Oncology Research & Development

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Agenda

1. *hhc* company: Eisai
2. Oncology Research & Development
3. History of Oncology Research in Eisai
4. Establishing Oncology Franchise
1. *hhc* company: Eisai
hhc company: Eisai

*human health care* is our goal. We give first thought to patients and their families, and to increasing the benefits health care provides.

- Providing meaningful contributions under any healthcare system
- Observing the highest legal and ethical standards
- Providing integrated healthcare solutions
Thoughts of Cancer Patients

- **Desire of patients**
  - Become healthy, become cured; Effective therapy
  - Maintain the current condition; Live actively as long as possible
  - Live with normal life; Not suffering

- **Be Physician in Charge**
  - Know cancer and understand my situation
  - Understand the therapy and responsible for the determination

- **Effort to make evidence**
  - Join the clinical trial
  - Effort to evaluate objectively

- The cancer treatment stands close
  the thoughts of patients and their families
2. Oncology Research & Development
Major differences in Oncology Research & Development

- Many different kinds of Research Approach
- Lower Probability of Success
- Pharmacological evaluation
- Manufacturing of Clinical Trial Material
- Clinical Studies/Clinical Development Strategy
Many Different Kinds of Research Approach

- Novel Cytotoxics
- Hormone Therapy
- Tyrosine Kinase Inhibitors
- Angiogenesis Inhibitors
- Signal Transduction Inhibitors
- Monoclonal Antibodies
- Cytokines
- Gene Therapy
- Cancer Vaccines
- Others

Research project is created based on the consideration of “research approach”, but clinical development & indication/labeling based on tumor type
Sales Forecast
(Except for Hormone, Immunological and Supportive Therapy)

From “Cancer Market Outlook” Business Insight
Lower Probability of Success

- POS from First-in-man to NDA/MAA Submission
  - Oncology: 5%
  - Cardiovascular: 20%
  - Infectious Disease: 16%
  - Metabolic Disease: 11%
  - Urological Disease: 9%
  - CNS: 8%

Nature Review Drug Discovery 3, 711, 2004
Pharmacological Evaluation

- Many kinds of Pharmacological models
- Difference of the effect size based on the mechanism of action, cytotoxic vs cytostatic
- Sensitivity difference between host (mouse) and transplanted tumor (human)
- Narrow therapeutic window
- Difference of endpoint between animal model and clinical
- Correlation between pharmacological action and anti-tumor effect, immediate vs delayed
Clinical Studies/ Clinical Development Strategy

- Multi Dosing Schedules
- Optimum Dose selection for Mono and Combination Therapy
- Selection of Multiple Target Tumor Types
- Selection of Patient Population (1st line, 2nd line, 3rd line)
- Accelerated Approval vs Full Approval
- Labeling/Indication based on Tumor Types and Treatment Line
- Pharmacogenomics and Biomarkers
3. History of Oncology Research in Eisai
Aiming to enter into oncology area

- Examination in a project (1986)
- After a research group starts, the policy is re-examined. (1987)
  ⇒ Aim to create candidates at the following three points.
  - Novel mechanism of action
  - Novel chemical structure
  - Prominent *in vivo* anti-tumor effects
Our policy for oncology R&D

1. We do not research analogs of existing classes for which competitors accumulate lots of knowledge.

2. We aim what we can demonstrate unique advantages of our own research.

3. We setup a goal of improving survival rate and survival time when we start research programs.

4. We setup endpoints and efficacy criteria in animal models corresponding to the feature and the objectives of the theme.

