Roche late-stage pipeline update III

London, 1 October 2013
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Roche late-stage pipeline update III

Agenda

14:30-14:35  Opening remarks
              Karl Mahler, Head of Investor Relations

14:35-14:40  Introduction
              Alan Hippe, CFO

14:40-15:45  Late-stage pipeline update III
              Hal Barron, MD Global Development and Chief Medical Officer

15:45-16:15  Q&A
Strong progress in non-oncology assets

2009

Launched

- Xolair
- Lucentis
- Rituxan/MabThera RA

Phase III

- Ocrelizumab RA
- Actemra

Phase II

- 4 phase II

2013

Launched

- Xolair
- Lucentis
- Rituxan/MabThera RA
- Actemra

- Bitopertin
- Ocrelizumab MS
- Gantenerumab
- Lebrikizumab
- Etrolizumab

Phase III

- Lampalizumab

Phase II

- 2 phase II
- 4 phase II

1 FPI expected 1H 2014; 2 Phase III decision pending
Innovation-driven resource allocation

Alan Hippe, Roche CFO
Roche strategy: Focused on medically differentiated therapies

Regulators:
Optimised benefit / risk ratio

Payors:
Optimised benefit / cost ratio
Pharma market drivers and constraints

Balance of these factors will determine future growth

- Major advances in science and medicine
- Growth and aging of world population
- Increasing wealth and access (in Emerging Markets)

- Patent expirations
- Global economic slowdown
  - Slower expansion of budgets in emerging markets
  - Increased pricing hurdles in developed world
Innovation through patient stratification
Benefit for all stakeholders, including the industry

Today
- Reduced patient pool
- Higher probability of success

Benefit from patient stratification
- Lower development costs
- Time to market
- Pricing power
- Increased market share

Future
Access becoming more important

Need for tailored systems

<table>
<thead>
<tr>
<th>Business challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Moving towards value based pricing</td>
</tr>
<tr>
<td>• Ensure access while rewarding value</td>
</tr>
<tr>
<td>• Multiple indications and combinations</td>
</tr>
</tbody>
</table>

Today  Future

Pack based pricing  Value based pricing

Undifferentiated $ by vial

Episode-of-care based

Combinations

Indication based

Need for patient based information
3 Economies and pricing/access

Important value drivers for Pharma outlook

Example: Pharma market growth in Europe

<table>
<thead>
<tr>
<th>Year</th>
<th>High GDP growth: increasing pharma spend</th>
<th>GDP challenges: austerity measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>7%</td>
<td></td>
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<tr>
<td>2005</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>5%</td>
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<tr>
<td>2007</td>
<td>6%</td>
<td></td>
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<tr>
<td>2008</td>
<td>5%</td>
<td></td>
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<tr>
<td>2009</td>
<td>3%</td>
<td>2%</td>
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<tr>
<td>2010</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>2011</td>
<td>-1%</td>
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<tr>
<td>2012</td>
<td>-1%</td>
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</tr>
<tr>
<td>2013</td>
<td>-1%</td>
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</tr>
<tr>
<td>2014</td>
<td>-1%</td>
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</tr>
<tr>
<td>2015</td>
<td>-1%</td>
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<td>2016</td>
<td>-1%</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>-1%</td>
<td></td>
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</table>

Source: IMS

- Limits to public access will continue
- Recognition and rewards for innovation
R&D allocation

*Mix of qualitative and quantitative factors*

**Research & Early Development**
- Annual budget allocation
- Ensure expertise in the field
- Plausibility of scientific hypotheses

**Late Stage Development**
- Market potential
- Efficient development
- Probability of technical success

Top down  Project driven
Roche: R&D well balanced from a risk & disease point of view

Industry average probability of success – Phase I to Registration

Source: Bernstein Equity Research, Tufts University and Roche analysis
Where science takes us

**Oncology**
- 9 drugs launched
- 5 Phase III
  - Avastin
  - MabThera
  - Herceptin
  - Xeloda
  - Tarceva
  - Zelboraf
  - Erivedge
  - Perjeta
  - Kadryla
  - MetMab
- 10 phase II
- Strong and growing

