

Madrid, 9 de mayo de 2012

USCAP & AACR HIGHLIGHTS

La visión clínica de los biomarcadores en Oncología

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UNIVERSIDAD DE VALENCIA



Fundación Investigación Clínica de Valencia
Instituto de Investigación Sanitaria – INCLIVA



VNIVERSITAT
DE VALÈNCIA



THE MULTIDISCIPLINARY TEAM

“Strategic choices determine the options”

Surgeon



Collabo

ess

di

**MOLECULAR PROFILING
SHOULD BE ADDED TO
THE DECISION PROCESS**

Oncologist



Radiologist



Nurse



Histopathologist

BIOMARCADORES EN ONCOLOGÍA

- **PRONÓSTICOS**
 - INESTABILIDAD DE MICROSATÉLITES EN CA. COLON
- **PREDICTIVOS**
 - KRAS EN CA COLON
 - BRAF EN MELANOMA
- **FARMACODINÁMICOS**
 - DESARROLLO DE FÁRMACOS

BIOMARCADORES PRONÓSTICOS

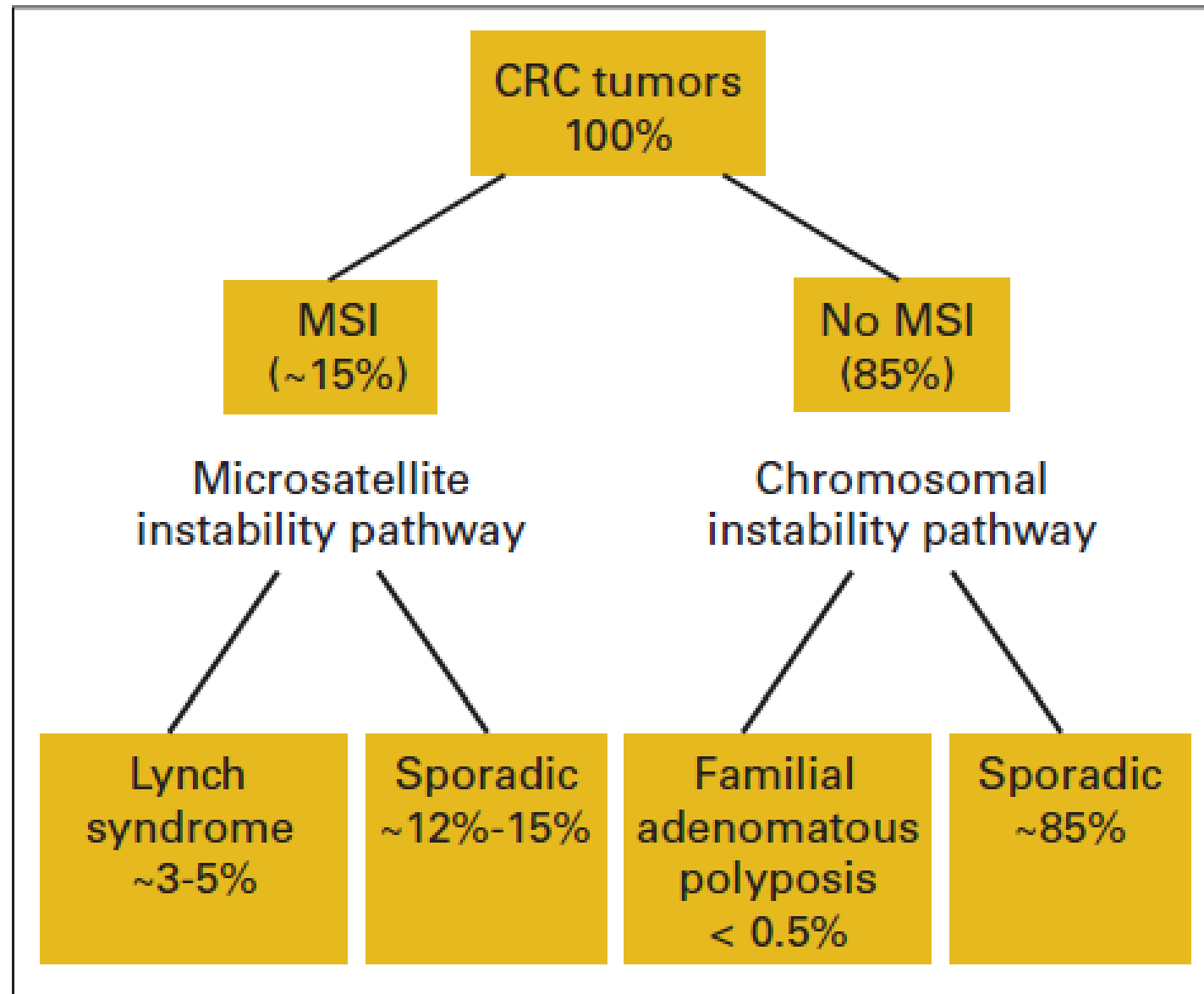
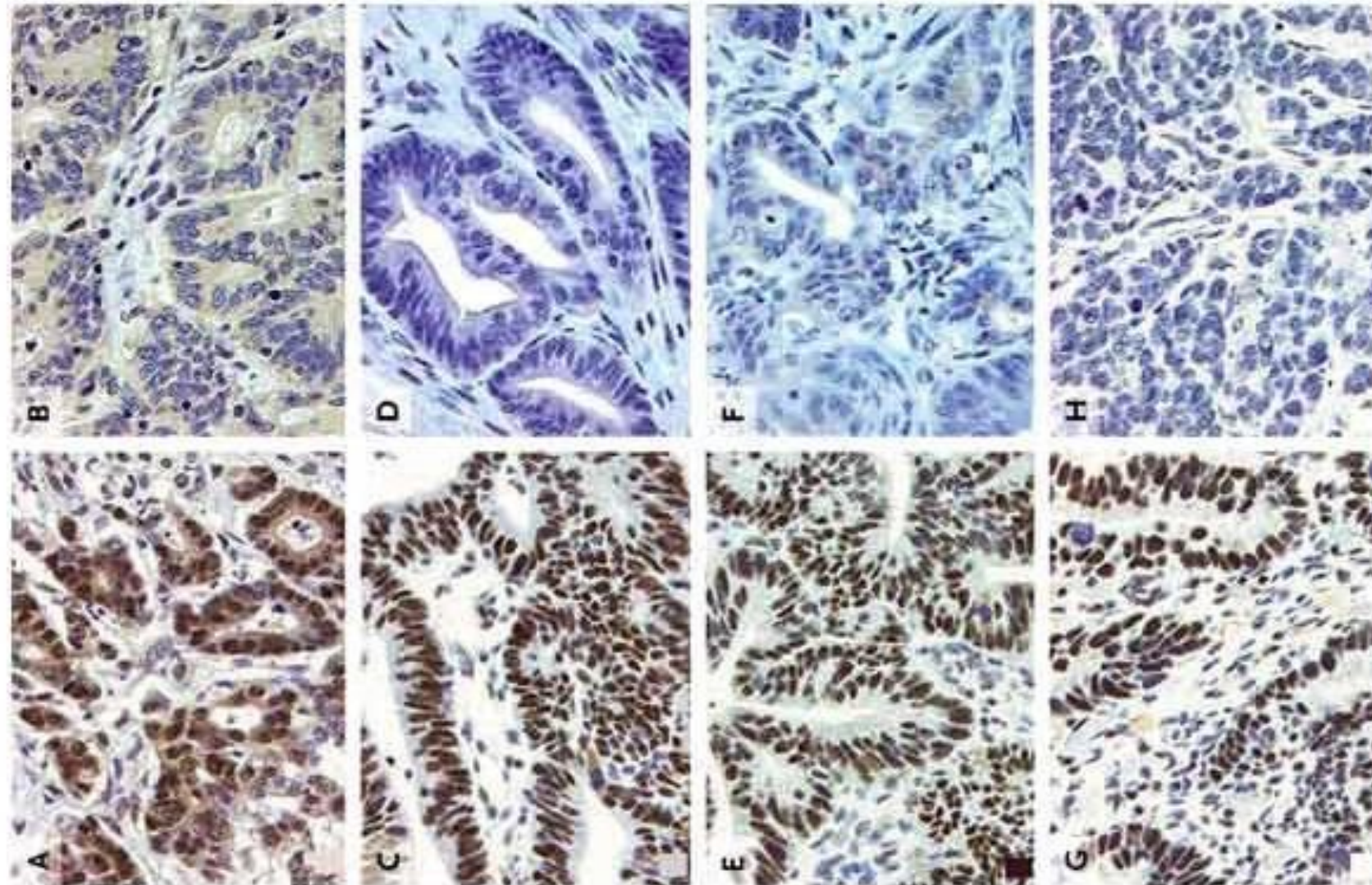


Fig 3. Schematic classification of colorectal cancers (CRCs). MSI, microsatellite instability.

