DEVELOPPING NEW THERAPIES: A LOOK AT THE FUTURE

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Fundación Investigación
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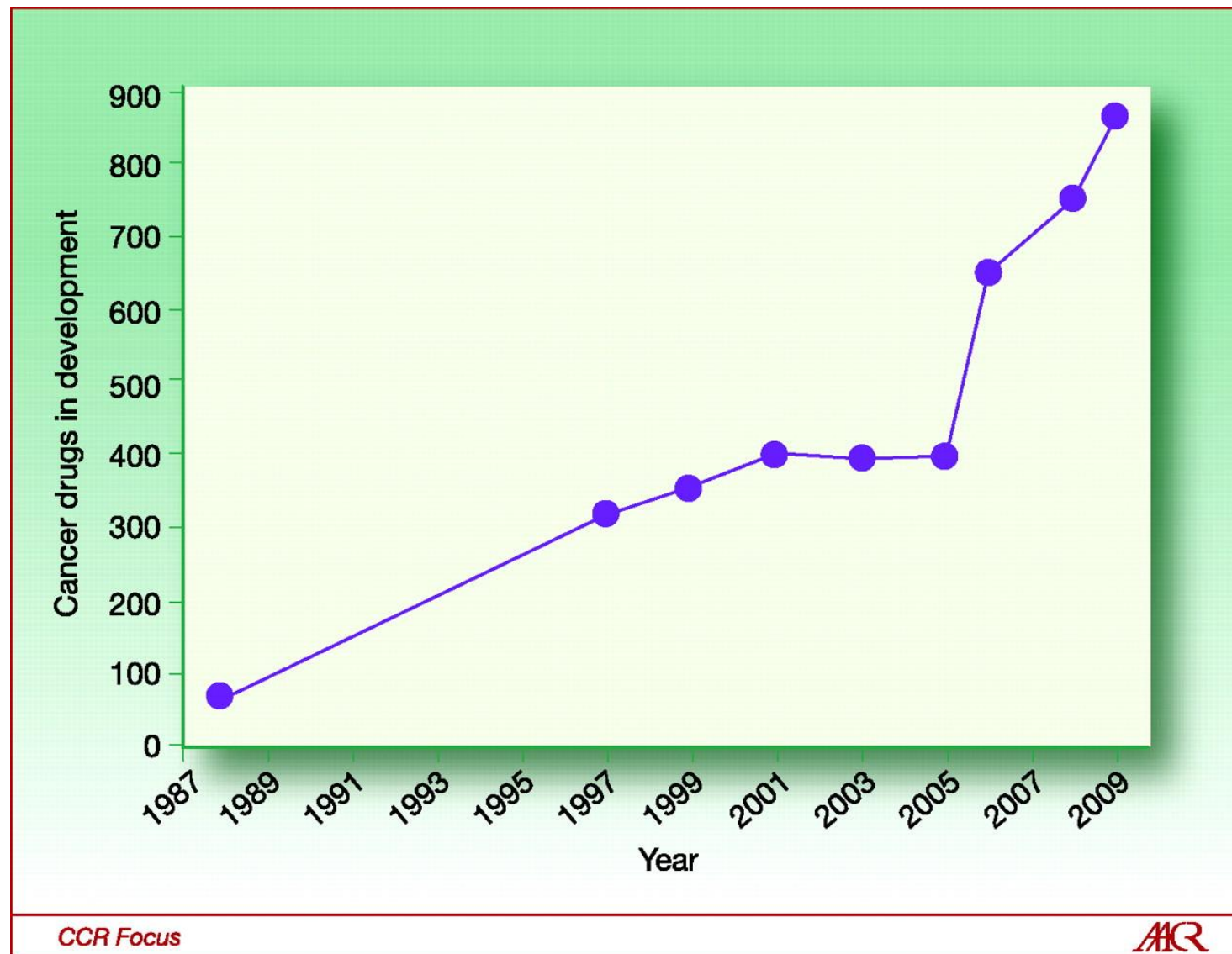**incliva**
Instituto de Investigación Sanitaria

VNIVERSITAT
DE VALÈNCIA

CANCER DRUGS TESTED IN CLINICAL TRIALS OR UNDER U.S. FDA REVIEW BY YEAR

LoRusso P M et al. Clin Cancer Res 2010;16:1710-1718

AIMS OF A PHASE I (FIRST IN HUMAN) TRIAL

- **Safety**
- **Tolerability**
- **Pharmacokinetics**
- **Pharmacodynamics**
- **To document any evidence of antitumor effect**
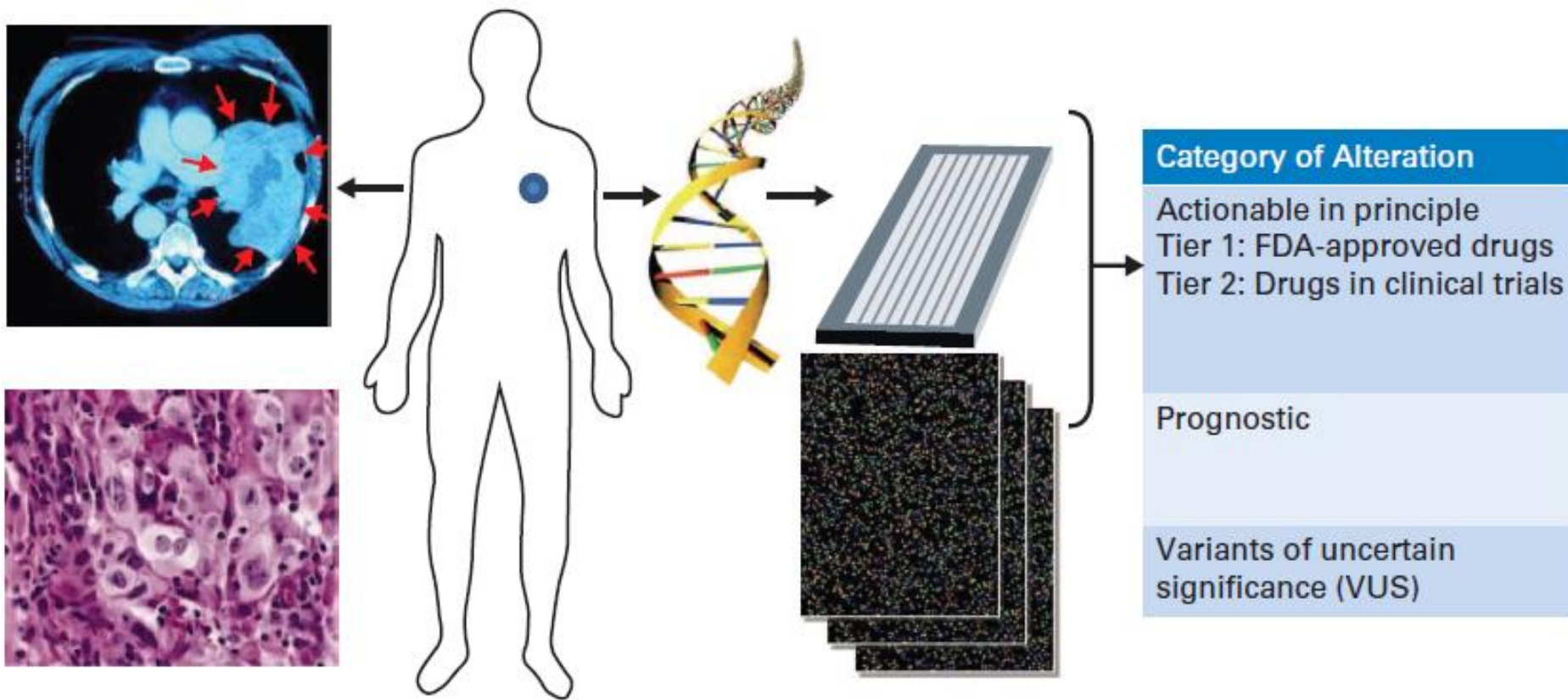- **To determine a recommended dose for a phase II trial**

AIMS OF A PHASE I (FIRST IN HUMAN) TRIAL

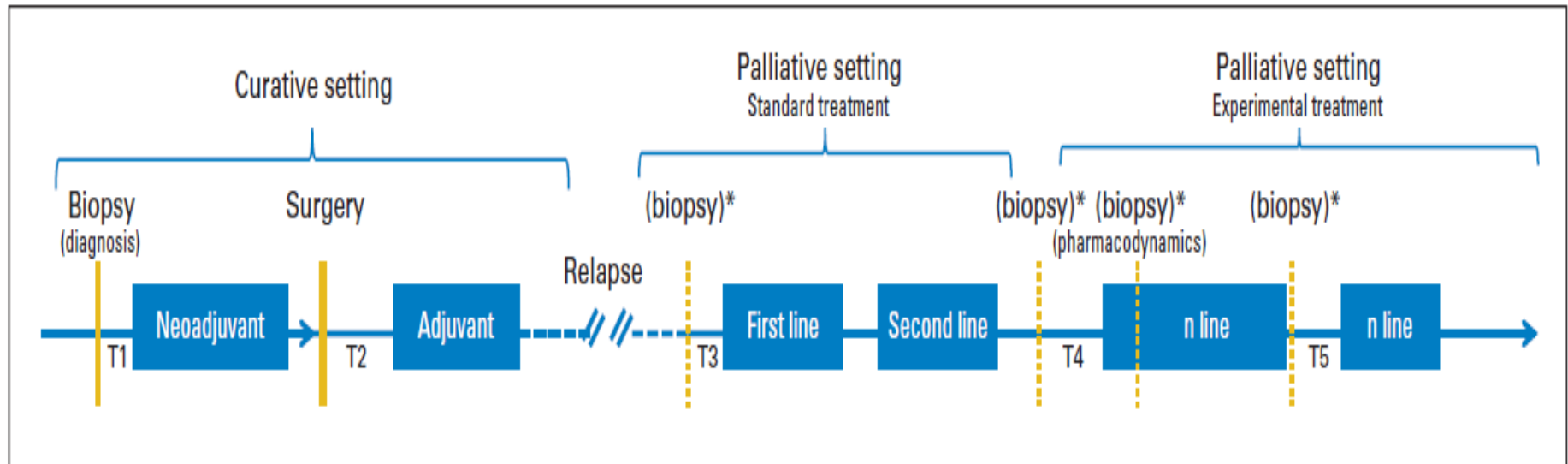**Maximum tolerated dose (cytotoxic agents)**

