5th R & D Meeting

10 December, 2010

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

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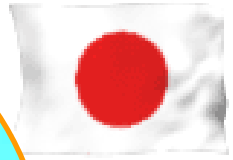
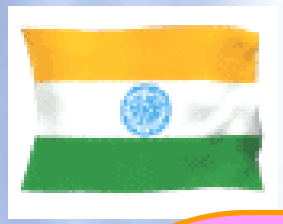
Agenda

- Reorganization of Research Facilities
- R&D Project Highlights in FY2010
- Edoxaban (Oral Factor Xa inhibitor)
- INAVIR® (Laninamivir Anti-Influenza Drug)
- Oncology Project Overview
- Olmesartan Lifecycle Management

Reorganization of Research Facilities

Global Research Functions





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/Daiichi Sankyo RD Associe

Oncology, Cardiovascular-Metabolics
and Frontier Areas
Low molecular medicines and biologics
Original lead generation
and lead optimization
Translational Research

RCI*

Inflammatory and
Infectious diseases
Low molecular medicines
Original lead generation
and lead optimization

U3 Pharma

Oncology
Biologics

Asubio Pharma

Inflammation
Regeneration
Low molecular and
peptide medicines
Original lead generation
and lead optimization

* Daiichi Sankyo Life Science Research Centre in India

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Integration of Research Functions and Locations

- **Purpose**
  - Integrate dispersed functions and locations to consolidate operation and manage
  - Effective use of limited resource, time and opportunity to enhance competitive advantage
- **Concentration of Research Functions**
  - Transfer New Drug Discovery Research function of Ranbaxy to DS
  - Asubio Pharma
- **Integration of Locations**
  - Research facilities in Japan
  - Asubio Pharma
- **Establishment of new Research Laboratories**
  - Oncology, CV-M and Frontier Research Laboratories

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RCI（DS Life Science Research Centre in India）

RCI established in July in Gurgaon, India

- **RCI Mission**
  - **Drug discovery research** (A part of the global research function)
    - Low molecular weight infectious and inflammatory disease drugs
- **Function**
  - **Medicinal Chemistry**
    - Chemical compounds library
    - Analytical chemistry
  - **Pharmacology**
    - *In vivo*, *in vitro*, Microbiology
    - Molecular biology
  - **Early phase screening**
    - Safety and metabolism profiling

RCI Office

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ASUBIO PHARMA

- **Business: Business Reorganization in Apr. 2010**
  - Focus on drug discovery (from discovery to POC)
- **Location: Relocation to Kobe in Sep. 2010**
  - Move to the Kobe Biomedical Innovation Cluster
    - A cluster of medical-related industries ranging from basic research to clinical application
      - •Academia
        (the RIKEN Kobe Institute, Kobe Univ., etc)
      - •A number of medical facilities (about 185)
    - Future development
      - •Next generation supercomputer
    - Infrastructures
      - •Good access to transportation
      - •Available rental facilities

ASUBIO PHARMA

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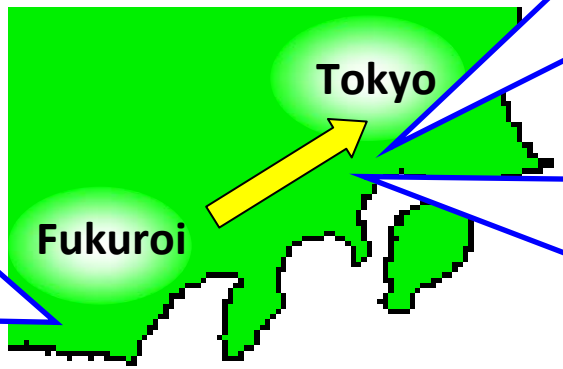
Integration of Research Centers in Japan

- **Transfer the Fukuroi Research Center functions to Tokyo Area**
  - **Transfer is planned in the 2nd half of FY2013.**
  - **Fukuroi Research Center will be closed after the transfer**
- **Purpose of the integration**
  - **Closer contact and stronger cooperation among R&D Functions**
  - **Effective use of resources and time**


Fukuroi Research Center



Fukuroi: approx.200km south west from Tokyo


Kasai R&D Center


Shinagawa R&D Center

R&D Project Highlights in FY2010

Global

- Edoxaban, Engage AF-TIMI 48 patient enrollment completed
- Edoxaban, Hokusai VTE Phase III patient enrollment underway
- ARQ 197, Top line results of Phase II study in patients with non-small cell lung cancer (NSCLC) presented, decision made to move forward into Phase III
- Olmesartan/calcium channel blocker/diuretic, three-in-one combination, approved and launched in US

Japan

- Edoxaban (prevention of venous thromboembolism after major orthopedic surgery), NDA filed
  - Top line results of preventing VTE Ph III study in patients total knee replacement (TKR) and total hip replacement (THR)
- Rezaltas® combination tablets (olmesartan 10 mg/azelnidipine 8 mg, olmesartan 20 mg/azelnidipine 16mg), launched
- Loxonin® Gel 1%, approved and launched
- Inavir® Dry Powder Inhaler 20 mg, approved and launched
- Cravit® IV (500 mg/100ml IV bags and 500 mg/20ml injections), approved
- Memantine was endorsed by Committee on Drug in MHLW
- AMG 162 (skeletal-related event from bone metastases), NDA filed

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Denosumab Development Overview

Indication	Dosage	Development Stage	
		Japan	US/EU (Amgen)
Osteoporosis	60 mg every 6 months, SC	Ph III	**Launched**
Bone metastasis (skeletal-related event)	120 mg every 4 weeks, SC	NDA[1)] submitted	**Approved (US)** Under review (EU)
Bone metastasis (prevention[2)])	120 mg every 4 weeks, SC[3)]	Ph III (global study)	
Rheumatoid arthritis	TBD	Ph II	Ph II

[1)]New Drug Application (NDA)
[2)]Adjuvant breast cancer setting
[3)] 120mg subcutaneously (SC) every 4 weeks for 6 months followed by 120mg SC every 3 months for the next 4 and a half years

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Edoxaban (DU-176b)

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	*Thromb Haemost (2010)*	ENGAGE AF-TIMI 48 Started in Nov. 2008 Enrollment completed in Nov. 2010
	Japan	ACC (2009), ISTH (2009) and ASH (2009)	
	Asia	APHRS (2009)	
VTE Prevention of post-surgical thromboembolic event	Japan	*TKR (J Thromb Haemost 2010)*	ICT 2010 (TKR and HFS Ph III) ASH 2010 (THR Ph III) J-NDA filed (Mar. 2010)
	US/EU	*THR (Thromb Haemost 2010)*	
VTE Acute treatment and long-term prevention of thromboembolic event in patient with DVT/PE	US/EU Japan Asia		HOKUSAI VTE Started in Jan. 2010

DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism

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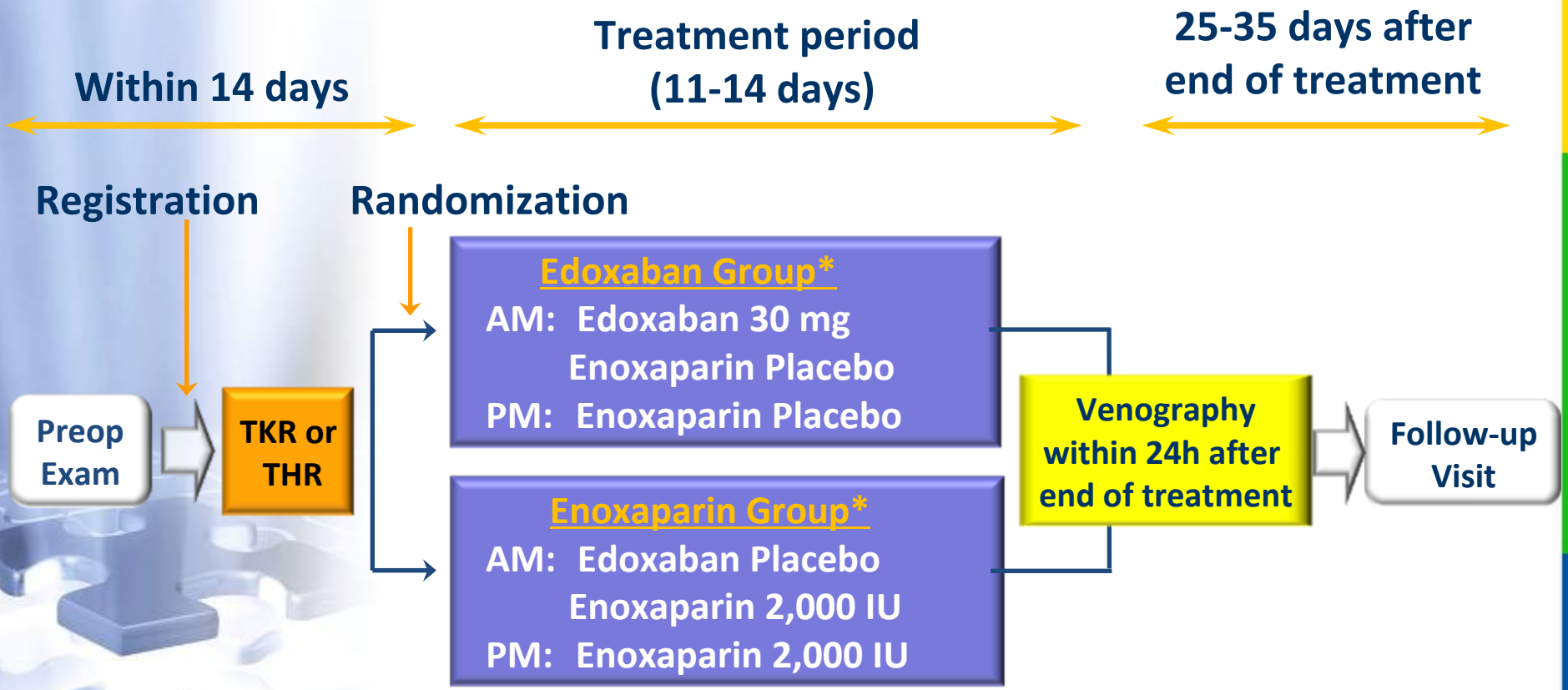
Total Knee Replacement (TKR) Total Hip Replacement (THR) Study design



*Edoxaban or edoxaban placebo was initiated within 6-24 hours after surgery and enoxaparin or enoxaparin placebo was initiated within 24-36 hours after surgery.

