R&D Roundtable

Martin Mackay, President, R&D

June 14th, 2012
Our vision for R&D

Performance

- Approval of valued medicines
- Positive return on investment

Portfolio

- Consistent productivity
- High quality late-stage pipeline

People

- Strong leadership cadre
- Smaller workforce

Operating Model

- Simpler footprint
- Innovative operating models

Cost

- Lower costs
- Higher external percentage
Transforming R&D 2010-12

Investing in the future of R&D

People

31 of the top 50 (60%) are new hires

Mene Pangalos
Innovative Medicines

Briggs Morrison
Global Medicines Development

Capabilities

>$200M over 5 years

• Personalised Healthcare
• Predictive Science
• Payer Evidence
• Clinical Trial Design

Portfolio

>40% of pipeline sourced externally

AMGEN

RIGEL

Bristol-Myers Squibb

Ardea Biosciences
Transforming R&D 2010-12

Managing the cost of R&D

People

23% reduction

Property

21 → 12 facilities

Portfolio

18% reduction
Building a high quality pipeline

5 Rs

Assurance Mapping

Real-World Evidence
# Potential 2012-13 phase III investment decisions

<table>
<thead>
<tr>
<th>Assets</th>
<th>Area under investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD6244 – selumetinib (MEK Inhibitor)</td>
<td>NSCLC / Melanoma</td>
</tr>
<tr>
<td>MEDI-1123 – tremelimumab (anti-CTLA-4 MAb)</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>AZD8931 (erbB kinase inhibitor)</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>CXL (beta lactamase inhibitor/cephalosporin)</td>
<td>MRSA</td>
</tr>
<tr>
<td>CAZ AVI (beta lactamase inhibitor/cephalosporin)</td>
<td>HAP/VAP</td>
</tr>
<tr>
<td>AZD9773 (anti-TNF-alpha polyclonal antibody)</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>MEDI-575 (anti-PDGFR-alpha MAb)</td>
<td>Glioblastoma / NSCLC</td>
</tr>
<tr>
<td>AMG-827 – brodalumab (anti-IL-17 MAb)</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>MEDI-563 – benralizumab (anti-IL-5R MAb)</td>
<td>Asthma</td>
</tr>
<tr>
<td>AZD1981 (CRTh2 receptor antagonist)</td>
<td>Asthma</td>
</tr>
</tbody>
</table>

As of 31 Dec 2011
### Late stage pipeline progress

<table>
<thead>
<tr>
<th>Phase III</th>
<th>Submitted</th>
<th>New indications</th>
<th>Launched/Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxegol</td>
<td>Further markets</td>
<td><strong>onglyza</strong> Renal impairment USA, Europe</td>
<td>Europe USA, Canada, Brazil</td>
</tr>
<tr>
<td>CAZ AVI</td>
<td>Russia</td>
<td><strong>onglyza</strong> Add-on to insulin Europe</td>
<td>China USA</td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>Further markets</td>
<td><strong>IRESSA</strong> 1st Line Japan</td>
<td>Europe Europe</td>
</tr>
<tr>
<td>IRESSA LCM</td>
<td>COPD Japan</td>
<td><strong>kombiglyze XR</strong> Add-on to insulin USA</td>
<td>USA</td>
</tr>
<tr>
<td>Faslodex LCM</td>
<td>SMART Asthma TBH Japan</td>
<td><strong>RANMARK</strong></td>
<td>Japan</td>
</tr>
<tr>
<td>Lesinurad*</td>
<td>EU</td>
<td><strong>komboglyze</strong> EU</td>
<td>EU USA</td>
</tr>
</tbody>
</table>

*subject to approval of Ardea acquisition

As of 31 Dec 2011
Our priorities for R&D

1. Deliver the late-stage portfolio
2. Secure high value late-stage partnerships
3. Achieve 8-11 positive POCs in 2012-14
4. Maximise LCM and emerging markets

