Personalized Healthcare (PHC) Approach in Chugai

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October 28, 2011

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the "Company"). These statements reflect the Company's current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company's businesses.

Concept of Personalized Healthcare: PHC

A heterogeneous group → Stratified to homogeneous groups

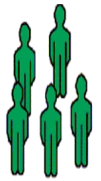
Method for stratification to specific properties

Biomarkers

One therapy (medicine) for all

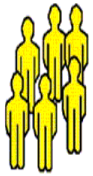
Efficacy (-)
Risk of adverse response (AR) (+)

Standard therapy as of today

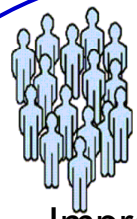


Efficacy (+)
Risk of AR (+)

Efficacy (-)
Risk of AR (+)



Efficacy (-)
Risk of AR (-)



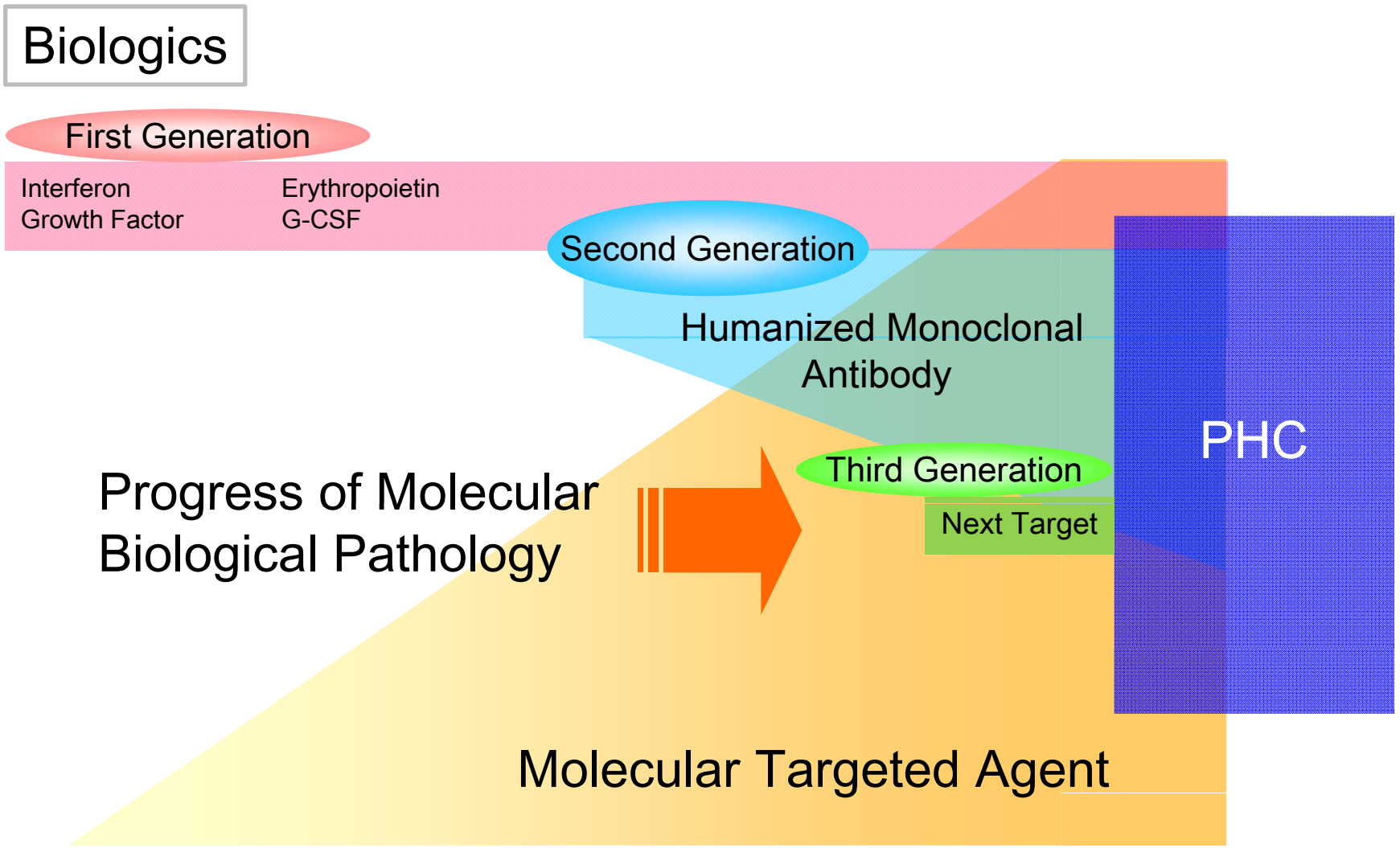
Efficacy (+)
Risk of AR (-)

Tailored therapy

Improving quality of the therapy

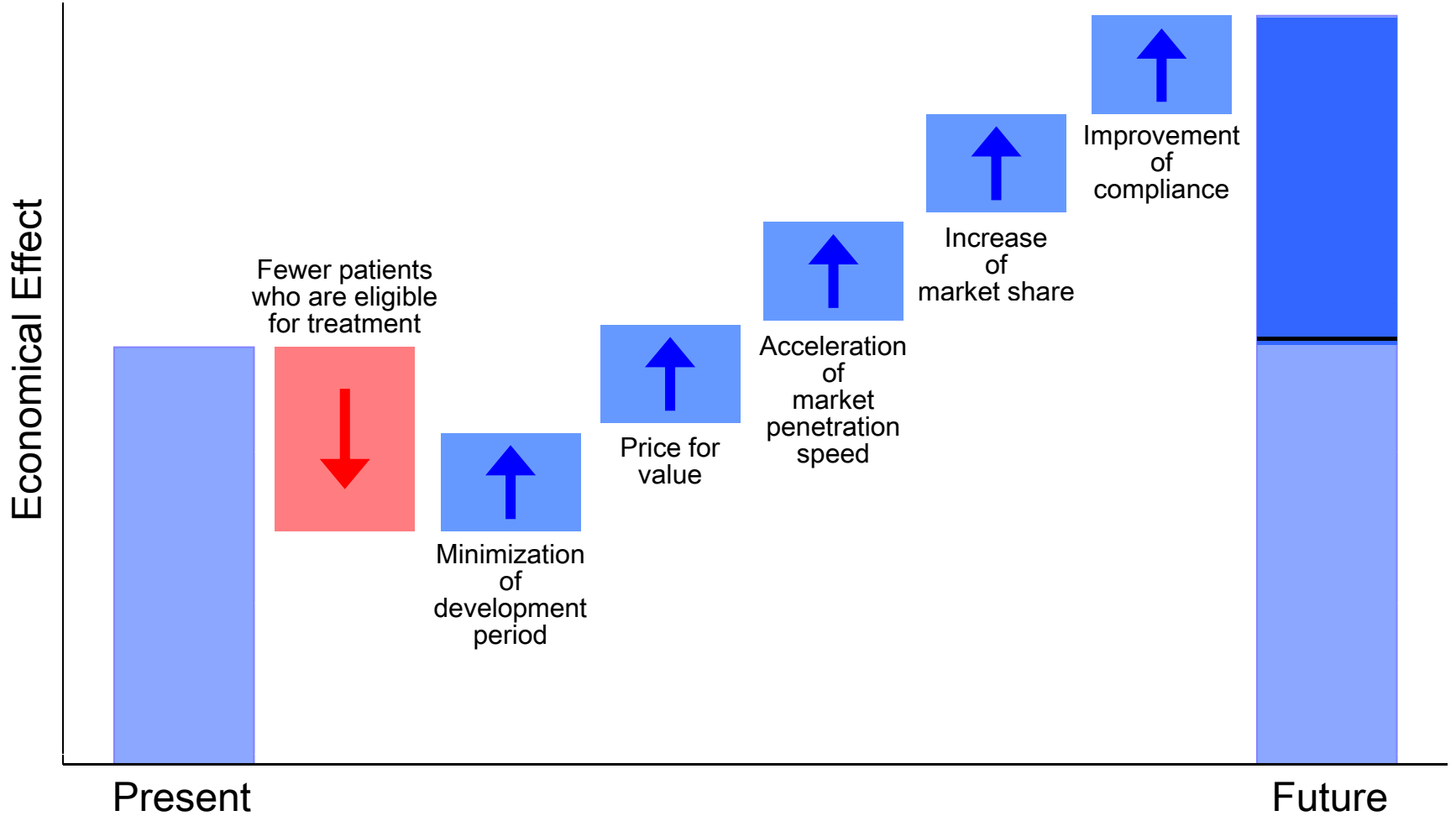
Personalized

Transition in Pharmaceutical Development



Economical Effect of PHC Approach in Pharmaceutical Companies

PHC approach benefits pharmaceutical Companies



PHC Benefits

PHC offers benefits to all stakeholders of Chugai, such as patients and physicians

Patients

→ Access to best treatment available

Physicians & Healthcare Providers

→ Maximum benefit

→ Minimum toxicity

PHC

Burden of national healthcare cost

→ Efficient use of healthcare budgets

Regulators & Policy Makers

→ Increased efficacy & safety

PHC Approach in Chugai

By leading PHC,

- ◇Chugai will accelerate paradigm shift in healthcare, and will offer benefits to all stakeholders of Chugai, including patients and physicians.
- ◇Chugai will be the leading company to accelerate innovation of new drugs, to penetrate market faster, and to contribute to new era of healthcare.

Scheme for PHC Approach in Chugai

Build collaboration scheme with Roche Diagnostics to conduct research and development of biomarkers from early stage

Development of pharmaceuticals

Pre-Clinical → P1 → P2 → P3 → Launch

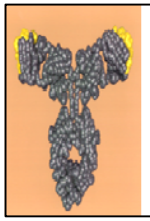
Development of diagnostics

Chugai to search biomarkers to stratify patients

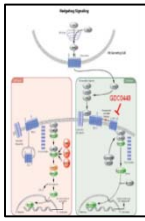
- Biomarker selection
- Optimization
- Development of diagnosis method

