European Commission

Designing clinical trials for personalised medicine

1-2 June 2016, Brussels

Sabine Tejpar MD PhD

University Hospital Leuven, Belgium

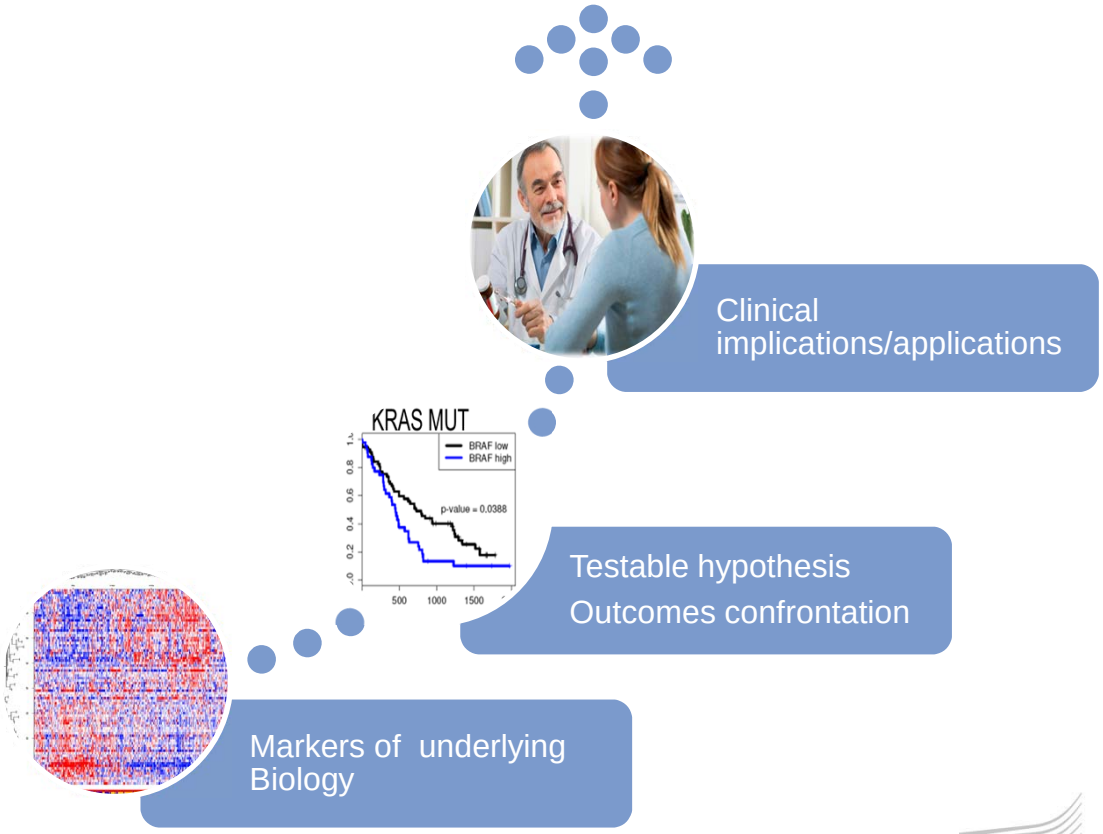
Research and Innovation

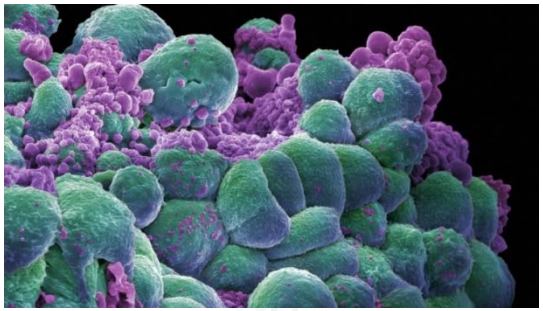
Perspective

- Cancer

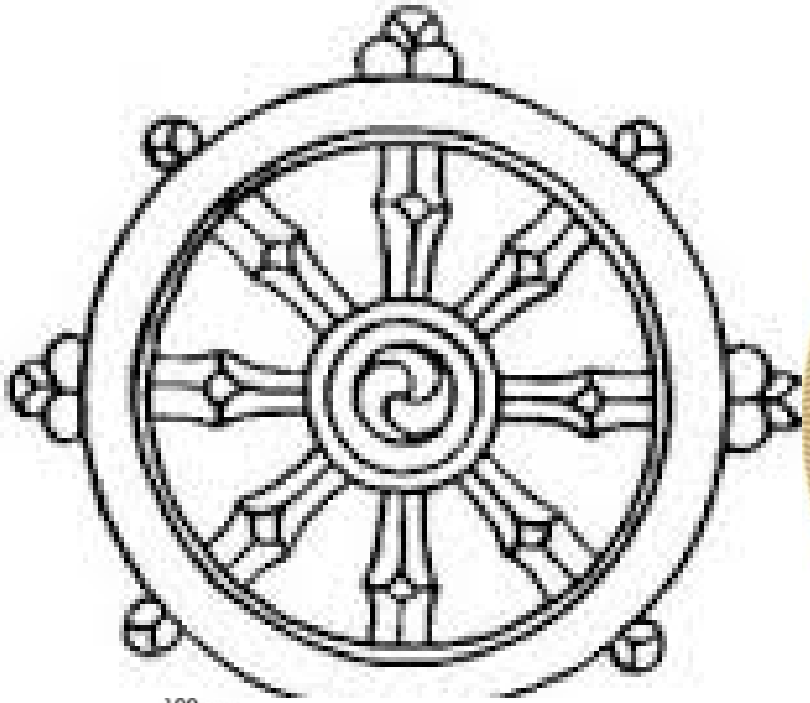
- Unmets needs:
  - Better Science
  - Better return to Patients, Society
  - For profit drug development
  - Academia competition

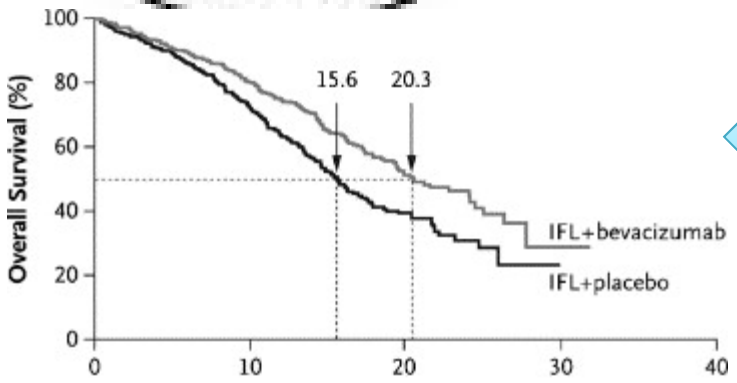
- Novel models


Clinical implications/applications
KRAS MUT
BRAF low
BRAF high
p-value = 0.0388
Testable hypothesis
Outcomes confrontation
Markers of underlying Biology