5. Initiate Clinical studies in Japan quickly based on our strategy and project status.
History of Oncology Research at Tsukuba (TRL) and Boston (ERI)

1. E7010 (ABT-751): Sulfonamide tubulin polymerization inhibitor (1987); TRL
2. Topoisomerase II inhibitor (1991); TRL
3. Farnesyl transferase inhibitor for ras, an oncogene product (1991); Full Collaboration
4. E7070: Sulfonamide G1 phase targeting agent (1992); TRL
5. E7820: Anti-angiogenesis (1992); TRL
6. E7389: microtubule growth suppressor, synthetic analog of halichondrin B (1992); ERI
7. E6020: TLR-4 agonist, Vaccine adjuvant (1997); ERI
8. E7974: Hemiasterlin-type microtubule polymerization inhibitor (1998); ERI
9. E7080: VEGFR kinase inhibitor, anti-angiogenesis (1999); TRL
10. E7107: RNA splicing modulator, pladienolide derivative (2000); TRL
11. E6201: MEK-1 & MEKK-1 kinase inhibitor (2002); ERI
12. E7050: c-met & VEGFR kinase dual inhibitor (2003); TRL
4. Establishing Oncology Franchise
Approach for establishing oncology franchise

- Steady progress of clinical development of our pipeline; Prioritization
- Product acquisition of launched products; Lymphoma Products
- Development of infrastructure of antibody research; Acquisition of Morphotek
- Establishment of Oncology Franchise; Acquisition of MGI Pharma
Oncology Pipeline/Products

**Preclinical**
- **Novel Cytotoxic Anti-cancer**
  - GPI21016: Cancer therapy, Radiotherapy sensitizer
- **Anti-Angiogenesis Anti-proliferation**
  - E7050: C-met & VEGFR Tyrosine Kinase Inhibitor
- **Monoclonal Antibody**
  - MORAb-004: Antibody
  - MORAb-009: Anti Mesothelin mAb
  - MORAb-028: Antibody
- **Vaccine**
  - E6020: Vaccine Adjuvant
- **Supportive care**
  - GCPII Inhibitor Chemo induced neuropathy

**Early phase clinical studies**
- **Novel Cytotoxic Anti-cancer**
  - E7070: Cell Cycle G1 Phase Targeting Agent
  - E7974: Hemastatin Type Tubulin Polymerization Inhibitor
  - E7107: RNA Splicing Modulator
- **Anti-Angiogenesis Anti-proliferation**
  - E7820: Alpha-2 Integrin Expression Inhibitor
  - E7080: VEGF Receptor Tyrosine Kinase Inhibitor
  - E6201: Novel natural product-inspired MEK-1/MEKK-1 Kinase Inhibitor
- **Monoclonal Antibody**
  - ZYC300: Cancer Therapeutic DNA Vaccine
- **Vaccine**
  - AKR-501: Thrombocytopenia

**Late phase clinical studies**
- **Novel Cytotoxic Anti-cancer**
  - E7974: Hemastatin Type Tubulin Polymerization Inhibitor
  - Irifulven: Semi-synthetic Derivative of Toxin Illudin S
- **Anti-Angiogenesis Anti-proliferation**
  - E7080: VEGF Receptor Tyrosine Kinase Inhibitor
  - E6201: Novel natural product-inspired MEK-1/MEKK-1 Kinase Inhibitor

**Launched**
- **Novel Cytotoxic Anti-cancer**
  - Dacogen®: DNA Methyltransferase Inhibitor, MDS
  - ONTAK®: CD25 Positive Cutaneous T-cell Lymphoma
  - Targetacin®: (Capsule & Gel) Cutaneous T-cell Lymphoma
  - Hexalen®: Ovarian Cancer
  - Panretin® gel: AIDS-related Kaposi's Sarcoma

**Biologics**
- Eisai
- MGI Pharma
- Ligand Pharmaceuticals

**Other**
- Fospropofol: Procedural Sedation for Minor Surgery/Diagnostics
- Fragmin®: Anti-clotting Agent
- Alox® postoperative nausea and vomiting (injection)
- Alox® Chemotherapy induced nausea & vomiting (injection, oral)
- Salagen®: Symptoms for Radiation-induced Dry Mouth in Head and Neck Cancer Patients

**Morphotek**
Taxol and E7389 have opposing effects on spindle microtubule dynamics.

- **Taxol** enhances spindle-microtubule polymerization.
- **E7389** induces spindle-microtubule shortening.

