49th ASCO Annual Meeting, Chicago

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Sunday, June 2, 2013
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Agenda

Introduction
Karl Mahler, Head of Investor Relations

Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities):
Final stage 1 results of the CLL11 (BO21004) phase III trial
Valentin Goede, MD, German CLL Study Group; Dept. I of Internal Medicine, University Hospital Cologne and Dept. of Geriatric Medicine and Research St. Marien-Hospital Cologne

Oncology pipeline update
Hal Barron, M.D., Chief Medical Officer and Head Global Product Development

Oncology business update
Daniel O’Day, Chief Operating Officer Roche Pharmaceuticals

Q&A followed by dinner
Roche oncology sales evolution
A portfolio of distinctive medicines

Sales at 2012 exchange rates
Roche oncology: From 1 medicine in 1 tumor types to 9 medicines in 14 tumor types

- **Kadcyla**
  - 2L HER 2+ BC

- **Perjeta**
  - 1L HER 2-positive BC
  - Basal Cell Carcinoma

- **Erivedge**
  - Melanoma

- **Zelboraf**
  - Pancreatic cancer

- **Tarceva**
  - Lung cancer

- **Avastin**
  - Ovarian
  - Renal cancer
  - Recurrent glioblastoma
  - Metastatic breast cancer (1st, 2nd line)
  - Lung cancer
  - Metastatic colorectal cancer (1st, 2nd line, TML)

- **Xeloda**
  - Colorectal cancer
  - Breast cancer

- **Herceptin**
  - HER2-positive gastric cancer
  - Early HER2-positive breast cancer
  - HER2-positive metastatic breast cancer

- **MabTheraRituxan**
  - CLL
  - Agressive NHL
  - Indolent NHL

**Timeline:**
- **1997:**
  - 1L HER 2-positive BC

- **2005:**
  - Basal Cell Carcinoma

- **2013:**
  - HER2-positive metastatic breast cancer
Strategies beyond great medicines
HER2 franchise

- Herceptin + chemo
- Lapatinib + chemo
- Kadcyla
- Perjeta
- Replace and extend

Medical value

Replace
Extend

EMILIA / MARIANNE
CLEOPATRA
MARIANNE
Strategies beyond great medicines

Hematology

Replace and extend

Replace

Extend

Medical value

MabThera

GA101

Chemo

MabThera

BCL2

ADCs

ADC 22

ADC 79b

Our vision

CLL11 etc.

Romulus

GA101

BCL2

ADCs

ADC 22

ADC 79b

Medical value

MabThera

GA101

Chemo

MabThera

BCL2

ADCs

ADC 22

ADC 79b

Our vision

CLL11 etc.

Romulus

GA101
Obinutuzumab (GA101): CLL11 study

Valentin Goede, MD

German CLL Study Group
Dept. I of Internal Medicine, University Hospital Cologne and
Dept. of Geriatric Medicine and Research St. Marien-Hospital Cologne
Obinutuzumab (GA101) + chlorambucil (Clb) or rituximab (R) + Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): final stage I results of the CLL11 (BO21004) phase 3 trial

**CLL11: Rationale**

- High number of elderly patients with CLL and co-existing medical conditions\(^1,2\)

- In this patient population:
  - No conclusive evidence that currently available treatments are superior to chlorambucil (Clb) monotherapy\(^3\)
  - Encouraging phase 2 data to develop combinations of Clb with anti-CD20 mAb\(^4,5\)
  - Encouraging phase 1/2 data to evaluate chemoimmunotherapy with novel type 2 anti-CD20 mAb obinutuzumab (GA101)\(^6,7\)

**Aims:** To show that in CLL patients with co-existing medical conditions...

... Clb plus anti-CD20 mAb is superior to Clb monotherapy (Stage I)

... GA101 plus Clb is superior to rituximab plus Clb (Stage II)

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GA101: Mechanisms of action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa

Lower CDC
Type II versus Type I antibody

ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
CLL11: Study design

- GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
- Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb
Patient disposition

Stage Ia

Enrolled patients
G-Clb, n = 238
Clb, n = 118
2 received no treatment

Received treatment
G-Clb, n = 236
Clb, n = 116
46 (19%) withdrawn from treatment

Stage Ia data cutoff
July 11, 2012
Median observation time:
Clb 13.6 months
G-Clb 14.5 months

Stage Ib

Clb, n = 118
R-Clb, n = 233
2 received no treatment
3 received no treatment

Clb, n = 116
R-Clb, n = 230
26 (11%) withdrawn from treatment

Stage Ib data cutoff
August 10, 2012
Median observation time:
Clb 14.2 months
R-Clb 15.3 months
### Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Stage Ia</th>
<th>Stage Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clb (n = 118)</td>
<td>G-Clb (n = 238)</td>
</tr>
<tr>
<td>Male, %</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>72 (43–87)</td>
<td>74 (39–88)</td>
</tr>
<tr>
<td>Aged ≥ 65 years, %</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Aged ≥ 75 years, %</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>Median ECOG PS</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Median CIRS score</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>CIRS score &gt; 6, %</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>Median CrCl, ml/min*</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>CrCl &lt; 70 ml/min, %</td>
<td>61</td>
<td>68</td>
</tr>
<tr>
<td>CrCl &lt; 50 ml/min, %</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>

CrCl data available for 117/118 patients in the Clb arms.
## Baseline disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Stage Ia Clb (n = 118)</th>
<th>Stage Ia G-Clb (n = 238)</th>
<th>Stage Ib Clb (n = 118)</th>
<th>Stage Ib R-Clb (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphocyte count, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25 x 10^9/l*</td>
<td>84</td>
<td>76</td>
<td>84</td>
<td>71</td>
</tr>
<tr>
<td>≥ 100 x 10^9/l*</td>
<td>37</td>
<td>24</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td><strong>Binet stage, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>20</td>
<td>23</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>B</td>
<td>42</td>
<td>41</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>C</td>
<td>37</td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td><strong>Cytogenetics, %</strong></td>
<td>(n = 96)</td>
<td>(n = 203)</td>
<td>(n = 97)</td>
<td>(n = 196)</td>
</tr>
<tr>
<td>17p–</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>11q–</td>
<td>15</td>
<td>16</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Tri12</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>13q–</td>
<td>33</td>
<td>29</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Other abnormality</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>16</td>
<td>24</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td><strong>IGHV status, %</strong></td>
<td>(n= 99)</td>
<td>(n= 210)</td>
<td>(n= 100)</td>
<td>(n =204)</td>
</tr>
<tr>
<td>Unmutated</td>
<td>59</td>
<td>61</td>
<td>58</td>
<td>62</td>
</tr>
</tbody>
</table>

* Circulating lymphocyte counts available for 116/118 patients in the Clb arms, 237/238 in the G-Clb arm, and 231/233 patients in the R-Clb arm.
## End-of-treatment response rates

