Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

December 14 2015

Research and Development at Daiichi Sankyo

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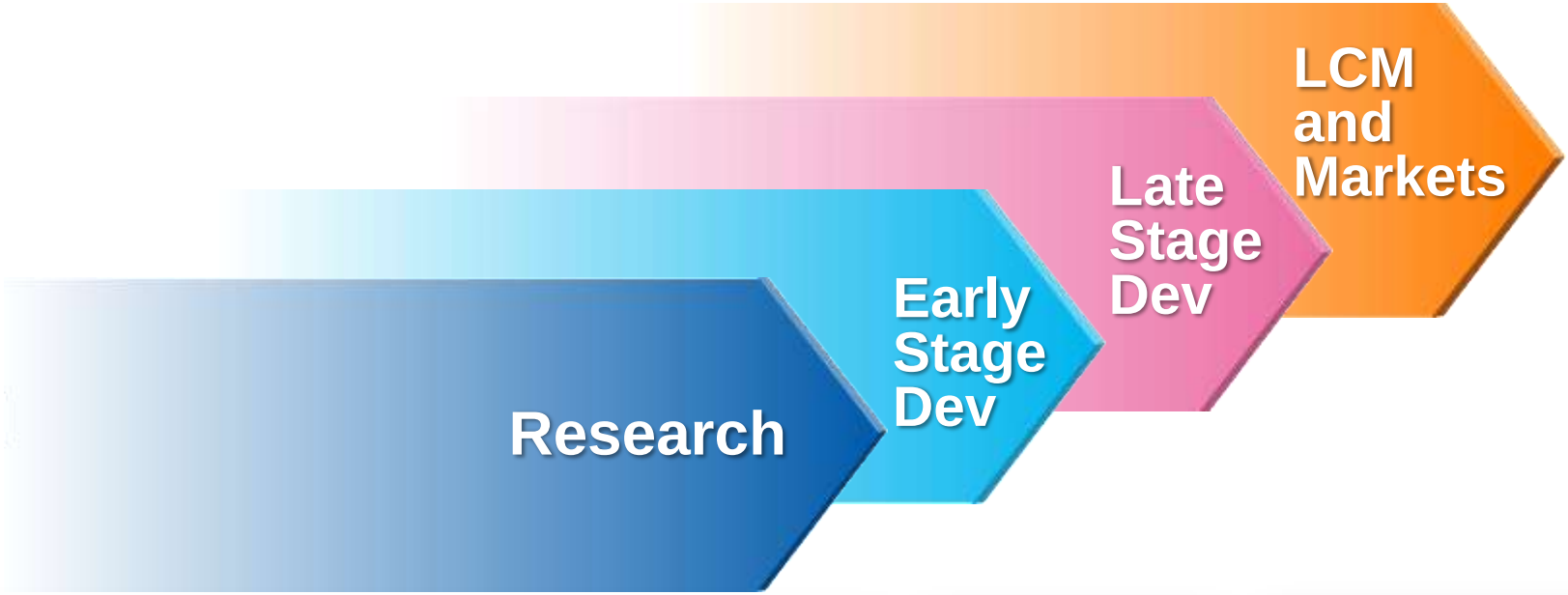
Senior Executive Officer, Global R&D Head

Daiichi Sankyo Co., Ltd.

Agenda

- **Pipeline overview**
- **Pipeline update : Thrombosis, Diabetes and Pain**
- **Focus on Oncology**

R&D Focus Therapeutic Areas



Priority Areas for Discovery*
- **Oncology**
- **CV-M**
- **Pain**

Oncology	**Thrombosis**
CV-M	**Hypertension**
Pain	**Pain**

*Discovery：Research and Early Development up to Proof of Concept

Major R&D pipeline

As of October 2015

Daiichi-Sankyo

Therapeutic area	Phase 1	Phase 2	Phase 3	Application
Cardio vascular-Metabolics	■ **DS-1040** (Acute ischemic stroke / TAFIa inhibitor) ■ **DS-8312** (Hypertriglyceridemia) ■ **DS-2330** (Hyperphosphatemia) ■ **DS-9231/TS23** (Thrombosis / α2-PI inactivating antibody)	■ **CS-3150 (JP)** (Hypertension・DM nephropathy / MR antagonist) ■ **DS-8500 (JP)** (Diabetes / GPR119 agonist)	■ **Prasugrel (JP)** (CS-747 / Ischemic stroke / anti-platelet agent) ■ **Prasugrel (US)** (CS-747 / sickle cell disease / anti-platelet agent)	■ **Edoxaban (ASCA etc.)** (DU-176b / AF / oral factor Xa inhibitor) ■ **Edoxaban (ASCA etc.)** (DU-176b / VTE / oral factor Xa inhibitor)
Oncology	■ **DS-3032 (US/JP)** (MDM2 inhibitor) ■ **PLX7486 (US)** (FMS / TRK inhibitor) ■ **PLX8394 (US)** (BRAF inhibitor) ■ **DS-6051 (US)** (NTRK/ROS1 inhibitor) ■ **PLX9486 (US)** (KIT inhibitor) ■ **U3-1565 (US/JP)** (Anti-HB-EGF antibody) ■ **DS-8895 (JP)** (Anti-EPHA2 antibody) ■ **DS-8273 (US)** (Anti-DR5 antibody) ■ **DS-5573 (JP)** (Anti-B7-H3 antibody) ■ **DS-8201 (JP)** (Anti-HER2 ADC)	■ **Patritumab (US/EU)** (U3-1287 / anti-HER3 antibody) ■ **Pexidartinib (US)** (PLX3397 / FMS/KIT/FLT3-ITD inhibitor)	■ **Tivantinib (US/EU)** (ARQ 197 / HCC / MET inhibitor) ■ **Denosumab (JP)** (AMG 162 / breast cancer adjuvant / anti-RANKL antibody) ■ **Nimotuzumab (JP)** (DE-766 / gastric cancer / anti-EGFR antibody) ■ **Vemurafenib (US/EU)** (PLX4032 / melanoma adjuvant / BRAF inhibitor) ■ **Quizartinib (US/EU)** (AC220 / AML / FLT3-ITD inhibitor) ■ **Pexidartinib (US/EU)** (PLX3397/TGCT / FMS/KIT/FLT3-ITD inhibitor)	
Others	■ **DS-1093** (Anemia of chronic kidney disease / HIF-PH inhibitor) ■ **DS-3801** (Chronic obstipation / GPR38 agonist) ■ **DS-1971** (Chronic pain) ■ **DS-1501** (Osteoporosis / Anti-Siglec-15 antibody) ■ **DS-7080** (AMD / Angiogenesis inhibitor) ■ **VN-0102/JVC-001 (JP)** (MMR vaccine)	■ **SUN13837 (US/EU)** (Spinal cord injury / modulator of bFGF signaling system) ■ **Laninamivir (US/EU)** (CS-8958 / anti-influenza / out-licensing with Biota)	■ **Mirogabalin (US/EU)** (DS-5565 / fibromyalgia / α2δ ligand) ■ **Mirogabalin (JP/Asia)** (DS-5565 / DPNP/ α2δ ligand) ■ **Mirogabalin (JP/Asia)** (DS-5565 / PHN / α2δ ligand) ■ **Denosumab (JP)** (AMG 162 / rheumatoid arthritis / anti-RANKL anti-body) ■ **Hydromorphone (JP)** (DS-7113 / cancer pain / opioid μ-receptor regulator) ■ **CHS-0214 (JP)** (Etanercept BS / rheumatoid arthritis / TNFα inhibitor) ■ **CL-108 (US)** (Acute pain / opioid μ-receptor regulator) ■ **VN-0105 (JP)** (DPT-IPV/Hib vaccine) ■ **VN-0107/MEDI3250 (JP)** (Nasal spray flu vaccine vaccine)	■ **Intradermal Seasonal Influenza Vaccine (JP)** (VN-100 /prefilled i.d. vaccine for seasonal flu) ■ **VN-101 (JP)** (Cell-culture H5N1 Influenza vaccine)

Targets for Approval and Launch

	FY2015	FY2016	FY2017	FY2018	≥ FY2019
Japan	Cravit® Injection	Hydromorphone Cancer Pain	Pralia® RA	Mirogabalin DPNP & PHN	
	Cravit® Tuberculosis	Lacosamide Epilepsy			
	Artist® Chronic AF		Efient® CVA		
US		CL108 Acute Pain & OINV		Tivantinib HCC	
		Effient® Sickle Cell		Quizartinib AML	
Western Europe	Lixiana® AF			Tivantinib HCC	
	Lixiana® VTE			Quizartinib AML	
Other Regions	Lixiana® AF&VTE (China・LTAM etc.)				

Oncology
Nimotuzumab
Patritumab
Pexidartinib
Quizartinib (JPN)
Zelboraf® (LCM)
Ranmark®
(BC adj)

CV-M
CS-3150 (MRA)
DS-8500 (GPR119)
Effient® (LCM)
Lixiana® (LCM)

Pain
Mirogabalin

Other

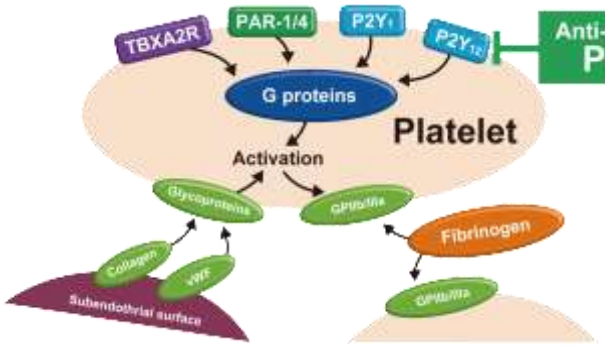
Agenda

- Pipeline overview
- **Pipeline update : Thrombosis, Diabetes and Pain**
- Focus on Oncology

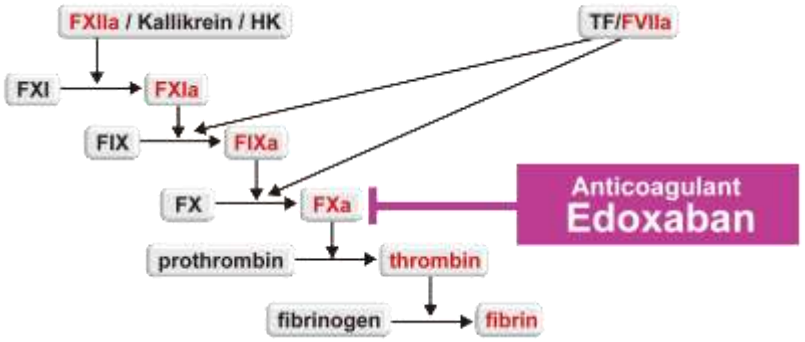
Medical Management of Thrombosis

Daiichi-Sankyo

Platelet aggregation

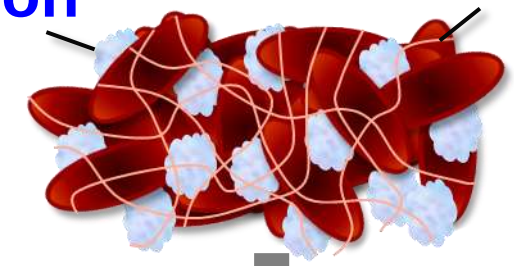


Blood coagulation



Platelet aggregation

Fibrin



Thrombus

TAFIa inhibitor (DS-1040) Fibrinolysis enhancer

TAFIa

Thrombin-activatable fibrinolysis inhibitor

Plasmin

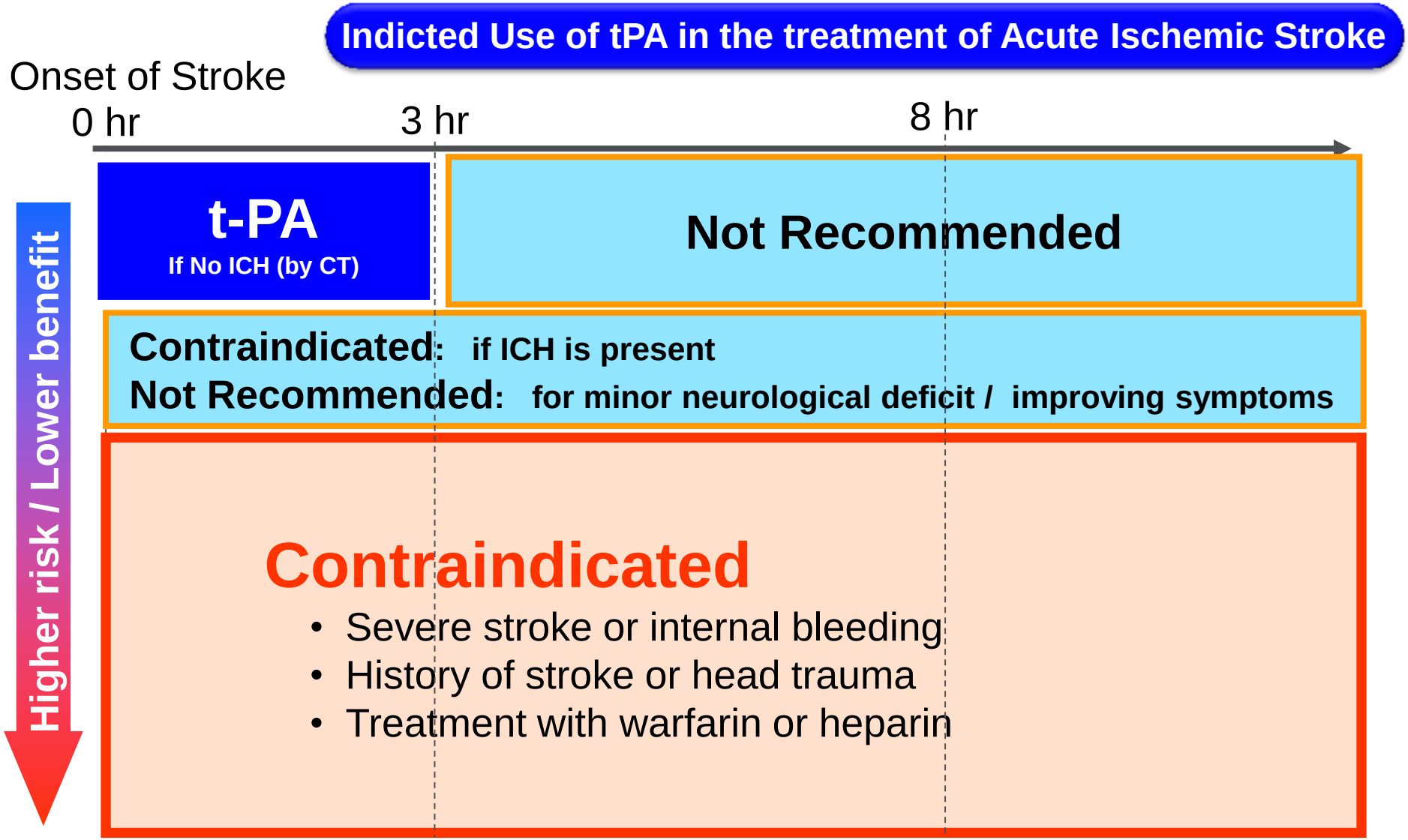
α2-PI

α2-PI inhibitor (DS-9231) Fibrinolysis enhancer

Fibrinolysis

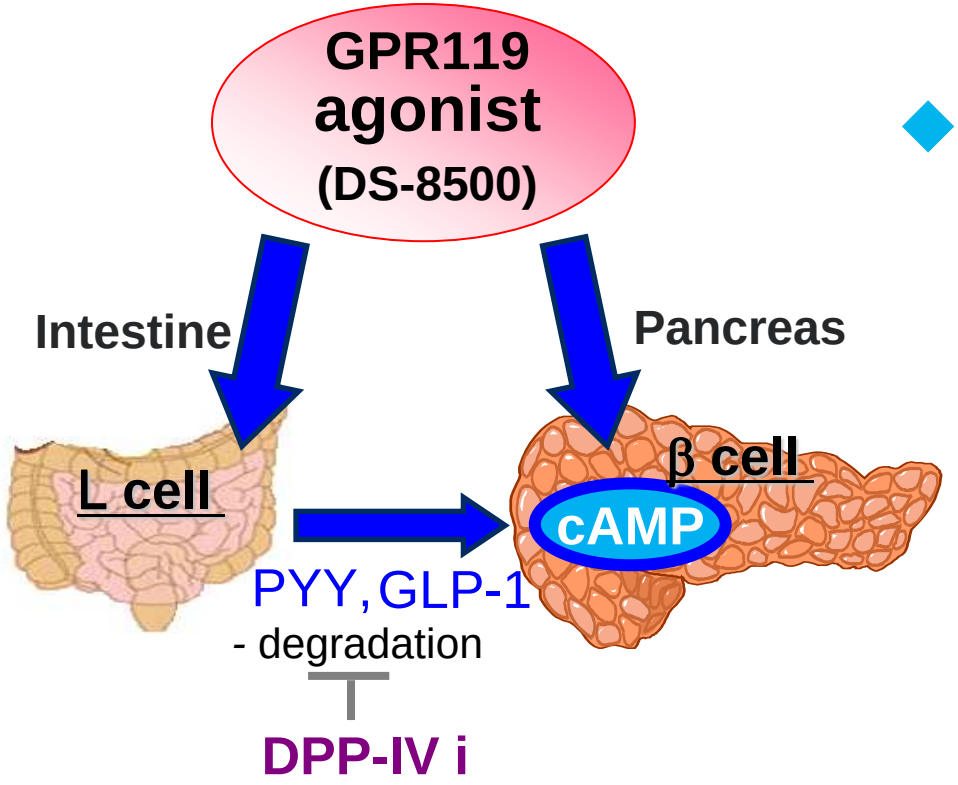
(α2-plasmin inhibitor)