All at the right cost and demonstrating progressive return on invested capital
R&D Roundtable

Mene Pangalos, Executive VP, Innovative Medicines

June 14th, 2012
The people behind our science

Susan Galbraith
Oncology iMed
Track record of delivery in cancer biology and drug development
Joined from Bristol-Myers Squibb

Manos Perros
Infection iMed
Led Novartis Institute for Tropical Disease
Former VP and Head of Antiviral Research at Pfizer

Maarten Kraan
R&I iMed
Experienced rheumatologist and clinician
Formerly of Roche, Bristol-Myers Squibb and Schering-Plough

Mike Poole
Neuroscience iMed
Twenty years experience in pharmaceutical clinical research
Former Chief Medical Officer at Link Medicine

Gunnar Olsson
CVGI iMed
Over 30 years of experience in cardiology
With AstraZeneca since 1989

Clive Morris
New Opportunities iMed
Former late stage development director for Oncology within Clinical Development
Accountability at every stage

Martin Mackay  President R&D

Innovative Medicines (IM)  Global Medicines Development

Target Selection  →  Proof of Concept  Late-stage development

IM Research Board  Product Development Committee  Product Review Board

Internal and external opportunities

Portfolio Investment Board

Martin Mackay  President R&D

Innovative Medicines (IM)  Global Medicines Development

Target Selection  →  Proof of Concept  Late-stage development

IM Research Board  Product Development Committee  Product Review Board

Internal and external opportunities

Portfolio Investment Board
Driving quality, not quantity

**Benefits**
- Increasing our focus on key projects and competitive position
- Increasing the odds of pipeline to deliver
- Removing low value projects early
- Staffing projects to be competitive
- Freeing resources to innovate, and re-invest in business priorities

**Impact**
- 30% decrease in IM portfolio volume
- 83% of projects stopped in pre-clinical phases

**Right target**

**Right tissue/Right exposure**

**Right safety**

**Right patients**

**Right commercial**
# Small molecule led NME’s

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3/registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD5363 (AKT) Solid tumors</td>
<td>AZD6244 (Selumetinib) (MEK) Solid tumors</td>
<td>Caprelsa™ (VEGFR/EGFR) MTC</td>
</tr>
<tr>
<td>AZD3514 (AR down regulator) Prostate cancer</td>
<td>Fostamatinib (SYK) Haematological malignancies</td>
<td>Fostamatinib (SYK) Rheumatoid arthritis</td>
</tr>
<tr>
<td>AZD2014 (mTOR1&amp;2) Solid tumors</td>
<td>AZD8931 (erbB) BC chemo combi/solid tumors</td>
<td>Forixga (SGLT2) Diabetes</td>
</tr>
<tr>
<td>AZD1480 (JAK1/2) Solid tumors</td>
<td>AZD4547 (FGFR) Solid tumors</td>
<td>Brilinta™ (ADP) Arterial thrombosis</td>
</tr>
<tr>
<td>Olaparib (PARP-gBRCA) Solid tumors</td>
<td>AZD8568 (Muscarinic antagonist) COPD</td>
<td>Naloxegol (Oral peripherally acting opioid antagonist) QIC</td>
</tr>
<tr>
<td>AZD6244/MK2206 (Selumetinib) (MEK/AKT) Solid tumors</td>
<td>AZD5423 (iSEGRA) COPD</td>
<td>Zinforo (Ceftaroline) Pneumonia/skin infections</td>
</tr>
<tr>
<td>AZD2115 (MABA) COPD</td>
<td>AZD5069 (CXR2) COPD</td>
<td>CAZ AVI (BLI /cephalosporin) SBI</td>
</tr>
<tr>
<td>AZD2820 (MC4r) Obesity</td>
<td>AZD2423 (CCR2b) COPD</td>
<td></td>
</tr>
<tr>
<td>CAT-354 (Tralokinumab) (IL-13) Ulcer, colitis</td>
<td>AZD1981 (CRTh2) Asthma/COPD</td>
<td></td>
</tr>
<tr>
<td>AZD5213 (H3R) Alzheimer’s/ADHD</td>
<td>AZD4017 (11BHSO) Glaucoma</td>
<td></td>
</tr>
<tr>
<td>AZD3839 (BACE1) Alzheimer’s</td>
<td>AZD22927 (ion channel blocker) Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>AZD3241 (MPO) Parkinson’s Disease</td>
<td>AZD6765 (NMADA) MDD</td>
<td></td>
</tr>
<tr>
<td>AZD1446 (a4b2 NNR) Alzheimer’s</td>
<td>AZD3480 (a4b2 NNR) AD</td>
<td></td>
</tr>
<tr>
<td>AZD5847 (Oxazolidine antibacterial inhibitor) TB</td>
<td>AZD2423 (CCR2b) Pain</td>
<td></td>
</tr>
<tr>
<td>AZD5099 (GyrB) Serious infections</td>
<td>CXL (BLI /cephalosporin) MRSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AZD9772 (aTNF polyclonal) Severe sepsis</td>
<td></td>
</tr>
</tbody>
</table>