<table>
<thead>
<tr>
<th>Response rate, %</th>
<th>Stage Ia (Cr/CRi 22.2%)</th>
<th>Stage Ib (Cr/CRi 22.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>30.2 (n = 106)</td>
<td>75.5 (n = 212)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>0</td>
<td>22.2</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>30.2</td>
<td>53.3</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>21.7</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>25.5</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Not evaluable</strong></td>
<td>22.6</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>MRD-negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0 (0/80)</td>
<td>31.1 (41/132)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0 (0/30)</td>
<td>17.0 (15/88)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response rate, %</th>
<th>Stage Ib (Cr/CRi 22.2%)</th>
<th>Stage Ib (Cr/CRi 22.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>30.0</td>
<td>65.9</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>30.0</td>
<td>57.6</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>20.9</td>
<td>13.4</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>28.2</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Not evaluable</strong></td>
<td>20.9</td>
<td>9.2</td>
</tr>
<tr>
<td><strong>MRD-negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>0 (0/82)</td>
<td>2.0 (3/150)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0 (0/32)</td>
<td>2.8 (2/72)</td>
</tr>
</tbody>
</table>

---

a Not reached by cutoff in 12 patients in Stage Ia Clb arm, 26 patients in G-Clb arm, eight patients in Stage Ib Clb arm, and 16 patients in the R-Clb arm; as assessed by iwCLL criteria.

b Includes CR with incomplete hematologic recovery.

c Includes nodular PR.

d As measured by central laboratory assessment (ASO-RQ-PCR); bone marrow samples were usually only taken from patients thought to be in CR.
**Investigator-assessed PFS (months)**

**Stage Ia**
- G-Clb: Median 23.0 mo*  
- 1-year PFS 84%
- Stratified HR: 0.14  
- 95% CI: 0.09–0.21  
- \( p < 0.0001 \) (log-rank)
- Clb: Median 10.9 mo  
- 1-year PFS 27%
- Stratified HR: 0.32  
- 95% CI: 0.24–0.44  
- \( p < 0.0001 \) (log-rank)

**Stage Ib**
- R-Clb: Median 15.7 mo  
- 1-year PFS 63%
- Clb: Median 10.8 mo  
- 1-year PFS 27%

---

Type 1 error controlled through closed test procedure; p-value of the global test was <.0001.

* In the G-Clb arm < 10% of patients had reached the median at cutoff; therefore, in contrast to the Clb arm the G-Clb median PFS could not be reliably estimated due to the few patients at risk at time of G-Clb median.

Independent Review Committee (IRC) - assessed PFS was consistent with investigator-assessed PFS.
Stage Ia: PFS subgroup analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>356</td>
<td>0.14</td>
<td>0.10–0.21</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75</td>
<td></td>
<td>205</td>
<td>0.13</td>
<td>0.07–0.22</td>
</tr>
<tr>
<td>≥ 75</td>
<td></td>
<td>151</td>
<td>0.18</td>
<td>0.10–0.31</td>
</tr>
<tr>
<td>&lt; 65</td>
<td></td>
<td>68</td>
<td>0.03</td>
<td>0.01–0.13</td>
</tr>
<tr>
<td>≥ 65</td>
<td></td>
<td>288</td>
<td>0.18</td>
<td>0.12–0.27</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>215</td>
<td>0.18</td>
<td>0.11–0.29</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>141</td>
<td>0.10</td>
<td>0.05–0.20</td>
</tr>
<tr>
<td>Binet stage at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>79</td>
<td>0.09</td>
<td>0.04–0.21</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>148</td>
<td>0.14</td>
<td>0.07–0.26</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>129</td>
<td>0.19</td>
<td>0.10–0.37</td>
</tr>
<tr>
<td>CIRS score at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td></td>
<td>85</td>
<td>0.12</td>
<td>0.05–0.30</td>
</tr>
<tr>
<td>&gt; 6</td>
<td></td>
<td>271</td>
<td>0.14</td>
<td>0.09–0.23</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70 ml/min</td>
<td></td>
<td>232</td>
<td>0.18</td>
<td>0.11–0.28</td>
</tr>
<tr>
<td>≥ 70 ml/min</td>
<td></td>
<td>123</td>
<td>0.07</td>
<td>0.03–0.15</td>
</tr>
<tr>
<td>&lt; 50 ml/min</td>
<td></td>
<td>94</td>
<td>0.19</td>
<td>0.08–0.42</td>
</tr>
<tr>
<td>≥ 50 ml/min</td>
<td></td>
<td>261</td>
<td>0.13</td>
<td>0.08–0.21</td>
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<tr>
<td>β2–microglobulin (mg/l)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.5</td>
<td></td>
<td>228</td>
<td>0.13</td>
<td>0.08–0.22</td>
</tr>
<tr>
<td>≥ 3.5</td>
<td></td>
<td>118</td>
<td>0.16</td>
<td>0.08–0.30</td>
</tr>
<tr>
<td>IgHV mutational status</td>
<td></td>
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</tr>
<tr>
<td>Mutated</td>
<td></td>
<td>112</td>
<td>0.10</td>
<td>0.04–0.24</td>
</tr>
<tr>
<td>Unmutated</td>
<td></td>
<td>187</td>
<td>0.17</td>
<td>0.10–0.28</td>
</tr>
<tr>
<td>Chromosomal abnormalities at baseline (hierarchical model)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17p–</td>
<td></td>
<td>26</td>
<td>0.42</td>
<td>0.15–1.17</td>
</tr>
<tr>
<td>11q–</td>
<td></td>
<td>47</td>
<td>0.09</td>
<td>0.03–0.27</td>
</tr>
<tr>
<td>+12</td>
<td></td>
<td>49</td>
<td>0.24</td>
<td>0.08–0.76</td>
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<tr>
<td>13q–</td>
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<td>90</td>
<td>0.15</td>
<td>0.06–0.35</td>
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<tr>
<td>Other</td>
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<td>24</td>
<td>0.20</td>
<td>0.05–0.79</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>63</td>
<td>0.12</td>
<td>0.04–0.34</td>
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</tbody>
</table>
Stage Ib: PFS subgroup analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>351</td>
<td>0.34</td>
<td>0.25–0.46</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt; 75</td>
<td>203</td>
<td>0.35</td>
<td>0.23–0.52</td>
</tr>
<tr>
<td></td>
<td>≥ 75</td>
<td>148</td>
<td>0.32</td>
<td>0.20–0.52</td>
</tr>
<tr>
<td></td>
<td>&lt; 65</td>
<td>73</td>
<td>0.27</td>
<td>0.14–0.52</td>
</tr>
<tr>
<td></td>
<td>≥ 65</td>
<td>278</td>
<td>0.36</td>
<td>0.25–0.51</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>224</td>
<td>0.40</td>
<td>0.27–0.58</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>127</td>
<td>0.25</td>
<td>0.14–0.42</td>
</tr>
<tr>
<td>Binet stage at baseline</td>
<td>A</td>
<td>73</td>
<td>0.32</td>
<td>0.12–0.45</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>150</td>
<td>0.33</td>
<td>0.21–0.53</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>128</td>
<td>0.39</td>
<td>0.23–0.67</td>
</tr>
<tr>
<td>CIRS score at baseline</td>
<td>≤ 6</td>
<td>92</td>
<td>0.28</td>
<td>0.15–0.52</td>
</tr>
<tr>
<td></td>
<td>&gt; 6</td>
<td>259</td>
<td>0.35</td>
<td>0.25–0.51</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>&lt; 70 ml/min</td>
<td>226</td>
<td>0.32</td>
<td>0.22–0.47</td>
</tr>
<tr>
<td></td>
<td>≥ 70 ml/min</td>
<td>124</td>
<td>0.38</td>
<td>0.23–0.64</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 ml/min</td>
<td>81</td>
<td>0.32</td>
<td>0.16–0.65</td>
</tr>
<tr>
<td></td>
<td>≥ 50 ml/min</td>
<td>269</td>
<td>0.35</td>
<td>0.25–0.50</td>
</tr>
<tr>
<td>β₂–microglobulin (mg/l)</td>
<td>&lt; 3.5</td>
<td>216</td>
<td>0.24</td>
<td>0.16–0.37</td>
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<tr>
<td></td>
<td>≥ 3.5</td>
<td>125</td>
<td>0.50</td>
<td>0.31–0.79</td>
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<tr>
<td>IgHV mutational status</td>
<td>Mutated</td>
<td>107</td>
<td>0.12</td>
<td>0.06–0.23</td>
</tr>
<tr>
<td></td>
<td>Unmutated</td>
<td>184</td>
<td>0.43</td>
<td>0.29–0.65</td>
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<tr>
<td>Chromosomal abnormalities at baseline (hierarchical model)</td>
<td>17p–</td>
<td>19</td>
<td>0.55</td>
<td>0.18–1.72</td>
</tr>
<tr>
<td></td>
<td>11q–</td>
<td>52</td>
<td>0.52</td>
<td>0.25–1.06</td>
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<td></td>
<td>+12</td>
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<td>0.30</td>
<td>0.12–0.76</td>
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<tr>
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<td>13q–</td>
<td>87</td>
<td>0.26</td>
<td>0.13–0.52</td>
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<tr>
<td></td>
<td>Other</td>
<td>26</td>
<td>0.26</td>
<td>0.09–0.77</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>57</td>
<td>0.20</td>
<td>0.08–0.48</td>
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</table>
Overall survival

