vejle Hospital, Denmark; University Medical Center Utrecht, Netherlands; Copenhagen University Hospital, Denmark; Karolinska Institutet, Stockholm, Sweden; Genmab A/S, Copenhagen, Denmark; Dana-Farber Cancer Institute, Boston, MA, USA

### Daratumumab A Human CD38 mAb with Broad-Spectrum Killing Activity



# Daratumumab: GEN501

Phase I/II Study of Monotherapy in Relapsed and Relapsed -Refractory Multiple Myeloma

#### Objectives

#### Primary

• Establishment of the safety profile of daratumumab

#### Secondary

- To establish the pharmacokinetic profile of *daratumumab*
- Evaluation of the efficacy of *daratumumab* according to International Myeloma Workshop Consensus Panel 1, Blood 2011;117:4691-5
- Evaluation of the immunogenicity of daratumumab

### Daratumumab Main Inclusion Criteria

- Patients with advanced Multiple Myeloma requiring systemic therapy
- Patients with relapsed or relapsed and refractory disease with at least 2 prior lines of therapy and without further established treatment options
- Patients with ECOG performance status of 0-2
- Patients having a life expectancy > 3 months



### Daratumumab Patient Characteristics

Cohort	No. of subjects	Age <sup>a</sup>	No. of treatments <sup>a</sup>	Len <sup>b</sup>	Thal <sup>b</sup>	Bor⁵	Dex/ Pred <sup>b</sup>	Chemo <sup>b,c</sup>	ASCT <sup>b</sup>
≤1 mg/kg	17	63 (42-76)	5 (2-8)	88%	71%	100%	88%/41%	100%	65%
2 mg/kg	3	64 (60-71)	8 (6-10)	100%	100%	100%	100%/100%	100%	100%
4 mg/kg	3	64 (62-66)	6 (3-6)	100%	33%	100%	100%/33%	100%	67%
8 mg/kg	3	60 (56-68)	11 (5-12)	100%	67%	100%	100%/67%	100%	100%
16 mg/kg	3	55 (54-59)	7 (4-8)	67%	67%	100%	100%/33%	100%	100%
24 mg/kg	3	58 (50-69)	5 (4-6)	100%	67%	100%	100%/33%	100%	67%

ASCT=autologous stem cell transplant; Bor=bortezomib; Chemo=chemotherapy; Dex=dexamethasone; Len=lenalidomide; No.=number; Pred=prednisolone; Thal=thalidomide.

Note: These results are based on data before database lock.

a Median (range).

b Number of subjects exposed to the drug/treatment.

c Vincristine, doxorubicin, cyclophosphamide, melphalan, and others.

### Daratumumab Safety Findings

#### • Infusion-related reactions were observed during the initial infusions

- 9% during the pre-dose infusion
- 26% during the first full infusion with a gradual decrease in frequency during the subsequent infusions
- No dose relationship
- Two events grade 3, the remaining grade 1-2
- Onset of events within 3 to 4 hours of infusion
- Five late reactions:
  - 2 events of bronchospasm, 1 event each of headache, dyspnoea and fever
  - Patients with bronchospasm had a medical history of chronic bronchitis and asthma
- No major changes in platelet count or hemoglobin were observed over time
- A dose-dependent decrease in NK cells as measured in the peripheral blood was observed, with full recovery after treatment

# Daratumumab

Safety Findings

- Six SAEs were assessed as related to daratumumab:
  - One patient: anemia grade 3 (DLT) and thrombocytopenia grade 4 (0.1 mg/kg)
  - One patient: AST grade 3 (DLT) (1 mg/kg)
  - One patient: cytokine release syndrome grade 2 (0.1 mg/kg)
  - One patient: bronchospasm grade 3 (2 mg/kg)
  - One patient: bronchospasm grade 2 (24 mg/kg)
- In total, 2 DLT events reported; 3 more patients were enrolled in the 0.1 mg/kg and 1.0 mg/kg cohorts
- All patients recovered after relevant treatment

### Daratumumab Pharmacokinetics



- Plasma peak levels after first full dose: as expected for IgG
- Rapid clearance at low dose: indicates target-mediated clearance
- High inter-patient variability suggests effect of tumor load on PK
- 2 mg/kg: pre-dose trough levels far below prediction
- 4 mg/kg and upwards: sustained trough levels > 10 µg/ml indicate that the impact of target-mediated clearance becomes negligible at higher doses