Modification and development for products to commercialize

Chugai's Strength



Achievement of Herceptin in Japan

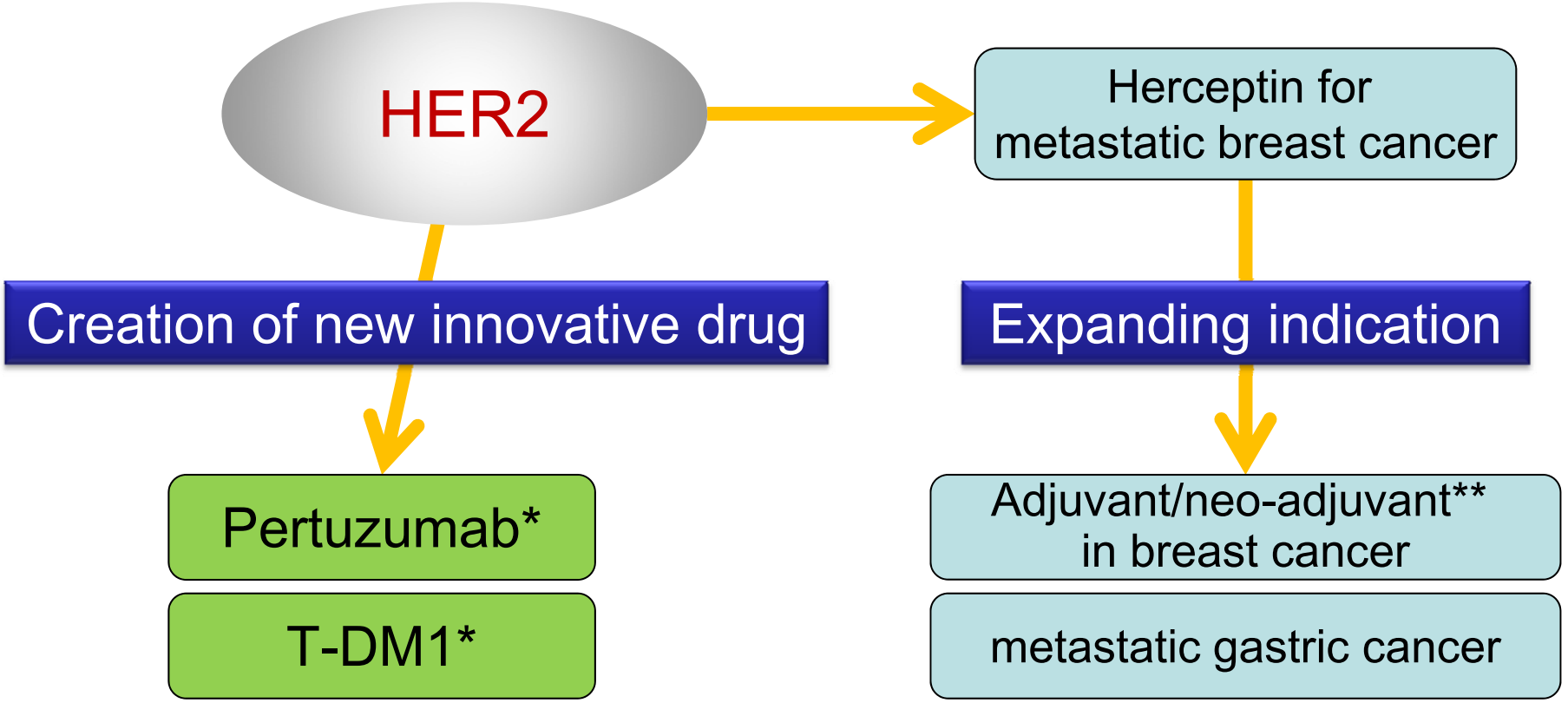


Accumulation of development know-how in oncology area where PHC is useful

Collaboration with Roche Diagnostics Division

Maximization of Product Value and Enlargement of Opportunity to Create New Drugs

PHC helps faster market penetration and leads to innovation of new drugs

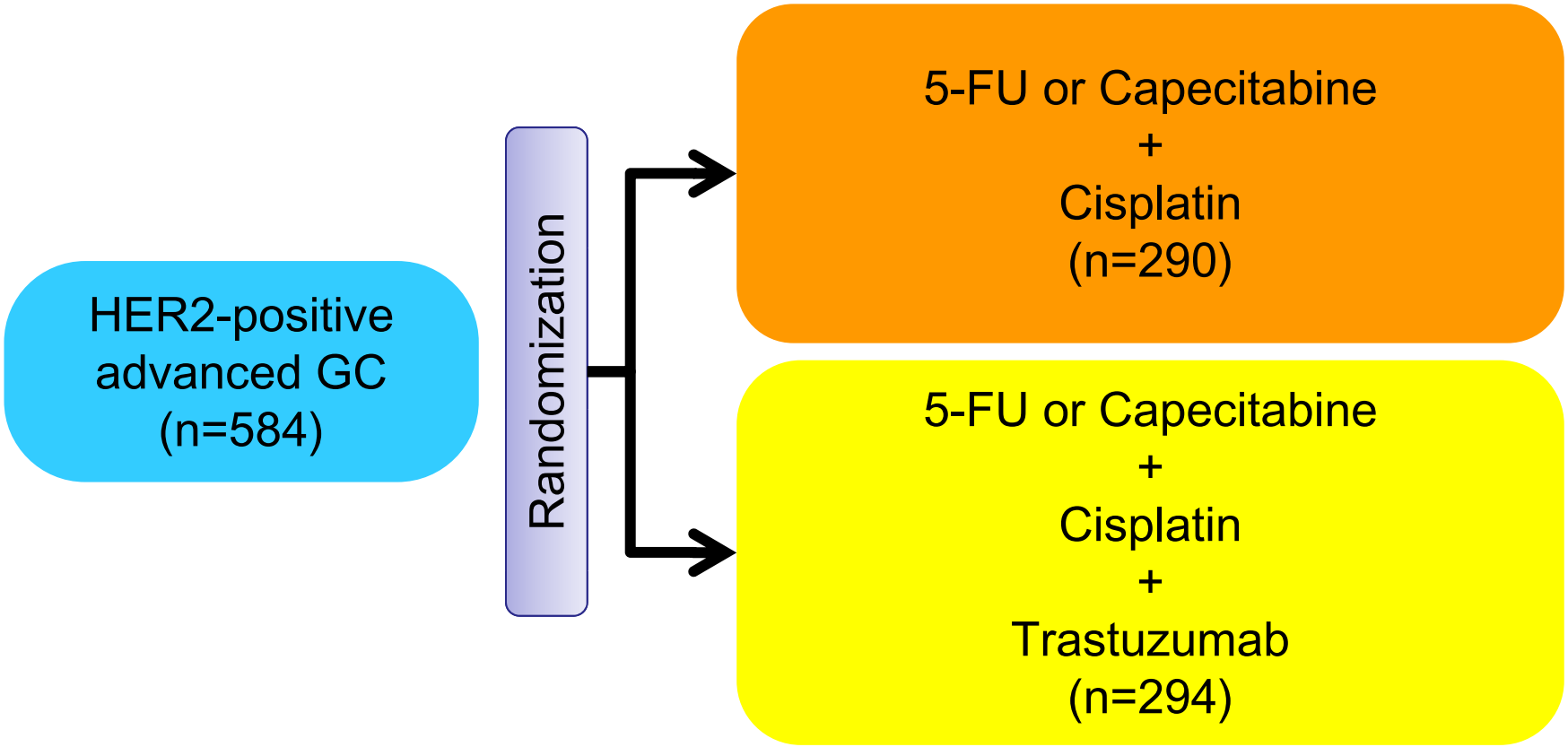


* Under development

** Neo-adjuvant indication is currently in review process by the health authority

ToGA Study
(Trastuzumab for GAstric Cancer)

Phase III, randomised, open-label, international, multicenter study



Bang YJ et al. : Lancet 376, 687-397, 2010

Development Compounds Targeting HER2

1. Pertuzumab

- ✓ An anti-HER2 monoclonal antibody which inhibits HER2-HER family dimerization
- ✓ In development as first line treatment in HER2-positive metastatic breast cancer in combination with Trastuzumab plus Docetaxel

  (CLEOPATRA, presented at SABCS in December, 2011)
  - ➢ The combination of Pertuzumab and Trastuzumab plus Docetaxel chemotherapy significantly extended the progression-free survival (PFS) compared to Trastuzumab and Docetaxel

2. T-DM1

- ✓ The first HER2-targeted antibody-drug conjugate (ADC) developed in breast cancer
- ✓ A phase II trial in the first line HER2-positive metastatic breast cancer conducted to evaluate clinical efficacy of T-DM1 vs. Trastuzumab plus Docetaxel

  (TDM4450g, presented at EMCC 2011)
  - ➢ T-DM1 significantly extended PFS (median PFS 14.2 months / T-DM1 vs. 9.2 months / Trastuzumab plus Docetaxel)
  - ➢ A favorable overall safety profile in T-DM1 group

R&D Portfolio based on PHC Strategy

	Phase I	Phase II	Phase III	Filed
Oncology	AF802 - NSCLC (PI/II) CIF/RG7167 - Solid tumors CKI27/RG7304 - Solid tumors GC33 - Liver cancer PA799 - Solid tumors WT4869 - Myelodysplastic syndromes (PI/II) - Solid tumors RG3638/MetMAb - NSCLC Vemurafenib (PI in preparation) - Melanoma	MRA/Actemra - PC (PI/II) RG435/Avastin * - Glioblastoma (relapsed) RG1415/Tarceva - NSCLC (1st line)	RG435/Avastin * - GC - aBC - Glioblastoma RG1273/Pertuzumab - BC RG3502 (T-DM1) - BC GA101/RG7159 - Indolent NHL - Aggressive NHL	EPOCH/Epogin - CIA
Bone & Joint	SA237 * - Rheumatoid arthritis (RA)	RG484/Bonviva (oral) - Osteoporosis	MRA/Actemra - RA (sc) RG484/Bonviva (inj) - Osteoporosis (PII/III)	
Others	RG1450 - Alzheimer's disease RG3637/Lebrikizumab -Asthma RG7090 * - Major depressive disease RG7128 - HCV		Tofogliflozin (CSG452) - Diabetes RG1678 (GLYT1) - Schizophrenia	

Letters in Red: Projects based on PHC *:Projects under searching companion biomarkers

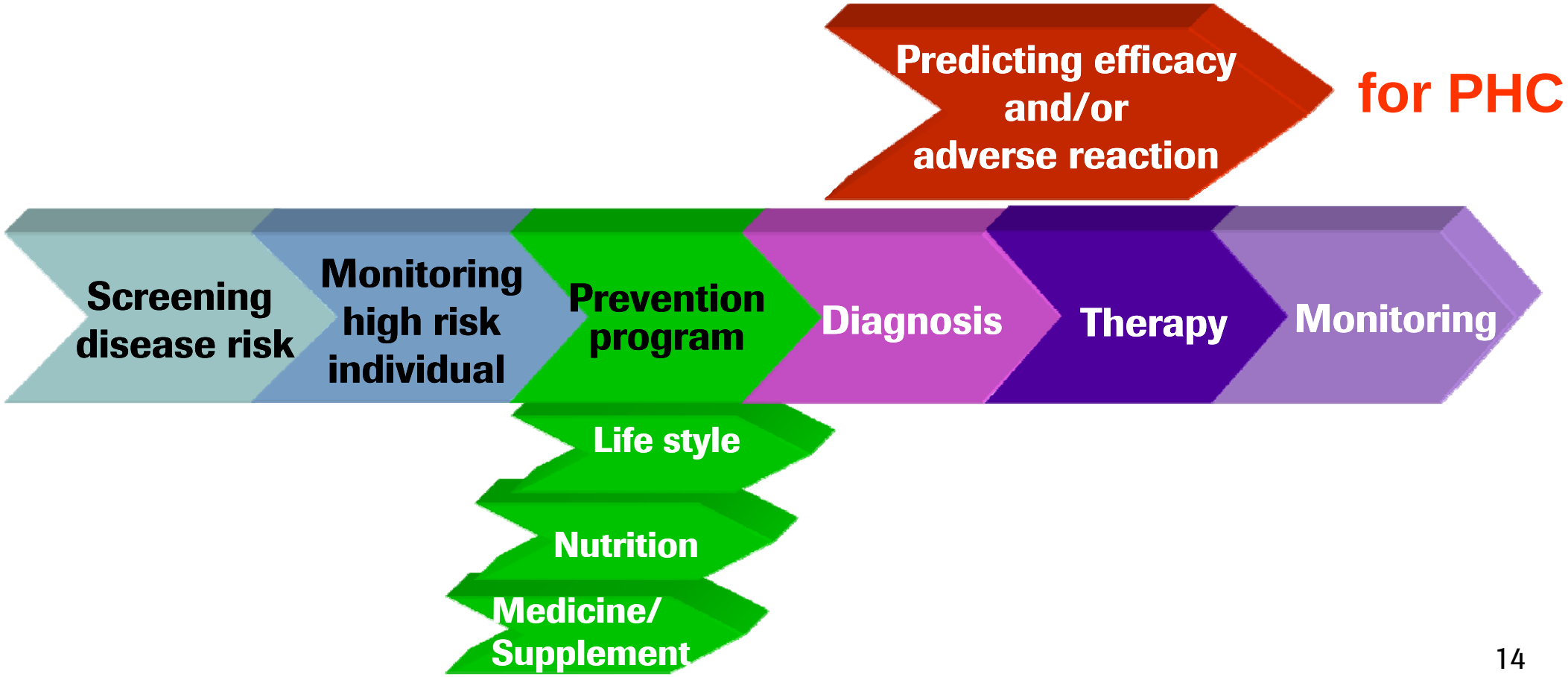
Role of Clinical Diagnostics for The Personalized Healthcare (PHC)

Yoshiaki Tazawa
Roche Diagnostics KK
Lifecycle Management of Molecular Diagnostics
October 28, 2011

Various Roles of Diagnostic Tests throughout the Medical Scenes

Roche

Diagnostics test has been getting more important for improving quality of advanced therapy

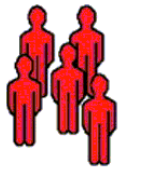


Ideal concept of Personalized Healthcare: PHC

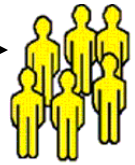
Illnesses are not always homozygous

Pharmaco-genomics(PGx)

Companion Diagnostics (CoDx)



Efficacy: low
Risk of AR: high



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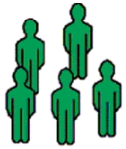


Efficacy: high
Risk of AR: high

One therapy for all

Efficacy: low
Risk of adverse response (AR): high

Efficacy: high
Risk of AR: low

Standard therapy as of today

Improving quality of the therapy

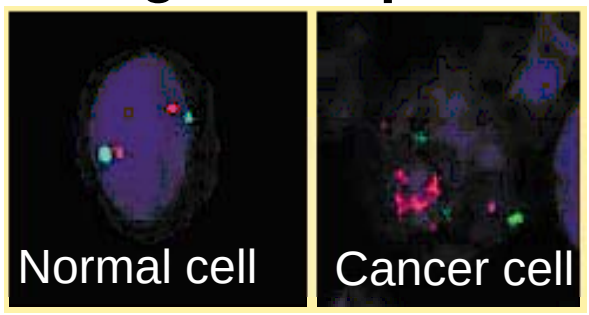
More therapies and designated Companion Dxs now available in the medical practice

Disease	Pharmaceuticals	CoDxs
Breast cancer	Herceptin (Trastuzumab)	Expression of HER-2/neu protein or gene
Stomach cancer		
NSCLC	Iressa (Gefitinib)	Mutation of EGFR gene
Colorectal cancer	Erbitux (Cetuximab)	Mutation of KRAS gene
	Vectibix (Panitumumab)	
CML	Glivec (Imatinib)	bcr-abl chimeric gene

Herceptin Therapy and HER2 Test (Breast Cancer)

HER2 test to identify HER2 amplification level to stratify patients for treatment with Herceptin or Tykerb

HER-2 test
(FISH: gene amplification)

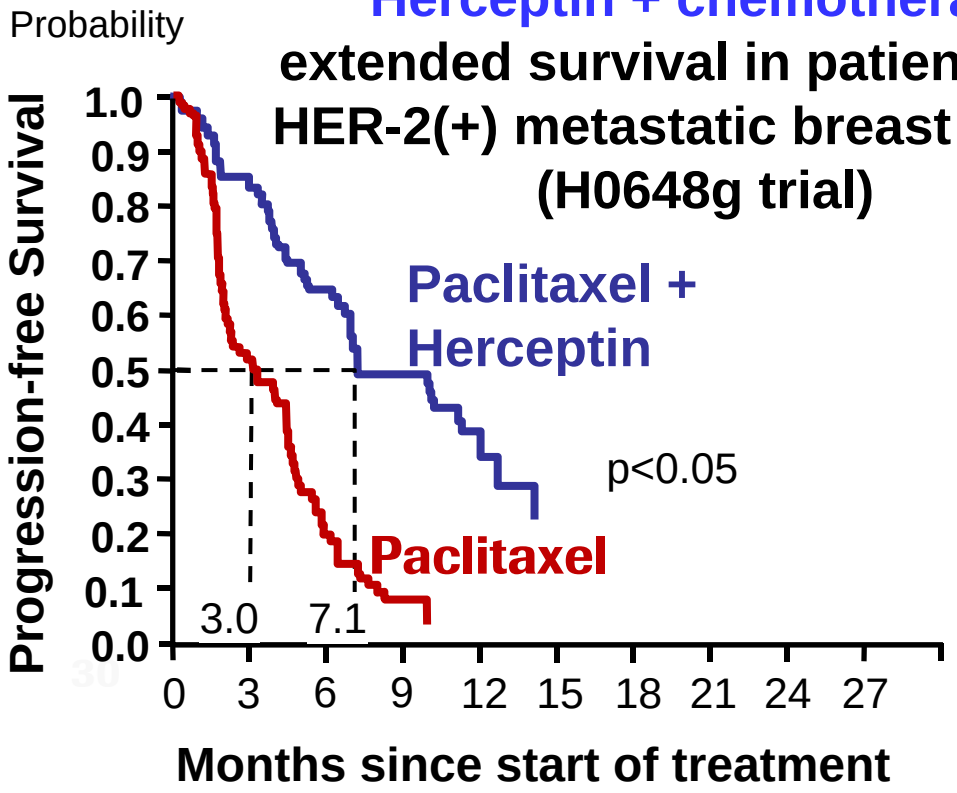


Herceptin efficacy
(metastatic breast cancer)

HER-2	Response Rate
FISH+	***34%*** (27/79)
FISH-	***7%*** (2/29)