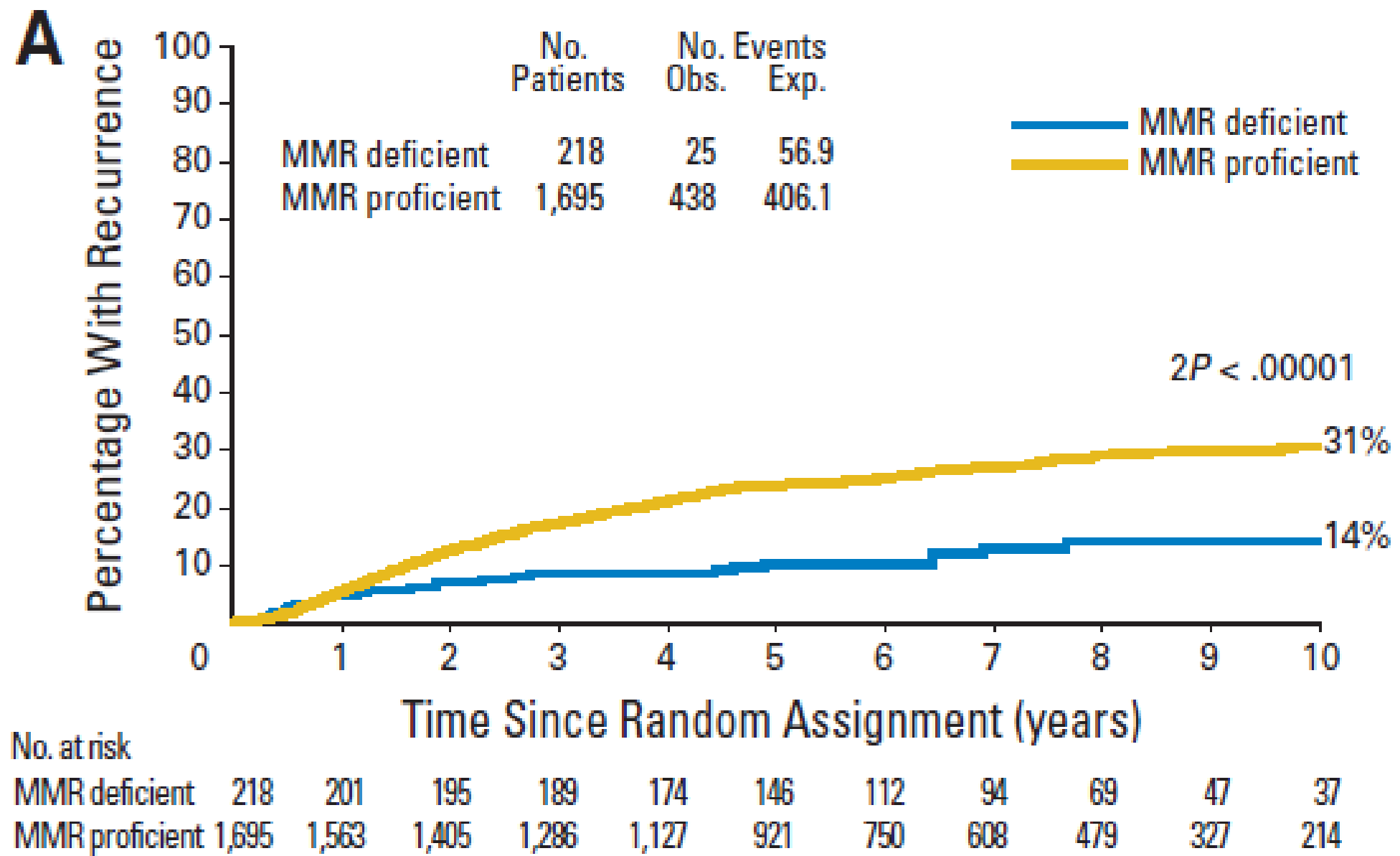
BIOMARCADORES PRONÓSTICOS

Immunohistochemical Staining for Mismatch-Repair Proteins in Colorectal Adenocarcinoma