Green : microtubule  
Blue : chromosome
E7389
Microtubule Growth Suppressor

- Synthetic analog of halichondrin B, marine sponge natural product
- Novel chemical structure
- Unique effect on microtubule dynamics*
  - blocks microtubule polymerization
  - no effect on depolymerization
  - sequesters tubulin into non-functional aggregates

E7389
Microtubule Growth Suppressor

- Phase II studies in breast cancer and non-small cell lung cancer (NSCLC) demonstrated promising efficacy and safety profile
  - Observed antitumor effect in breast cancer patients who were pretreated with anthracycline, taxane and capecitabine (ORR by Independent Review 9.3%, Investigator-assessed ORR 14.1%)
  - Potential advantage in safety profile in peripheral neuropathy
  - E7389 appears to show activity in NSCLC patients who have previously received taxane therapy (ORR 9.7%)

- Breast cancer (pretreated with anthracycline, taxane and capecitabine)
  - FDA agreed Eisai may submit NDA using breast cancer 305 study
  - US NDA, EU MAA, J-NDA planned in FY 2009

- Prostate cancer
  - Now in final stage of Phase II POC study

- Sarcoma
  - Phase II POC study ongoing for four types of sarcoma, two-stage design
  - Confirmed activity in 1st stage for leiomyosarcoma and decided to advance into 2nd stage

- Non-small cell lung cancer
  - Phase Ib/II combination study with carboplatin ongoing
MORAb-003
<mAb targeting folate receptor alpha>
Current status

✓ Phase I results
  - Well tolerated up to 400 mg/m² (10mg/kg/wk)
  - Radiolabel demonstrated tumor localization

✓ Phase II study for ovarian cancer ongoing
  - Innovative clinical trial design to direct best use of mAb
  - Platinum-sensitive ovarian cancer after 1st relapse
  - Monotherapy and combination with carboplatin + taxane
  - To date, 6 out of 12 patients have 2nd remission longer than 1st remission in combination with carb. + taxane
    - Occurs in < 1% of patients on carbo + taxane

(Oral presentation “Exploratory Phase II efficacy study of MORAb-003, a monoclonal antibody against folate receptor alpha, in platinum sensitive ovarian cancer in first relapse” in ASCO annual meeting, Chicago, USA, May 30 – June 3, 208)
MORAb-003
<mAb targeting folate receptor alpha>
Future Plan

- Phase III study; Platinum-sensitive relapsed ovarian cancer
  - Current Regulatory Status
    - FDA End of Phase II Meeting in Jan 2008
      - Invited to submit SPA for full approval
      - CMC review meeting with FDA on April 17th 2008 (CMC plan agreed to)
    - SPA package submission July 2008
      - Seeking EMEA scientific advice
  - Final protocol 3Q FY2008
    - Dependent on FDA review/feedback
  - Target BLA submission FY2012

- Phase II study; Platinum-resistant relapsed ovarian cancer
  - Weekly paclitaxel +/- MORAb-003
MORAb-009
<Anti-mesothelin Monoclonal Antibody>

– Phase I study completed
– Phase II study for pancreatic cancer (1st line)
  • MORAb-009 + gemcitabine vs. placebo + gemcitabine
  • Target: 152 patients (76 patients/arm)
  • Primary endpoint: overall survival
  • FPI achieved in December 2007
– Preparing for Phase II study for mesothelioma
MORAb-028

<Anti-GD2 Monoclonal Antibody>

- Human IgM antibody to cell surface tumor antigen “GD2 (ganglioside2)”
- Targets melanoma, NSCLC, SCLC and brain tumors
- Biology of target antigen ”GD2” associated with transformation
- Antibody suppresses growth of tumors in vivo
- MOA via complement dependent killing
- L72 (human anti-GD2 IgM) antibody tested in 8 patient clinical study and shown to have anti-tumor activity
- MORAb-028 established from L72 producing hybridoma line MORPHODOMA technology
Inhibition of all VEGF receptor family (VEGFR1: Flt-1, VEGFR2: KDR, VEGFR3: Flt-4) and other angiogenesis-related molecules such as FGFR1 and PDGFRβ