Versus

Optimal or effective dose
Relevant level of target modulation

GENOMICS DRIVEN CANCER MEDICINE

Garraway LA, Verwey J, Ballman K. J Clin Oncol 2013

SCHEDULING OF TUMOR BIOPSIES AND THE OPORTUNITIS FOR GENOMIC ANALYSIS

Dienstmann R, Rodón J, Tabernero J. J Clin Oncol 2013

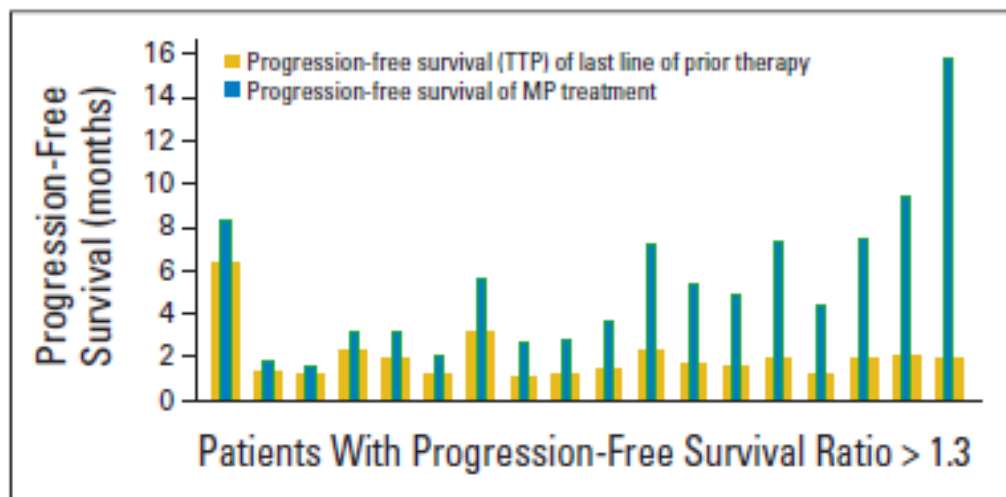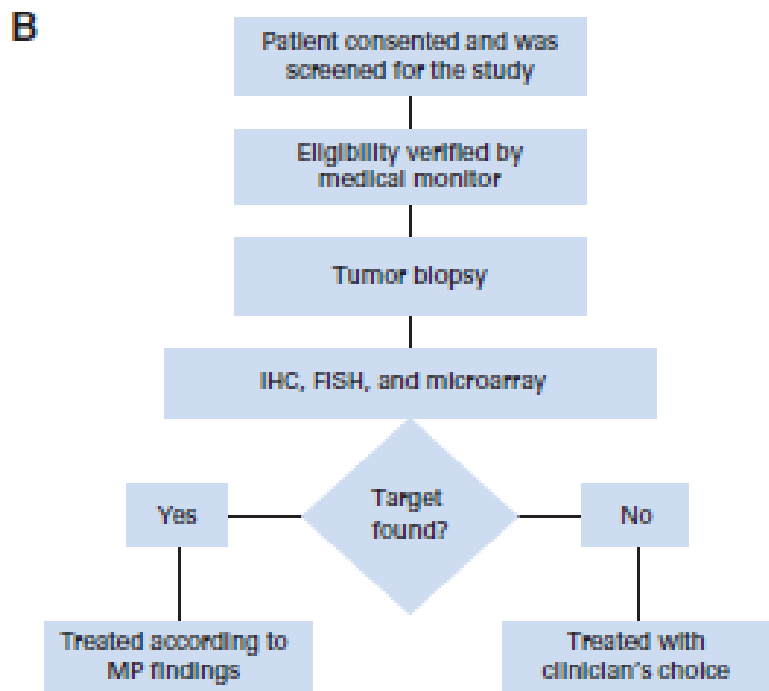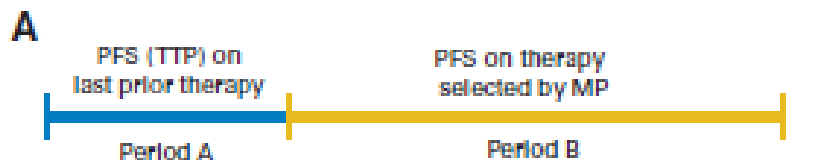# TREATMENT OF REFRACTORY TUMORS AFTER THEIR MOLECULAR PROFILLING

A

PFS (TTP) on last prior therapy — Period A

PFS on therapy selected by MP — Period B

B

Patient consented and was screened for the study

Eligibility verified by medical monitor

Tumor biopsy

IHC, FISH, and microarray

Target found?

Yes → Treated according to MP findings
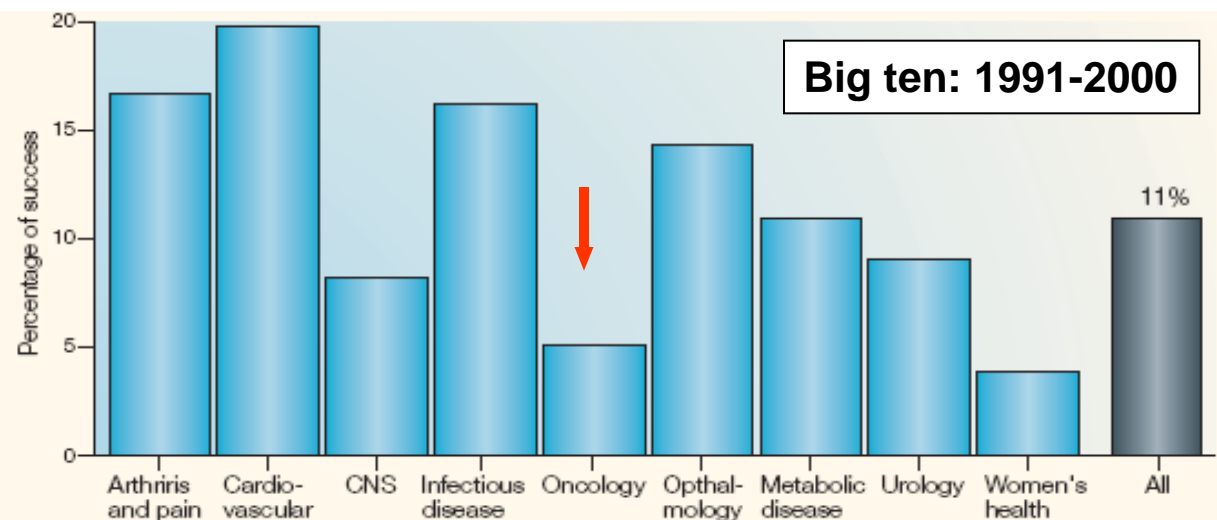
No → Treated with clinician's choice

Fig 3. Comparisons of progression-free survival (PFS) on molecular profiling (MP) therapy (blue bars) versus PFS (time to progression [TTP]) on prior therapy (gold bars) for the 18 patients with a PFS ≥ 1.3.

Von Hoff D, et al. J Clin Oncol 2010

ATTRITION RATE IN ONCOLOGY DRUG DEVELOPMENT

Big ten: 1991-2000

- Failure rate:
  - Phase III:
    45% (all) vs 59% (Onc)
  - Registration:
    23% (all) vs 30% (Onc)

- Causes:
  - Lack of efficacy (30%)
  - Safety (30%)
  - Pharmacokinetic (10%)
  - Other (30%)

Kola et al, Nat Rev Drug Discover 2004
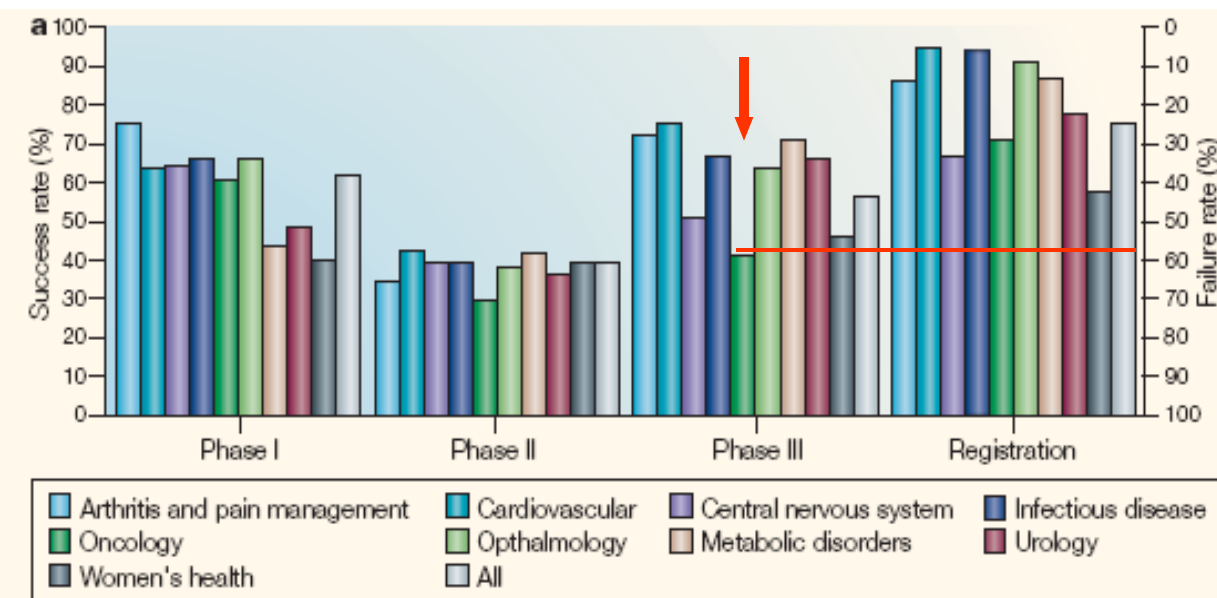
ATTRITION RATE IN ONCOLOGY DRUG DEVELOPMENT

1995-2007 period: 800 oncology drugs, 150 kinase inhibitors

Oncology drugs	Ph I → Ph II	Ph II → Ph III	Ph III → Market	Attrition rate
	(Transition probability)			
All	0.8	0.49	0.59	77%
Kinase inhibitors	0.88	0.75	0.83	45%

Evolution: 95% → 77% → 45% (kinase inhibitors)

Causes:
• Clinical trial design
• Patient stratification
• More representative preclinical animal models
• Use of biomarkers

HOW TO REDUCE ATTRITION IN ONCOLOGY DRUG DEVELOPMENT?

