Herzlich Willkommen
zum Treffen des
AK Regulatorische Toxikologie
am
18. November 2005
Our Strategy is the Successful Discovery, Development and Commercialization of Anticancer Drugs

- Founded in 1997
- IPO in 2000 on Frankfurt Stock Exchange (FSE: GPC)
- NASDAQ ADRs since June 2004 (GPCB)
- Market cap as of Sept. 29, 2005: €313m
- Cash and equivalents: €121.6m
-Indices: TecDAX, NASDAQ Health Care Index

* Shares, cash and employee figures as of June 30, 2005
1D09C3
Anti-MHC Class II Monoclonal Antibody for Oncology

Treffen des AK Regulatorische Toxikologie
18. November 2005

Benno Rattel
GPC Biotech AG
Agenda

• At the Start
• Project Goal
• Searching for an Antibody
• Looking for Activity
• Gearing up for the Clinics:
  CMC (Chemistry, Manufacturing, Control)
  Bioanalytical methods
  Toxicology
• First Into Man (FIM) Studies
At the Start...

- Activation of T helper cells triggered by foreign antigen bound to MHC (major histocompatibility complex) class II, also called HLA (human-leucocyte-associated antigen)
2. Elimination von Fremdantigenen (z. B. Bakterien)
At the Start...

- MHC class II is selectively expressed on antigen-presenting cells
- Anti-class II antibodies could be drug candidates for selective immunosuppressive treatment
mAbs against MHC-II can
- inhibit Th cell response
- be cytotoxic on EBV-transformed and mitogen-pre-activated B-cells

Select and develop human anti-MHC class II monoclonal antibodies from human antibody gene libraries that cause selective, programmed death of MHC class II positive malignant cells
GPC Biotech and MorphoSys collaborate on human therapeutic antibodies against autoimmune diseases and lymphoid malignancies

Munich, Germany, April 16th 1999 –

GPC Biotech AG [...] and MorphoSys AG [...] today announced an agreement under which the two Munich-based firms will collaborate in the development of human therapeutic antibodies against proprietary GPC immunology targets. No financial terms were disclosed.

Under the terms of the collaboration, MorphoSys will apply its Human Combinatorial Antibody Library (HuCAL) technology to generate human antibodies against specific major histocompatibility complex (MHC) class II molecules, crucial components of the immune system which are able to distinguish between own tissue (‘self’) and foreign organisms. Any irregularities in this precise mechanism of action can result in the development of autoimmune disease. The goal of the programme is to develop a new generation of highly specific therapeutics to treat a variety of key autoimmune diseases, including rheumatoid arthritis and multiple sclerosis (MS), graft versus host disease, transplant rejection, as well as certain MHC class II-positive lymphoid malignancies. [...]
Searching for a Human mAb (Panning) Phage Display Screening

MorphoSys HuCal® Library ®

- Single Chain Fvs
- MHC+ve cell
- Human MHC
- Chimeric MHC
- Red mouse
- Black human
- HuCal®
- Affinity-
- Maturations

@ Complementarity Determining Regions

* Human Combinatorial Antibody Library
# Killing of Lymphoid Tumors by anti-HLA-DR mAbs