Opportunity for a new fibrinolysis enhancer



Global sales for alteplase: $1.1 B in 2014 (Source: EvaluatePharma)

DS-8500 : GPR119 agonist



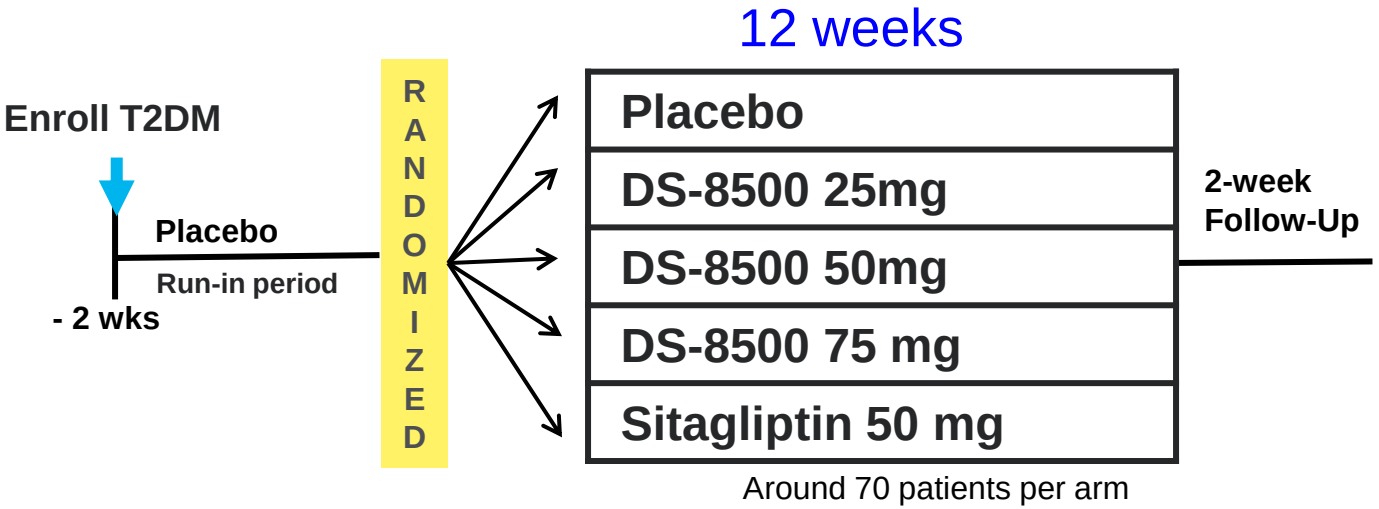
- **Mechanism of Action**
  - **Amplify glucose-stimulated insulin secretion**
  - **Improve β-cell function**
  - **Stimulate GLP-1 secretion**

DPP-IV i : Dipeptidyl Peptidase-4 inhibitor
GLP-1: Glucagon-Like Peptide-1
PYY: Peptide YY

Results of Phase 2a study are anticipated to be published in 1H 2016

DS-8500 : GPR119 agonist

Phase 2b: 12-week study has just started



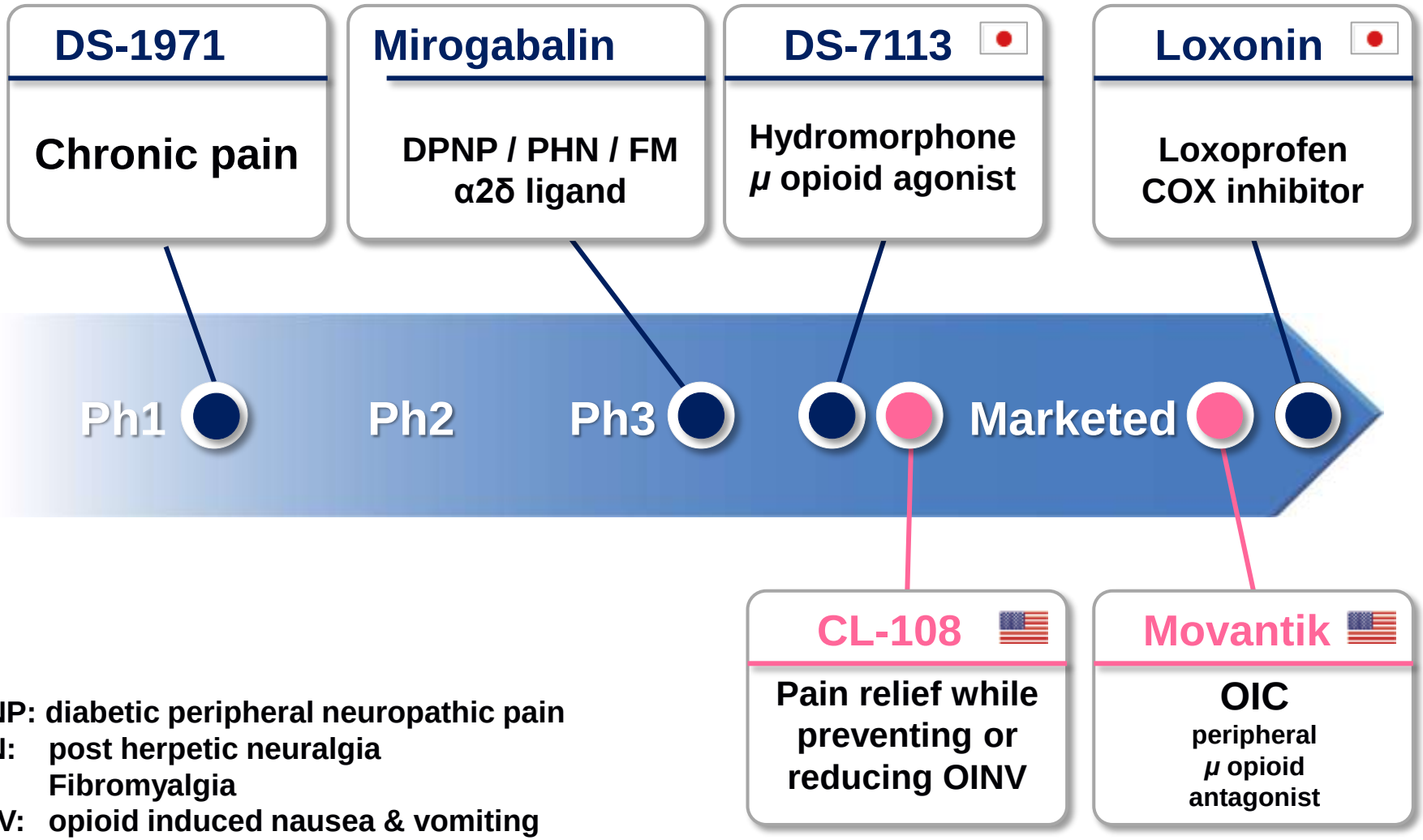
Around 70 patients per arm

Subject	T2DM patients
Region	Japan
Study endpoints	Primary endpoint: HbA1c
	Safety: adverse events, hypoglycemia
Study timeline	Nov 2015 (FPI)～ 4Q FY2016 (TLR anticipated)

FPI: First Patient In
TLR: Top Line Results

http://www.clinicaltrials.jp/user/cteSearch_e.jsp JapicCTI-153068

Pipeline for the Treatment of Pain



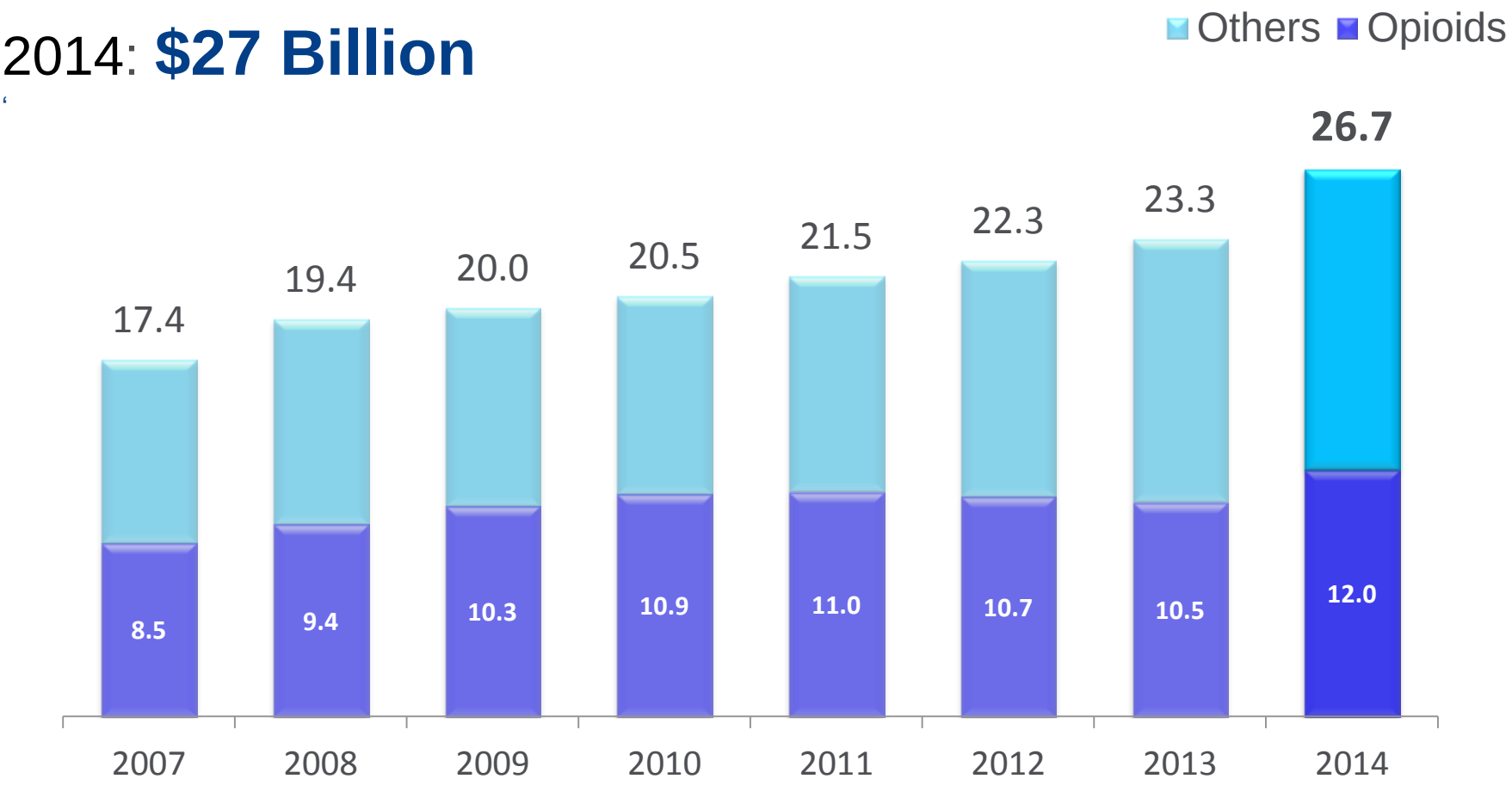
DPNP: diabetic peripheral neuropathic pain
PHN: post herpetic neuralgia
FM: Fibromyalgia
OINV: opioid induced nausea & vomiting
OIC: opioid induced constipation

U.S. Pain Market Holds Great Opportunity

Large, Growing Market

U.S. Pain Market Gross Sales (US $ Billion)

2014: **$27 Billion**



Source: Symphony Health PHAST Audit, Encuity

Update on CL-108

Third Phase 3 study recently completed :

- **Double-Blind, Active- and Placebo-Controlled study**
- **Population: 550 patients, with pain after bunionectomy surgery**
- **Results: co-primary endpoints were met:**
  - **Pain relief and prevention or reduction of OINV* (both p<0.001)**
- **Results are planned to be published in 2016**

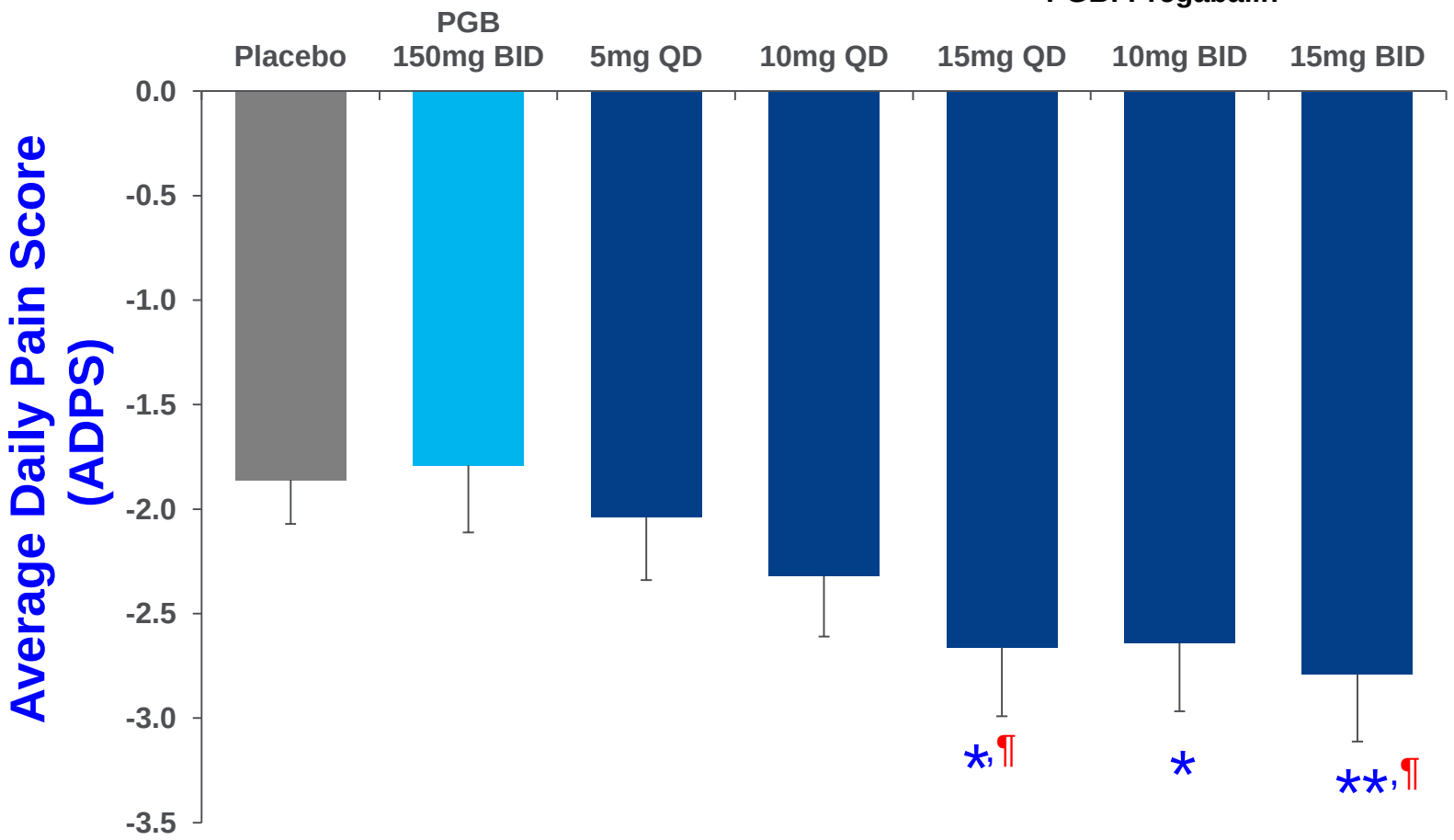
OINV: opioid-induced nausea and vomiting