- **Strong proof of concept evidence:**
  - **Target, target relevance, target dependency**
- Minimize toxicity:
  - Gene knockouts, RNAi, preclinical toxicology
- Appropriate animal models:
  - Genetic (transgenic or knockout animals) and "xenopatients" rather than xenograft models
- **Identification of biomarkers:**
  - **Phase I: POC studies, correct dosing/schedule**
  - **Phase I/II: Target "population"**
- **Appropriate phase I**, phase II and phase III designs
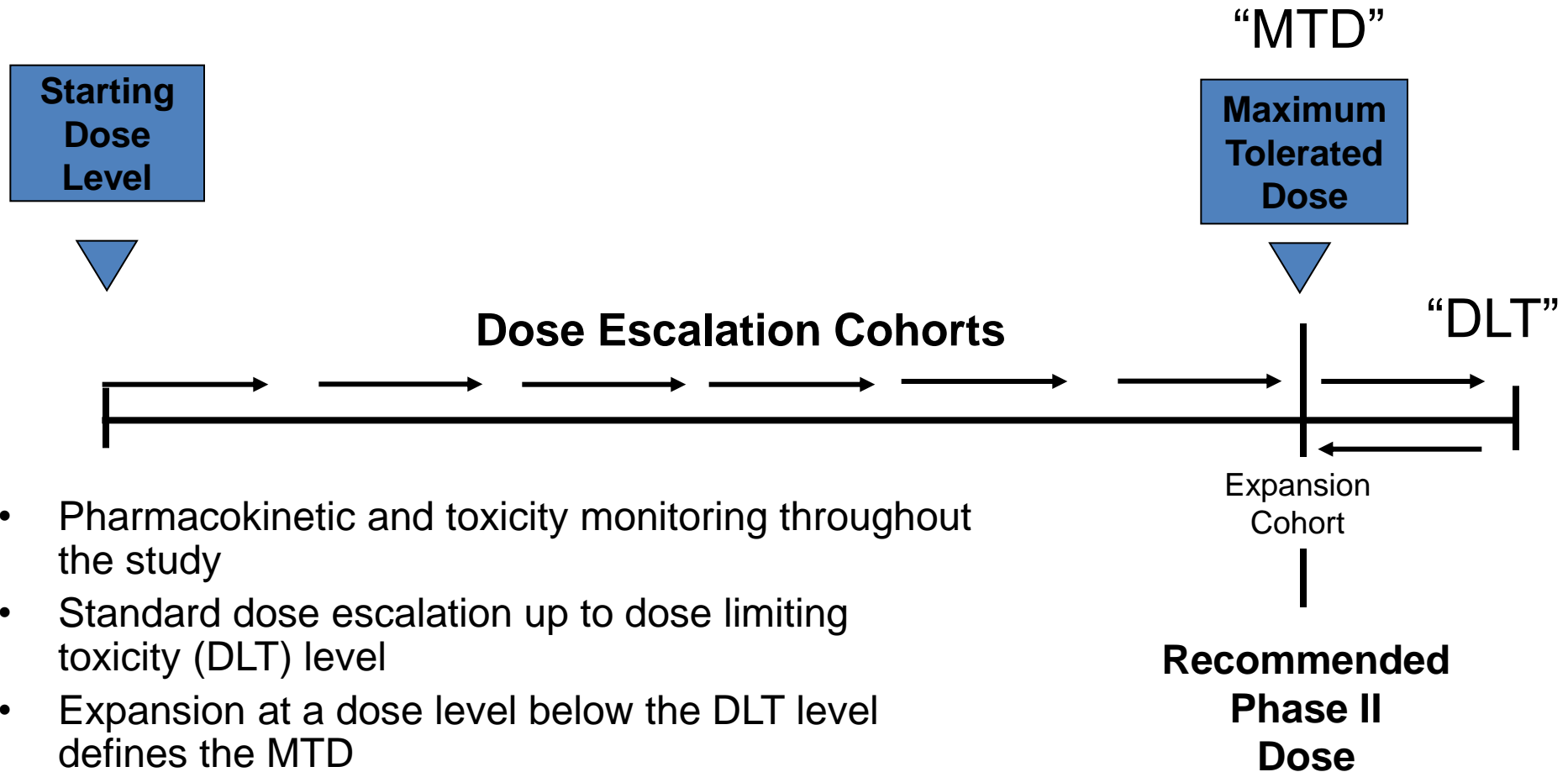- Early discontinuation for "commercial" reasons

BIOMARKERS IN DRUG DEVELOPMENT

- **Pharmacodynamic/Mechanism of Action Biomarkers**
  - Inform about a drug's pharmacodynamic actions
  - Most relevant to early development
    - Dose and schedule selection
    - Define pharmacological behaviour in patients
    - Goal: Improve efficiency of early development

- **Predictive Biomarkers**
  - Identify patients who will/will not respond to treatment
  - Most relevant to mid/late development
    - Basis for stratified/personalized medicine
    - Develop co-diagnostic biomarker assays
    - Goal: Enrich treatment population to maximize benefit

The biomarker hypothesis

→ Early investment (phase I-II) in biomarkers will accelerate development time lines and reduce costs

- Increase probability of registrational success through increased scientific understanding of the drug, target and pathway:
  - Proof of mechanism of action
  - Proof of mechanism of resistance (primary and secondary)
  - PD exploration: right schedule and dose
- Permit focused clinical studies with higher probability of demonstrating benefit:
  - Adaptative study designs
  - Prospective screening of patients for enrolment

TRADITIONAL ONCOLOGY PHASE I STUDY DESIGN

"MTD"

Starting Dose Level

Maximum Tolerated Dose

Dose Escalation Cohorts

"DLT"

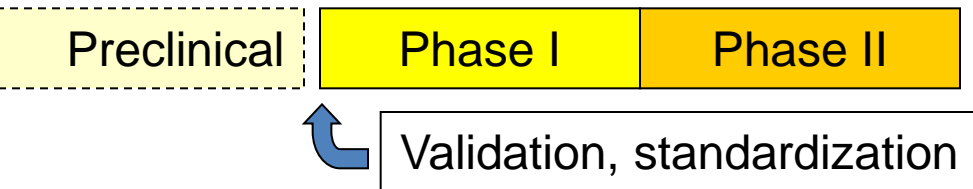Expansion Cohort

Recommended Phase II Dose

- Pharmacokinetic and toxicity monitoring throughout the study
- Standard dose escalation up to dose limiting toxicity (DLT) level
- Expansion at a dose level below the DLT level defines the MTD
- MTD is the recommended Phase II dose for further study

Provided by Chris Takimoto

BIOMARKER DEVELOPMENT IN DRUG APPROVAL TIMELINES

Drug approval time lines

| Preclinical | Phase I | Phase II | Phase III | Registrational |

MoA/PD Biomarkers

| Preclinical | Phase I | Phase II |

Validation, standardization

Predictive Biomarkers

| Preclinical | Phase I | Phase II | Phase III |

Validation, standardization
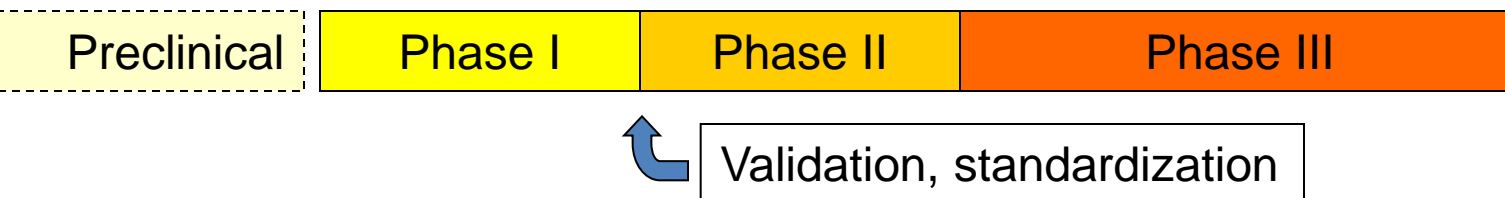
- Ph. II trials are the 1st opportunity for correlative studies with sufficient patients exposed to a RD
- Novel markers discovered in late ph. II will delay ph. III entry
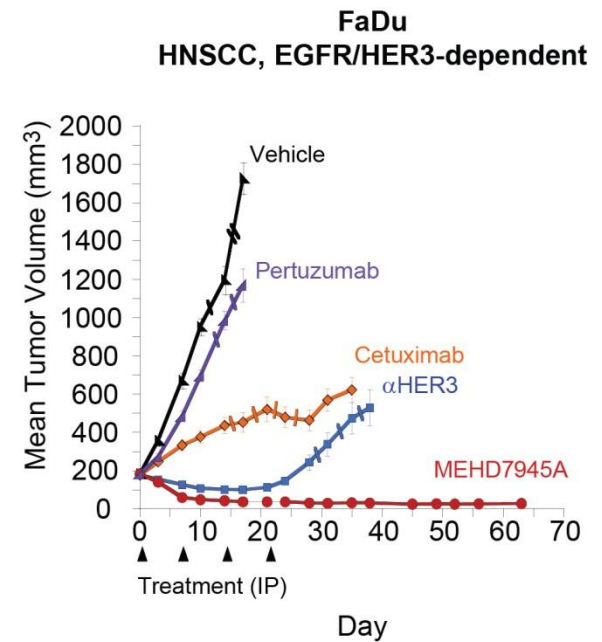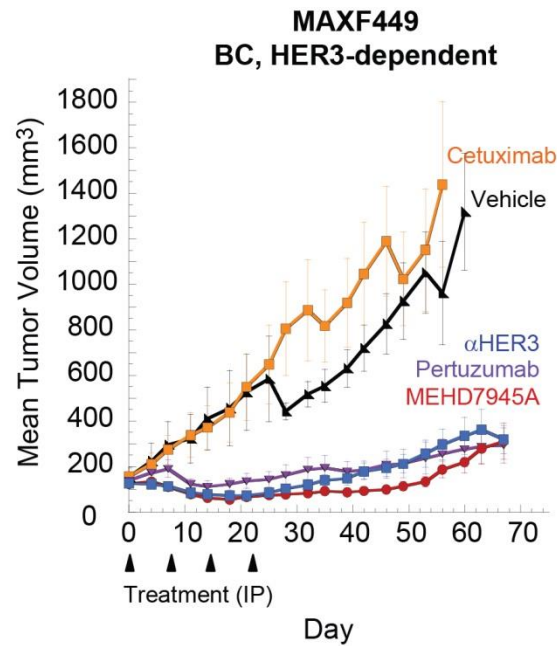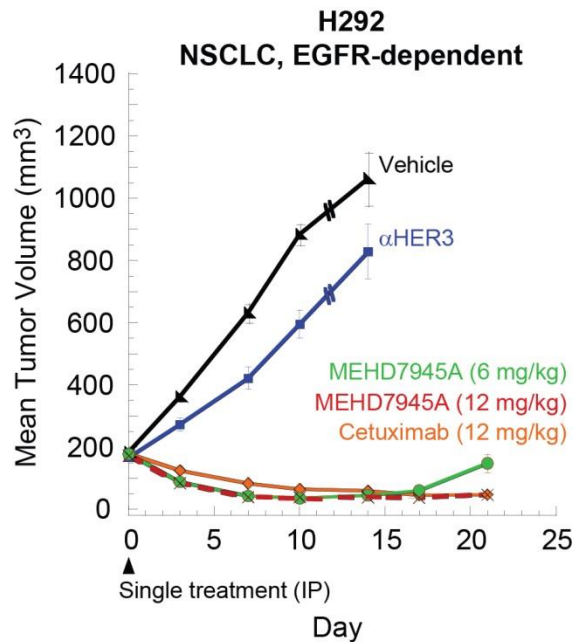
Anti-EGFR/HER3 Dual-action Fab: MEHD7945A