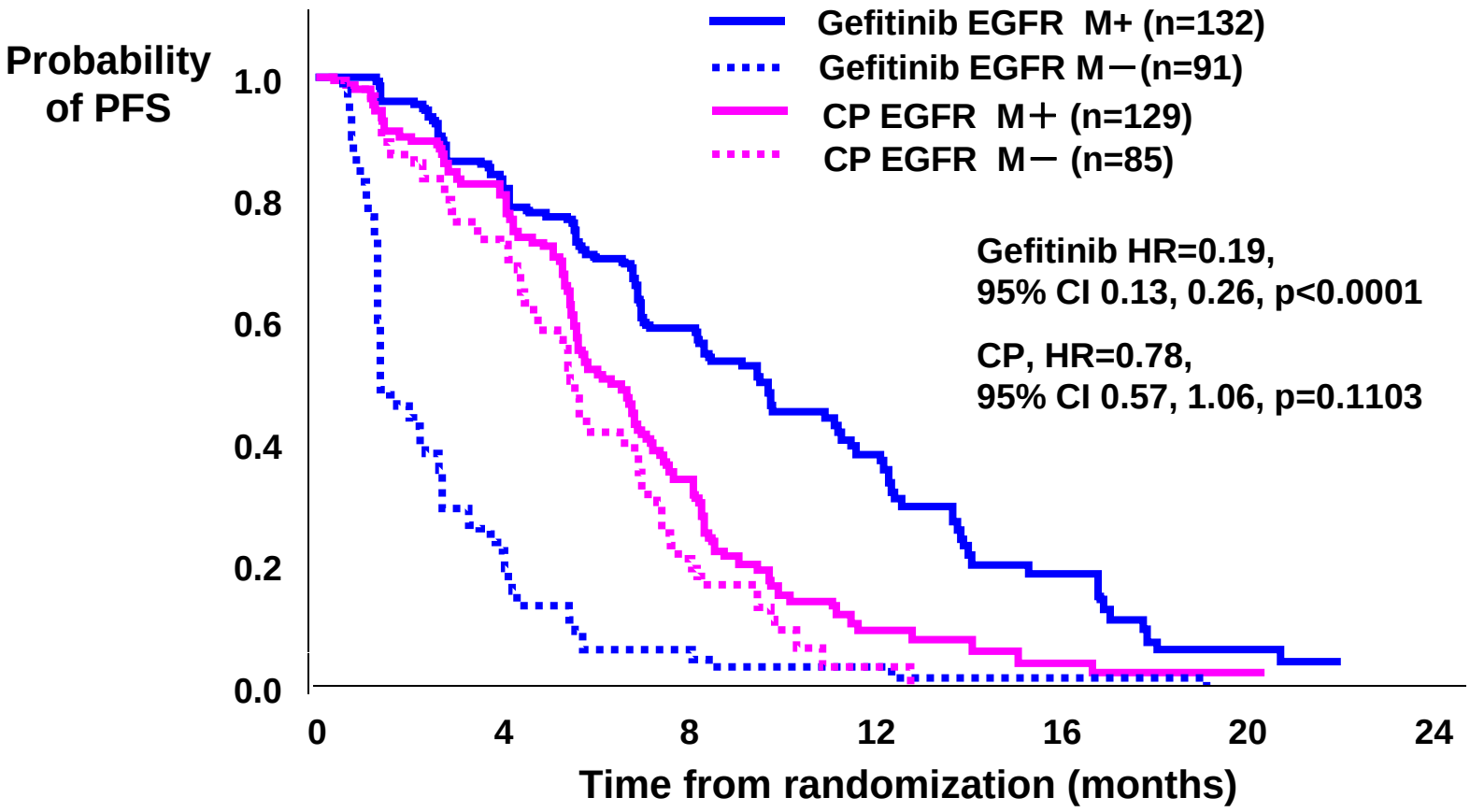
(*JCO*, 20:719-726, 2002)

Herceptin + chemotherapy
extended survival in patients with HER-2(+) metastatic breast cancer (H0648g trial)



Roche data on file; Smith et al 2001

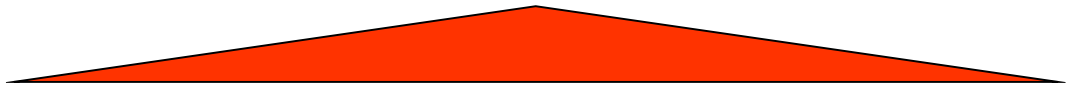
Efficacy of Gefitinib and EGFR mutation in NSCLC (IPASS trial)



CP: Carboplatin / paclitaxel , M+, mutation positive; M－, mutation negative

The Current Progress of PHC Approach

- **New drugs with CoDx currently approved by FDA**
  - **Aug 17: vemurafenib and BRAF V600E Mutation assay**
  - **Aug 26: crizotinib and ALK *in-situ* hybridization**
- **R&D collaboration currently stimulated**
  - **Kyowa Hakko Kirin and Kyowa Medex**
  - **Pfizer and Qiagen**



Draft Guidance for Industry and Food and Drug Administration Staff

Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

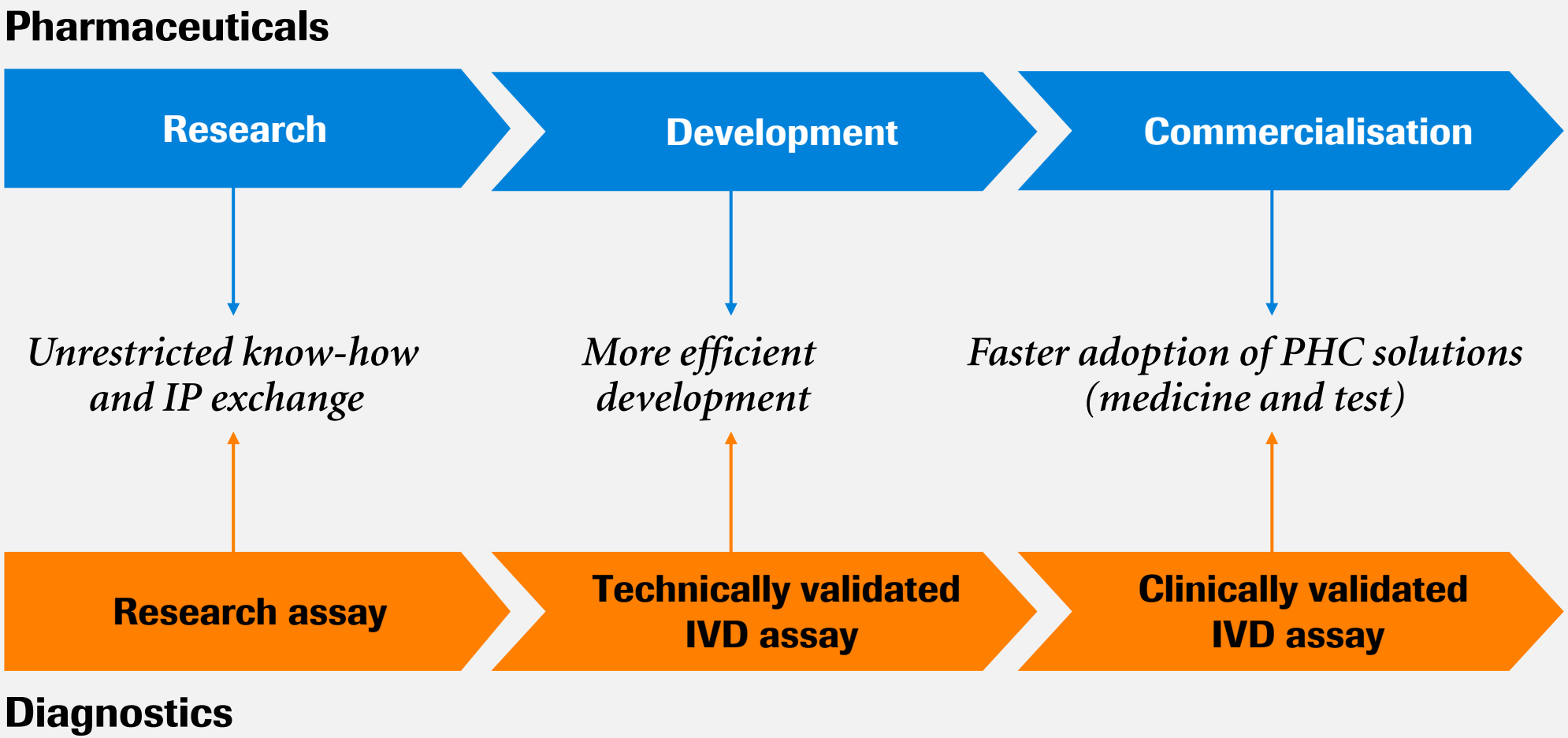
This guidance document is being distributed for comment purposes only.

Document issued on: July 14, 2011

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

PHC: Leveraging Pharma & Diagnostics

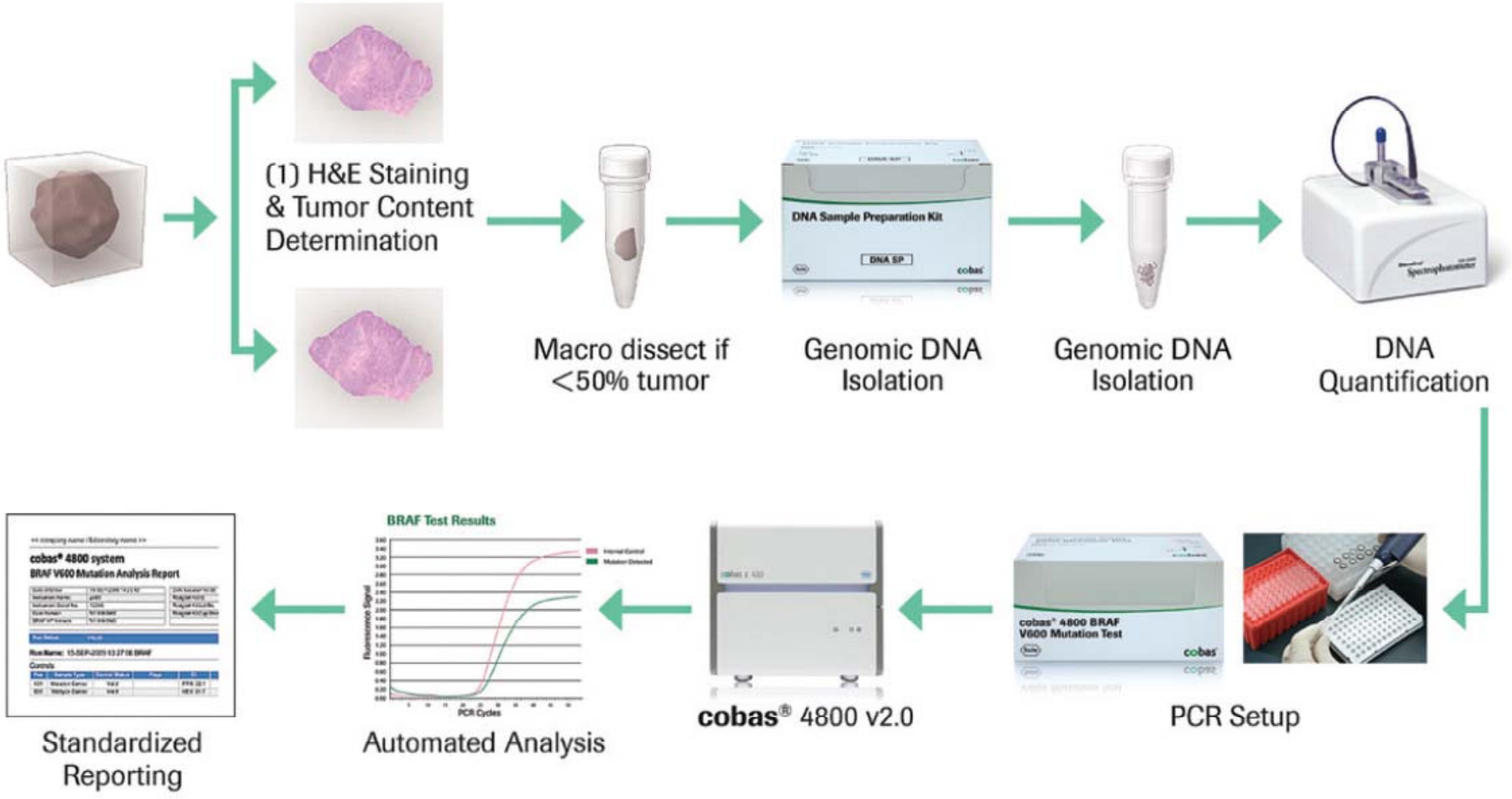
Collaborating throughout discovery to market



Core Dx technologies and Platforms to enhance CoDx development

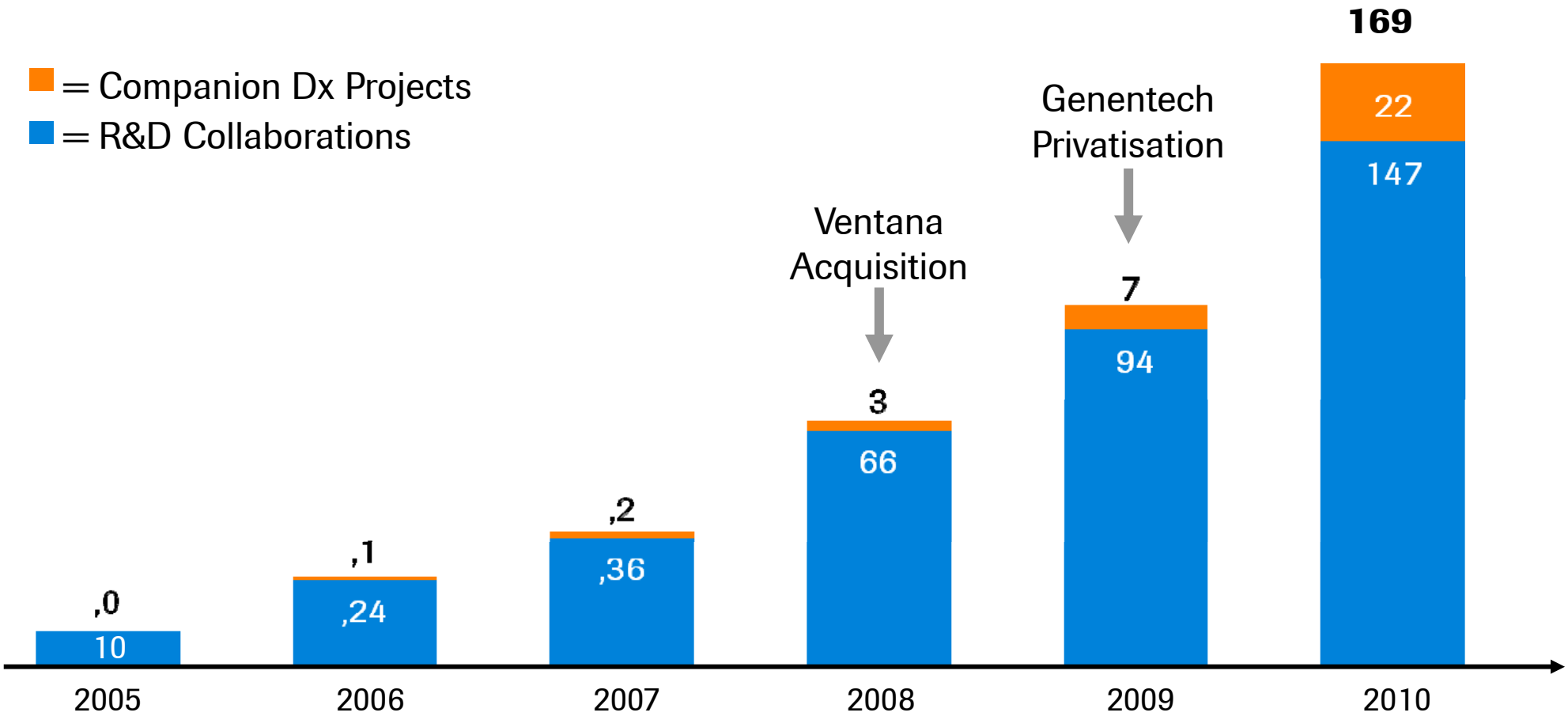
Life Sciences	In Vitro Diagnostics				
Applied Science	Molecular Diagnostics	Professional Diagnostics		Tissue Diagnostics	Diabetes Care*
 *Academia/Pharma*	 *Molecular Lab*	 *Central Lab*	 *Doc. Office, Wards*	 *Pathology Lab*	 *Patient*
Biochemicals/IB	Blood Screening	SWA High/Mid Volume Platforms	Workflow & IT	Advanced Staining Assays	Single Strip bGM
qPCR/NAPI	Genomics & Oncology	SWA Low Volume Platforms	Hospital POC	Advanced Staining Platforms	Integrated bGM
Arrays	HPV & Microbiology	Clin Chem, ID, Onco, Endo	Ambulatory Care	Primary Staining	Lancing Systems
Sequencing	NewGen	Cardio-Renal, Crit. Care & WH		Advanced Workflow	Insulin Delivery Systems
Cellular	Virology	Specialty Testing			