NDA submission: anticipated 4Q FY2015

Mirogabalin: Phase 2, DB Study in DPNP

Primary Endpoint at Week 5

DPNP: Diabetic Peripheral Neuropathic Pain
PGB: Pregabalin

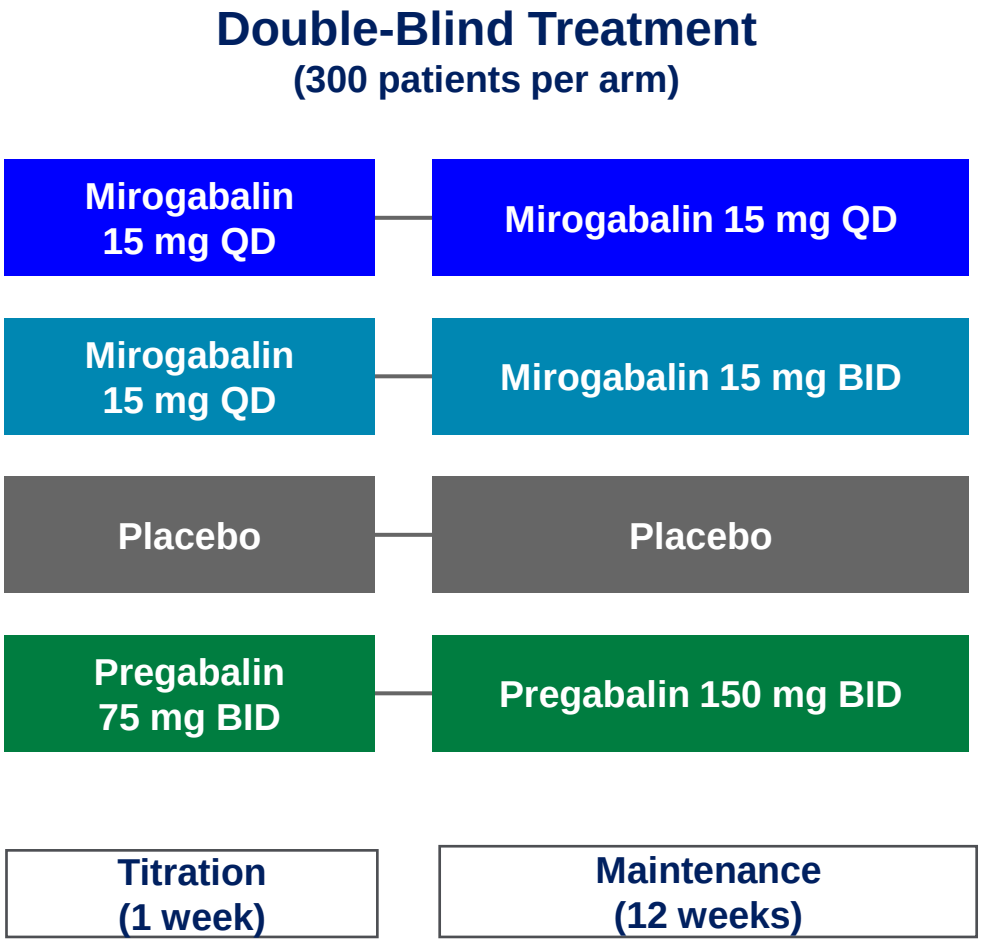


QD：once daily
BID：twice a day

- 3 doses reached statistical significance versus placebo ***: p<0.05, **: p<0.01**
- 2 doses reached statistical significance versus pregabalin **¶: p<0.05**

American Diabetes Association 74th Scientific Sessions; June 13-17, 2014; San Francisco, California.

West: Mirogabalin Phase 3 FM Study Design



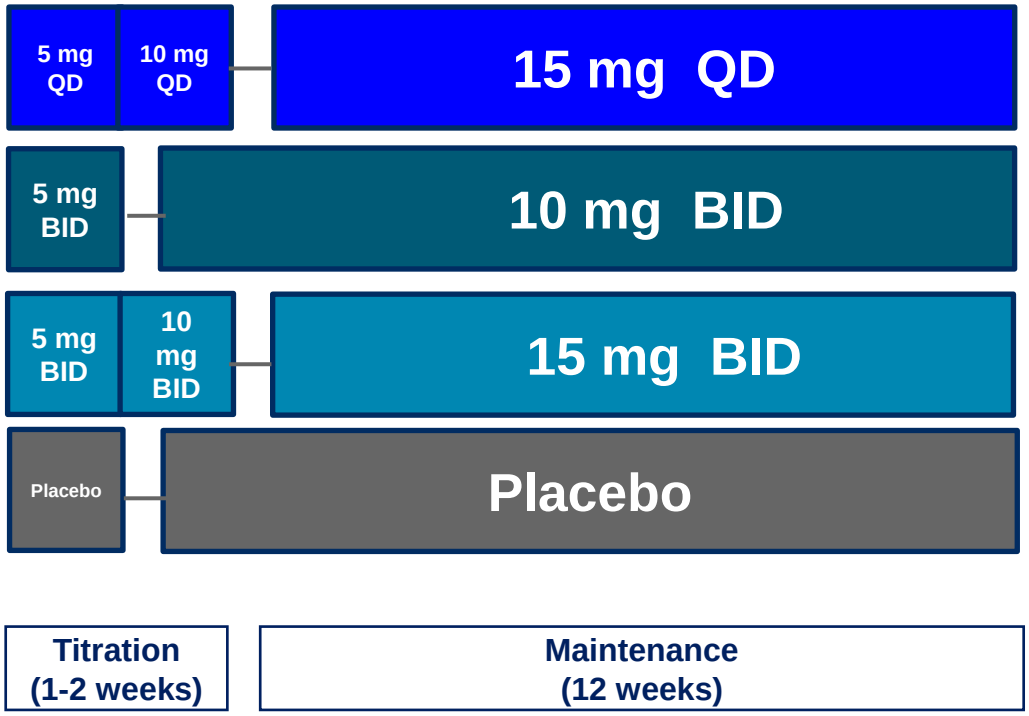
- **Primary outcome: change from baseline in the ADPS at week 13**

ADPS: Average Daily Pain Score
FM: Fibromyalgia

Top Line Results anticipated in 1H 2017

Asia: Peripheral Neuropathic Pain (PNP) Phase 3 Study Design

Double-Blind Treatment
(150 patients per Mirogabalin arm, 300 patients in placebo arm)



- **Primary outcome: change from baseline in the ADPS at week 14**

ADPS: Average Daily Pain Score
PNP : DPNP+PHN
DPNP: Diabetic Peripheral Neuropathic Pain
PHN: Post Herpetic Neuralgia

Top Line Results anticipated in 1H 2017

Agenda

- Pipeline overview
- Pipeline update: Thrombosis, Diabetes and Pain
- **Focus on Oncology**

Daiichi Sankyo Oncology Strategy

- Focus on FIC opportunities
- Develop Personalized medicine based therapies
- Maintain strong academic partnerships
  - National Cancer Center of Japan
  - UCSF
  - Max Planck
- Partner with innovative biotech companies
  - ArQule
- Strategic acquisitions
  - Plexxikon
  - Ambit

Oncology Clinical Pipeline

	Ph 1	Ph 2	Ph 3
Growth Survival Receptors	U3-1565 (HB-EGF) DS-3032 (MDM2) DS-8273 (DR5)	Patritumab (HER3)	Nimotuzumab (EGFR)
ADC	DS-8201 (HER2 ADC)		
ADCC	DS-8895 (EPHA2) DS-5573 (B7-H3)		
Kinase	DS-6051 (NTRK/ROS1) PLX7486 (FMS/TRK) PLX8394 (mBRAF) PLX9486 (mKIT)	Pexidartinib (FMS/KIT) GBM	Zelboraf® (BRAF) MM Adjuvant Tivantinib (MET) Quizartinib (FLT3) Pexidartinib (FMS/KIT) TGCT

ADC: Antibody Drug Conjugate

ADCC: Antibody Dependent Cellular Cytotoxicity

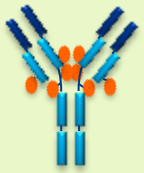
Small Molecule

Biologics

DS-8201: Phase 1

Innovative anti-HER2 antibody drug conjugate (ADC)

- **DS-8201 compared to T-DM1**



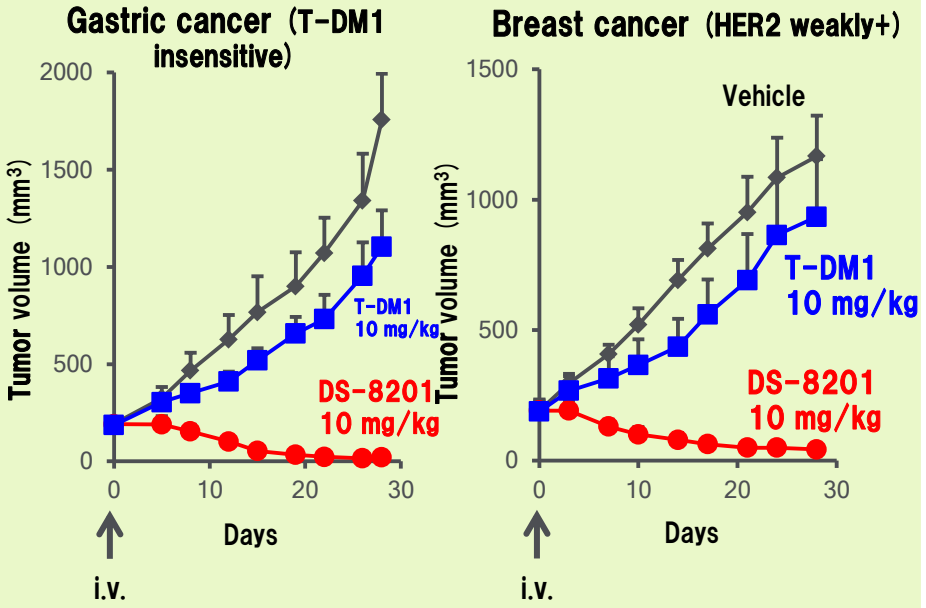
	DS-8201	T-DM1
Antibody	HER2 Ab	Trastuzumab
Conjugated toxin	Topoisomerase I inhibitor	Tubulin inhibitor
DAR*	7-8	3.5

*DAR: Drug to Antibody Ratio

- **Differentiation from T-DM1**
  - Different conjugated toxin
  - Original ADC technology
  - Higher drug to antibody ratio

- **Mechanism of action**
  - Ab binds HER2 receptor and is internalized
  - Conjugated toxin is released inside cell
  - Toxin causes targeted cell death

- **Patient-derived tumor xenograft models**



DS-8201demonstrated potent anti-tumor efficacy against:

T-DM1 insensitive model
HER2 weakly-positive model

Next Generation of DS Oncology Portfolio

Immune-oncology

- Immune checkpoint inhibitors
- Cell therapy

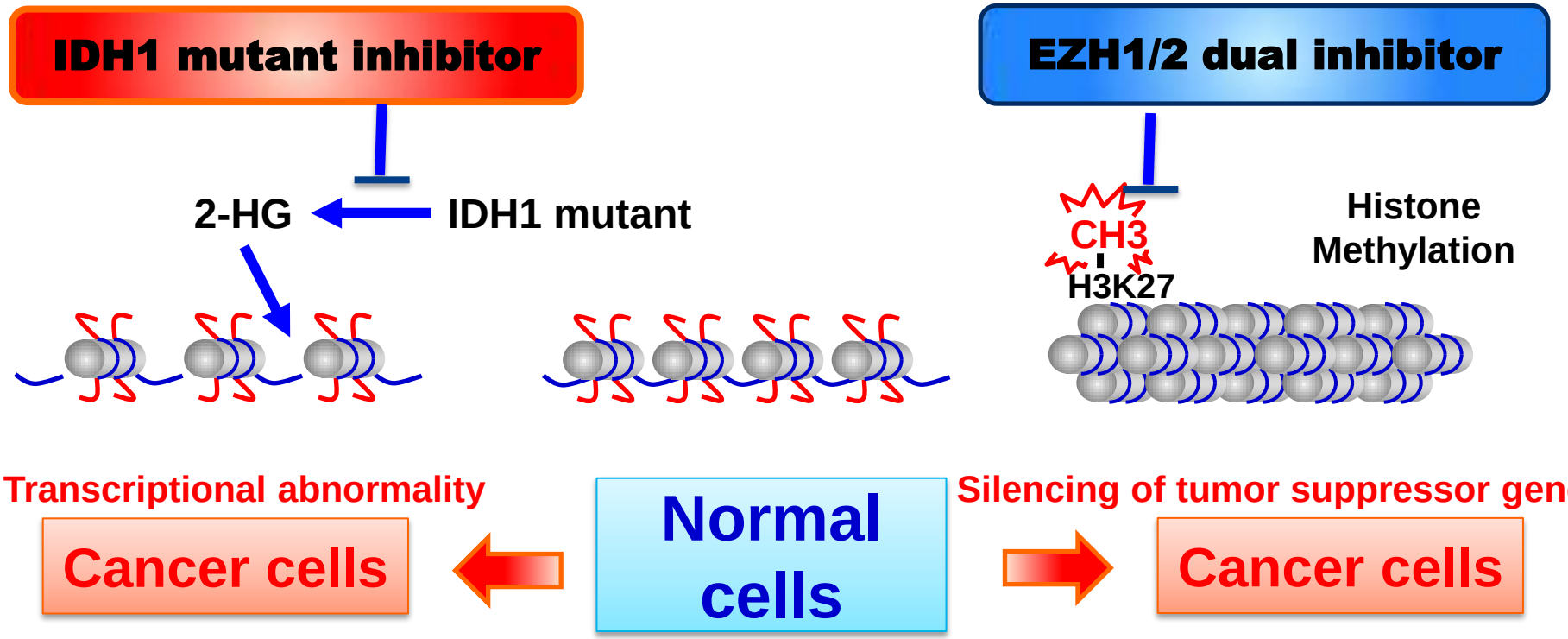
Epigenetics

- IDH1 mutant inhibitor
- EZH 1/2 inhibitor

Epigenetic Targeting of Cancer Cells

IDH1 mutant inhibitor and EZH1/2 dual inhibitor

- IDH1 mutant inhibitor decreases 2-hydroxyglutarate (2-HG) and improve transcriptional abnormality
- EZH 1/2 inhibitor decreases histone methylation and increases transcription of tumor suppressor genes
- Clinical studies of both inhibitors planned for 2016



Focus on Late Stage Oncology Projects

Four novel compounds targeting unique pathways in Phase 2/3 registration trials

Quizartinib (Ph3)

Acute myeloid leukemia (AML)

Pexidartinib (Ph3)

Tenosynovial giant cell tumor (TGCT)

Tivantinib (Ph3)

Hepatocellular carcinoma (HCC) in partnership with ArQule

Patritumab (Ph2/3)

Non-small cell lung cancer (NSCLC)

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Quizartinib

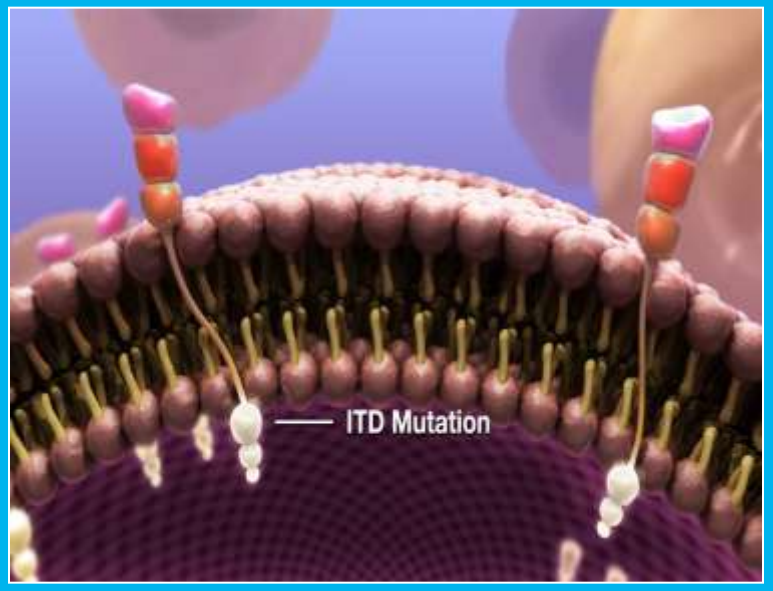
Investigational FLT3 Inhibitor

Acute Myeloid Leukemia (AML)

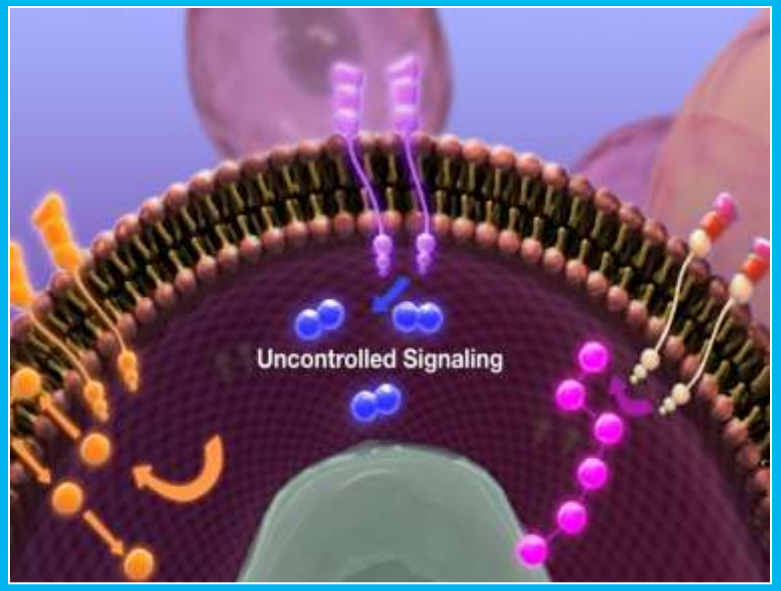
Granted Orphan Drug Designation by the FDA and EMA

Granted Fast Track Status by the FDA

Quizartinib: a Selective Inhibitor of ITD mutated FLT3 receptor



Reference:
Levis M, et al. Leukemia. 2003;17:1738-52.