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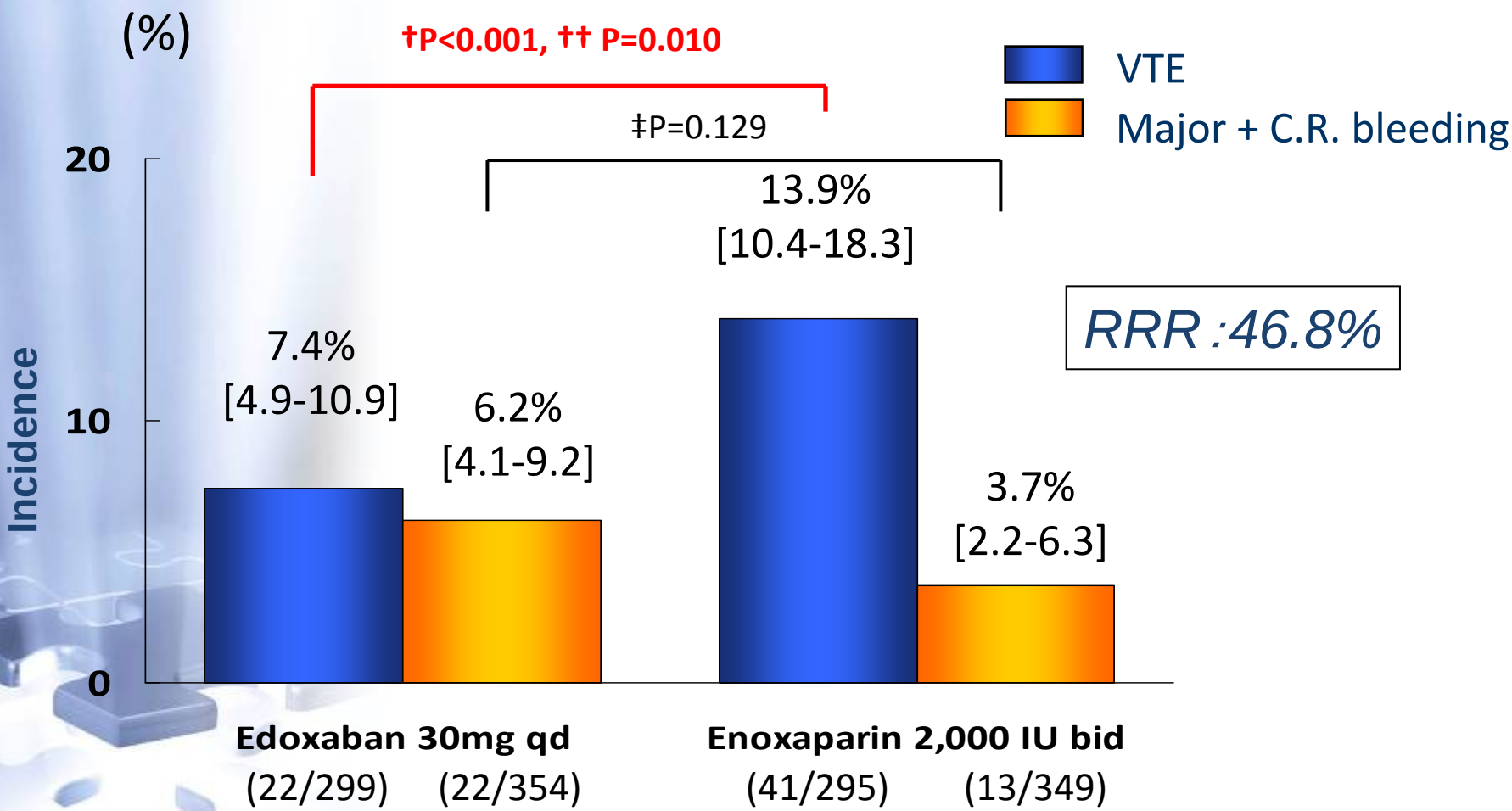
Total Knee Replacement (TKR) Phase III



Efficacy: † Non-inferiority: Z-test (Significant level : One-sided P<0.025)
†† Superiority : χ^2 test (Significant level : Two-sided P<0.05)

Safety : ‡ χ^2 test (Significant level : Two-sided P<0.05)

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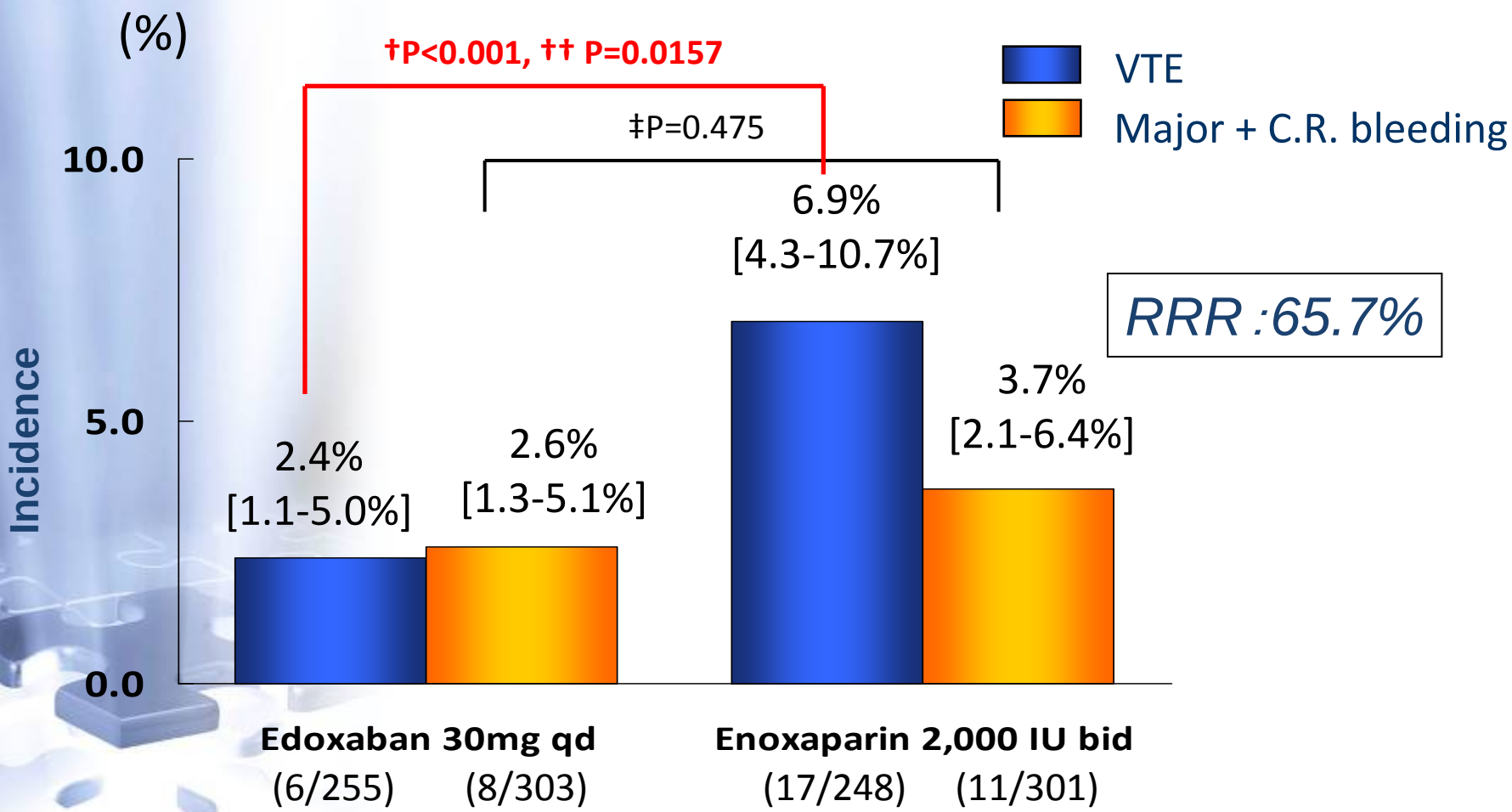
Total Hip Replacement (THR) Phase III



Efficacy: † Non-inferiority: FM-test (Significant level : One-sided P<0.025)
† † Superiority : FM-test (Significant level : Two-sided P<0.05)

Safety : ‡ χ^2 - test (Significant level : Two-sided P<0.05)