Assay Procedure of cobas BRAF V600E kit



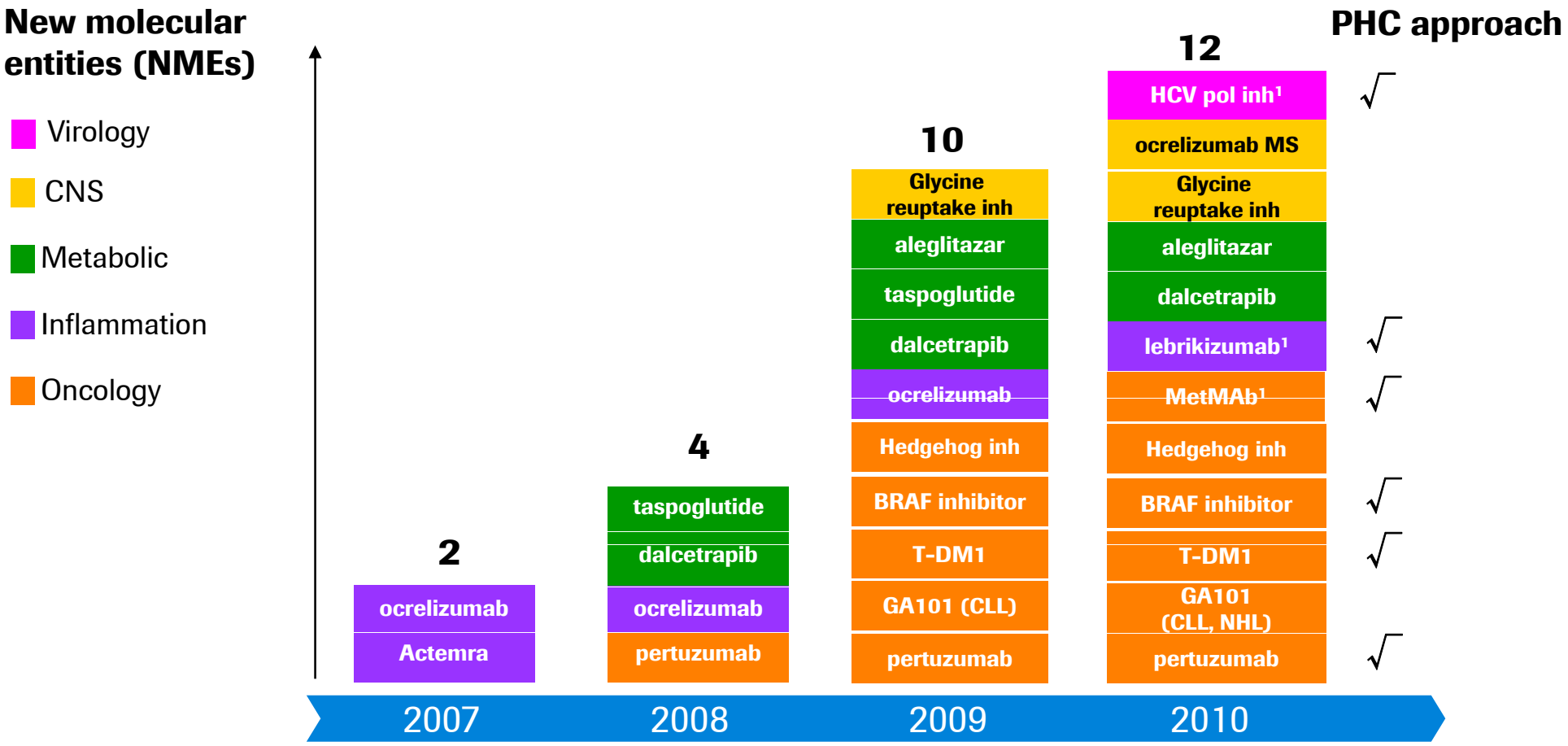
PHC: Roche internal collaborations

Significant increase due to focused PHC strategy



Roche Pharma: a leading pipeline

12 NMEs in late-stage development



[1] LIP decision made, phase III start pending

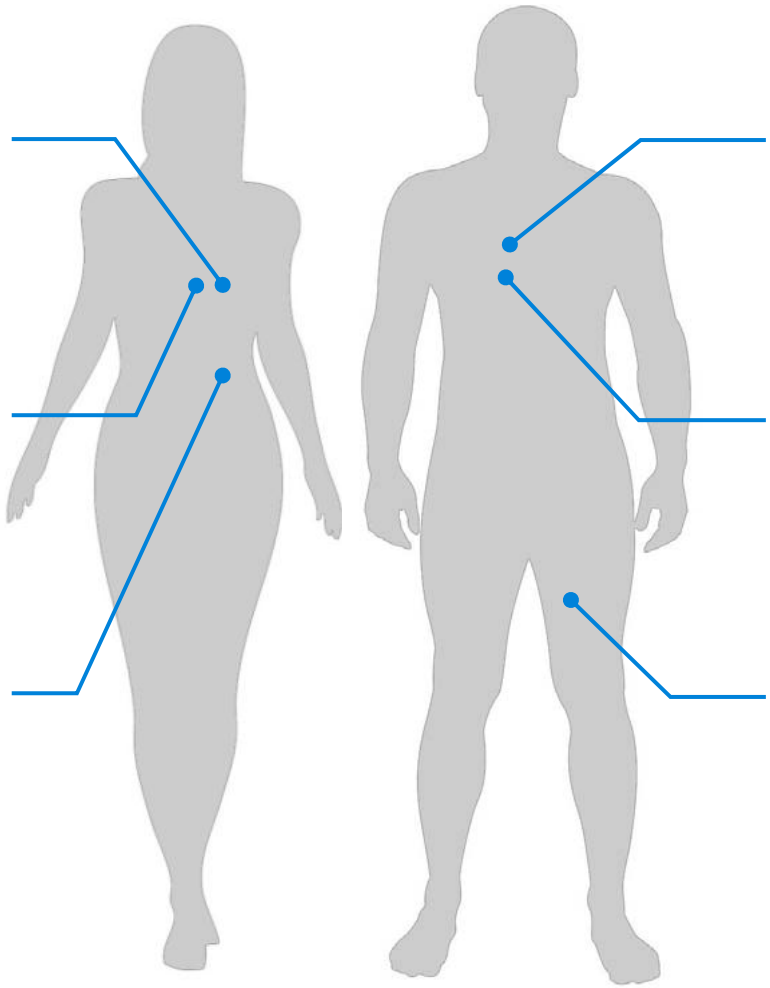
Personalised Healthcare becoming a reality

Six late-stage compounds require a companion diagnostics test

T-DM1
Metastatic breast cancer
(HER-2 expression level)

Pertuzumab
Metastatic breast cancer
(HER-2 expression level)

RG 7128[1]
Hepatitis C
(HCV viral load, genotype)



MetMAb[1]
Non-small cell lung cancer
(MET status)

Lebrikizumab[1]
Asthma
(periostin level)

Zelboraf
Metastatic melanoma
(BRAF V600E mutation)

[1] LIP decision made, phase III start pending

We Innovate Healthcare

R&D Portfolio Based on PHC Approach in Chugai

CHUGAI PHARMACEUTICAL CO., LTD.
Portfolio Management Unit
Department Manager of
R&D Portfolio Management Dept.
Hisanori Takanashi

October 28, 2011

R&D Portfolio Based on PHC Approach

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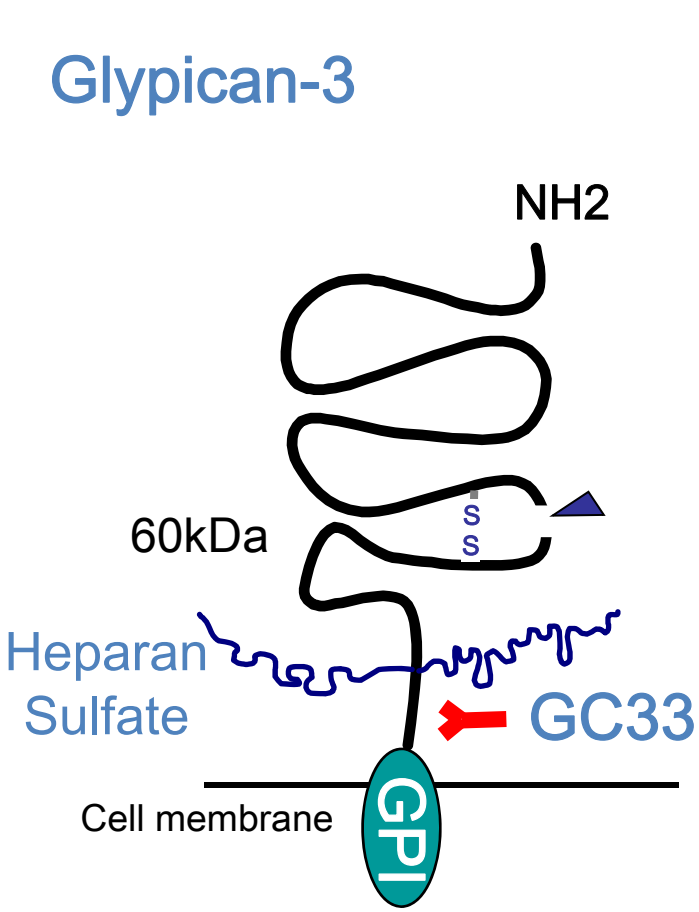
Letters in Red: Projects based on PHC *:Projects under searching companion biomarkers

GC33

A recombinant humanized antibody against glypican-3 positive hepatocellular carcinoma

Glypican-3 and GC33



Glypican-3 (GPC3)

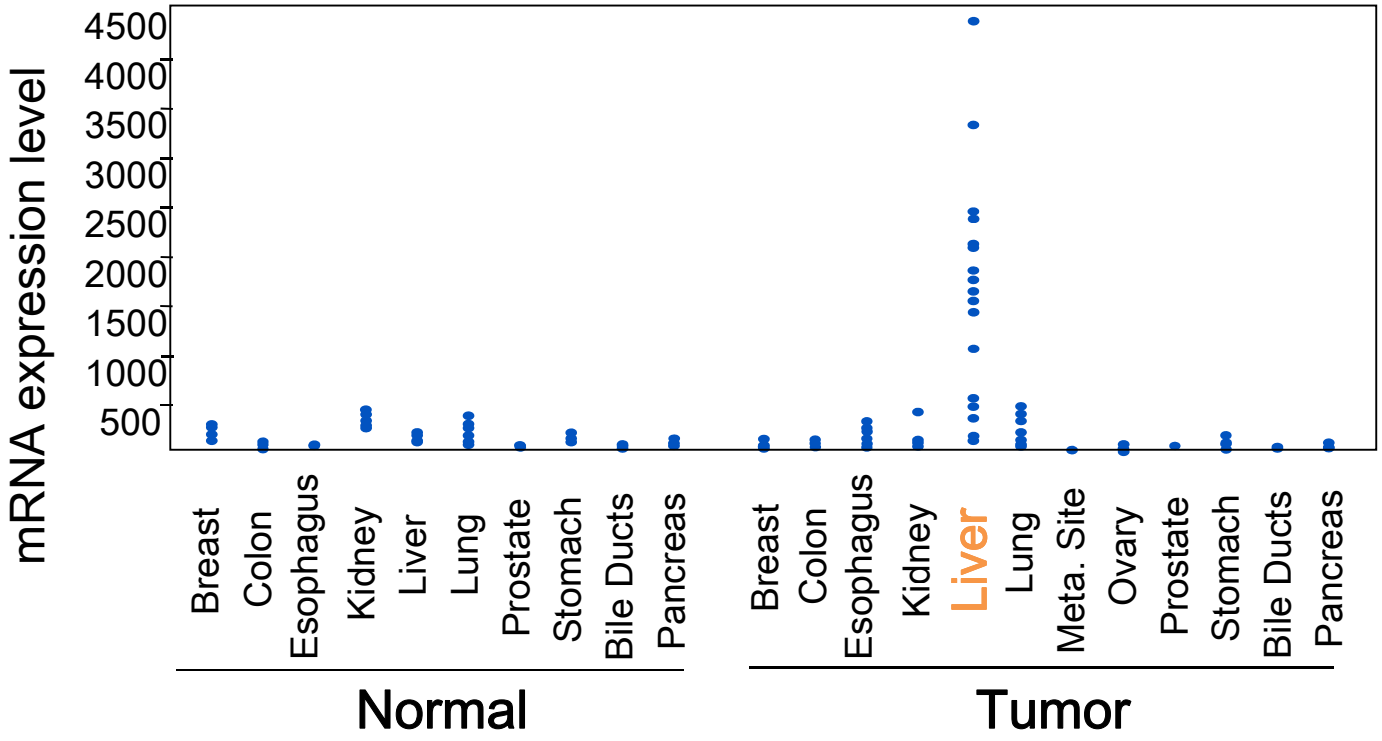
- GPI-anchored heparan sulfate proteoglycan
- It is highly expressed in the majority (70–100%) of hepatocellular carcinoma (HCC)
- One of onco-fetal antigen
- Said to play a role in tumor growth

GC33

- A recombinant humanized antibody against glypican-3 (GPC3)
- Shows potent antitumor activity in GPC3 positive HCC models

GPC3 mRNA Expression Profile

Clinical Tissue Samples

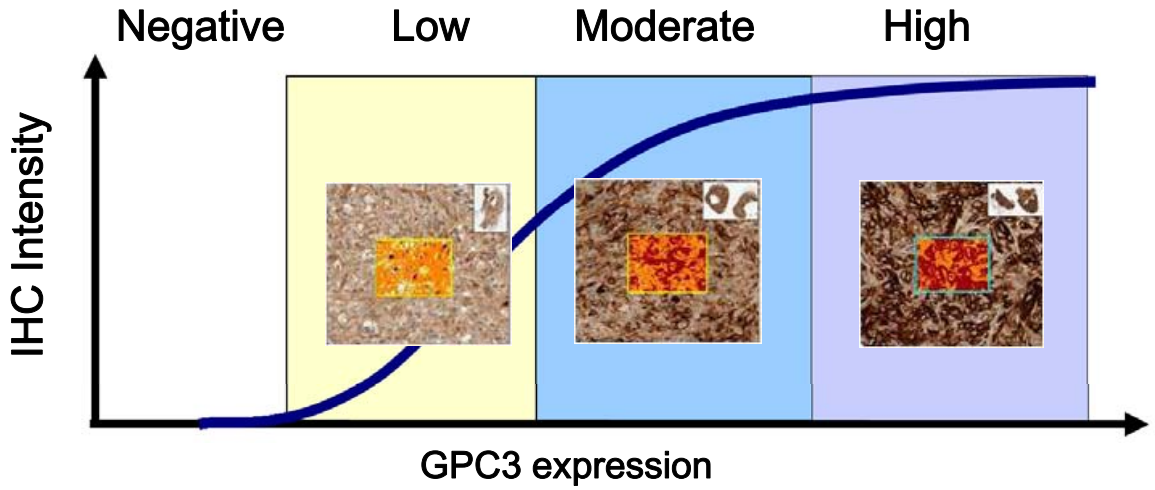


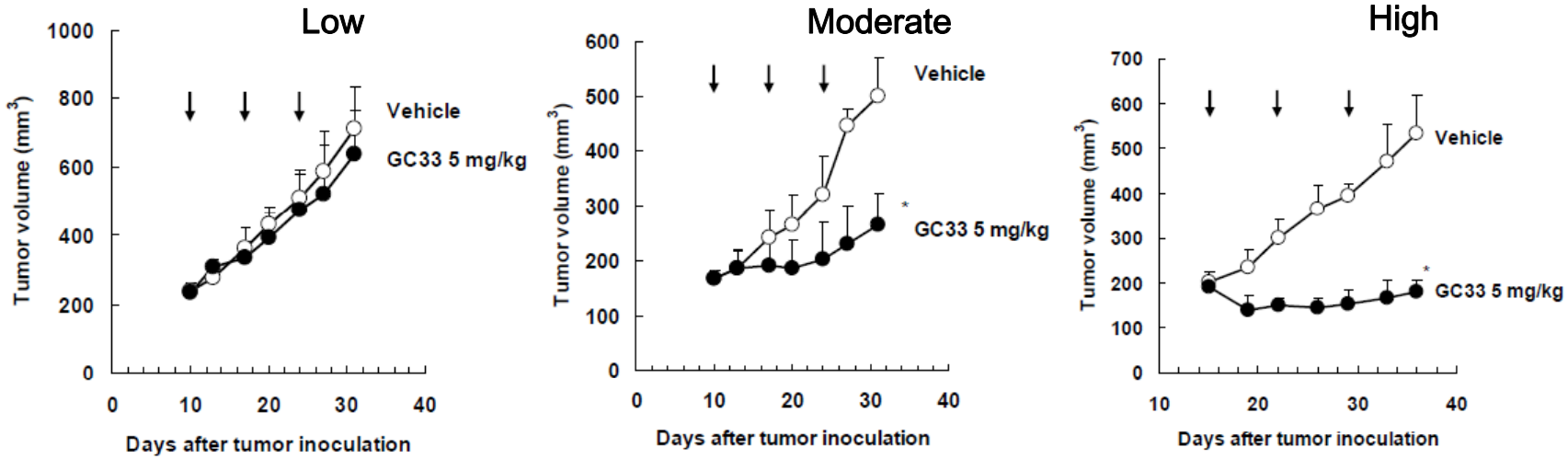
GPC3 expression was specifically upregulated in liver tumor, but is less so in other tumor or normal tissues.