Reference:
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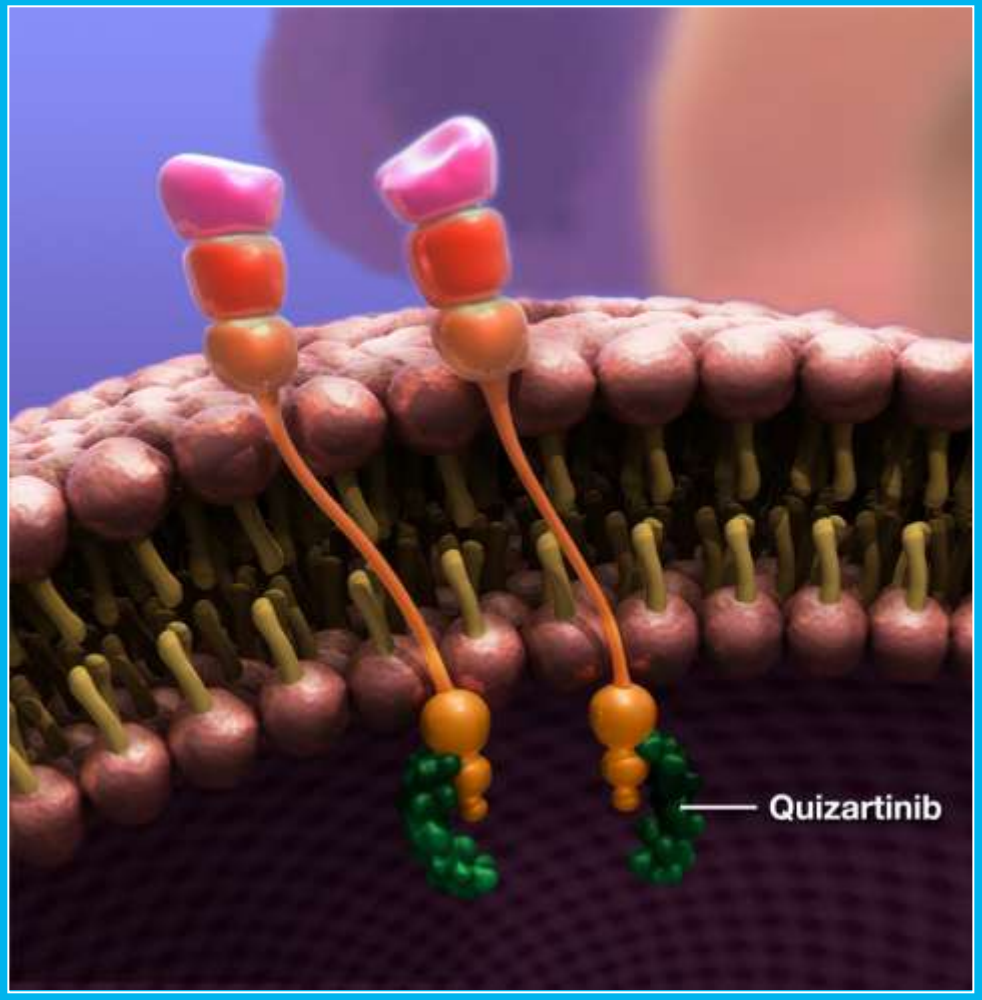
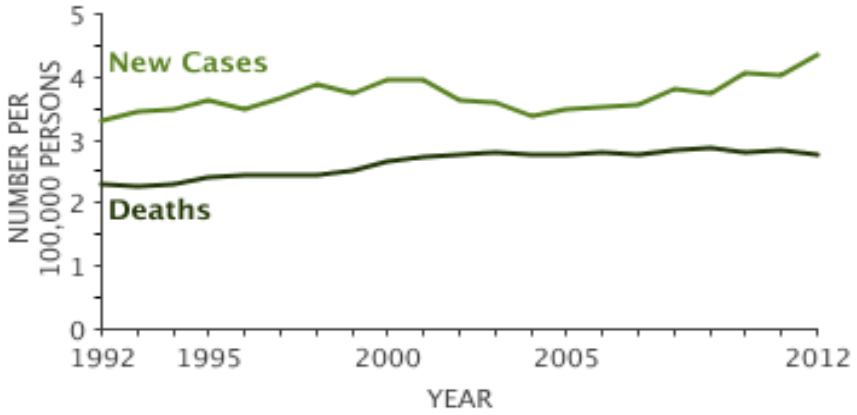


References:
Zarrinkar PP, et al. Blood. 2009;114(14):2984-92.
Sexauer A, et al. Blood. 2012;120(20):4205-14.

Acute Myeloid Leukemia

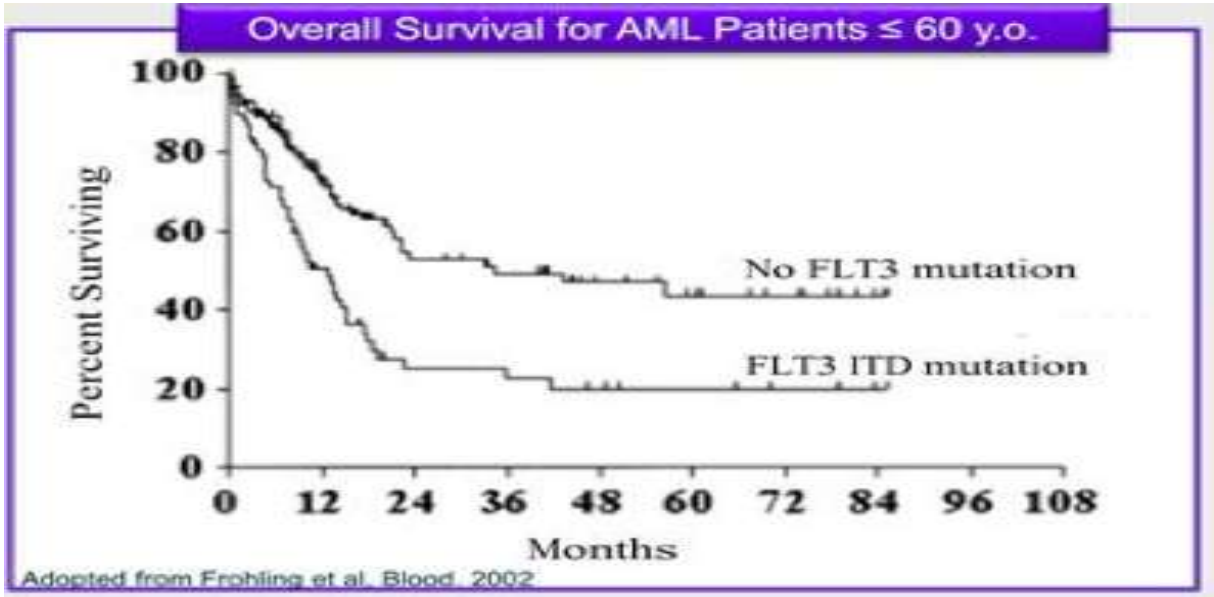
- Epidemiology in US

Estimated New Cases in 2015	20,830
% of All New Cancer Cases	1.3%
Estimated Deaths in 2015	10,460
% of All Cancer Deaths	1.8%

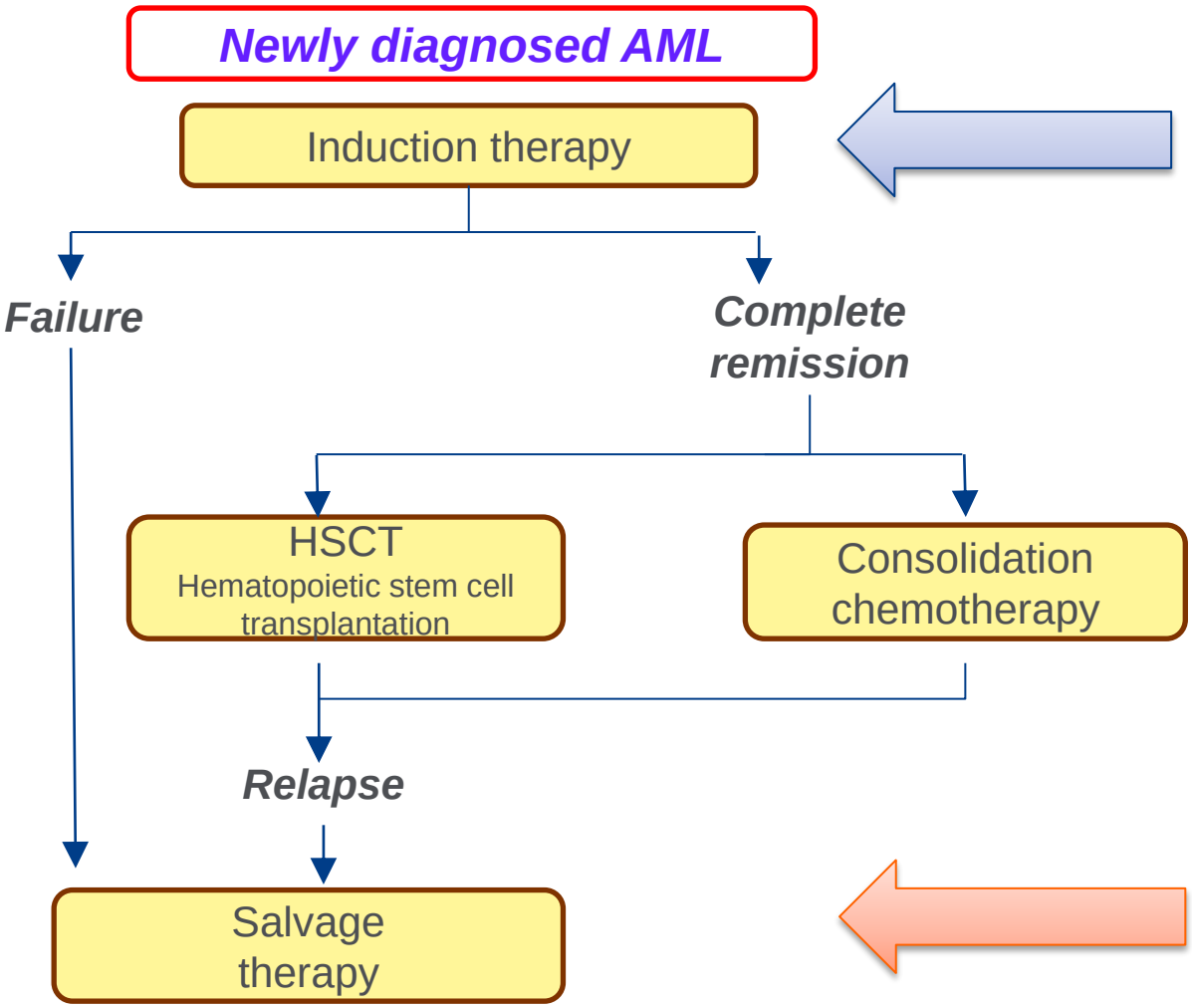


Percent Surviving 5 Years
25.9%
2005–2011

FLT3-ITD mutation: 23% of AML
survival rate lower than patients without this mutation

