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

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

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**

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.**

1. **E7010 (ABT-751): Sulfonamide tubulin polymerization inhibitor (1987); TRL**
2. **Topoisomerase II inhibitor (1991); TRL**

4. Establishing Oncology Franchise

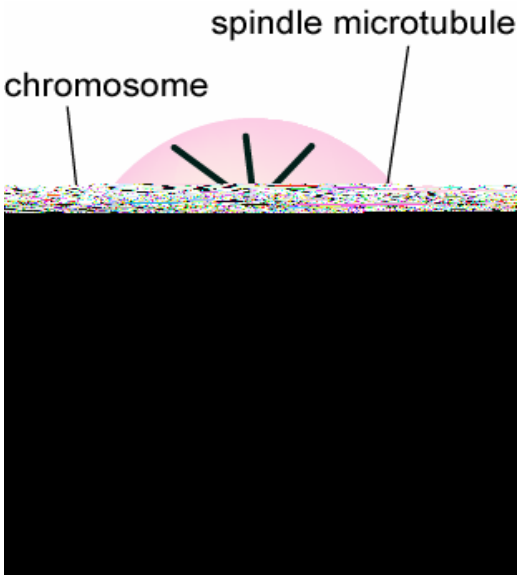
Approach for establishing oncology franchise

- **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**

Taxol and E7389 have opposing effects on spindle microtubule dynamics

<u>Taxol</u> enhances spindle-microtubule polymerization.

<u>E7389</u> induces spindle-microtubule shortening.



Green : microtubule
Blue : chromosome

E7389
Microtubule Growth Suppressor

➢

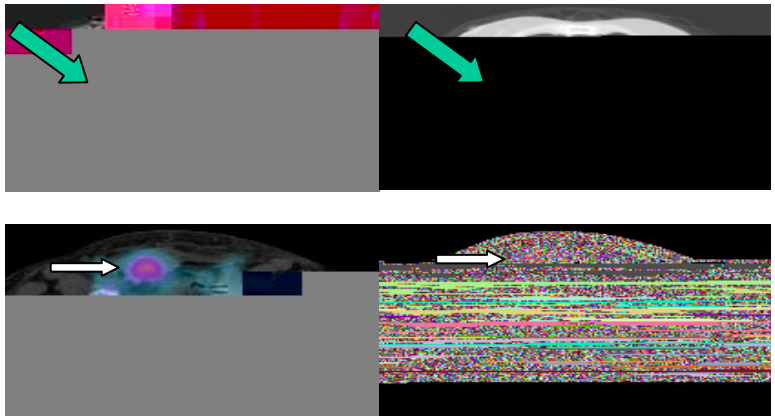
MORAb-003

<mAb targeting folate receptor alpha>

Current status

✓ Phase I results

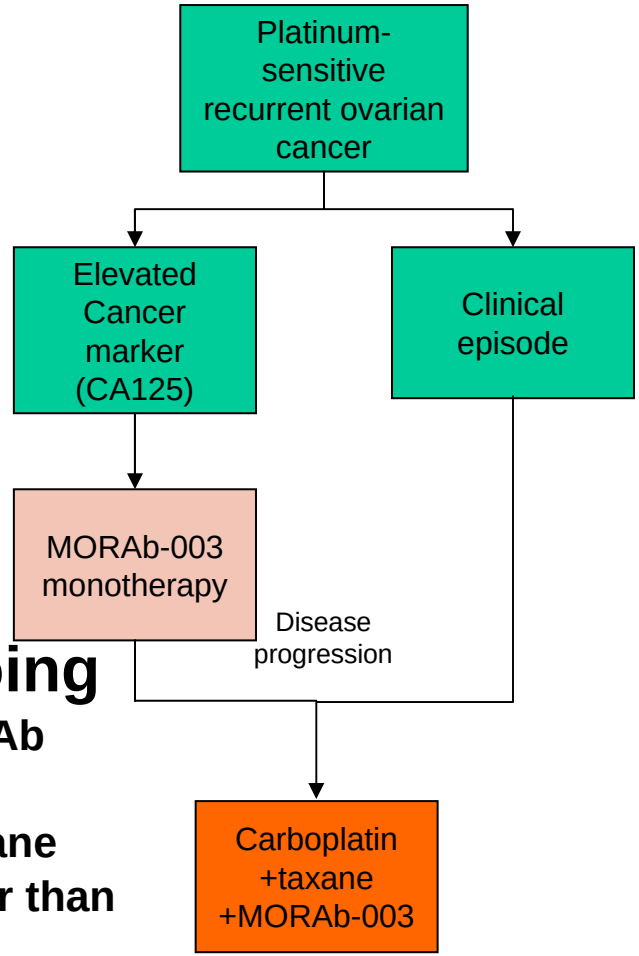
- **Well tolerated up to 400 mg/m² (10mg/kg/wk)**
- **Radiolabel demonstrated tumor localization**