MEHD7945A: A novel, first in class, two in-one antibody

Light Chain

HER3

Heavy Chain

EGFR
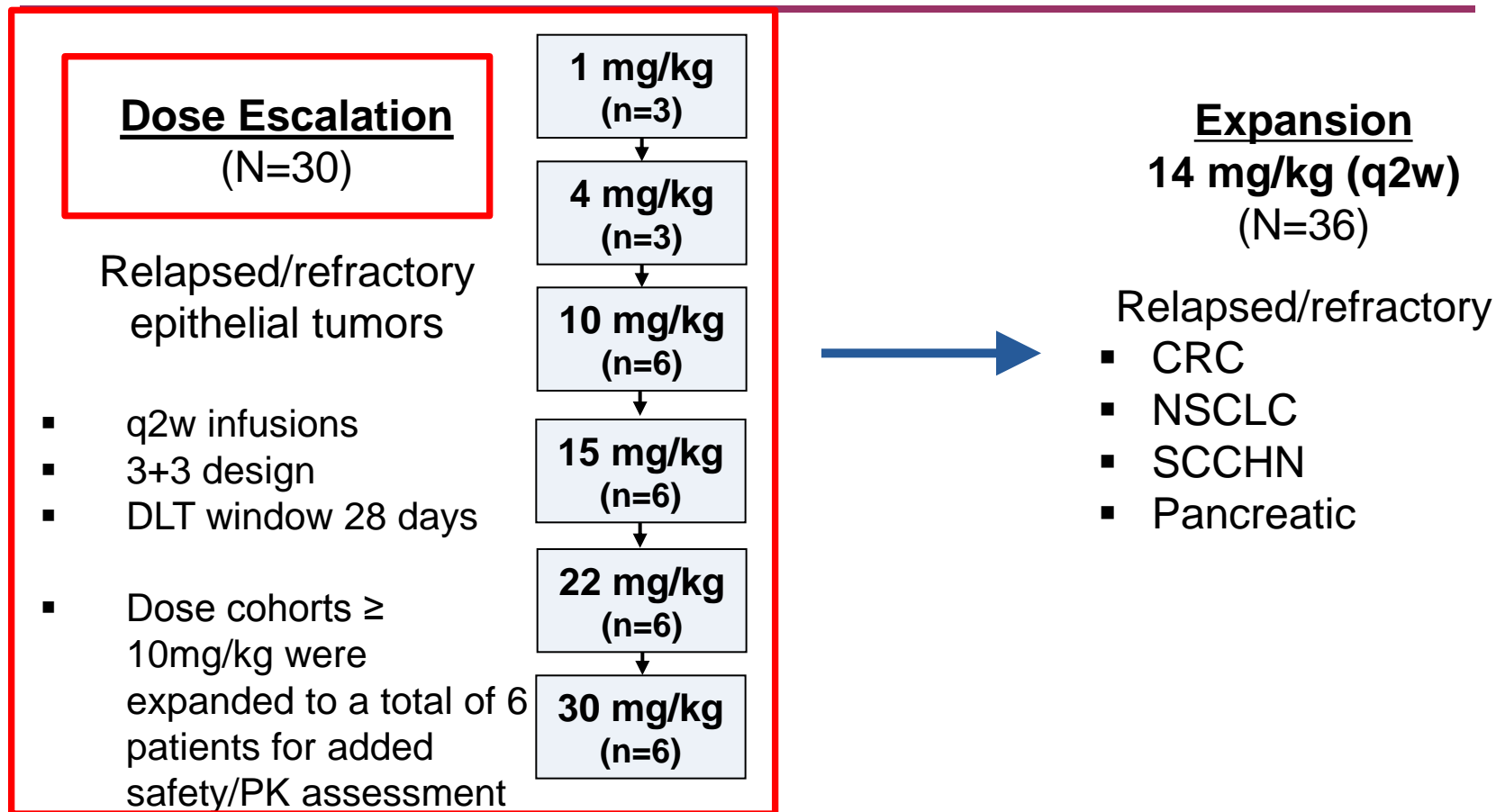
Antigen-binding fragment

Fc
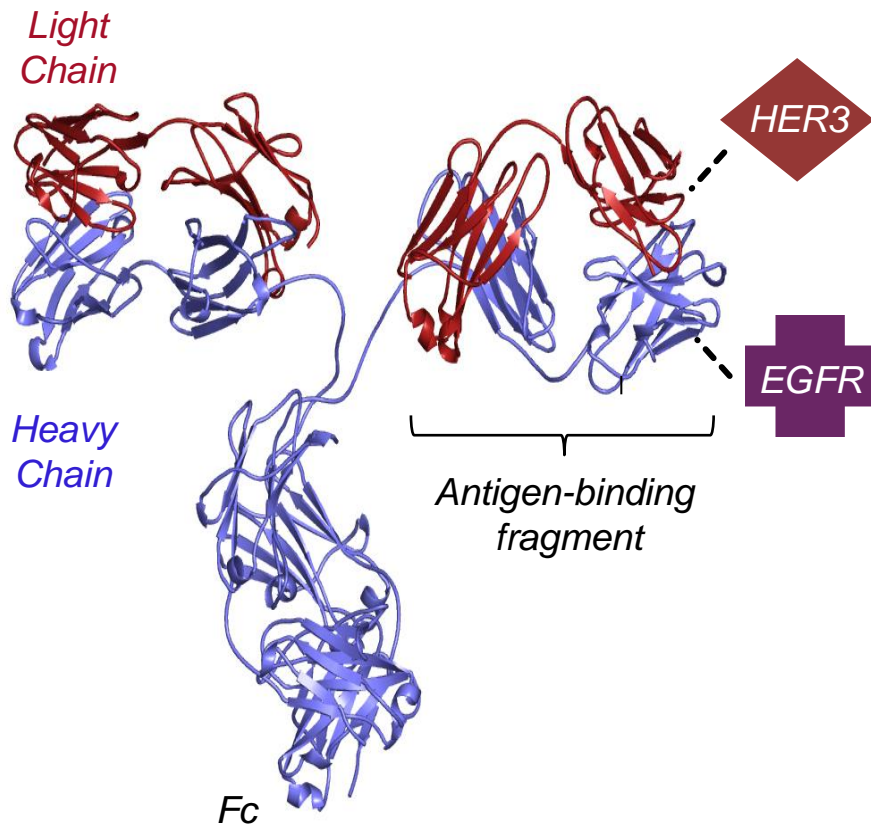
- Affinity-matured, human IgG1
- Dual binding specificity:
  - Each Fab binds to either EGFR or HER3 with high affinity
  - Simultaneously blocks ligand-binding to EGFR and HER3
    - Binding affinity to EGFR: $K_d = 1.9$ nM
    - Binding affinity to HER3: $K_d = 0.4$ nM
- Inhibits signaling by all major ligand-dependent HER-family dimers
- Mediates ADCC

Schaefer et al., Cancer Cell, 2011.

MEHD7945A: Activity vs. Monospecific Antibodies

- As active as cetuximab in EGFR-driven tumor models
- Efficacy seen in HER3-driven tumor types where cetuximab has no effect
- Increased activity over other HER monospecific antibodies in models where both EGFR and HER3 signaling contribute to tumor growth

Schaefer et al., Cancer Cell, 2011.

FIRST-IN-HUMAN PHASE I STUDY DESIGN (DAF4873G)

Dose Escalation
(N=30)

Relapsed/refractory epithelial tumors

- q2w infusions
- 3+3 design
- DLT window 28 days

- Dose cohorts ≥ 10mg/kg were expanded to a total of 6 patients for added safety/PK assessment

Dose
1 mg/kg (n=3)
4 mg/kg (n=3)
10 mg/kg (n=6)
15 mg/kg (n=6)
22 mg/kg (n=6)
30 mg/kg (n=6)

Expansion
14 mg/kg (q2w)
(N=36)

Relapsed/refractory
- CRC
- NSCLC
- SCCHN
- Pancreatic

- **Eligibility**: Patients with relapsed/refractory epithelial tumors
- **Endpoints**: PK, safety, DLT, objective response, exploratory PD
  - **PD markers**: FDG-PET, tumor biopsies (IHC/RPPA for pRAS40, pRbS6, and pERK), plasma biomarkers (e.g., amphiregulin, IL-8)

ANTI-HER3/EGFR ACTIVITY IN SCCHN PATIENT (1)

Baseline

C3, D8 (at week 5, after 3 infusions)

C5,D1 (at week 8, after 4 infusions)

| Line of Therapy	Treatment	Best Response
Dx (T4N2M0) Nov-2007	-	-
Induction therapy	Taxotere/platinum/5-FU (Nov-Dec 2007)	(Completed Regimen)
Concurrent chemo with radiation	RT 70Gy + carbo qw (Jan-Mar 2008)	CR
1L	Cetuximab (Oct 2009-Jun 2010)	SD (then PD)
2L	Cetuximab/carbo (Jul-Sep 2010)	PD
3L	Cetuximab/paclitaxel (Oct 2010-Mar 2011)	SD (then PD)
4L	Capecitabine (March-May 2011)	PD
5L	DAF 14 mg/kg (July 2011-present)	C2D2: better phonation, less pain, FDG-PMR C3D8: appreciable shrinkage of visible tumor C4D8: CT-PR (70% reduction in SLD)

ANTI-HER3/EGFR ACTIVITY IN SCCHN PATIENT (2)

Baseline
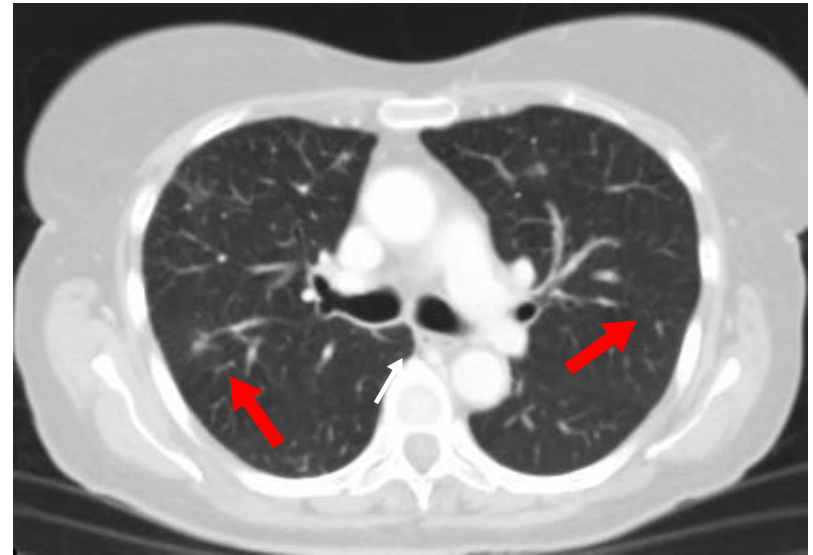
Pre-C5, D1 (CT at week 8, after 4 infusions)

- SCCHN of the tongue, diagnosed in 1994, ost recently metastatic to the lung
- Prior therapies include multiple surgeries and chemoradiation
- MEHD7945A at 14 mg/kg IV q2w since 09/11
- Confirmed PR and clincial improvement (regained ability to swallow)
- Remains active on study (> 6 months)

ANTI-TUMOR ACTIVITY IN SCCHN PATIENTS WITH HIGHEST TUMOR EXPRESSION OF HRG
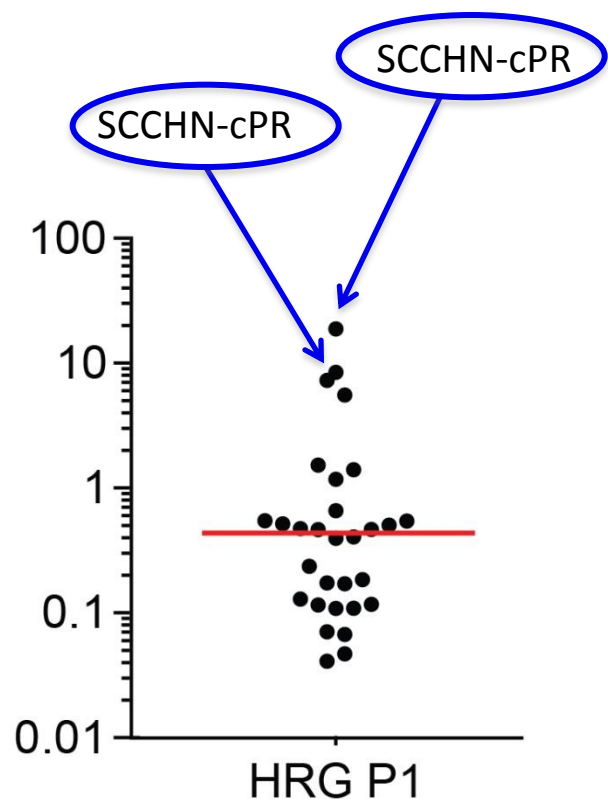

	SCCHN-cPR	SCCHN-cPR
First diagnosis	2007	1994
Tumor location	Larynx	Tongue + pulmonary mets
Prior anti-EGFR	Cetuximab 3x (± chemo)	None
MEHD7945A Line of treatment DOR (weeks)	5L +26	2L +18