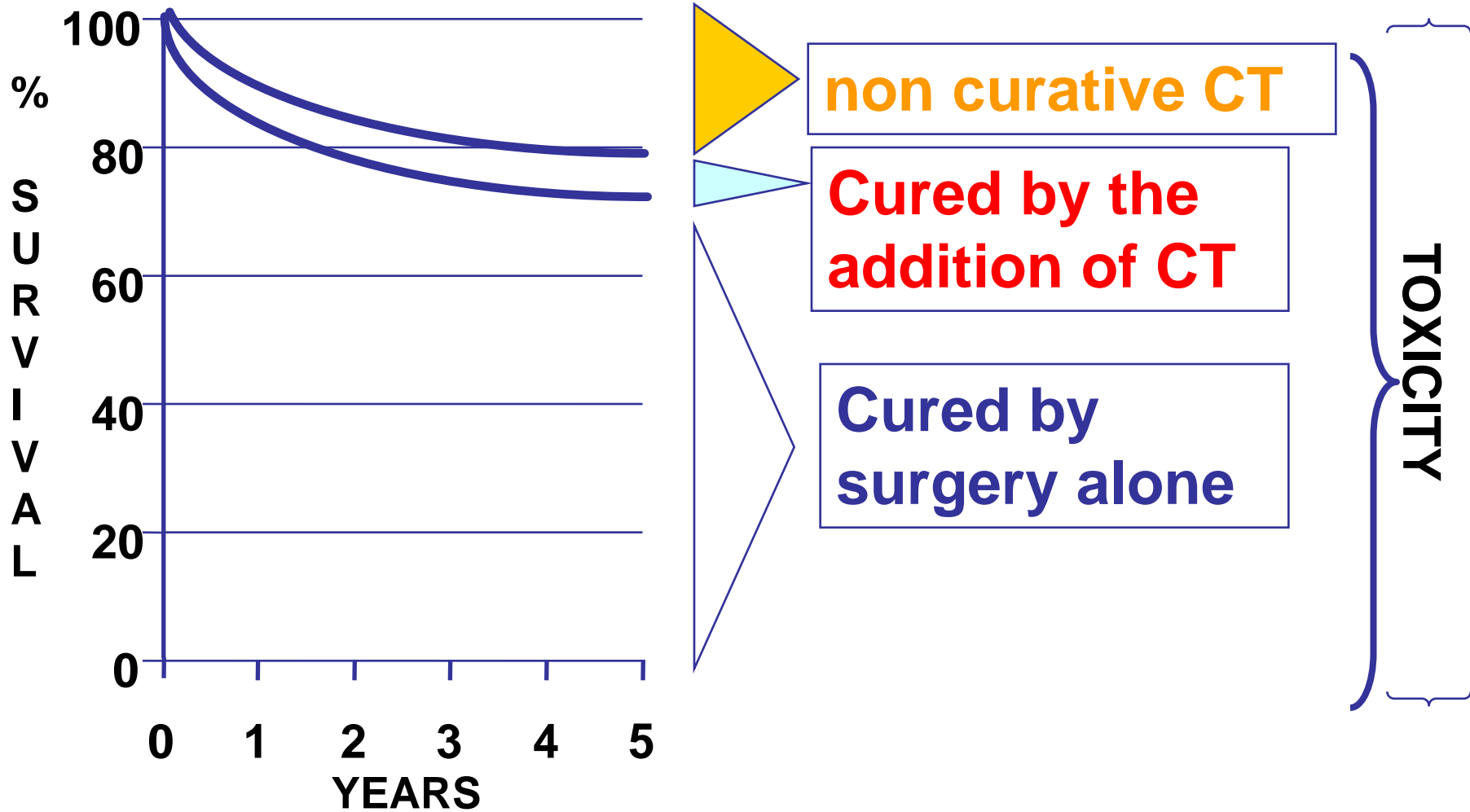


Hampel H , N Eng J Med 2005;352:1851

BIOMARCADORES PRONÓSTICOS



INTERPRETATION OF RESULTS OF TRIALS WITH ADJUVANT CT IN STAGE II COLON CANCER



BIOMARCADORES PREDICTIVOS

FÁRMACOS APROVADOS EN EUROPA CON INDICACIONES RESTRINGIDAS DE BIOMARCADORES-1

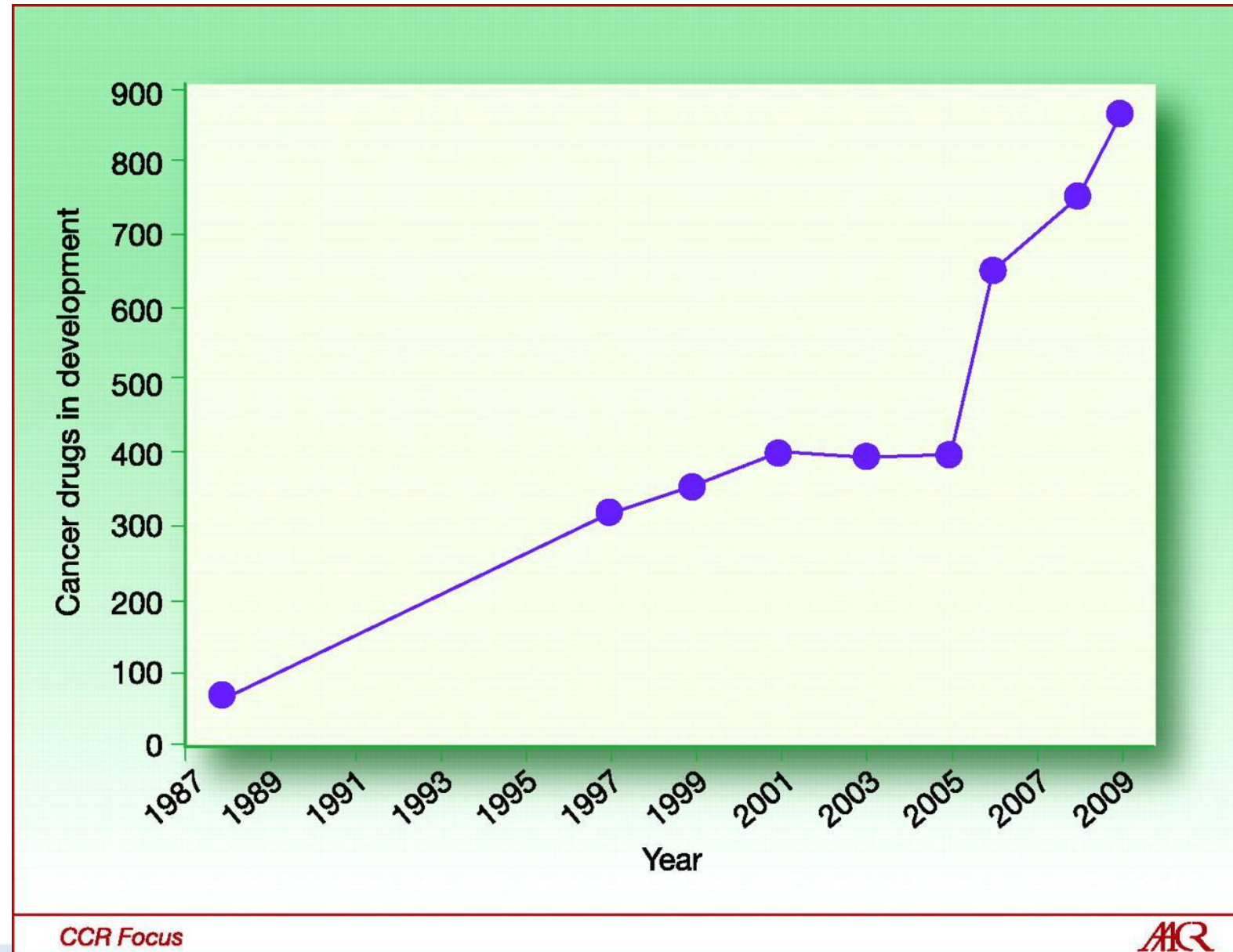
FÁRMACO	INDICACIÓN	BIOMARCADOR
CETUXIMAB	CA. COLON	KRAS No MUTADO
PANITUMUMAB	CA. COLON	KRAS No MUTADO
ERLOTINIB	CA. PULMÓN NO MICRO	Mutación EGFR
CRIZOTINIB	CA. PULMÓN NO MICRO	TRASLOCACIÓN ALK MEK
GEFITINIB	CA. PULMÓN NO MICRO	Mutación EGFR
LAPATINIB	CA. MAMA	Her2 SOBREENPRESION
TRASTUZUMAB	CA. MAMA/GÁSTRICO	Her2 SOBREENPRESION
VEMURAFENIB	MELANOMA	BRAF MUTADO V600

BIOMARCADORES PREDICTIVOS

FÁRMACOS APROVADOS EN EUROPA CON INDICACIONES RESTRINGIDAS DE BIOMARCADORES-2

FÁRMACO	INDICACIÓN	BIOMARCADOR
CATUMAXUMAB	ASCITIS MALIGNA	EpCam POSITIVO
DASATINIB	L MIELOIDE CRÓNICA	BCR-ABL
NILOTINIB	L MIELOIDE CRÓNICA	BCR-ABL
⁹⁰ Y-IBRITUMOMAB	LINFOMA FOLICULAR	CD20 POSITIVO
RITUXIMAB	LINFOMAS	CD20 POSITIVO
IMATINIB	L MIELOIDE CRÓNICA S. MIELODISPLÁSICOS GIST HIPEREOSINOFILIA	BCR-ABL REORDENAMIENTO GEN PDGFR c-KIT REORDENAMIENTO <i>FIP1L1</i> -PDGFR

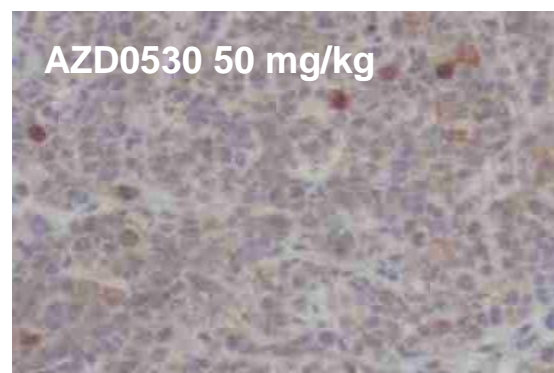
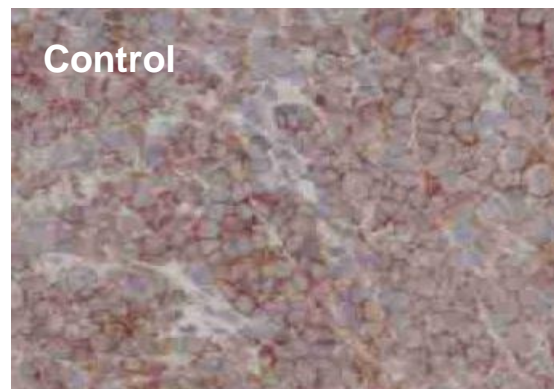
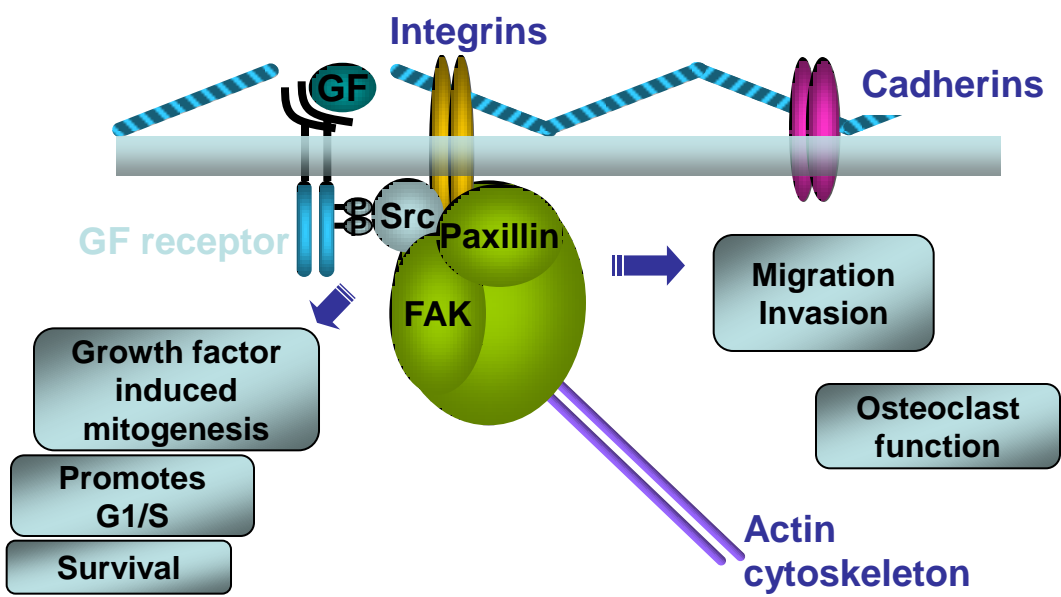
CANCER DRUGS TESTED IN CLINICAL TRIALS OR UNDER U.S. FDA REVIEW BY YEAR



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

BIOMARCADORES FARMACODINÁMICOS

P-FAK AND P-PAXILLIN – BIOMARKERS OF SRC INHIBITION



Src phosphorylation of FAK and paxillin is critical for the migratory phenotype

Methodologies using FAK pY861 and paxillin pY31 antibodies have been validated in preclinical models

Src inhibition by AZD0530 decreases phosphorylation of FAK and paxillin in preclinical models

Clinical Cancer Research

Cancer Therapy: Clinical

Phase I Safety, Pharmacokinetics, and Inhibition of Src Activity Study of Saracatinib in Patients with Solid Tumors

José Baselga¹, Andres Cervantes², Erika Martinelli¹, Isabel Chirivella², Klaas Hoekman³, Herbert I. Hurwitz⁴, Duncan I. Jodrell⁵, Paul Hamberg⁶, Esther Casado¹, Paul Elvin⁷, Alan Swaisland⁷, Renee Iacona⁷, and Josep Tabernero¹

