4th R&D Meeting

11 December, 2009

GEMRAD Co-Chairperson
Dr. Kazunori Hirokawa
Dr. Glenn J. Gormley

Daiichi-Sankyo

R&D Highlights in FY2009

- Effient®, Approved and Launched in U.S.
- New Formulations of Cravit®, Approved and Launched in Japan
- Edoxaban, Top line result of Post-Surgical VTE Ph III
- Edoxaban, New multinational Ph III study is scheduled for VTE in patients with DVT/PE.
- Laninamivir, Positive top line results for Flu treatment, and launch of new Ph III study for Flu prevention
- CS-866AZ, Olmesartan combination drug with Azelnidipine was endorsed by Committee on Drug in MHLW

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U3 Pharma relocation (2009/09/05)

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Edoxaban (DU-176b)

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Novel Anticoagulants: Compound Profiles

Compound	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
T_{max}	2-4 hr	1-4 hr	1.25-3 hr	1-2 hr
Bioavailability	57-86 % (animals)	49 % (human)	6.5 % (human)	50 % (monkey)
Potential drug interactions	CYP3A4/ P-gp inhibitors	CYP3A/ P-gp inhibitors	P-gp inhibitors	NR
Protein binding	92-95 %	87 %	35 %	40-59 %
$t_{1/2}$	9-13 hr	8-15 hr	12-14 hr	9-11 hr
Renal excretion	66%	25%	80%	35%

NR: not reported

Clin Pharmacokinet, 2009, 48, 1-22 (modified)
Drug Metab Dispos, 2009, 37, 74-81
Am Coll Clin Pharmacol, Sep 2009
Am Assoc Pharm Sci, Nov 2009

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Oral Factor Xa Inhibitor: Edoxaban

- Phase IIb and Phase III studies

Indication	Phase IIb		Phase III
AF Prevention of thromboembolic event in atrial fibrillation	US/EU	Presented at ISTH (Jul 2009)	ENGAGE AF-TIMI 48 Started in Nov 2008
	Japan	Presented at ACC (Mar 2009), ISTH (Jul 2009) and ASH (Dec 2009)	
	Asia	Presented at APHRS (Oct 2009)	
VTE Prevention of post-surgical thromboembolic event	Japan	Presented at ASH (TKR Ph IIb, Dec 2008, THR Ph IIb, Dec 2009)	TKR Ph III Completed in 4Q 2009
	US/EU	Presented at ESC (THR Ph IIb)	
VTE Prevention of thromboembolic event in patient with DVT/PE	US/EU Japan Asia		HOKUSAI-VTE Plan to start in Dec 2009

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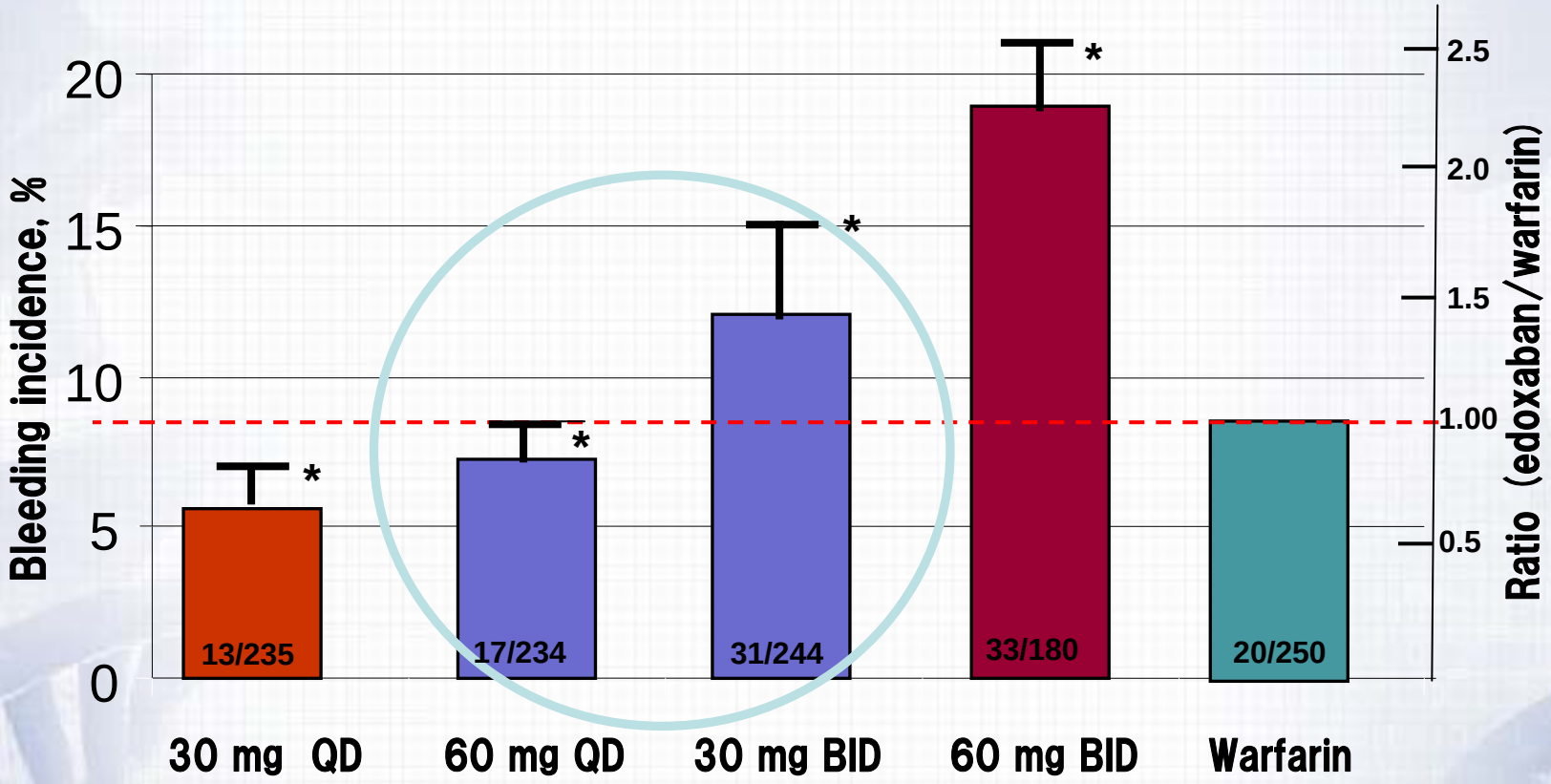
Identify 2 dose regimens for the ENGAGE AF-TIMI 48
-All Bleeds for Edoxaban Relative to Warfarin-



For the same total daily dose of 60 mg, higher bleeding observed for 30 mg BID compared with 60 mg QD

- Upper bound for one-sided 67% CI for ratio of incidence rates (edoxaban/warfarin): 0.80, 1.04, 1.79 and 2.58
- QD: Once daily, BID: Twice daily

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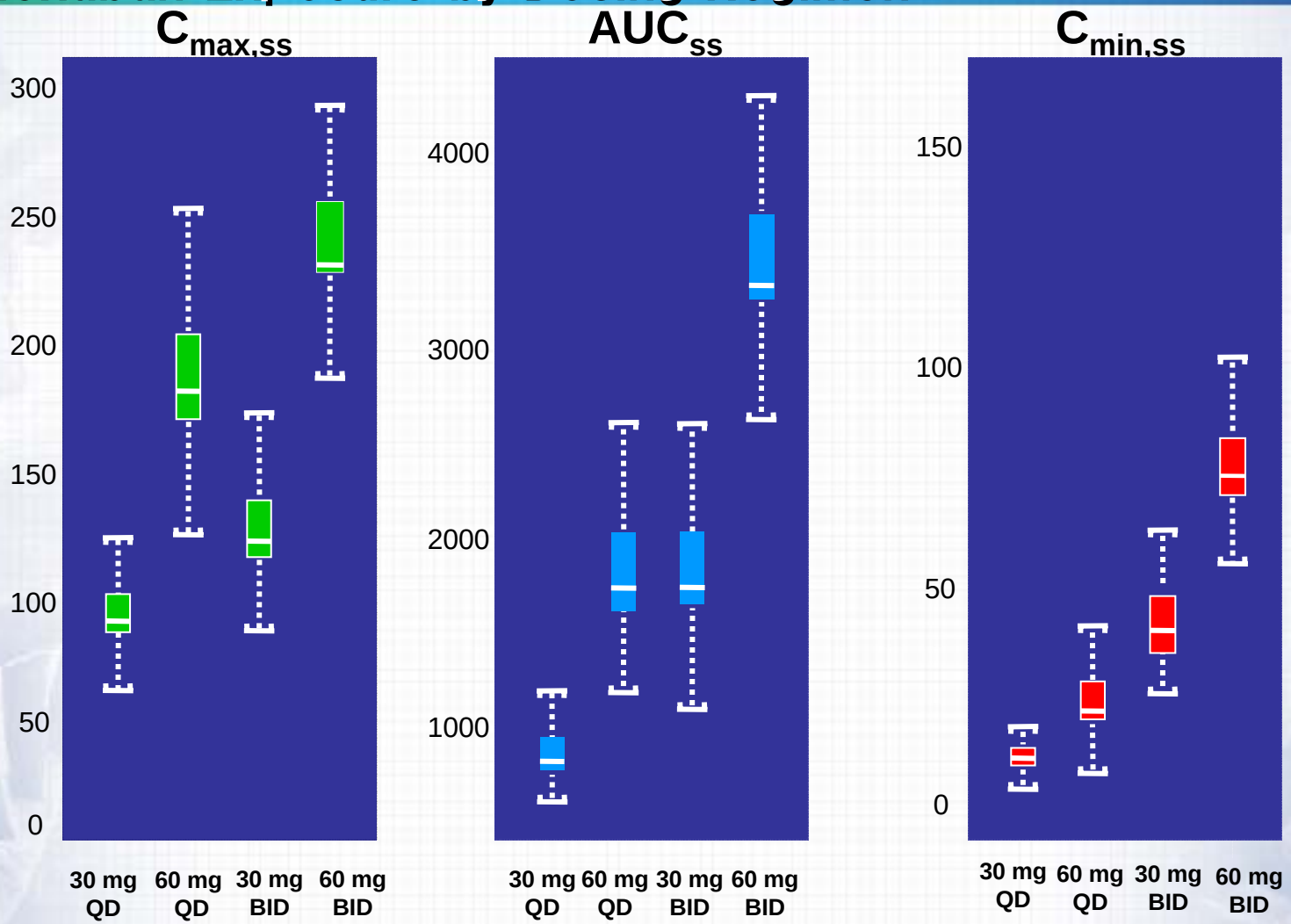
Identify 2 dose regimens for the ENGAGE AF-TIMI 48
-Edoxaban Exposure by Dosing Regimen-