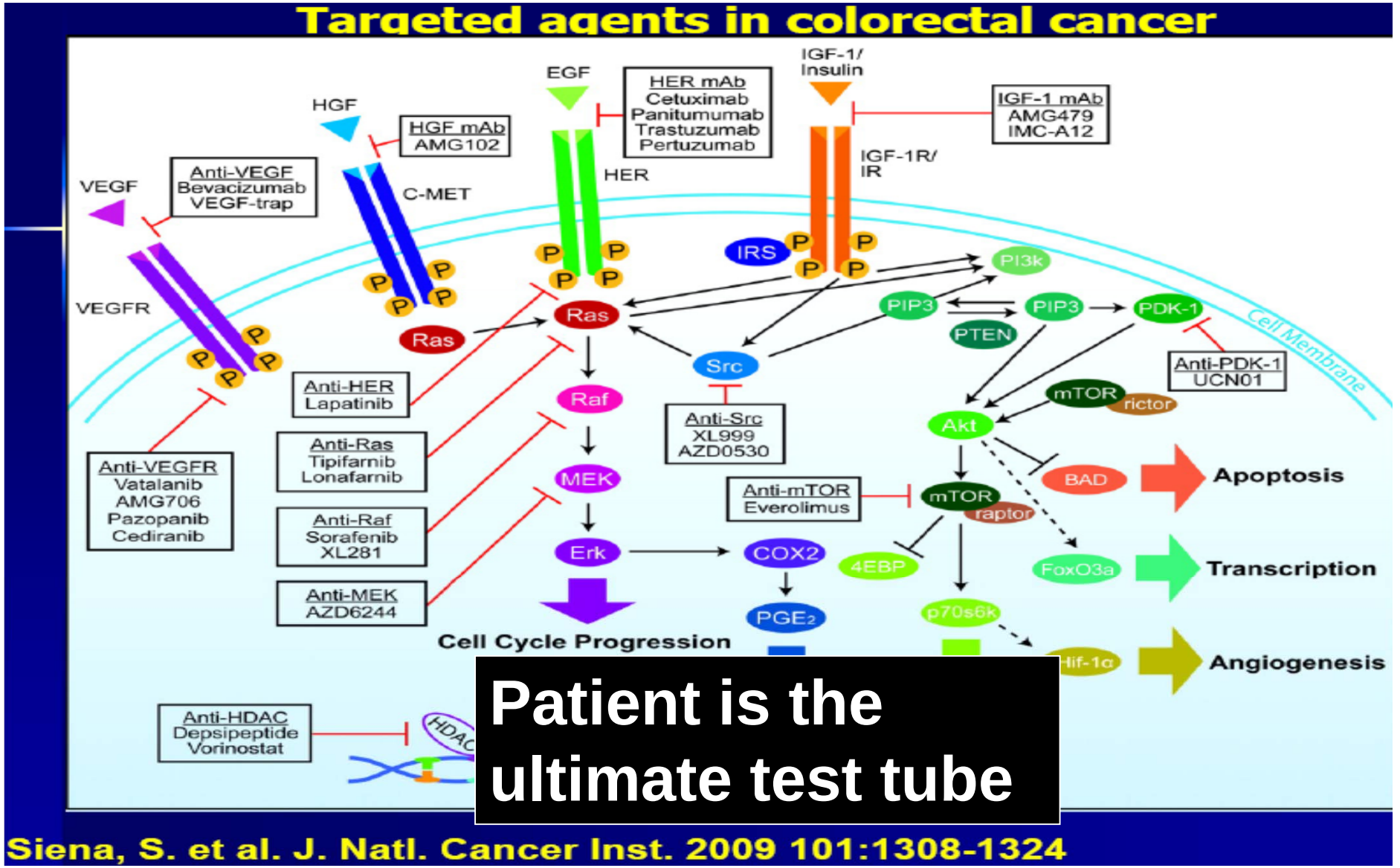


Did we ask the right question?
Is it the right target?
Is there a subgroup?