Clin Cancer Res 2010; 29:1261

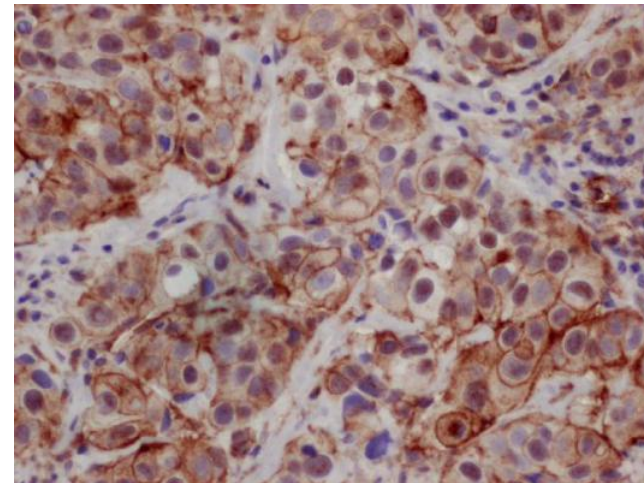


BIOMARCADORES FARMACODINÁMICOS

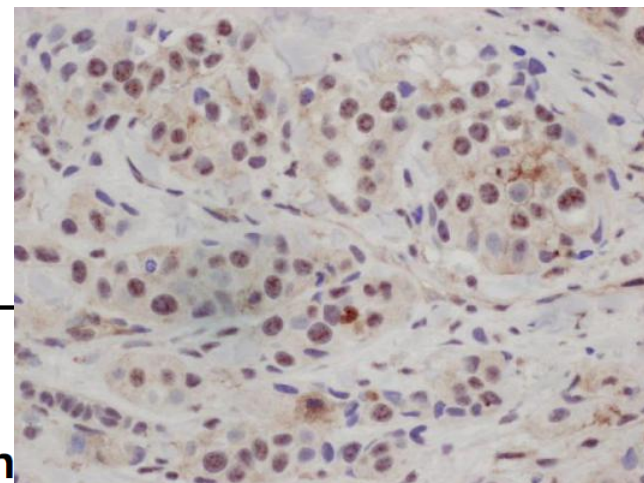
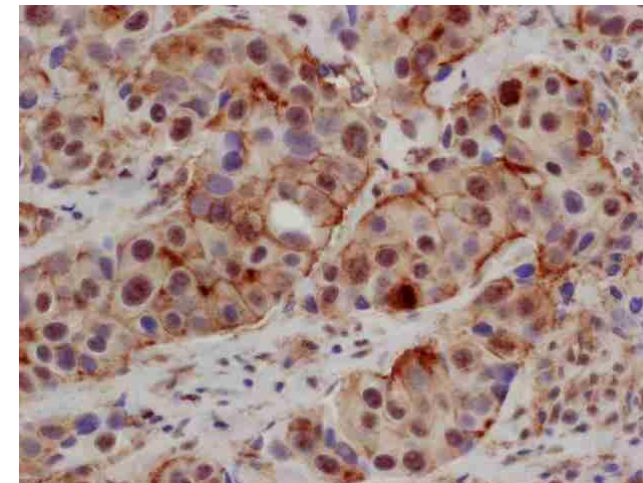
P-FAK AND P-PAXILLIN – BIOMARKERS OF SRC INHIBITION PRE AND POST AZD0530 TREATMENT

p-FAK

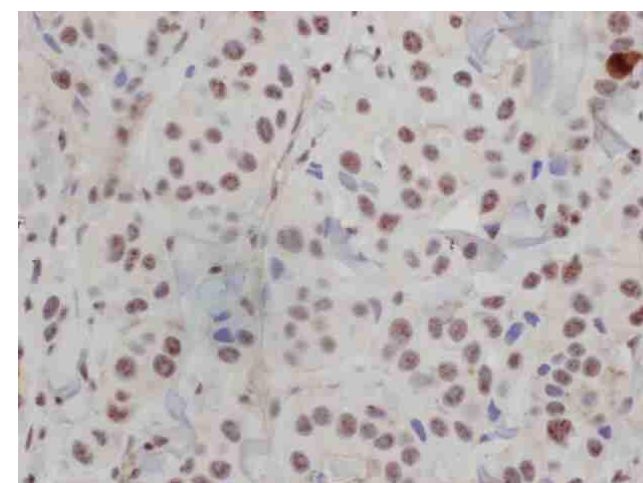
p-paxillin



Day -1



Day 28



Clinical
Cancer
search

Cancer Therapy: Clinical

**Phase I Safety, Pharmacokinetics, and
Activity Study of Saracatinib in Patients with Solid Tumors**

José Baselga¹, Andres Cervantes², Erika Martinelli¹, Isabel Chirivella², Klaas Hoekman³, Herbert I. Hurwitz⁴,
Duncan I. Jodrell⁵, Paul Hamberg⁶, Esther Casado¹, Paul Elvin⁷, Alan Swaisland⁷, Renee Iacona⁷, and Josep Tabernero¹

Clin Cancer Res 2010; 29:1261



Phase I Study of MEHD7945A, a First-in-class HER3/EGFR Dual Action Antibody, in Patients with Locally Advanced or Metastatic Epithelial Tumors

D. Juric,¹ R. Dienstmann,² W. Messersmith,³ A. Cervantes,⁴
G. Blumenschein,⁵ J. Baselga,¹ J. Tabernero,² A. Jimeno,³ A. Calles,⁶
D. Roda,⁴ Y. Xin,⁷ A. Kapp,⁷ S. Chandler,⁷ A. Pirzkall,⁷ M. Hidalgo⁶

¹Massachusetts General Hospital Cancer Center, Boston, MA

²Vall d'Hebron Institute of Oncology, Barcelona, Spain

³University of Colorado Cancer Center, Denver, CO

⁴INCLIVA Health Research Institute, University of Valencia, Valencia, Spain

⁵University of Texas MD Anderson Cancer Center, Houston, TX

⁶Spanish National Cancer Research Center, Madrid, Spain

⁷Genentech, Inc., South San Francisco, CA



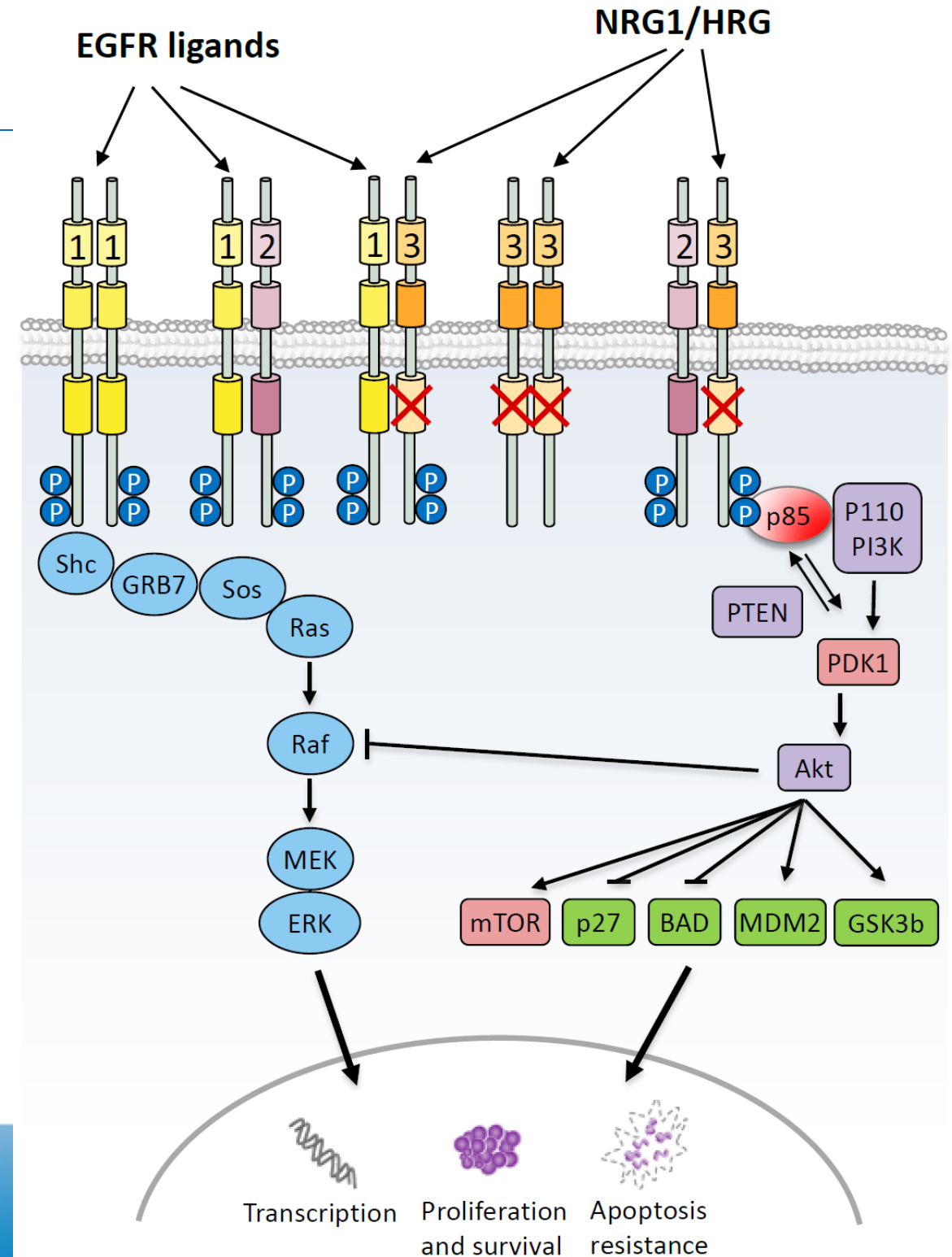
HER3 AND EGFR DYSREGULATION IN A VARIETY OF CANCERS

HER3

- Ubiquitously expressed in epithelial tumors
- Tightly regulated level of expression
- Most potent driver of PI3K/Akt pathway
- Exclusive co-receptor role
 - Dimerizes with other HER receptors upon ligand binding
 - Activated as a result of compensatory pathways (PI3K-Akt, Met, EGFR, FGFR2, IGFR-1)
 - Plays a crucial role in EGFR-driven and HER2-driven tumors
- Mediates acquired resistance to other RTKs