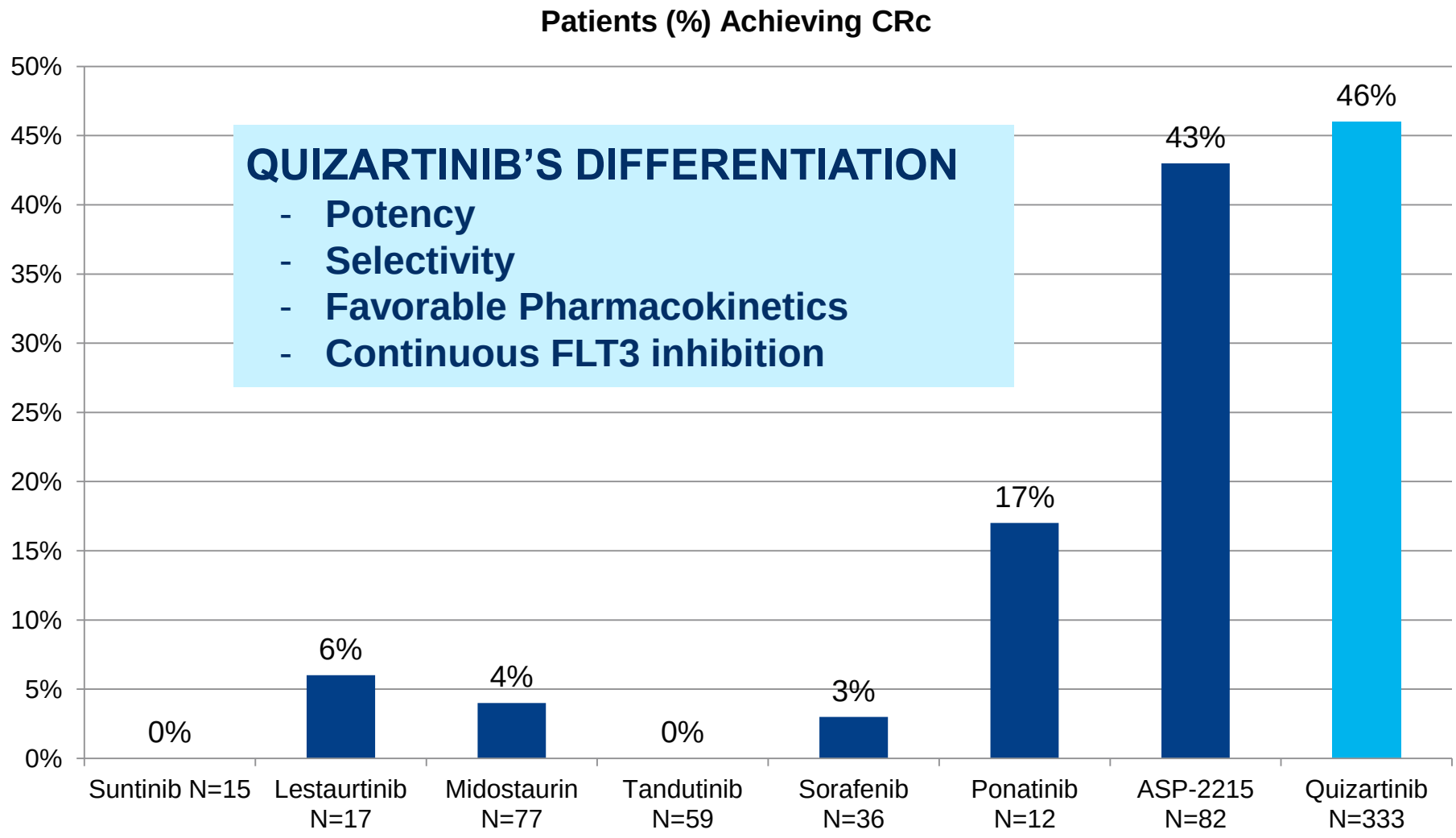


Paradigm for the Treatment of AML



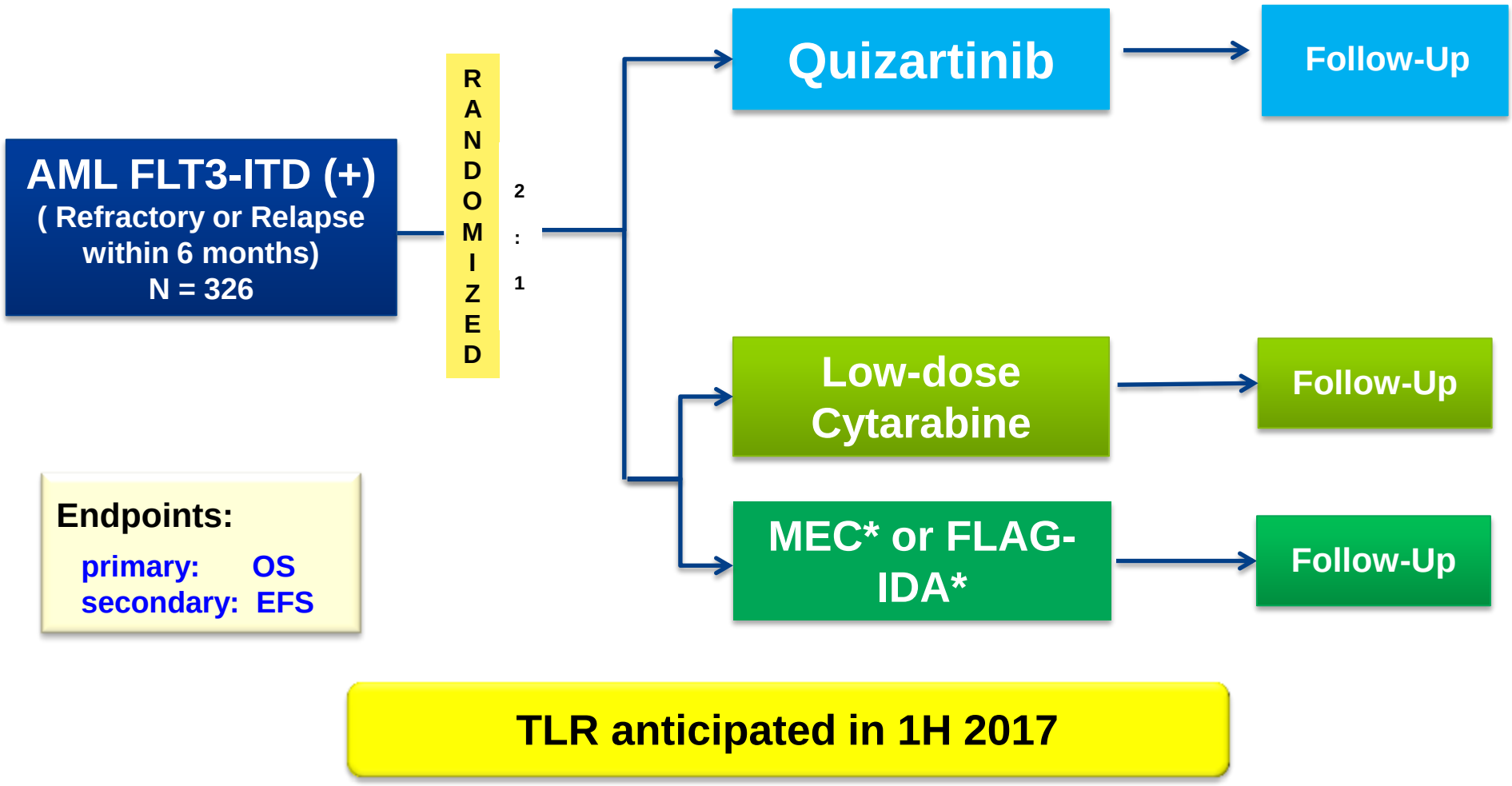
Quizartinib: Effect in FLT3-ITD(+) AML

Observed Response Rate for specific and non-specific FLT3 Inhibitors Administered as a Single Agent in FLT3-ITD(+) AML



Modified from Ambit Presentation & Knapper, S., 2011 and ASCO 2015

Quizartinib: QuANTUM-R Phase 3 Study



MEC: mitoxantrone, etoposide, and intermediate-dose cytarabine
FLAG-IDA: fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin

https://clinicaltrials.gov/show/NCT02039726

Plans to Maximize Value of Quizartinib

Ongoing program

QuANTUM-R (US, EU, Asia)

NDA

Approval

Planning Phase

JP study

1st line therapy

FY2014 | FY2015 | FY2016 | FY2017 | FY2018 | FY2019 | FY2020 -

Summary of Quizartinib

Highly Selective Treatment for Relapsed Refractory AML

- **Targeted therapy against ITD mutated FLT3 receptor**
- **Once daily oral dosing**
- **Well tolerated outpatient treatment**
- **Overall survival in Phase 2: 6 months**

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Compassion for Patients.™

Pexidartinib： PLX3397

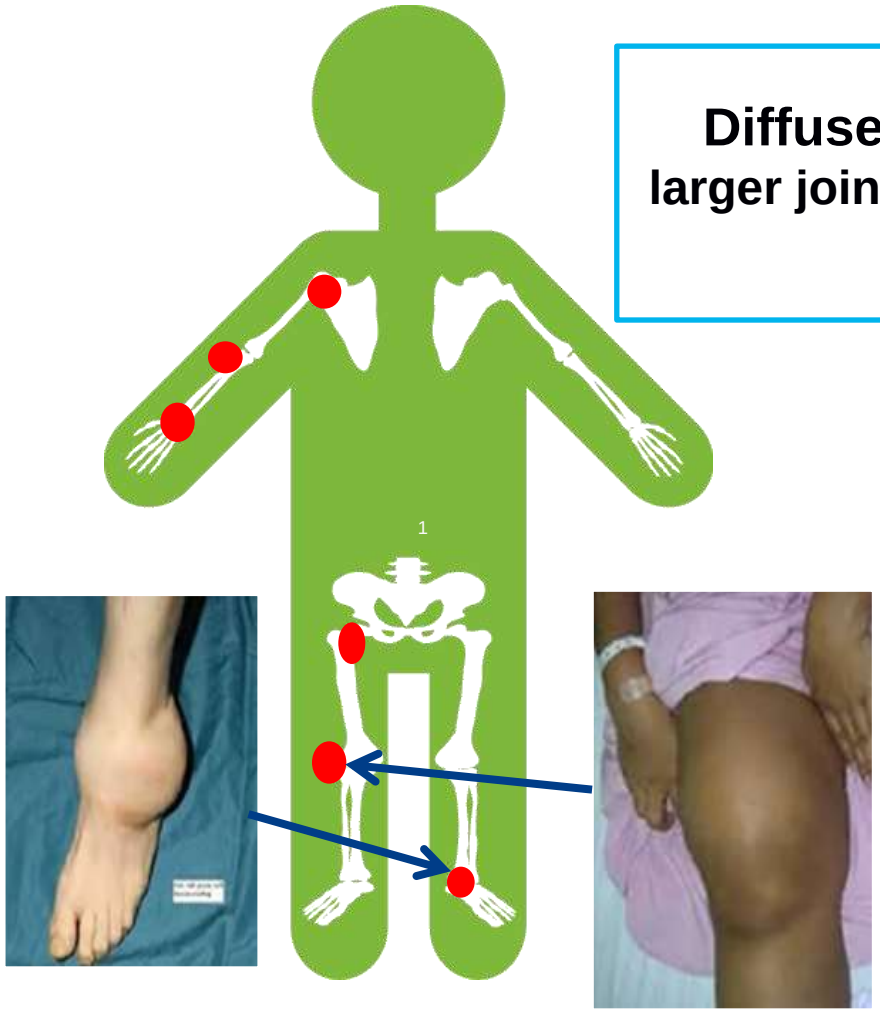
Investigational CSF-1R Inhibitor

Tenosynovial Giant Cell Tumor (TGCT)

Granted Orphan Drug Designation by the FDA and EMA

Granted Breakthrough Therapy designation by FDA

No Approved Systemic Therapies for TGCT



Diffuse TGCT: a rare disease that affects larger joints such as knee, hip, ankle, shoulder, elbow[1]

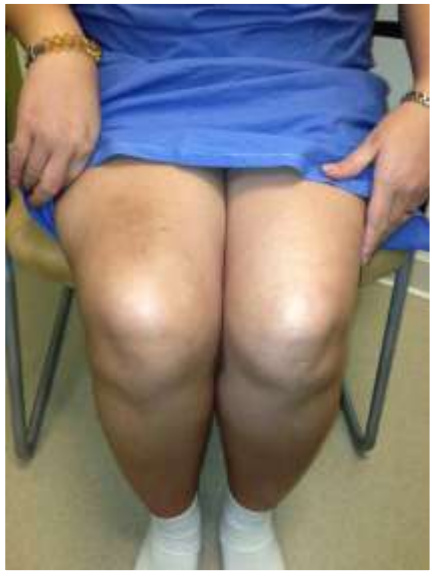
75% of diffuse cases involve the knee

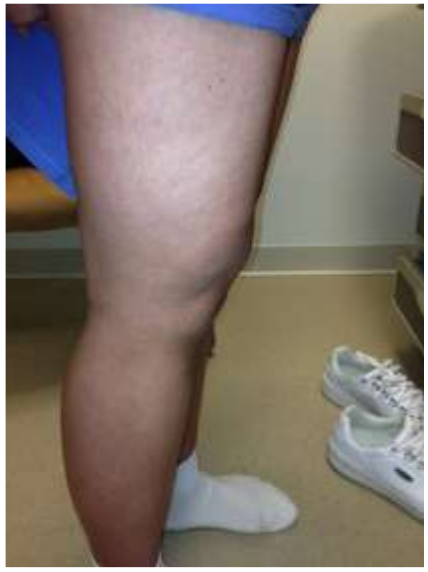
Recurrent, diffuse TGCT may require multiple surgeries and even amputation

[1]*Ravi V, et al. Curr Opin Oncol. 2011;23:361-6*

Early Results in Treatment of TGCT

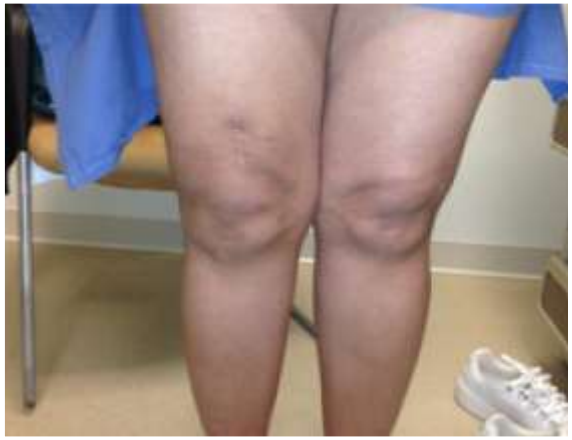
4 months on pexidartinib





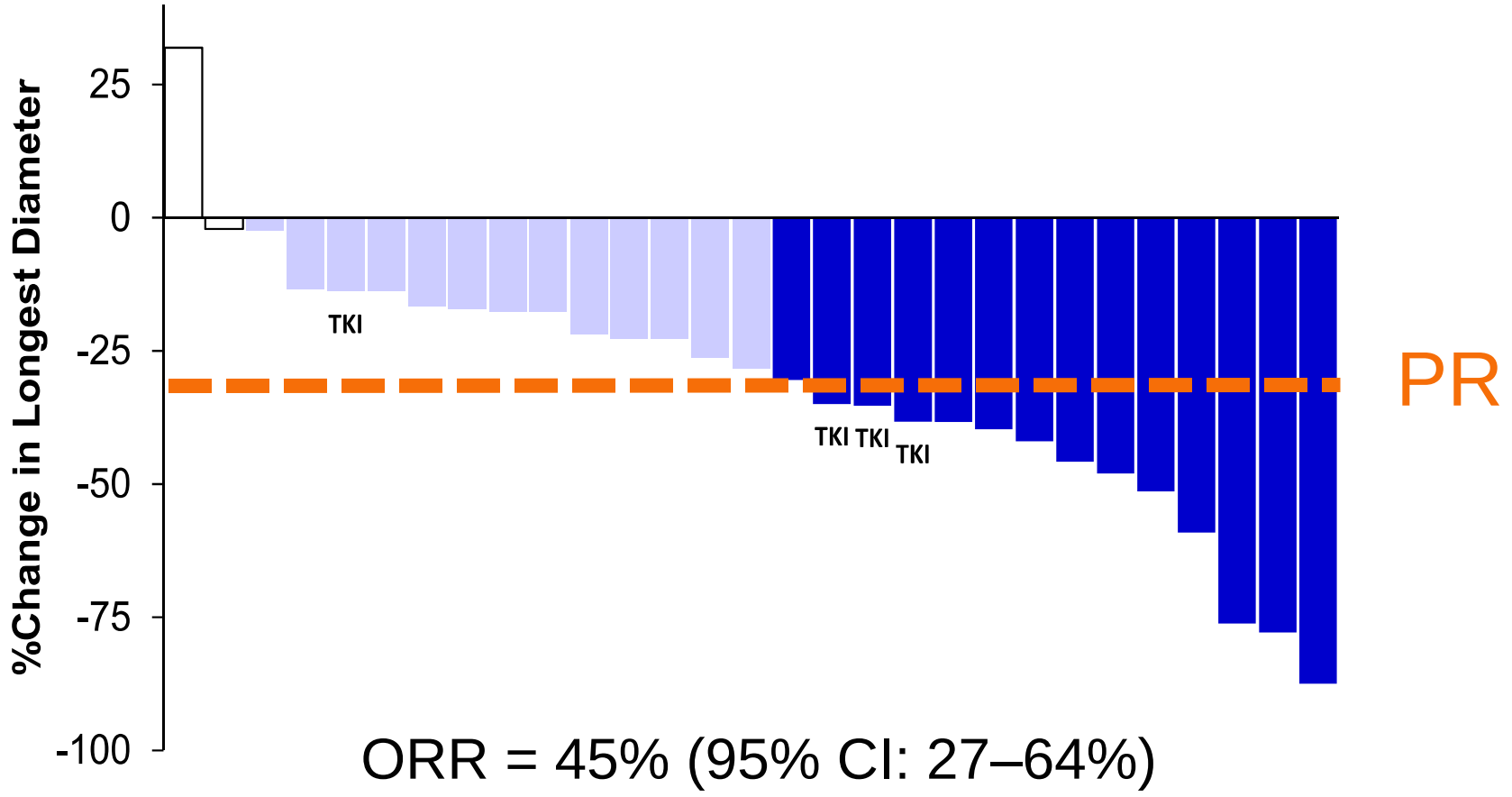
Walking with cane
Unable to straighten knee
Narcotics for pain
Unable to work
Amputation considered

Walking unassisted
Improved range of motion
Off narcotics
Back to work



Tap et al, ASCO 2014

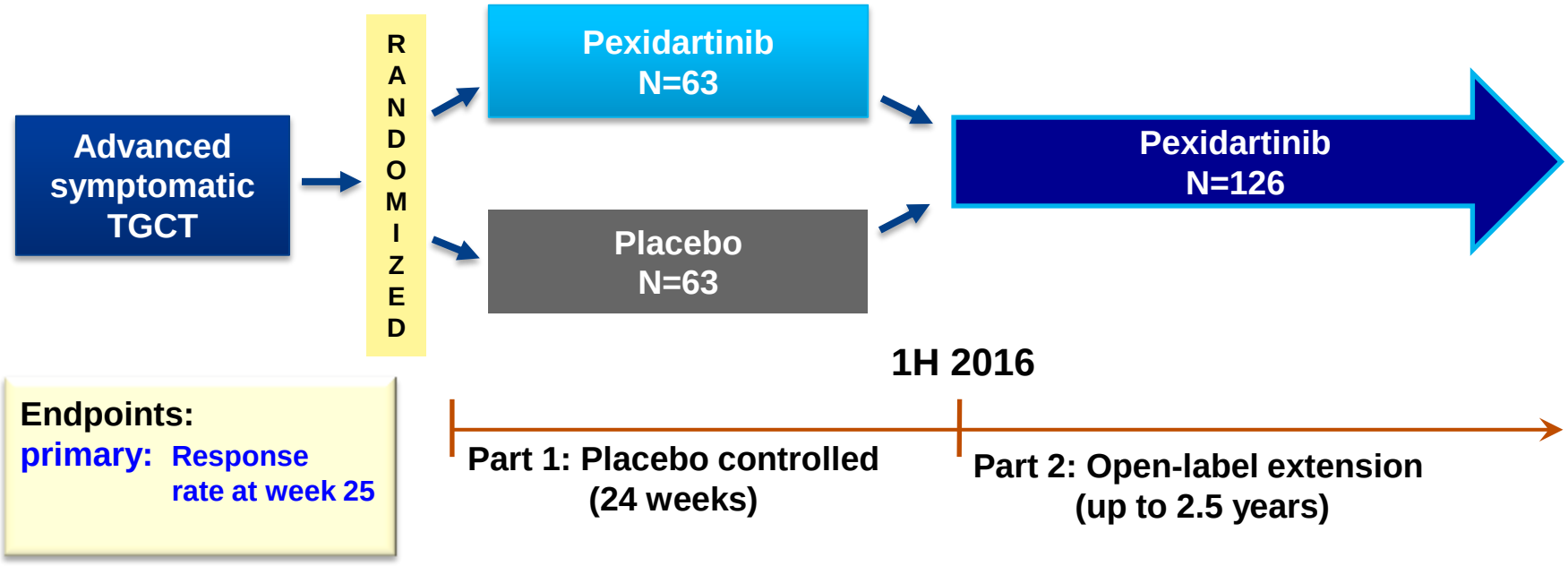
Efficacy Evaluation by RECIST 1.1 Criteria