Stage Ia
Median follow-up 14.2 months

Deaths at cutoff:
G-Clb 5.5%
Clb 7.6%

n at risk

<table>
<thead>
<tr>
<th></th>
<th>Clb</th>
<th></th>
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<tbody>
<tr>
<td>G-Clb</td>
<td>238</td>
<td>226</td>
<td>218</td>
<td>179</td>
<td>139</td>
<td>115</td>
<td>72</td>
<td>37</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Clb</td>
<td>118</td>
<td>108</td>
<td>101</td>
<td>78</td>
<td>65</td>
<td>47</td>
<td>30</td>
<td>16</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Stage Ib
Median follow-up 15.2 months

Deaths at cutoff:
R-Clb 7.7%
Clb 10.2%

n at risk

<table>
<thead>
<tr>
<th></th>
<th>Clb</th>
<th></th>
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</thead>
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<tr>
<td>R-Clb</td>
<td>233</td>
<td>227</td>
<td>223</td>
<td>190</td>
<td>158</td>
<td>125</td>
<td>78</td>
<td>44</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Clb</td>
<td>118</td>
<td>108</td>
<td>104</td>
<td>83</td>
<td>71</td>
<td>56</td>
<td>34</td>
<td>23</td>
<td>8</td>
<td>1</td>
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</table>
### Relevant AE during treatment

<table>
<thead>
<tr>
<th></th>
<th>Stage Ia</th>
<th>Stage Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clb (n = 116)</td>
<td>G-Clb (n = 240)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any AE grade ≥ 3, %</td>
<td>41.4</td>
<td>66.7</td>
</tr>
<tr>
<td>IRR&lt;sup&gt;b&lt;/sup&gt;, %</td>
<td>n/a</td>
<td>21.3</td>
</tr>
<tr>
<td>Neutropenia, %</td>
<td>14.7</td>
<td>34.2</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>5.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>3.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Infection, %</td>
<td>11.2</td>
<td>6.3</td>
</tr>
<tr>
<td>AE leading to withdrawal from study medication, %</td>
<td>14.7</td>
<td>19.6</td>
</tr>
<tr>
<td>AE leading to death, %</td>
<td>5.2</td>
<td>2.1</td>
</tr>
<tr>
<td>AE new malignancy, %</td>
<td>0.9</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Safety population for G-Clb includes four patients randomized to R-Clb who received one infusion of GA101 in error.

<sup>b</sup>Infusion Related Reactions (IRR)
Stage Ia: IRR by cycle

- **All grades**
  - Day 1: 69%
  - Day 8: 3%
  - Day 15: 0%

- **Grade 3-4**
  - Day 1: 21%
  - Day 8: 0%
  - Day 15: 0%

(No deaths due to IRR)
**Stage Ia:** The addition of G to Clb was associated with:

- **Improved PFS** (HR: 0.14, 95% CI: 0.09–0.21, \( p < 0.0001; 23.0 \text{ vs } 10.9 \text{ mo} \))
- **Higher CR rate** (22.2% vs 0%)
- **MRD negativity** (31.1% vs 0% in blood; 17.0% vs 0% in bone marrow)
- **Increased rate of grade ≥ 3 neutropenia** (34% vs 15%)
- **Grade ≥ 3 IRR occurring at first infusion only** (21%)

**Stage Ib:** The addition of R to Clb was associated with:

- **Improved PFS** (HR: 0.32, 95% CI: 0.24–0.44, \( p < 0.0001; 15.7 \text{ vs } 10.8 \text{ mo} \))
- **Higher CR rate** (8.3% vs 0%)
- **Increased rate of grade ≥ 3 neutropenia** (25% vs 15%)
First large and pivotal, phase 3 trial reporting on an elderly CLL patient population with co-existing medical conditions

First direct comparison of Clb vs Clb plus anti-CD20 mAb demonstrating that addition of GA101 or rituximab is beneficial in these patients

Acceptable safety profile for G-Clb (and R-Clb); IRR and neutropenia are the most important adverse events

The protocol specified final analysis of G-Clb vs R-Clb will occur in stage 2 of the study
Oncology Pipeline Update

Hal Barron, M.D.
Executive Vice President
Global Development and Chief Medical Officer
Agenda