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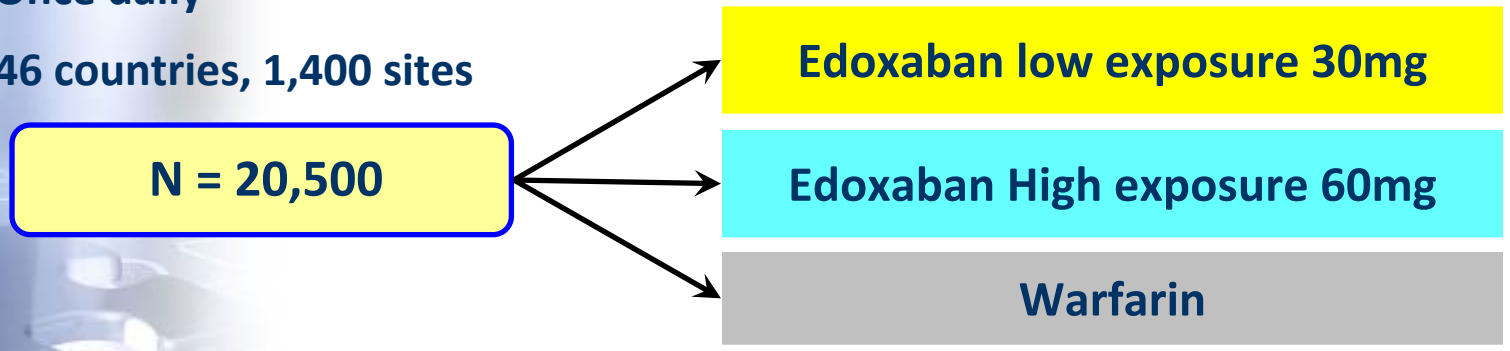
Summary of Post Surgical VTE (TKR, THR)

- Non-inferior and also superior to enoxaparin sodium confirmed in edoxaban in prevention of VTE in TKR and THR
- No significant difference observed between edoxaban and enoxaparin sodium in the incidence of major and clinically relevant non-major bleeding
- J-NDA filed for ‘the prevention of VTE after major orthopedic surgery’ in Mar. 2010

ENGAGE AF-TIMI 48 (Edoxaban AF Ph III)

Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation *(Am Heart J 2010)*

- **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

Patient enrollment completed

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Robustness of ENGAGE AF-TIMI 48

- Two doses (30 mg QD and 60 mg QD) selected as optimum dose regimens from the results of 3 phase II studies in US/EU, Asia and Japan
- Enough sample size secured based on the projected event rate
- Paying attention to time in therapeutic range to increase the quality of the study
- Double blind and double dummy design enables rigid evaluation of net clinical benefit of Edoxaban in comparison with warfarin

Summary of Edoxaban

- **Pharmacological profile: Predictive PK-PD relationship**
  - **Bioavailability more than 60%**
  - **Minimal food effect**
  - **No significant drug-drug interactions except potent P-glycoprotein inhibitors**
  - **Dual mechanism of excretion: one-third via kidneys and remainder in feces**
- **Optimized dose regimens (30 mg QD and 60 mg QD) of edoxaban for ENGAGE AF-TIMI 48**
- **Superior efficacy to enoxaparin sodium in prevention of VTE in post orthopaedic surgeries in Japan**

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INAVIR ®

(Laninamivir, Anti-Influenza Drug)

Status Update on Laninamivir (Anti-Influenza Drug)

- 10 September, 2010 : NDA Approval
- 19 October, 2010: Launched

Approved Labeling of Inavir

Brand name	INAVIR® DRY POWDER INHALER 20 mg
Generic name	Laninamivir Octanoate Hydrate (JAN)
Indication	Treatment of influenza A and B virus infection
Dosage and Administration	• For adult patients: Single dose inhalation of 40 mg • For pediatric patients <10-year old: Single dose inhalation of 20 mg • For pediatric patients ≥10-year old: Single dose inhalation of 40 mg

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Clinical Development Strategy (’08-’09 flu season)

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

Under 10 years	10-19 years (restriction on use of Tamiflu®)	Over 20 years
Phase II/III study CS-8958 *vs* Tamiflu® (Assessments of Efficacy, Safety)	Phase III open labeled study (Assessments of Efficacy, Safety)	Multinational Phase III study （MARVEL
PK study （below 15 years ）		Phase II Multi Dose Study
		Phase III study for Device Switching

- The patient enrollments of all the clinical trials for CS-8958 in this flu season were successfully finished.
- The total numbers of the patients for these studies are more than 1,500.

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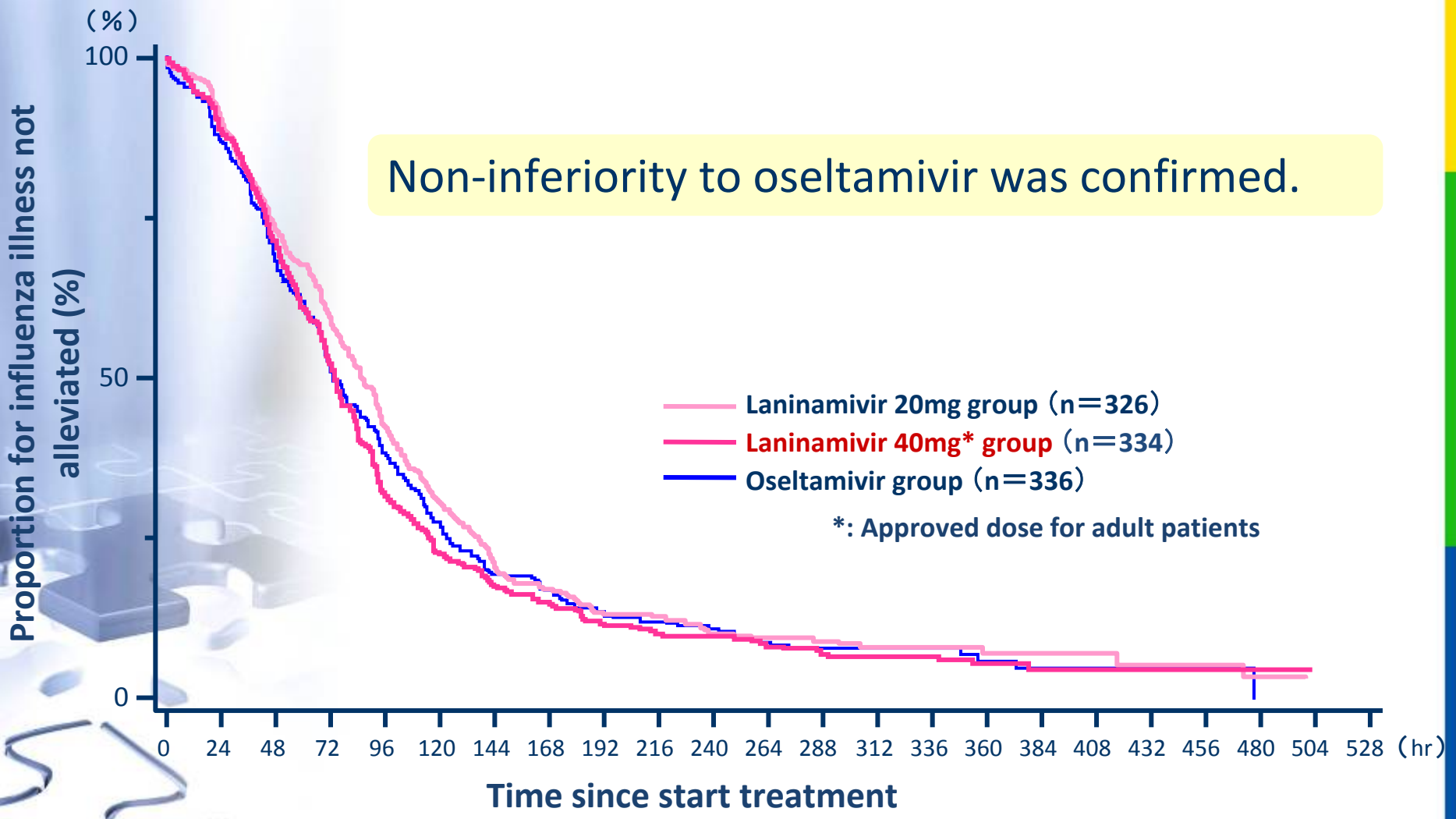
MARVEL Study

- Time to alleviation of influenza illness



Non-inferiority to oseltamivir was confirmed.