PR: Partial Response

Tap *et al,* NEJM 2015

Pexidartinib: Phase 3 Study Design



Endpoints:
primary: Response rate at week 25

TLR anticipated in 1H 2018

https://clinicaltrials.gov/show/NCT02371369

Target Population of Phase 3 Study

- **Treatable patients in the US, EU and Japan are estimated to be around 38,000**
  - **Often under-diagnosed**
  - **Affected patients have normal life expectancy**
- **High unmet need**
  - **High morbidity**
  - **No systemic therapies approved**

Further Investigations of Pexidartinib

Collaboration with Merck :

Pexidartinib in combination with anti-PD-1 therapy for advanced melanoma and multiple other solid tumors

Other potential indications :

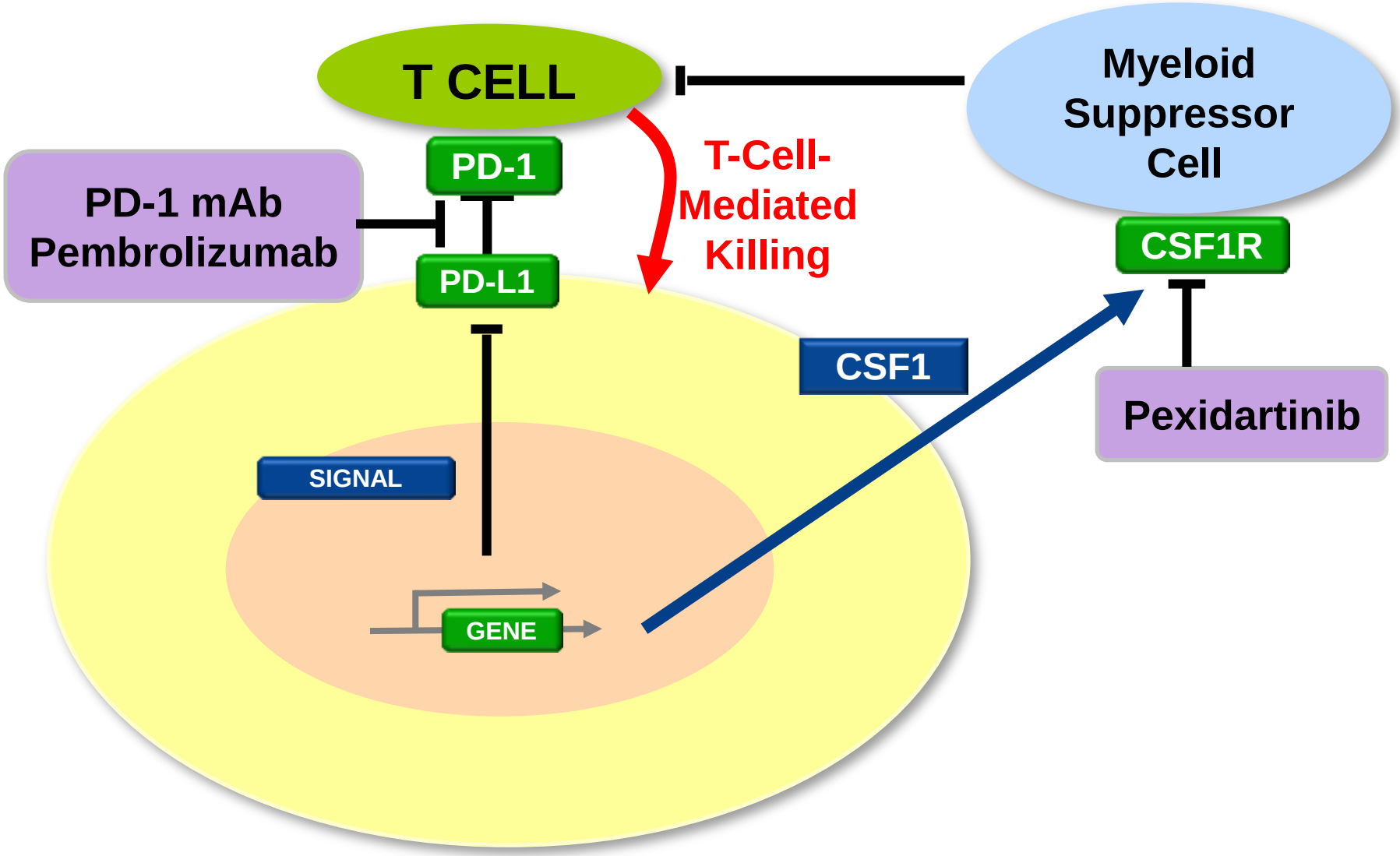
Glioblastoma

Ovarian cancer

Breast cancer

Sarcomas

Pexidartinib in Combination with anti-PD-1 Therapy for Advanced Solid Tumors



Combination study of Pexidartinib and Pembrolizumab

Phase 1 / 2a study outline

	Part 1: Dose-escalation phase	Part 2: Expansion phase
Dose	Pexidartinib: dose escalation + Pembrolizumab: 200 mg every 3wks	Pexidartinib: RP2D + Pembrolizumab: 200 mg every 3wks
Target patients for enrollment	Advanced solid tumors N=24	Advanced melanoma (+ other Solid tumors) N=376
Outcome measures	Primary: Safety during 1 year treatment Secondary: Objective response rate (rate of a complete response or partial response relative to historical control)	

TLR for part 2 anticipated in 2H 2019

RP2D=Recommended phase 2 Dose

https://clinicaltrials.gov/show/NCT02452424

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Tivantinib

Investigational MET Inhibitor for treatment of Hepatocellular Carcinoma (HCC)

Daiichi-Sankyo

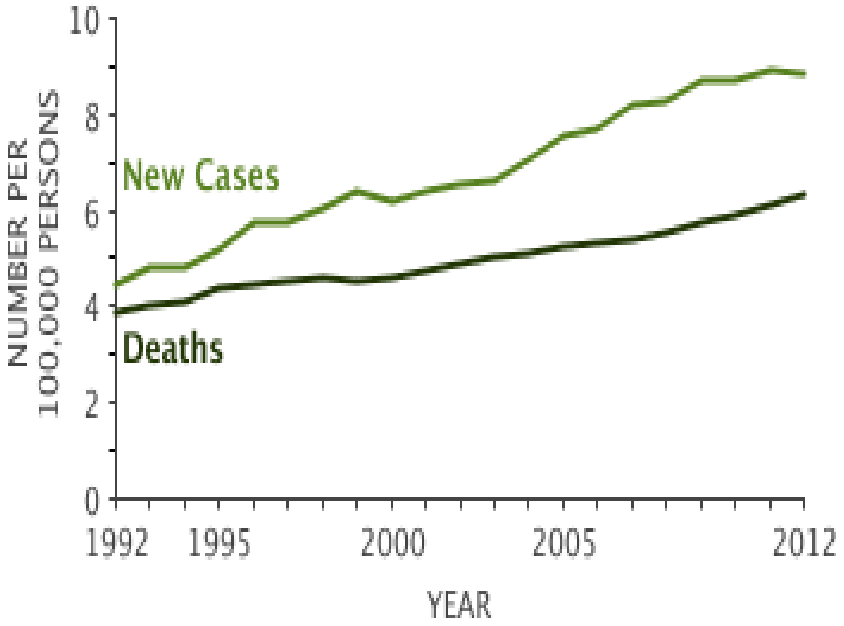
ArQule

Granted Orphan Drug Designation by FDA and EMA

Liver and Intrahepatic Bile Duct Cancer

- Epidemiology in US[1)]

Estimated New Cases in 2015	35,660
% of All New Cancer Cases	2.2%
Estimated Deaths in 2015	24,550
% of All Cancer Deaths	4.2%



Percent Surviving 5 Years
17.2%
2005-2011

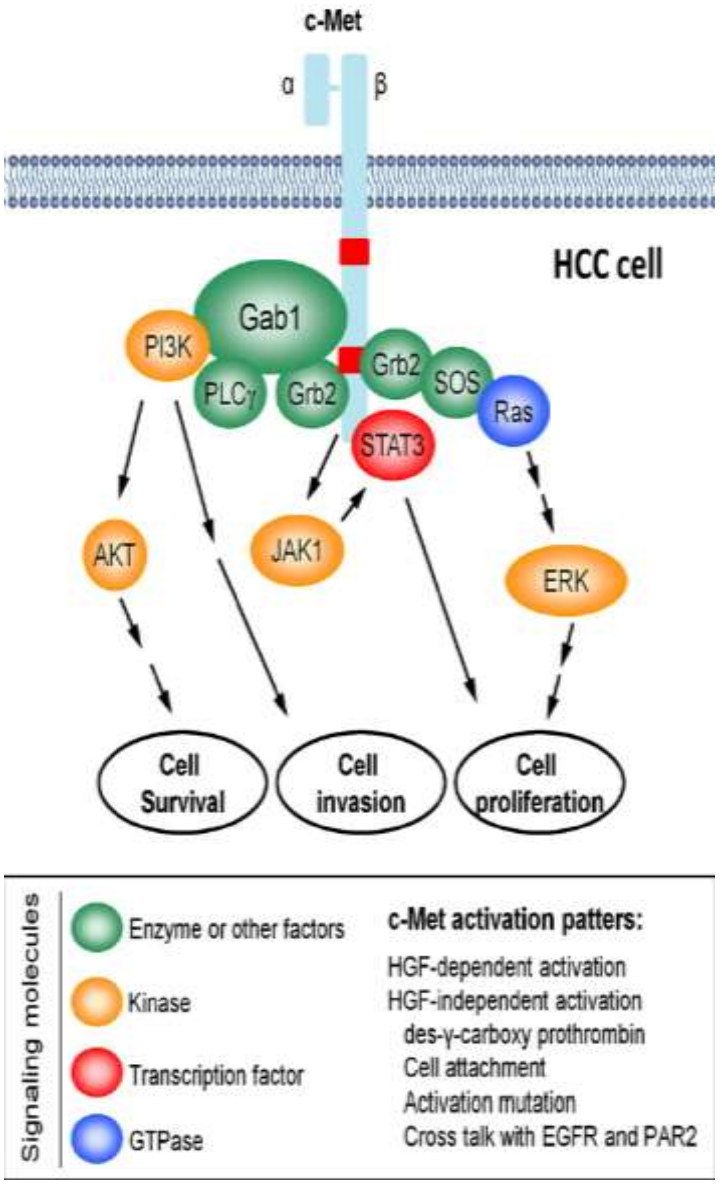
1) http://seer.cancer.gov/statfacts/html/livibd.html accessed 17 Nov 2015

Tivantinib: Selective, oral MET inhibitor

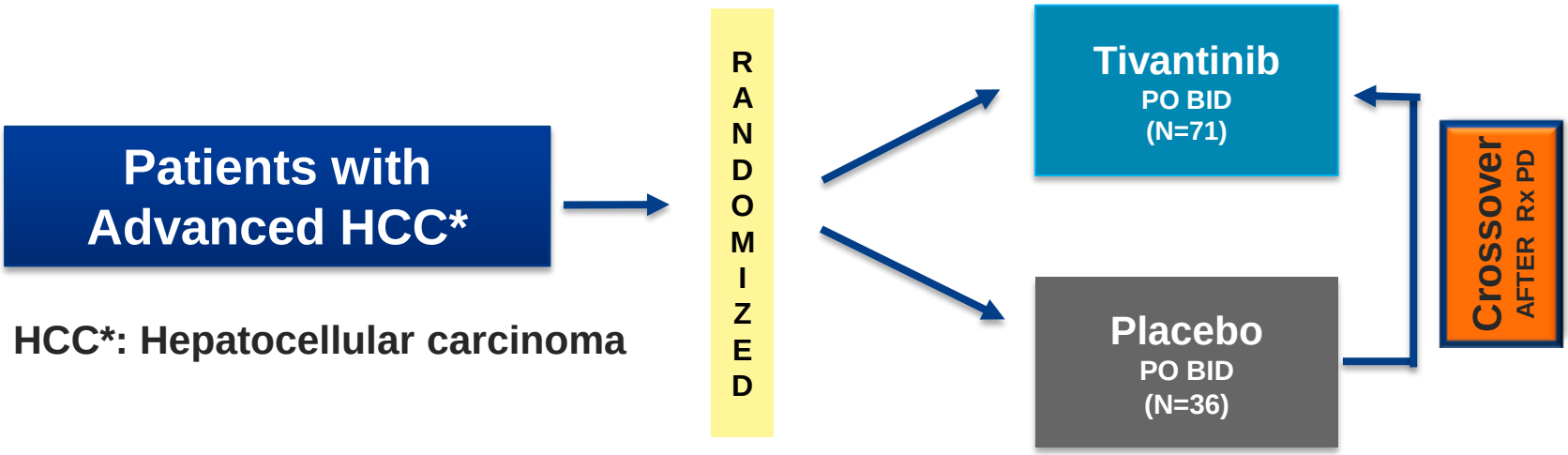
Role of MET in HCC

- MET is the only receptor for hepatocyte-growth factor (HGF) leading to :
  - Cell survival
  - Cell invasion
  - Cell proliferation

- MET expression is correlated with poor prognosis in patients with HCC



Tivantinib: Phase 2 Study in 2nd line HCC



HCC*: Hepatocellular carcinoma

Endpoints:

- **primary:** TTP
- **secondary:** PFS, OS, ORR
- **tertiary:** TTP, PFS, OS in subgroups by MET Diagnostic status (high vs low levels)

Lancet Oncol 2013;14:55-63

Successful Results of the Phase 2 Study

- Treatment with Tivantinib met the primary endpoint of the study, with a 56% improvement in TTP (data not shown here)
  - TTP: HR=0.64 p=0.04
- Pronounced benefit was observed in patients with high expression of MET
  - TTP: HR = 0.43 p= 0.03
  - OS: HR = 0.38 p= 0.01
- These are the first randomized data in HCC showing OS advantage with a MET inhibitor and identifying a subgroup responding to a targeted therapy