Cells sensitive to EGFR/HER2 TKIs exhibit high levels of HRG/NRG1 and pHER3: suggestive of autocrine signaling

Autocrine HER3 signaling is inhibited by anti-HER3 portion of MEHD7495A

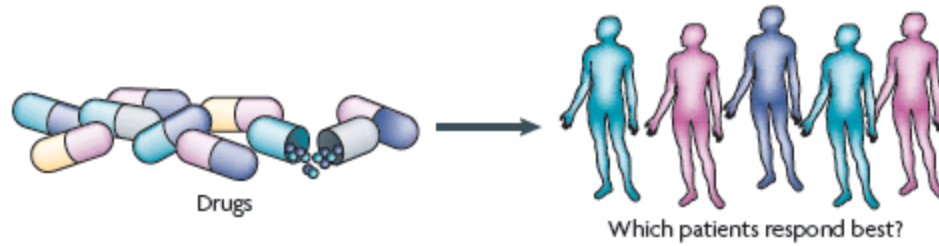*Wilson et al., Cancer Cell, 2011.*
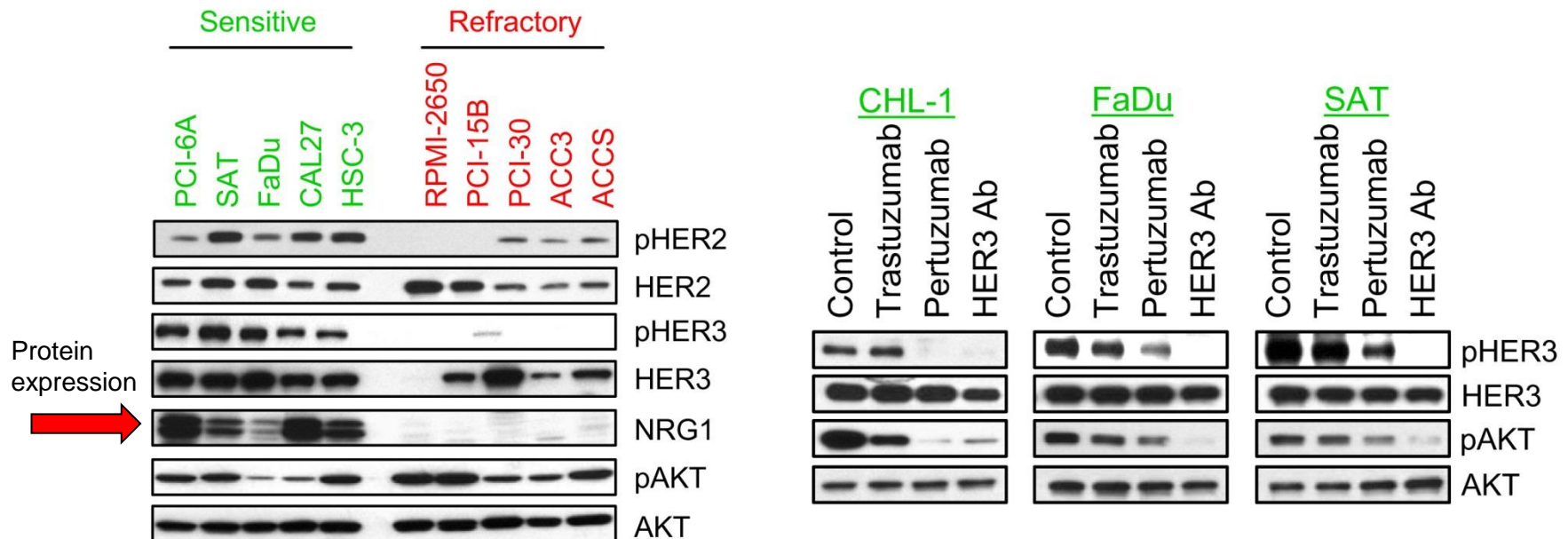
A NEW APPROACH

- Translational Phase I study with Biomarker Defined Endpoints
  - A new study design for targeted oncology agents
- PD/MoA biomarkers are formal study endpoints
  - Biologically effective dose (BED): biomarker defined
  - Maximum tolerated dose (MTD): toxicity defined
  - Recommended Phase 2 dose range: toxicity and biomarker defined
- Allows for the objective evaluation of the PhAT benchmarks

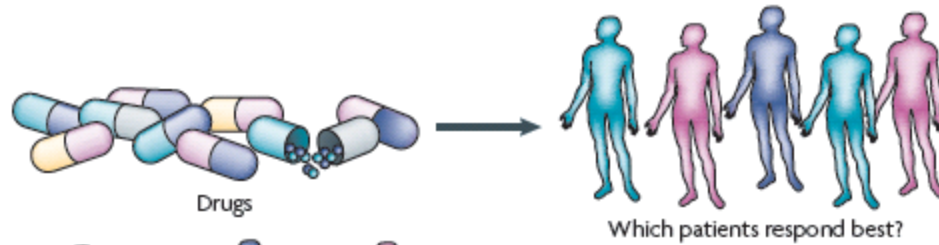# TRANSLATIONAL PHASE I STUDY WITH BIOMARKER-DEFINED ENDPOINTS

"BED"

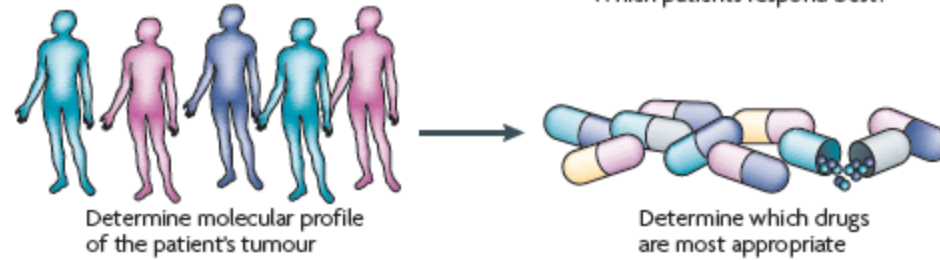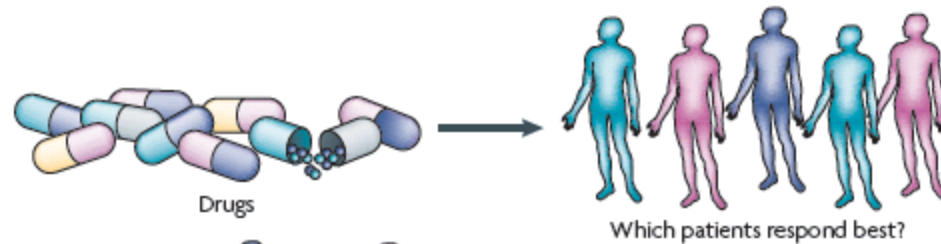"MTD"

Starting Dose Level

Target biomarker effect in surrogate tissues or if any clinical activity

Potential Phase 2 Dose Range

Maximum Tolerated Dose

Dose Escalation with biomarker monitoring in surrogate tissue

"DLT"

Expansion Cohort 3

Expansion Cohort 2

Expansion Cohort 1

- Biologically effective dose (BED) defined in by
  - Prespecified change in biomarker seen in a defined fraction of patients, or
  - Any clinical antitumor activity
- Maximum tolerated dose (MTD) defined in standard manner
- Expansion cohorts have mandatory tumour biopsies
- Phase 2 dose range defined by BED in tumour biopsies and by MTD

Tumour biopsy cohorts for biomarker evaluation

Provided by Chris Takimoto

The shift

Past

Drugs → Which patients respond best?

The shift

Past

Present & Future

Drugs → Which patients respond best?

Determine molecular profile of the patient's tumour → Determine which drugs are most appropriate
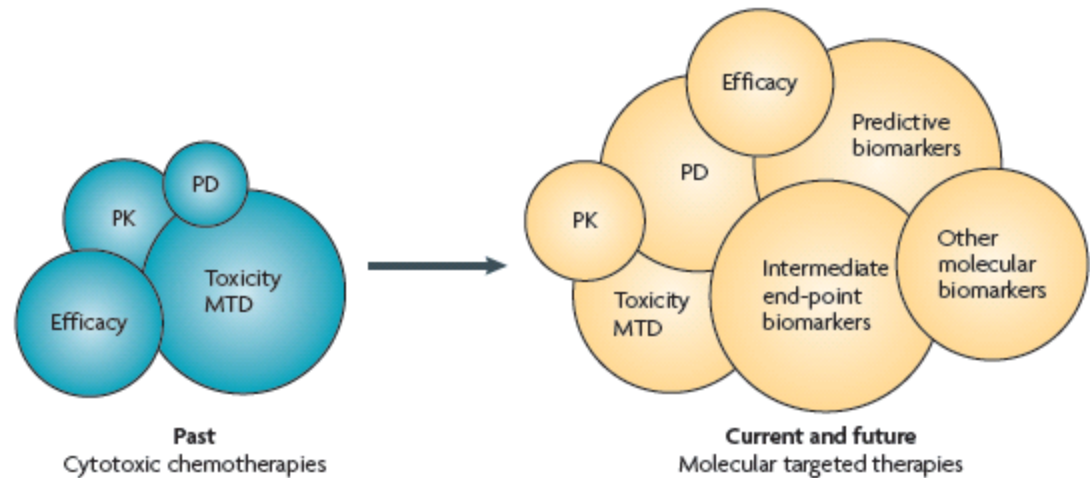
Yap et al, Nature Rev Cancer 2010
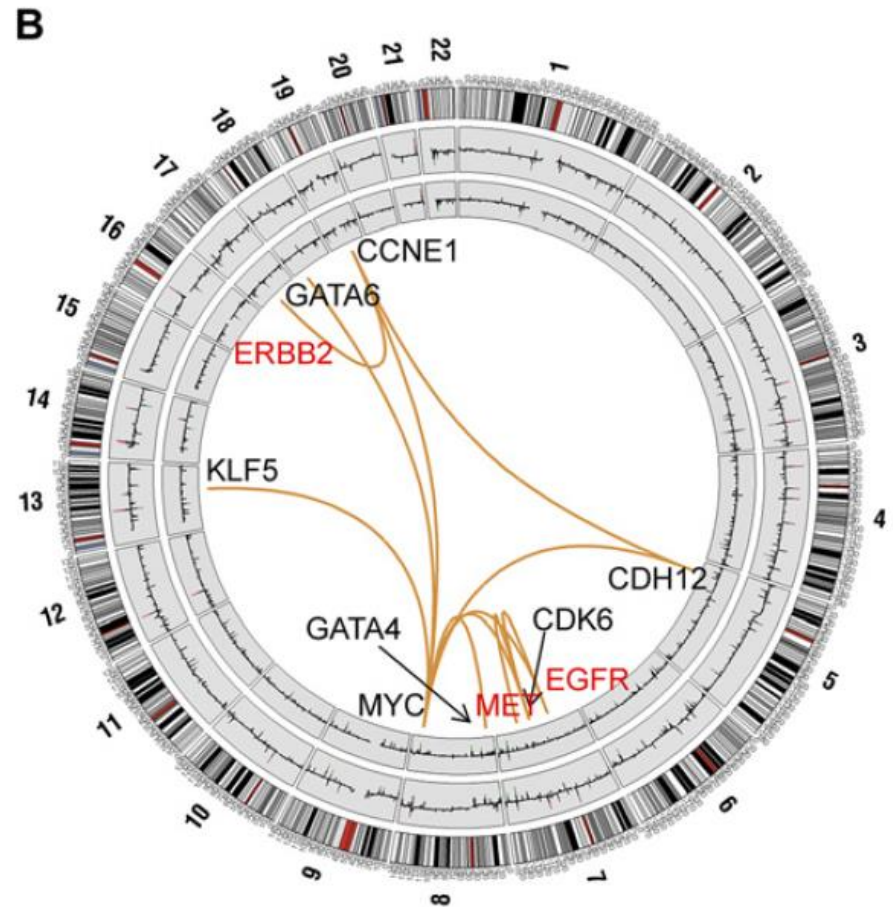
The shift