✓ 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**

MORAb-003
Phase II ovarian cancer



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-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 PDGFRb

- Three Phase I studies are almost completed
  - Three Phase I studies in parallel in U.S., EU and Japan
  - C_{max} and AUC appear to increase proportionally to dose
  - PK-PD using biomarkers indicates C

E7080

Study objectives

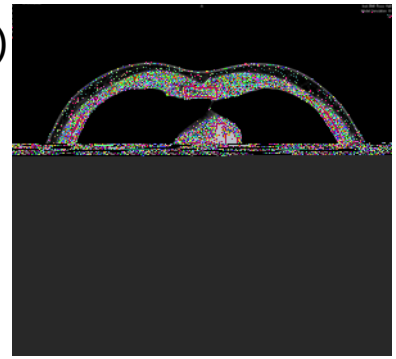
Primary objective

- 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.

(a)



(b)

Best response	Number of patients
Partial Response	5
Disease Stabilisation	25
Progressive Disease	9

E7080

Tumour type	Starting dose (mg)	Best response	TTP (weeks)
Melanoma	0.8	NA	<8
	12.5	NA	NA
	16	PD	8
	20	PD	8
	25	SD	32
	32	SD	40
	32	PR	44+
	32	PR	49+
	25	SD	36+
Renal	3.2	SD	76
	20	PR	68+
	25	PR	36+
Sarcoma	3.2	PD	8
	6.4	NA	7
	12.5	SD	44
	12.5	PR	24
	16	SD	56
	16	SD	24
	25	SD	36
	32	SD	12

Conclusion

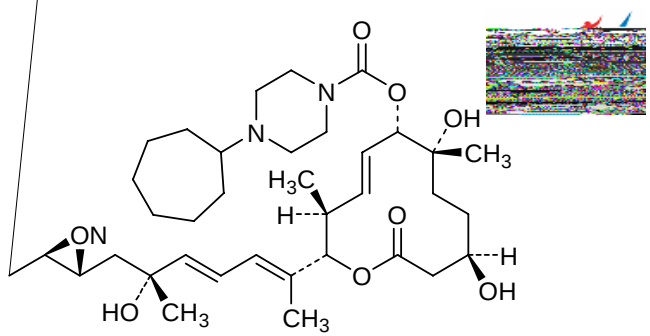
- E7080 displays linear pharmacokinetics and is safe and well tolerated at doses up to 25 mg daily.

- Very promising early indications of anti-cancer activity have been observed, especially in patients with melanoma, renal cell carcinoma and sarcoma.