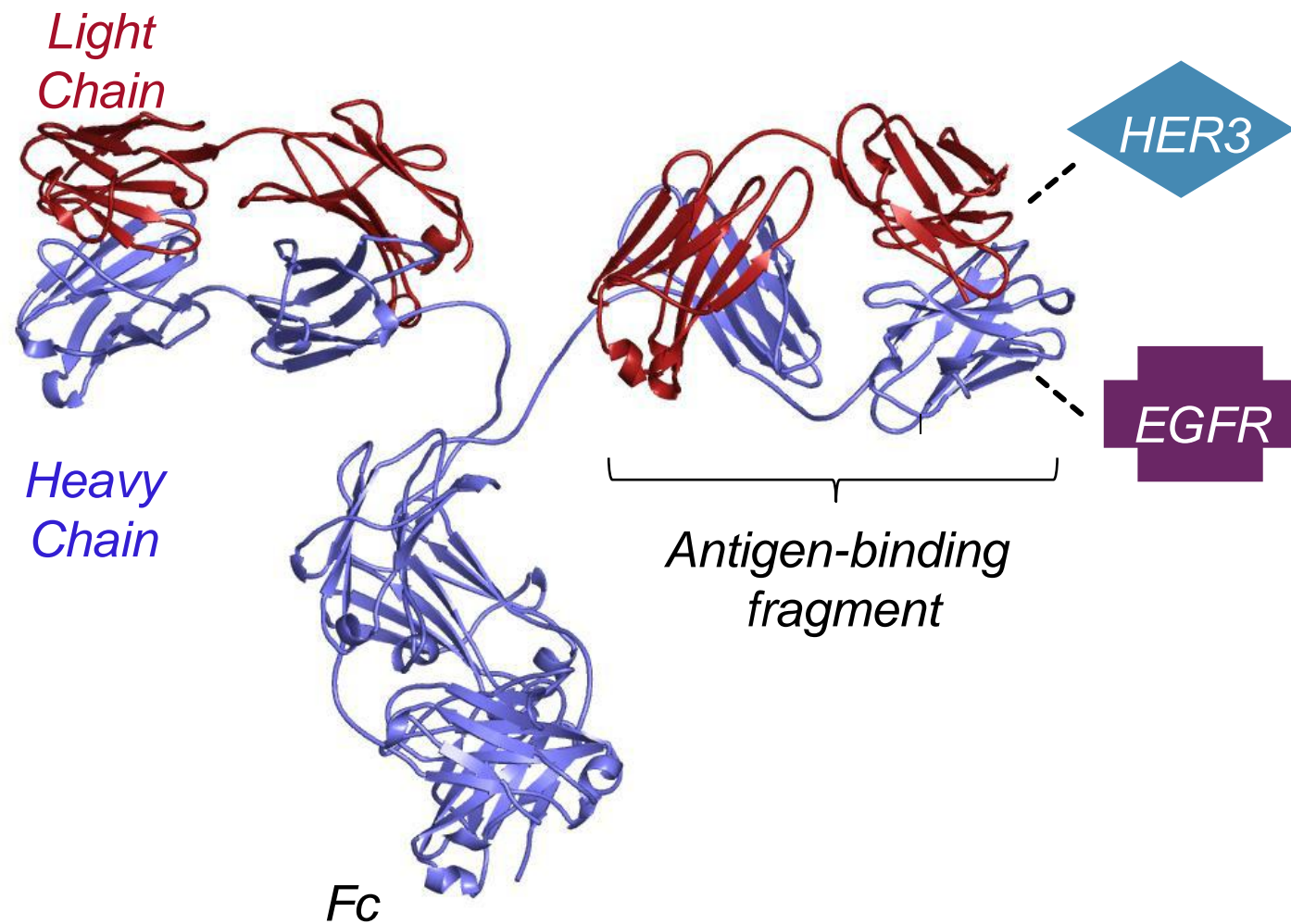
Epidermal Growth Factor Receptor (EGFR)

- Clinically validated target in CRC, SCCHN, NSCLC, Pancreatic cancer



ANTI-EGFR/HER3 DUAL-ACTION FAB: MEHD7945A

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



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: $K_d = 1.9 \text{ nM}$

Binding affinity to HER3: $K_d = 0.4 \text{ nM}$

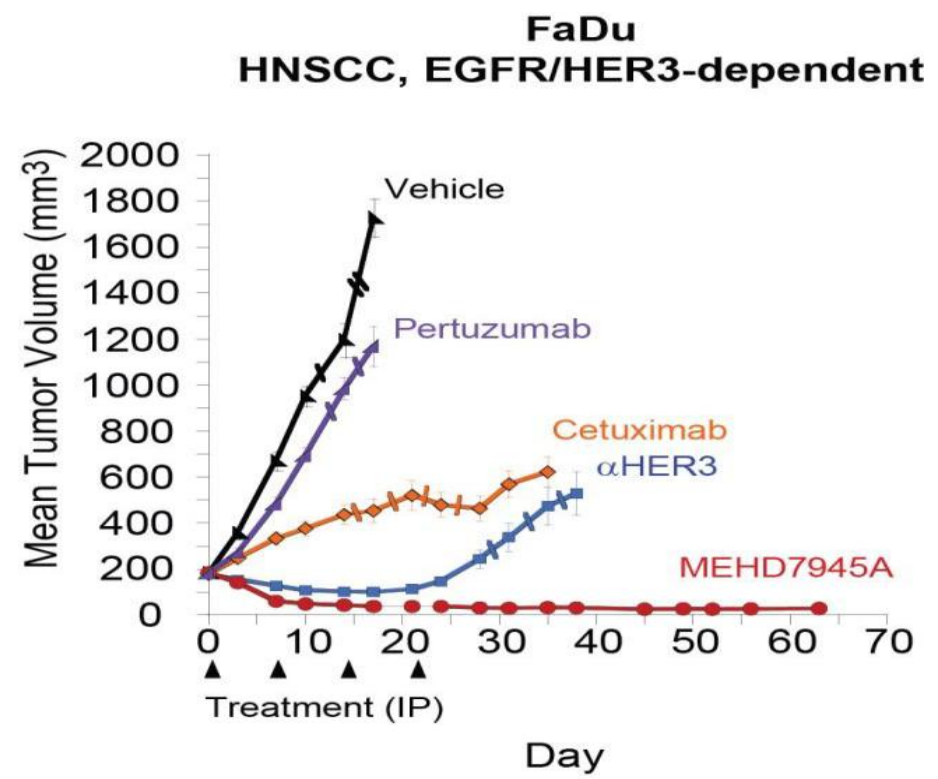
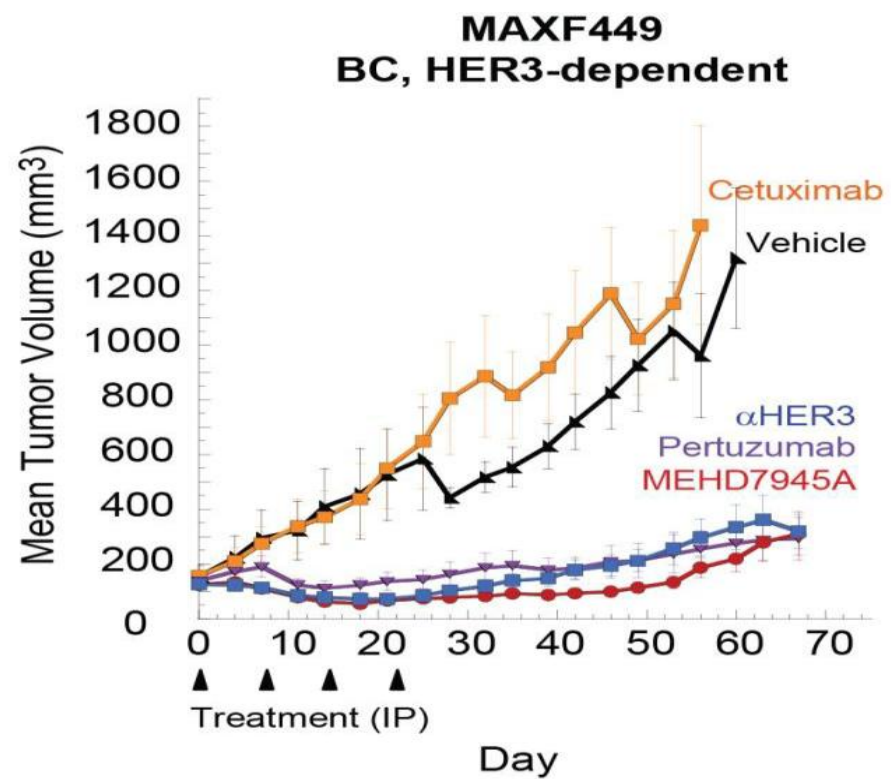
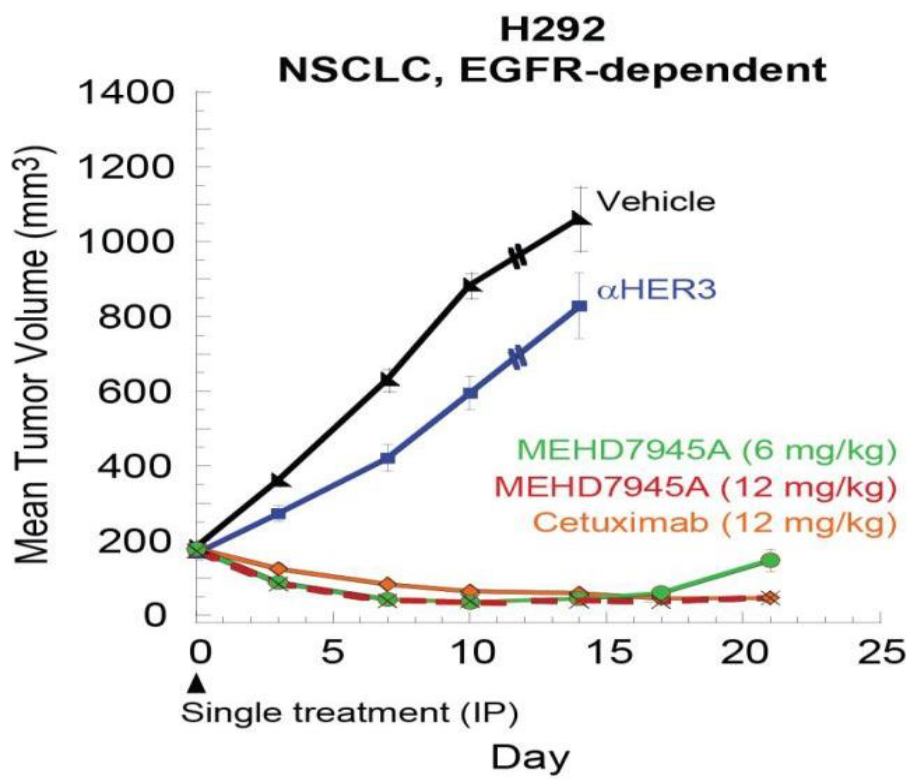
Inhibits signaling by all major ligand-dependent HER-family dimers