[Watanabe *et al., Clin. Infect. Dis.*, 2010, 51(10) 1167–1175]

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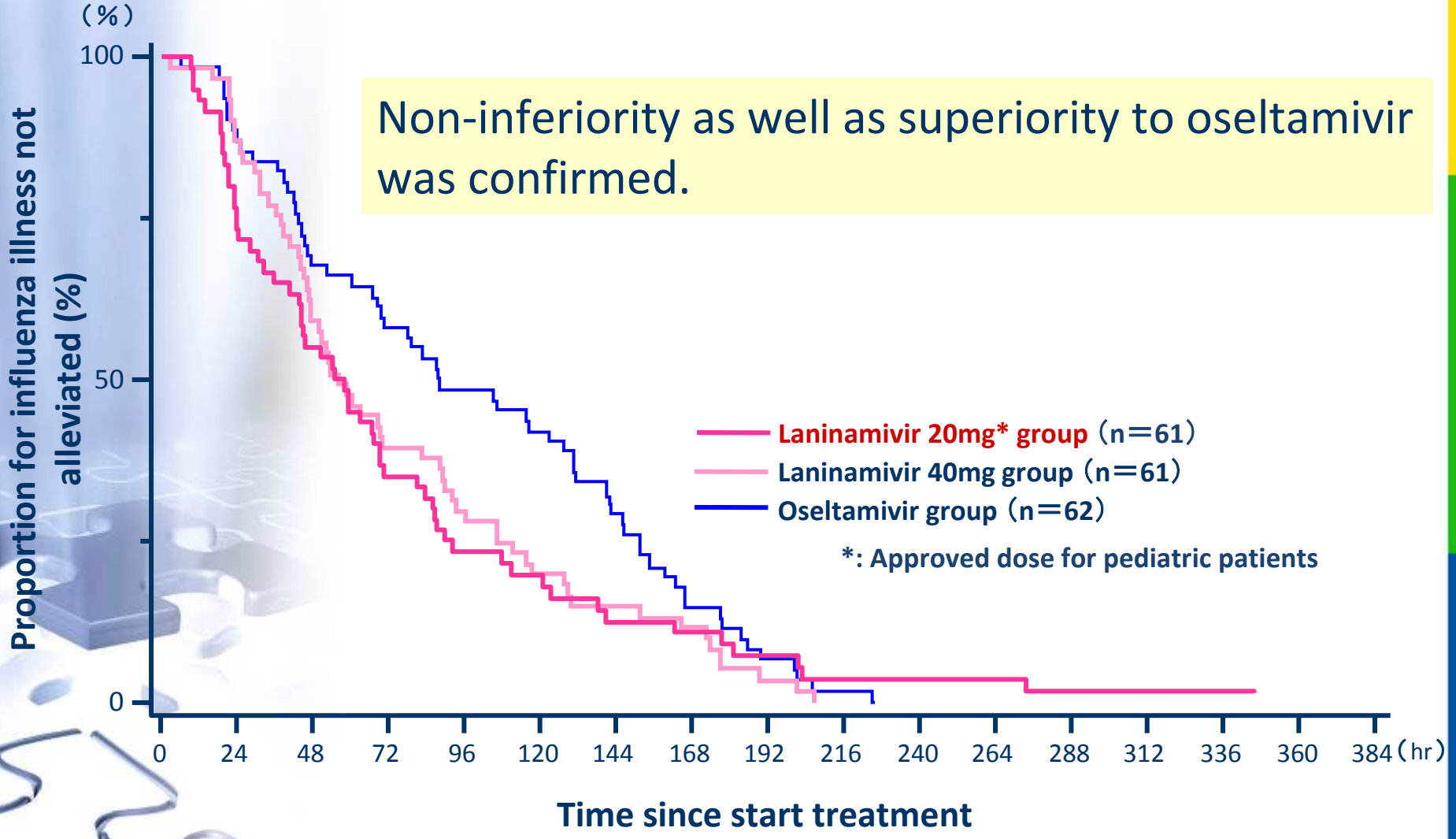
Pediatric Study (Under 10 years)

- Time to alleviation of influenza illness



Non-inferiority as well as superiority to oseltamivir was confirmed.

[Sugaya *et al. Antimicrob. Agents. Chemother.,* 2010; 54(6): 2575-2582]

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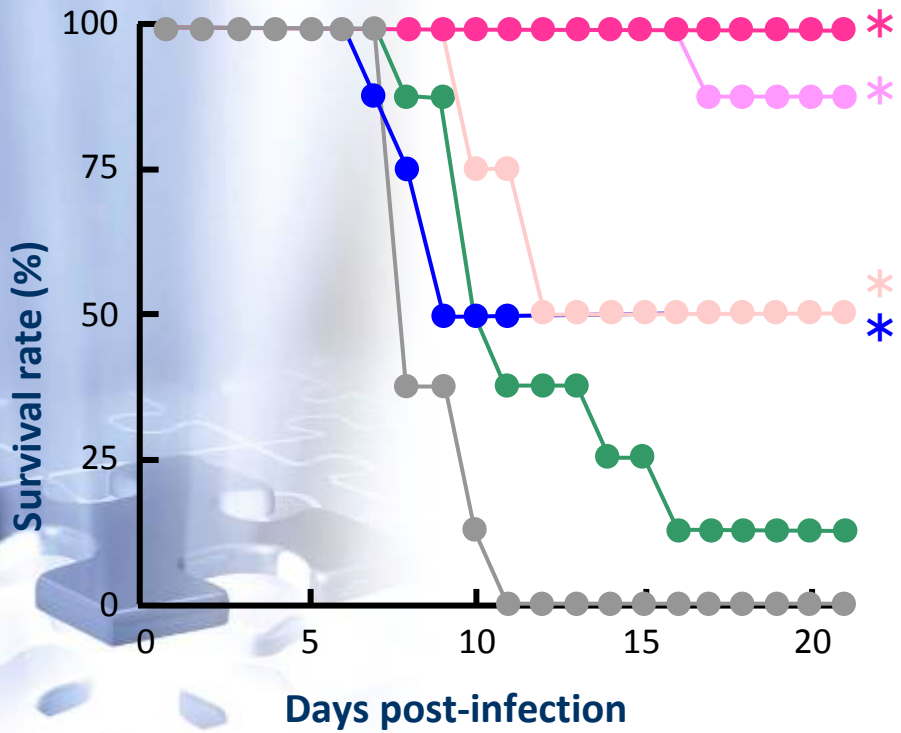
Therapeutic Efficacy to High Pathogenic H5N1 Influenza Virus（Clinical Isolates, oseltamivir-resistant) in Mice

Single Dose of laninamivir (CS-8958) vs Repeated Dose of Oseltamivir

VN1203-H274Y



- CS-8958 (1,500 μg/kg, single, intranasally)
- CS-8958 (750 μg/kg, single, intranasally)
- CS-8958 (75 μg/kg, single, intranasally)
- Oseltamivir (50 mg/kg, twice daily for 5 days, orally)
- Oseltamivir (5 mg/kg, twice daily for 5 days, orally)
- Control (saline and water)

***p<0.05**

-M. Kiso. *et al.* PloS Pathogens, February 2010, Volume 6, Issue 2, e1000786 -

Single Dose of laninamivir (CS-8958) is efficacious to high pathogenic H5N1 influenza virus.

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Conclusion on Laninamivir

- For adult patients, 40mg of single administration of laninamivir showed comparable effect to twice daily administration of Tamiflu® for 5days. (75mg x 2 x 5days).
- For pediatric patients (<10-year old), 20mg of single administration of laninamivir shows better efficacy, compared to Tamiflu®.
- Laninamivir can also be administered to teenaged-patients (40mg of single dose inhalation).
- Preclinical data reveal that laninamivir might be efficacious to high pathogenic H5N1 and 2009pdm H1N1 influenza virus clinically.

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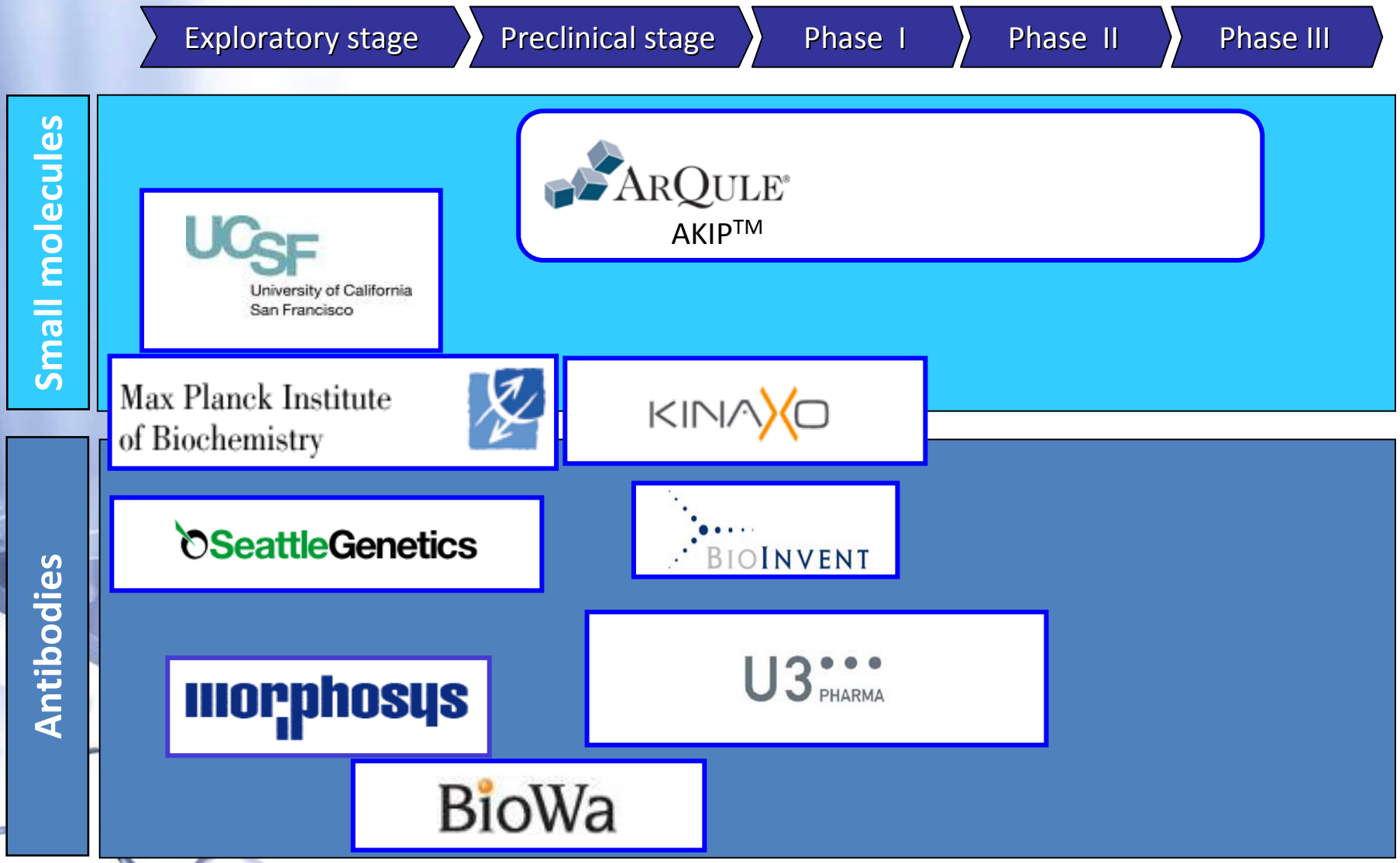
Oncology Overview