### Daratumumab Response Maximal Change in Paraprotein



### Daratumumab Response

Max Reduction of M-Component/FLC/BM PCs and by IMWG Criteria

		Max. reduction in M-component (%)		Max. reduction in	Max reduction in	
Cohort (mg/kg)	N	Serum	Urine	between involved and uninvolved FLC (%)	plasma cells in BM smear (%) [Baseline value (%)]	Response according to IMWG <sup>a</sup>
4	3	49	*	*	80 [12.5]	MR
		100	87	96	89 [23]	PR
		64	*	*	97 [19]	PR
8	3	4	*	*	-29 [14]	SD
		39	*	*	93 [7.5]	MR
		*	*	*	_	NE
16	3	-3	*	-12		PD
		50	*	88	100 [31.5]	MR
		*	-12	55	100 [2]	SD
24	3	*	*	80 <sup>b</sup>	51 [18.5]	PR
		29 <sup>b</sup>	*	*	17 [3.0]	MR
		58 <sup>b</sup>	89	93	C	PR

Notes:

- \* no measurable disease/normal at Baseline
- data not available
- a Evaluation based on maximal reduction in M-component or FLC, according to the consensus on uniform reporting of clinical trials
- b Follow-up still ongoing
- c Data not yet available

### Daratumumab Progression free survival vs. Exposure



#### Daratumumab Conclusion 1/2

- Daratumumab has shown a favorable safety profile in the monotherapy study treating relapsed or relapsed and refractory Multiple Myeloma patients
- In 15 of 32 (47%) heavily pre-treated evaluable Multiple Myeloma patients receiving 8 weeks of daratumumab as monotherapy in doses up to 24 mg/kg, a reduction in paraprotein has been observed, corresponding to preliminary responses of:
  - 4 patients achieving PR (13%)
  - 6 patients achieving MR (19%)
  - 5 patients achieving SD (16%)
- At doses 4 mg/kg and above, 8 of the 12 patients had at least MR (67%)

# Daratumumab

Conclusion 2/2

- Biochemical response was accompanied by clearance of myeloma cells from the bone marrow
- At higher dose levels, observed plasma concentrations are close to those predicted
- MTD has not been reached
- Increased daratumumab exposure correlated with longer progression free survival
- Future directions: Extended exposure up to 24 months in MM patients with 8 mg/kg daratumumab as monotherapy and combination studies



# News from the Clinic

Ofatumumab Highlights from ASH

Presented by Nikolai C Brun, MD, PhD VP Medical dept. Genmab





### Ofatumumab Development Program Timeline to Primary Data – Per December 2012



# Ofatumumab Plus CHOP in Previously Untreated FL Study Design

- FL, grade 1-3, stage II/IV, or bulky stage II
- CD20+ (lymph node biopsy)
- No prior therapy
- ECOG performance status 0, 1, or 2
- Aged  $\geq$  18 years
- 59 patients randomized to ofatumumab 500 mg (n=29) or 1000 mg (n=30) with CHOP
- Follow-up continued until 24 mos. after last infusion (Figure 1)



Figure 1. Study Schema

## Ofatumumab Plus CHOP in Previously Untreated FL Key Safety Findings

- 97% of patients completed all 6 treatment cycles
- With exception of infusion-related reactions associated with ofatumumab, AEs and SAEs were consistent with those of CHOPbased therapy
- No unexpected AEs were reported
- No deaths and no hematologic SAEs during follow-up period
- Non-hematologic SAEs during follow-up period
- 500 mg 1 case of pneumonia
- 1000 mg abdominal hernia, erysipelas, intervertebral disc protrusion, menisus lesion and vulval cancer
- None related to ofatumumab



### Ofatumumab Plus CHOP in Previously Untreated FL Key Efficacy Findings

#### Figure 2. Ofatumumab Treatment Response



ORR, overall response rate; PR, partial response; CRu, complete response unconfirmed; CR, complete response. Error bars indicate 95% confidence interval; response rates shown are by IRC evaluation.