ASCO 2011: # 4085

Anti-tumor Efficacy
Correlation to GPC3 Levels

In GC33, antigen level dependent antitumor activities observed

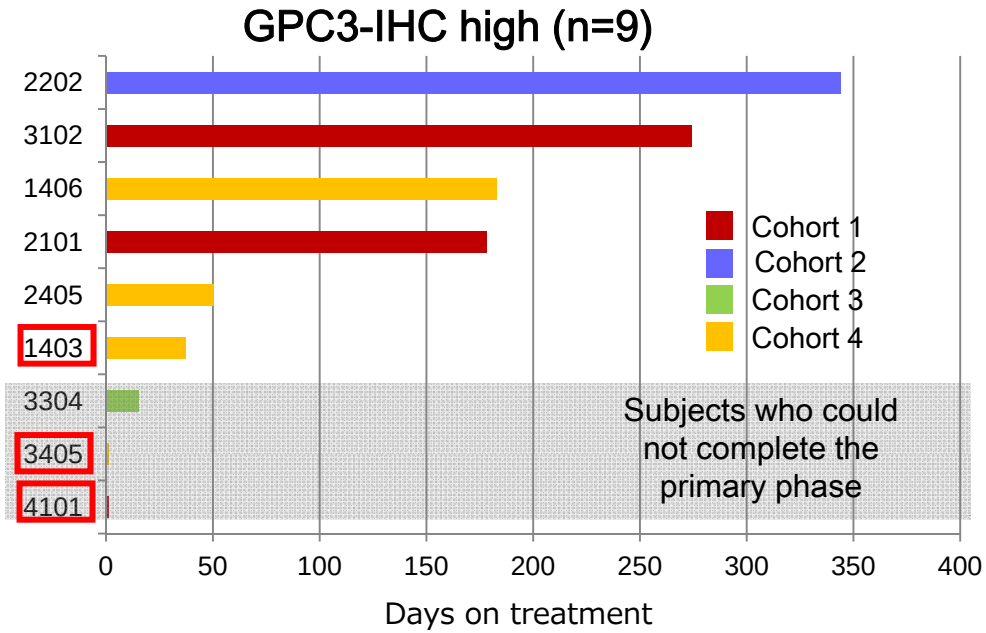


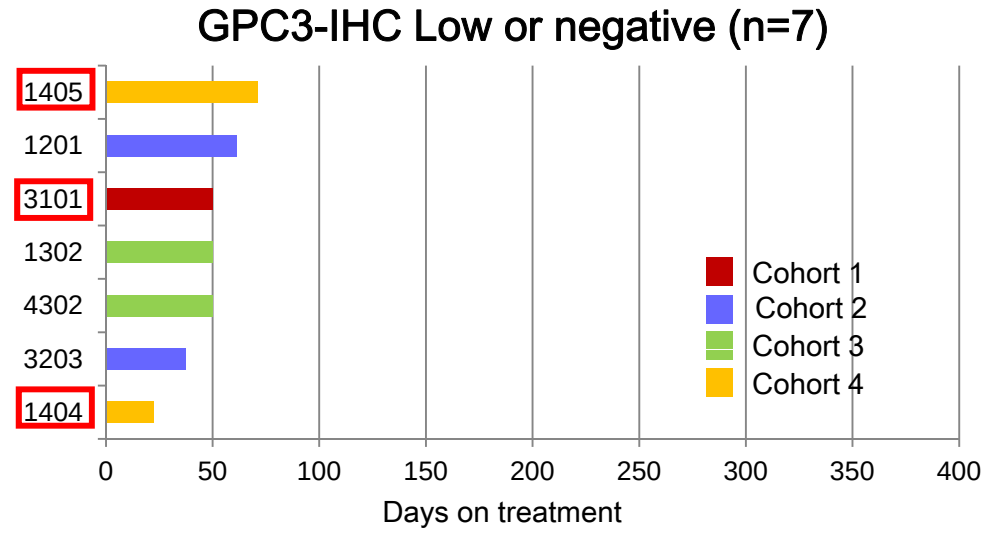


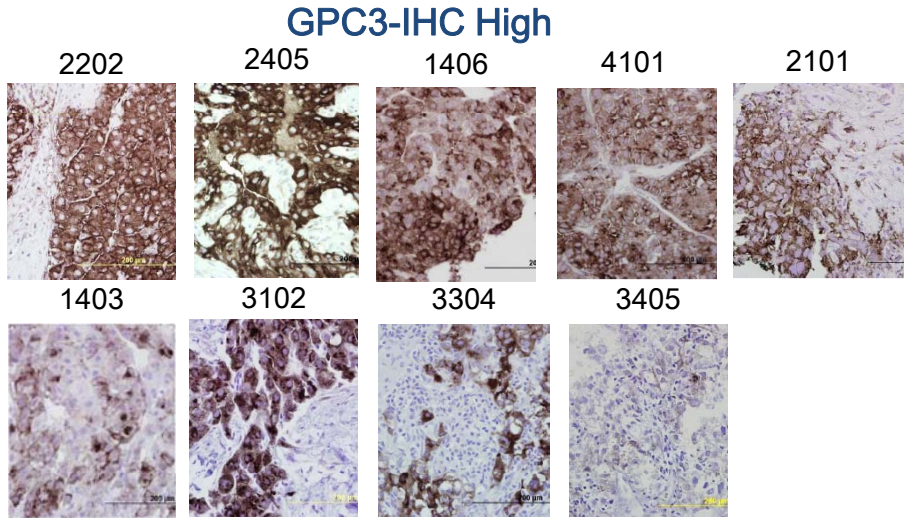
AACR 2010: # 2426

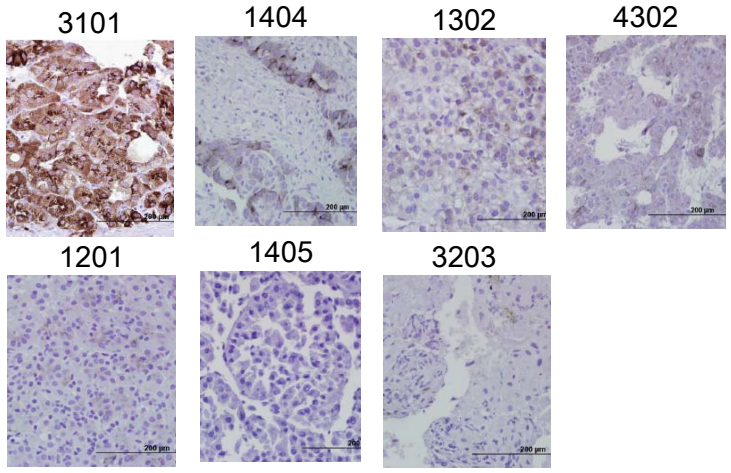
Treatment Duration and GPC3 Expression

Analysis of Phase I Study





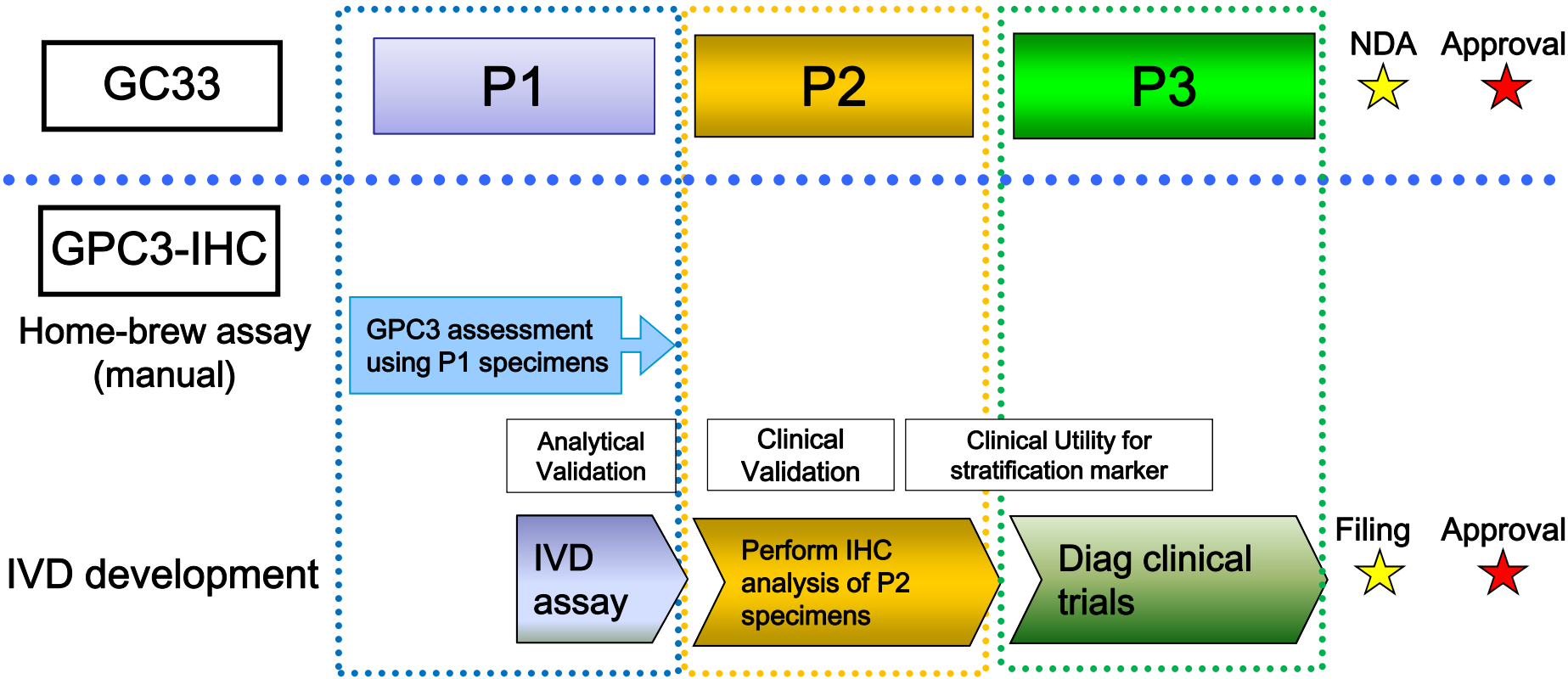




Child-Pugh B

ASCO 2011: # 4085

GPC3 IHC Development Plan



- Standardization of IHC assay using automated system
- Define scoring criteria for IVD assay and cut-off for patient selection

AF802: High Sensitivity to ALK

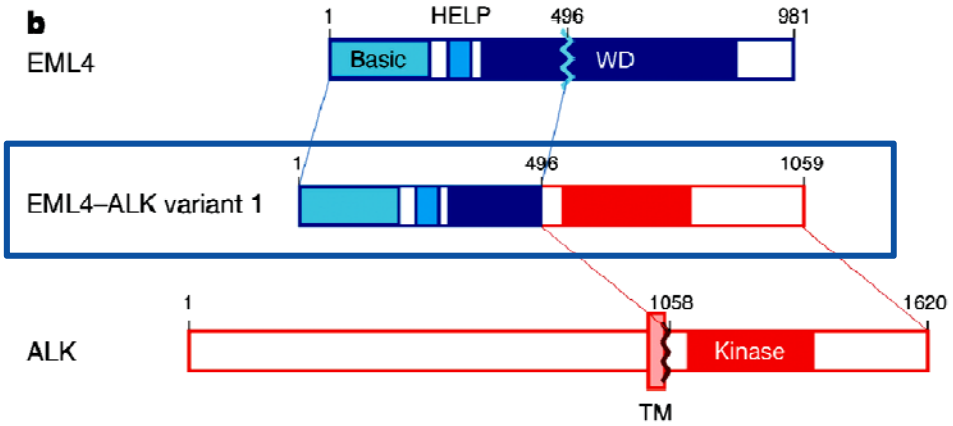
A new selective treatment against ALK mutation positive non-small cell lung cancer

EML4-ALK Fusion Gene

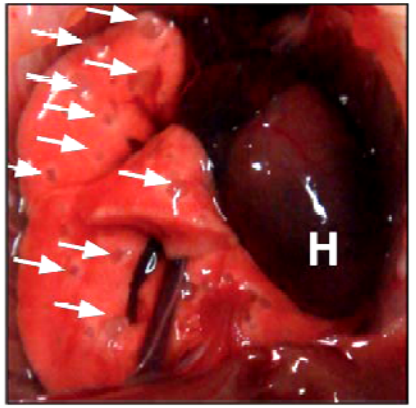
A New Target for Non-small Cell Lung Cancer

Identification of the transforming EML4-ALK fusion gene in non-small cell lung cancer