(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)

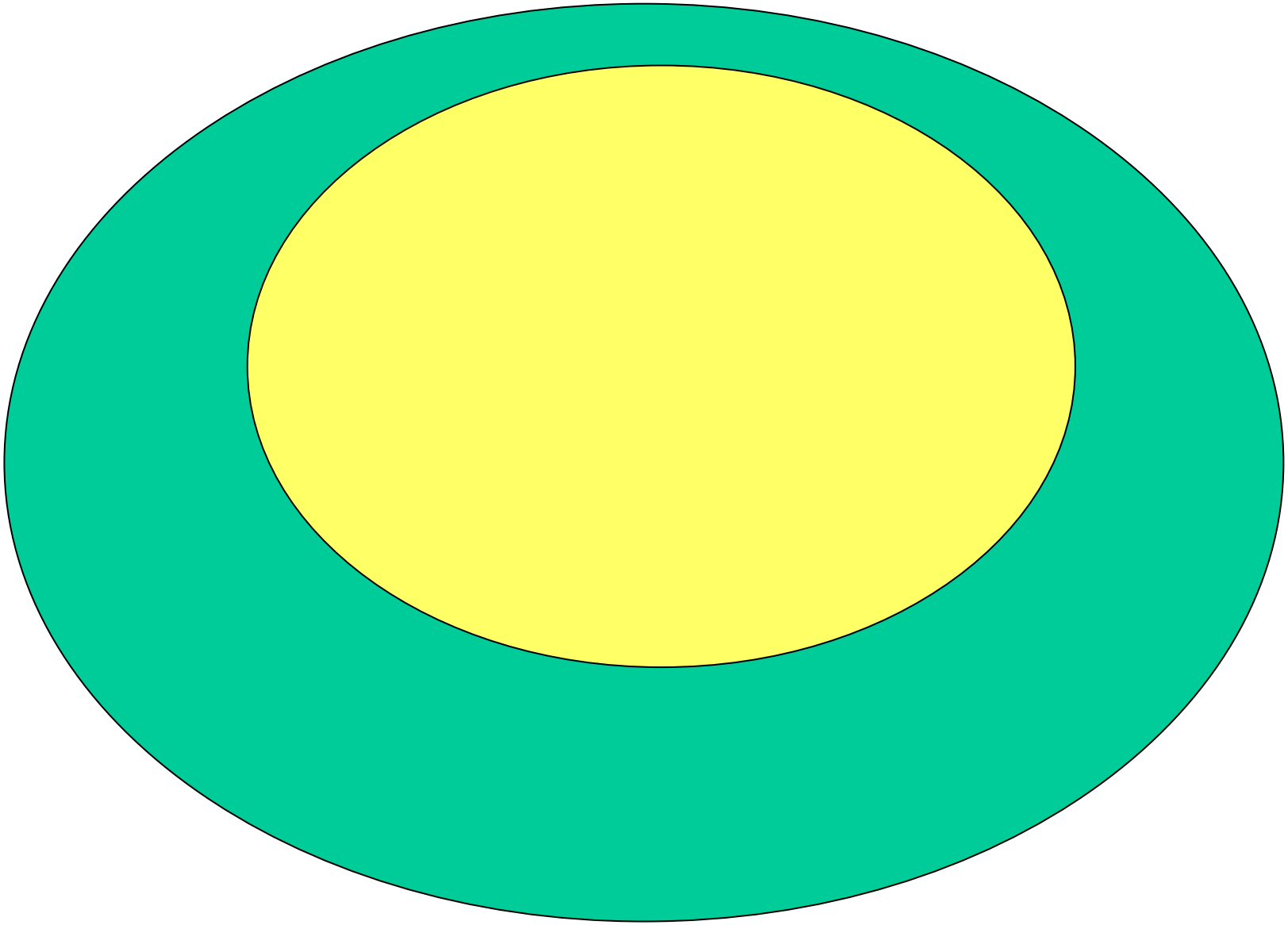
- Current Status:
  - Two Phase I studies in US & EU progressing rapidly
  - Biomarker studies based on MOA

Letter

Splicing factor SF3b as a target of the antitumor natural product pladienolide

Yoshihiko Kotake, Koji Sagane, Takashi Owa, Yuko Mimori-Kiyosue, Hajime Shimizu, Mai Uesugi, Yasushi Ishihama, Masao Iwata & Yoshiharu Mizui