Oncology Pipeline Collaborations



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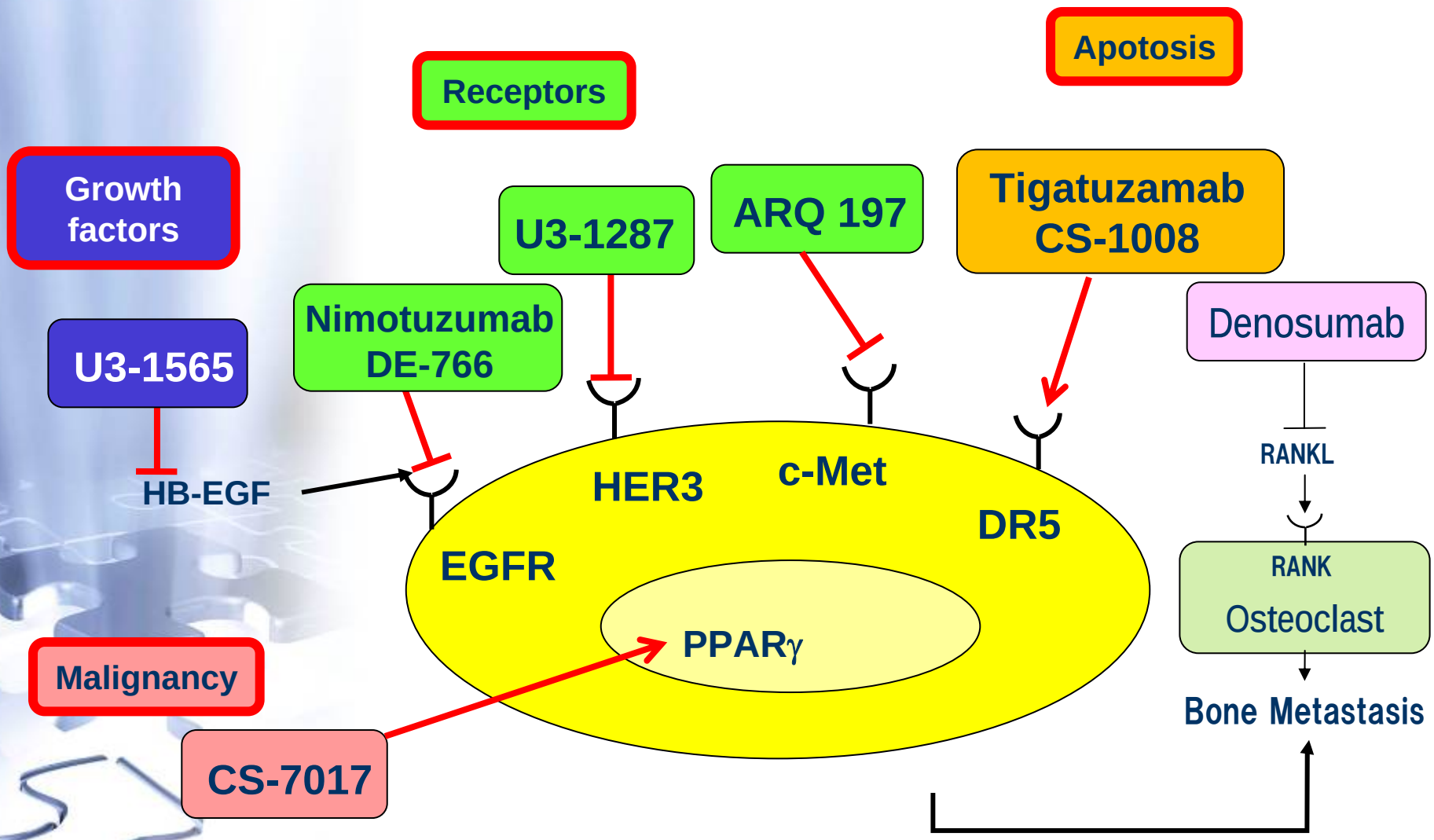
Oncology Research Targets



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AKIP™ (ArQule Kinase Inhibitor Platform)

- Kinases play pivotal roles in modulating diverse cellular activities
- AKIP™ technology is based on a novel binding mode that does not compete with the ATP binding site on the Kinase enzyme
- Non ATP-competitive inhibitors may have fewer off target effects
- ARQ 197 is the most advanced AKIP™ based inhibitor
- The agreement initially signed Nov. 2008 has now been expanded for 2 additional years and establishes a third therapeutic target for the collaboration in the field of Oncology

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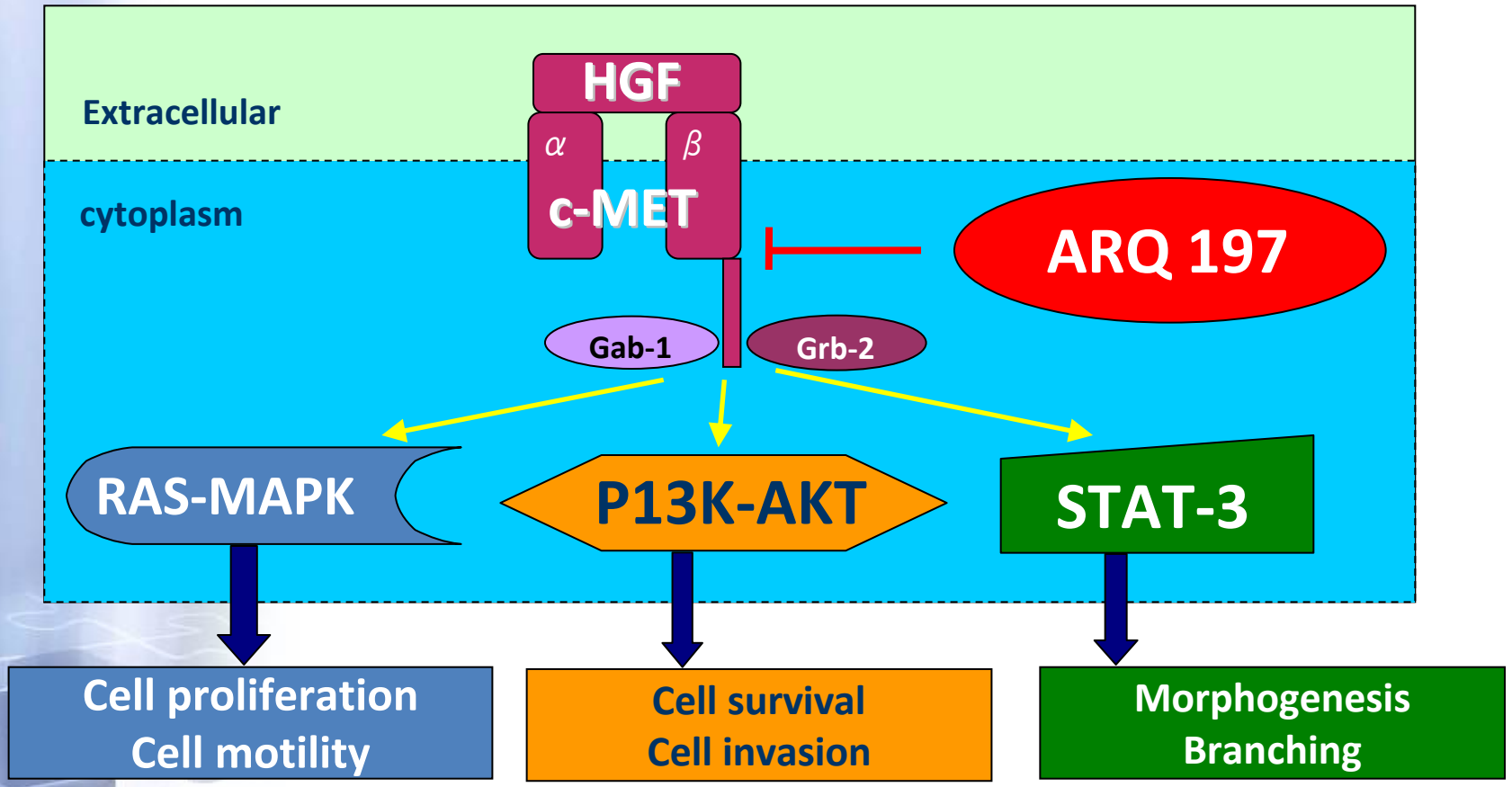
ARQ 197: First-in-class c-Met Inhibitor