Combinations: Future of cancer care

Improving the standard of care in hematology

Anti-PDL1: Promising immunotherapy

Avastin in GBM and Cervical cancer
### Best-in-class oncology pipeline

**39 NMEs and 32 AIs supporting long-term growth**

<table>
<thead>
<tr>
<th>Phase I (26 NMEs)</th>
<th>Phase II (8 NMEs+ 11 AIs)</th>
<th>Phase III (3 NMEs+17 AIs)</th>
<th>Registration (2 NMEs+ 4 AIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM2 ant</td>
<td>Perjeta</td>
<td>Avastin</td>
<td>MabThera&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>HER3 MAb</td>
<td>BC neoadjuvant</td>
<td>HER2+ BC adj</td>
<td>NHL sc formulation</td>
</tr>
<tr>
<td>CSF-1R MAb</td>
<td>Perjeta</td>
<td>Avastin</td>
<td>Avastin&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>MEK inh</td>
<td>HER2+ mBC 2&lt;sup&gt;nd&lt;/sup&gt;  line</td>
<td>HER2-neg. BC adj</td>
<td>glioabloma 1&lt;sup&gt;st&lt;/sup&gt; line</td>
</tr>
<tr>
<td>Tweak MAb</td>
<td>Perjeta</td>
<td>Avastin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Herceptin&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ang2-VEGF MAb</td>
<td>RAF &amp; MEK dual inh</td>
<td>Avastin</td>
<td>HER2+ BC sc form</td>
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<tr>
<td>CD44 MAb</td>
<td>solid tumors</td>
<td>Avastin</td>
<td>Tarceva&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDM2 ant</td>
<td>solid &amp; hem tumors</td>
<td>Avastin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NSCLC EGFR mut 1&lt;sup&gt;st&lt;/sup&gt; line</td>
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<tr>
<td>MEK inh</td>
<td>solid tumors</td>
<td>Avastin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Kadcyla&lt;sup&gt;4&lt;/sup&gt;(T-DM1)</td>
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<tr>
<td>AKT inhibitor</td>
<td>solid tumors</td>
<td>Avastin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>HER2+ pretr. mBC</td>
</tr>
<tr>
<td>CD-L1 MAb</td>
<td>prostate ca.</td>
<td>Perjeta</td>
<td>advanced BCC</td>
</tr>
<tr>
<td>Steap 1 ADC</td>
<td>ovarian ca.</td>
<td>Zelboraf</td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>multiple myeloma</td>
<td>Zelboraf</td>
<td></td>
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<tr>
<td>Steap 1 ADC</td>
<td>ovarian ca.</td>
<td>Zelboraf</td>
<td></td>
</tr>
<tr>
<td>Bcl-2 inh</td>
<td>CLL and NHL</td>
<td>Zelboraf</td>
<td></td>
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<tr>
<td>Chk1 inh</td>
<td>solid tum &amp; lymphoma</td>
<td>Zelboraf</td>
<td></td>
</tr>
<tr>
<td>PI3K inh</td>
<td>solid tumors</td>
<td>Zelboraf</td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>metastatic melanoma</td>
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<tr>
<td>PI3K inh</td>
<td>solid tumors</td>
<td>Zelboraf</td>
<td></td>
</tr>
<tr>
<td>Chk1 inh(2)</td>
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<tr>
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<td>NSCLC</td>
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<tr>
<td>PI3K inh</td>
<td>solid tumors</td>
<td>Zelboraf</td>
<td></td>
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<tr>
<td>WT-1 peptide</td>
<td>cancer vaccine</td>
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<tr>
<td><strong>New Molecular Entity (NME)</strong></td>
<td></td>
<td></td>
<td>1 US only: ongoing evaluation for FDA submission</td>
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<tr>
<td><strong>Additional Indication (AI)</strong></td>
<td></td>
<td></td>
<td>2 Submitted in EU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 Approved in US, submitted in EU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 Approved in EU, submitted in US</td>
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Status as of March 31, 2013
R&D cycle: Translating learnings from the clinic into preclinical research
Improving cancer treatment with combinations

29 internal combinations with 18 compounds in over 9 tumor types, and increasing

<table>
<thead>
<tr>
<th>Solid tumors</th>
<th>Colon cancer</th>
<th>Lymphoma</th>
<th>Gastric, brain, kidney and others</th>
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<tr>
<td><strong>Breast cancer</strong></td>
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<td>Perjeta</td>
<td>Herceptin Ph3</td>
<td>Anti-CD22 ADC Rituxan Ph2</td>
<td>Perjeta Herceptin Ph3</td>
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<td>Herceptin Ph3</td>
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<td>Onartuzumab Avastin Ph2</td>
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<tr>
<td>Kadcyla</td>
<td>Perjeta Ph3</td>
<td>Bcl2 inh</td>
<td>Anti-EGFL7 Avastin Ph2</td>
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<tr>
<td>Kadcyla</td>
<td>Perjeta Ph3</td>
<td></td>
<td>Anti-PDL1 Avastin Ph1</td>
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<tr>
<td>Perjeta</td>
<td>Herceptin Ph3</td>
<td></td>
<td>Melanoma Cobimetinib Zelboraf Ph3</td>
</tr>
<tr>
<td>Onartuzumab</td>
<td>Avastin Ph2</td>
<td></td>
<td>Melanoma Anti-PDL1 Zelboraf Ph1</td>
</tr>
<tr>
<td>Pictilisib (PI3Ki)</td>
<td>Kadcyla Ph1</td>
<td></td>
<td>Melanoma Cobimetinib AKT inh Ph1</td>
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<td>Pictilisib (PI3Ki)</td>
<td>Herceptin Ph1</td>
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<td>Avastin Ph2</td>
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<td>Avastin Ph2</td>
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<td>Pictilisib (PI3Ki)</td>
<td>Avastin Ph1</td>
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<td>Tarceva Ph1</td>
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<tr>
<td><strong>Colon cancer</strong></td>
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<td>Onartuzumab</td>
<td>Avastin Ph2</td>
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<td>Avastin Ph1</td>
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<td>Avastin Ph1</td>
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<td>Tarceva Ph1</td>
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<td><strong>Gastric, brain, kidney and others</strong></td>
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<td>Herceptin Ph3</td>
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<td>Onartuzumab</td>
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<tr>
<td>Anti-EGFL7</td>
<td>Avastin Ph2</td>
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<tr>
<td>Anti-HER3 MAb</td>
<td>Tarceva Ph1</td>
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</table>

✓ Studies read out/filed/approved

Roche

29
Combinations: Future of cancer care

Improving the standard of care in hematology

Anti-PDL1: Promising immunotherapy

Avastin in GBM and Cervical cancer
Hematology franchise
Multiple compounds targeting distinctive pathways

**Improving the backbone (anti-CD20)**

- **Obinutuzumab (GA101)**
  - CLL filed US/EU
  - Phase III rituximab ref. NHL, 1L DLBCL and 1L iNHL+maintenance

- **MabThera Rituxan**
  - Oncology indications:
    - CLL
    - iNHL
    - aNHL/DLBCL

**Exploring combinations with complementary MoA**

**Bcl-2 inh +/- anti-CD20**

- Phase III R/R CLL, Bcl-2 + rituximab FPI Q1 2014
- Phase II CLL (17p del) FPI Q3 2013
- Phase I GA101+Bcl-2

**ADC + anti-CD20**

- Phase II NHL (FL+DLBCL) CD22+rituximab vs. CD79b+rituximab

---

**CLL**: Chronic Lymphocytic Leukemia; **NHL**: Non-Hodgkin’s Lymphoma (i=indolent, a=aggressive); **DLBCL**: Diffuse Large B-cell Lymphoma; **FL**: Follicular Lymphoma; **R/R**: Rituximab Refractory
GA101: glyco-engineered, type II CD20 antibody

Increasing efficacy vs. Rituxan/MabThera

**Increased direct cell death**
Type II vs. Type I antibody

**Lower CDC activity**
Type II vs. Type I antibody

**Enhanced ADCC**
Glyco-engineering for increased affinity to FcγRIIIa

ADCC = Antibody-Dependent Cell-mediated Cytotoxicity;
CDC = Complement Dependent Cytotoxicity

*Mössner E, et al. Blood. 2010; June 3; 115:4393-4402*
GA101 in NHL: Phase III development

**GADOLIN study**

- **Rituximab-refractory iNHL (n=360)**
  - **Induction**: GA101 + bendamustine x 6 cycles, Bendamustine x 6 cycles
  - **Maintenance**: GA101 q2mo x 2 years

**Primary end-point**: PFS
**Expect data**: 2015

**GOYA study**

- **Previously untreated DLBCL (n=1,400)**
  - **Induction**: GA101 x 8 cycles + CHOP x 6 or 8, MabThera x 8 cycles + CHOP x 6 or 8
  - **Maintenance**: MabThera x 8 cycles + CHOP x 6 or 8

**Primary end-point**: PFS
**Expect data**: 2015

**GALLIUM study**

- **First-line iNHL (n=1,400)**
  - **Induction**: GA101 x 8 cycles + CHOP x 6 or 8, GA101 x 6 cycles + benda. x 6, MabThera x 8 cycles + CHOP x 6 or 8, MabThera x 8 cycles + CVP x 8 or 8, MabThera x 6 cycles + benda. x 6
  - **Maintenance**: GA101 q2mo x 2 years
  - **CR, PR**

**Primary end-point**: PFS
**Expect data**: 2017
GDC-0199 (Bcl-2 inhibitor)

Apoptosis: Why should a cell commit suicide?