Past

Present & Future

Vision & Investment

A

B
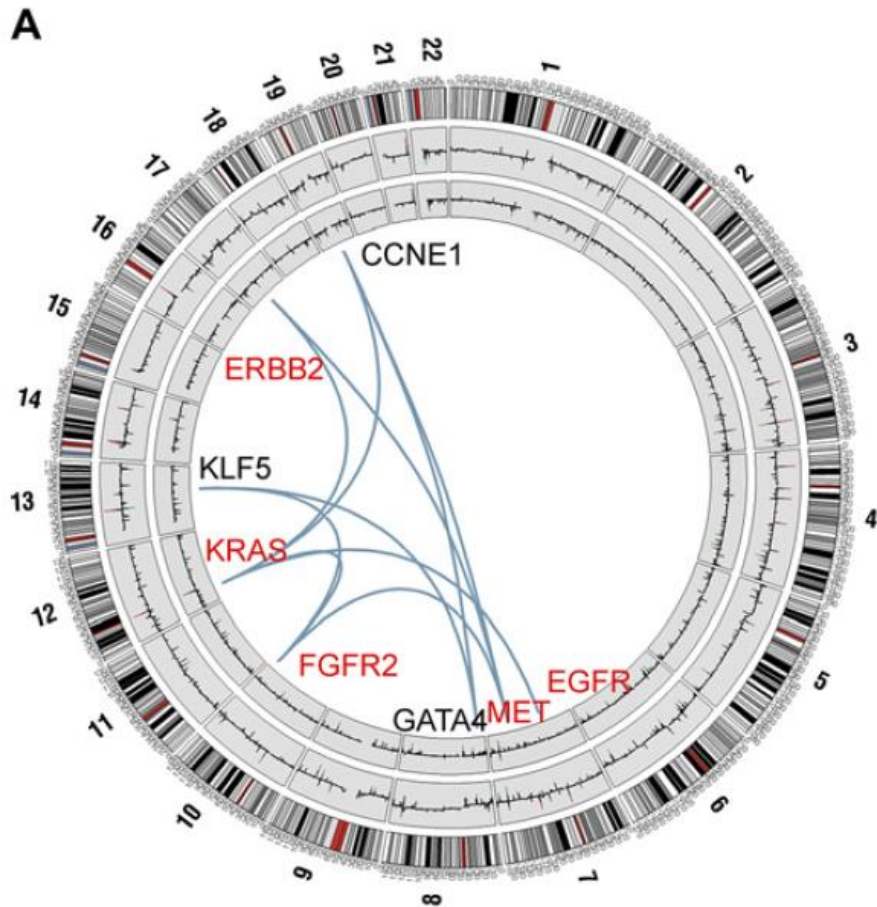
Mutually exclusive amplification
Co-amplification

DENG N, et al. GUT 2012; 62:673-684

LAUREN'S CLASSIFICATION OF GASTRIC NEOPLAMS
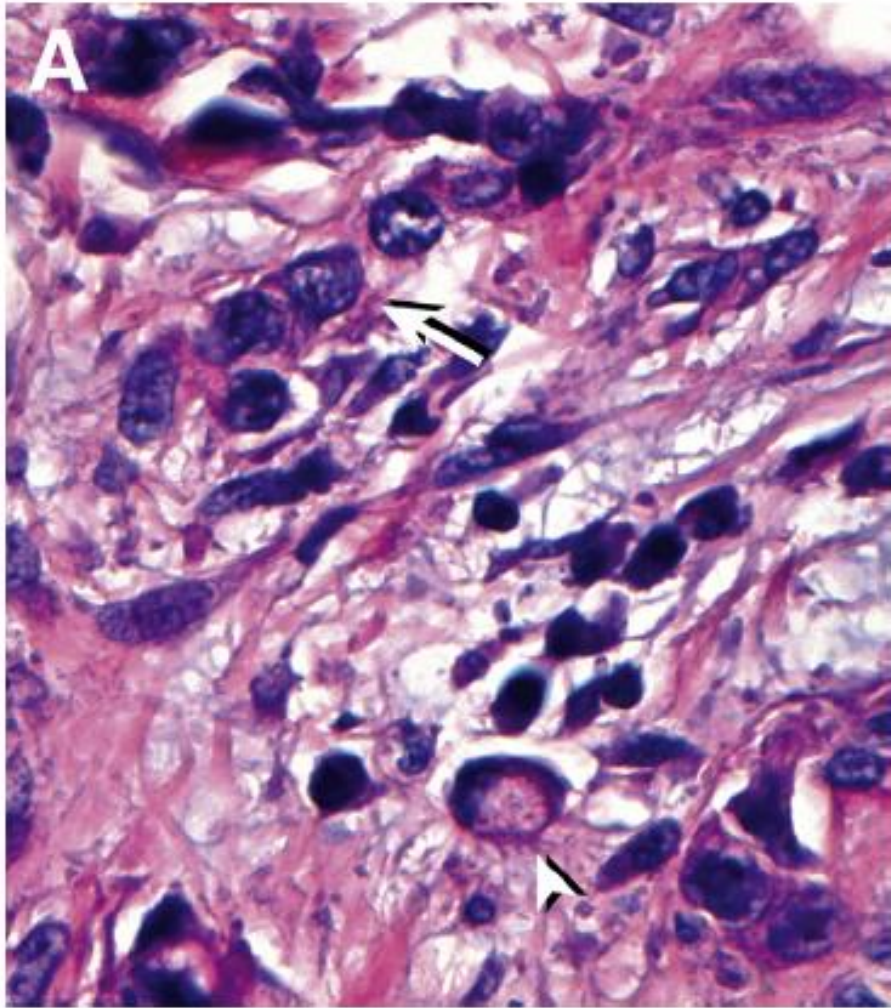
DIFFUSE
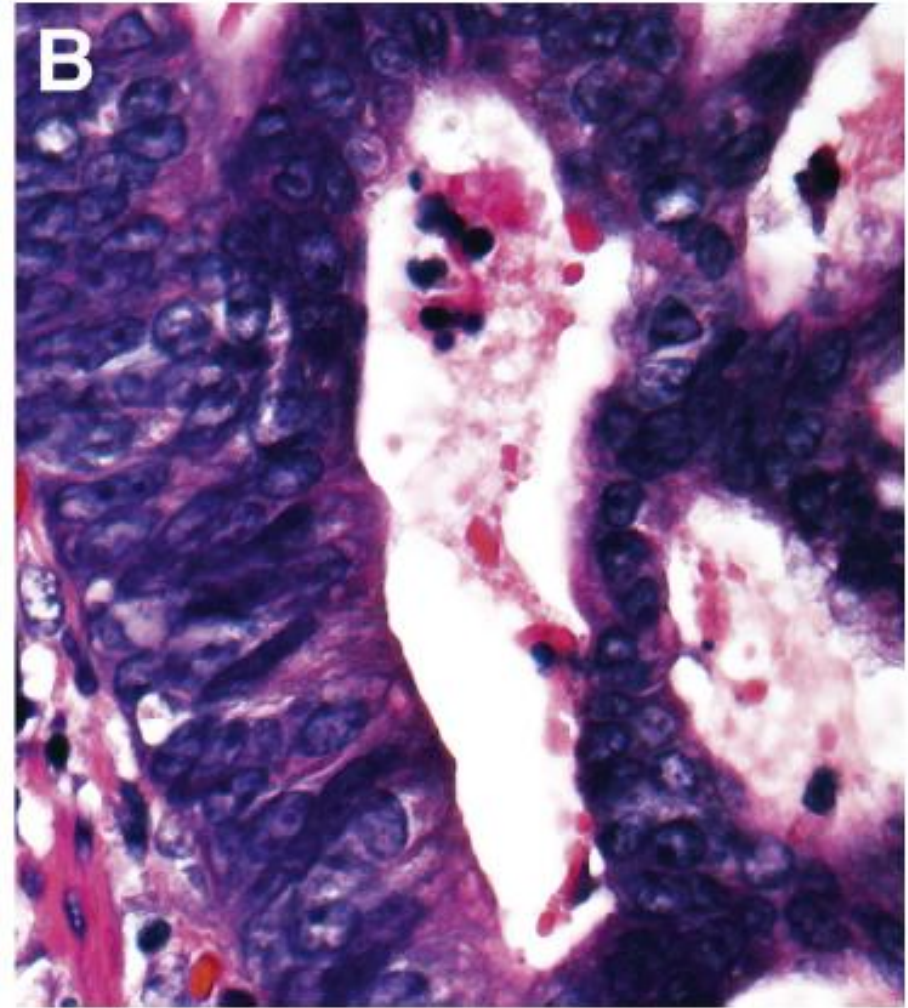
INTESTINAL

Table 1. Gastric Adenocarcinoma Classifications

	Lauren (1965)		Lei et al. (2013)		
	Diffuse	Intestinal type	Mesenchymal	Proliferative	Metabolic
Intestinal type morphology	0%[a]	100%[a]	30%[a] (7%)[a]	74%[a] (71%)[b]	54%[a] (84%)[b]
Diffuse morphology	100%[a]	0%[a]	59%[a] (93%)[b]	17%[a] (29%)[b]	41%[a] (16%)[b]
Intestinal metaplasia	55%	91%			
Chronic gastritis	45%	88%			
Copy number alteration			Low	High	
Amplified genes				CCNE1, MYC, ERBB2, KRAS	
Aberrant methylation			Hypermethylation	Hypomethylation	
TP53 mutations			Low	High	Low