<table>
<thead>
<tr>
<th>Cell line</th>
<th>HLA-DR expression mean-FL</th>
<th>% Killing by mAb</th>
<th>murine mAbs</th>
<th>human mAbs</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>L243 8D1 1D09C3</td>
<td>C7277</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LG-2</td>
<td>1.1 B-lymphoblastoid</td>
<td>458 79 85 87 88</td>
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<tr>
<td>Priess</td>
<td>4.4 B-lymphoblastoid</td>
<td>621 87 83 88 93</td>
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<tr>
<td>ARH-77</td>
<td>12 B-lymphoblastoid</td>
<td>301 88 73 85 88</td>
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<tr>
<td>GRANTA-519</td>
<td>2.11 B cell non-Hodgkin</td>
<td>1465 83 56 78 78</td>
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<tr>
<td>KARPAS-422</td>
<td>2.4 B cell non-Hodgkin</td>
<td>211 25 32 66 68</td>
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<td>KARPAS-299</td>
<td>1.2 T cell non-Hodgkin</td>
<td>798 78 25 82 79</td>
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<tr>
<td>DOHH-2</td>
<td>1.2 B cell lymphoma</td>
<td>444 29 23 59 60</td>
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<tr>
<td>SR-786</td>
<td>1.2 T cell lymphoma</td>
<td>142 3 8 53 44</td>
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<tr>
<td>MHH-CALL-4</td>
<td>1.2 B-ALL</td>
<td>358 35 41 63 46</td>
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<tr>
<td>MN-60</td>
<td>10.13 B-ALL</td>
<td>1120 46 22 69 72</td>
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<tr>
<td>BJAB</td>
<td>12.13 Burkitt lymph.</td>
<td>338 53 59 70 67</td>
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<tr>
<td>RAJI</td>
<td>10.17 Burkitt lymph.</td>
<td>617 69 64 84 86</td>
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<tr>
<td>L-428</td>
<td>12 Hodgkin's lymph.</td>
<td>244 82 81 91 91</td>
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<tr>
<td>HDLM-2</td>
<td>Hodgkin's lymph.</td>
<td>326 77 73 88 84</td>
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<td>HD-MY-Z</td>
<td>Hodgkin's lymph.</td>
<td>79 35 39 69 57</td>
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<td>KM-H2</td>
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<td>619 81 56 86 88</td>
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<td>L1236</td>
<td>Hodgkin's lymph.</td>
<td>41 52 62 63 66</td>
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<tr>
<td>BONNA-12</td>
<td>hairy cell leuk.</td>
<td>2431 92 91 92 91</td>
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<tr>
<td>HC-1</td>
<td>hairy cell leuk.</td>
<td>372 88 89 93 86</td>
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<tr>
<td>NALM-1</td>
<td>1.4 CML</td>
<td>1078 44 4 82 78</td>
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<tr>
<td>L-363</td>
<td>plasma cell leu.</td>
<td>49 6 5 26 24</td>
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<tr>
<td>EOL-1</td>
<td>AML (eosinophil)</td>
<td>536 22 13 69 49</td>
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<tr>
<td>LP-1</td>
<td>multiple myeloma</td>
<td>315 12 0 73 70</td>
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<tr>
<td>RPMI-8226</td>
<td>multiple myeloma</td>
<td>19 6 0 29 26</td>
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<tr>
<td>MHH-PREB-1</td>
<td>B cell non-Hodgkin</td>
<td>175 3 3 4 8</td>
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<td>OPM-2</td>
<td>multiple myeloma</td>
<td>3 13 0 1 4</td>
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<td>KASUMI-1</td>
<td>AML</td>
<td>5 0 0 10 10</td>
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<tr>
<td>HL-60</td>
<td>AML</td>
<td>3 18 0 15 9</td>
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<td></td>
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<tr>
<td>LAMA-84</td>
<td>CML</td>
<td>7 7 9 11 5</td>
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</tr>
</tbody>
</table>

% Killing: 100 - % viable cells after a 4h treatment with 200 nM murine or 50 nM human mAb at 37°C.
**Ex Vivo Efficacy of Anti-DR mAbs on CLL Cell Samples from Patients**

**Resting cells**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>4h</th>
<th>24h</th>
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</thead>
<tbody>
<tr>
<td>h4.None</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>h4.10F12</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>h4.L243</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>h4.B8</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>h4.1C7277</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>h4.1D09C3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Activated cells**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>4h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>h4.None</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>h4.10F12</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>h4.L243</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>h4.B8</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>h4.1C7277</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>h4.1D09C3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**CLL: Chronic Lymphatic Leukemia**

13
• 4 different types of lymphoma
• 2 non-neoplastic lymph nodes
• 1D09C3 was immunoreactive for lymphocytes only and not for other non-lymphoid tissues


In vitro Efficacy on a Panel of Tumor Cell Lines

- Killing is dependent on MHC (HLA-DR) expression
- Killing is HLA-DR allotype independent
- Cell lines of various tumor types killed effectively
- Potency higher than that of previously known mouse antibodies
Characteristics of MHC Class II Mediated Cell Death