$C_{min,ss}$ follows a similar pattern to that observed in edoxaban bleeding

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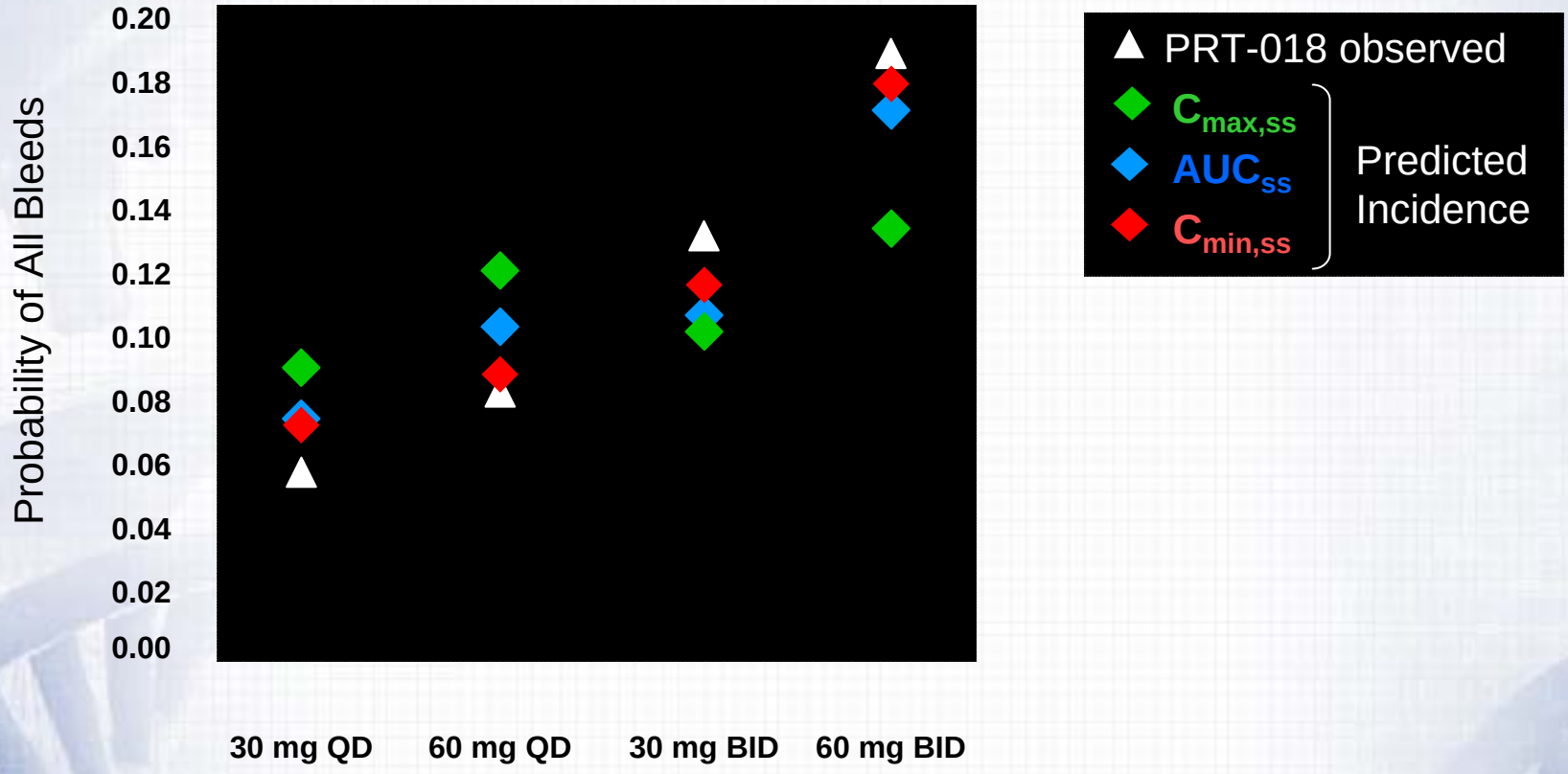
Identify 2 dose regimens for the ENGAGE AF-TIMI 48

-Cmin,ss: Best Predictor for the Probability of All Bleeds-



Bleeding as predicted by $C_{min,ss}$ most closely matched observed bleeding

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Summary: Optimization of Edoxaban Dose Regimen

- 60 mg QD and 30 mg QD had similar and less bleeding to warfarin, respectively
- Once-daily edoxaban dosing regimens were associated with less bleeding than twice-daily regimens
- Cmin,ss was the most robust predictor of bleeding
- This analysis allowed the optimization of edoxaban dose regimen (30 mg QD and 60 mg QD) for the Phase III study, ENGAGE AF-TIMI 48

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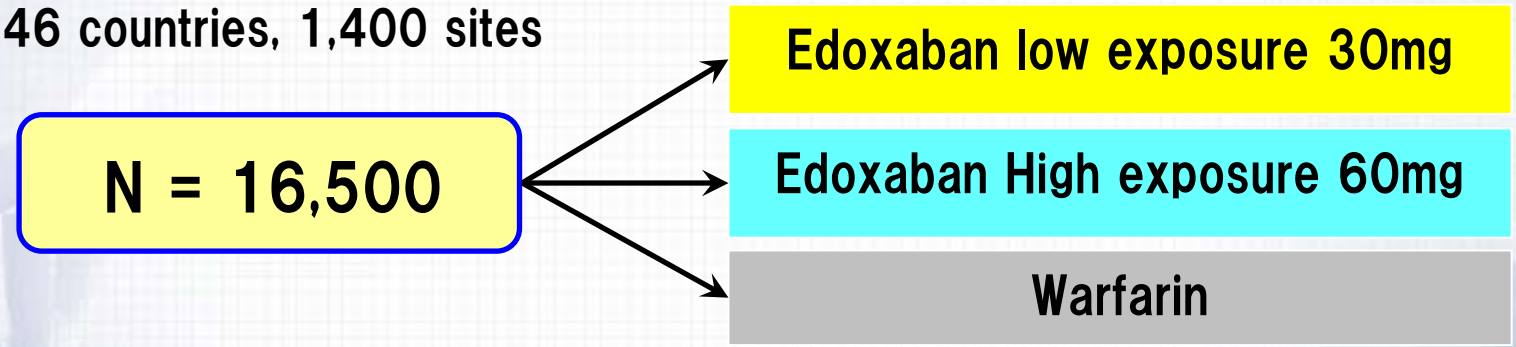
ENGAGE AF-TIMI 48 (Edoxaban AF Ph III)

Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation

- Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi- Center, Multi-National
- Evaluation of efficacy and safety of edoxaban in AF patients in comparison with those of warfarin
- Once daily
- 46 countries, 1,400 sites



Primary efficacy endpoint: stroke, systemic embolism
Secondary efficacy endpoint: stroke, systemic embolism, all-cause mortality
Safety endpoint: major bleeding, clinically relevant bleeding

Post-Surgical VTE (TKR) Ph III in Japan/Taiwan

- Primary Objective
  - Assess the efficacy of edoxaban in the prevention of VTE vs. enoxaparin sodium in TKR

TKR: total knee replacement

- Patient population
  - Patients undergo elective TKR
- Design
  - Randomized, double-blind
- Dose, Treatment period and First dosing
  - 30mg once daily for 11-14 days , 6 to 24 hours after surgery
- Number of patients
  - 716

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Summary of TKR Ph III in Japan/Taiwan

- Non-inferiority to enoxaparin sodium confirmed in edoxaban in prevention of VTE
- No significant difference observed between edoxaban and enoxaparin sodium in the incidence of either major or clinically relevant non-major bleeding

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HOKUSAI VTE (Edoxaban VTE Ph III)

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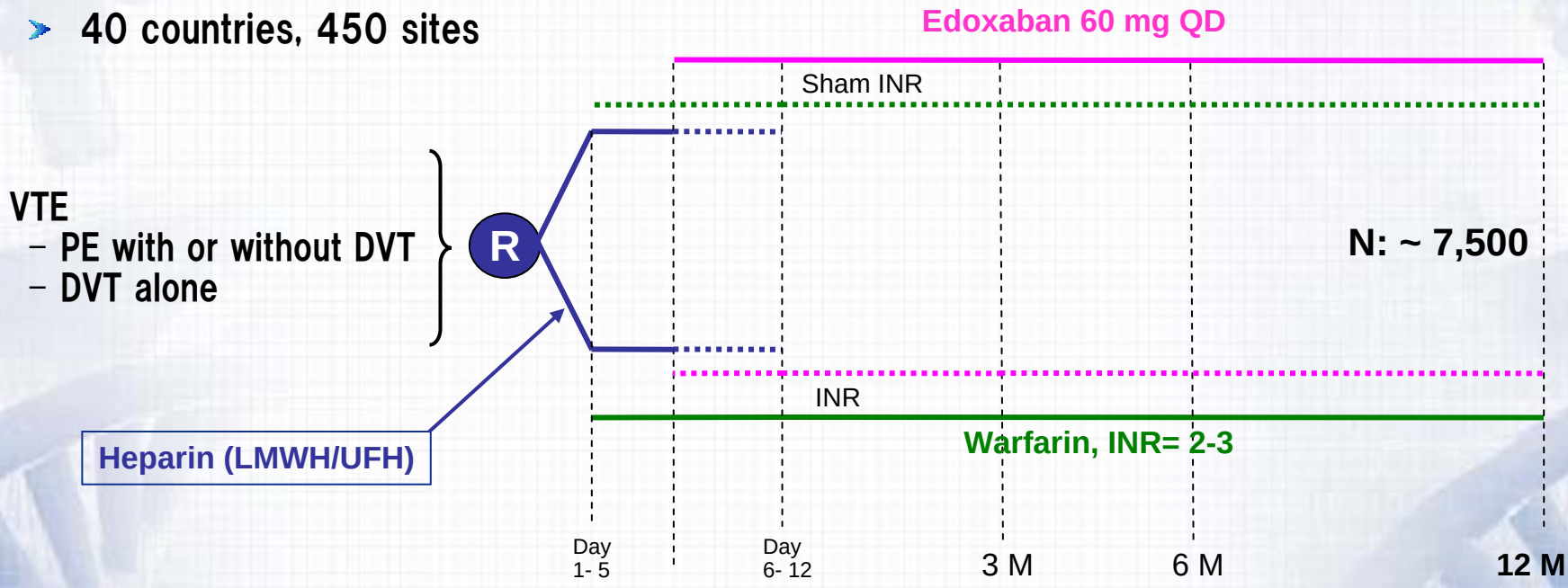
HOKUSAI VTE (Edoxaban VTE Ph III)

- Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi- Center, Multi-National
- Evaluation of efficacy and safety of Edoxaban in patients with symptomatic DVT and/or PE in comparison with those of warfarin
- 40 countries, 450 sites



Primary efficacy endpoint: symptomatic recurrent VTE
Secondary efficacy endpoint: symptomatic recurrent VTE, all-cause mortality
Safety endpoint: major bleeding, clinically relevant bleeding