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



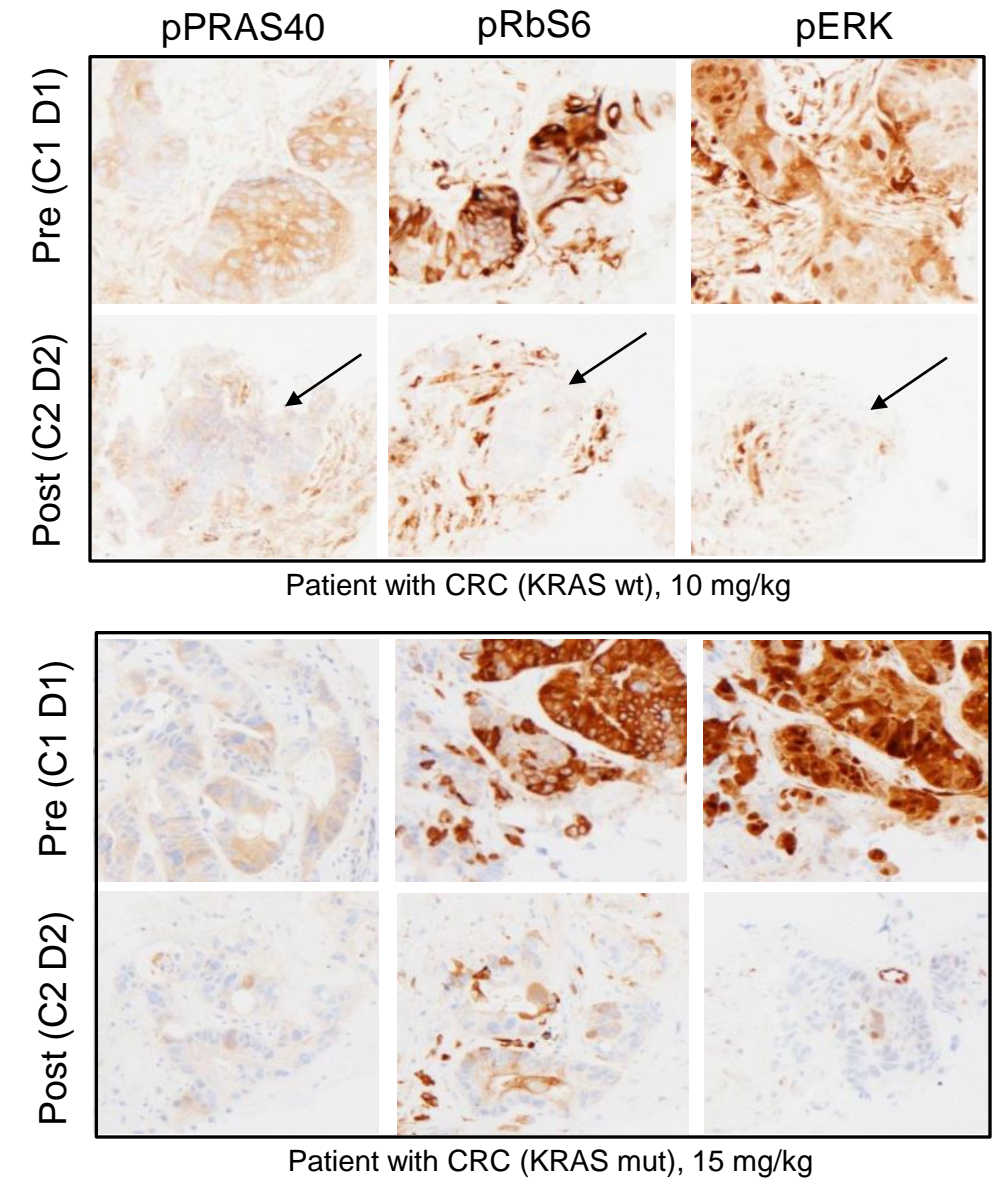
Schaefer et al., Cancer Cell, 2011.

PD ASSESSMENT BY IHC IN TUMOR BIOPSIES

Pharmacodynamic (PD) evidence of target inhibition detected at 10 and 15 mg/kg q2w

Decreased phosphorylation of markers downstream of HER3/EGFR measured in 4/8 patients with biopsies

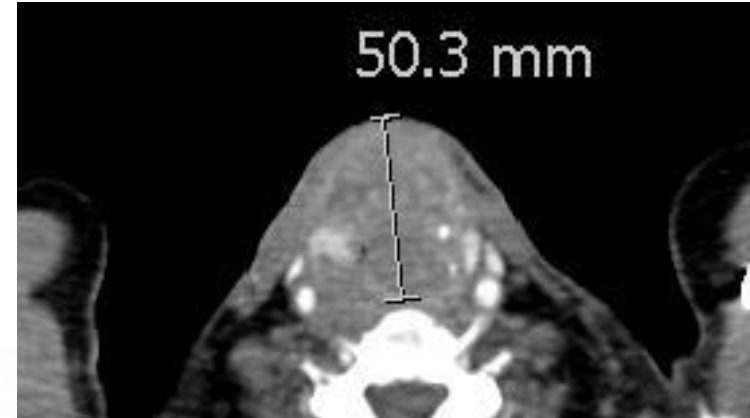
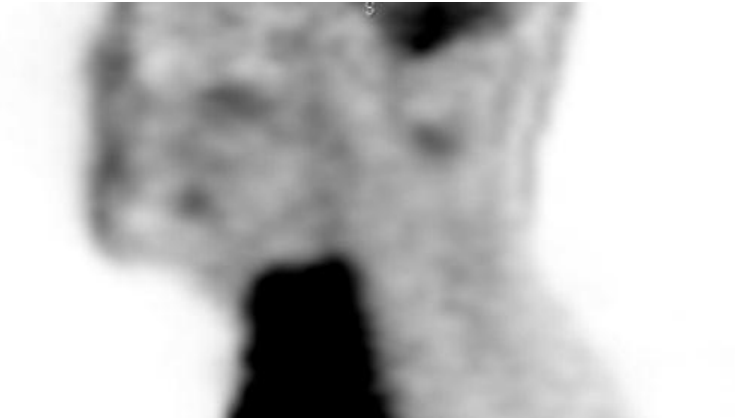
pPRAS40
pRbS6
pERK