Role of apoptosis

Proper development

- Resorption of the tadpole tail
- Formation of fingers and toes of the fetus
- Sloughing off of the inner lining of the uterus
- Formation of proper connections between neurons in the brain

Cell destruction

- Cells infected with viruses
- Cells of the immune system
- Cells with DNA damage
- Cancer cells

Bcl-2 inhibitor: pro-apoptotic small molecule

- GDC-0199: highly selective, orally bioavailable, small molecule Bcl-2 inhibitor
- Attractive therapeutic target in CLL
- >100-fold improved functional selectivity for Bcl-2 over Bcl-xL in assays with tumor cell lines
## Bcl-2 in R/R NHL: Best response

<table>
<thead>
<tr>
<th></th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DLBCL (n=8)</strong></td>
<td>1 (13)</td>
<td>2 (25)</td>
<td>1 (13)</td>
<td>4 (50)</td>
</tr>
<tr>
<td><strong>Follicular lymphoma (n=11)</strong></td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>8 (73)</td>
<td></td>
</tr>
<tr>
<td><strong>Mantle cell lymphoma (n=8)</strong></td>
<td></td>
<td>8 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Waldenstrom macroglobulinemia (n=3)</strong></td>
<td>1 (33)</td>
<td>2 (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marginal zone lymphoma (n=1)</strong></td>
<td></td>
<td></td>
<td>1 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple myeloma (n=1)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1 (100)</td>
</tr>
<tr>
<td><strong>Total (n=32)</strong></td>
<td></td>
<td></td>
<td></td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

Overall Best Response Rate = (PR + CR) = 17/32 (53%)
MCL Overall Best Response Rate = 8/8 (100%)

*2 patients discontinued due to PD prior to first response assessment (1 MZL and 1 DLBCL)
Bcl-2 in R/R CLL: Dose escalation phase I study

Phase I in CLL (n=55)

May-2012

Jan-2013

Partial response ongoing >1 year

Blood

Lymph nodes

Bone marrow

ASCO 2013
### Efficacy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Best Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Evaluable (n=55)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Overall response rate</td>
<td>46 (84)</td>
</tr>
<tr>
<td></td>
<td>Complete response (CR/CRi)</td>
<td>10 (18)</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
<td>36 (65)</td>
</tr>
<tr>
<td></td>
<td>Stable disease</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>Disease progression</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 subject has not reached Week 6 for evaluation by scan; 4 patients discontinued prior to Week 6 assessment.

### Safety

**Tumor Lysis Syndrome (TLS)**

- Clinical TLS occurred in 2 subjects in this trial and 1 in another phase 1 trial
  - All had bulky lymphadenopathy ≥10 cm
- TLS can be associated with rapid tumor reduction
  - Titrated dosing scheme combined with more aggressive prophylaxis, monitoring, and management may provide adequate protection for patients
  - Dose and schedule evaluation will continue

---

ASCO 2013
**Bcl-2 development program in CLL**

**Phase I study Relapsed/Refractory CLL**

- Relapsed/Refractory CLL → Bcl-2 dose-escalation
  - 4 cohorts (100-400 mg)
- Combination
  - GA101+Bcl-2
  - 6 cycles
- Single agent Bcl-2
  - to progression

- Establish the dose of Bcl-2 and safety of the combination (Q4 2013)
- Activity in expansion cohorts (2H 2014)

**Adjunct Phase II study Relapsed/Refractory CLL with 17 p deletion**

- Relapsed/Refractory CLL with 17 p deletion → GDC-0199
  - 400 mg
- Treatment to progression

- Primary end-point: Overall Response Rate
- **FPI:** Q3 2013
- **Expect data:** end 2014

**Phase III Relapsed/Refractory CLL**

- Relapsed/Refractory CLL → Rituximab + GDC-0199
  - X 6 cycles
- GDC-199
  - 2 years
- Observation

- Primary end-point: PFS
- **FPI:** Q1 2014
- **Expect data:** 2016
Anti-CD22 and anti-CD79b: Novel drug candidates in CD20-positive B-cell malignancies

**Surface immunoglobulin (sIg)**
- **CD79a/b (Igα/β)**
- **CD22**

**Anti-CD79b**
- Signaling component of Ig B-cell receptor (with CD79a)
- Negative regulator of B-cell function
- Restricted to B-cell lineage
- Internalized & trafficked to a lysosomal compartment
- Expressed on the surface of >98% of NHLs
- Strong activity in multiple xenograft models of NHL

<table>
<thead>
<tr>
<th></th>
<th>Anti-CD79b</th>
<th>Anti-CD22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Signaling component of Ig B-cell receptor (with CD79a)</td>
<td>Negative regulator of B-cell function</td>
</tr>
</tbody>
</table>

**Graphs**
- **Granta MCL**
  - Tumor volume (mm³)
  - Comparison of treatments: RTX, CHOP, R-CHOP, 2 & 5 mg/kg Anti-CD79bvcE

- **Ramos (BL)**
  - Tumor volume (mm³)
  - Comparison of treatments: 2 mg/kg Anti-CD22vcE, 5 mg/kg Anti-CD22vcE, R-CHOP
ADCs in hematology: Anti-CD22 and anti-79b phase I data

Anti-tumor responses observed by histology

**Anti-CD22**

**Anti-CD79b**

Presented at ASH 2012
ADCs in hematological cancers: Anti-CD22 and anti-CD79b

**ROMULUS phase II**

NHL (R/R FL and 2/3 line DLBCL)  
N=120

- anti-CD22 ADC + rituximab
- anti-CD79b ADC + rituximab

Primary end-point: Progression Free Survival  
Expect data: 2014 (Up to first progression)
Combinations: Future of cancer care

Improving the standard of care in hematology

Anti-PDL1: Promising immunotherapy

Avastin in GBM and Cervical cancer
Tumor PD-L1 enables cancer immune evasion
Anti-PDL1 inhibits binding of PD-L1 to PD-1 and B7.1
**MPDL3280A: Rationale for third generation IgG1 engineered anti-PDL1 antibody**

1st generation

*IgG1 wt*

- **ADCC intact**
  - Potential to deplete activated T cells and Tumor Induced Lymphocytes (TILs) and diminish activity
  - *Blocks PD-1/PD-L2 interaction in lungs*
  - Potential for autoimmune pneumonitis