ORR, overall response rate; PR, partial response; Cru, complete response unconfirmed; CR, complete response Response rates shown are by IRC evaluation

### Ofatumumab Plus CHOP in Previously Untreated FL Conclusions

- O-CHOP achieved durable remissions in previously untreated patients with FL
- O-CHOP was effective in patients with high-risk FLIPI scores
- CR/CRu and PFS not affected by FLIPI scores
- Results indicate O-CHOP is effective upfront therapy in FL and demonstrated non-inferior anti-tumor activity in high-risk FLIPI subset
- Data support future evaluation of O-CHOP in FL



# Salvage Treatment with Ofatumumab & ESHAP in Relapsed/Refractory Classical Hodgkin's Lymphoma

- Phase II interim analysis
- 45 patients with relapsed/refractory classical Hodgkin's lymphoma after 1<sup>st</sup> line chemotherapy

	Response to first-line chemotherapy			
Response after O-ESHAP	Relapsed or partial response (n=17)	Refractory (n=16)		
OR	16 (94%)	7 (44%)		
CR	14 (82%)	3 (19%)		
PR	2 (12%)	4 (25%)		
Refractory	1 (6%)	9 (56%)		

#### **Conclusion**:

Preliminary results of this ongoing trial suggest that addition of ofatumumab to ESHAP in patients with relapsed/refractory HL candidates to ASCT:

- Is safe
- Allows PBSCs collection in most treated patients
- And has a promising clinical activity with an ORR at least similar to that obtained with other salvage regimens and it has a high efficacy in patients with relapsed HL or PR HL after 1<sup>st</sup> line therapy



# Phase I/II Trial of Ofatumumab/Lenalidomide in Relapsed/Refractory B-Cell NHL



#### **Conclusion:**

The combination of lenalidomide and of a tumumab was well tolerated by most patients. The patients with FL had a high response rate of 83 % and a 1 year PFS of 67%.



Ofatumumab: Improved Anti-Tumor Activity in Vitro and in Vivo in Mantle Cell Lymphoma (MCL)

Pre-clinical models have demonstrated that OFA was more potent than rituximab (RIT) in vitro and in vivo.




Ofatumumab: Improved Anti-Tumor Activity in Vitro and in Vivo in Mantle Cell Lymphoma (MCL)

### Conclusions

- Data suggest that of atumumab is more potent than RTX against Ara-C-sensitive and –resistant MCL cells in vitro
- Ofatumumab delays tumor growth and prolongs survival compared to RTX in an in vivo MCL SCID mouse model
- Ofatumumab retains CDC activity despite low CD20 and high complement inhibitory protein (CIP) surface expression levels
- Ofatumumab appears to be promising in MCL



Phase II Trial of Intracycle Sequential Ofatumumab and Lenalidomide in Relapsed/Refractory CLL

### 17 patients

Ofatumumab2000 mg IV on day 1 (300 mg on the first cycle)Lenalidomide10 mg PO from days 8-28 (5 mg on the first cycle)



Source: #3933, Costa et al - ASH Oral Presentation Dec 10, 2012



Phase II Trial of Intracycle Sequential Ofatumumab and Lenalidomide in Relapsed/Refractory CLL

- PR 10/16 = 62% (95% C.I. 39%-81%)
- SD 3/16 = 19% (95% C.I. 7%-43%)
- PD 3/16 = 19% (95% C.I. 7%-43%)
- Tumor flare reaction (TFR) 8/18 = 44%
- 2/18 (11%) early termination due to toxicity
  - Increase in AST/ALT
  - Thrombocytopenia
- Dose reduction (or no planned increased) of lenalidomide seen in 14/18 patients (78%)
- Most common grade 3/4 toxicity was neutropenia in 14/18 patients (78%)
- Fever and neutropenia in 2/18 patients (11%)

#### Conclusions

- OFA + LEN is active in high risk R/R CLL
- TFR is common and manageable, not requiring treatment interruptions
- Most frequent toxicity is neutropenia but infections are uncommon
- Expected trial completion in 06/13



# Phase II Trial of Ofatumumab in Previously Untreated CLL or SLL

- 77 pts with untreated CLL or SLL (Small Lymphocytic Leukemia)
- Older patients (≥ 65 y.o.) & patients who refuse fludarabine-based regimens – Study Design:





# Phase II Trial of Ofatumumab in Previously Untreated CLL or SLL – Results:

	-			-	-		-
<u>Responses</u>	<u>Cohort 1</u> <u>N=44</u> 2000 mg OFA	<u>Cohort 2</u> <u>N=33</u> 1000 mg OFA	Total Pts	<u>Responses</u>	<u>Cohort 1</u> <u>N=44</u> 2000 mg OFA	<u>Cohort 2</u> <u>N=33</u> 1000 mg OFA	<u>Total Pts</u>
CR	2 (5%)	1 (3%)	3 (4%)	CR	2 (5%)	1 (3%)	3 (4%)
PR	25 (57%)	9 (27%)	34 (44%)	PR	36 (82%)	18 (55%)	54 (70%)
SD	17 (38%)	19 (58%)	36 (47%)	SD	6 (13%)	10 (30%)	16 (21%)
PD	0	0	0	PD	0	0	0
UE	0	4 (12%)	4 (5%)	UE	0	4 (12%)	4 (5%)
ORR*	27/44 (62%)	10/33 (30%)	37/77 (48%)	ORR*	38/44 (86%)	19/33 (58%)	57/77 (74%)