[a]Classification based on criteria of Lauren (1965).[11]
[b]Classification based on criteria of Tan et al. (2011).[7]

A

B

| Mesenchymal | Proliferative | Metabolic |

Pathway seed gene set

KANNAN_P53
P53_BRCA1
JECHLINGER_EMT
TGFBETA_ALL
TGFBETA_C1
TGFBETA_C2
TGFBETA_C3
TGFBETA_C4
TGFBETA_C5
TGFBETA_EARLY
TGFBETA_LATE
VEGF_HUVEC
VEGF_HUVEC_30MIN
VEGF_MMMEC_12HRS
VEGF_MMMEC_3HRS
VEGF_MMMEC_6HRS
VEGF_MMMEC_ALL
BOQUEST_CD31PLUS_VS_CD31MINUS
HINATA_NFKB
PARENT_MTOR_SIGNALING
SHH_LAURENDEAU
CSC_RBIRNIE
CSC_SHIPITSIN
BILD_E2F3
E2F1_DNA
STANELLE_E2F1
LEE_MYC_E2F1
LEE_MYC
SCHUMACHER_MYC
LEE_MYC_TGFA
MENSSEN_MYC
BILD_MYC
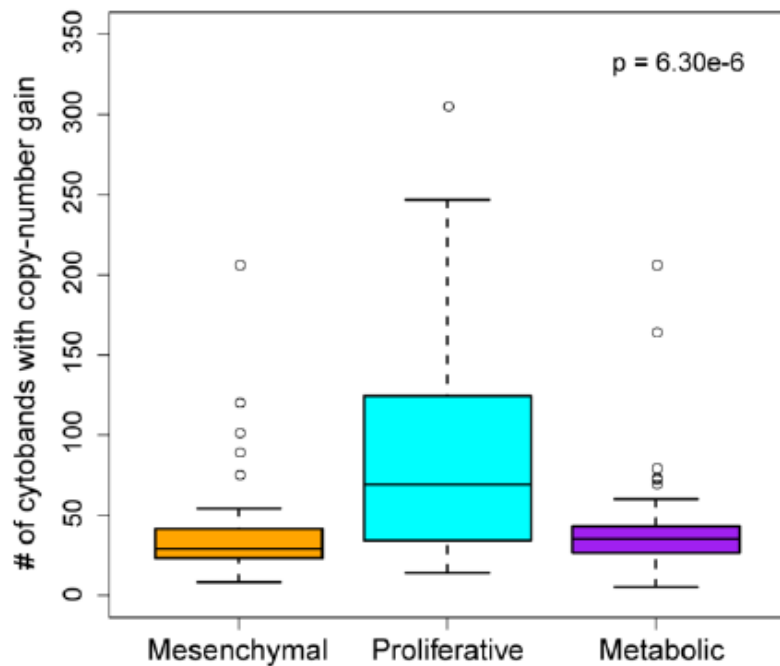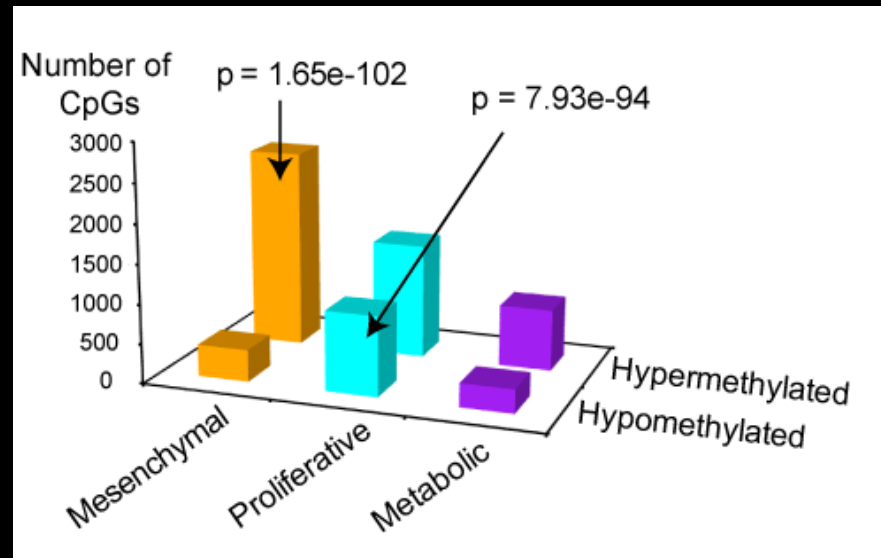ZELLER_MYC
BILD_RAS
SPEM_HJLEE

LEI Z et al. GASTROENTEROLOGY 2013; 145:554-565

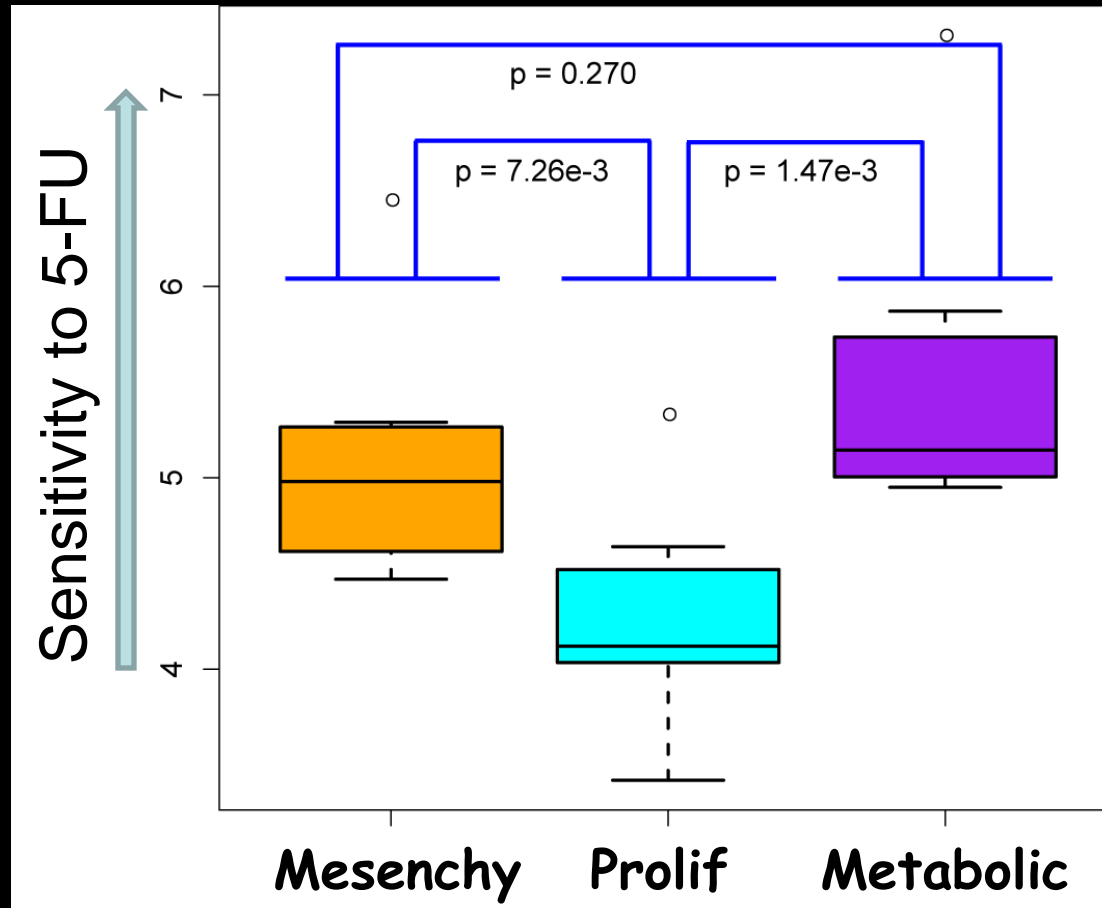# Proliferative GCs Have More Copy Number Alterations (*ERBB2*, *KRAS*) and *TP53* Mutations

Mesenchymal GCs Have Increased DNA Methylation
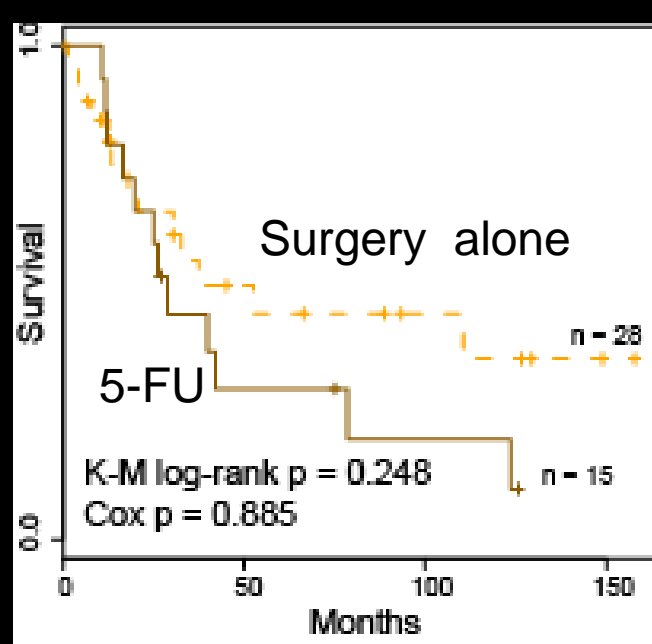

P53 mutations (p=0.003)

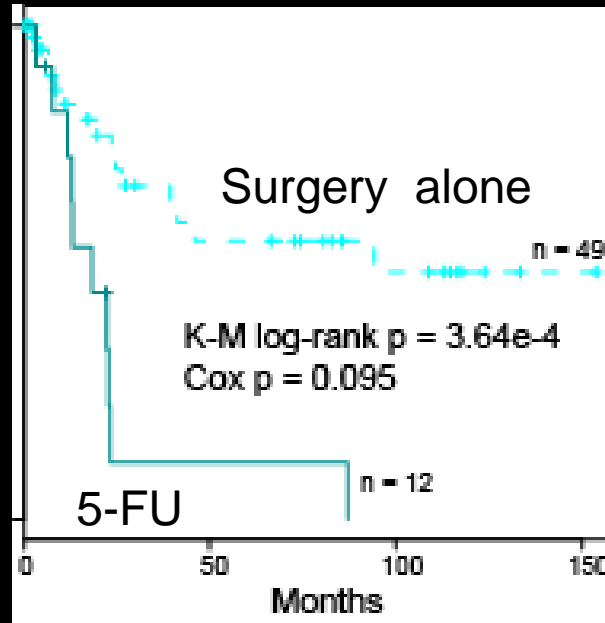# Metabolic GC Cell Lines Show Sensitivity to 5-Fluorouracil Treatment *in vitro*