Nature, 2007: 448, 561-6

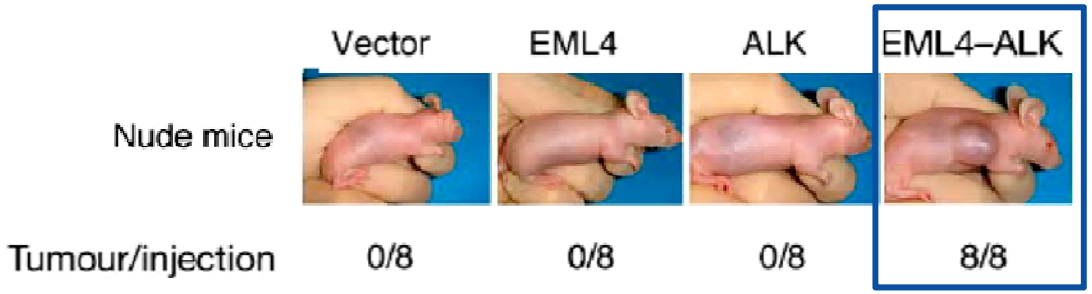


Development of lung adenocarcinoma in EML4-ALK transgenic mice



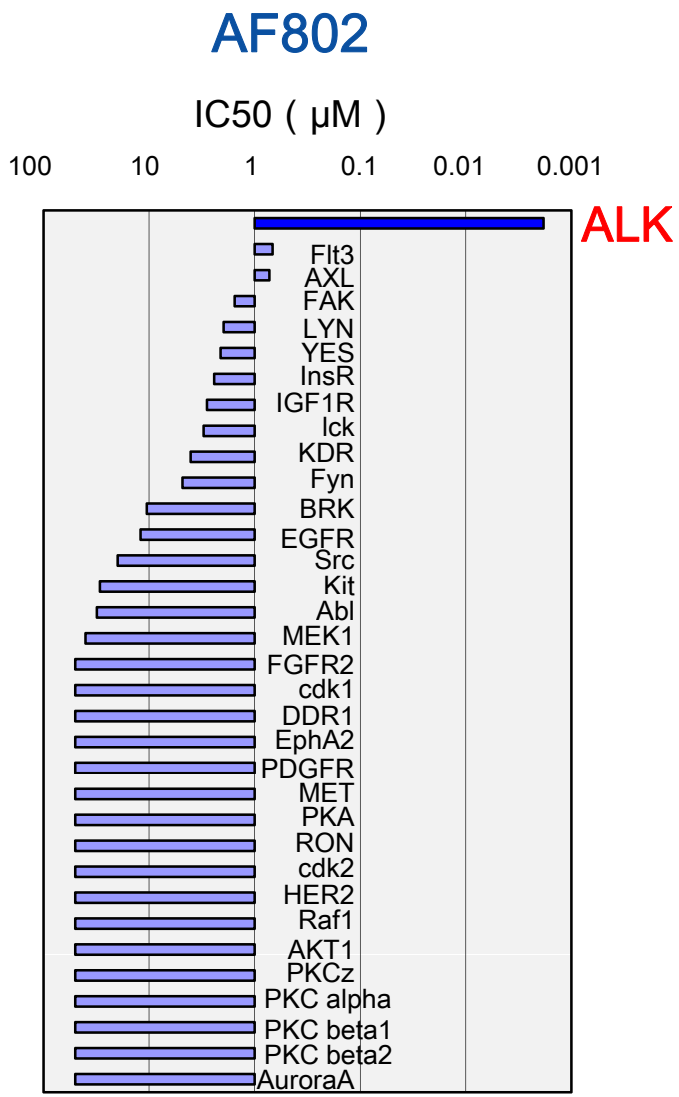
PNAS, 2008: 105, 19893-7

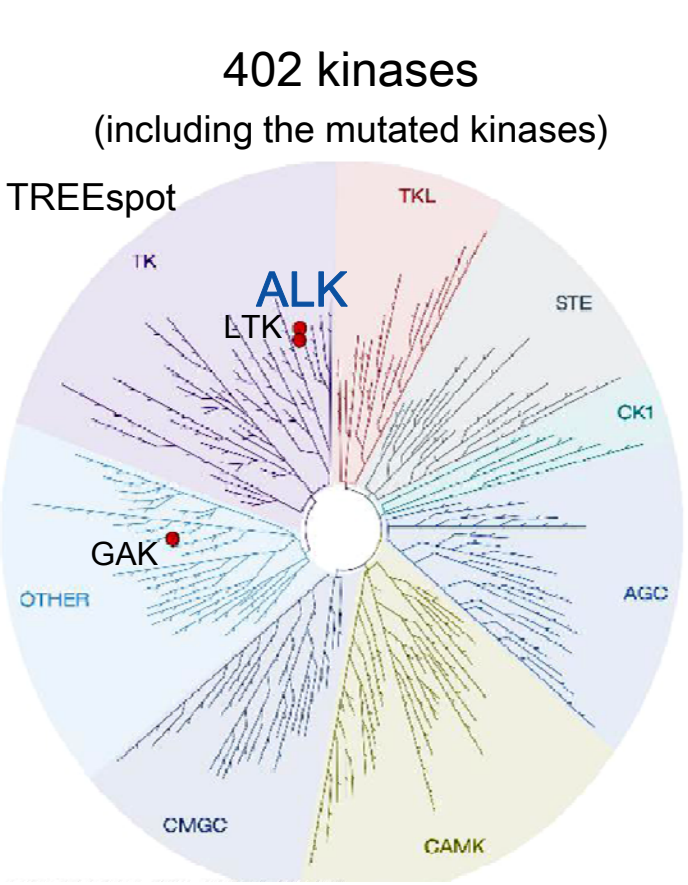
Subcutaneous injection of the transfected 3T3 cells into nude mice



EML4-ALK (~5%)

AF802: High Sensitivity to ALK



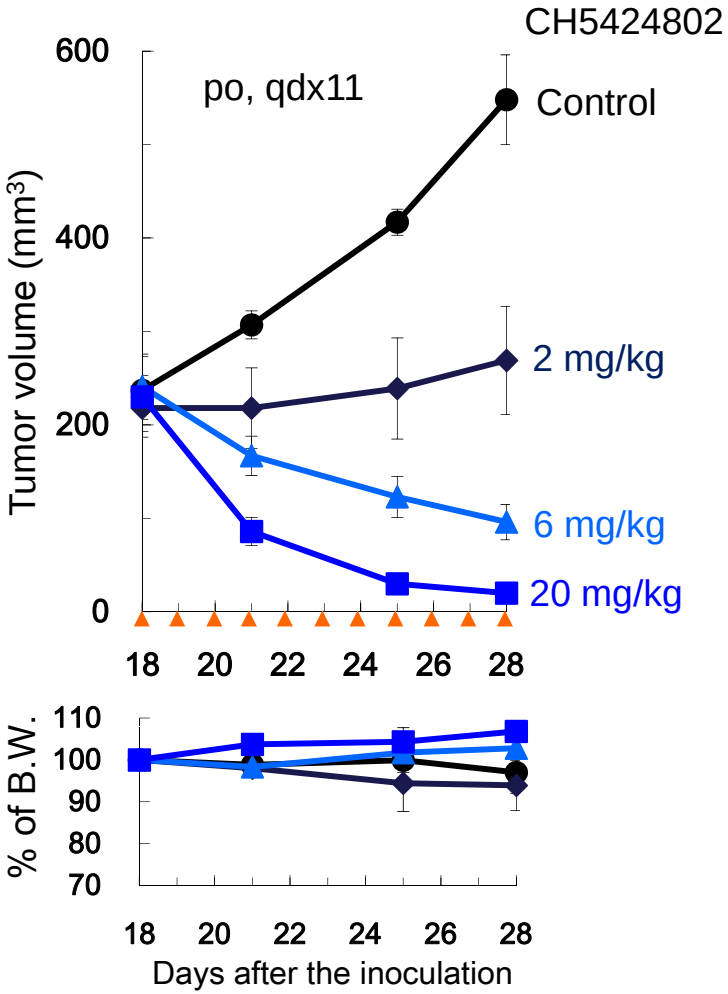


● >50% inhibition at 10 nM AF802 in kinase binding assay

Cancer Cell *19,* 679 (2011)

Efficacy of AF802
Xenograft Model

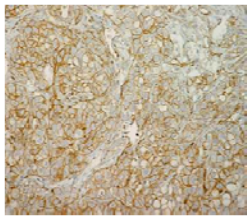
NCI-H2228: ***EML4-ALK***



Xenograft Tumors

p-ALK (IHC)

Control



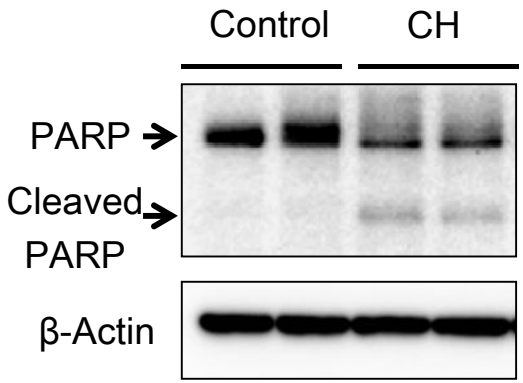
AF802

20 mg/kg

4h after single oral administration

Apoptosis

Cleaved PARP



Vehicle or 20 mg/kg AF802, 4 h after qd x 2

Cancer Cell *19,* 679 (2011)

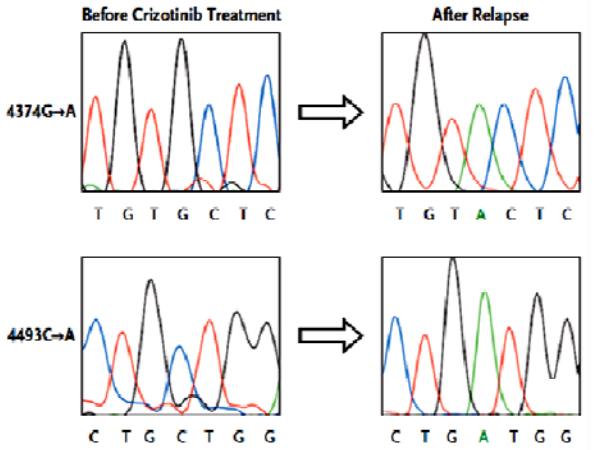
Crizotinib-resistant Mutations

EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors

Young Lim Choi, M.D., Ph.D., Manabu Soda, M.D., Ph.D., Yoshihiro Yamashita, M.D., Ph.D., Toshihide Ueno, Ph.D., Junpei Takashima, M.D., Takahiro Nakajima, M.D., Ph.D., Yasushi Yatabe, M.D., Ph.D., Kengo Takeuchi, M.D., Ph.D., Toru Hamada, M.D., Hidenori Haruta, M.D., Ph.D., Yuichi Ishikawa, M.D., Ph.D., Hideki Kimura, M.D., Ph.D., Tetsuya Mitsudomi, M.D., Ph.D., Yoshiro Tanio, M.D., Ph.D., and Hiroyuki Mano, M.D., Ph.D., for the ALK Lung Cancer Study Group

Choi, et al., N. Eng. J. Med. 363, 1734-1739 (2010)

Secondary mutations within EML4-ALK

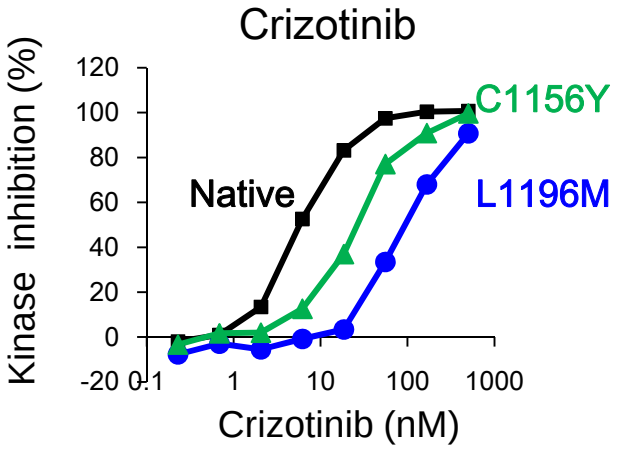


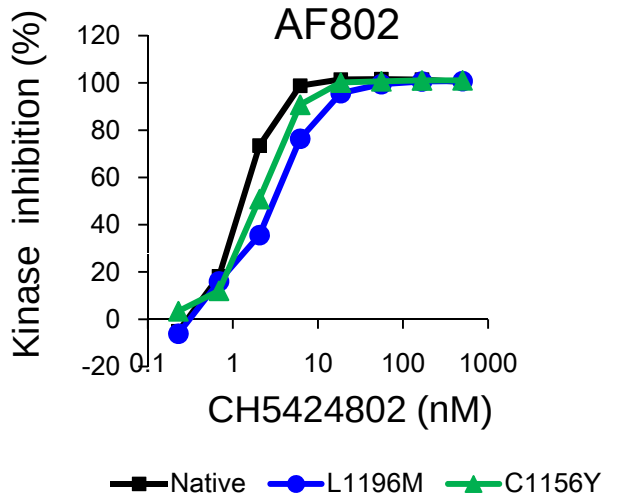
C1156Y

L1196M

Gatekeeper mutation

Cell-free kinase inhibition



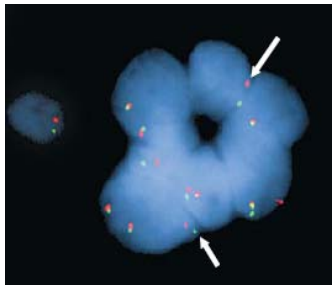


Cancer Cell *19*, 679 (2011)

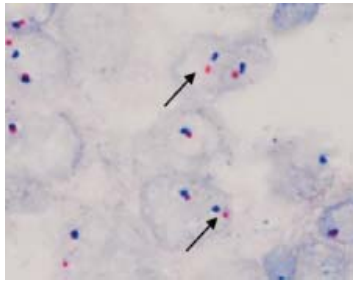
ALK Diagnosis:
as a Prerequisite for the Treatment

- In situ hybridization
  - Fluorescence in situ hybridization (FISH)
  - Chromogenic in situ hybridization (CISH)
- Immunohistochemistry (IHC)
- Real-time polymerase chain reaction (RT-PCR)

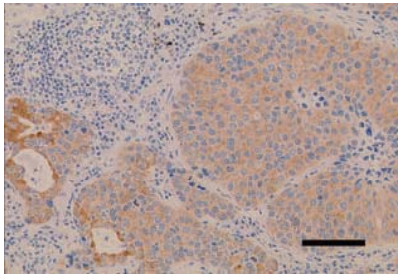
FISH (1)



CISH (2)



IHC (3)



RT-PCR (4)

(1) N Eng J Med 363; 1693-1703 (2010)
(2) J Thorac Oncol 6; 1359-1366 (2011)
(3) Clin Cancer Res 15; 3143-3149 (2009)
(4) Clin Cancer Res 14; 6618-6624 (2008)