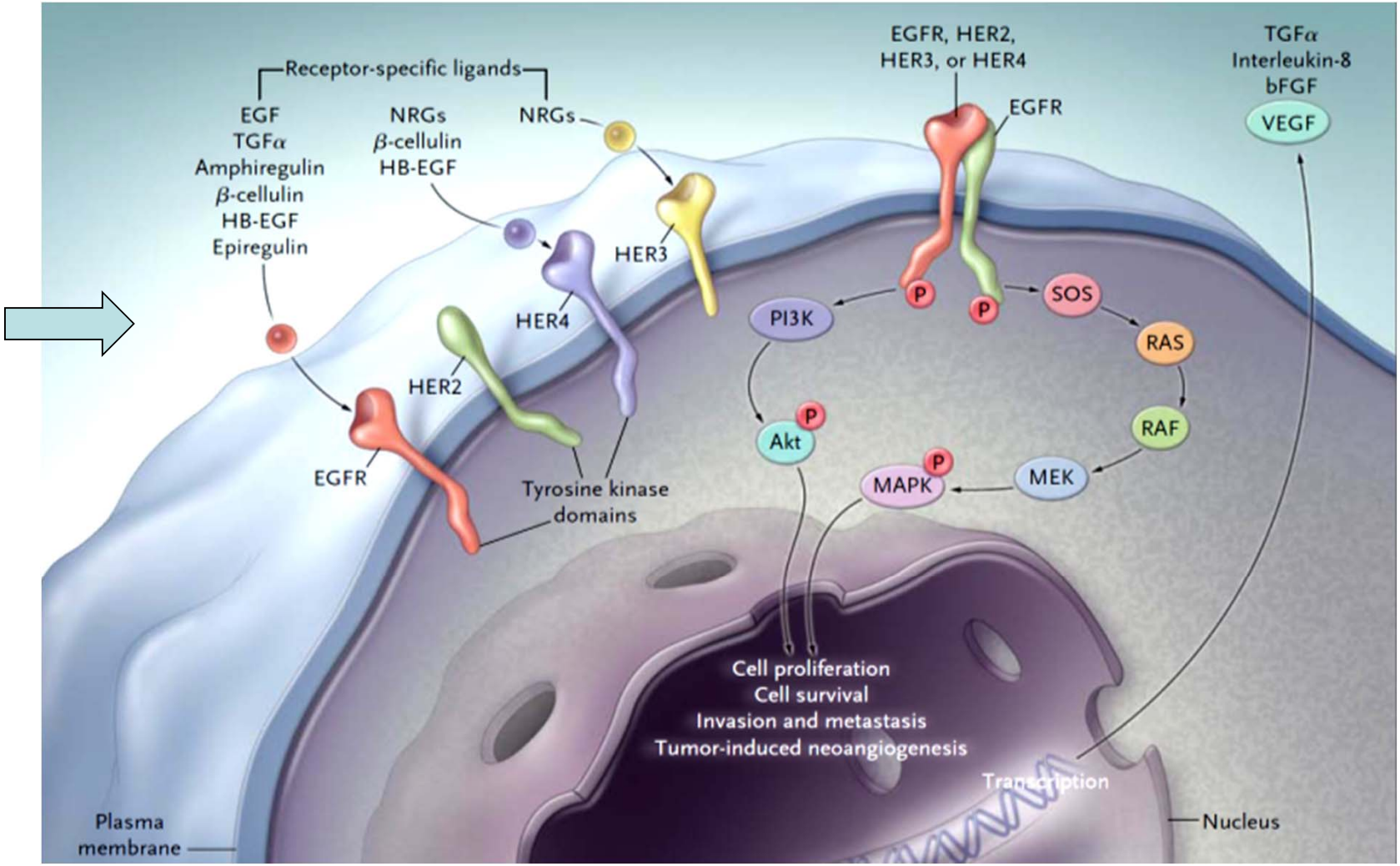




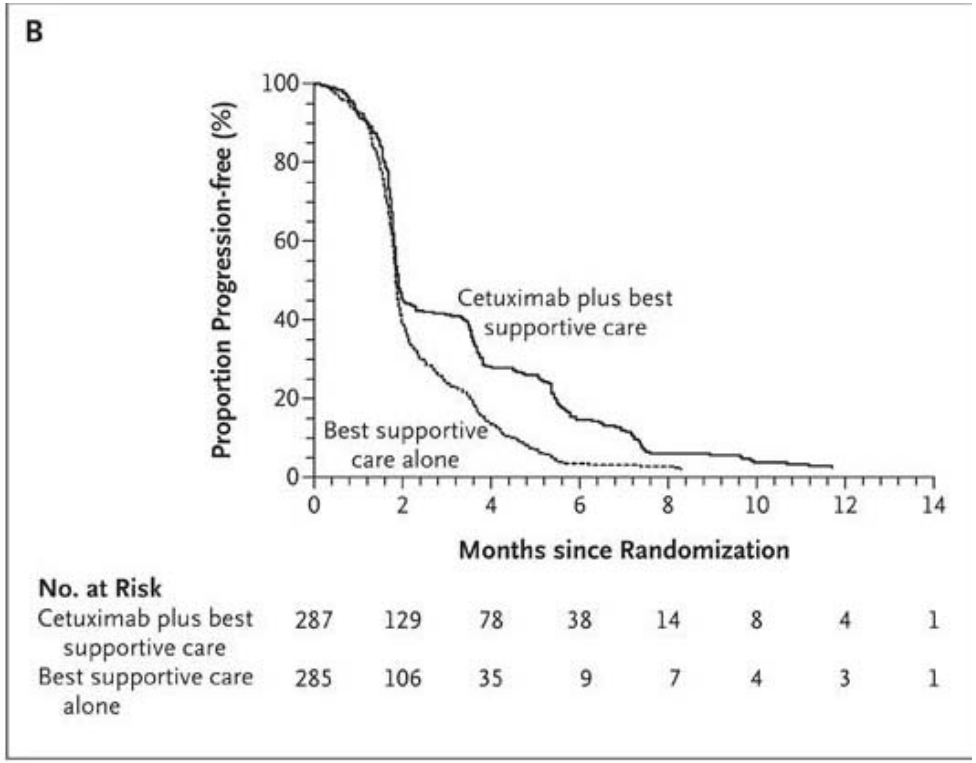
Test a hypothesis


Targeted agents in colorectal cancer
EGF
HER mAb
Cetuximab
Panitumumab
Trastuzumab
Pertuzumab
IGF-1/
Insulin
IGF-1 mAb
AMG479
IMC-A12
HGF
HGF mAb
AMG102
C-MET
HER
IGF-1R/
IR
VEGF
Anti-VEGF
Bevacizumab
VEGF-trap
VEGFR
IRS
PI3k
Ras
PIP3
PIP3
PDK-1
PTEN
Cell Membrane
Src
Anti-PDK-1
UCN01
mTOR
rictor
Akt
Anti-HER
Lapatinib
Raf
Anti-Src
XL999
AZD0530
Anti-Ras
Tipifarnib
Lonafarnib
MEK
Anti-mTOR
Everolimus
BAD
Apoptosis
mTOR
raptor
Anti-VEGFR
Vatalanib
AMG706
Pazopanib
Cediranib
Anti-Raf
Sorafenib
XL281
Erk
COX2
4EBP
FoxO3a
Transcription
Anti-MEK
AZD6244
PGE2
p70s6k
Cell Cycle Progression
Hif-1α
Angiogenesis
Anti-HDAC
Depsipeptide
Vorinostat
HDAC
Patient is the ultimate test tube
Siena, S. et al. J. Natl. Cancer Inst. 2009 101:1308-1324

Oncogenic addiction to EGFR in CRC



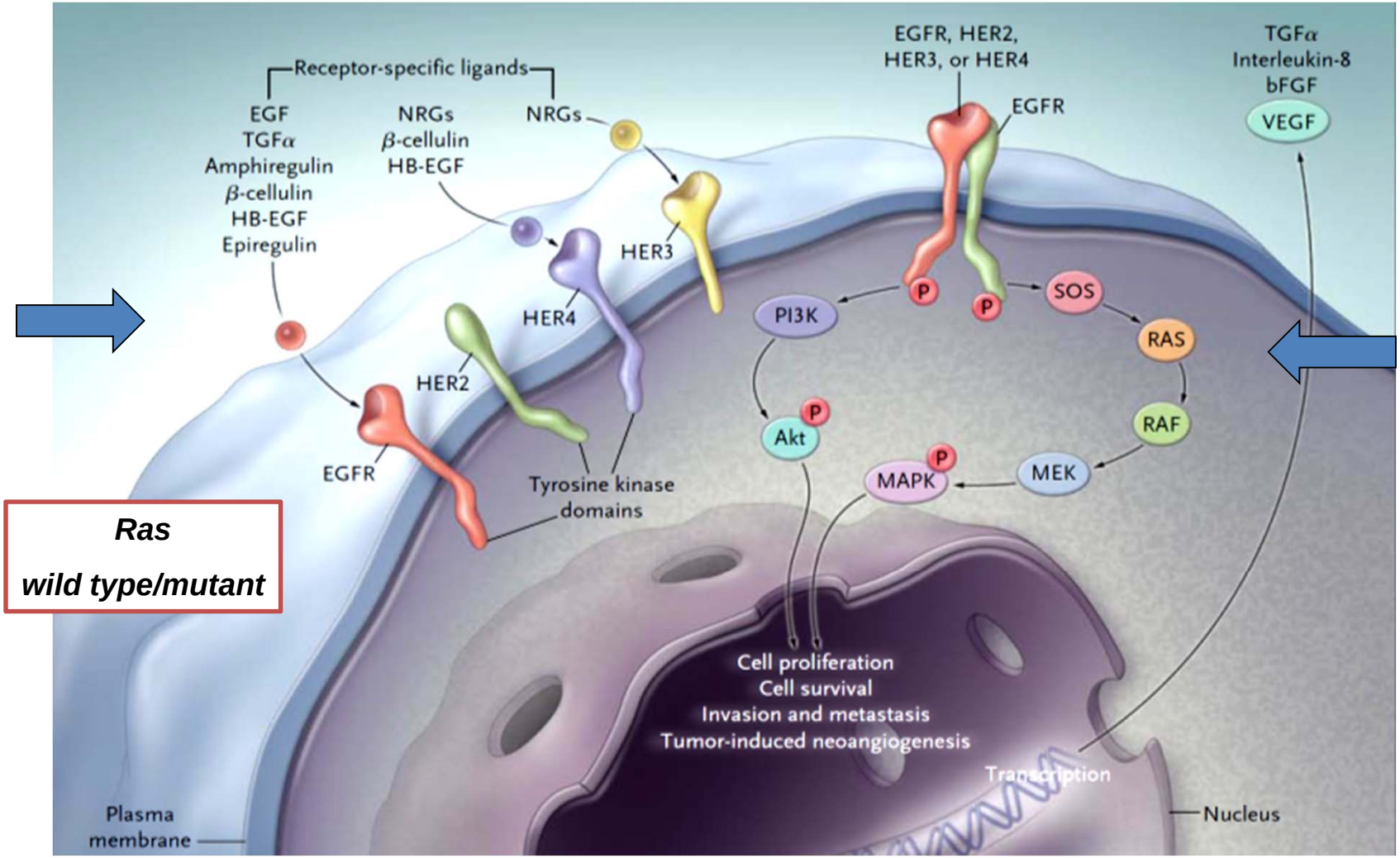
From Ciardiello F & Tortora G. N Engl J Med 2008;358:1160–117