2nd generation

*IgG4 hinge mutant*

- **40% reduced ADCC**
  - Potential to deplete activated T cells and Tumor Induced Lymphocytes and diminish activity
  - *Blocks PD-1/PD-L2 interaction in lungs*
  - Potential for autoimmune pneumonitis

3rd generation

*IgG1 engineered MPDL3280A Anti-PD-L1*

- **No ADCC**
  - Minimal potential to deplete activated T cells and TILs
  - *Leaves PD-1/PD-L2 interaction in lungs intact*
  - *Blocks PD-L1/B7.1 interaction*
  - Potential for enhanced priming and durability of response

*ADCC=Antibody-Dependent Cell-Mediated Cytotoxicity*
Prolonged response potentially a hallmark of immunomodulation

Patients dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.
Assessing benefits of immunotherapy agents

RECIST1.1 does not capture:
- Patients who progress initially per RECIST 1.1 but then go on to respond
- Patients who have a mixed response or new lesions, but whose overall tumor burden decreases

RECIST (Response Evaluation Criteria In Solid Tumors): rules that define when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments; irRECIST = immune related RECIST
Rapid response in an NSCLC patient treated with anti-PDL1 monotherapy

64-year-old male with squamous NSCLC s/p R lobectomy, cisplatin + gemcitabine, docetaxel, erlotinib, PD-L1 positive

Images represent data from patient enrolled after Aug 1, 2012.
Hospital Universitario Vall D Hebron (Tabernero).
Complexity in evaluating response

Multiple subcutaneous metastases started resolving days after initiating aPDL1.

First CT scans at 6 weeks demonstrated significant regression of multiple lung metastases

Sarcomatoid Renal Cell Carcinoma (10 mg/kg anti-PDL1)
Anti-PDL1: Salvage of BRAF-mutant metastatic melanoma patient after progression on Zelboraf

**Baseline**

**Week 6**

**Week 12**

**Week 18**

**Images** include data from after Feb 1, 2013.

Dana Farber Cancer Institute (Ibrahim/Hodi).
PD-L1 is broadly expressed in human cancers

- Positive PD-L1 staining in lung cancer (proprietary GNE/Roche PD-L1 IHC)
- High sensitivity and specificity in Formalin-Fixed, Paraffin-Embedded (FFPE) samples

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Estimated PD-L1 prevalence (≈ %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (Squamous-cell carcinoma)</td>
<td>50</td>
</tr>
<tr>
<td>NSCLC (Adenocarcinoma)</td>
<td>45</td>
</tr>
<tr>
<td>Colorectal</td>
<td>45</td>
</tr>
<tr>
<td>Melanoma</td>
<td>40</td>
</tr>
<tr>
<td>Renal</td>
<td>20</td>
</tr>
</tbody>
</table>

Nearly all human cancer types can express PD-L1

*Based on staining of archival tumor tissue from patients (not on study) with metastatic cancer (Genentech data).
## Selecting the patients most likely to benefit

**Companion diagnostics**

<table>
<thead>
<tr>
<th>Anti-PDL1 immunohistochemistry</th>
<th>Companion diagnostics factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>(proprietary Genentech/Roche PD-L1 IHC)</td>
<td>- Highly sensitive and specific anti-PDL1 antibody used for IHC</td>
</tr>
<tr>
<td><img src="image" alt="Image of PD-L1 staining" /></td>
<td>- PD-L1 expression on tumor cells</td>
</tr>
<tr>
<td><img src="image" alt="Image of PD-L1 staining" /></td>
<td>- PD-L1 expression on tumor infiltrating immune cells</td>
</tr>
<tr>
<td><img src="image" alt="Image of PD-L1 staining" /></td>
<td>- Appropriate diagnostic cut-off</td>
</tr>
<tr>
<td><img src="image" alt="Image of PD-L1 staining" /></td>
<td>- Prospective evaluation of diagnostic</td>
</tr>
</tbody>
</table>

- **PD-L1**: Protein that is expressed on the surface of immune cells to prevent them from attacking cancer cells
- **T cell**: Type of white blood cell that plays a role in the immune response
- **Cancer cell**: Cell that is abnormal and can cause disease
Anti-PDL1: Phase I data in solid tumors

**Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Response rates&lt;sup&gt;1&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All comers&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Dx-positive&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Overall Phase I experience</td>
<td>21% (29/140)</td>
<td>36% (13/36)</td>
</tr>
<tr>
<td>Metastatic NSCLC</td>
<td>22% (9/41)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>29% (11/38)</td>
<td>27% (4/15)</td>
</tr>
<tr>
<td>Metastatic RCC</td>
<td>13% (6/47)</td>
<td>20% (2/10)</td>
</tr>
</tbody>
</table>

26 of 29 responders continued to respond at last assessment (time on study of 3 to over 15 months)

**Safety**

<table>
<thead>
<tr>
<th>Grade 3/4 adverse events</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grade 3/4 Events</td>
<td>43% (73/171)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5% (9/171)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4% (7/171)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>3% (5/171)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3% (5/171)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3% (5/171)</td>
</tr>
</tbody>
</table>

- No grade 3-5 pneumonitis observed
- Immune-related Grade 3-4 AEs observed in 4 patients (2%)
- Treatment-related Grade 3-4 AEs in 22 patients (13%)

---

<sup>1</sup> Efficacy evaluable subjects first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013; ORR includes unconfirmed PR/CR and confirmed PR/CR by RECIST 1.1

<sup>2</sup> All patients include PD-L1-positive, PD-L1-negative and patients with unknown tumor PD-L1 status; 3 Diagnostic positivity based on Roche PD-L1 IHC
Anti-PDL1: Disease control rate
Phase I

Overall disease control rate

Disease control rate by tumor type

<table>
<thead>
<tr>
<th>Disease Control Rate (ORR¹ + SD)</th>
<th>All comers¹</th>
<th>Dx-positive²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Phase I experience</td>
<td>61% (86/140)</td>
<td>86% (31/36)</td>
</tr>
<tr>
<td>Metastatic NSCLC</td>
<td>54% (22/41)</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>58% (22/38)</td>
<td>87% (13/15)</td>
</tr>
<tr>
<td>Metastatic RCC</td>
<td>72% (34/47)</td>
<td>80% (8/10)</td>
</tr>
</tbody>
</table>

Best response:
- Complete response
- Partial response
- Stable disease

¹ All patients include PD-L1-positive, PD-L1-negative and patients with unknown tumor PD-L1 status; ² Diagnostic positivity based on Roche PD-L1 IHC
Anti-PDL1 development: NSCLC

**FIR Study: Phase II Dx-positive advanced mNSCLC**

Stage IIIB/IV
Diagnostically positive NSCLC
N=100

Anti-PDL1 1200 mg IV Q3 weeks

Primary end-point: Overall Response Rate

**OAK Study: Phase III 2/3L mNSCLC**

Metastatic NSCLC (2/3L)