- Affects only activated/tumor transformed cells
- Resting B cells, macrophages, dendritic cells resistant
- mAb must recognize the first (N-terminal) domain (membrane-distal) of class II to induce cell death
- Cytotoxicity consequence of MHC-cross-linking
- Inherent tumoricidal activity independent of complement and ADCC
Characteristics of MHC Class II Mediated Cell Death

• Lack of apoptotic nuclear morphology, and is resistant to caspase inhibitors

• Increase of reactive oxygen species (apoptosis prevented by ROS scavenger Tiron)

• Phosphorylation and activation of Jun kinase (JNK)

• Depolarization of mitochondrial membrane

• Release of apoptosis-inducing factor (AIF) from mitochondria
In Vivo Mouse Tumor Model

- Subcutaneous or intravenous administration of Granta 519 cell line (non-Hodgkin’s lymphoma) to SCID mice
- 1D09C3 Dosing Days 5, 7 and 9

Mouse #2, untreated, Day 32; tumor area 4.76 cm²

Mouse #13, mAb i.v., Day 32; tumor area 0.01 cm²
In vivo Efficacy: Subcutaneous Tumor (NHL)
*In vivo* Efficacy: Subcutaneous Tumor (NHL)
1D09C3 Treatment of Chronic Lymphocytic Leukemia

- JVM-2 + 1D09C3_1 mg (n = 10)
- JVM-2 + 1D09C3_2 mg (n = 10)
- JVM-2 + 1D09C3_3 mg (n = 14)
- Control (n = 16)
Synergism Between 1D09C3 and Rituxan in Birkitt`s Lymphoma

1D09C3 dosing:
Days 5 and 12
Synergism Between 1D09C3 and Rituxan in NHL

Disease endpoint: Paraplegia or death
Manufacturing of Drug Substance/Product

Cell Line
- Stably expressing mAb
- High productivity

GMP* Master Cell Bank
- 20 * 1 ml

GMP Fermentation Process
- Reproducible
- High end titer
- 200 * 1 ml
- 1000-3000 L

GMP Purification Process
- High capacity
- Virus removal step
- 100-300 g

Drug Product Manufacturing

* Good Manufacturing Practice
CMC Analytics

- Characteristics
e.g. Appearance, pH, Osmolarity, Turbidity

- Content/Activity
e.g. Protein Content, Biol. Activity, ELISA, Amino Acid Comp.

- Purity
e.g. SEC-HPLC, SDS-PAGE Reduced/Non-Reduced

- Impurity/Safety
e.g. Sterility, Endotoxin, Host Cell Protein/DNA, Protein A/G

- Identity/Composition
e.g. IEF, IEC, Peptide Mapping, N/C-Terminal Sequ., Carbohydrates MALDI-TOF MS
Quantitation of 1D09C3 in Serum Humans

Mouse α-human IgG4 - AP conjugate

MHC-II HLA
DRA1*0101
DRB1*0401

1. Coating

2. Capture

3. Detection
Quantitation of anti-1D09C3 Antibodies Monkeys and Humans

1. Coating
   Human serum;
   Surrogate:
   Rabbit α-1D09C3 idiotype

2. Capture
   1D09C3
   HRP conjugate

3. Detection
   1D09C3- HRP conjugate
   HRP
Inhibiting anti-1D09C3 Antibodies
Monkey and Humans

1. Coating
   - MHC-II HLA
     - DRA1*0101
     - DRB1*0401

2. Competition + Capture
   - 1D09C3-Biotin conjugate

3. Detection
   - Biotin
   - SA
   - Anti-1D09C3 antibody
   - AP
MHC-II Receptor Saturation
FACS

- blood sample + isotype control

- blood sample + xs 1D09C3

- MHC-II B-cell + CD20-PE, CD14-PC5, αhuIgG4-FITC

- MHC-II B-cell B-cells, Monocytes, HuIgG4
Toxicology
Selection of a Relevant Animal Species

A relevant species is one in which the test article is pharmacologically active due to the expression of the receptor or epitope.
Toxicology
Species Selection

• Cynomolgus monkey B cells bind 1D09C3

• Cross reactivity study in 32 human and Cynomolgus monkey tissues

• Cynomolgus monkey tissues showed the same cross reactivity pattern like the human tissues

• Cynomolgus monkey model is valid
Cross Reactivity Study with 1D09C3 Human Liver
Cross Reactivity Study with 1D09C3 Human Lung
DRF Study