onotherapy Erbitux Unselected patients

NEJM 2007

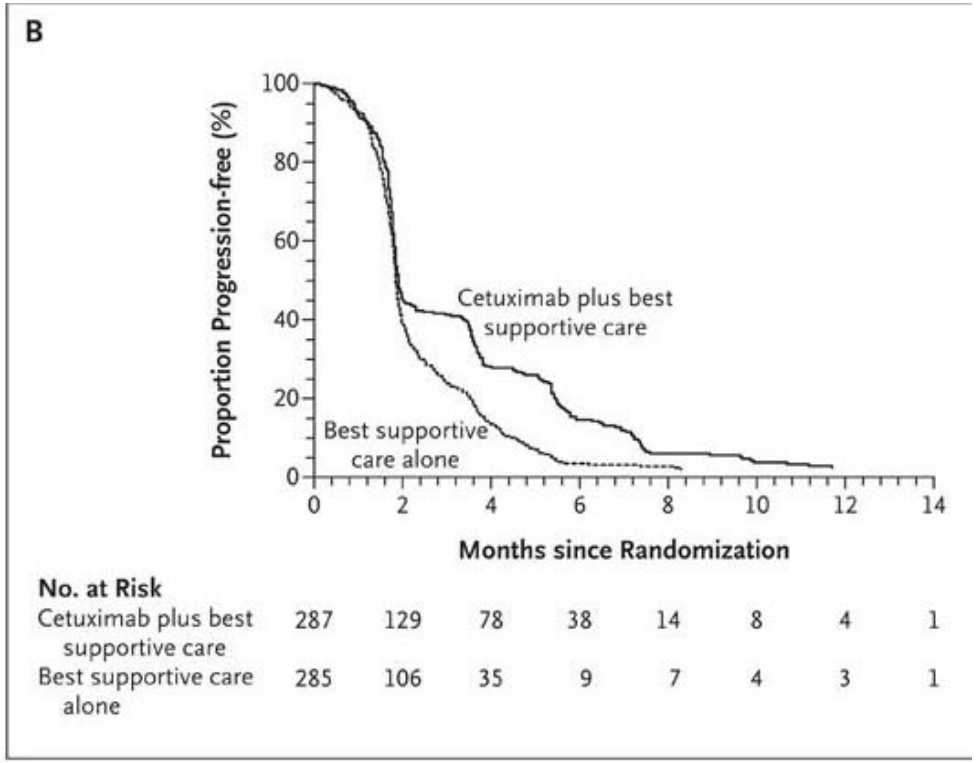
Oncogenic addiction to EGFR in CRC



Ras

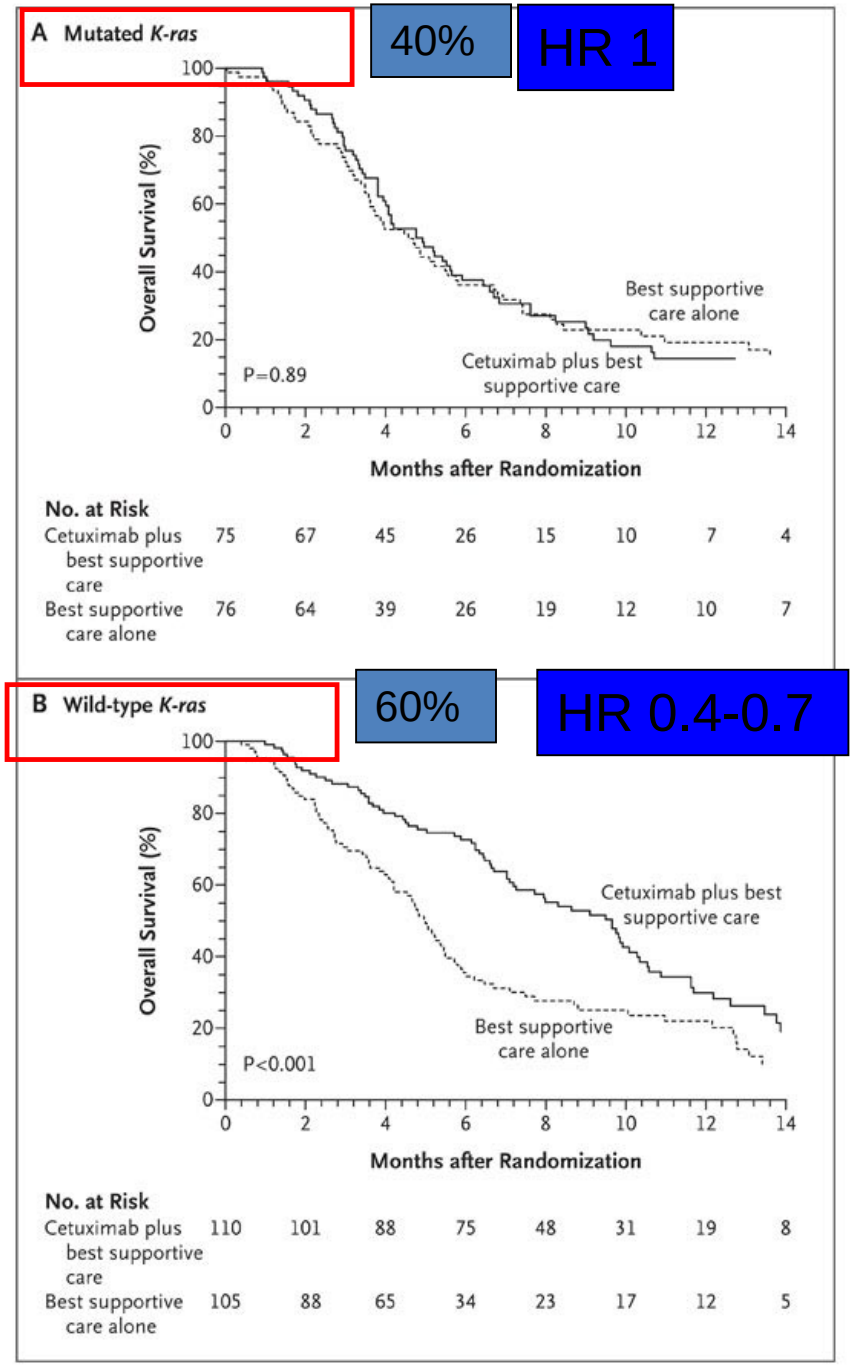
wild type/mutant

From Ciardiello F & Tortora G. N Engl J Med 2008;358:1160–117



onotherapy Erbitux Unselected patients
NEJM 2007

7 Monotherapy Kras selected patients
NEJM 2008



THE LANCET Oncology

60%, harm

< Previous Article Volume 11, No. 8, p753–762, August 2010 Next Article >

Articles

Effects of *KRAS, BRAF, NRAS*, and *PIK3CA* mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis

Wendy De Roock, MD, Bart Claes, MSc, David Bernasconi, MSc, Jef De Schutter, MSc, Bart Biesmans, MSc, Prof George Fountzilas, MD, Konstantine T Kalogeras, MD, Vassiliki Kotoula, MD, Demetris Papamichael, FRCP, Prof Pierre Laurent-Puig, MD, Prof Frédérique Penault-Llorca, MD, Prof Philippe Rougier, MD, Bruno Vincenzi, MD, Daniele Santini, MD, Prof Giuseppe Tonini, MD, Federico Cappuzzo, MD, Milo Frattini, PhD, Francesca Molinari, PhD, Piercarlo Saletti, MD, Sara De Dosso, MD, Miriam Martini, PhD, Prof Alberto Bardelli, PhD, Prof Salvatore Siena, MD, Andrea Sartore-Bianchi, MD, Prof Josep Tabernero, MD, Teresa Macarulla, MD, Frédéric Di Fiore, MD, Alice Oden Gangloff, MD, Prof Fortunato Ciardiello, MD, Prof Per Pfeiffer, MD, Camilla Qvortrup, MD, Tine Plato Hansen, MD, Prof Eric Van Cutsem, MD, Prof Hubert Piessevaux, MD, Prof Diether Lambrechts, PhD, Mauro Delorenzi, PhD, Prof Sabine Tejpar, MD

Published Online: 08 July 2010

1022 tumour DNA samples (73 from fresh-frozen and 949 from formalin-fixed, paraffin-embedded tissue) from patients treated with cetuximab between 2001 and 2008 were gathered from 11 centres in seven European countries

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Panitumumab–FOLFOX4 Treatment and *RAS* Mutations in Colorectal Cancer

Jean-Yves Douillard, M.D., Ph.D., Kelly S. Oliner, Ph.D., Salvatore Siena, M.D., Josep Tabernero, M.D., Ronald Burkes, M.D., Mario Barugel, M.D., Yves Humblet, M.D., Ph.D., Gyorgy Bodoky, M.D., Ph.D., David Cunningham, M.D., Jacek Jassem, M.D., Ph.D., Fernando Rivera, M.D., Ph.D., Ilona Kocákova, M.D., Ph.D., Paul Ruff, M.D., Maria Błasińska-Morawiec, M.D., Martin Šmakal, M.D., Jean Luc Canon, M.D., Mark Rother, M.D., Richard Williams, M.B., B.S., Ph.D., Alan Rong, Ph.D., Jeffrey Wiezorek, M.D., Roger Sidhu, M.D., and Scott D. Patterson, Ph.D.

N Engl J Med 2013; 369:1023-1034 | September 12, 2013 | DOI: 10.1056/NEJMoa1305275

BACKGROUND

Patients with metastatic colorectal cancer that harbors *KRAS* mutations in exon 2 do not benefit from anti–epidermal growth factor receptor (EGFR) therapy. Other activating *RAS* mutations may also be negative predictive biomarkers for anti-EGFR therapy.

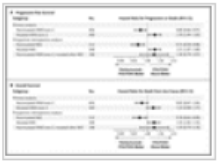
Full Text of Background...

METHODS

In this prospective–retrospective analysis, we assessed the efficacy and safety of panitumumab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) as compared with FOLFOX4 alone, according to *RAS* (*KRAS* or *NRAS*) or *BRAF* mutation status. A total of 639 patients who had metastatic colorectal cancer without *KRAS* mutations in exon 2 had results for at least one of the following: *KRAS* exon 3 or 4; *NRAS* exon 2, 3, or 4; or *BRAF* exon 15. The overall rate of ascertainment of *RAS* status was 90%.

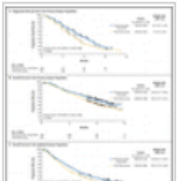
MEDIA IN THIS ARTICLE

FIGURE 1



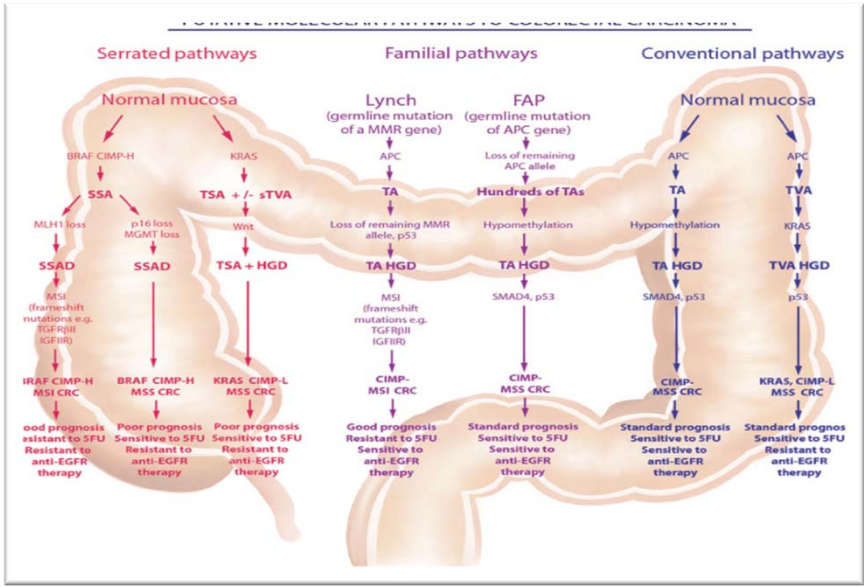
Hazard Ratio for Disease Progression or Death and Hazard Ratio for Death from Any Cause, According to *KRAS* and *RAS* Mutation Status.