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Laninamivir octanoate（CS-8958）

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Concept of Anti-influenza drug, Laninamivir octanoate

Long Acting Neuraminidase Inhibitor

LANI

Long Acting Anti-influenza Drug

Neuraminidase inhibitors in the market

Relenza (inhalation)
Tamiflu (oral agent)

- Twice daily for 5 days for treatment (10 times)
- Once daily for 7-10 days for prophylaxis

Laninamivir octanoate (inhalation)

- Single administration for treatment
- Once weekly for prophylaxis expectedly

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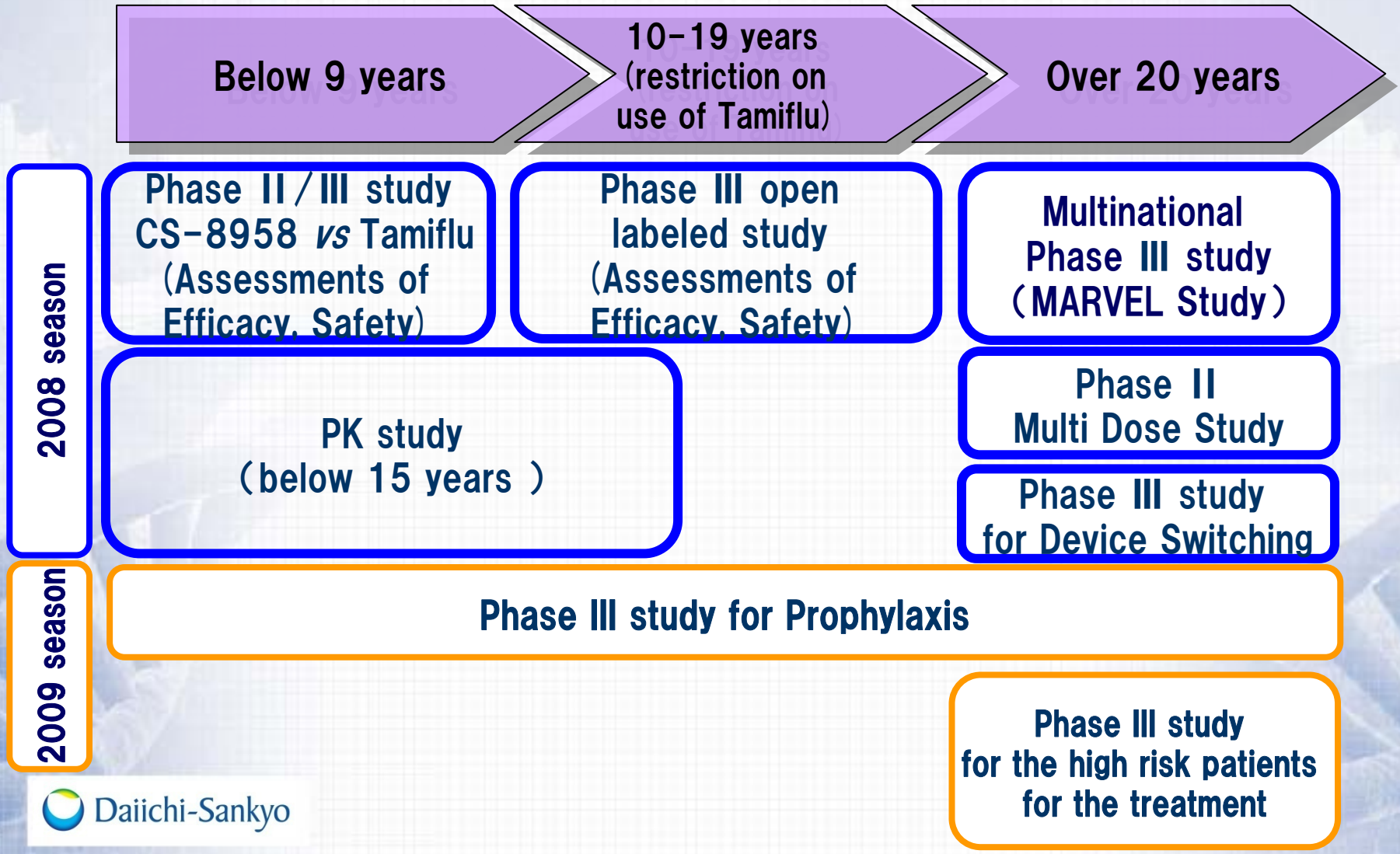
Clinical Development Strategy

- Wide-Range of Clinical Use, from Pediatrics to Elderly -



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Conclusion of Clinical Studies

- According to the results of the Phase 3 (MARVEL) study, non-inferiority of Laninamivir octanoate to Tamiflu was proven.

- 20mg and 40mg of single administration of Laninamivir octanoate showed comparable effect to twice daily administration of Tamiflu for 5days. (75mg x 2 x 5days).

- Pediatric studies indicates that 20mg, 40 mg of single administration of Laninamivir octanoate shows better efficacy, compared to Tamiflu.

- To maximize the values of the features on broad spectrum of anti-virus activity and quick recovery from influenza symptoms for pediatric, 40 mg of single administration is the appropriate dose regimen for adult and pediatrics.

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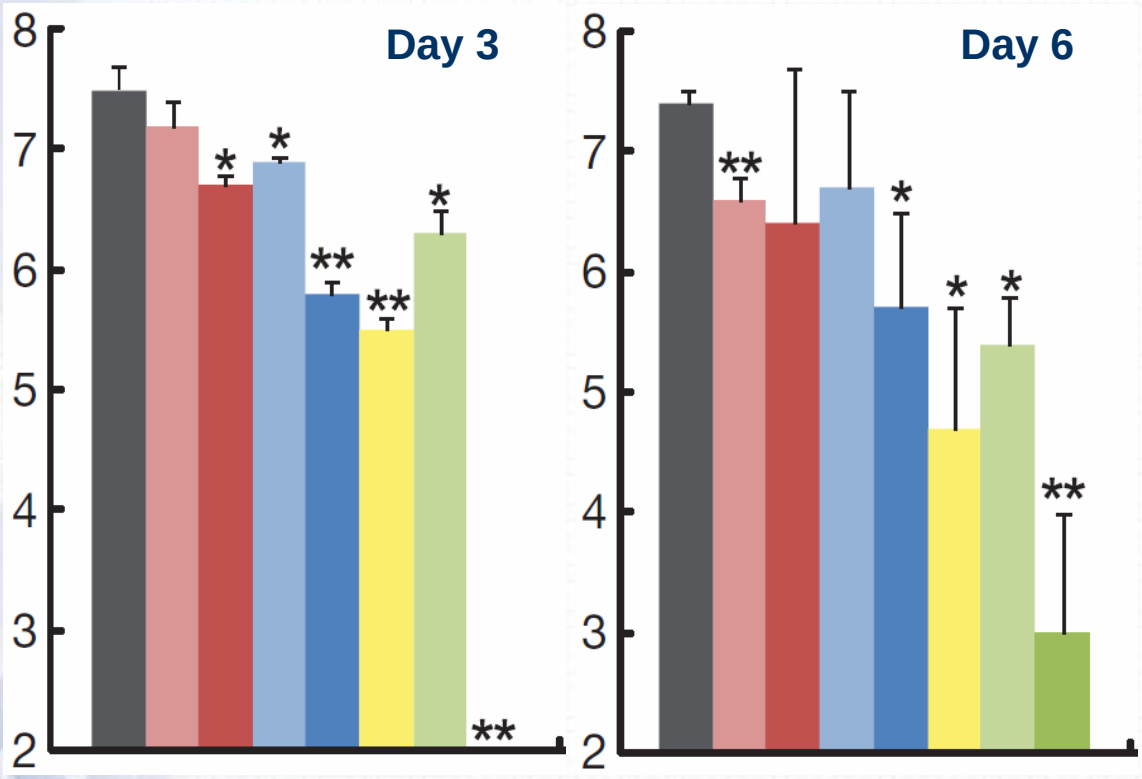
Pre-clinical update

- Laninamivir shows anti-viral activity to the clinical isolates of oseltamivir-resistant strains.
  (Antimicorbial Agent Chmotherapy 53: 186-192 (2009))
- Laninamivir shows good efficacy to swine-origin H1N1 influenza viruses.
- Laninamivir octanoate shows the potential in mice that it is efficacious to swine-origin influenza.
  (Nature 460 Number 7258: 1021 (2009))

Swine-Originated H1N1 Influenza Virus sensitivity to antiviral compounds in mice



- Control
- Osel. 4 mg/kg bid x 5d *po*
- Osel. 40 mg/kg bid x 5d *po*
- Zan. 0.8 mg/kg qd x 5d *in*
- Zan. 8 mg/kg qd x 5d *in*
- CS-8958 700 μg/kg x once *in*
- T-705 30 mg/kg bid x 5d *po*
- T-705 150 mg/kg bid x 5d *po*

Zan: Relenza
Osel: Tamiflu
CS-8958: Laninamivir octanoate

Infection：10,000 PFU of A/California/04/09 (H1N1)
∗: $P<0.05$, ∗∗ : $P<0.01$ *vs* control groups

Ito Y. *et al.* Nature 460 Number 7258:1021 (2009)

Laninamivir octanoate shows good efficacy to Swine-originated H1N1 influenza in mice

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Denosumab（AMG 162）

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Development Overview

Indication	Dosage	Development Stage	
		Japan	US/EU
Bone Metastasis	120 mg every 4 weeks SC	Ph III	Ph III
Osteoporosis	60 mg every 6 months SC	Ph III	BLA submitted
HALT-induced bone loss	60 mg every 6 months SC	N/A	BLA submitted
Rheumatoid Arthritis	TBD	TBD	Ph II

HALT: hormone ablation therapy, N/A: not applicable, BLA: Biological License Application
SC: Subcutaneous Injection