**Immunology/Inflammation**
- 4 drugs launched
- 1 Phase III
  - Xolair
  - Lucentis
  - Rituxan/MabThera RA
  - Actemra
- 4 phase II
- Strongly emerging

**Neuroscience**
- 3 Phase III
- 4 phase II
- Earlier stage

1 FPI expected 1H 2014; 2 Phase III decision pending
## Focus on innovation and growth

1. **Strategic focus on innovation and driving Personalised Healthcare**

2. **Growth facilitated by tailored access models**

3. **Leading product pipeline providing value for the future**
We follow the science

Hal Barron, MD
Global Development and Chief Medical Officer
Oncology drug development
Understanding of tumour biology is expanding

Example of melanoma
Translating science into new medicines requires innovation in development

**Biology of the disease**

**Personalized Healthcare**
- Increase success rate
- Improve outcome
- Reduce side effects

**Combinations**
- Target multiple pathways
- Reduce resistance
- Improve outcomes

**Innovative design with smart surrogate end-points**
- pCR in early breast cancer
- MRD in hematology
- GA lesion size in dry AMD
Good and bad surrogate end-points

Why don’t they always work?

- The surrogate is not in the causal pathway of the disease process
- The intervention has mechanisms of action independent of the disease process
- The surrogate is not in the pathway of the intervention’s effect or is insensitive to its effect.
- Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate

Good surrogate end-points

**Good surrogate endpoint is in the causal pathway of the disease**

Some surrogate end-points that might expedite drug development

- **pCR** – Pathological Complete Response in early breast cancer
- **MRD** – Minimal Residual Disease in lymphomas
- **GA area** – GA area change in Geographic Atrophy
Late-stage pipeline update

**Oncology**
- **Kadcyla**
  - Phase III
  - HER2-positive BC and gastric cancer
- **obinutuzumab GA101**
  - Phase III
  - Hem. cancers
- **Bcl-2i (GDC 0199)**
  - Phase III
  - Hem. cancers
- **anti-PDL1**
  - Phase III
  - NSCLC

**Immunology, ophthalmology and infectious diseases**
- **lebrikizumab**
  - Phase III
  - Asthma
- **etrolizumab**
  - Phase III
  - IBD
- **lampalizumab**
  - Phase II
  - GA

**CNS**
- **bitopertin**
  - Phase III
  - Schizophrenia
- **ocrelizumab**
  - Phase III
  - Multiple Sclerosis
- **gantenerumab**
  - Phase III
  - Alzheimer Disease
- **lampalizumab**
  - Phase II GA
- **etrolizumab**
  - Phase III
  - IBD
- **mercitabine**
  - Phase II
  - Chronic Hepatitis C
Oncology: HER2 and Hematology franchises

Never Settle For Great – 2.0 !
Never Settle for Great 1.0
HER2 franchise

Replace and extend

**Medical value**
- Herceptin + chemo
- Lapatinib + chemo

**Replace**
- Kadcyla

**Extend**
- Perjeta
- Herceptin + chemo

**Kadcyla**
- EMILIA / MARIANNE

**Perjeta**
- CLEOPATRA

**Kadcyla**
- MARIANNE
**TH3RESA: Kadcyla vs. physicians choice in 3L HER2-positive BC**

**HER2-positive (central) advanced BC**  
≥2 prior HER2-directed therapies for MBC  
N=600

**Treatment of physician’s choice**

**Kadcyla**  
3.6 mg/kg q3w IV

PD

PD

Kadcyla
Optional crossover

**Co-primary endpoints:**  
- PFS by Investigator  
- OS

Kadcyla in collaboration with ImmunoGen Inc.
TH3RESA: Progression-free survival and overall survival

**Progression Free Survival (PFS)**

<table>
<thead>
<tr>
<th></th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>3.3</td>
<td>6.2</td>
</tr>
<tr>
<td>No. of events</td>
<td>129</td>
<td>219</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>0.528</td>
<td>(95% CI, 0.422, 0.661)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.0001</td>
<td></td>
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</tbody>
</table>