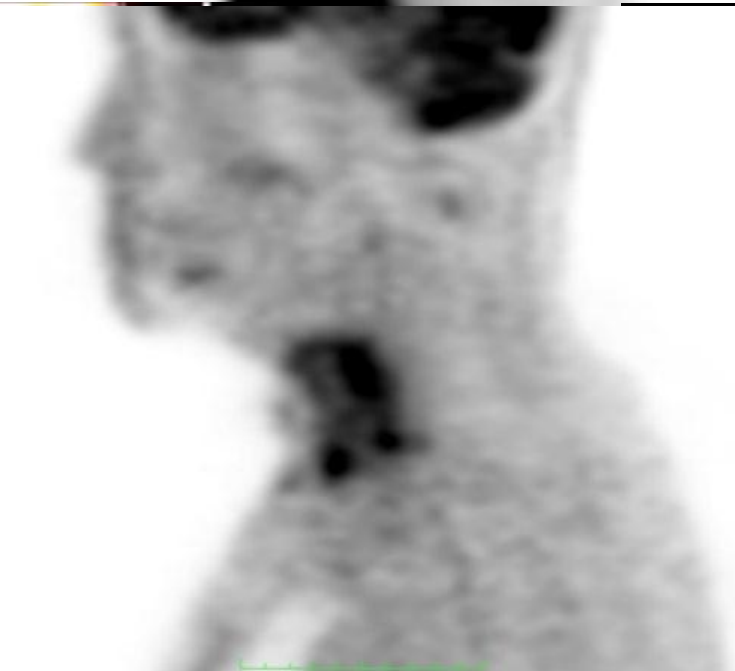
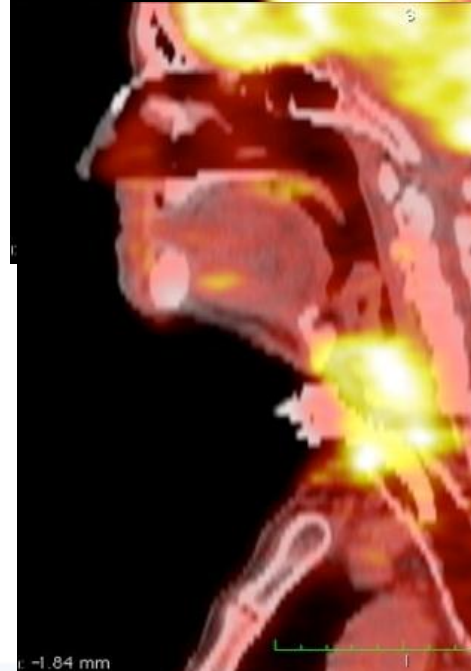
Schaefer et al., Cancer Cell, 2011.

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

Screening



Cycle 2, Day 2



CETUXIMAB-RELAPSED SCCHN OF THE LARYNX, INVADING TRACHEOSTOMY SITE



Baseline



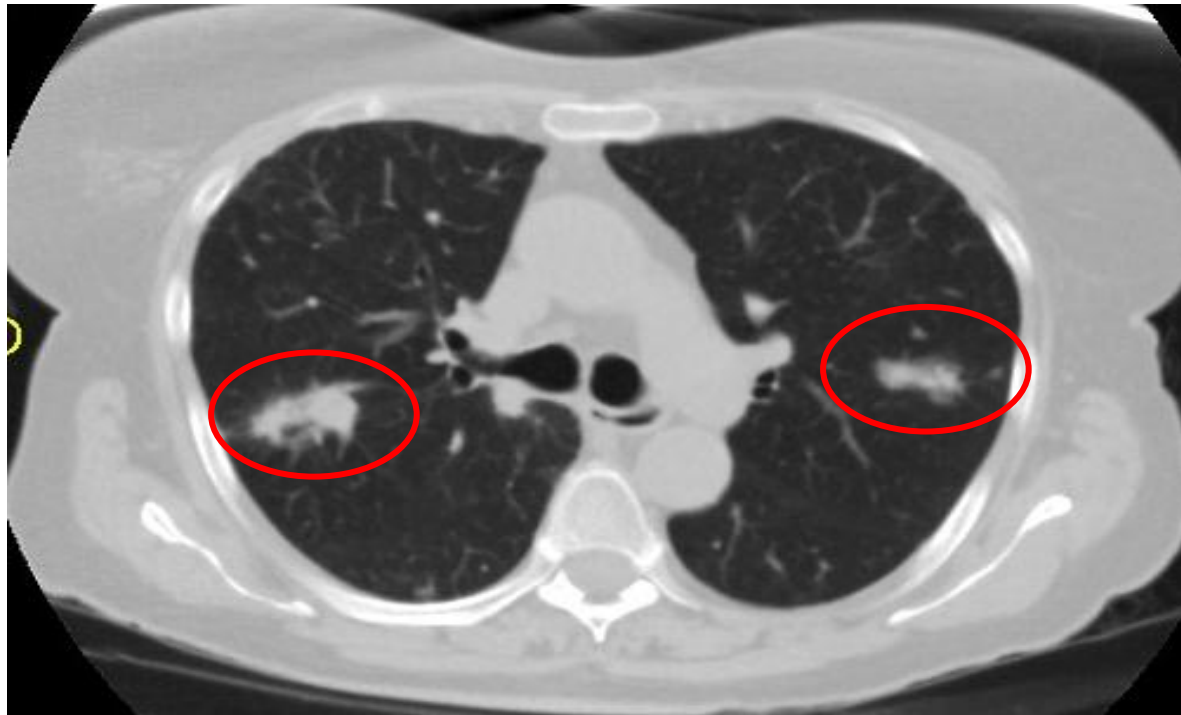
C3, D8 (at week 5, after 3 infusions)



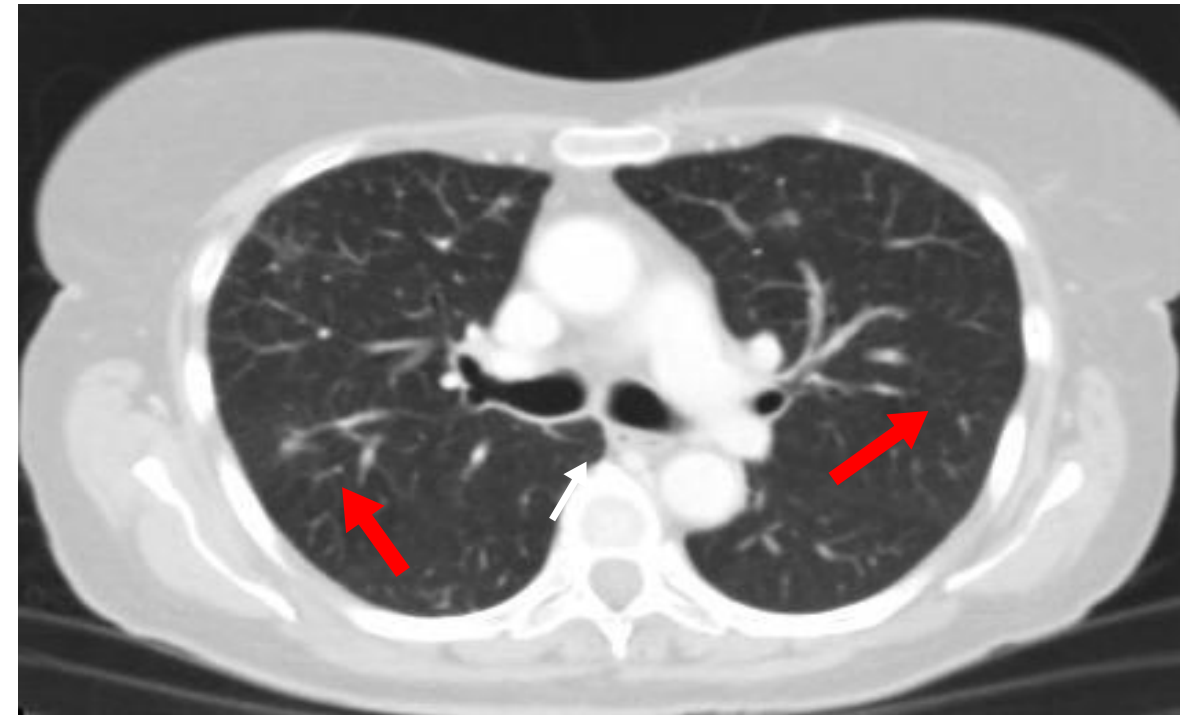
C5, D1 (at week 8, after 4 infusions)

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)