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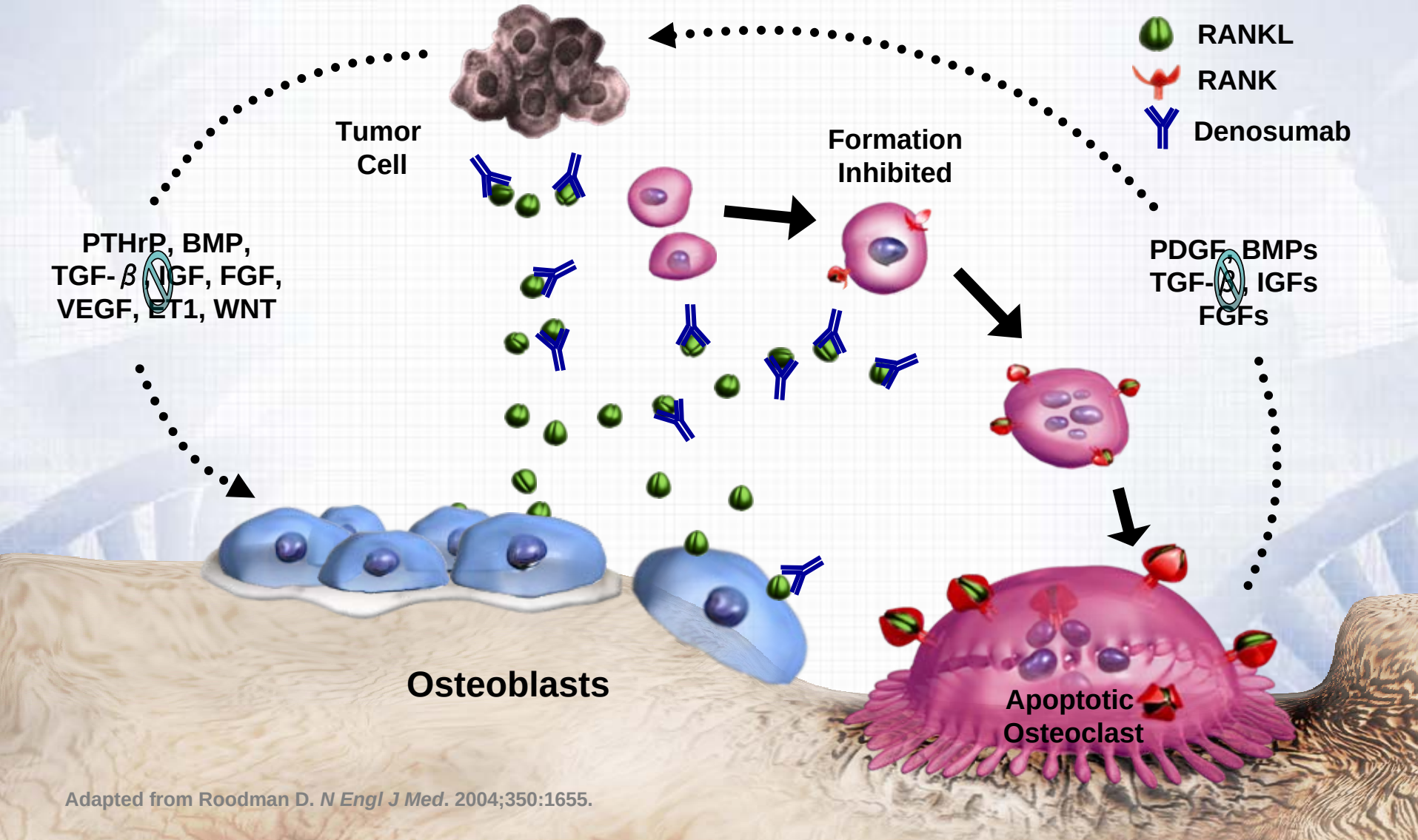
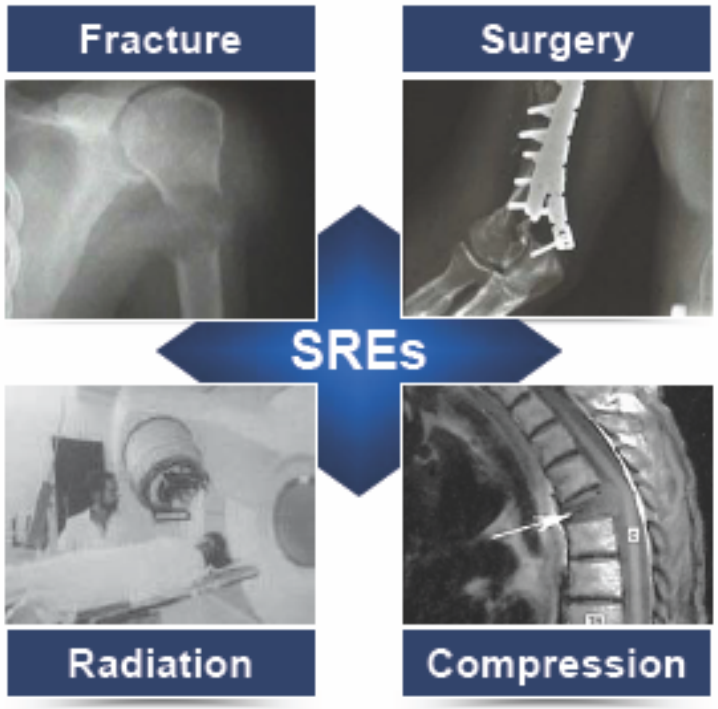
Denosumab May Interrupt The "Vicious Cycle" of Cancer-Induced Bone Destruction



Adapted from Roodman D. *N Engl J Med*. 2004;350:1655.

Skeletal-Related Events (SRE) Are Grievous Complications of Cancer Metastatic to Bone

- **SRE Studies**
  - Treating complications of disease
  - Patients with established bone metastases



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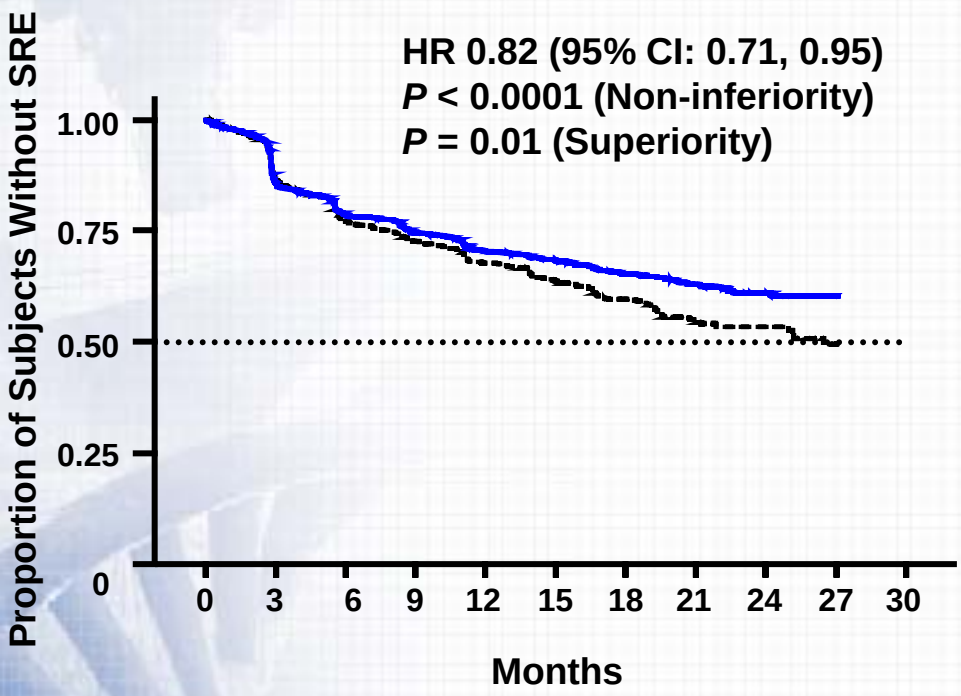
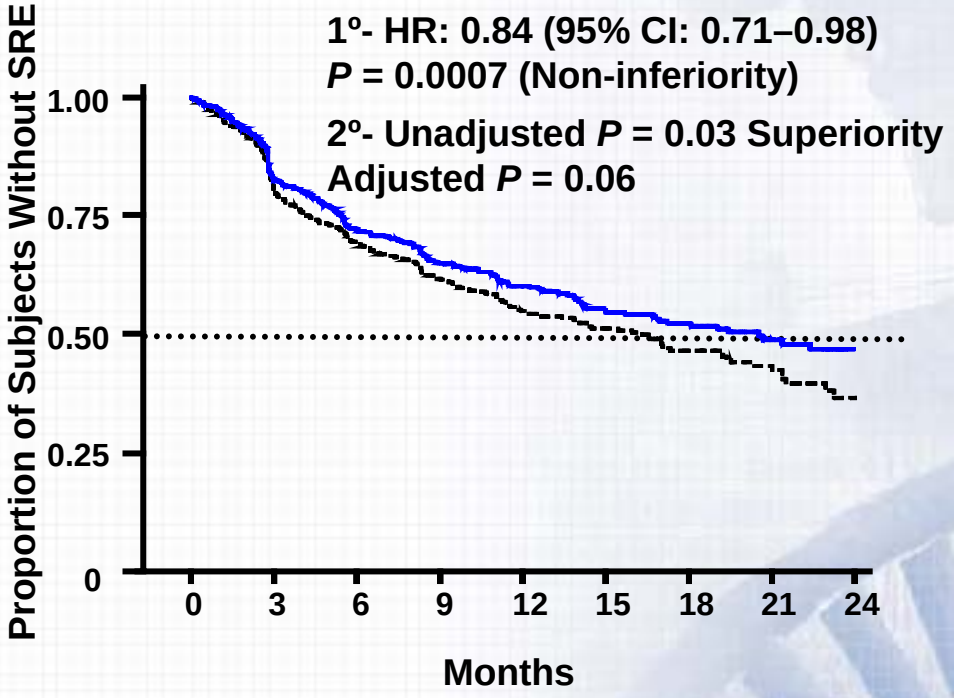
SRE Studies
Primary Endpoint: Time to First On-Study SRE

Breast Cancer



Solid tumors or Multiple Myeloma



denosumab: 120mg every 4 weeks, SC

---- Zometa®: 4mg every 4 weeks, IV

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Global Development Status: Bone Metastasis

- **Phase III global studies:**
  - **Three global SRE studies explore the effects of denosumab in different tumor types**
  - **Denosumab reduces SREs in patients with metastatic bone disease**
  - Denosumab demonstrates superiority over Zometa® in reducing the incidence of SREs with advanced breast cancer patients (Including Japanese patients)
    - Sponsor in Japan: Daiichi Sankyo
  - Denosumab is non-inferior to Zometa® in reducing the incidence of SREs in patients with a variety of solid tumors or multiple myeloma
  - Results of above two studies were presented at ECCO/ESMO 2009. Data from the prostate cancer SRE study is expected in 1Q 2010

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Development Status: Osteoporosis in Japan

- Phase III study (DIRECT*): Enrollment completed
  - A Randomized, double-Blind, placebo-controlled study evaluating efficacy and safety of denosumab in patients with osteoporosis
  - Primary endpoints
    - Incidence of vertebral fractures

*DIRECT stands for "Denosumab fracture Intervention Randomized Placebo Controlled Trial in Japanese patients with osteoporosis"

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Development Status: Osteoporosis Indication Overseas

- PMO* and HALT-induced bone loss indications
  - BLA/MAA submitted globally in Dec, 2008 - Jan, 2009
  - FDA Reproductive Health Drugs Advisory Committee (RHDAC) reviewed the potential use of denosumab on August 13
  - RHDAC recommended approval of denosumab for the treatment of PMO and for the treatment of bone loss in patients undergoing hormone ablation for prostate cancer
  - FDA issued Complete Response Letters for PMO and HALT in October 2009