Observed 21% of targeted events

**Overall Survival (OS) - Interim**

<table>
<thead>
<tr>
<th></th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>14.9</td>
<td>NE</td>
</tr>
<tr>
<td>No. of events</td>
<td>44</td>
<td>61</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>0.552</td>
<td>(95% CI, 0.369, 0.826)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.0034</td>
<td></td>
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</tbody>
</table>

Presented at ECC 2013

* Investigator Assessment; TPC=Treatment of Physician’s Choice
TH3RESA: PFS for patients treated with Herceptin-containing regimens

<table>
<thead>
<tr>
<th></th>
<th>TPC (H-containing) n=149</th>
<th>T-DM1 n=404</th>
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</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>3.2</td>
<td>6.2</td>
</tr>
<tr>
<td>No. of events</td>
<td>101</td>
<td>219</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>0.558 (95% CI, 0.437, 0.771)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
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</tbody>
</table>

Presented at ECC 2013
First-line HER2-positive mBC: MARIANNE trial
Kadcyla and Perjeta vs. standard of care

Primary end-point
• Progression-free survival
• Recruitment started Q3 2010
• Expect data H2 2014
Neo-adjuvant HER2-positive breast cancer
Potentially completely new indication in the US

**Annual US incidence**

<table>
<thead>
<tr>
<th>Early BC</th>
<th>Neo-adjuvant</th>
</tr>
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<tbody>
<tr>
<td>37’000</td>
<td>~9’250</td>
</tr>
<tr>
<td>~25%</td>
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</table>

**Evaluating the effect of neo-adjuvant treatment**

- **Neo-adjuvant treatment**
  - Pre-surgery, 4-6 cycles
- **Adjuvant treatment**
  - Post-surgery
  - up to 1 year

**Pathological complete response, pCR**
Absence of cancer cells
pCR as surrogate end-point in early breast cancer

**Association of pCR with Event-free survival (EFS) in HER2-positive BC**

Perjeta in neo-adjuvant setting (NEOSPHERE)

CTNeoBC Meta-analysis, FDA

Perjeta recommended for approval in neo-adjuvant setting
Kadcyla neo-adjuvant study
*pCR as surrogate end-point*

**Primary endpoint**
- Pathological complete response, pCR (ypT0N0)

**Secondary endpoints**
- DFS, breast conservation, safety, pCR by other definitions

**6 cycles**
- Herceptin + docetaxel + carboplatin
- Herceptin & Perjeta + docetaxel + carboplatin
- Kadcyla & Perjeta

**Primary Endpoint**
- pCR

**Up to 1 year**
- Herceptin
- Herceptin & Perjeta
- Kadcyla & Perjeta

HER2 positive eBC

**FPI expected Q2 2014**
**Expect pCR data: end 2015**
Never Settle for Great 2.0
Hematology franchise

Medical value

Replace

Extend

BCL2
ADCs
ADC CD22
ADC CD79b

Our vision

Replace and extend

MabThera

GA101

Chemo

MabThera

CLL11 etc.

Romulus

GA101
Never Settle for Great 2.0
Hematology franchise development overview

Oncology indications:
- CLL
- iNHL
- aNHL/DLBCL

- CLL filed US/EU
- Phase III rituximab ref. NHL, 1L DLBCL and 1L iNHL+maintenance
- Phase III R/R CLL, Bcl-2 +rituximab FPI Q1 2014
- Phase II CLL (17p del) FPI Q3 2013
- Phase I GA101+Bcl-2

Improving the backbone (anti-CD20)

Obinutuzumab (GA101)

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

ADC + anti-CD20

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

Exploring combinations with complementary MoA

MabThera Rituxan

- CD20
- CD22
- Bcl-2
- CD79b

Bcl-2 inh +/- anti-CD20
GA101 in Chronic Lymphocytic Leukemia (CLL)

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

Previously untreated CLL with comorbidities
- Total CIRS* score > 6 and/or creatinine clearance < 70 ml/min
- Age ≥ 18 years
- N = 780 (planned)