#### By 1996 criteria (Rituximab approval):

\*Fisher's exact test (2 sided p-value) P=0.01

By 2008 criteria:

\*Fisher's exact test (2 sided p-value) P=0.008

#### **Conclusion:**

Single-agent of atumumab is well tolerated as front-line therapy in CLL/SLL.

"Response rates & PFS compare favorably to our previous studies with RTX using the same response criteria. Optimal single-agent dose of OFA in the front-line setting remains to be determined." [abstract]

Source: #719, Flinn et al – ASH Oral Presentation Dec 10, 2012



Combination of Ofatumumab and Lenalidomide Relapsed CLL: Results of a Phase II Trial

Design: 36 (34 evaluable) pts with R/R CLL – All previously FCR exposed

Lenalidomide and Ofatumumab in Relapsed CLL: Treatment Schedule



- Lenalidomide dose adjustment permitted for toxicity
- Allopurinol 300 mg d1-14
- No mandated antibiotic, anti-viral, DVT or tumor lair prophylaxis

Source: #720, Ferrajoli et al – ASH Oral Presentation Dec 10, 2012



# Combination of Ofatumumab and Lenalidomide Relapsed CLL: Results of a Phase II Trial

Lenalidomide+Rituximab <sup>1</sup> vs	Lenalidomidet	Ofatume		
		Oratumumab <sup>2</sup>		
Characteristic	L+R	L+O		
Study Time	2008-9	2010-11		
No. of Patients	59	34		
Median age, yrs (range)	62 (42-83)	64 (34-82)		
Median B2M (mg/L)	3.5	4.1		
# prior therapies (range)	2 (1-9)	2 (1-8)		
FDR refractory (%)	20			
17 p del (%)	25	26		
ORRICE (%)	66/12	68/24		
	00,12			
OS	PFS			
	The state			
	I have			
2 0.0- 5	1	and the second se		
	\$ 0.00	The second se		
	e			
TOTAL DED	- Len-Ofatumu	mab 14 22 59 42		
Len-Rituximab 59 17	0.0 1 Convenience	the star the		
ó é 12 18 24 30 36 Months		Abstr		

- Lenalidomide and ofatumumab is an effective salvage combination for CLL
- ORR: 68% with 24% CR and 16 month PFS
- Lenalidomide and ofatumumab is safe and the most common toxicity is myelosuppresion. Tumor flare reactions were mild.
- This study confirms the clinical activity of Lenalidomide and ofatumumab in CLL



## Key Learnings from ASH: Ofatumumab Demonstrates Sustained Effect in Multiple Indications

- Ofatumumab shows superiority compared to RTX in head-to-head pre-clinical study
- O-CHOP in Front line FL, 100% ORR
  - 67% in patients with high FLIPI score
- Up to 94% response rate in Relapsed / refractory Hodgkin's lymphoma
- 86% ORR and 80% PFS at 1 year as single agent in elderly front-line CLL pts who refuse fludarabine-based regimens
- Lenalidomide/Ofatumumab combination: In patients previously exposed to FCR with relapsed / refractory CLL: 68% ORR and 24%CR





# Clinical Pipeline Q&A

Torben Plesner, *Vejle Hospital*; Paul Richardson, *Dana Farber Cancer Institute*; Nikolai Brun & Jan van de Winkel, *Genmab* 





# Pre-clinical Pipeline & Technology

**Innovation Fueling Our Pipeline** 

Jan van de Winkel, PhD





# Therapeutic Antibody Landscape

2009 • 2010 • 2011 • 2012 • 2013 • 2014 • 2015 • 2016 • 2017 • 2018 • 2019 • 2020 • 2021 • 2022 • 2023 • 2024 • 2025