- **c-Met:** Receptor tyrosine kinase of hepatocyte growth factor (HGF)
  - Multiple roles in intracellular signal transduction
- **High expression of c-Met**
  - Found in Colorectal, Liver, Breast, Pancreatic cancer
  - Associated with poor prognosis

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ARQ 197-209: Phase II Study Design

Randomized, placebo-controlled, double-blind clinical trial

NSCLC

- Inoperable, locally adv or metastatic dz.
- ≥1 prior chemo

(no prior EGFR TKI)

→ RANDOMIZE →

Erlotinib 150 mg PO QD
+ ARQ 197 360 mg PO BID
28-day cycle

Erlotinib 150 mg PO QD
+ placebo PO BID
28-day cycle

PD

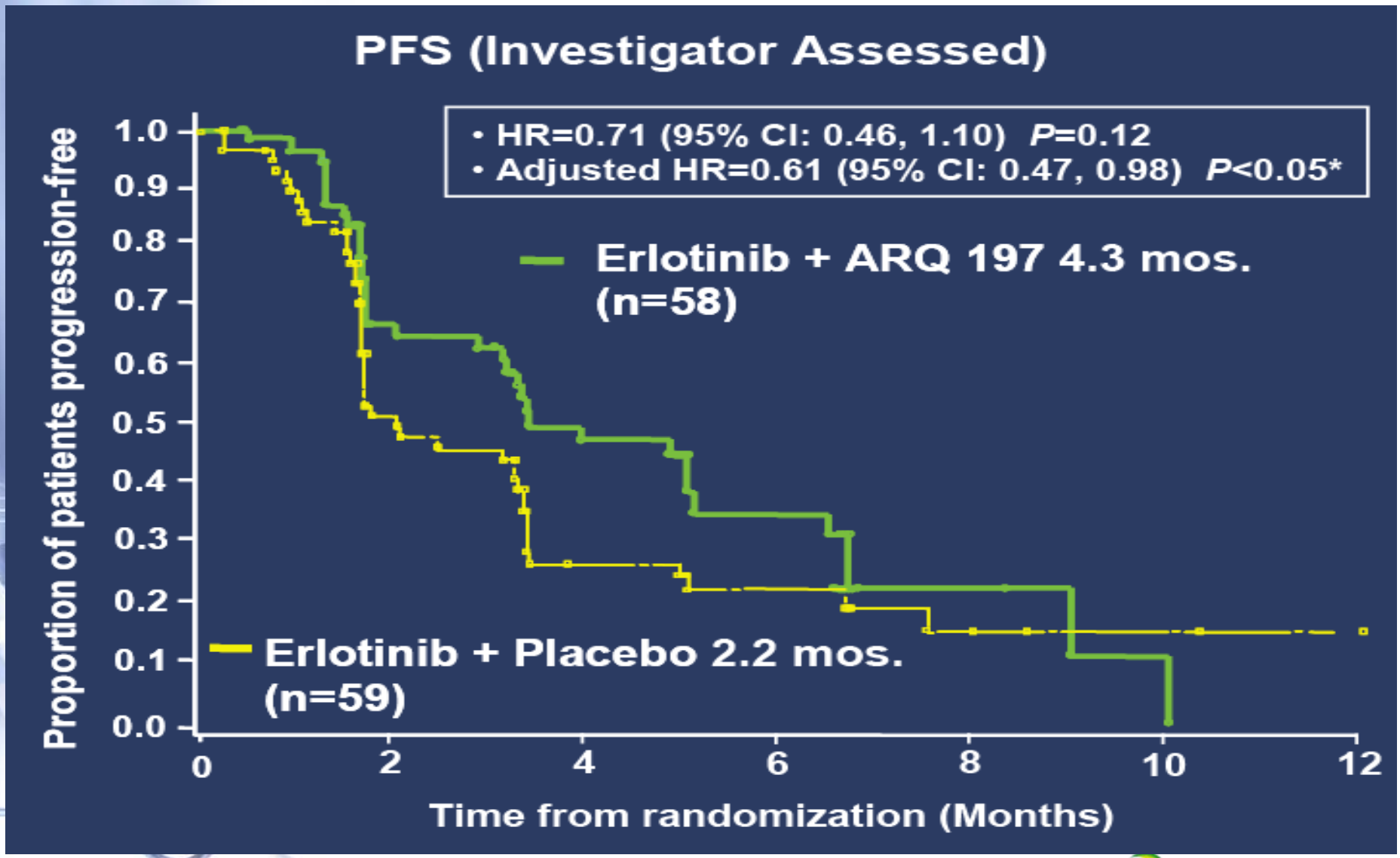
Endpoints

- 1° PFS
- 2° ORR, OS
- Subset analyses
- Crossover: ORR

- 33 sites in 6 countries
- Study accrual over 11 months
- Randomization stratified by prognostic factors : sex, age, smoking, histology, performance status, prior therapy, best response, and geography (US vs. ex-US)

Schiller et. al. ASCO 2010

ARQ 197-209: Progression Free Survival Non-Squamous Cell NSCLC Patients (n=117)



* Cox regression model

Schiller et. al. ASCO 2010

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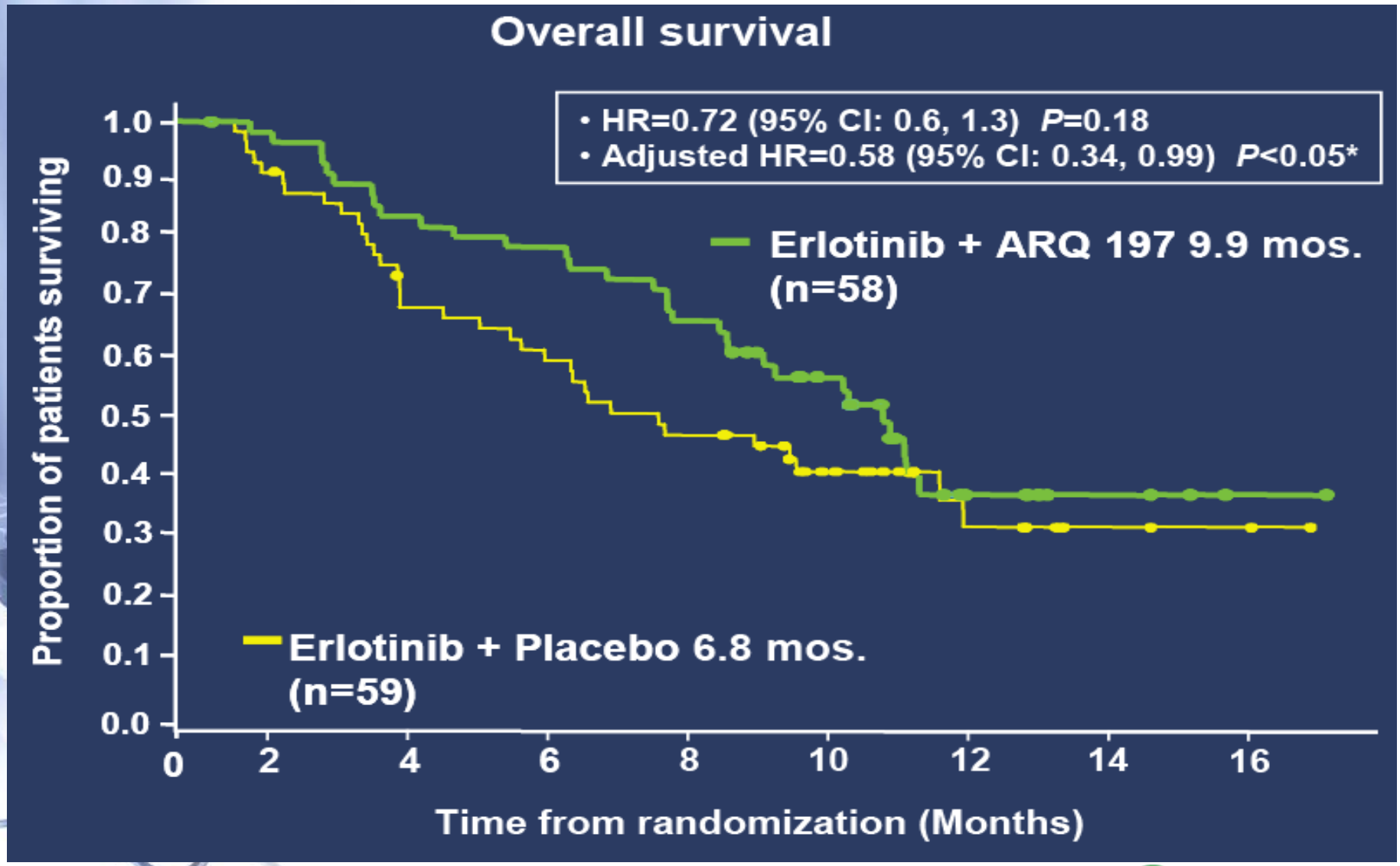
ARQ 197-209: Overall Survival Non-Squamous Cell NSCLC Patients (n=117)



* Cox regression model

Schiller et. al. ASCO 2010

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ARQ 197-209: Phase II Study Conclusions

- The ARQ 197/erlotinib combination is well-tolerated
- PFS is prolonged with ARQ 197/erlotinib vs. placebo/erlotinib
  - Statistically significant HR after adjusting for imbalances in Cox analysis
- Improvements in median OS parallel PFS
- PFS and OS benefits more pronounced in non-squamous patients
- Benefits in EGFR wild-type, KRAS mutation positive, and c-MET over expressing patients merit further investigation
- Exploratory analyses reveal meaningful increase in time to new metastatic lesions in the ARQ 197-erlotinib group