Phase I/II study of AF802 in Japan

Target

- Non-small cell lung cancer with ALK fusion gene

Objectives

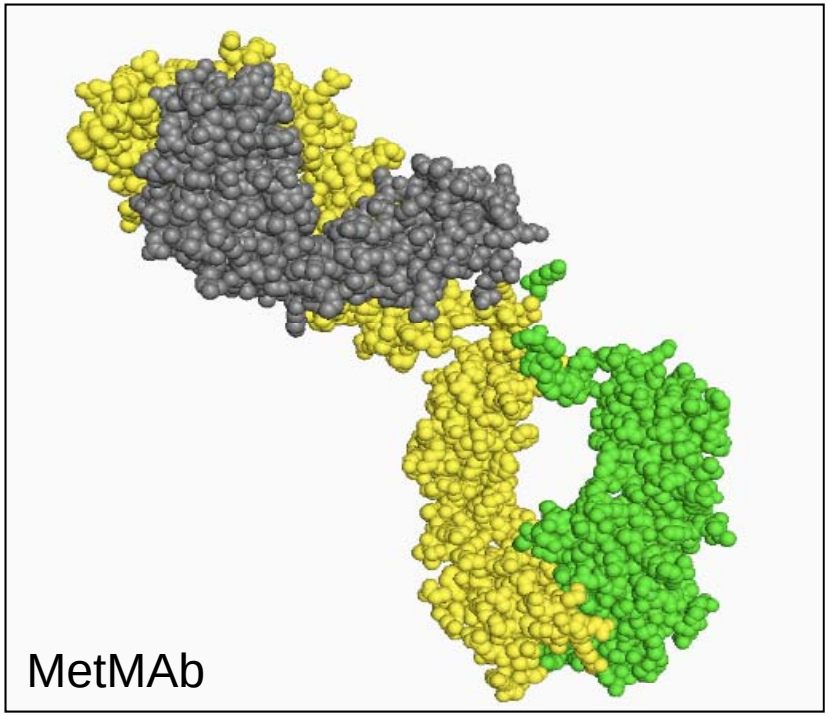
- PI part: dose finding (initial dose: 40 mg/day)
  - To investigate the safety, tolerability, and PK parameters of CH5424802
  - To determine the recommended dose of CH5424802 in PII part
- PII part: investigation at recommended dose
  - To investigate the efficacy and safety of CH5424802

Global study in preparation

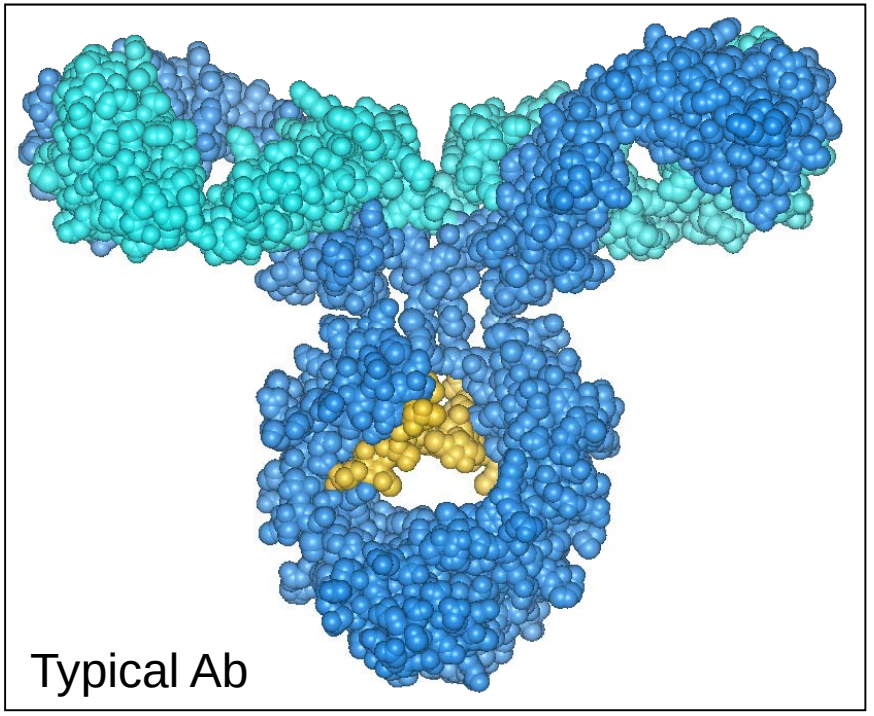
MetMAb

A recombinant humanized antibody
against cMet positive
non-small cell lung cancer

Unique Features of MetMAb



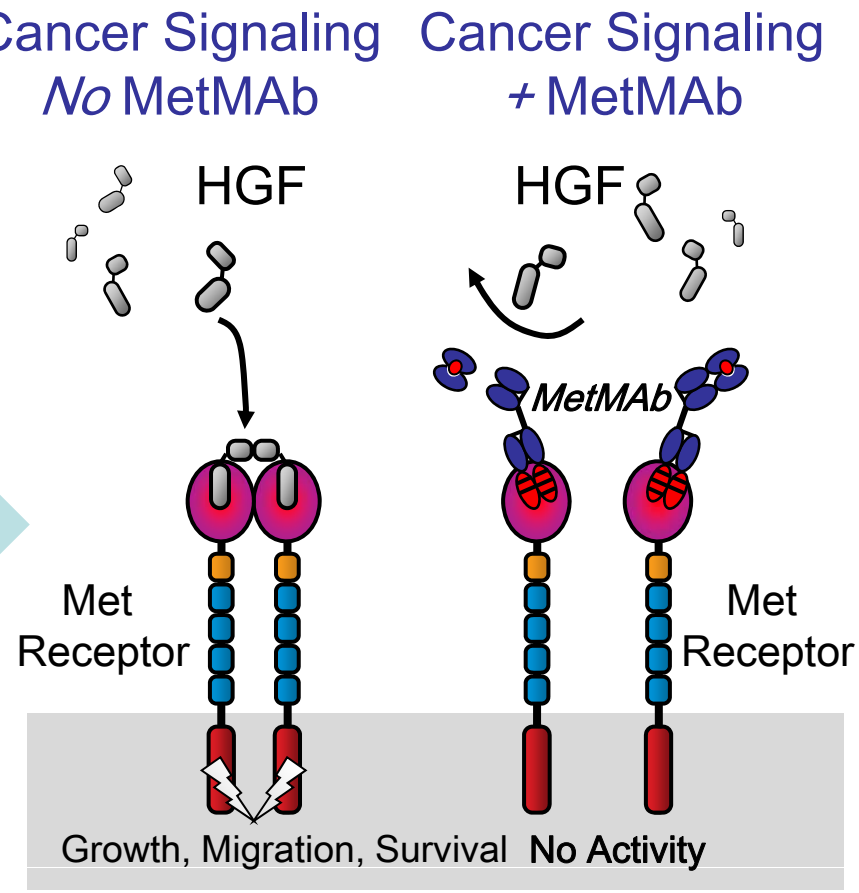
- Monovalent: Does not dimerize Met
- Produced in *E.coli*
- Non-glycosylated (No ADCC)



- Bivalent: Potential for Met dimerization
- Produced in CHO
- Glycosylated antibody (ADCC)

NSCLC: cMet Oncogene is a Therapeutic Target in Non-small Cell Lung Cancer

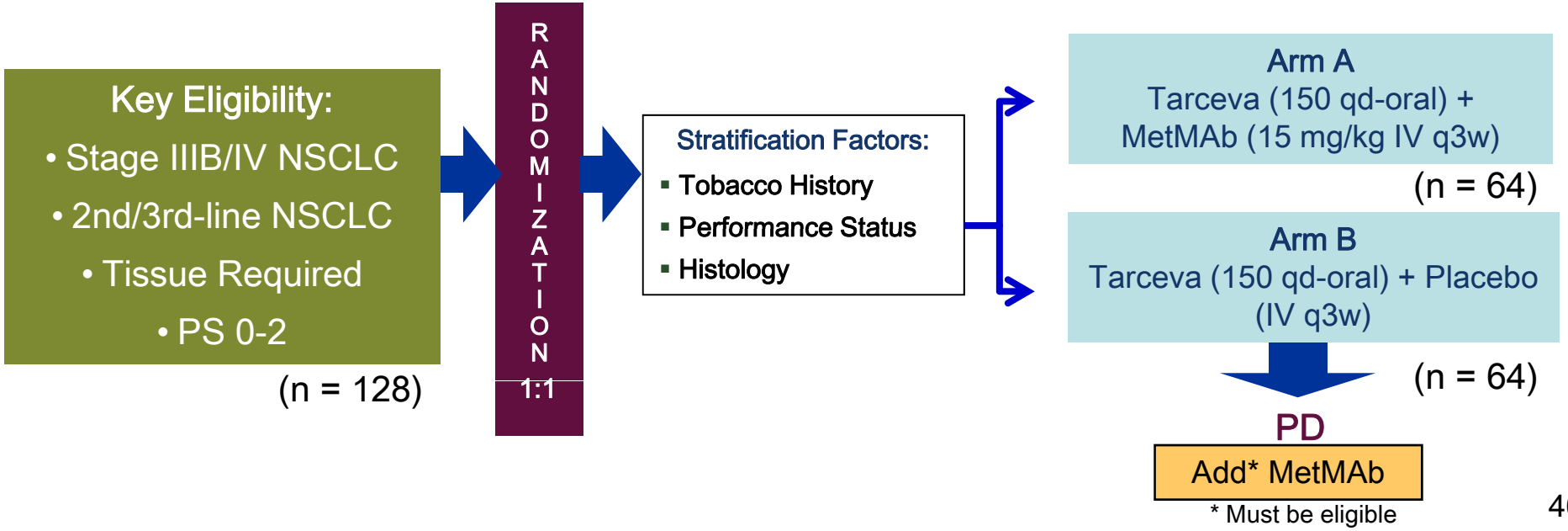
- Met is amplified, mutated, overexpressed in many tumours, including NSCLC. Associated with a worse prognosis in NSCLC
- Met activation is implicated in resistance to Tarceva in patients with EGFR mutations
- MetMAb is a one-armed antibody designed to prevent HGF-mediated stimulation of pathway
- Showed preclinical activity across multiple tumor models, and increased efficacy in combination with Tarceva



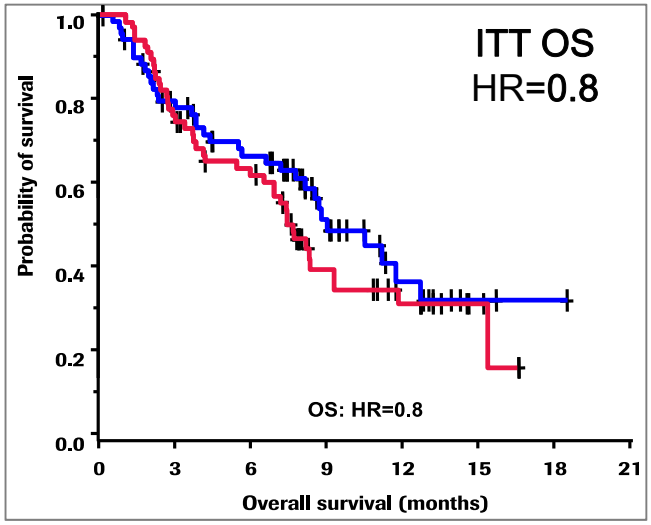
HGF = Hepatocyte growth factor

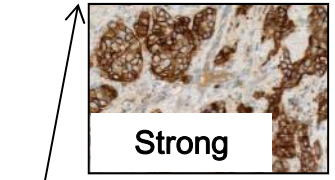
A Phase II Study Testing Tarceva ± MetMAb in Second-/third-line NSCLC

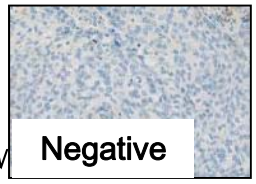
Design	A randomized, phase II, multicenter, double-blind, placebo-controlled study evaluating the safety and activity of MetMAb, in combination with Tarceva (Erlotinib)
Population	Adult patients (> 18 yrs) who have inoperable locally advanced or metastatic (stage IIIb/IV, PS 0-2) NSCLC and have received at least one but no more than two prior regiments
Sample size	128 (IHC was evaluated in 121)
Dose	15 mg/kg (IV, Q3W) + 150 mg Tarceva (qd-oral)
1st endpoint	PFS in patients with Met positive tumors as well as overall
2nd endpoint	OR, duration of OR

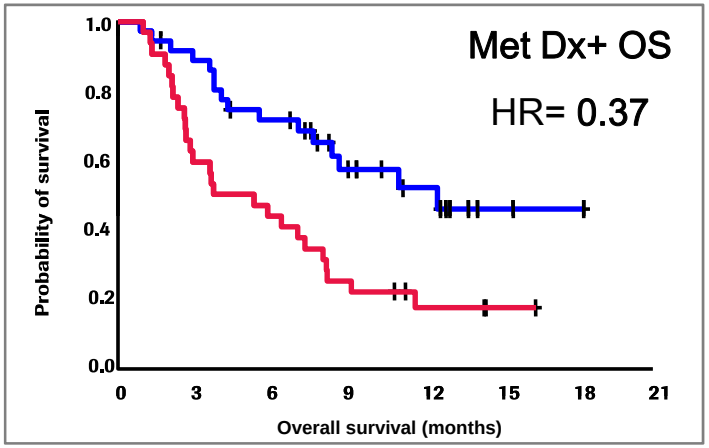


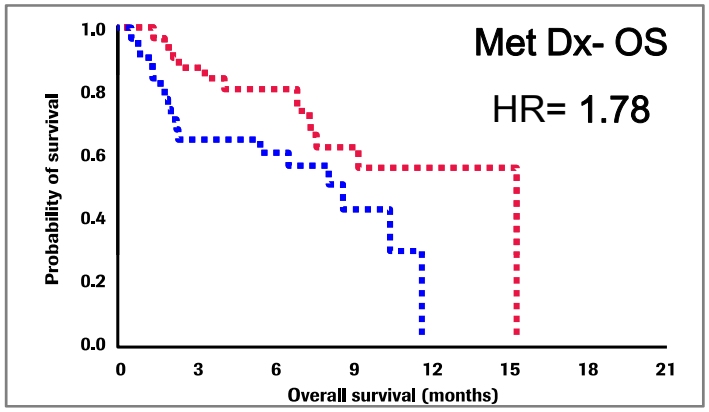
NSCLC: Significant Survival Benefit in Dx+ 2/3 line NSCLC Treated with MetMAb + Tarceva