Stage I, n = 590

Stage Ia
G-Clb vs Clb

Stage Ib
R-Clb vs Clb

Stage II
G-Clb vs R-Clb

Additional 190 patients to complete stage II

*Cumulative Illness Rating Scale
GA101 in CLL

Progression-free survival (PFS)

- 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

Presented at ASCO 2013
**GA101 in CLL**

**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

---

**Stage I, n = 590**

- RANDOMIZE
  - Previously untreated CLL with comorbidities
    - Total CIRS* score > 6 and/or creatinine clearance < 70 ml/min
    - Age ≥ 18 years
    - N = 780 (planned)

**Stage Ia**
- G-Clb vs Clb

**Stage Ib**
- R-Clb vs Clb

**Stage II**
- G-Clb vs R-Clb

---

**Additional 190 patients to complete stage II**

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*Cumulative Illness Rating Scale
Never Settle for Great!

Stage two results for GA101 in CLL11

- GA101 plus chlorambucil was superior to MabThera/Rituxan plus chlorambucil in helping people with previously untreated chronic lymphocytic leukemia live longer without their disease worsening (7/24/13)

- To be presented at the American Society of Hematology’s 55th Annual Meeting in December, 2013
GA101 in Non Hodgkin’s Lymphoma
Multiple Head-to-head phase III trials vs MabThera

**GADOLIN study**

- **Induction**
  - MabThera-refractory iNHL (n=360)
  - GA101 + bendamustine x 6 cycles
  - Bendamustine x 6 cycles

- **Maintenance**
  - CR, PR, SD
  - GA101 q2mo x 2 years

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

**GOYA study**

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

**Maintenance**

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

**GALLIUM study**

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

**Primary end-point:** PFS
**Expect data:** 2017
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

Bcl-2 inhibitor in collaboration with AbbVie

Presented at 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:** Q2 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
ADCs in hematology: Anti-CD22 and anti-CD79b
Phase I responses in multiple histologies

Anti-tumor responses observed by histology

ADCs in collaboration with Seattle Genetics

Presented at ICML 2013
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
Improving the standard of care in Hematology

**Objectives**

- Increase **cure rate** or extend **treatment-free remissions**
  - Improve upon individual agents in current SOC
  - Add novel agents to current SOC
- Manage/decrease **toxicity**
  - Evaluate chemo-free regimens

**Anti CD20 + Chemo + Biologic modifier**

- Rituxan or GA101
- Eliminate or replace with ADC
- Add a targeted agent (Bcl-2, BTKi, Pi3K, aPD-L1)
MRD (Minimal Residual Disease) as surrogate end-point for longer remission and/or cure

**MRD detection**

- Early relapse
- Late relapse
- Cytomorphology detection limit
- Immunophenotypic and PCR detection limit
- ‘Cure’

**Follow-up time**

- Induction
- Maintenance

**MRD as prognostic factor: CLL8 study**

- Peripheral blood
  - MRD level
    - $< 10^{-4}$
    - $\geq 10^{-4}$ to $< 10^{-2}$
    - $\geq 10^{-2}$

- Bone marrow

Follow-up time:

- 0 6 12 18 24 36 48 60 72 78

J Clin Oncol. 2012 Mar 20;30(9):980-8

Roche
CLL market fragmented between two treatment approaches

**Short course combinations** that induce **deep responses** followed by long **treatment-free remissions**

**Chronic treatments** with agents that are **effective, safe, and convenient**

MRD-negative responses followed by long remissions

Long remissions from safe, tolerable, chronic therapy

### MRD rates in CLL

<table>
<thead>
<tr>
<th>Line</th>
<th>GDC-0199&lt;sup&gt;1&lt;/sup&gt;</th>
<th>GA101-chlorambucil&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R-chlorambucil&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R-FC&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Ibrutinib&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Idelalisib&lt;sup&gt;5&lt;/sup&gt;</th>
<th>R-Benda-Ibrutinib&lt;sup&gt;6&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>N</td>
<td>56</td>
<td>238</td>
<td>233</td>
<td>408</td>
<td>31</td>
<td>61</td>
<td>54</td>
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<tr>
<td>ORR</td>
<td>84%</td>
<td>75.5%</td>
<td>65.9%</td>
<td>90%</td>
<td>71%</td>
<td>67%</td>
<td>56%</td>
</tr>
<tr>
<td>CR</td>
<td>20% CR/CRi</td>
<td>22.2% CR/CRi</td>
<td>8.3% CR/CRi</td>
<td>44%</td>
<td>10%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>MRD</td>
<td>BM: 35-50%*</td>
<td>PB: 31% (41/132) BM: 17% (15/88)</td>
<td>PB: 2% (3/150) BM: 3% (2/72)</td>
<td>PB: 63% (90/143)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

MRD: minimal residual disease; R/R: relapsed/refractory; 1L: first-line; BM: bone marrow; PB: peripheral blood

* MRD tests performed in local unvalidated laboratories in a small number of patients; in patients with a CR who have been tested

**References:**
1. John Seymour, iwCLL 2013
Anti-PDL1

*Immunotherapy*
Anti-PDL1 overview

**Differentiation**

- Potential for better safety
- Potential for personalized approach
- Potential for longer response

**Development**

- NSCLC
- Melanoma
- RCC
- Combo w Avastin
- Solid tumours
- Combo w Zelboraf
- Melanoma
- Multiple combos start
- 2H13/1H14

Differentiation Development
MPDL3280A Phase Ia: Efficacy Summary

<table>
<thead>
<tr>
<th></th>
<th>Single Agent RECIST 1.1 Response Rate (ORR&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>SD of 24 Weeks or Longer</th>
<th>24-Week PFS Rate</th>
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<tbody>
<tr>
<td><strong>Overall population</strong></td>
<td>21%</td>
<td>19%</td>
<td>42%</td>
</tr>
<tr>
<td>(N = 175)</td>
<td></td>
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<tr>
<td><strong>NSCLC</strong></td>
<td>23%</td>
<td>17%</td>
<td>45%</td>
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<tr>
<td>(n = 53)</td>
<td></td>
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<tr>
<td><strong>Non-squamous</strong></td>
<td>21%</td>
<td>17%</td>
<td>44%</td>
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<td>(n = 42)</td>
<td></td>
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<tr>
<td><strong>Squamous</strong></td>
<td>27%</td>
<td>18%</td>
<td>46%</td>
</tr>
<tr>
<td>(n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> ORR includes investigator-assessed unconfirmed and confirmed PR. 6 patients that did not have a post-baseline scan were included as non-responders. Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria et al, ECCO 2013
## MPDL3280A Phase Ia in NSCLC: Best response by PD-L1 IHC Status

<table>
<thead>
<tr>
<th>Diagnostic Population&lt;sup&gt;a&lt;/sup&gt; (n = 53)</th>
<th>ORR&lt;sup&gt;b&lt;/sup&gt; % (n/n)</th>
<th>PD Rate % (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3</td>
<td>83% (5/6)</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>IHC 2 and 3</td>
<td>46% (6/13)</td>
<td>23% (3/13)</td>
</tr>
<tr>
<td>IHC 1/2/3</td>
<td>31% (8/26)</td>
<td>38% (10/26)</td>
</tr>
<tr>
<td>All Patients&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23% (12/53)</td>
<td>40% (21/53)</td>
</tr>
</tbody>
</table>

<sup>a</sup> IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.

<sup>b</sup> ORR includes investigator-assessed unconfirmed and confirmed PR.

<sup>c</sup> All patients includes patients with IHC 0/1/2/3 and 7 patients have an unknown diagnostic status.

Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.  
Soria et al, ECCO 2013
Duration of treatment in responders

Sustained response in majority of responders

Duration of Treatment and Response

<table>
<thead>
<tr>
<th>Histology</th>
<th>IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsquamous</td>
<td>IHC 0</td>
</tr>
<tr>
<td>Squamous</td>
<td>IHC 3</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 0</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 1</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 0</td>
</tr>
<tr>
<td>Squamous</td>
<td>IHC 2</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 3</td>
</tr>
<tr>
<td>Squamous</td>
<td>IHC 3</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 3</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 0</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 3</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>IHC 1</td>
</tr>
</tbody>
</table>

On study, on treatment
On study, post treatment
Treatment discontinued
Ongoing response
First response
First PD

Time (Weeks)

Soria et al, ECCO 2013

Patient experiencing ongoing benefit per investigator.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.
**Anti-PDL1 Development: NSCLC**

**FIR Study: Phase II Dx-positive advanced mNSCLC**
- PDL1 positive NSCLC
- Anti-PDL1 1200 mg IV Q3 weeks
- **Ongoing**
- **Primary end-point:** Overall Response Rate

**POPLAR Study: Phase II 2/3L mNSCLC**
- Metastatic NSCLC (2/3L)
- Docetaxel 75 mg/m2 IV Q3 wk
- Anti-PDL1 1200 mg IV Q3 wk
- **Ongoing**
- **Primary end-point:** Overall Survival

**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

Combination of anti-PDL1 and Avastin (Study GP28328, solid tumors)
T cell-directed therapeutics: Multiple possibilities

Safety issues

- **Pros:** Stimulate $T_{\text{eff}}$ and inhibit $T_{\text{reg}}$ production (or activity), CTLA4 - possibly PD1 - are clinically validated

- **Cons:** Can amplify auto-reactive T cell responses, disregulate T cell proliferation & cytokine production

Clinical validation

Novel molecules in cancer immunotherapy:

Preliminary pre-clinical molecules

**Preliminary pre-clinical data: NME1 + anti-PD-L1**

- Co-blockade induces tumor rejection and creates resistant to tumor re-challenge

**Preliminary pre-clinical data: NME2**

- Tumor volume reduction seen in pre-clinical models with NME2
Etrolizumab

Anti-β7 Integrin in Inflammatory Bowel Disease
Inflammatory Bowel Disease (IBD) overview

Two distinct diseases with high unmet medical need

**Ulcerative colitis**
- Age of onset 20-30 yrs
- Continuous mucosal distal disease
- Confined to sigmoid/colon
- Bloody, frequent bowel movements
- Progressive over time

**Crohn’s disease**
- Age of onset 15-30 yrs
- Patchy transmural disease
- Most common in ileum and ascending colon
- Abdominal pain, diarrhea, vomiting, weight loss
- Fistulæ and strictures

**Medical need**
- Higher sustained remission rates
- Decreased risk of severe infections
- Avoidance of surgery and hospitalizations
Inflammatory Bowel Disease (IBD)

Epidemiology and current treatment options

**Epidemiology**

<table>
<thead>
<tr>
<th>Prevalence (000)</th>
<th>Mild</th>
<th>Moderate-Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>5EU</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5EU</td>
<td></td>
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<td>5EU</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5EU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Current treatment options**

- Surgery
- anti-TNFs
- cyclosporine
- Immunosuppressants (azathioprine, 6-MP)
- 5-amniosalicylates (5-ASAs)
- Antibiotics, Alternative therapies

5EU=UK, Germany, France, Italy, Spain
Etrolizumab: Gut-selective anti-β7 integrin with dual mode of action and no expected CNS effect

**Etrolizumab: Anti-β7**
Blocks leukocyte trafficking and lymphocyte retention

**Vedolizumab: Anti-α4β7**
- Blocks leukocyte trafficking only
  - No apparent effect on CNS

**Natalizumab (Tysabri): Anti-α4**
- Blocks leukocyte trafficking only
- Affects trafficking to CNS, associated with PML
Evaluating efficacy in Ulcerative Colitis

Importance of induction and sustainability of remission

* Most trial designs utilize randomized withdrawal design to assess maintenance of remission.
Etrolizumab phase II study in Ulcerative Colitis
Compelling remission rates