**Legend**

- **Oncology**
- **Respiratory & Inflamm.**
- **CVGI**
- **Neuroscience**
- **Infection**

As of 31 Dec 2011
Does not reflect partner projects
‘Hot’ science ...

**CXCR2 (AZD5069) – Phase Ila**
Severe Asthma

**OPPORTUNITY**
- Asthma is one of the most prevalent chronic conditions, affecting over 300 million worldwide. Every decade, it’s prevalence increases 50%.

**DIFFERENTIATION POTENTIAL**
- First-in-class COPD therapy and reducing exacerbations in severe asthma

Proof of Mechanism achieved – Phase Ila study showed 67% reduction in neutrophils from baseline

**Mean neutrophil count (10^6/g) sputum neutrophils**

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre-treatment</th>
<th>AZD5069 80mg BD, 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>-67%</td>
</tr>
</tbody>
</table>

**NMDAr (AZD6765) – Phase IIb**
Major depressive disorder (MDD)

**OPPORTUNITY**
- Globally 450 million people suffer a mental or behavioral disorder. By 2020 it is estimated that depression will be the leading cause of disease burden.

**DIFFERENTIATION POTENTIAL**
- Treatment for refractory depression that could occupy a unique market position – following ineffective generics and before expensive hospital procedures

Efficacious in Phase Ila without psychomimetic effects – confirmed with fMRI and gamma-EEG; well-tolerated intermittent IV infusions

**Single infusion very well tolerated in Phase Ila**

Smith et al 2012, NCDEU
Partnering for success
Progress with the virtual iMed

**Optimised resources**
- Small headcount
- Simplified footprint
- Flexible collaborations replacing brick and mortar labs
- Cost-effective suppliers
- Sharing risk & cost

**Improved productivity**
- Leadership in place
- Autonomous drug ‘hunters’
- Based in major neuroscience hubs
- Rapid, efficient execution

**Partnering with the best**
- Proprietary discovery across network of partners
- Tapping into richest science available
- Access to AZ capabilities and global reach
- Sharing successes

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[Logos of partner institutions]
R&D Roundtable

Bahija Jallal, Executive VP R&D, MedImmune

June 14th, 2012
MedImmune’s pipeline comprises over 40% of the total AstraZeneca pipeline and potential 2012-13 Phase 3 investment decisions.
New approaches to building the R&D pipeline

INNOVATIVE AMGEN PARTNERSHIP

- MedImmune and Amgen are jointly developing and commercializing five monoclonal antibodies from Amgen’s inflammatory disease portfolio
- The assets have novel profiles with the potential to deliver multiple indications per asset
- The lead asset in the collaboration is Brodalumab (AMG827) in Phase 2 development for psoriasis, psoriatic arthritis, and asthma with Phase 3 investment decisions upcoming