*PMO: postmenopausal osteoporosis

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Oncology Franchise

- Research Targets
- Collaboration
- ARQ 197
- Tigatuzumab, CS-1008
- CS-7017
- Nimotuzumab, DE-766
- U3-1287

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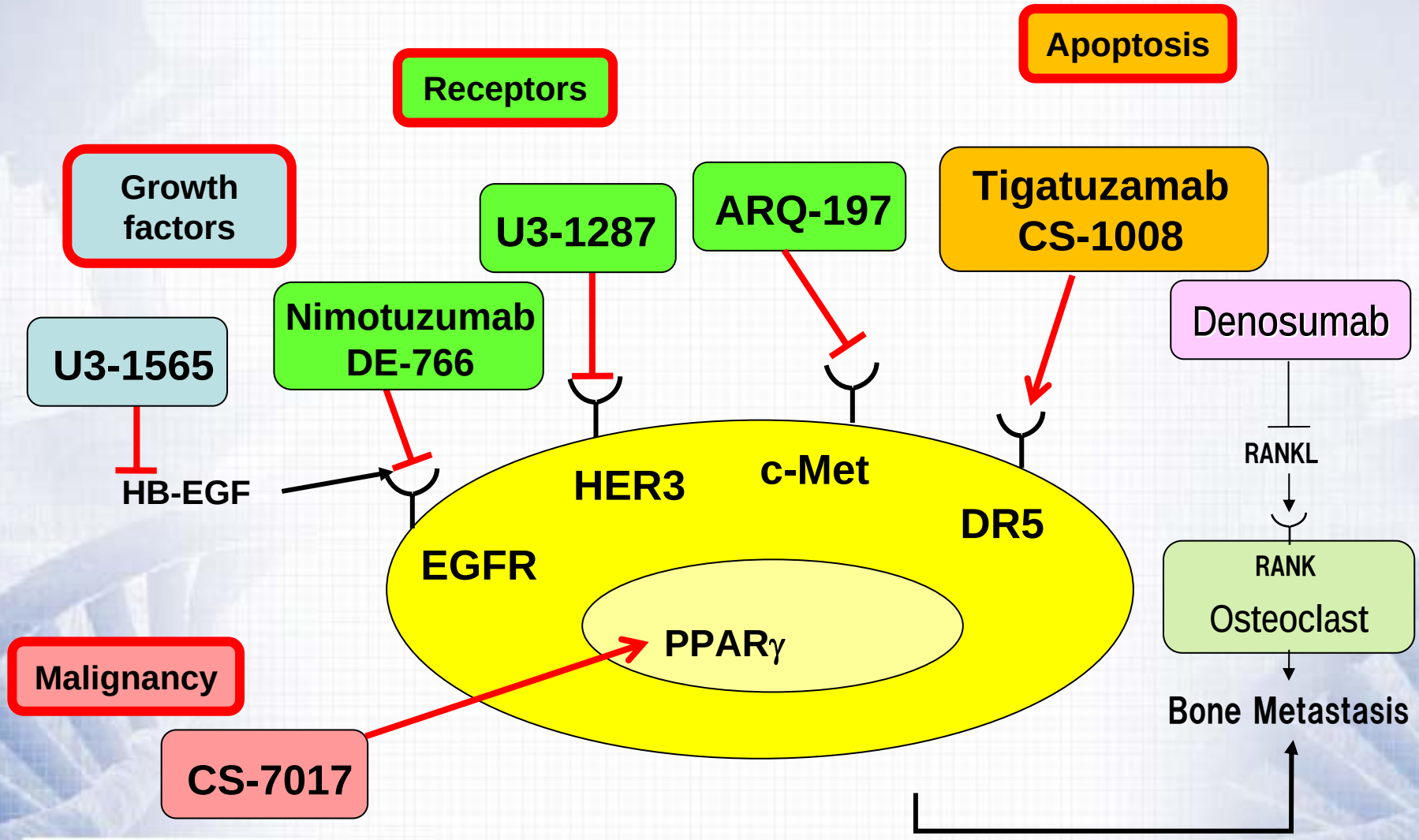
Oncology Research Targets



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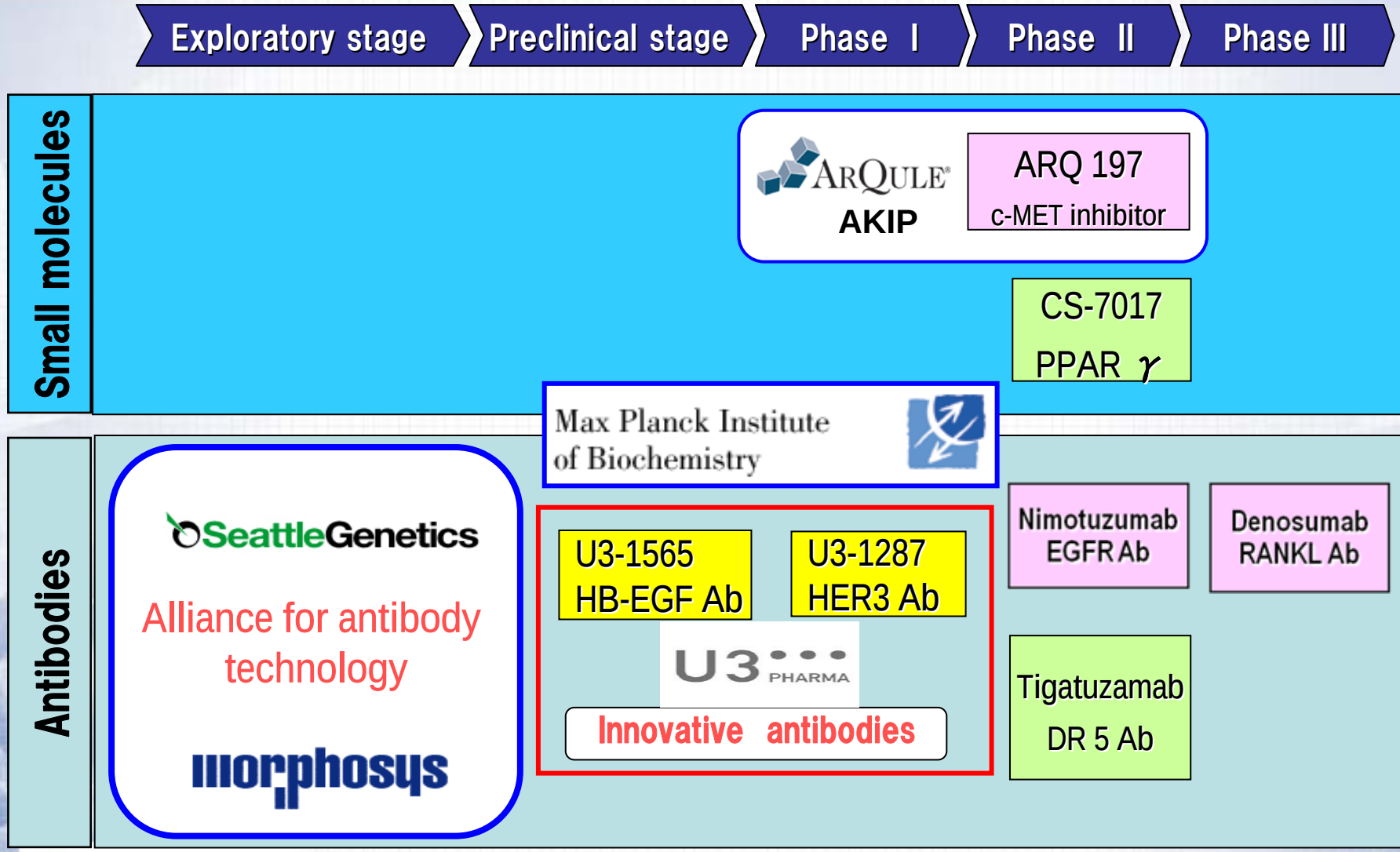
Oncology Pipeline Collaborations



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In-house projects | In-licensed projects | U3 projects

Progress in U3 Pharma after acquisition

U3 PHARMA

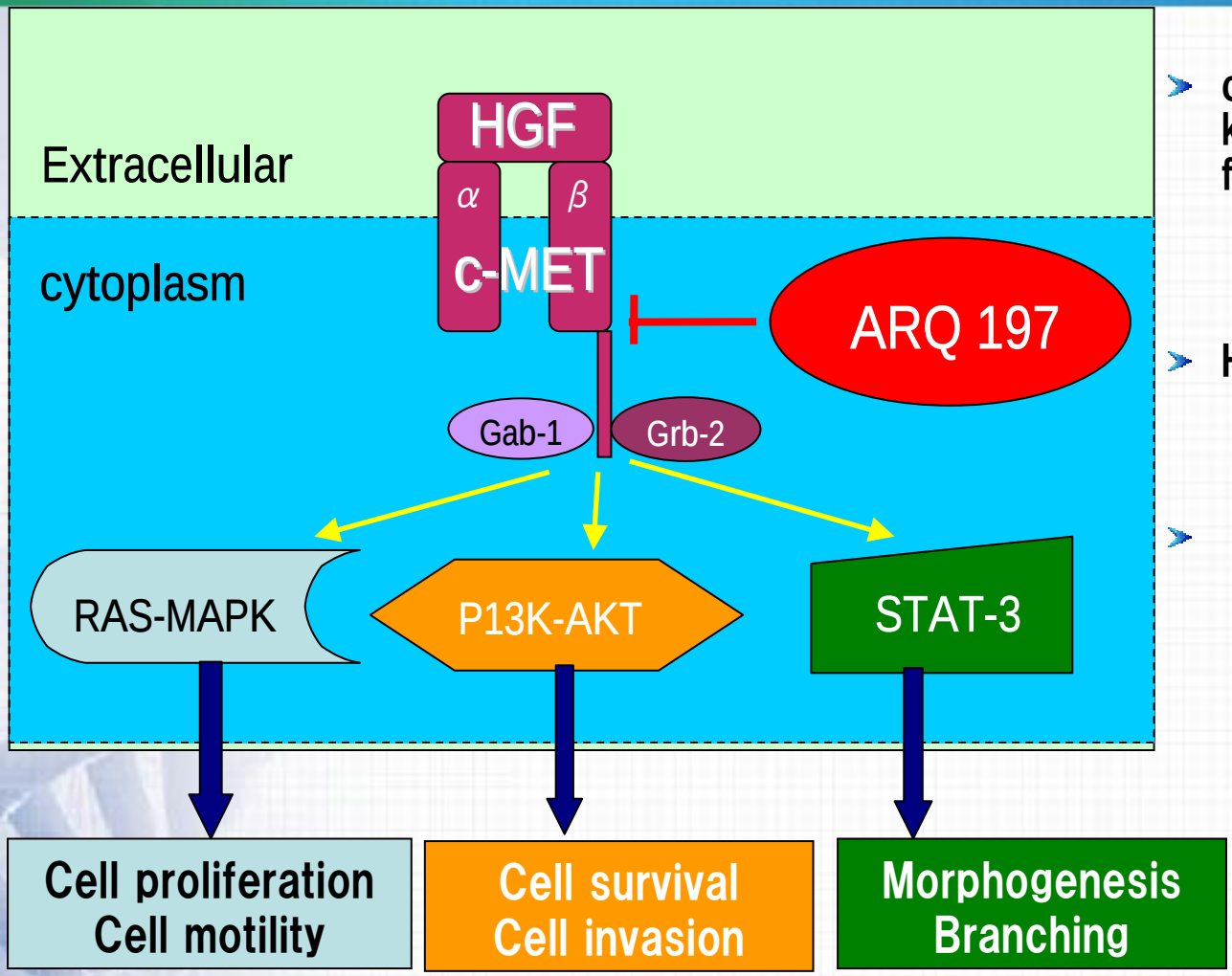
- Increasing number of PROJECTS added to portfolio
  - Under collaboration with Prof. Ullrich (MPI*)