Three Phase I studies are almost completed
- Three Phase I studies in parallel in U.S., EU and Japan
- $C_{\text{max}}$ and AUC appear to increase proportionally to dose
- PK-PD using biomarkers indicates $C_{\text{trough}}$ level exceeded pharmacological active concentration
- E7080 treatment decreased c-kit(+) CEP and c-kit(+) CEC
- Many PR and long (> 6 months) SD were observed in renal, sarcoma, melanoma, thyroid cancer, colorectal cancer

(CEP: Circulating endothelial progenitors, CEC: Circulating endothelial cells)
**Study objectives**

**Primary objective**
- To determine the maximum tolerated dose (MTD) in a continuous once daily dosing schedule.

**Secondary objectives**
- To determine the dose limiting toxicities (DLTs).
- To explore the safety and tolerability of E7080.
- To determine the pharmacokinetic profile.
- To explore the anti-tumor efficacy.
- To identify and validate pharmacodynamic biomarkers and explore the biological effects.

<table>
<thead>
<tr>
<th>Best response</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>5</td>
</tr>
<tr>
<td>Disease Stabilisation</td>
<td>25</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>9</td>
</tr>
</tbody>
</table>

(Poster “A phase I dose escalation and pharmacokinetic study of E7080, a small molecule tyrosine kinase inhibitor, in patients with advanced malignancies” in ASCO annual meeting, Chicago, USA. May30-Jun 3.)
**E7080**

**Conclusion**
- E7080 displays linear pharmacokinetics and is safe and well tolerated at doses up to 25 mg daily.
- Very promising early indications of anti-cancer activity have been observed, especially in patients with melanoma, renal cell carcinoma and sarcoma.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Starting dose (mg)</th>
<th>Best response</th>
<th>TTP (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>0.8</td>
<td>NA</td>
<td>&lt;8</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>16</td>
<td>PD</td>
<td>8</td>
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<tr>
<td></td>
<td>20</td>
<td>PD</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>SD</td>
<td>32</td>
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<tr>
<td></td>
<td>32</td>
<td>SD</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td><strong>PR</strong></td>
<td>44+</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td><strong>PR</strong></td>
<td>49+</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>SD</td>
<td>36+</td>
</tr>
<tr>
<td>Renal</td>
<td>3.2</td>
<td>SD</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td><strong>PR</strong></td>
<td>68+</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td><strong>PR</strong></td>
<td>36+</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3.2</td>
<td><strong>PD</strong></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td>NA</td>
<td>7</td>
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<tr>
<td></td>
<td>12.5</td>
<td>SD</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td><strong>PR</strong></td>
<td>24</td>
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<td>16</td>
<td>SD</td>
<td>56</td>
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<td>SD</td>
<td>24</td>
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<td>25</td>
<td>SD</td>
<td>36</td>
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<tr>
<td></td>
<td>32</td>
<td>SD</td>
<td>12</td>
</tr>
</tbody>
</table>

(Poster “A phase I dose escalation and pharmacokinetic study of E7080, a small molecule tyrosine kinase inhibitor, in patients with advanced malignancies” in ASCO annual meeting, Chicago, USA. May30-Jun 3.)
E7107
(Pladienolide derivative)
RNA Splicing Modulator

- New Molecular target; Splicing factor SF3b
- Pladienolide was discovered from the fermentation broth of *streptomyces platensis* Mer-11107
- Different antitumor spectrum from existing anticancer drugs
- Most potent tumor regression activity in nude mouse xenograft models (human cancer cells)

- Current Status:
  - Two Phase I studies in US & EU progressing rapidly
  - Biomarker studies based on MOA

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Splicing factor SF3b as a target of the antitumor natural product pladienolide
Yoshihiko Kotake, Koji Sagane, Takashi Owa, Yuko Mimeri-Kiyosue, Hajime Shimizu, Mai Uesugi, Yasushi Ishihama, Masao Iwata & Yoshinari Mizui
Published online: 22 July 2007 | doi:10.1038/nchembio.2007.16
**Novel Anti Tumor Mechanism**

Controlling Splicing

[Diagram of cell with nuclear and splicing elements, showing the process of splicing and its impact on mature mRNA and protein synthesis necessary for cancer cells.]