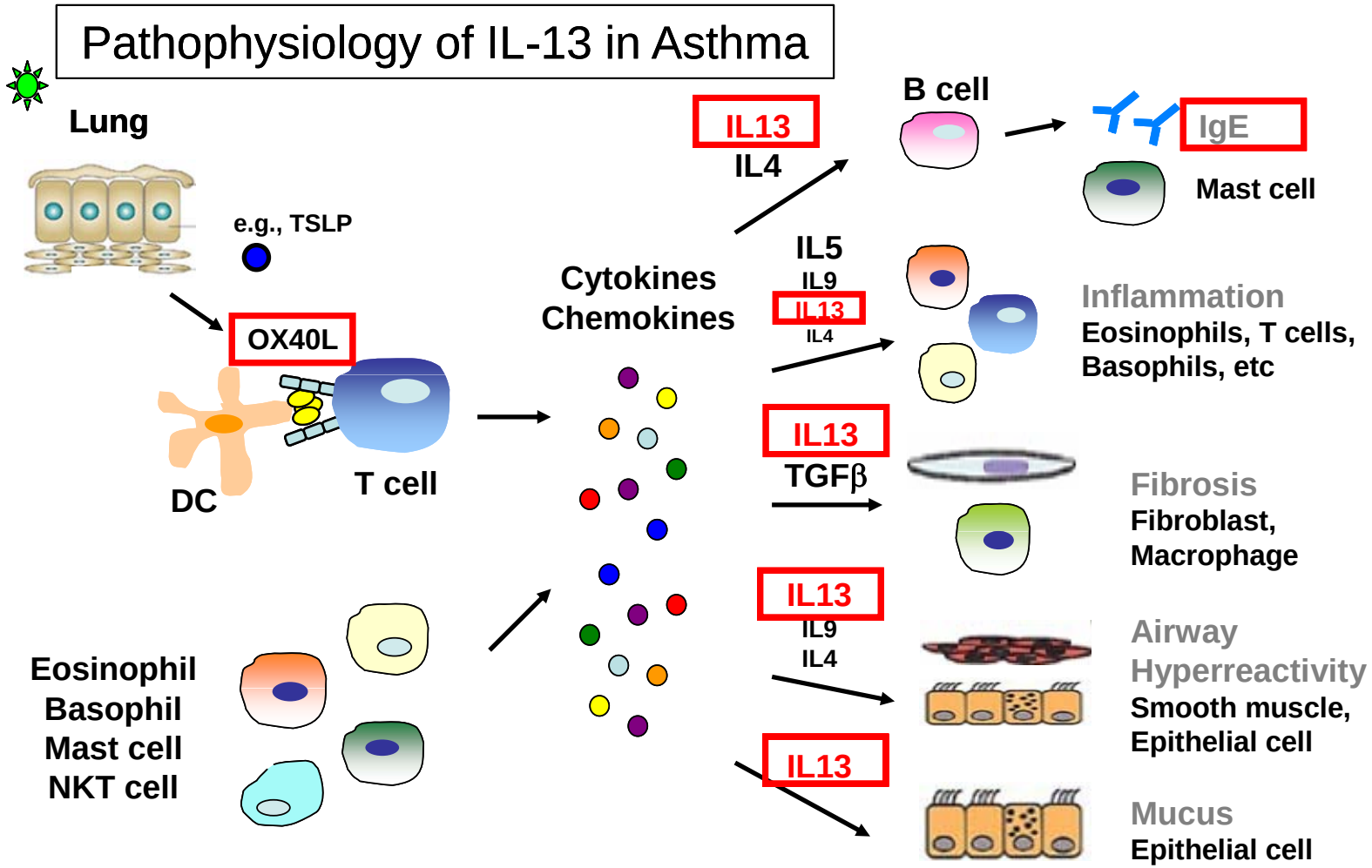




Lebrikizumab

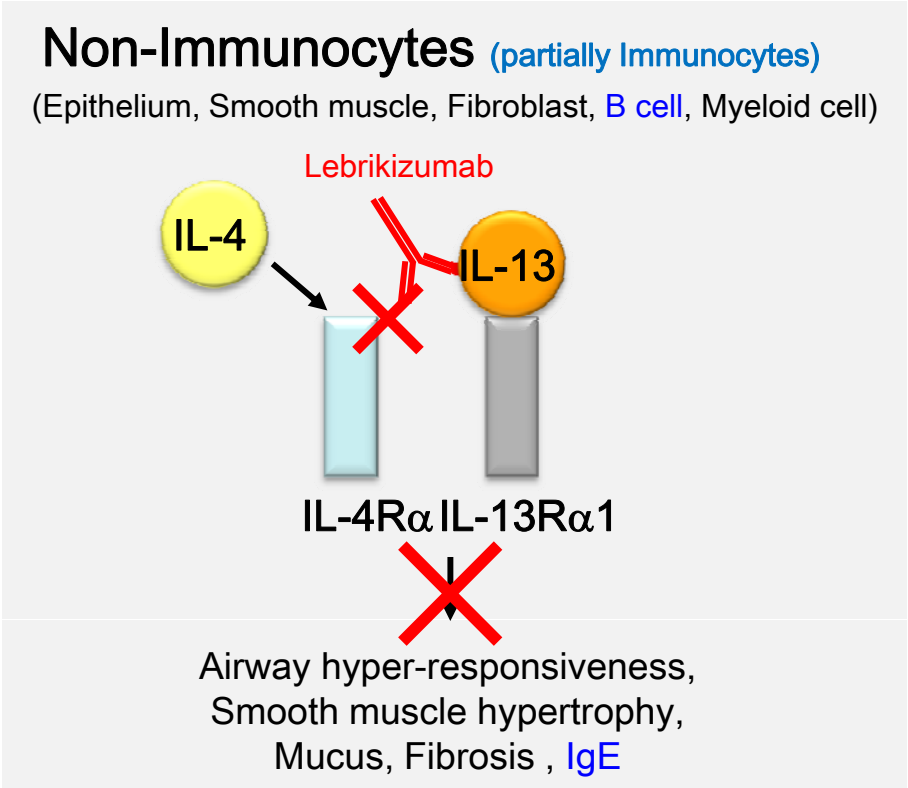
A recombinant humanized anti-IL-13 antibody against periostin high asthma

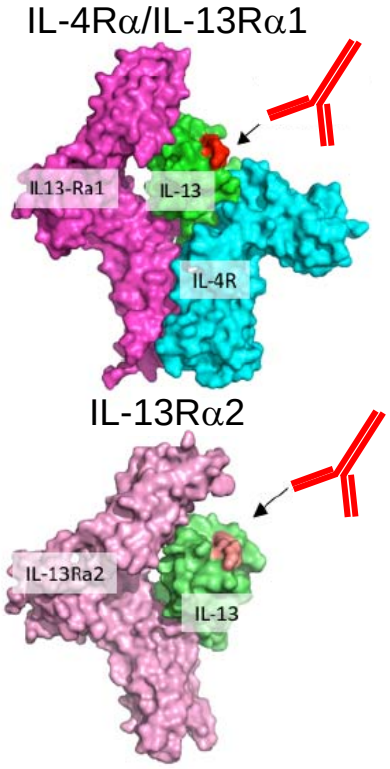
Lebrikizumab :
Science Rationale of IL-13 for Asthma



Mode of Action：Blocks IL-13 Binding to IL-4Rα and Inhibits IL-13 Signaling through IL-4/IL-13Rα1

- Lebrikizumab
  - Inhibits recruiting IL-4Ra to IL-4Ra/IL-13Ra1 complex after binding lebrikizumab/IL-13 complex to IL-13
  - Is expected to have effect on airway hyper reactivity, mucus production and fibrosis in the lung

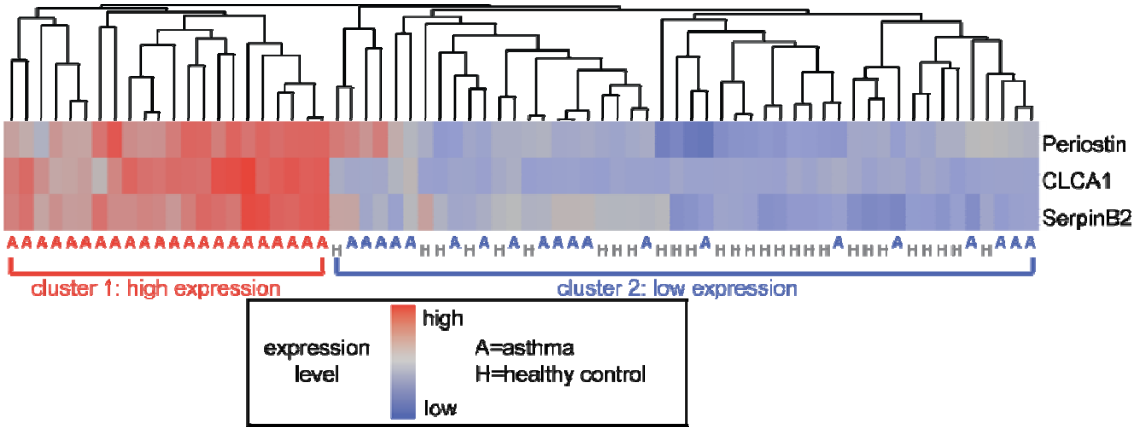




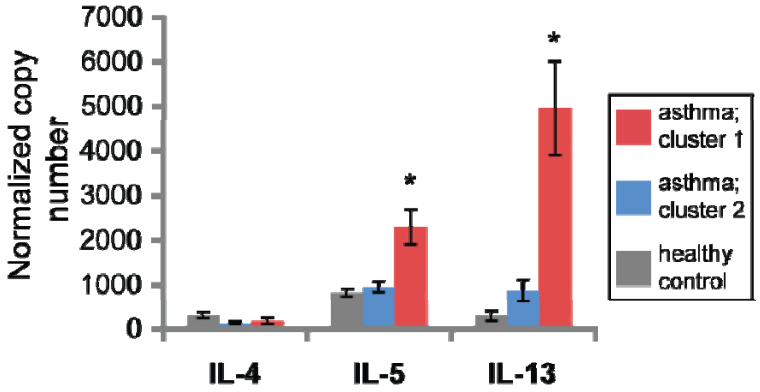
Periostin Gene is Highly Expressed in Bronchial Epitherial Cells in Half of Asthmatics

IL-13 responsive gene signature in bronchial epithelium

asthmatics asthmatics & controls



Th2 cytokine expression in bronchial biopsies

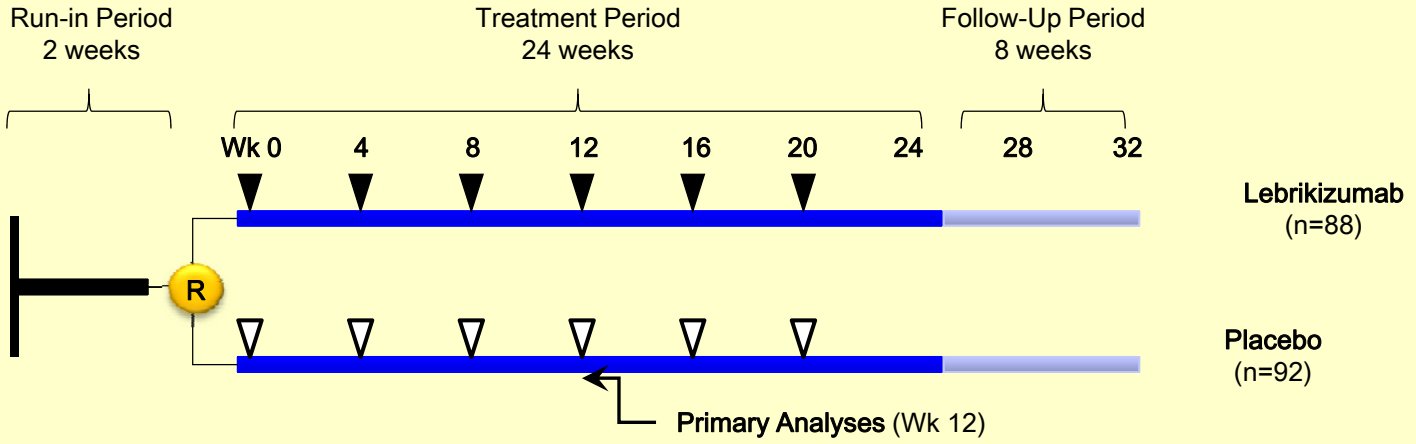


Level of periostin induced by IL-13 is projected to correlate with asthmatic symptom of patients with level of IL-13.

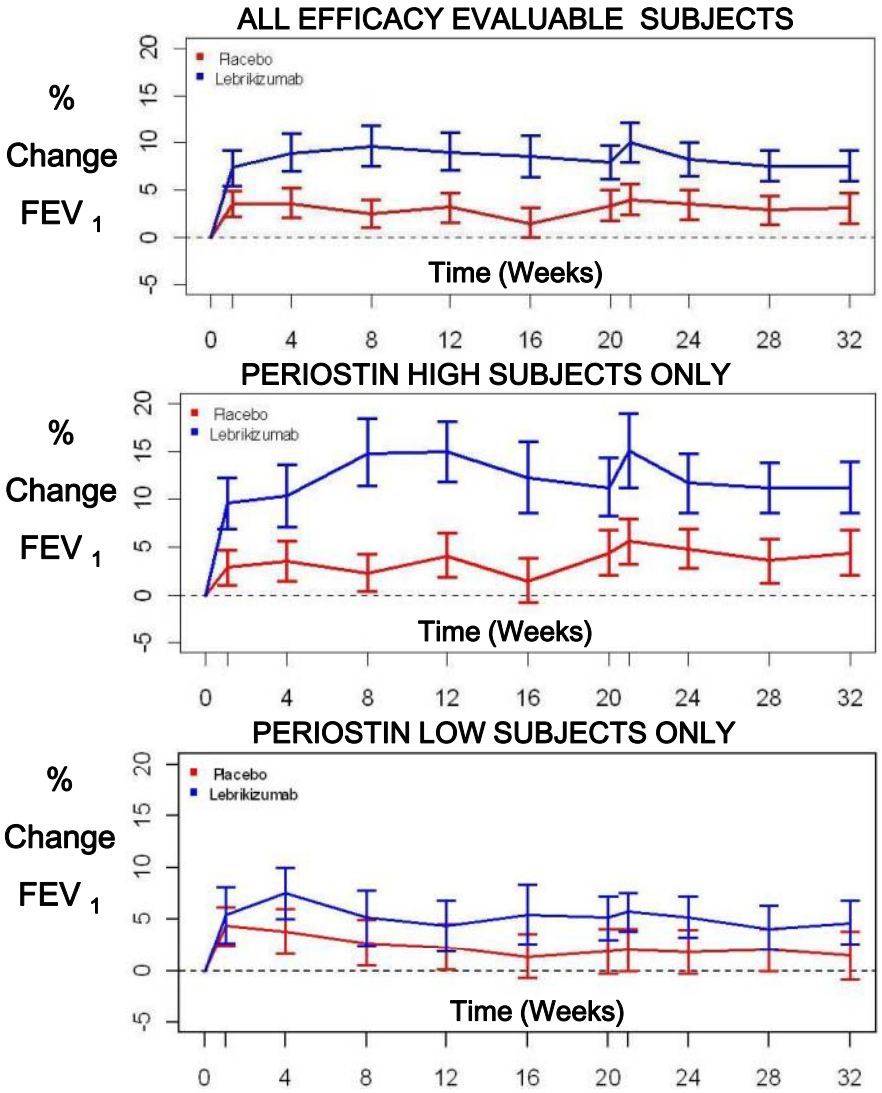
Woodruff PG et al, *AJRCCM* **180**:388 (2009)

Study Overview of P2 (MILLY)

Design	1:1 randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of lebrikizumab vs placebo
Population	18-65 year old patients with asthma who are inadequately controlled on inhaled corticosteroids (ICS)
Sample Size	218 [200 originally planned] 180 were evaluated
Study Duration	2 week screening period, 24 week treatment period, 8 week safety follow-up period
Dose	250 mg, SC, every 28 days, for a total of 6 doses
1° endpoint	Relative change in FEV1 from baseline to Week 12
2° endpoints	Relative change in FEV1 from baseline to Week 24 Rate of asthma exacerbations during the 24-week period



Asthma: Relative Change in FEV1* from Baseline in Asthma Patients Treated with Lebrikizumab



	Relative Mean FEV1 change at week 12		
	Total ITT population	Periostin High	Periostin Low
Placebo	4.3%	5.8%	3.5%
Lebrikizumab	9.8%	14.0%	5.1%
Difference	5.5% (p=0.02)	8.2% (p=0.03)	1.6% (p=0.61)

cobas e 601

Periostin assay

*FEV1: Forced Expiratory Volume in 1 second

Corren et al. NEJM, 2011

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