- **Species:** Cynomolgus monkey
- **Number of Animals:** 3 males
- **Route:** Intravenous slow bolus
- **Dosages:** 1 and 10 mg/kg
- **Schedule:** Sequentially on Days 1 and 8
DRF Study Sampling Schedule

- 1 week: hematology; clinical pathology
- Day 1: predose hematology

1st Dosing (1mg/kg)
- 2h (TK), 4h, hematology
- Day 2: 24h hematology; TK
- Day 3: 48h hematology
- Day 4: 96h hematology; TK
- Day 8: predosing hematology

2nd Dosing (10mg/kg)
- 30 min, 2h (TK), 4h, hematology
- Day 9: 24h hematology; TK
- Day 10: 48h hematology
- Day 12: 96h hematology; TK; clinical pathology;
- Day 16: 192h hematology; necropsy
DRF Studies

- 1 mg/kg
  - MHC Class II molecules in peripheral blood not fully saturated

- 10 mg/kg
  - Full saturation MHC Class II molecules in peripheral blood
Multiple Dose Finding Study

- **Species:** Cynomolagus monkey
- **Number of Animals:** 1 male + 1 female per group
- **Dosages:** 10 and 30 mg/kg
- **Route:** Intravenous slow bolus
- **Schedule:** 3 dosages in weekly intervals
According to ICH S6 Guideline

- **Species:** Cynomolgus monkeys, purpose bred from Mauritius
- **Route:** Intravenous infusion 100 min
- **Formulation:** used as supplied in vials
- **Cycles:** 5 once every week
- **Sequence:** by group (1+2, 3+4)
### Pivotal Repeat Dose Toxicity Study

**Groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage (mg/kg)</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>3+2</td>
<td>3+2</td>
</tr>
<tr>
<td>1D09C3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1D09C3</td>
<td>10</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1D09C3</td>
<td>30</td>
<td>3+2</td>
<td>3+2</td>
</tr>
<tr>
<td>1D09C3</td>
<td>0.3, 1</td>
<td>3</td>
<td>(single dose)</td>
</tr>
</tbody>
</table>

- **Interim necropsy:** after cycle 5 infusion
- **Recovery necropsy:** after 4 week post-dose observation
Pivotal Repeat Dose Toxicity Study

- **Ophthalmoscopy:**
  - pretreatment, between cycles 4 and 5

- **ECG:**
  - pretreatment, Cycle 3: 2h and 24 h after dosing

- **Hematology:**
  - Cycles 1, 3, 5: predosing, pre-1D09C3
  - Cycles 1, 3, 5: 1h after dosing with 1D09C3
  - Recovery
• Subtyping and MHC class II expression (FACS):
  ✓ Cycles 1, 3, 4, 5: predosing, pre-1D09C3
  ✓ Cycles 1, 3, 4, 5: 1h after dosing with 1D09C3
  ✓ Recovery
# Pivotal Repeat Dose Toxicity Study

## Clinical Pathology Parameters

### Haematology:
- Haematocrit
- Haemoglobin
- Erythrocyte count
- Reticulocytes
- Total leucocyte count
- Differential leucocyte count
- Abnormalities
- Platelet count
- Mean cell haemoglobin
- Mean cell volume
- Mean cell haemoglobin concentration
- Prothrombin time
- Activated partial thromboplastin time

### Flow Cytometry:
- Total B lymphocytes (CD20+)
- Total T lymphocytes (CD3+)
- CD4 T lymphocytes (CD3+CD4+CD8-)
- CD8 T lymphocytes (CD3+CD4-CD8+)
- NK cells (CD3-CD56+)
- Monocytes (CD14)

### Blood Chemistry:
- Alkaline phosphatase
- Alanine amino-transferase
- Glucose
- Bilirubin
- Cholesterol
- Triglycerides
- Creatinine
- Urea
- Total protein
- Protein electrophoretogram
- Albumin/globulin ratio
- Sodium
- Potassium
- Chloride
- Calcium
- Phosphorous
• **Blood Chemistry:**
  - Pretreatment
  - Cycles 3, 5: 1h after dosing
  - Recovery

• **Urinalysis:**
  - Pretreatment, between cycles 4 and 5
Pivotal Repeat Dose Toxicity Study