Docetaxel
75 mg/m2 IV Q3 wk

Anti-PDL1
1200 mg IV Q3 wk

Expect FPI: Q1 2014

Primary end-point: Overall Survival
Anti-PDL1 in combination with Avastin

**Anti-VEGF combination:**
*preclinical data*

- **Cloudman melanoma**
  - Control
  - a-PD-L1
  - a-VEGF
  - a-PD-L1 + a-VEGF

**Combination of anti-PDL1 and Avastin**
*(Study GP28328, solid tumors)*

**Arm A (n=6)**
- Anti-PDL1 q3w
- Bevacizumab 15mg/kg q3w + chemo

**Arm B (n=6)**
- Anti-PDL1 q2w
- Bevacizumab 10mg/kg q2w

**Dose escalation**
- Anti-PDL1 q3w @selected dose
- Bevacizumab 15mg/kg q3w

**Dose expansion**
- Anti-PDL1 q2w @selected dose
  - Bevacizumab 10mg/kg q2w
  - + chemo
Combinations: Future of cancer care

Improving the standard of care in hematology

Anti-PDL1: promising immunotherapy

Avastin in GBM and Cervical cancer
Avastin in glioblastoma
AVAglio and RTOG 0825 study

**Progression free survival**

- AVAglio:
  - RT/TMZ/Pb (n=463)
  - RT/TMZ/BEV (n=458)

- Stratified HR: 0.64
  - (95% CI: 0.55–0.74)
  - p<0.0001 (log-rank test)

- 10.6 mo

**Overall survival**

- AVAglio:
  - Stratified HR: 0.88
  - (95% CI: 0.76–1.02)
  - P=0.0987

- RTOG 0825:
  - HR: 0.79
  - (95% CI: 0.66–0.94)
  - P=0.007

  - HR: 1.13
  - (95% CI: 0.93–1.37)
  - P=0.21

---

Both AVAglio and RTOG demonstrated an improvement in PFS
No survival benefit
Avastin cervical cancer: GOG240 study

Randomized, open label Phase III trial utilizing a 2x2 factorial design

Stage IVB, recurrent or persistent carcinoma of the cervix N=450

- Cisplatin + Paclitaxel
- Topotecan + Paclitaxel
- Cisplatin + Paclitaxel + Bevacizumab (15mg/kg)
- Topotecan + Paclitaxel + Bevacizumab (15mg/kg)

Treatment to progression or toxicity

Overall survival

Stratified HR: 0.71 (95% CI: 0.54–0.94) P=0.0035

Data to be discussed with healthcare authorities
Oncology business and strategy update

Daniel O’Day
COO Roche Pharmaceuticals
Agenda

Oncology strategy

Avastin update

Improving the standard of care in hematology

Combinations: Future of cancer treatments
Roche strategy: Focused on medically differentiated therapies

Regulators:
Optimised benefit / risk ratio

Payors:
Optimised benefit / cost ratio
## Best-in-class oncology pipeline

### Personalised approach for majority of projects

### Phase I (26 NMEs)
- MDM2 ant: solid & hem tumors
- HER3 MAb: solid tumors
- CSF-1R MAb: solid tumors
- MEK inh: solid tumors
- Tweak MAb: oncology
- Ang2-VEGF MAb: oncology
- Raf & MEK dual inh: solid tumors
- CD44 MAb: solid tumors
- MDM2 ant: solid & hem tumors
- MEK inh: solid tumors
- AKT inhibitor: solid tumors
- PD-L1 MAb: solid tumors
- Steap 1 ADC: prostate ca.
- ADC: ovarian ca.
- ADC: multiple myeloma
- ADC: oncology
- ADC: acute myeloid leukemia
- Bcl-2 inh: CLL and NHL
- Chk1 inh: solid tumor & lymphoma
- PIsK inh: solid tumors
- ADC: metastatic melanoma
- PIsK inh: glioblastoma 2L
- Chk1 inh(2): solid tumors
- ALK inhibitor: NSCLC
- PIsK inh: solid tumors
- WT-1 peptide: cancer vaccine

### Phase II (8 NMEs+ 11 AIs)
- Perjeta: BC neoadjuvant
- Perjeta: HER2+ mBC 2nd line
- Perjeta: HER2+ gastric cancer
- Kadcyla: HER2+ gastric cancer
- Envedge: operable BCC
- Onartuzumab: TNmBC, 1st/2nd line
- Onartuzumab: mCRC 1st line
- Onartuzumab: NSCLC sq. 1st line
- Onartuzumab: NSCLC sq. 2nd line
- Onartuzumab: glioblastoma 2nd line
- Zeolboraf: papillary thyroid cancer
- Imageztumab (GA201): solid tumors
- Pictilisib (PisK inh): solid tumors
- Pl3k/mTOR inh: solid & hem tumor
- Parsatuzumab (EGF/L7 Mab): solid tumor
- CD22 ADC: hem tumors
- CD79b ADC: hem tumors
- HER3/EGFR: m. epithelial tumors
- Glypican-3 MAb: liver cancer

### Phase III (3 NMEs+17 AIs)
- Avastin: HER2+ BC adj
- Avastin: HER2-neg. BC adj
- Avastin: NSCLC adj
- Avastin: high risk carcinoid
- Avastin: rel. ovarian ca. Pt-resistant
- Avastin: rel. ovarian ca. Pt-sensitive
- Perjeta: HER2+ early BC
- Tarceva: NSCLC adj
- Kadcyla: HER2+ mBC 3rd line
- Kadcyla: HER2+ mBC 1st line
- Kadcyla: HER2+ early BC
- Onartuzumab: gastric cancer
- Obinutuzumab: iNHL relapsed
- Obinutuzumab: DLBCL
- Obinutuzumab: iNHL front-line
- Zeolboraf: m. melanoma adj
- Onartuzumab: NSCLC 2nd/3rd line
- Obinutuzumab: CRL

### Registration (2 NMEs+4 AIs)
- MabThera: NHL sc
- Avastin: glioblastoma 1st line
- Herceptin: HER2+ BC sc
- Tarceva: NSCLC EGFR mut 1st line
- Kadcyla: HER2+ pretr. mBC
- Envedge: advanced BCC

---

**New Molecular Entity (NME)**

**Additional Indication (AI)**

1. US only: ongoing evaluation for FDA submission
2. Submitted in EU
3. Approved in US, submitted in EU
4. Approved in EU, submitted in US

---

**Status as of March 31, 2013**
Expanding leadership in oncology with new platforms

**Future:**
Leading in further outcome improvements

**Present:**
Three transformative approaches

<table>
<thead>
<tr>
<th>Combinations</th>
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<tr>
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<tr>
<td><strong>Immunotherapy</strong></td>
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<tr>
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<tr>
<td><strong>Antibody-drug conjugates</strong></td>
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<tr>
<td><strong>New pathways (MET, PI3K, apoptosis)</strong></td>
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<tr>
<th>HER2 targeting</th>
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<tbody>
<tr>
<td>Kadcyla</td>
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<tr>
<td>Perjeta</td>
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<tr>
<td>Herceptin</td>
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<tr>
<th>Anti-CD20</th>
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<tbody>
<tr>
<td>Rituxan / MabThera GA101</td>
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<tr>
<th>Anti-angiogenesis</th>
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<tbody>
<tr>
<td>Avastin</td>
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</table>
Expanding patient access in Emerging markets

Global oncology sales

%: proportion of sales in International region

All sales at 2012 exchange rates
Oncology strategy

Avastin update

Improving the standard of care in hematology

Combinations: Future of cancer treatments
# Avastin: Standard of care in multiple tumor types with the largest breadth of data