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ARQ 197: Development Status

- **Phase III**
  - NSCLC in North/Latin America and EU: in preparation
- **Phase II**
  - MiT in the US: enrolment completed
  - GCT in the US and EU: ongoing
  - HCC in EU: ongoing
  - CRC in the US, EU and Russia: ongoing

NCSCL = Non Small Cell Lung Cancer, GCT = Germ Cell Tumors, HCC = Hepatocellular Carcinoma, MiT = Microphthalmia Transcription Factor Associated tumors, CRC = Colorectal Cancer

ARQ 197: Phase III Clinical Trial in NSCLC

NSCLC

- Inoperable locally adv/metastatic dz.
- Non-squamous histology
- 1-2 regimens prior chemo (no prior EGFR TKI)
- Prior adjuvant/ maintenance therapy allowed

→ **RANDOMIZE**

→ **Erlotinib 150 mg PO QD +ARQ 197 360 mg PO BID 28-day cycle**

→ **Erlotinib 150 mg PO QD + Placebo 28-day cycle**

1° Endpoint OS

2° Endpoints incl:

- PFS
- OS and PFS in EGFR WT patients
- Safety and toxicity

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Olmesartan Lifecycle Management

CS-8635: A triple combination antihypertensive with Amlodipine and HCTZ

- US: Launched August 2010
  Brand name: Tribenzor™
- EU: NDA Filed in December 2009
  Anticipated approval soon

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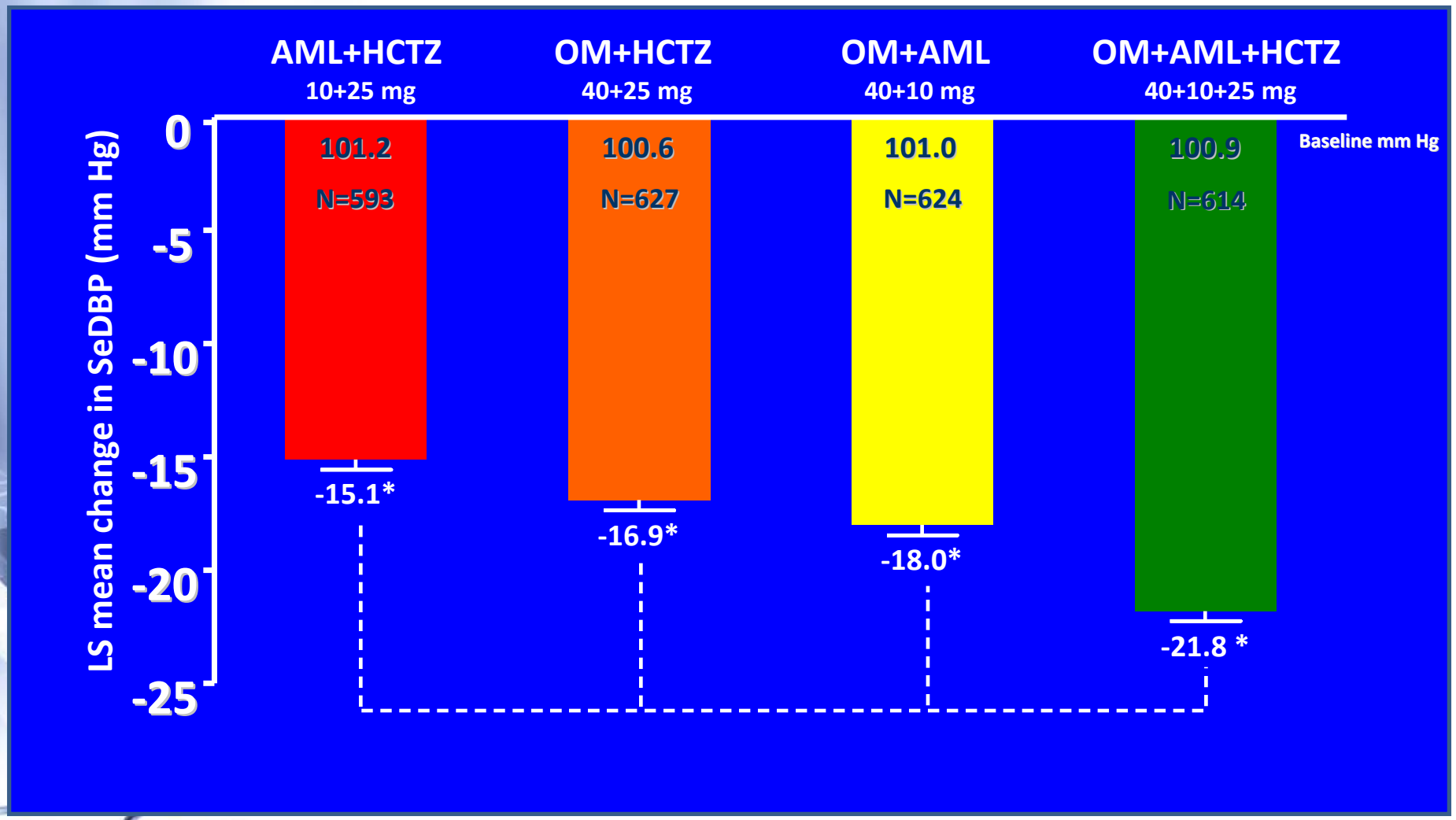
Tribenzor™: US Phase III Primary Endpoint: Mean Change from Baseline in SeDBP at Week 12



* *P*<0.0001 for all dual vs triple combinations

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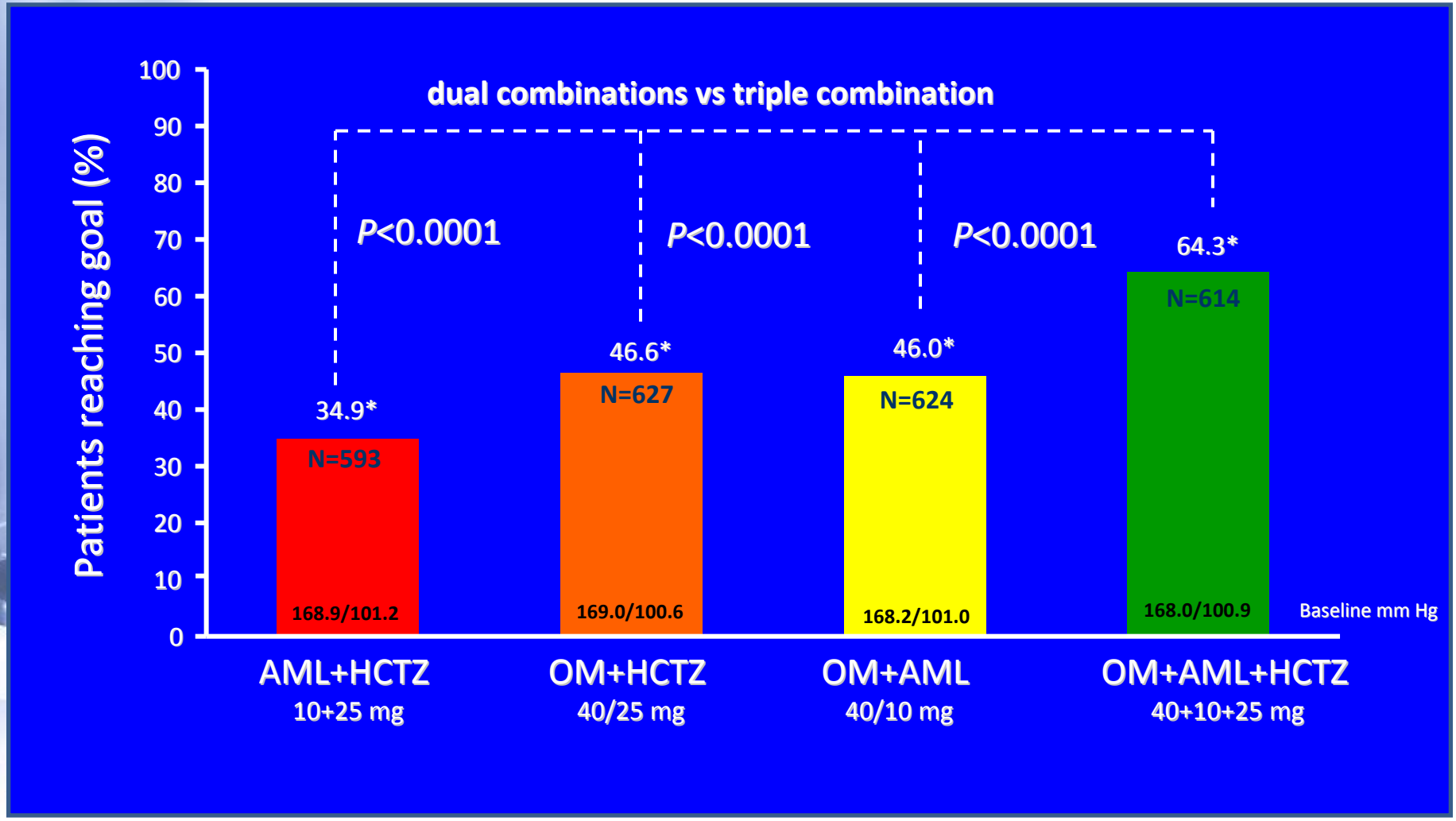
Tribenzor™: US Phase III Secondary Endpoint: Proportion of Patients Achieving BP Goal at Week 12