**NAKED ANTIBODIES** 

**ANTIBODY FRAGMENTS & SCAFFOLDS** 

**ANTIBODY-DRUG CONJUGATES** 

**POTENCY-ENHANCED ANTIBODIES** 

**BISPECIFIC ANTIBODIES** 

**ANTIBODY & FORMAT COMBINATIONS** 



# Robust Technology & IND Engine to Produce Better Cancer Therapeutic Antibodies

#### **UltiMAb®** Platform

- Validated technology
  - 5 approved products
  - 29 in development
- Naked & potency-enhanced antibodies

### DuoBody<sup>®</sup> Platform

- Genmab proprietary -
- Creates bispecific antibodies with ability to bind to 2 targets
- Potential in: cancer, infectious disease, autoimmune & CNS
- Collaborations with Novartis, Janssen, and KHK

#### **Antibody-Drug Conjugates**

- Major new advancement in antibody technology
- Collaboration with Seattle Genetics
- Research agreement with undiscl. pharma (DuoBody-ADC)

#### HexaBody<sup>™</sup> Platform

- Genmab proprietary -
- Enhances natural killing ability of antibodies
- Creates novel, differentiated products
- Potential in: cancer & infectious disease



# Genmab Product Innovation





# Innovative Pre-clinical Pipeline IND Candidates





# The Genmab Advantage

- Streamlined antibody selection
- Automated creation of very large libraries of antibodies
- Expert capabilities in analysis of antibody characteristics
- Unsurpassed antibody validation
- Discovery integrated with clinical development
- Suite of next generation proprietary technologies





# Pre-clinical Pipeline & Technology

HuMax-TF-ADC Aimed at the Clinic

Jan van de Winkel, PhD





### HuMax<sup>®</sup>-Tissue Factor-ADC

- Fully human antibody-drug conjugate
- Targets Tissue Factor (TF)
- Potential in multiple solid cancers including pancreatic, lung, bladder, cervix, ovarian, and prostate cancer
- IND submission prepared for 2013
- Collaboration with Seattle Genetics





# TF – An Excellent ADC Target





# TF – An Excellent ADC Target





## TF – An Excellent ADC Target





# HuMax-TF-ADC Efficient Tumor Cell Killing in Laboratory Models

- Models
  - Cell line derived xenograft models in vivo (in house)
  - Human biopsy derived xenograft models in vivo (Oncotest GmbH)



# HuMax-TF-ADC Effective Inhibition Tumor Outgrowth in *in vivo* Models

human epidermoid carcinoma model



Genmab



## HuMax-TF-ADC Efficacy in Tumor with Heterogeneous TF Expression



- Isotype control
- Isotype control-ADC
- HuMax-TF-ADC
- Treatment





## HuMax-TF-ADC On Track to 2013 IND

Good non-clinical safety profile

- Multiple cynomolgus monkey toxicity studies
  - HuMax-TF well-tolerated up to high doses in dose-escalation study
  - HuMax-TF-ADC
    - Acceptable toxicity profile in dose-escalation study
    - Well-tolerated in 10-week repeat dose toxicity study
    - 13-week repeat dose tox study ongoing
- HuMax-TF & HuMax-TF-ADC tissue cross-reactivity studies completed





# Pre-clinical Pipeline & Technology

Trend-setting Next-Generation Antibody Technologies

Paul Parren, PhD





## Genmab Product Innovation Exploiting the Ways Antibodies Work





# DuoBody® Platform Turning Science into Medicine

DuoBody platform is based on **Fab-arm exchange**, a naturally occurring process for generating bispecificity



Natural process for bispecificity

- IgG4
- Naturally occurs in human body
- Dynamic reaction



DuoBody process for bispecificity

- IgG1
- Controlled laboratory conditions
- Unidirectional reaction



# DuoBody Platform Efficient Bispecific Antibody Production

- Combines two IgG1 antibodies into one bispecific antibody
  - Dual target binding
  - Increased potency
- Retains regular IgG1 structure, function & stability
- Easily applied to both drug discovery and large-scale development
- Broad therapeutic potential





## DuoBody Platform Bispecific Antibody Discovery





# DuoBody Platform Robust, Scalable & Efficient Manufacturing



67



## Application for Bispecific Antibodies Immune Effector Cell Recruitment



68

### Genmab

# DuoBody Platform Preferred Technology for Bispecific Antibody Therapeutics





# Introducing HexaBody<sup>TM</sup> Creating Differentiated Antibody Products





# HexaBody Platform Enhancing Natural Killing Mechanisms

- Potentiates the **natural** ability of antibodies to kill targets by specific clustering after target binding
- Enhancement of **multiple** killing mechanisms
- Highly suitable for therapy in major therapeutic areas with broad market potential including cancer & infectious disease