FIGURE 2

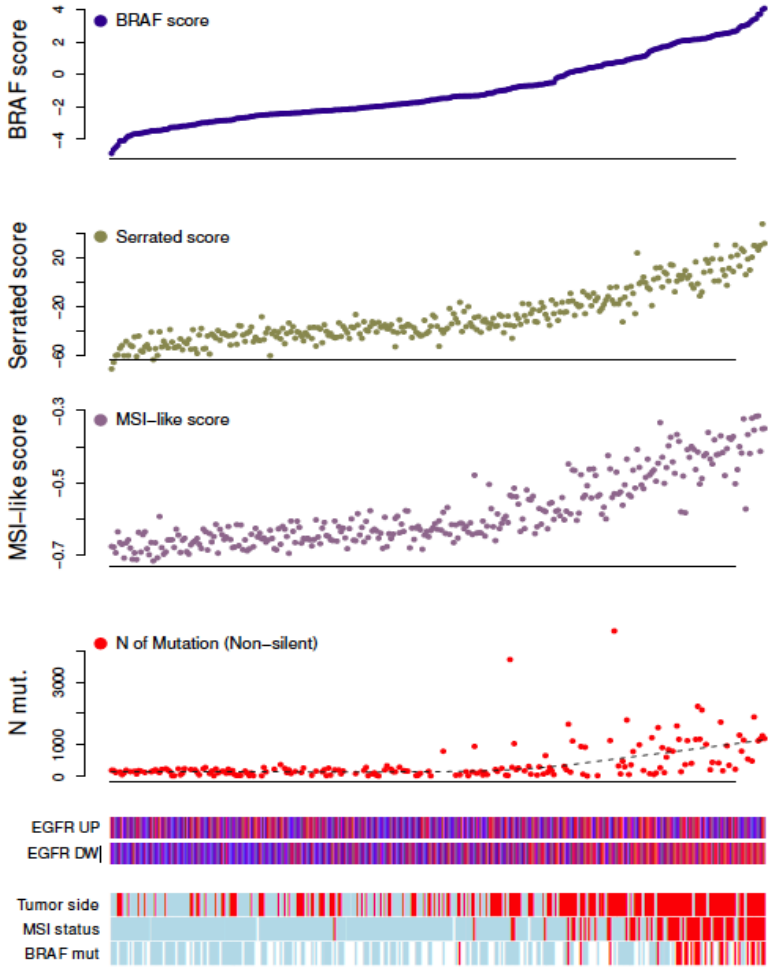


Colon Site Trends

left



right

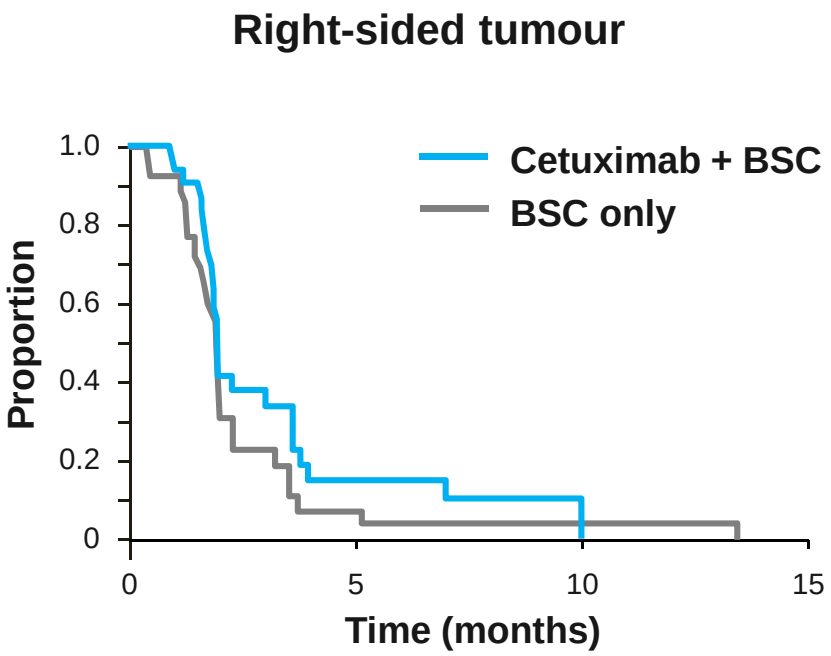


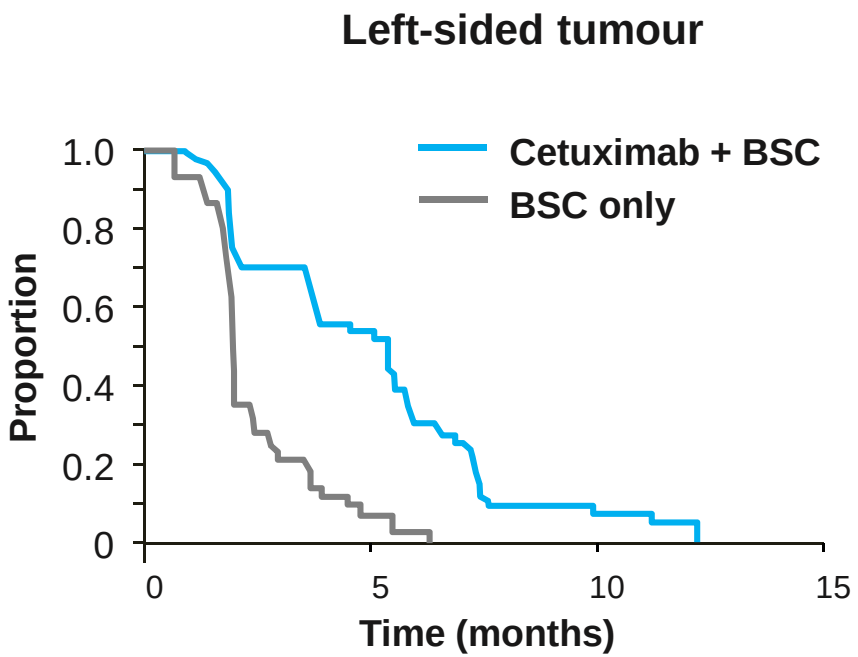
MSI, microsatellite instability.

Bettington, et al. *Histopathology*. 2013; Missiaglia, et al. *Ann Oncol*. 2014.

Tumour Location: A Predictive Marker for Cetuximab Benefit in *KRAS* WT?

- In **CO.17 trial,** left-sided primary tumour location was a strong predictor of PFS benefit in patients with *KRAS* WT refractory mCRC treated with cetuximab

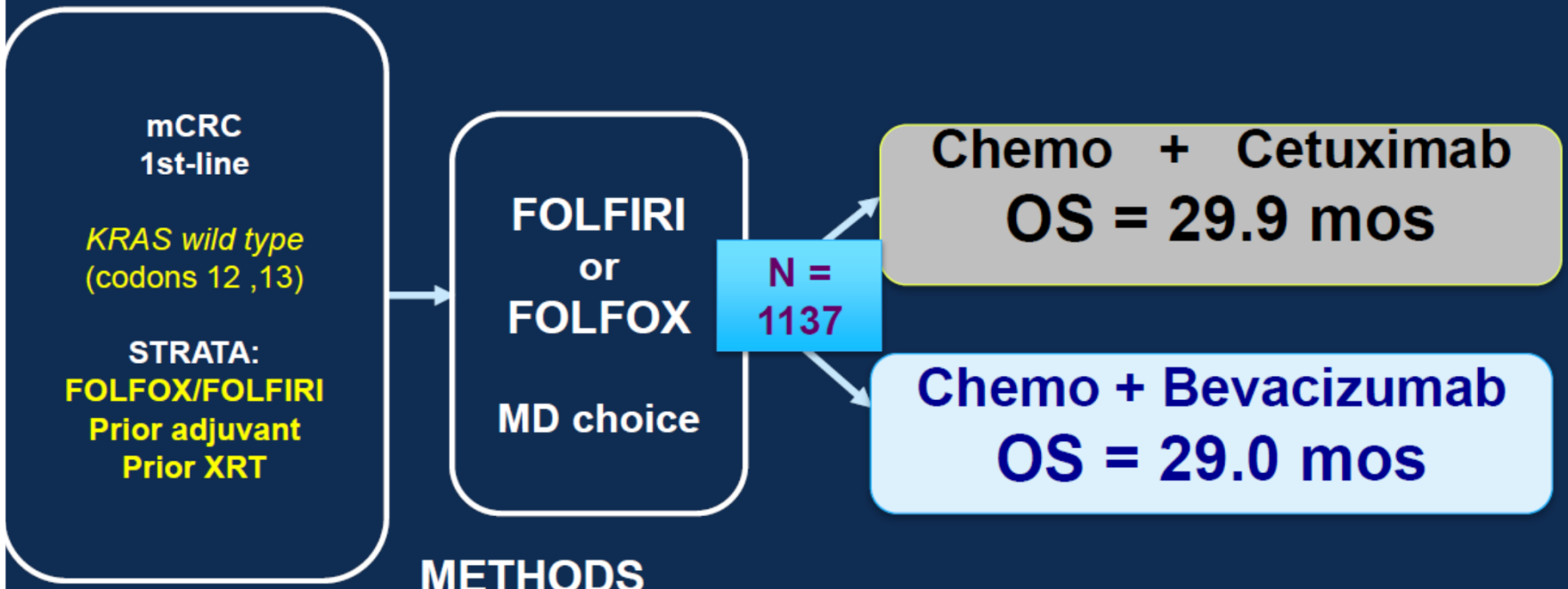




- Merck: CRYSTAL (2011)
- FIRE3 (2015)
- CALGB 80405 ASCO 2016
- Amgen: PRIME, ….? regulatory

BSC, best supportive care; mCRC, metastatic colorectal cancer; PFS, progression-free survival; WT, wild type.
Brule, et al. ASCO 2013.