<table>
<thead>
<tr>
<th>Asset</th>
<th>Indications</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodalumab</td>
<td>Psoriasis &amp; Psoriatic Arthritis</td>
<td>2b</td>
</tr>
<tr>
<td>AMG 827</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMG 139</td>
<td>Asthma</td>
<td>2a</td>
</tr>
<tr>
<td>AMG 157</td>
<td>Crohn’s</td>
<td>1</td>
</tr>
<tr>
<td>AMG 181</td>
<td>Ulcerative Colitis &amp; Crohn’s</td>
<td>1</td>
</tr>
<tr>
<td>AMG 557</td>
<td>SLE</td>
<td>1</td>
</tr>
<tr>
<td>All Assets</td>
<td>LCM</td>
<td>TBD</td>
</tr>
</tbody>
</table>

Brodalumab Efficacy in Psoriasis
Benralizumab (MEDI-563): Asthma (Phase 2b)
Anti IL-5 receptor mAb that depletes eosinophils and basophils

UNMET MEDICAL NEED
• Eosinophilic asthma represents ~40-60% of all patients with asthma and is characterized by more frequent exacerbations and higher risk of near-fatal events

MECHANISM OF ACTION
• MEDI-563 binds with high affinity to the IL-5 receptor alpha thereby depleting eosinophils and basophils. It is believed that reduction in sputum eosinophil count is associated with better asthma control and increases in sputum eosinophil counts are associated with asthma/COPD exacerbations

DIFFERENTIATION
• Incorporation of PHC strategy
• Improved outcomes vs. SoC/competitors
• Convenience of dosing vs. SoC

BIOLOGICS MARKET SIZE
• Estimated at $9-13B
Sifilimumab (MEDI-545): SLE (Phase 2b)
Anti IFNα mAb that prevents signaling through the Type I IFN receptor

UNMET MEDICAL NEED
• There is a significant unmet need in SLE for therapies that can reduce long-term steroid use and its associated side effects. Type 1 IFNs play a key role in SLE disease pathogenesis with IFN-α being an important Type 1 IFN subtype

MECHANISM OF ACTION
• MEDI-545 binds to IFN-α and prevents signaling through the Type I IFN receptor. IFN-α activates multiple cell types including monocytes, dendritic cells, neutrophils, T cells and B cells, and drives multiple pathways believed to be central to SLE

DIFFERENTIATION
• Improved outcomes vs SoC
• Reduced chronic steroid use
• Incorporation of PHC strategy

BIOLOGICS MARKET SIZE
• Opportunity estimated at $4-5B

Inhibition of type I IFN-inducible genes (Day 0–28)
Effect on SLE Skin Lesion (Day 0-28)
Moxetumomab pasudotox (CAT-8015): ALL (Ph 1b)
Anti CD22 immunotoxin that uniquely delivers toxins to malignant B-cells

UNMET MEDICAL NEED
• Anti-CD therapy with rituximab has improved outcomes for cancer patients. However, many patients relapse and stand to benefit from new approaches

MECHANISM OF ACTION
• Moxetumomab has a unique MoA whereby it selectively binds to CD22, is internalized, and is processed which releases the cytotoxic portion leading to cancer cell death

DIFFERENTIATION
• Targeted therapy: CD22 target is broadly expressed and internalized in B-cell malignancies making it an ideal target for immunotherapy
• Demonstrated single agent clinical activity in both pediatric ALL and Hairy Cell Leukemia

BIOLOGICS MARKET SIZE
• Opportunity estimated at $1B
R&D Roundtable

Susan Galbraith, iMed Head, Oncology

June 14th, 2012
Our oncology pipeline

Phase I

Breast

- AZD2014 TOR kinase inhibitor
- MEDI-573 Anti-IGF MAb
- AZD3514 AR down-regulator