GC Patients with Metabolic Subtype Tumors Respond Better to 5-Fluorouracil Treatment
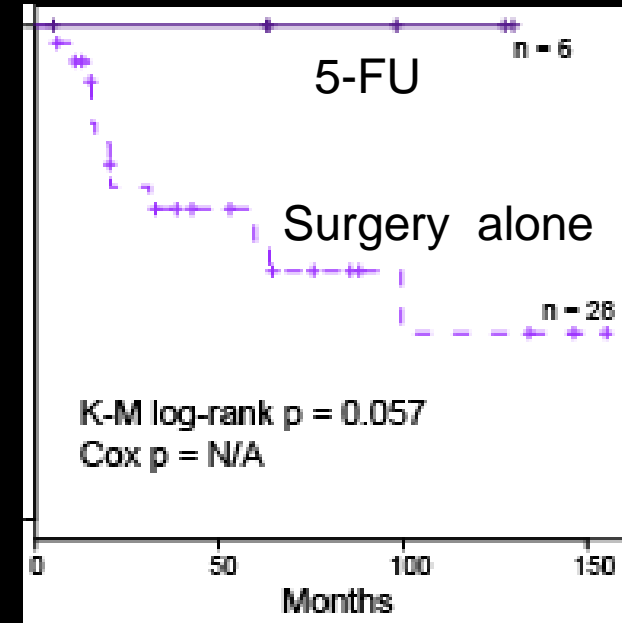
Mesenchymal

Surgery alone

5-FU

K-M log-rank p = 0.248
Cox p = 0.885

n = 28

n = 15

Proliferative

Surgery alone

K-M log-rank p = 3.64e-4
Cox p = 0.095

5-FU

n = 49

n = 12

Metabolic

5-FU
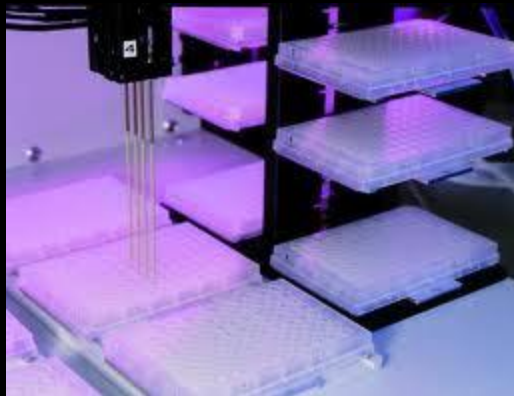
Surgery alone

K-M log-rank p = 0.057
Cox p = N/A

n = 6

n = 28

Note : Patients with more severe disease were more often treated with 5-FU

P-value for Interaction = 0.0012

Mesenchymal GC Lines are Sensitive to PIK3CA Inhibitors (High Throughput Drug Screening)

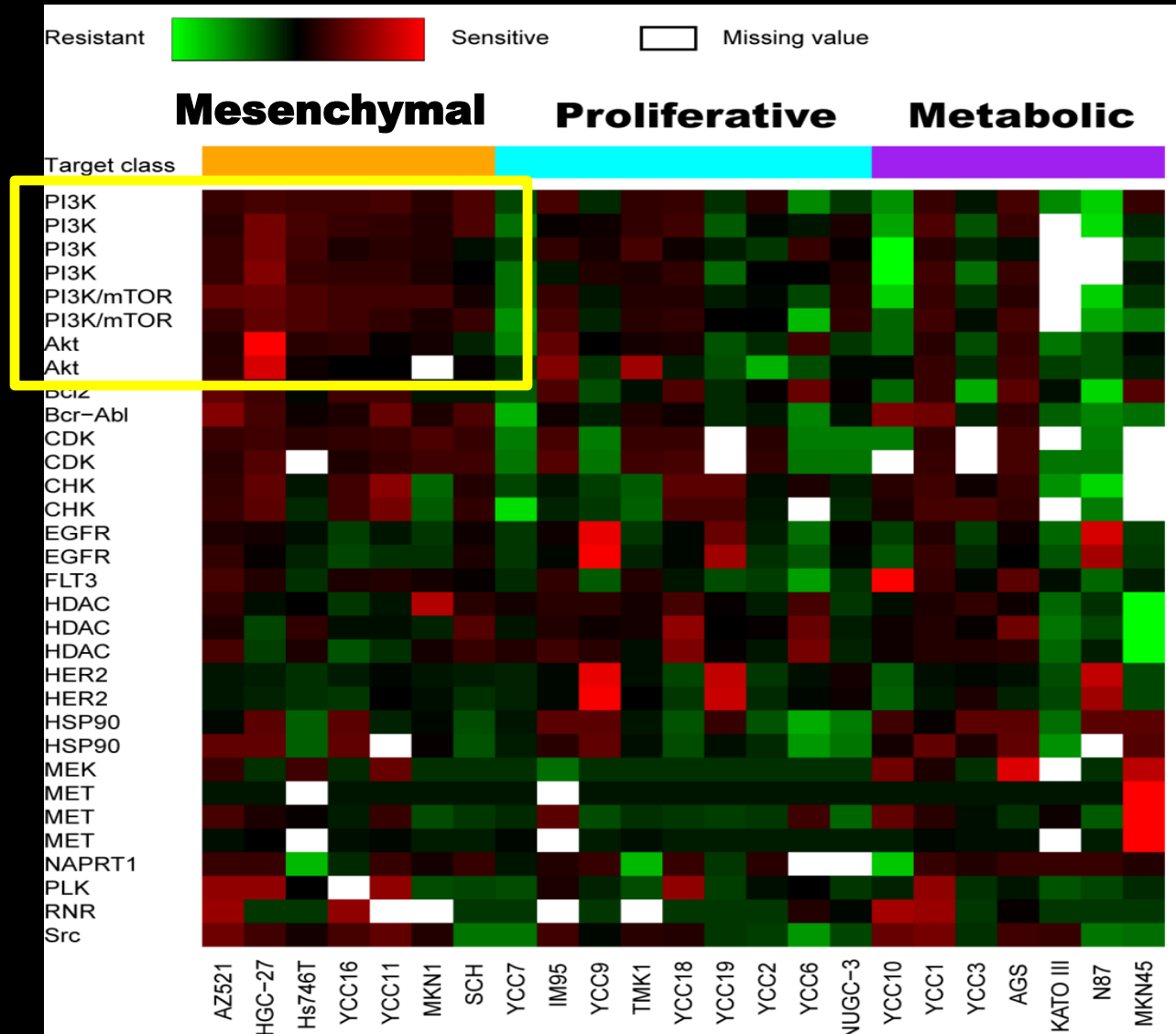Screening Performed By Experimental Therapeutics Centre, A-star

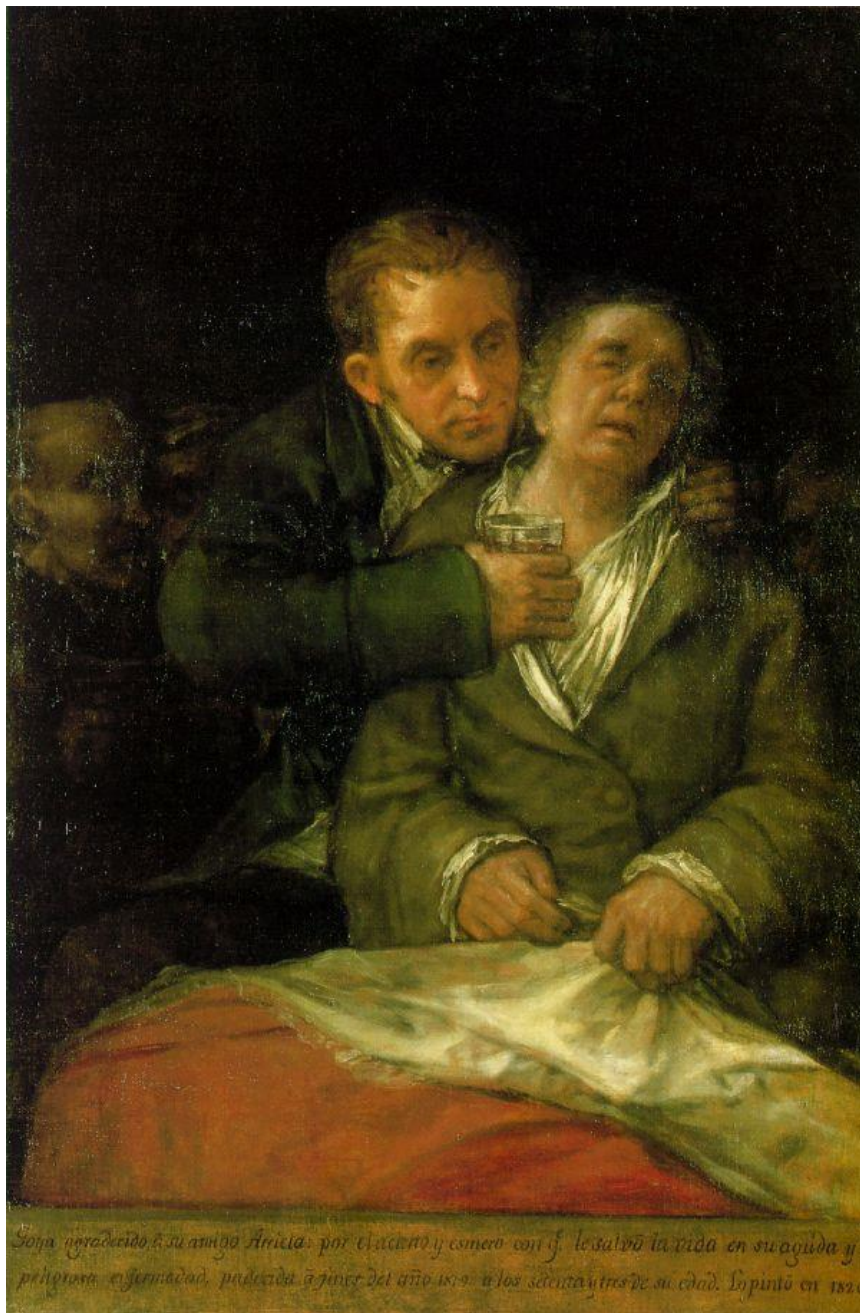**Table 3.** Characteristics of the Three Subtypes of Gastric Adenocarcinoma

Characteristic	Mesenchymal
5-FU effect on patient survival	No effect in Singapore cohort; beneficial in Australian cohort
Chemosensitivity in cell lines	PI3K–AKT–mTOR inhibitors
KEGG pathways associated with up-regulated genes	Focal adhesion, ECM-receptor interaction
GO biological processes associated with up-regulated genes	Cell adhesion, vasculature development, cell motility, angiogenesis
Pathway activation determined by BFRM	EMT, TGF-β, VEGF, NF-κB, mTOR, SHH, and CSC

Table 3. Characteristics of the Three Subtypes of Gastric Adenocarcinoma

Characteristic	Proliferative
5-FU effect on patient survival	No effect
Chemosensitivity in cell lines	-
KEGG pathways associated with up-regulated genes	Cell cycle, DNA replication
GO biological processes associated with up-regulated genes	M phase, mitotic cell cycle
Pathway activation determined by BFRM	E2F, MYC, and RAS

LEI Z et al. GASTROENTEROLOGY 2013; 145:554-565

Table 3. Characteristics of the Three Subtypes of Gastric Adenocarcinoma

Characteristic	Metabolic
5-FU effect on patient survival	Beneficial
Chemosensitivity in cell lines	5-FU
KEGG pathways associated with up-regulated genes	Metabolic processes
GO biological processes associated with up-regulated genes	Digestion, secretion
Pathway activation determined by BFRM	SPEM (spasmolytic polypeptide-expressing-metaplasia)

THANKS