BP goal: <140/90 mm Hg, or <130/80 mm Hg for patients with diabetes, chronic renal disease or chronic cardiovascular disease

* *P*<0.0001 for all dual combinations vs triple combination

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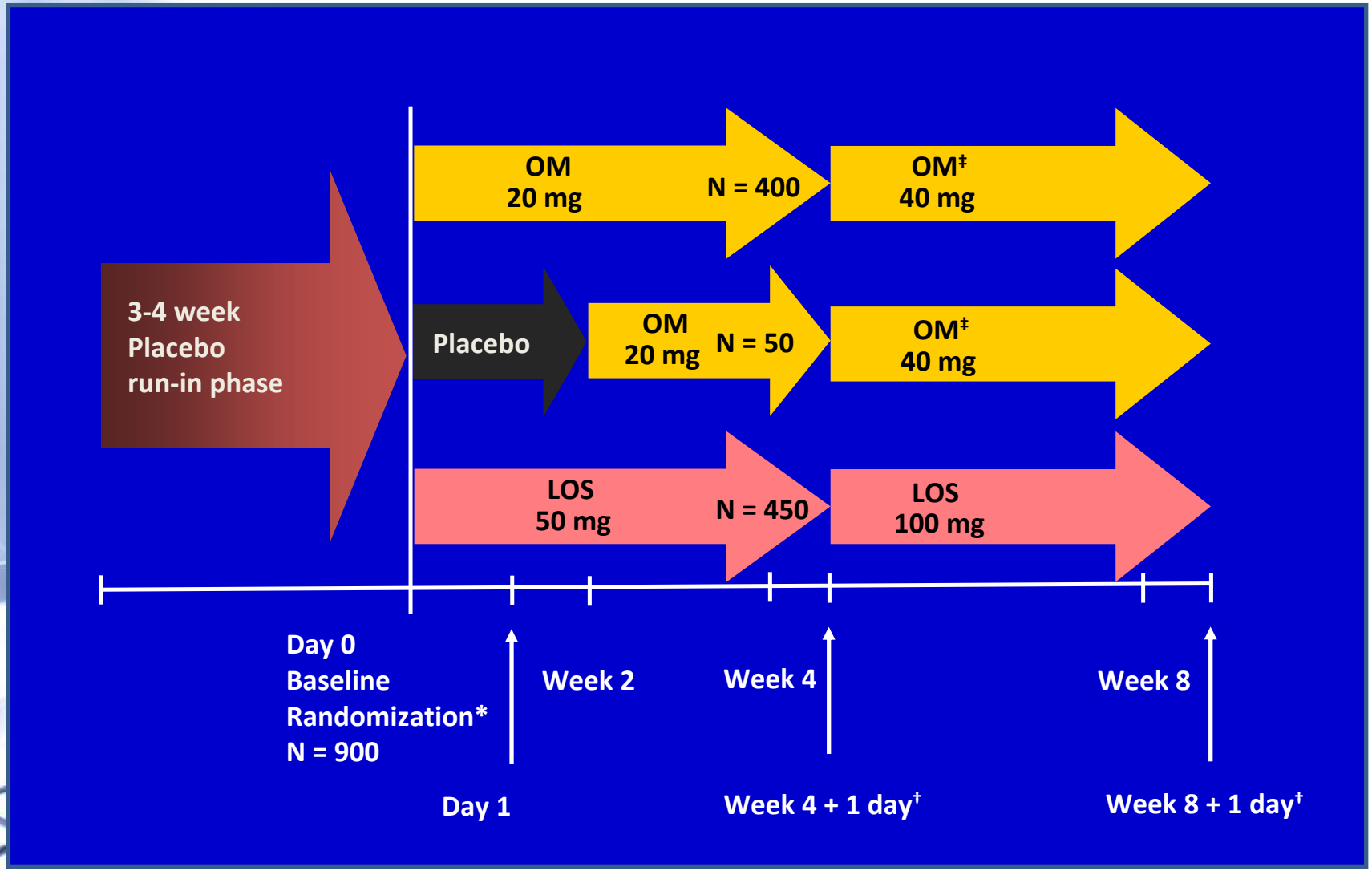
BeniVICTOR: Double-Blind, Randomized, Forced-Titration Comparison Trial of Olmesartan (OM) vs Losartan (LOS)



*Eligible subjects randomized in an 8:1:9 ratio to OM, placebo followed by OM, or LOS;
† Subjects undergoing ABPM at pre-selected participating sites;
‡Combined OM includes subjects who were randomized to OM or PLA-OM.

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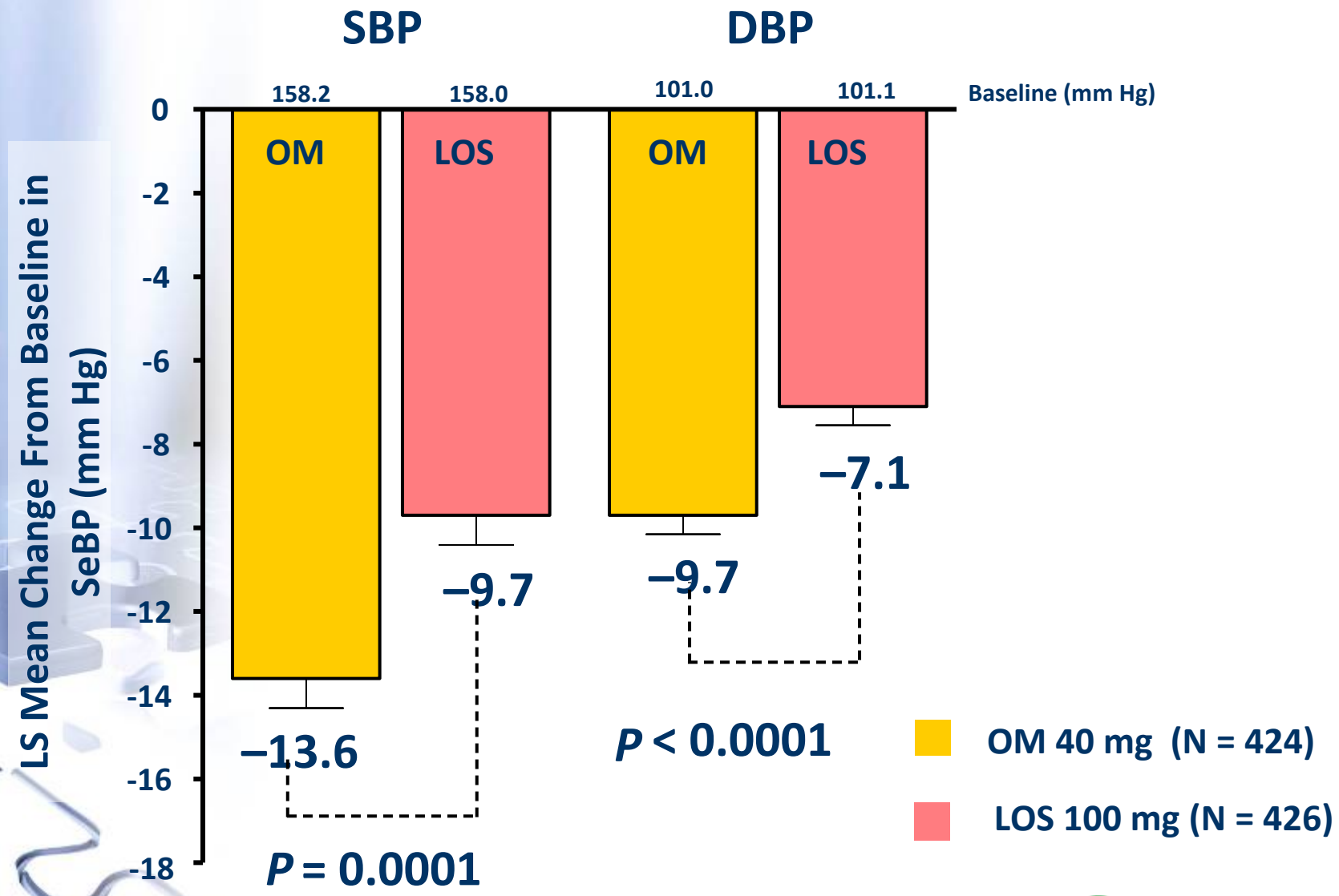
LS Mean (± SEM) Change From Baseline in SeDBP (Primary Endpoint) and SeSBP (Secondary Endpoint) at Week 8 LOCF



LS, least-squares; SEM, standard error of the mean.

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Conclusions on BeniVICTOR

- Treatment with olmesartan produced significantly greater reductions in SeBP, and more patients attained SeBP goals than patients treated with losartan
- Both agents were well tolerated

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Expected R&D Events in CY2011

- Memantine, approval and launch in Japan
- Edoxaban (prevention of venous thromboembolism after major orthopedic surgery), approval and launch in Japan
- Denosumab (skeletal-related event from bone metastases), approval and launch in Japan
- Olmesartan (ARB), calcium channel blockers and diuretics, three-in-one combination, launch in EU
- Nimotuzumab (DE-766), top line result of Phase II study in patients with gastric cancer

Contact address regarding this material

DAIICHI SANKYO CO., LTD.

Corporate Communications Department

TEL: +81-3-6225-1126 (Public Relations)
+81-3-6225-1125 (Investors Relations)

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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.