Clinical remission by MCS, Week 10

- Placebo
- Etrolizumab 100mg
- Etrolizumab 300mg+LD

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Clinical remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-comers</td>
<td>41</td>
<td>8 (20.5%)</td>
</tr>
<tr>
<td>TNF-naive</td>
<td>15</td>
<td>7 (43.8%)</td>
</tr>
<tr>
<td>TNF-IR</td>
<td>16</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>All-comers</td>
<td>39</td>
<td>10.3%</td>
</tr>
<tr>
<td>TNF-naive</td>
<td>39</td>
<td>25.0%</td>
</tr>
<tr>
<td>TNF-IR</td>
<td>25</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

TNF-IR patients without response at 10 weeks continued etrolizumab treatment to 14 weeks *

TNF-IR remitters at week 10 or 14

n=47

5 (10.6%)

MCS=Mayo Clinic Score, using central endoscopy reading; * 14 week remission as assessed by partial MCS
Etrolizumab among highest placebo-corrected remissions for TNF-naïve patients

Etrolizumab
(Only program to use central endoscopy reading)

Remicade ACT1 (Rutgeerts NEJM 05), Humira ULTRA2 (Sandborn GE12), Vedolizumab DDW ’12, Tofacitinib (Sandborn NEJM ’12), Etrolizumab (ENCALYPTUS);
Anti-integrins may sustain remission better than TNF-inhibitors: Learning from in-class compounds

**Remicade**
- Week 8: Placebo 14.9%, Active 38.8%
- Sustained week 54: Placebo 6.6%, Active 19.8%
- Change: -50%

**Humira**
- Week 8: Placebo 11.0%, Active 21.3%
- Sustained week 52: Placebo 6.2%, Active 10.7%
- Change: -50%

**Vedolizumab**
- TNF-Naive & TNF-IR
- Week 6: Placebo 24.0%
- Sustained week 52: Active 36.0%
- Change: -33%
αEβ7 may predict remission in TNF-naive patients: Potential for PHC approach

Remission at 10 weeks

Note: ~10% and 40% of patients were missing qPCR and IHC data, respectively
Potential for better efficacy in Crohn’s Disease

Higher concentration of αE in small bowel, often involved in Crohn’s Disease

Small bowel, often involved in Crohn’s Disease
Phase III outlook

Best-in-disease in Inflammatory Bowel Disease
>3000 patients program

- First subcutaneous gut-selective anti-integrin
- Better safety profile with reduced risk of severe infection or malignancy
- PHC through αE expression as potential companion diagnostics
- Further details after discussions with healthcare authorities

FPI 1H 2014. Expect first data 2018
Lampalizumab

Anti-factor D in Geographic Atrophy
Age-related macular degeneration (AMD)

Progression of the disease

- Normal retina
- Early or intermediate dry AMD
- Geographic atrophy
- Neovascular AMD

Clinical spectrum of AMD

Early AMD

Intermediate AMD

- Initially, visual acuity minimally affected; signs are anatomic (drusen and pigmentary changes) with symptoms of visual function impairment (e.g., dark adaptation, contrast sensitivity)

Advanced AMD

Geographic Atrophy

- non fovea-threatening
- fovea-threatening
- fovea-involved

Wet AMD

Arch Ophthalmol 2001;119:1417-1436
Epidemiology and current treatment options for Geographic Atrophy

**Prevalence of Geographic Atrophy**

![Graph showing prevalence of Geographic Atrophy in the US and EU.](image)

**Current treatment options**

- No treatments that showed improvement or disease slowdown
- High-dose antioxidant vitamins and zinc often recommended

Lampalizumab (anti-factor D): Selective inhibitor of the alternative complement pathway

**Molecule**
- Fab of a humanized monoclonal antibody
- Targets complement factor D of the alternative pathway

**Target**
- Complement factor D is a rate-limiting enzyme in the alternative pathway and present in relatively low abundance

MAC=Membrane Attack Complex; MBL=mannose-binding lectin
MAHALO Phase II study

**Study design**

- **Phase Ib**
  - Open-label safety run-in (N=14)