* Max-Planck-Institute

- Expansion of RESOURCES and FACILITIES
  - Talented researchers have been recruited
  - New facility opened with doubled capacity

- SYNERGY creation within DS Group
  - Established a successful global collaboration within DS Group for development candidate projects AND early stage research projects

c-Met inhibitor: ARQ 197



- c-Met: receptor for tyrosine kinase of hepatocyte growth factor (HGF)
  - Multiple roles in intracellular signal transduction
- High expression of c-Met
  - Colon, Hepatic, Breast Pancreatic, etc
- Development Status
  - US/EU Phase II studies
    - LPI achieved NSCLC*
    - Ongoing for MiT**, HCC
  - US/UK Phase I studies on-going

* Non Small Cell Lung Cancer, ** Microphthalmia Transcription factor associated (MiT) tumors

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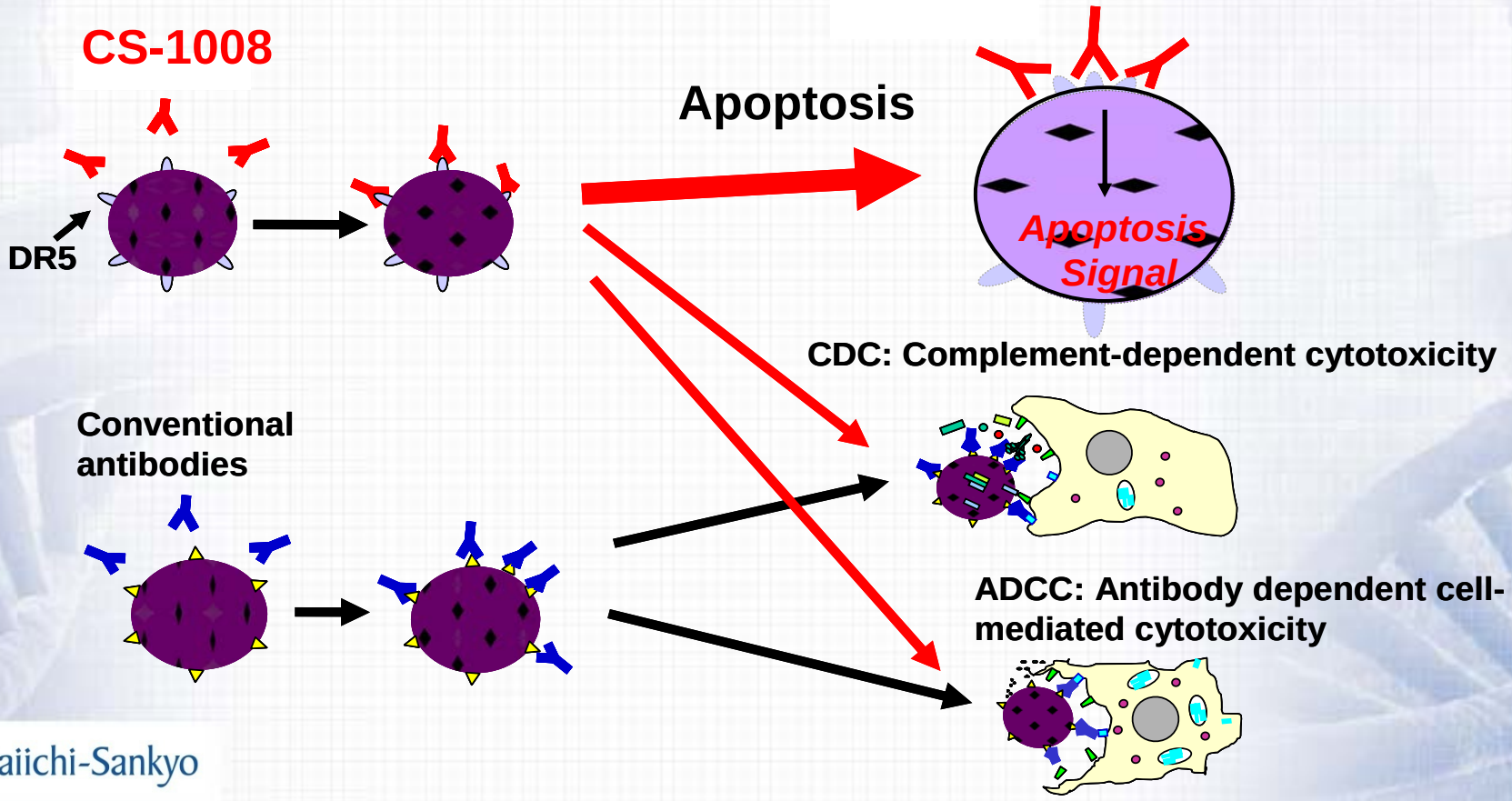
Tigatuzumab CS-1008 (1)

- Monoclonal Antibody (Mab) against human death receptor 5 (DR5)
  - Induces apoptosis, CDC and ADCC in tumors expressing DR5
  - Expected to show selectivity against tumor cells since DR5 is rare in normal tissues



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Tigatuzumab CS-1008 (2)

- Current Development Status
  - Japan Phase I study ongoing
  - US Pancreatic cancer Phase II
    - Good safety and tolerability profile in combination with Gemzar
  - Status of other Phase II studies
    - NSCLC and CRC: Initiated in EU
    - Ovarian cancer: FPI in October in the US
    - Other tumors: Under evaluation

NSCLC = Non Small Cell Lung Cancer, CRC = Colorectal Cancer

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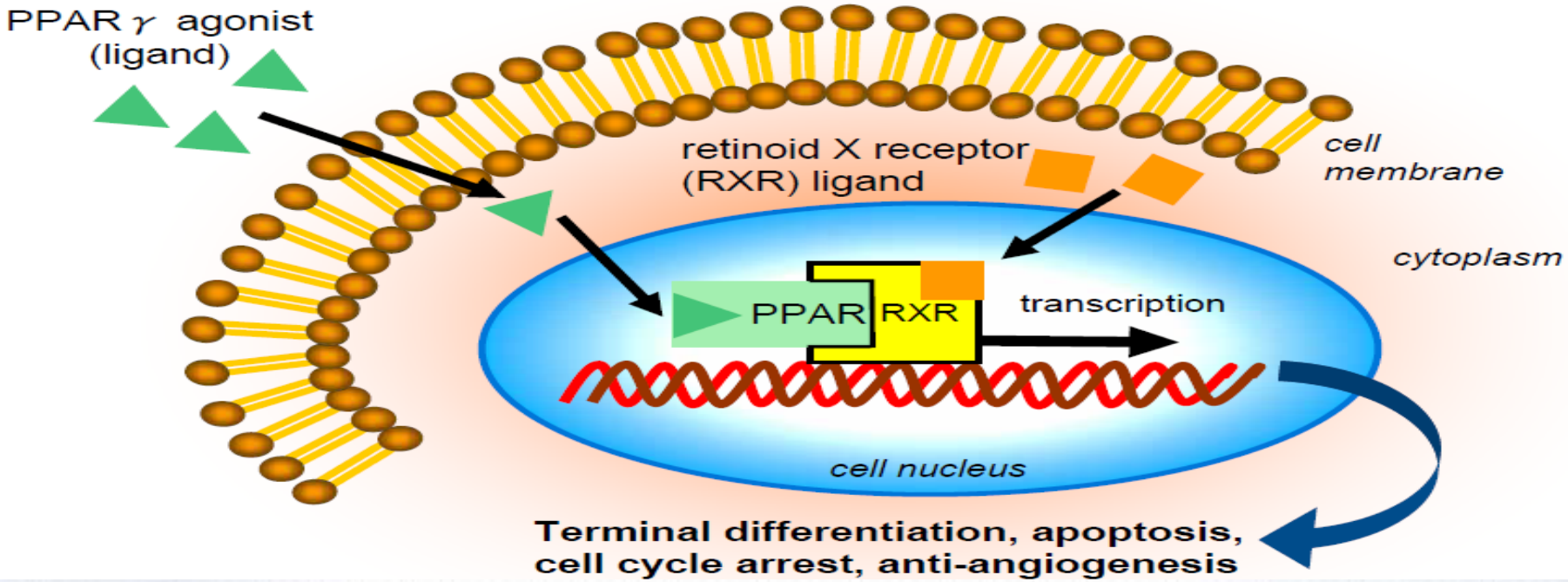
CS-7017 : PPAR-gamma activator



- Inhibits growth of tumor cells in vitro without killing those cell
- Effective against human tumor-implanted in vivo models
- Current Development Status
  - US Phase II studies on-going (ATC*, NSCLC, CRC)
  - Japan Phase I under preparation