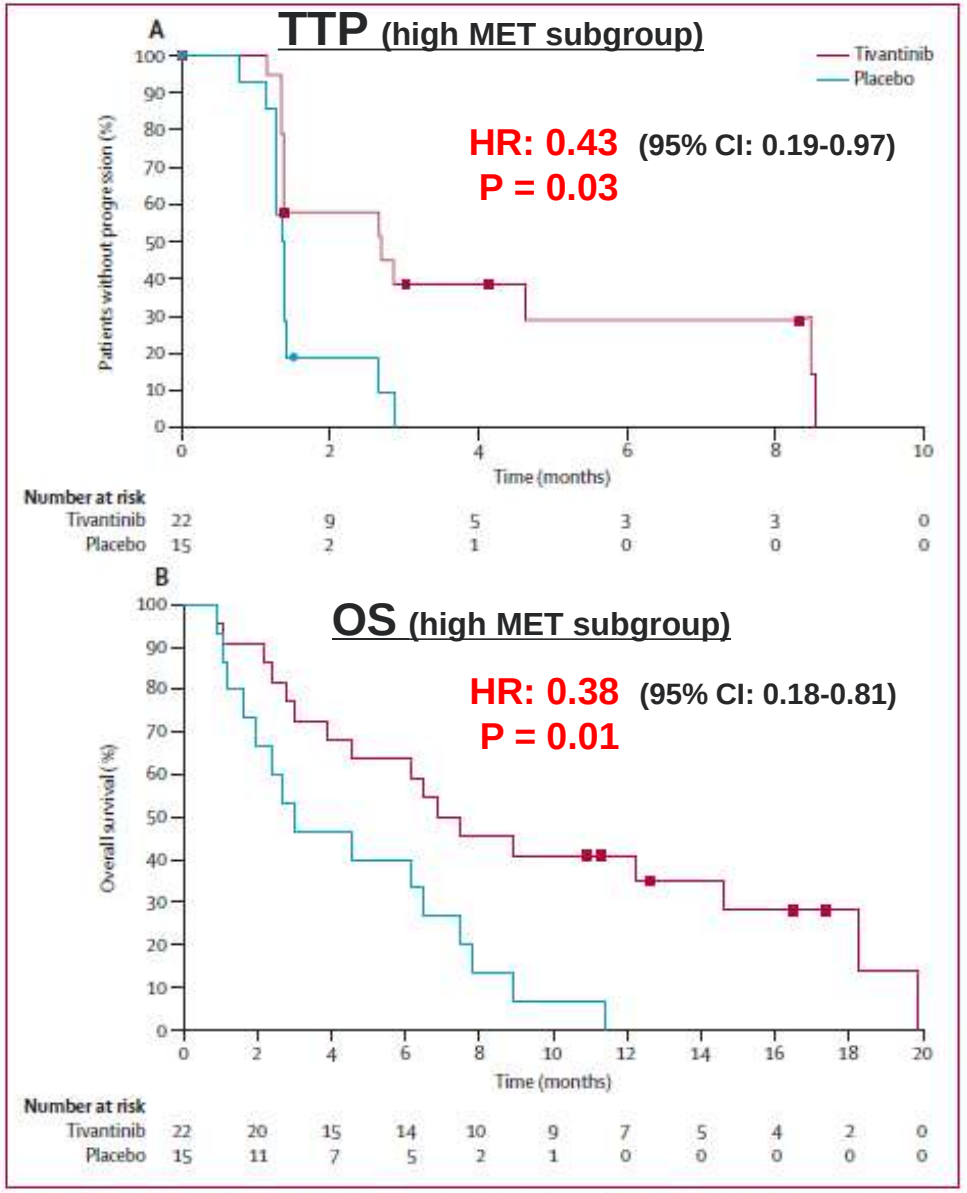
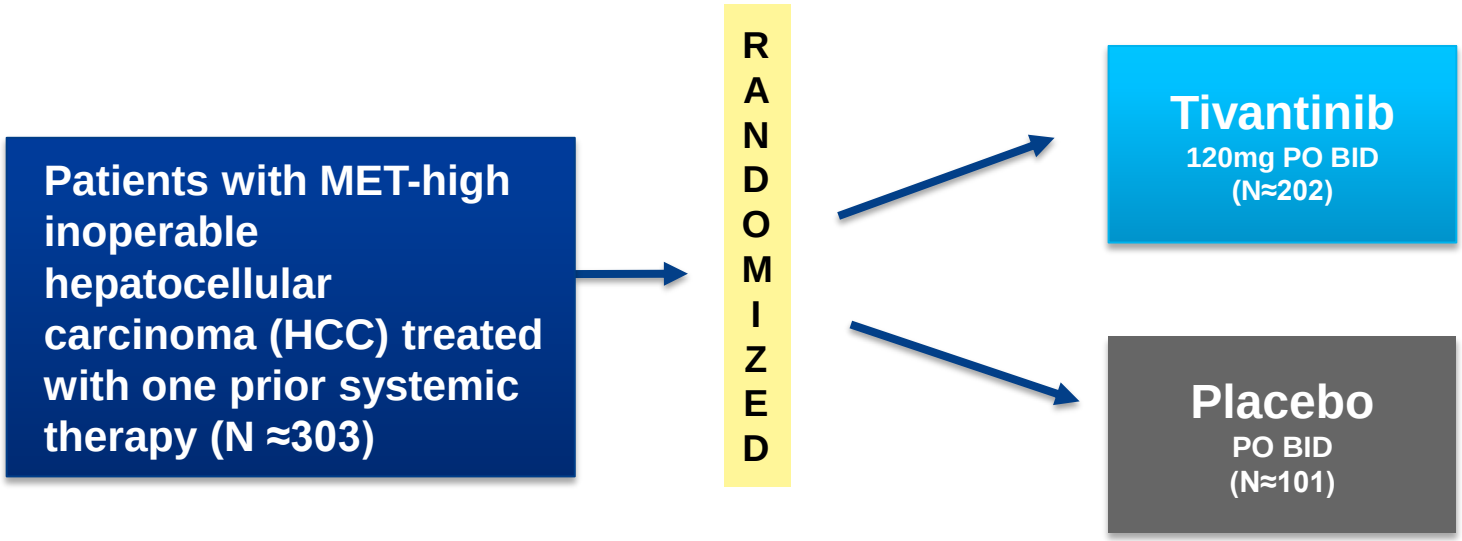


Figure 4: Kaplan-Meier estimate of time to progression (A) and overall survival (B) in the MET-high subgroup
Squares and circles represent censoring of data.

Lancet Oncol 2013;14:55-63

Tivantinib: METIV-HCC Phase 3 design



Endpoints:

primary: OS

secondary: PFS, safety

TLR anticipated in 1H 2017

https://clinicaltrials.gov/show/NCT01755767

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Patritumab

Investigational Anti-HER3 Monoclonal Antibody

Non-Small Cell Lung Cancer (NSCLC)

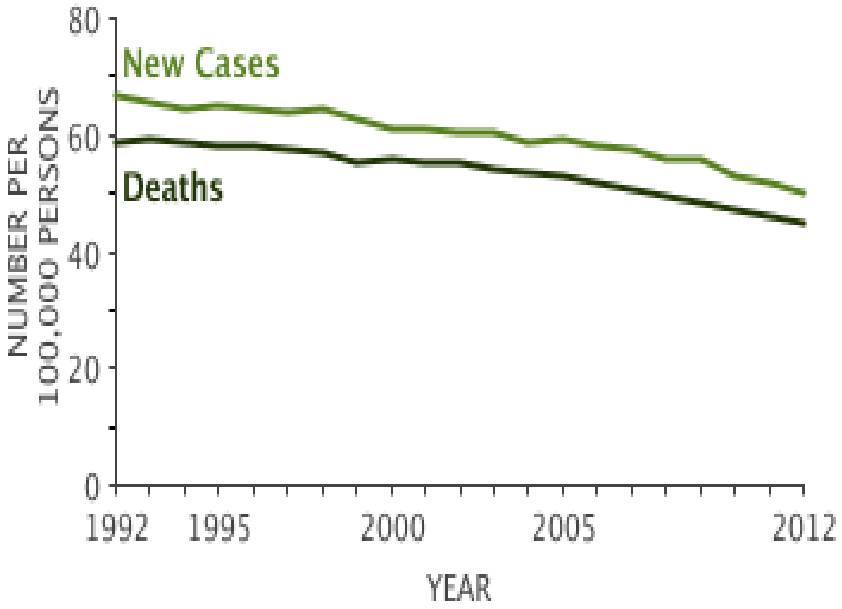
Head and Neck Cancer (H&N)

Daiichi-Sankyo

Lung and Bronchial Cancer

- Epidemiology in US[1)]

Estimated New Cases in 2015	221,200
% of All New Cancer Cases	13.3%
Estimated Deaths in 2015	158,040
% of All Cancer Deaths	26.8%

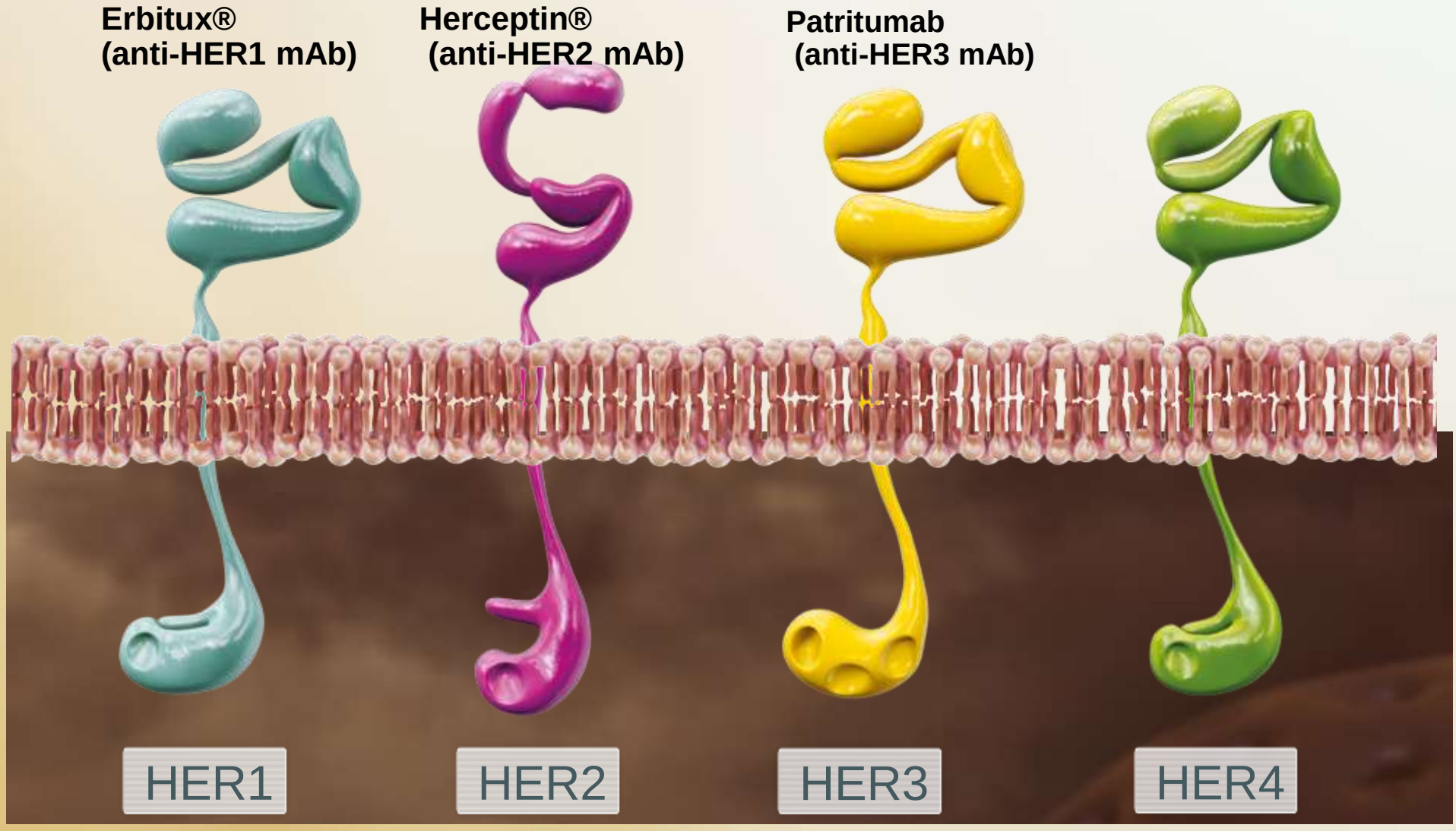


Percent Surviving 5 Years
17.4%
2005–2011

1) http://seer.cancer.gov/statfacts/html/alyl.html accessed 17 Nov 2015

The HER Family

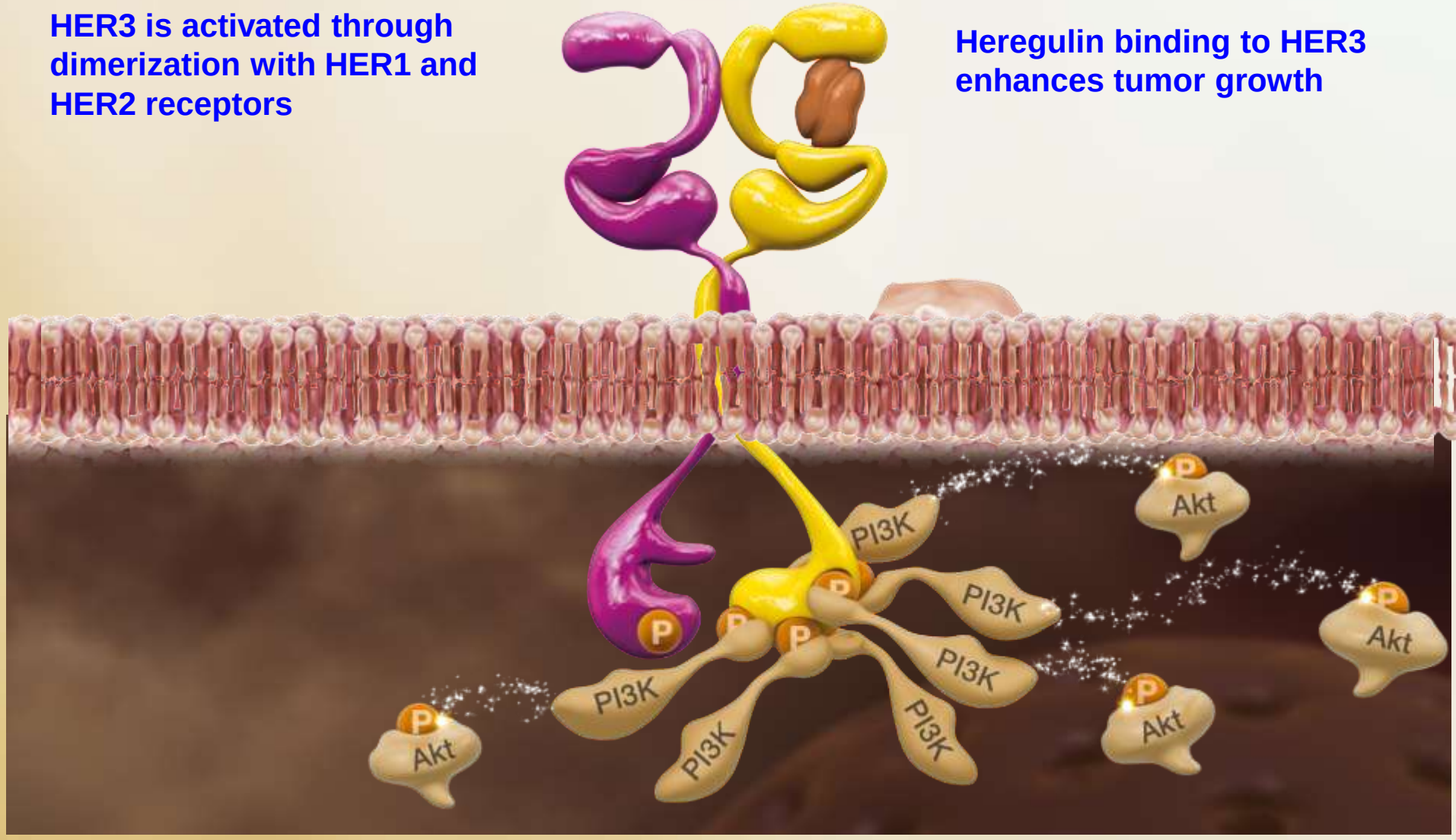
(human epidermal growth factor receptors)



Unique Property of HER3: Escape from Growth Inhibition associated with Current Treatments

HER3 is activated through dimerization with HER1 and HER2 receptors

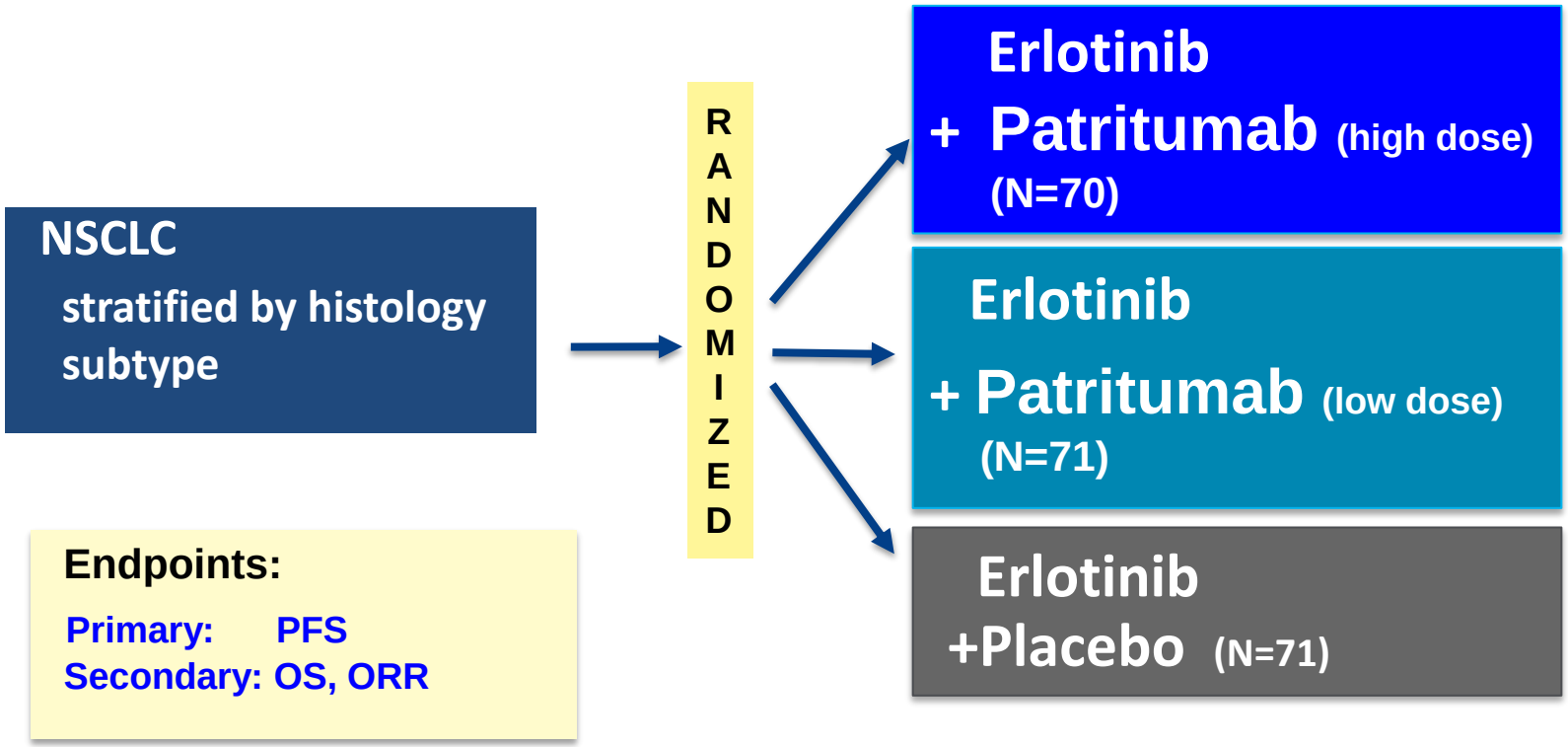
Heregulin binding to HER3 enhances tumor growth