- **Phase II (N=129)**
  - Randomized 1:2:1:2

- **Sham**
  - Monthly
  - N=21

- **Lampalizumab**
  - 10 mg, monthly
  - N=43

- **Sham**
  - Every 2 mths
  - N=21

- **Lampalizumab**
  - 10 mg, every 2 mths
  - N=44

- **Safety follow-up period or Open-label extension study**

**Primary Endpoint**

- Mean change in GA area from baseline to Month 18 assessed by fundus autofluorescence (FAF)


*N = 123 for pre-specified modified intent-to-treat population, which is the primary efficacy analysis population.*
Lampalizumab: Efficacy results I

*Data embargoed for printing until the publication in a scientific/medical journal*
Lampalizumab: Efficacy results II

*Data embargoed for printing until the publication in a scientific/medical journal*
Lampalizumab: Efficacy results III

Data embargoed for printing until the publication in a scientific/medical journal
Lampalizumab: Safety results I

Data embargoed for printing until the publication in a scientific/medical journal
AMD risk has a strong genetic component

**Identifying patients that benefit the most**

- Genetic factors account for ~55% of total variability in disease risk
- Lifetime AMD risk for individual of affected family member 50% compared to 12% for relatives of controls

19 confirmed loci in pathways related to:
- **Complement**
- **Lipid metabolism**
- **Angiogenesis**
- **Apoptosis**
- **Extracellular matrix**

**Strong biological rationale for lampalizumab biomarker**
- To be presented at AAO, November 16-19

Further development: Learning from the natural history of the disease I

Challenges
- Slow progressing disease
- No formal regulatory guidelines on end-points

Medical need
- No approved treatment options
- GA associated with visual loss

GA area progression over time*

“For all levels of baseline total atrophy, there was significant enlargement of atrophy over time, with only six eyes (7%) not demonstrating significant growth.”

*Ophthalmology. 1999 Sep;106(9):1768-79; DA=Macular Photocoagulation Study disc areas
Further development: Learning from the natural history of the disease II

**Challenges**
- Slow progressing disease
- No formal regulatory guidelines on end-points

**Medical need**
- No approved treatment options
- GA associated with visual loss

*Visual Acuity over time in patients with central GA*

- Mean BCVA of 63.6 ETDRS letters (approx. 20/50) one year prior to diagnosis of central GA
- 22-letter decrease by year 5 (BCVA of 41.9 letters, approx. 20/160) over 6 years

*AREDS Report Number 26, Archives of Ophthalmology 2009, 127:1168-74*
Smart development: Similarities between early BC and Geographic Atrophy

*Early Breast Cancer*  
*Geographic Atrophy*

**Slow progressing disease**
- Long survival
- Slow decline in visual function

**High unmet medical need with no approved treatments**

**Potentially long clinical trials**

**Biological rationale for surrogate end-point**
- pCR
- GA area change

*Perjeta&Herceptin: Approved for neoadjuvant HER2+ BC based on pCR*  
*Lampalizumab: Phase III design to be discussed with healthcare authorities*
## Summary: Successful 2013

### Regulatory achievements
- **US approvals:** Kadcyla, Avastin TML, Tarceva EGFR+ NSCLC, Lucentis (HARBOR)
- **EU approvals:** Perjeta, Avastin TML, Erivedge, Herceptin SC
- **Positive opinions:** Kadcyla (EU), Perjeta neoadjuvant (US)

### Late-stage read-outs
- **GA101** in CLL
- **Xolair** in Chronic idiopathic urticaria
- **Avastin** in GBM, Cervical cancer

### Positive proof-of-concept
- **Anti-PDL1** in solid tumours
- **Bcl-2 inh** in hematology
- **Lampalizumab** in dry AMD
- **Etrolizumab** in Inflammatory Bowel Disease
2011 to present: Strong pipeline progression
29 successful late-stage trials
NME submissions and their additional indications
Projects currently in phase 2 and 3

Unless stated otherwise, submissions are planned to occur in US and EU.
✓ indicates a submission which has occurred with regulatory action pending
# negative symptoms and sub-optimal control

Status as of June 30, 2013
Doing now what patients need next