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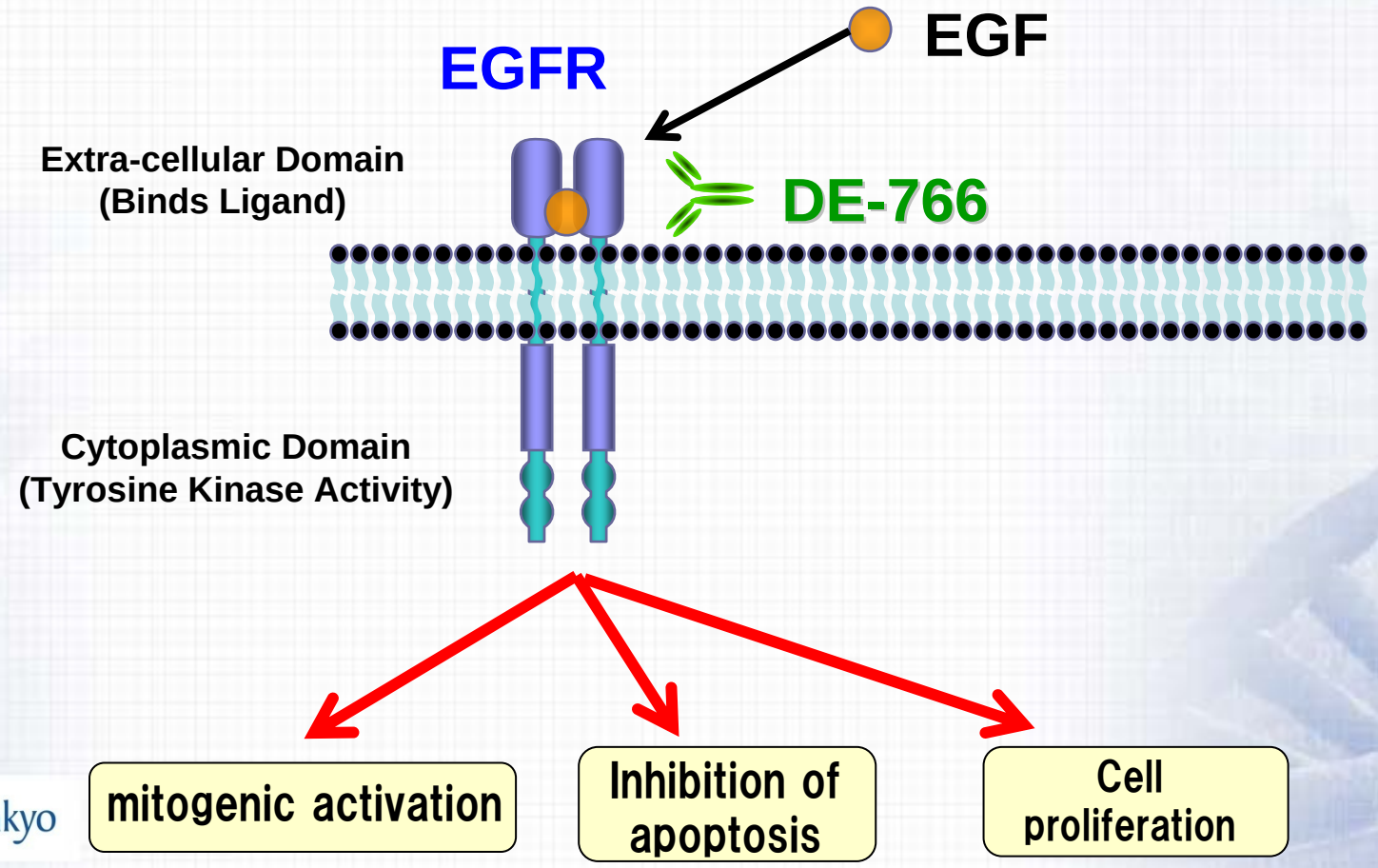
* Anaplastic Thyroid Cancer

Nimotuzumab DE-766 (1)

- A humanized monoclonal antibody that binds to extracellular ligand binding domain of epidermal growth factor receptor (EGFR)
- Blocks the intracellular tyrosine kinase (TK) domain



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Nimotuzumab DE-766 (2)

- Target indication: tumors expressing EGFR
  - Glioma, NSCLC, Esophagus, Gastric etc
- Development Status (Japan)
  - Phase I study: completed
  - Phase II study (Gastric) in Japan and Korea: on-going
  - Phase II study (NSCLC) : initiated in 2Q 2009
- Superior safety (skin rash) and comparable efficacy to other EGFR Mabs
- Current Status in Other Countries
  - Head & Neck cancer: Approved in Cuba, India, Latin America
  - Glioma: Approved in Cuba, Indonesia, Philippines, Brazil
  - Nasopharyngeal carcinomas: Approved in China

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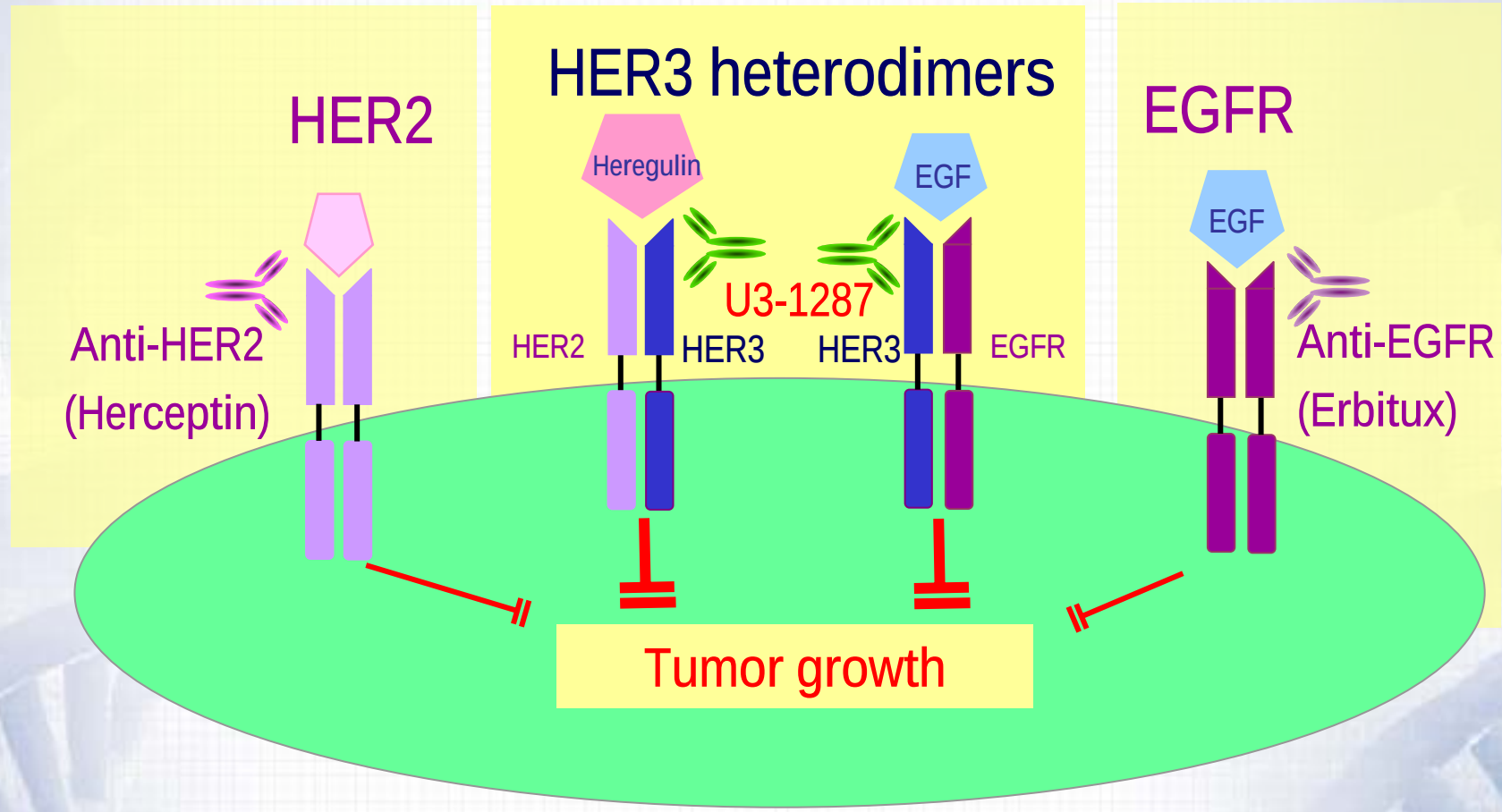
U3-1287: Anti-HER3



HER3: member of the EGFR family

Expression upregulated in several cancer cells (breast, lung, prostate, etc.)

HER3 heterodimers have higher mitogenic potential than HER2 homodimers or EGFR homodimers

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Prasugrel / Efient® / Effient®

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Major Milestones in 2009

- February 3 – FDA Cardio-Renal Advisory Committee unanimously recommended approval for prasugrel
- February 25 – EU approved EFIENT® for ACS PCI
- March 27 – EFIENT® first launch (UK)
- July 10 – US FDA approved EFFIENT® for ACS PCI
- August 3 – US launch

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Effient US Labeling

- **INDICATION STATEMENT: Acute Coronary Syndrome**

  - Effient is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI)

  - Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel.
    - The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death

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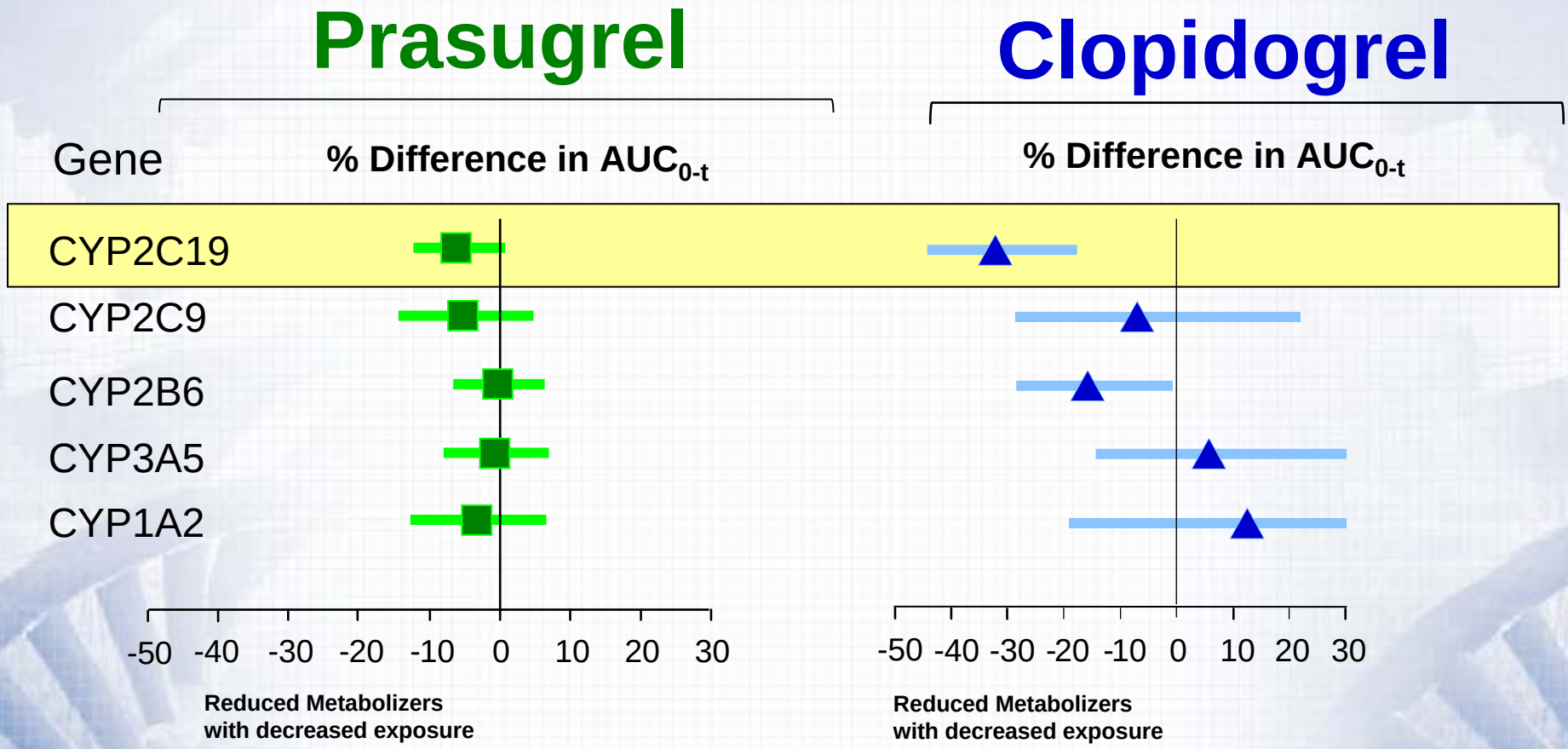
Genetic Effect on Pharmacokinetics