- **Pre-mRNA**
- **Mature mRNA**
- **Exon**
- **Intron**

**Splicing**

**E7107**

**SF3b**

**Anti-tumor effect**

Protein synthesis necessary for cancer cells
Human Papillomavirus (HPV) infection can result in pre-cancerous disease.

Non-invasive disease treatment option that does not damage healthy tissue.

If approved, amolimogene: would represent the first DNA vaccine therapy available for human use.

Amolimogene:
- A non-replicating, non-integrating DNA
- Expresses a HPV polyprotein (based on E6 and E7 proteins) to activate an immune response
- Encapsulated in PLG particles
- Lyophilized formulation
Amolimogene: Treatment vs. Prophylaxis for Cervical Dysplasia

Prophylactic Vaccine
- Goal: elicit antibody response
- Antibody binds and neutralizes virus
- Prevents infection

Medical Therapeutic Vaccine
- Goal: elicit immune response
- Immune cells migrate to cervix; recognize pre-cancer cells
- Eliminate diseased cells → cleared lesion

Prevent infection

Treat women with disease

Antibody

Immune cells
**Amolimogene Clinical Development: Cervical Dysplasia**

- **Phase I trials**
  - Demonstrated biologic activity
  - Clinical response in 100% of ≤25 year olds

- **Phase II investigator study**
  - Well tolerated; 67% clinical response overall and 100% clinical response in patients <25 years old

- **Phase II company sponsored trial**
  - 161 patients, randomized, controlled
  - Safe and well-tolerated
  - Resolution of CIN2/3 (all patients): 43% vs. 27%
  - Resolution of CIN2/3 (< 25 years old): 70% vs 23%; (p =0.001)

- **Pivotal program underway**
  - 2 pivotal trials
  - First trial (n=250) completed enrollment

CIN: cervical intraepithelial neoplasia
## Summary of Oncology Pipeline

<table>
<thead>
<tr>
<th>Product</th>
<th>Status and Details</th>
</tr>
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<tbody>
<tr>
<td><strong>E7389</strong></td>
<td>FDA agreed Eisai will submit NDA using breast cancer 305 study; simultaneous NDA/MAA submissions in Japan, U.S. and Europe; steady patient enrollment; targeting NDA/MAA submissions in FY2009</td>
</tr>
<tr>
<td><strong>MORAb-003</strong></td>
<td>Presented Phase I and II data at ASCO; confirmed potential anti-cancer effect against ovarian cancer; Phase III to be initiated; targeting NDA submission in FY2012</td>
</tr>
<tr>
<td><strong>MORAb-009</strong></td>
<td>Phase II study for pancreatic cancer (1st line) ongoing. Preparing for Phase II study for mesothelioma</td>
</tr>
<tr>
<td><strong>MORAb-028</strong></td>
<td>Phase I study in preparation.</td>
</tr>
<tr>
<td><strong>E7080</strong></td>
<td>Confirmed potential anti-cancer effect for multiple cancer types; targeting best-in-class drug and NDA/MAA submissions in FY2012</td>
</tr>
<tr>
<td><strong>E7107</strong></td>
<td>Two Phase I studies in US &amp; EU Progressing. Biomarker studies based on MOA.</td>
</tr>
<tr>
<td><strong>Amolimogene</strong></td>
<td>Achieved LPO (Last Patient Out) of Phase II/III study for treatment of CIN (Cervical Intraepithelial Neoplasia) in women under 25</td>
</tr>
</tbody>
</table>