Phase 2: HERALD Study Design

Subjects with Advanced NSCLC Who Have Progressed on at Least One Prior Chemotherapy

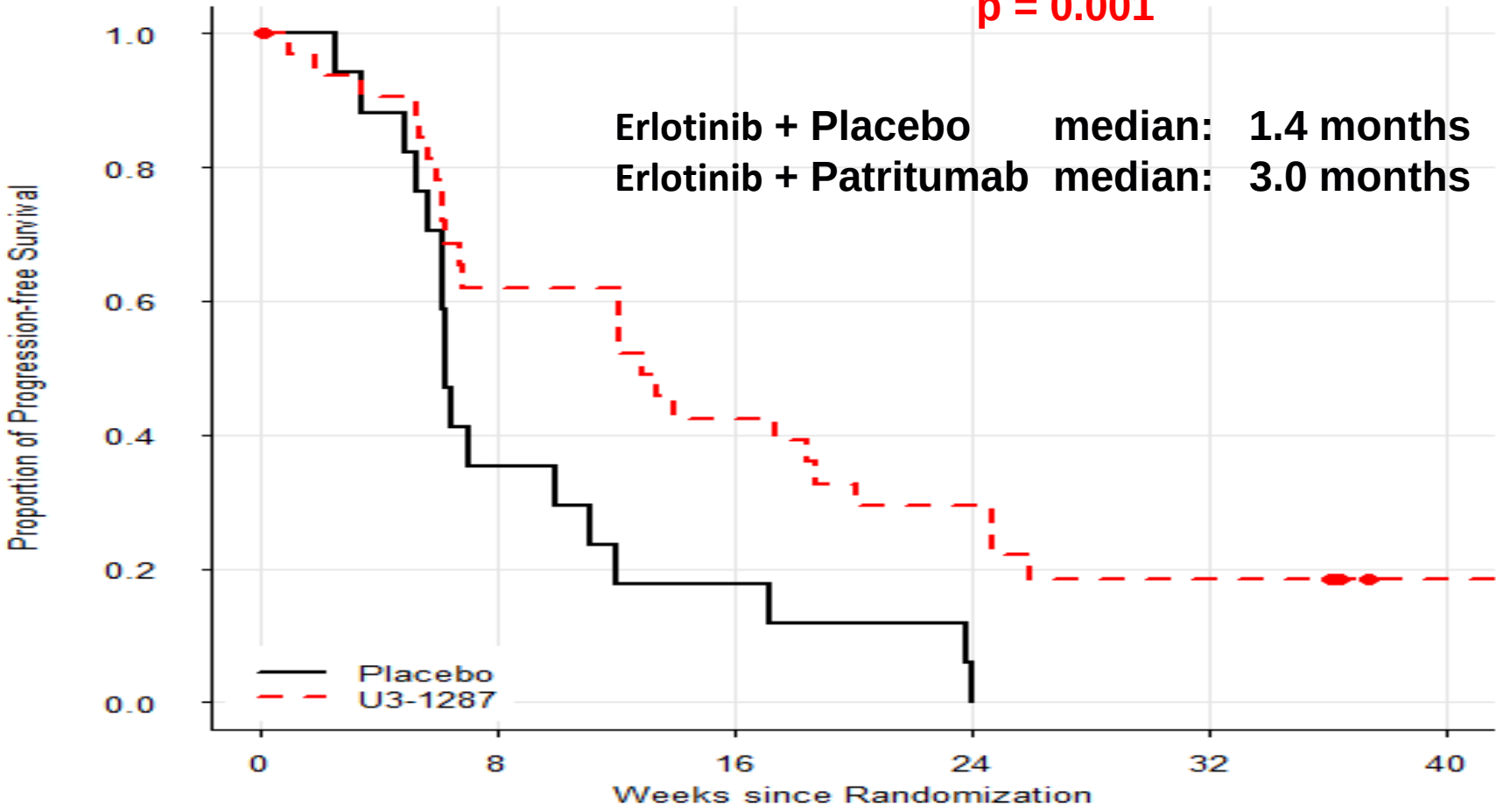
- **Biomarker Hypothesis : Patritumab will have the greatest benefit in patients with high expression of the HER3 ligand heregulin**



HERALD: PFS in patients with High levels of Heregulin

Daiichi-Sankyo

Patritumab vs placebo HR = 0.32 (95% CI: 0.16, 0.67)
p = 0.001

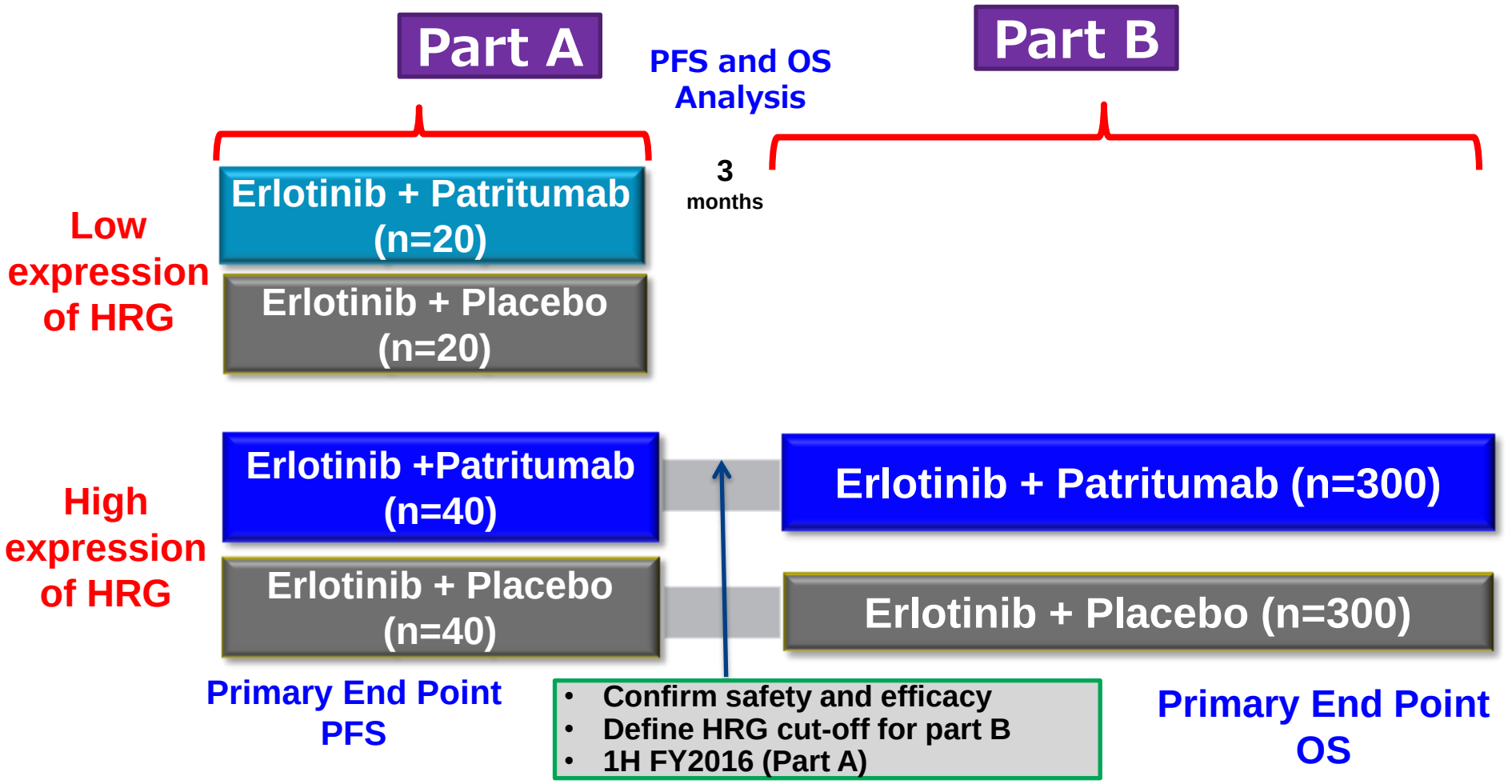


Biomarker positive group showed significant improvement in PFS

Joachim von Pawel et al. ASCO Annual Meeting 2014

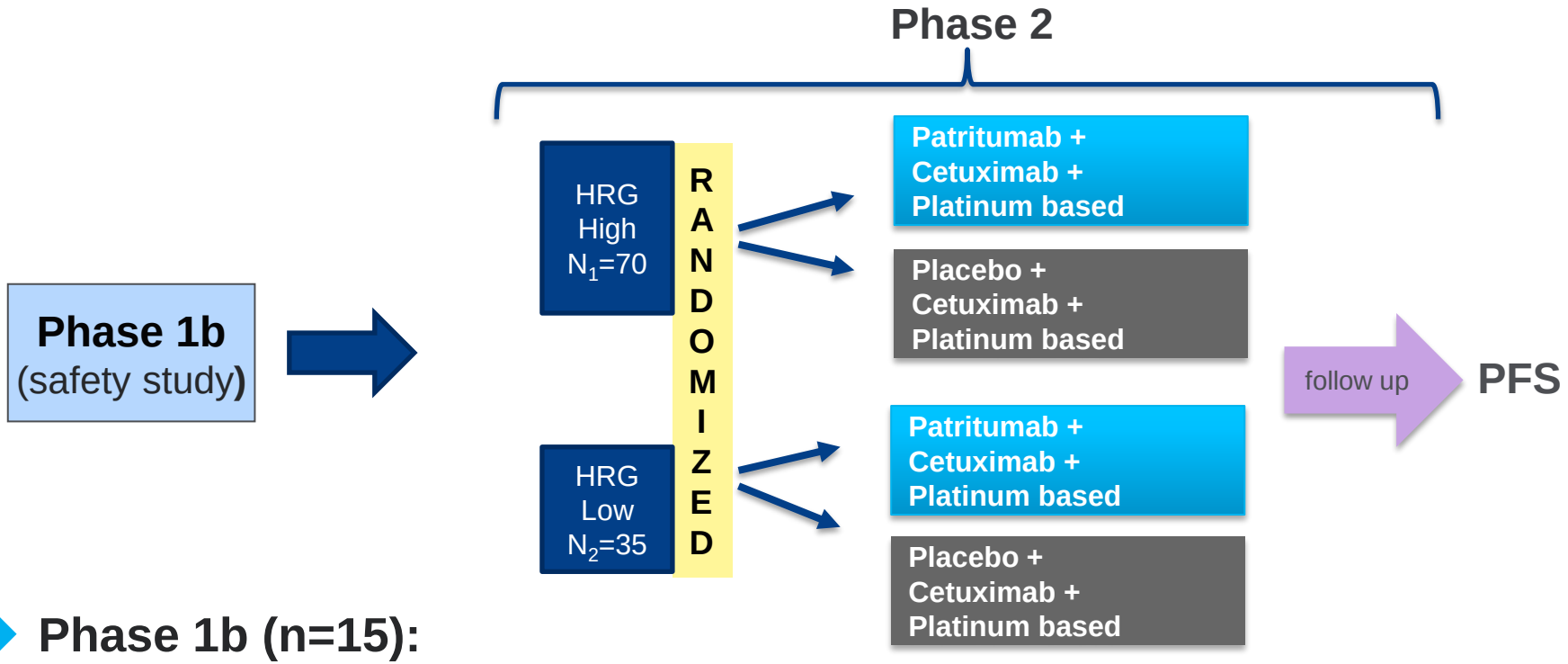
Patritumab: HER3 Lung Trial

2 Part Phase 2b / 3 Study



TLR (Part B) anticipated in 2H 2018

Patritumab: Head & Neck Cancer Indication



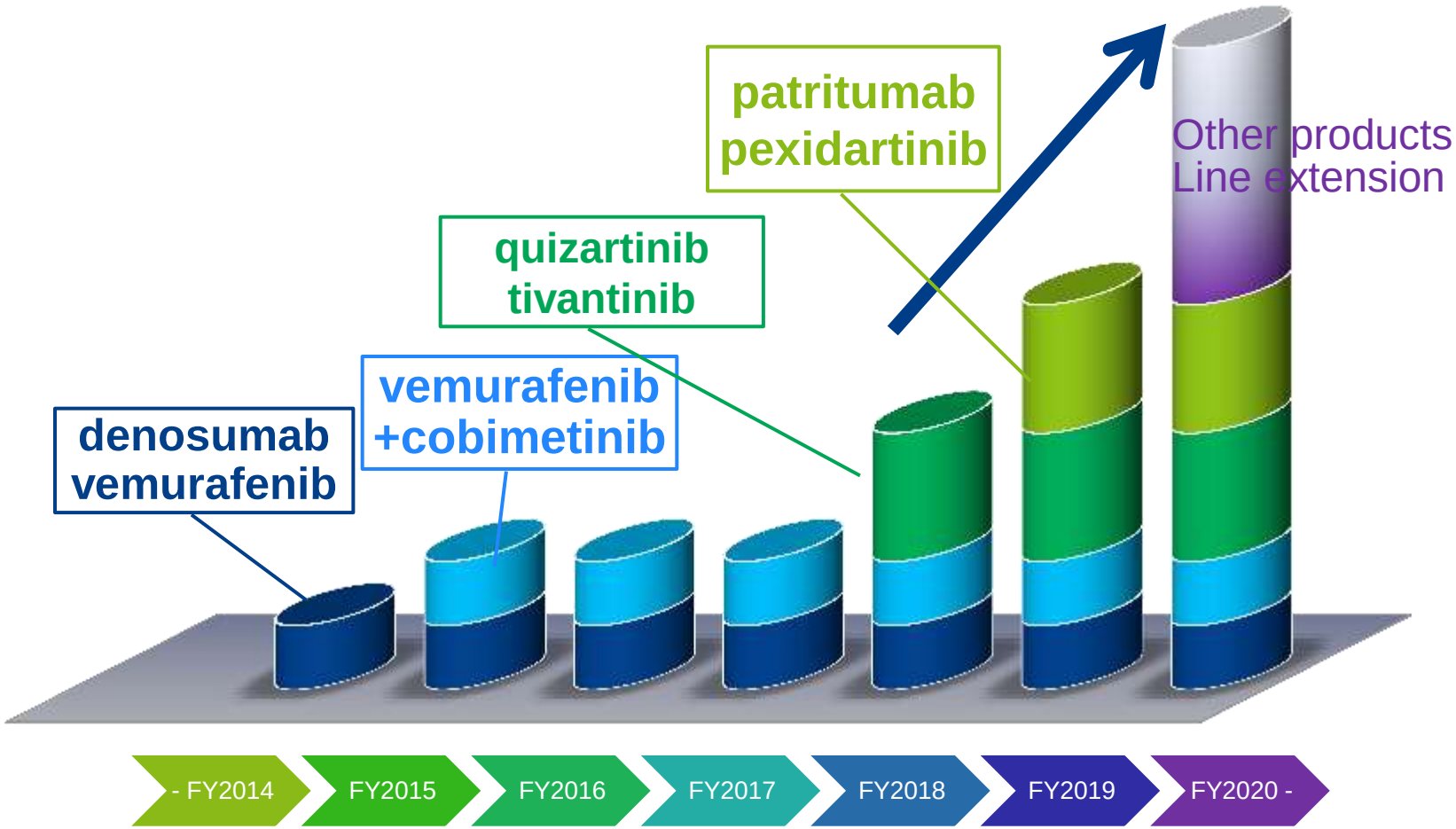
- **Phase 1b (n=15):**
  - Patients: R/M Head and Neck Cancer 1st Line
  - Cetuximab + Platinum chemo+ Patritumab
  - Enrollment completed
  - Results will be published in 1H 2016

- **Phase 2 (n=105)**
  - Enrollment to begin December 2015
  - 2:1 randomization: high vs low HRG

https://clinicaltrials.gov/show/NCT02350712

Launch Timeline of DS Pipeline in Oncology

Oncology pipeline is a key driver for DS future growth



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Thank you

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