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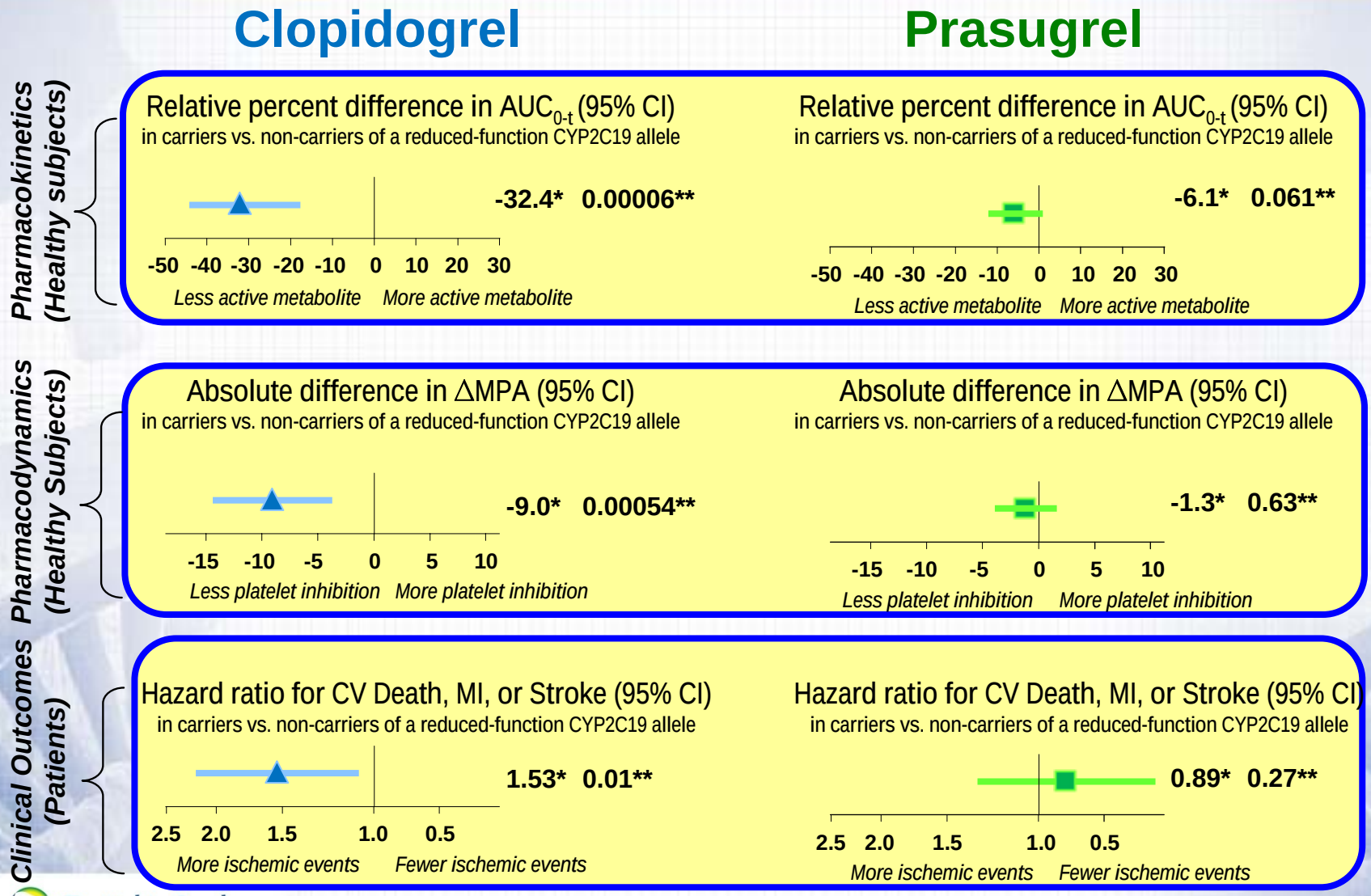
Mega J et al. *NEJM* 2009; 360(4):354-362
Mega JL et al. *Circulation* 2009;119:19:2553-2560

CYP2C19 Genetic Classification
Pharmacokinetics, Pharmacodynamics and Clinical Outcomes



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AUC = area under the concentration curve; MPA = maximal platelet aggregation;
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction *point estimate; **p-value

Mega JL et al. *Circulation* 2009;119:19:2553-2560

Clopidogrel Labeling Change (Revised Autumn, 2009)

- New statement added to ***WARNINGS*** section
  - Avoid use of PLAVIX in patients with impaired CYP2C19 function due to known genetic variation or due to drugs that inhibit CYP2C19 activity.
  - Patients with genetically reduced CYP2C19 function have diminished antiplatelet responses and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function
- Update made to ***PRECAUTIONS*** section
  - *Information for patients*
    - They should tell their physician about any other medications they are taking, including prescription or over-the-counter omeprazole
  - *Drug interactions*
    - Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine (see WARNINGS).

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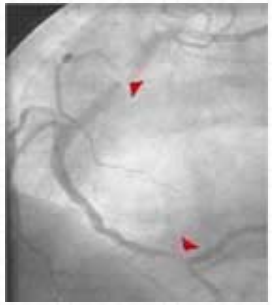
Treatment option for ACS

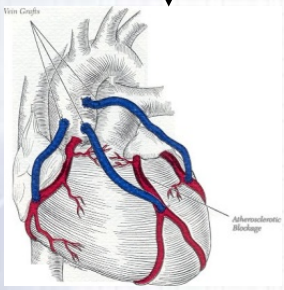
Ambulance vehicle

↓

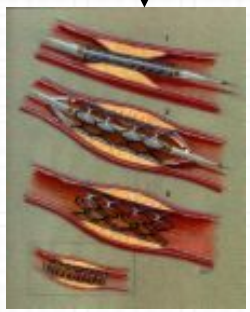
ICU →



diagnostic cardiac catheterization



CABG
(<10%)



PCI
(40-50%)

Medical management
(40-50%)

CRUSADE Registry
(Ezra A et al. presented at ACC, 2007)

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TRÎTON TIMI·38

TRILOGY ACS

Additional Indication (Medical Management)

- TRILOGY
  - Purpose: expand indication of Effient in ACS patients who are medically managed
  - An unmet medical need:
    - 40-50% of patients with ACS do not undergo revascularization during initial hospitalization in the US[1]
    - Medically managed ACS patients have a higher risk of adverse outcomes compared with PCI/CABG patients[2]

[1]ACTION Registry-GWTG DATA: July 1, 2007 – June 30, 2008 (n = 32,377)
[2]Chan M, JACC Cardiovasc Int 2008

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Additional Indication (Medical Management)

- TRILOGY
  - Double-blind, active control study to evaluate prasugrel against clopidogrel in reducing the risk of CV death, MI, or stroke in ACS patients who are medically managed
  - First Patient Visit occurred in June 2008
  - Target of10,000 patients in 800 hospitals in 40 countries
  - Will provide clinical information on the 5-mg dose of prasugrel in elderly or low weight patients

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DAPT Study

HARVARD CLINICAL RESEARCH INSTITUTE ENROLLS FIRST PATIENTS INTO DAPT STUDY TO ADVANCE UNDERSTANDING OF DUAL ANTIPLATELET THERAPY FOLLOWING DRUG-ELUTING STENT PROCEDURES

- Four-year, Public Health Study to be Conducted Through an Unprecedented Collaboration between Industry, FDA and Academia -

BOSTON – October 2, 2009 - The Harvard Clinical Research Institute (HCRI) announced today that the first patients have been enrolled in the DAPT Study, marking the official initiation of the four-year clinical trial to investigate the duration of dual antiplatelet therapy (DAPT, the combination of aspirin and a thienopyridine/antiplatelet medication to reduce the risk of blood clots) following drug-eluting stent implantations.

Olmesartan Franchise

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Olmesartan Combinations

US・EU

- CS-8663: Combination drug with Amlodipine
  - Launched in US, EU, ASCA countries
  - Brand name: AZOR® in US and Sevikar® in EU

- CS-8635: Combination drug with Amlodipine and Hydrochlorothiazide
  - NDA filed in US, September 2009
  - Phase III on-going in EU

Japan

- CS-866AZ: Combination drug with Azelnidipine*
  - NDA filed, December 2008

** Azelnidipine is marketed in Japan as brand name of Calblock*

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Olmesartan Lifecycle Management

<Mono>	Phase III	NDA filed	Marketing
US		Pediatric (sNDA)	Benicar ®
Europe			Olmetec ®
Japan		40mg tablet (approved)	Olmetec ®

<Combo>	Phase III	NDA filed	Marketing
US		CS-8635 (with AML and HCTZ)	Benicar HCT ® AZOR ®
Europe	CS-8635 (with AML and HCTZ)		Olmetec Plus ® Sevikar ®
Japan		CS-866AZ (with Calblock)	

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Daiichi Sankyo R&D pipeline continues to deliver on innovation

- **Global leadership in Cardiovascular Medicine is preserved**
  - Approval of Effient in the US and progression of TRILOGY for ACS-MM
  - Progression of edoxaban AF Phase III, ENGAGE AF study
  - Encouraging result of post-surgical VTE Phase III
  - Phase III HOKUSAI study ready to initiate for VTE indication
  - Olmesartan combinations expand medical indications and enhance value
- **Laninamivir shows positive top line results for Flu treatment, and new Phase III study for Flu prevention begins**
- **Our oncology pipeline continues to mature**
  - Denosumab demonstrates superiority over Zometa® in reducing the incidence of SREs with advanced breast cancer patients
  - Denosumab Phase III OP study, DIRECT, completes enrollment in Japan
  - Four compounds are progressing through Phase II
    - ARQ 197, CS-1008, DE-766, CS-7017

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Contact address regarding this material

DAIICHI SANKYO CO., LTD.

Corporate Communications Department

TEL: +81-3-6225-1126
FAX: +81-3-6225-1132

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- This material contains information on pharmaceuticals (including compounds under development), but this information is not intended to make any representations regarding the efficacy or effectiveness of these preparations nor provide medical advice of any kinds.