Urology

- AZD4547 FGFR TKI
- MEDI3617 Anti-ANG-2 MAb

Lung

- MEDI-565 Anti-CEA BiTE
- AZD4547 FGFR TKI

Gastrointestinal

- MEDI3617 Anti-ANG-2 MAb
- MEDI-565 Anti-CEA BiTE

Haematological

- Moxetumomab Anti-CD22 immunotoxin
- MEDI3617 Anti-ANG-2 MAb
- Olaparib PARP inhibitor
- MEDI-565 Anti-CEA BiTE
- MEDI-573 Anti-IGF MAb

‘Niche’/ Other

- MEDI-573 Anti-IGF MAb

Phase II

- AZD8931 erbB kinase inhibitor
- Selumetinib AZD6244 MEK inhibitor
- MEDI-575 Anti-PDGFR-alpha MAb
- MEDI-573 Anti-IGF MAb
- AZD4547 FGFR TKI

- Azumetinib Syk inhibitor
- Tremelimumab Anti-CTLA4 MAb

As of 31 Dec 2011
• Worldwide, lung cancer is the most common cause of cancer-related death (1.3M deaths)
• Traditional classification used morphology
• The most common types of Non-small Cell lung cancer described above

1987

• Discovery showed that NSCLC cells can harbor a single specific mutated KRAS oncogene
• KRAS is thought to be the primary genetic “driver” leading to cancer

2004

• 2001-04: AstraZeneca in collaboration with external groups show that clinical response to Gefitinib (IRESSA) correlates with EGFR mutations

2012

• 2012: Global genomics initiatives (e.g., TCGA) identify multiple additional primary genetic “drivers”
• Majority of lung cancer cases now have a ‘molecular diagnosis’ with further segmentation inevitable
MEK inhibitor
AZD6244 (Selumetinib) – Treatment for lung cancer

OPPORTUNITY

• KRAS mutation positive non-small cell lung cancer (NSCLC) represents ~20% of lung cancer and is a disease associated with a poor prognosis

DIFFERENTIATION POTENTIAL

• To drive and lead the establishment of MEK dependency as a key cancer treatment paradigm

SCIENTIFIC RATIONALE

• MEK/ERK pathway is activated as a consequence of KRAS mutation in NSCLC
• KRAS mutations are associated with resistance to Standard of Care and no effective follow-on therapies
• AZD6244 is a potent and selective inhibitor of MEK1/2

Distribution of gene changes in NSCLC
MEK inhibitor
AZD6244 (Selumetinib) – Treatment for lung cancer

WHY WE BELIEVE IN THIS APPROACH

• Phase I achieved Proof of Mechanism and Principle at tolerated dose
• Significant improvement in PFS with AZD6244/ chemotherapy combination vs chemotherapy alone in Phase IIb
• PHC strategy with Roche Molecular Systems to recruit patients with KRAS mutation only

<table>
<thead>
<tr>
<th></th>
<th>AZD6244 + docetaxel (N=43)</th>
<th>Placebo + docetaxel (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>16 (37%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-response</td>
<td>27 (63%)</td>
<td>40 (100%)</td>
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</table>

AZD6244 75 mg BD + Docetaxel
median = 5.3 vs 2.1 months
(HR 0.58, 80% CI (0.42, 0.79), p = 0.0138)

Improved progression-free survival demonstrated and trend to increased OS (median 9.4 vs 5.2 months) following AZD6244 combination treatment in Phase IIb
Fibroblast growth factor receptor (FGFR) inhibitor
AZD4547 – Treatment for gastric, lung and breast cancers

OPPORTUNITY
• Disregulation of FGF/FGFR signalling is associated with early relapse and poor survival, particularly in patients with gastric tumours

DIFFERENTIATION POTENTIAL
• A novel targeted therapy for FGFR-amplified cancers

SCIENTIFIC RATIONALE
• FGFR maintains the malignant properties of tumour cells – growth, survival and angiogenesis
• Disregulation of FGF/FGFR occurs in several tumour subsets due to gene amplifications/rearrangements/mutations