# HexaBody Platform Enhancing Natural Killing Mechanisms




#### HexaBody Platform Applicable to Wide Range of Targets

Target	Enhanced Effector Function by HexaBody
CD38	$\checkmark$
CD20	$\checkmark$
CD19	$\checkmark$
EGFR	$\checkmark$



### HexaBody Exploiting the Ways Antibodies Work

- Exploits natural clustering
- Activity restricted to target cells
- Multiple killing mechanisms are enhanced
- Minimal protein engineering
- Applicable to a wide range of targets
- Allows available libraries to be exploited
- Highly suitable for developing treatments in major therapeutic areas





## **Science-Driven Product Innovation**

- Genmab innovates immunotherapy by exploiting the ways antibodies work
- Validation of DuoBody platform
  - Partnerships with Janssen, Novartis, KHK & undisclosed pharma
- HexaBody platform to profoundly enhance natural killing mechanisms









# Key Takeaways & Looking Ahead

Jan van de Winkel, PhD





## Genmab Today – Positioned for Success

#### Sales

- Growing GSK sales
- 2011 Arzerra sales GBP 43.5M
- 2012 9 mo Arzerra sales GBP 45.5M
- Partner milestone payments

#### **Pipeline**

- Cancer focused
- Expanding potential of Arzerra
- Efforts to bring daratumumab to market
- 12 INDs in 12 years

#### **Partnerships**

- Amgen
- Roche
- GSK
- Seattle Genetics
- Lundbeck
- Emergent
- Undiscl. pharma
- Cormorant
- Novartis
- Janssen x2
- Kyowa Hakko Kirin



### HexaBody Platform New Business Opportunities

- Novel, differentiated products
  - Hematology, oncology, infectious diseases
- Attractive alternative to pay-load enhanced antibodies
- Other opportunities
  - Repurpose / rescue drug candidates that failed in Phase II or III
  - Life cycle management





#### In Summary Robust Pipeline Progress

- Expansion of Arzerra
  - Pivotal studies start to read out in 2013
  - Continued development in numerous indications
- Daratumumab partnership with Janssen
  - Multiple new studies involving > 3,500 patients
- HuMax-TF-ADC on track for 2013 IND
- Trend-setting next-generation antibody technologies
  - DuoBody Productive partnerships with Janssen, Novartis, and KHK
  - HexaBody Exciting new business opportunities









## 2013: A Year of Data and Deals

Priority	Milestone
Maximize value of ofatumumab	<ul> <li>» Ph III frontline CLL; ofa + chlorambucil vs chlorambucil data</li> <li>» Ph II front and 2nd line; ofa + bendamustine data</li> <li>» Ph III CLL; ofa maintenance safety interim data</li> <li>» Update progress ofa sc autoimmune development</li> </ul>
Expansion Arzerra	<ul> <li>» Approval in Japan</li> <li>» Launch &amp; reimbursement in new countries</li> </ul>
Fully exploit the potential of daratumumab	<ul> <li>Ph I/II MM monotherapy matured safety &amp; efficacy data</li> <li>Ph I/II MM combi therapy preliminary safety &amp; efficacy data</li> <li>Initiate additional MM clinical studies</li> </ul>
Expand pipeline	<ul> <li>File IND for HuMax-TF-ADC</li> <li>Initiate first in human trial with HuMax-TF-ADC</li> <li>Update progress pre-clinical programs including ADC and DuoBody projects</li> </ul>
Next generation technologies	<ul> <li>» Expand DuoBody technology collaborations</li> <li>» Validate and advance HexaBody platform</li> </ul>
Partnerships	<ul> <li>» Report progress partnered programs</li> <li>» Enter new collaboration</li> </ul>
Disciplined expense management, reduce cash burn	<ul> <li>» 2013 operating loss &lt; than in 2012</li> <li>» Reduce cash burn, lengthen cash runway</li> </ul>



### Creating Value: World Class Products & Technology

- Unique, world-class antibody expertise
- Therapeutic antibodies at the heart of cancer treatment
- Broad pipeline of differentiated products
- Innovative suite of cutting edge antibody technologies
- Working towards translating our technologies into products of the future
- Driving sustainable value and growth













# Genmab

# Glædelig Jul og Godt Nytår Holiday Greetings Prettige Feestdagen

Copenhagen | Princeton | Utrecht