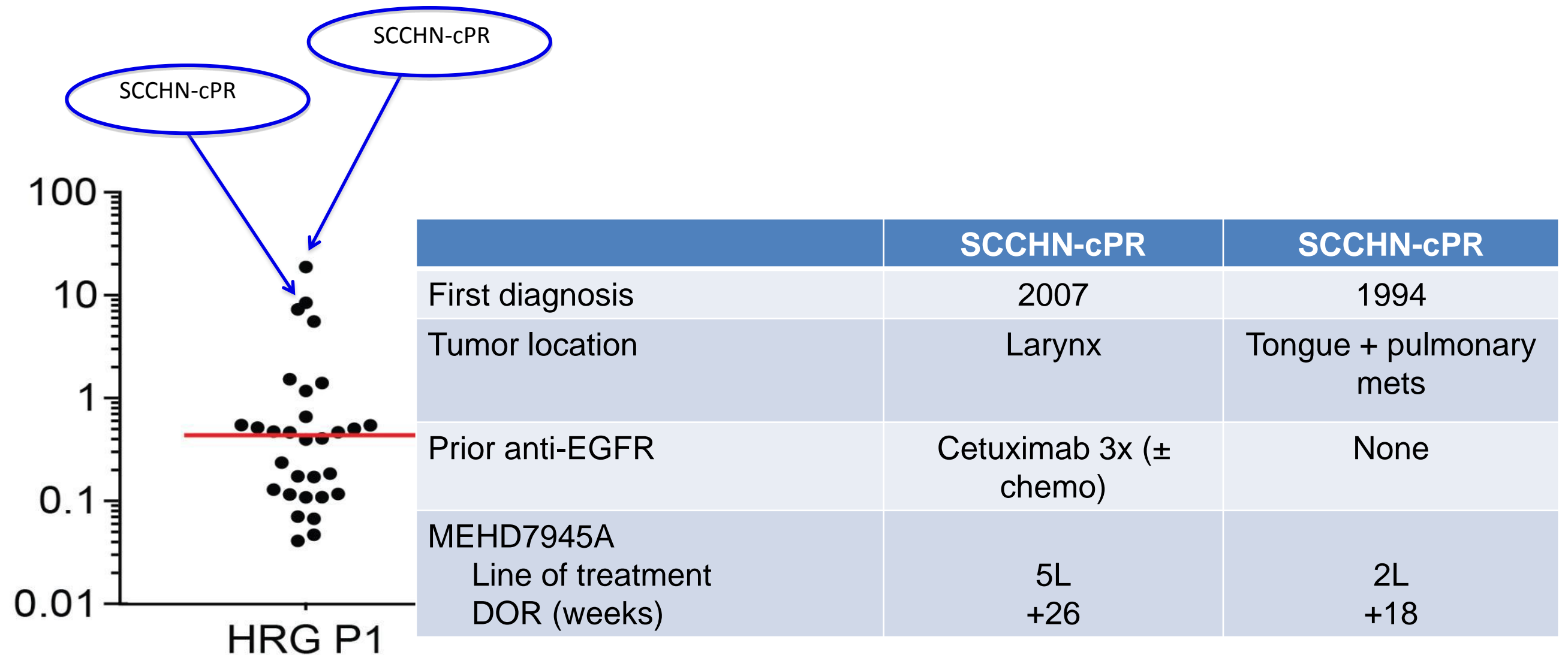
Baseline



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

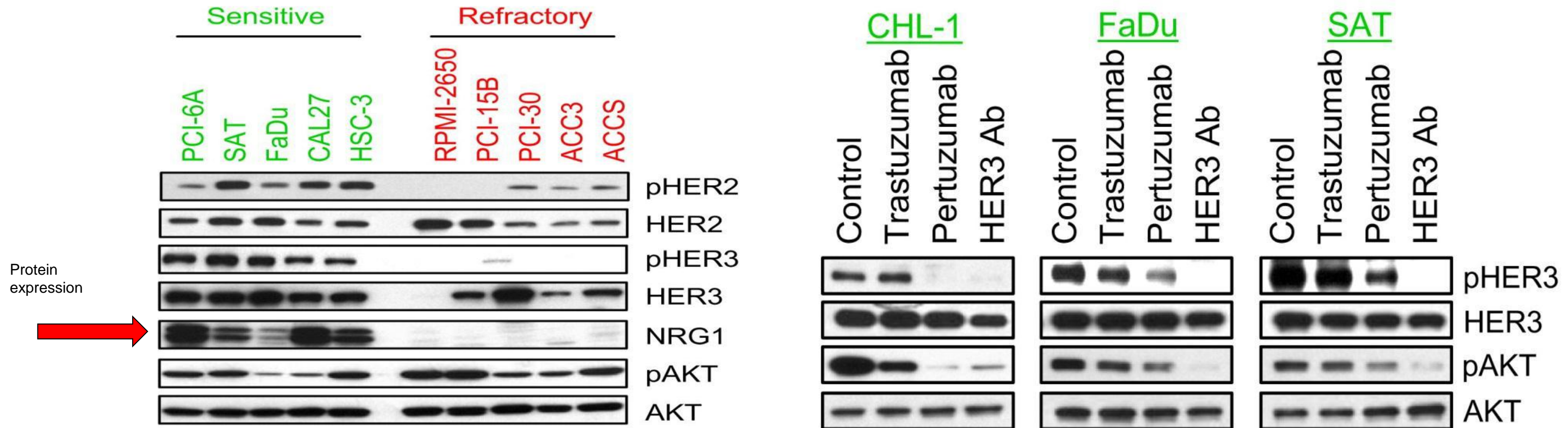
- SCCHN of the tongue, diagnosed in 1994, most recently metastatic to the lung
- Prior therapies include multiple surgeries and chemoradiation
- MEHD7945A at 14 mg/kg IV q2w since 09/11
- Confirmed PR and clinical improvement (regained ability to swallow)
- Remains active on study (> 6 months)

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



ANTI-TUMOR ACTIVITY IN HRG-HIGH SCCHN CONSISTENT WITH RECENT PRECLINICAL DATA

Cells sensitive to EGFR/HER2 TKIs exhibit high levels of Autocrine HER3 signaling is inhibited by anti-HER3 portion of MEHD7495A
 HRG/NRG1 and pHER3: suggestive of autocrine signaling



Wilson et al., Cancer Cell, 2011.

UNIDAD DE ENSAYOS FASE I

HOSPITAL CLÍNICO UNIVERSITARIO DE VALENCIA

SERVICIO DE HEMATOLOGÍA Y ONCOLOGÍA MÉDICA

Radiología Intervencionista: Jorge Guijarro, Ximo Gil, Juanma Sanchis

Patología: Samuel Navarro, Cristina Mongort, Antonio Ferrándis

Laboratorio polimorfismos y mutaciones: Javier Chaves, Charo Abellán

Oncología Médica: Desamparados Roda, Alejandro Pérez Fidalgo, Susana Roselló, Ana Bosch, Paloma Martín

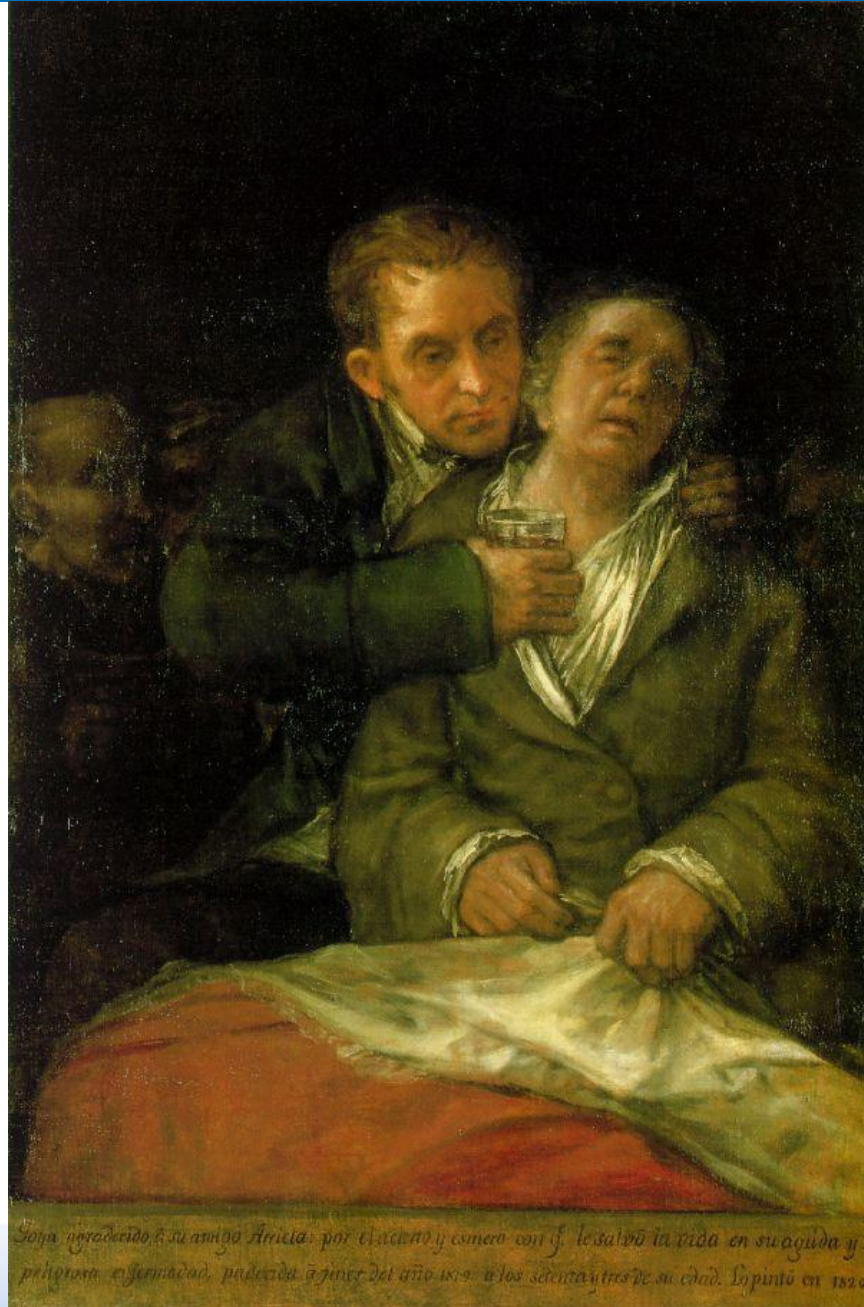
Enfermeras de Investigación: Inma Blasco, Amparo Domingo, María Higuera

Data Manager: Julia Peláez

Personal administrativo: Yolanda de la Cruz, Gabriela Pérez, Jessica Fraile

Jefe de Servicio: Ana Lluch

Biomarcadores en Oncología



GRACIAS