CALGB/SWOG 80405



METHODS

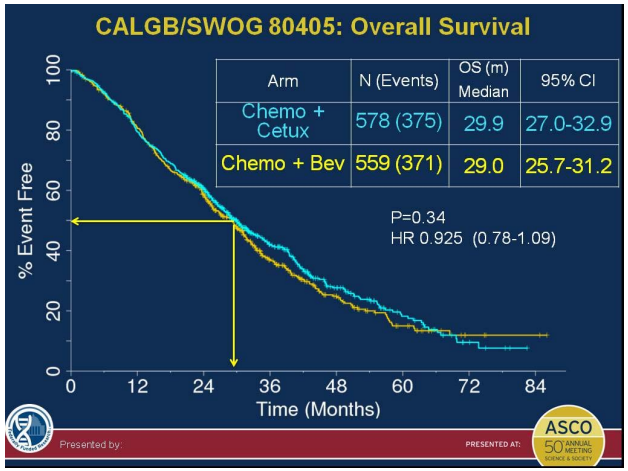
Main cohort 1° SIDE Distribution:

Right (293) Left (732) Transverse (66) uncertain (46)

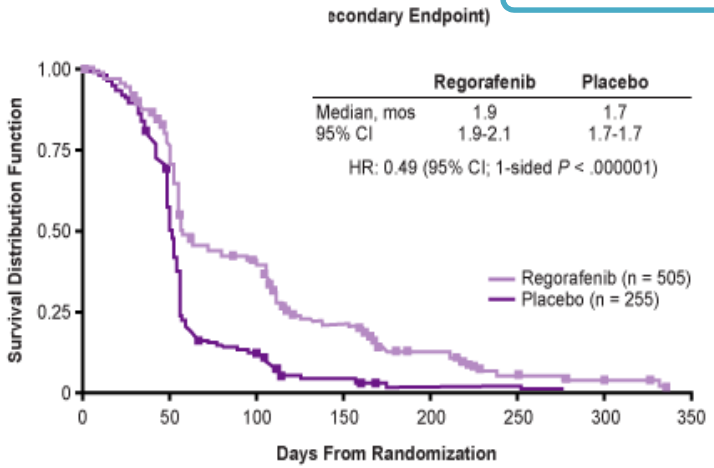
SIDE comparison: Right v left (exclude Transverse)

Pre-amendment KRAS *mutant* cohort: 213

Reanalysis of existing trials

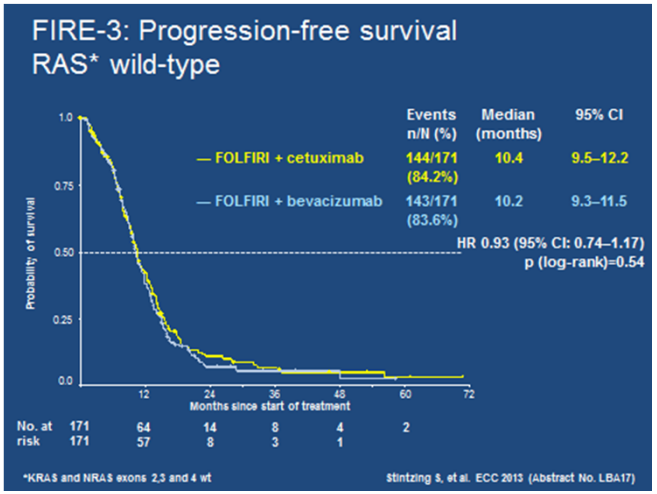


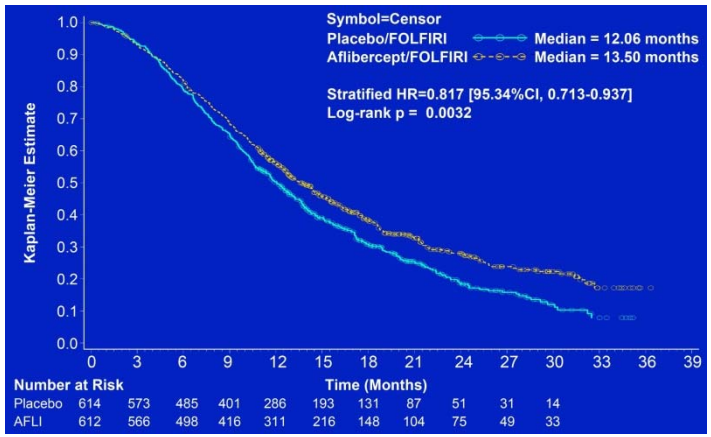
CORRECT+CONCUR



Major drug trials

-test biomarker–drug interactions





VELOUR+AFLAME

nature REVIEWS CLINICAL ONCOLOGY

ARTICLE PREVIEW

NATURE REVIEWS CLINICAL ONCOLOGY | PERSPECTIVES | OPINION

Integrating biomarkers in colorectal cancer trials in the West and China

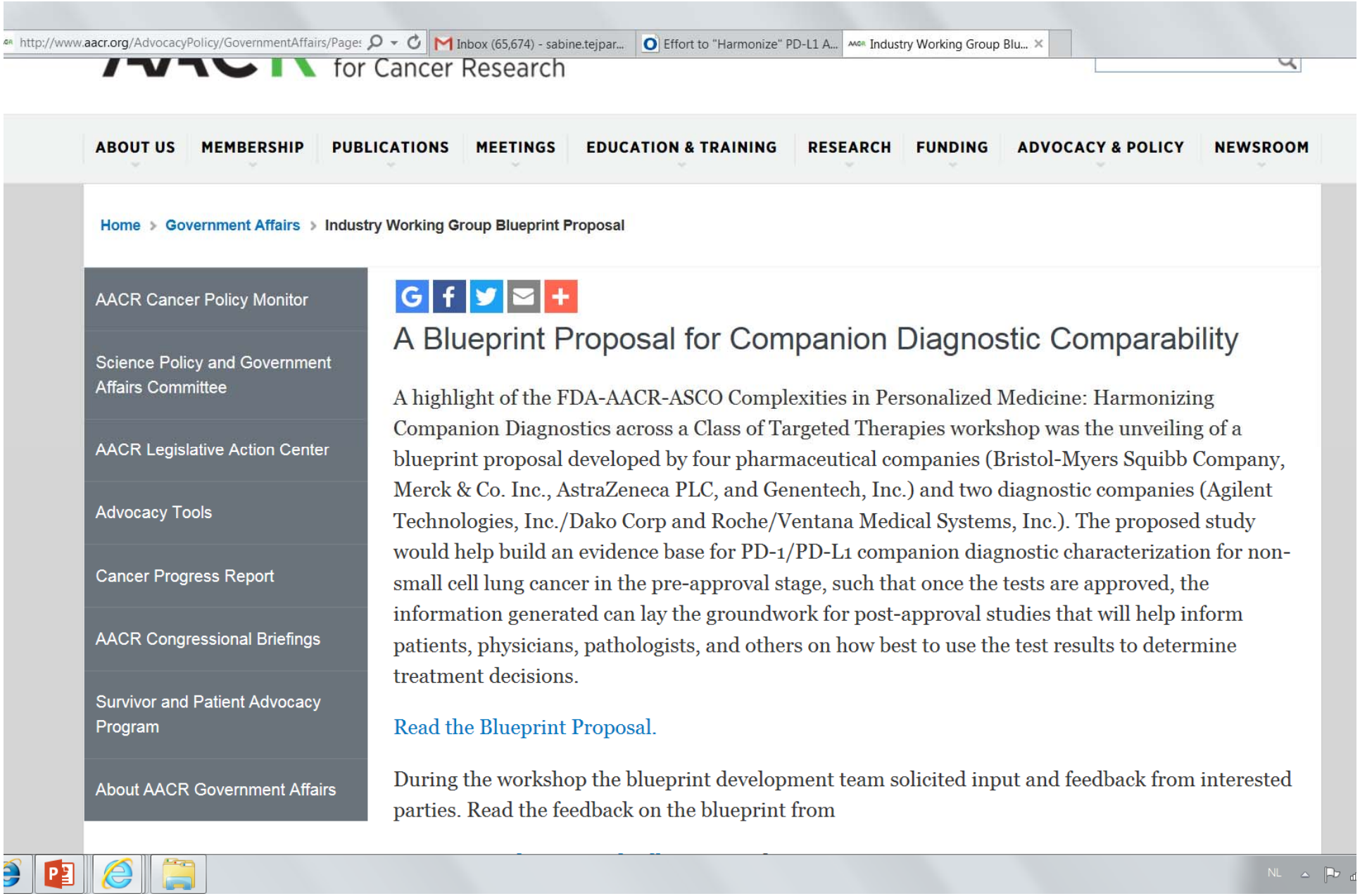
Sabine Tejpar, Lin Shen, Xicheng Wang & Richard L. Schilsky