Published online: 22 July 2007 | doi:10.1038/nchembio.2007.16

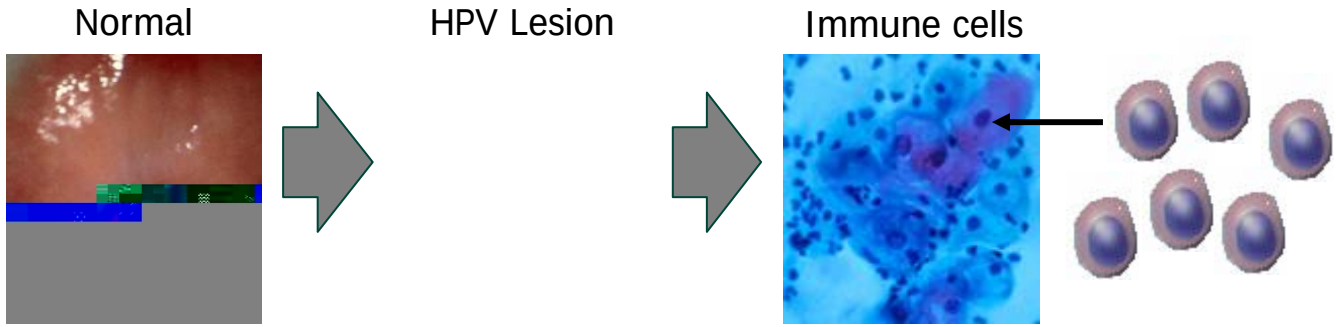


Amolimogene:
A Vaccine for Tre V
diated Disease

Amolimogene:

- **A non-replicating, g DNA**
- **Expresses a HPV po sed E6 and E7 pr e an response**
- **d in PLG particles**
- **lation**

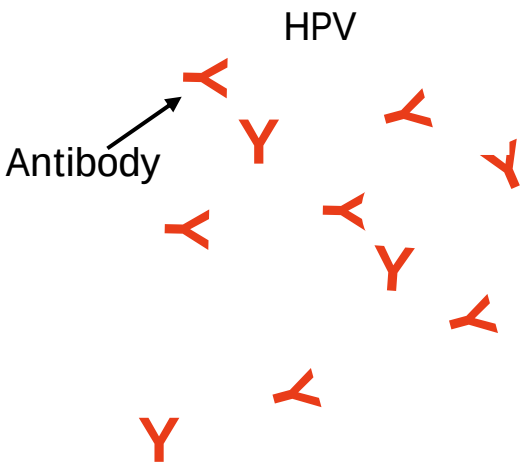
represent the first DNA vaccine available for human use.



Amolimogene:
Treatment vs. Prophylaxis for Cervical Dysplasia

Prophylactic Vaccine

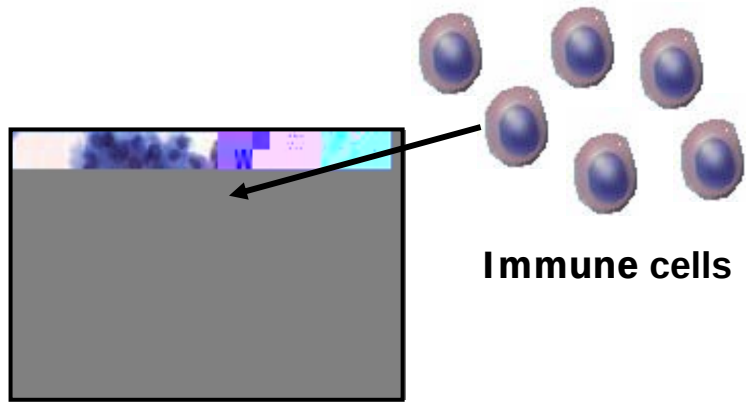
- Goal: elicit antibody response
- Antibody binds and neutralizes virus
- Prevents infection



Prevent infection

Medical Therapeutic Vaccine

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



Treat women with disease

Summary of Oncology Pipeline

E7389: 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

MORAb-003: Presented Phase I and II data at ASCO; confirmed potential

E7080: Confirmed potential anti-cancer effect for multiple cancer types; targeting best-in-class drug and NDA/MAA submissions in FY2012