• Toxicokinetics:
  ✓ Cycle 1: 30min, 4h, 8h, 24h, D3, D5, D8 (predose)
  ✓ Cycle 4: 30min, 4h, 8h, 24h, D3, D5, D8 (predose)

• Anti-1D09C3 Antibodies* and Protein Subfractions IgG/IgM/IgE):
  ✓ Predosing at each cycle: D1, D8, D15, D22, D29,
  ✓ Recovery

*amount, neutralizing potential, BiaCore characterization
Pivotal Repeat Dose Toxicity Study

• Terminal Studies:
  ✓ All animals: Standard procedure for necropsy
  ✓ Groups 1-4: Histopathology
  ✓ Flow cytometry on lymphnode and spleen (B-, T-, CD4 T- and CD8 T-lymphocytes)
  ✓ Snap frozen sections of lymph nodes, liver, kidneys, lungs, spleen, Payer`s Patches and thymus stored
Drug Regulatory Affairs

- IMPD (Investigational Medicinal Product Dossier) documentation prepared and filed
- Several Meetings with PEI
Clinical Starting Dose

• **In vitro killing assay**
  
  *Cell number* (KMH2 tumor): $1.21 \times 10^6$ (in 0.55 ml)
  
  *IC*$_{max}$ (conc. needed for maximal kill) of 1D09C3: 15nM = 1.24 µg (in 0.55 ml)
  
  (NB.: normal resting cells are not killed up to at least 50 nM)

• **Cynomologus Monkey**
  
  *B cells*: $1.5 \times 10^6$/ml; *Monocytes*: $5 \times 10^5$/ml; *Blood volume*: 250 ml

• **Humans**
  
  *B cells*: $1.25 \times 10^6$/ml; *Monocytes*: $4 \times 10^5$/ml; *Blood volume*: 5 liter

• **HLA-DR expression**
  
  *Resting normal cells*: $4 \times 10^5$/cell; *Tumor cells*: $8 \times 10^5$/cell

• **B cells and monocytes in lymphoid organs**
  
  50x of that in total blood (based on mouse data)
Clinical Starting Dose

• **In Vitro Tumor Cell Killing**
  
  Total number of cellular DR: $\sim 1 \times 10^{12}$
  
  Mab molecules at $IC_{max}$ (1.24 µg) = $5 \times 10^{12}$

• Thus, a 5 fold molar excess is required for total kill!

• **In Vivo Cynomologus Monkey**
  
  B+Mono in blood: $5 \times 10^8$, in lymphoid org.: $2.5 \times 10^{10}$, total = $2.55 \times 10^{10}$
  
  Total DR in cyno: $1.02 \times 10^{16}$
  
  Mab molecules needed: $\sim 5 \times 10^{16} = 12.5$ mg = 5 mg/kg (for 2.5 kg)

• This corresponds very well to the experimental DR-saturation dose, which was found to be between at approx 3 mg/kg!

• **In Vivo Human**
  
  B+Mono in blood: $8.25 \times 10^9$, in lymphoid org. $4.13 \times 10^{11}$, total = $4.21 \times 10^{11}$
  
  Human DR total: $1.68 \times 10^{17}$
  
  Mab molecules needed: $8.4 \times 10^{17} = 210$ mg = 3 mg/kg (for 70 kg)

• Start with $1/10^{th}$ of this dose.
Phase 1 clinical study program initiated in early 2005

- 1D09C3 tested in relapsed/refractory B-cell lymphomas, including non-Hodgkin’s lymphoma
- 1st site active: IOSI in Switzerland under Dr. Franco Cavalli - world-renowned oncology center
- Program also involves other leading academic centers in Europe
Summary
Monoclonal Antibody 1D09C3

• Active in B-cell and T-cell lymphomas
• Novel mechanism-of-action; targets MHCII
• Needs no immunological effector function
• Fully human, very high affinity (pM) antibody
• Potentially synergistic effect with Rituxan®
• Phase 1 clinical study program initiated in early 2005
  - Relapsed/refractory B-cell lymphomas, including Hodgkin’s and non-Hodgkin’s lymphomas
• Orphan drug designation granted in EU for Hodgkin’s lymphoma