Proportion of tumour subsets with FGFR amplification/mutations

- Gastric amp ~7%
- Bladder mut ~70%
- Myeloma trans ~20%
- Breast ~10%
- Squamous NSCLC ~15%
- Prostate up-reg

18 ligands
Fibroblast growth factor receptor (FGFR) inhibitor
AZD4547 – Treatment for gastric, lung and breast cancers

WHY WE BELIEVE IN THIS APPROACH

• Primary explant models from patients’ tumours with FGFR gene amplification show profound tumour regression with AZD4547

• Diagnostic development in Phase I enables faster transition to Phase III

• Tumour regression seen in a patient with squamous lung cancer and FGFR amplification in Phase I

STATUS

• Potential Phase IIb ID 2012-13 in Squamous Lung cancer

• PHC strategy to prospectively select patients with FGFR gene amplification using FISH diagnostic assay

Lung primary explants with FGFR1 gene amplification regress when treated with AZD4547 in vivo

FISH assay

28/3/2012 9/5/2012
R&D Roundtable

Bill Mezzanotte, GMed Head, Respiratory, Inflammation and Neuroscience

June 14\textsuperscript{th}, 2012
Increasing our success in late stage development

- Decrease our cycle time
- Reduce our costs
- Increase the analytic rigor in our programmes

INCREASE THE SUCCESS RATE
Phase III heat maps and probability of success

**Efficacy map**

1. What is the magnitude of your PoC Clinical signal relative to your base TPP?
2. How similar is your planned Phase III Clinical Programme to your PoC trial?

**Safety map**

1. What is the severity of your safety signal(s) prior to PhIII?
2. What is the frequency of safety signals prior to PhIII?
Repeated Critical Evaluation Over Time Helps to Identify the Most Promising Molecules

- High uncertainty
- Low knowledge
- Low uncertainty
- High knowledge

Pre-Clinical

Phase III

Critical Questions

Select Target

Select Lead Series

Select Candidate Drug

Proof of Mechanism

Proof of Principle

Proof of Concept

Efficacy/Safety Heat Maps
Regulatory rigour for greater success

**BRILINTA:**
First Regulatory Approval Achieved in Europe—December 2010

Achieved regulatory approvals in 38 countries across 5 continents within 6 months of first approval.
Increasing payer outcomes

We deliver clinical and economic evidence for payers to understand the value of our medicines in achieving better, cost effective healthcare

- **Payer Insights**
  - Customer engagement
  - Payer research
  - Payer advisory boards

- **Payer Analytics**
  - RCT design & analysis
  - Health economic modelling
  - Specialist statistics (Payer Analysis Plan)
  - Informatics

- **Payer Evidence Strategy**
  - Product strategy development
  - Payer scientific advice
  - Global reimbursable dossier generation
  - Informatics

- **Real World Evidence**
  - Customer & partner engagement
  - RWE study design & analysis
  - Informatics

- **Strategic & Operational Pricing**
  - Price modelling
  - Pricing research & analogue analysis
  - Contracting and price negotiation
Impressive clinical trial capability

**BRILINTA PLATO Trial**

Real World Design & Head to Head Superiority  
*Acute Coronary Syndrome*  
- Trial design reflected ACS treatment decisions – 18,700 patients in 43 countries  
- Superiority achieved against current ACS standard of care  
- Payer and physician needs addressed in study outcomes

**ONGLYZA SAVOR TIMI-53 Trial**

Elegant Design to Foster Recruitment Speed  
*Adults with Type 2 Diabetes*  
- Fast study recruitment – 16,500 patients completed in 19 months  
- Event-driven trial design powered for superiority  
- Complies with new FDA T2DM guidance regarding long-term CV risk
Significant improvement in R&D productivity: Example: Cost per patient

AZ has reduced “cost per patient” by more than 30% in the period 2010-2012

Source: R&D Clinical June 2012