<table>
<thead>
<tr>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line mCRC</td>
<td>✓</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line mCRC</td>
<td>✓</td>
</tr>
<tr>
<td>TML mCRC</td>
<td>✓</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line NSCLC</td>
<td>✓</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Ovarian</td>
<td>✓</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line Ovarian</td>
<td>✓</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line mRCC</td>
<td>✓</td>
</tr>
<tr>
<td>Recurrent Glioblastoma</td>
<td>✓*</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line mBC</td>
<td>✓</td>
</tr>
<tr>
<td>Recurrent Cervical</td>
<td></td>
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</tbody>
</table>

* Accelerated approval; 2012 US sales CHF ~170 m
Cervical cancer: 3rd most common cancer in women worldwide

**Patient population**

- Recurrent
- Stage IVb
- Stage I-IVa

**Unmet medical need**

- Very few treatment advances, chemo radiation established as standard of care in 1999 with ~80% platinum based therapies
- Patient population that generally lacks access to good health care
- Lack of HPV vaccination and lack of screening
- Highest incidence in Latin America and East Europe/Middle East/Africa regions
Avastin in glioblastoma

Avastin-eligible drug treated incidence

- Filed in EU based on AVAglío PFS, OS and quality of life
- Fully analyze Avastin data in GBM and discuss with the medical community and FDA in H2 2013
- 2012 US sales in relapsed GBM CHF ~170m

2012 estimates for number of patients

- US: Relapsed 5'900, Front line 9'600
- Top 5 EU: Relapsed 7'200, Front line 11'800
Oncology strategy

Avastin update

Improving the standard of care in hematology

Combinations: Future of cancer treatments
MabThera/Rituxan
Standard of care in multiple indications

**Oncology sales split by indications**

- **Indolent NHL** ~50%
- **Aggressive NHL** ~30%
- **CLL** ~20%

**Over 15 years of clinical practice**

- **1997**: Relapsed FL
- **2001**: DLBCL (EU)
- **2004**: 1st line FL (EU)
- **2006**: DLBCL (US)
- **2007**: 1st line FL (US)
- **2010**: CLL
- **2011**: 1st line FL maintenance

Follicular Lymphoma (FL) = ~70% of all indolent NHL; Diffuse large B-cell lymphoma (DLBCL) = ~90% of aggressive NHL
MabThera subcutaneous versus infusion

**MabThera IV administration can take all day**

<table>
<thead>
<tr>
<th>Waiting room</th>
<th>Pharmacy preparation</th>
<th>IV line</th>
<th>MabThera infusion + observation period</th>
</tr>
</thead>
</table>

**MabThera SC injection takes 5–7 minutes**

<table>
<thead>
<tr>
<th>Waiting room</th>
<th>Prep</th>
<th>Time saving SC vs IV administration</th>
</tr>
</thead>
</table>

No pharmacy dose preparation, no IV line, no mandatory observation period
Submitted to EMA Q4 2012
GA101 in CLL: Changing the standard of care in patients with comorbidities

Front line CLL patient populations

- ~55% Intolerant to aggressive chemotherapy
- ~45% Rituximab/FC or Rituximab/B based combinations

CLL11 study patient population

Treatment options today:

- 3-25% treated with chlorambucil (varies by country)
- ~30% other*

FC=fludarabine/cyclophosphamide; B=bendamustine; *Other: MabThera monotherapy, Fludarabin, fludarabin+cyclophosphamide (standard or lower dose), bendamustin and MabThera+Bendamustin
GA101 in CLL: Exploring safety in combination with other chemotherapies

Previously untreated chronic lymphocytic leukaemia (CLL)  
N=41

- First patient recruited: Q2 2011
- Recruitment completed
- Primary endpoint: Safety
- Expect presentation 2013

Cohort A
GA101 plus bendamustine

Cohort B
GA101 plus fludarabine and cyclophosphamide

Safety and tolerability of chemotherapies to support GA101 as the backbone therapy in CLL
Obinutuzumab (GA101) development
Faster recruitment expedites timelines

In collaboration with Biogen Idec
Strategies beyond great medicines

Hematology

Replace and extend

Replace

Extend

Medical value

MabThera

GA101

Chemo

ADC 22

ADC 79b

BCL2

ADCs

ADC 22

ADC 79b

Our vision

CLL11 etc.

Romulus

GA101

Medical value

MabThera

Chemo

ADCs

BCL2

Our vision

MabThera

ADC 79b

ADC 22

Roche

Replace

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BCL2

Our vision

MabThera

ADC 79b

ADC 22

Roche
Oncology strategy

Avastin update

Improving the standard of care in hematology

Combinations: Future of cancer treatments
Importance of combinations and diagnostics

1995 - 2005

- Anatomic diseases

2005 - 2012

- Disease subsets
- Emergence of specific treatment (Zelboraf, Xalkori)
- Companion diagnostic for single mutation

2012+

- Biologic subsets
- Targeted combinations
- Immune therapy
- Multiplex platforms
- Continuous diagnostics

Tumor Biology

- Little to no direct competition
- Primary “competition” was cytotoxics and inaction

Treatment

- Chemo + MAbs

Diagnostics

- IHC or nothing

Competition

- Increased investments in oncology
- Multiple molecules targeting same pathways (PI3K, MEK)
- Highly competitive
- Biosimilars
Cancer: Increasing ability to manage complexity

Potential driver mutations

- **MEKi + PI3Ki**
- **PI3K inh**
- **RG7321**
- **RG7422**
- **MetMAb**
- **KRAS**
- **EGFR**
- **EML4-ALK**
- **Tarceva**
- **NRAS**
- **PIK3CA**
- **HER2**
- **BRAF**
- **MET AMP**
- **MetMAb**

Overlapping biomarkers

- **Anti-PDL1**
- **ADC**
- **PDL1**
- **Met High**
- **Met Low**
- **NAPI3b**
- **PI3K mut**
- **PTEN loss**
- **KRAS mut**

Biomarker research

- Comprehensive diagnostics and understanding mechanisms of resistance
- Combinations & sequences of treatment
Enabling access through innovative pricing models

Pack based pricing

- Undifferentiated
  - $$$ by vial

Patient based pricing

- Episode-of-care based
- Combinations
- Indication based

Need for patient based information
**Avastin: Examples of successful capping programs**

**Indications likely to reach 10/11g per year limit**
- Breast cancer
- Ovarian cancer

**Status**
- Germany: ~50% insured patients covered by capping program
- Italy: ~30,000 patients tracked since 2009
Innovation remains rewarded: Example of Perjeta

**Illustrative pricing for metastatic breast cancer, ex-US**
Summary

Roche at ASCO 2013

• **Securing Hematology franchise:**
  GA101 in CLL, Bcl-2 advancing to pivotal studies

• **Immunotherapy:**
  Promising data for anti-PDL1 in multiple tumor types; advancing to pivotal studies

• **Further benefits of Avastin:**
  Cervical data to be discussed with Healthcare authorities, GBM data submitted in EU

Advancing the standard of care in Oncology

• **Rich portfolio:** Best-in-class portfolio, targeting multiple pathways

• **Combinations:** Improving clinical outcomes through complementary MoA

• **Unique commercial advantage:** Ability to offer patient-specific pricing models, including diagnostics and combination therapies to support access
Doing now what patients need next