Affiliations | **Contributions** | **Corresponding authors**

Nature Reviews Clinical Oncology **12**, 553–560 (2015) | doi:10.1038/nrclinonc.2015.88
Published online 12 May 2015 | Corrected online **28 May 2015**

Abstract

	Nivolumab (Opdivo)	Pembrolizumab (Keytruda)	Atezolizumab (MPDL3280A)	Durvalumab (MEDI4736)
mAb clone	28-8	22C3	SP142	SP263
Cells scored	"Tumor cell membrane"	"Tumor cell and stroma"	"Infiltrating immune cells"	Tumor cell membrane
Tissue	Archival	Recent	Archival/recent	Archival/recent
Positive cutoff	1%-5%	1%-50%	1%-10%	n/a
PD-L1–positive ORR	13%-31%	19%-47%	31%-83%	26%
PD-L1–negative ORR	10%-17%	9%-13%	18%-20%	10%
Drug developer	BMS	Merck	Genentech	AstraZeneca


http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages
Inbox (65,674) - sabine.tejpar...
Effort to "Harmonize" PD-L1 A...
Industry Working Group Blu...
for Cancer Research
ABOUT US
MEMBERSHIP
PUBLICATIONS
MEETINGS
EDUCATION & TRAINING
RESEARCH
FUNDING
ADVOCACY & POLICY
NEWSROOM
Home
Government Affairs
Industry Working Group Blueprint Proposal
AACR Cancer Policy Monitor
Science Policy and Government Affairs Committee
AACR Legislative Action Center
Advocacy Tools
Cancer Progress Report
AACR Congressional Briefings
Survivor and Patient Advocacy Program
About AACR Government Affairs
A Blueprint Proposal for Companion Diagnostic Comparability
A highlight of the FDA-AACR-ASCO Complexities in Personalized Medicine: Harmonizing Companion Diagnostics across a Class of Targeted Therapies workshop was the unveiling of a blueprint proposal developed by four pharmaceutical companies (Bristol-Myers Squibb Company, Merck & Co. Inc., AstraZeneca PLC, and Genentech, Inc.) and two diagnostic companies (Agilent Technologies, Inc./Dako Corp and Roche/Ventana Medical Systems, Inc.). The proposed study would help build an evidence base for PD-1/PD-L1 companion diagnostic characterization for non-small cell lung cancer in the pre-approval stage, such that once the tests are approved, the information generated can lay the groundwork for post-approval studies that will help inform patients, physicians, pathologists, and others on how best to use the test results to determine treatment decisions.
Read the Blueprint Proposal.
During the workshop the blueprint development team solicited input and feedback from interested parties. Read the feedback on the blueprint from
NL

Inflamed-Phenotype Gene Expression Signatures, and the Anti–PD-1 Antibody Pembrolizumab in PD-L1+ Hea

Tanguy Y. Seiwert,[1] Barbara Burtness,[2] Jared Weiss,[3] Joseph Paul Eder,[4] Jennifer Yearley,[5] Erin Murphy,[5] Michael Nebozhyn,[5] Terri McClanahan,[5] Mark Ayers,[5] Jare

[1]University of Chicago, Chicago, IL, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC,

INTRODUCTION

- Pembrolizumab (MK-3475) is a humanized IgG4 kappa monoclonal antibody that directly blocks the interaction between the programmed death 1 (PD-1) receptor and its 2 ligands, PD-L1 and PD-L2[1]
- In the nonrandomized, open-label, phase 1b KEYNOTE-012 trial (ClinicalTrials.gov, NCT01848834), the anti–programmed death 1 (PD-1) antibody pembrolizumab exhibited antitumor activity in a cohort of patients with PD-L1–positive (PD-L1+) recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) and was generally well tolerated[2]
  - Objective response rate was 19.6% (confirmed and unconfirmed)
- Baseline tumor features related to response or resistance to PD-1 blockade were not fully elucidated
  - Ongoing translational studies have allowed identification of biomarkers beyond tumor PD-L1 expression as potential enrichment biomarkers across a broad range of tumor types
- This hypothesis-confirming study tested 4 multigene immune-related gene expression signatures that were previously established in patients with melanoma who were treated with pembrolizumab[3]
  - These predefined signatures were then independently tested in patients with R/M HNSCC treated with pembrolizumab in the KEYNOTE-012 study

METHODS

Tissue Processing and NanoString Analysis

- The methodology for this analysis is outlined in **Figure 1**

Table 1. Immune-Related Gene Expression Signatures Identified in Melanoma

IFN-γ	Expanded Immune		TCR Signaling	De Novo		
IDO1	*CD3D*	*NKG7*	*CD27*	*IKZF3*	*SAMHD1*	*CD38*
CXCL10	*IDO1*	*HLA-E*	*TIGIT*	*HLA-DPB1*	*TIGIT*	*CRTAM*
CXCL9	*CIITA*	*CXCR6*	*CD8a*	*CD27*	*IL2RB*	*CD8A*
HLA-DRA	*CD3E*	*LAG3*	*CD3D*	*AMICA1*	*TARP*	*CXCL9*
STAT1	*CCL5*	*TAGAP*	*GRAP2*	*CD74*	*CD3D*	*HLA-C*
IFNG	*GZMK*	*CXCL10*	*LCK*	*LY9*	*CD3G*	*GPR18*
	CD2	*STAT1*	*PTPRCAP*	*CD4*	*HLA-B*	*IL18*
	HLA-DRA	*GZMB*	*CD4*	*HLA-DRA*	*IGJ*	*CX3CR*
	CXCL13		*CCL5*	*B2M*	*IRF1*	*CXCL1*
	IL2RG		*IL2RB*	*IGSF6*	*BST2*	*SIT1*
			IKZF3	*FASLG*	*PTPN7*	
			CD3G	*LCK*		
			CD74			

IFN-γ = interferon gamma; TCR = T-cell receptor.

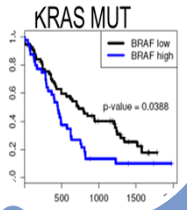
RESULTS

- Of the 61 patients enrolled, 43 had RNA expression profiling and survival data; 40 were evaluable for objective response and used for this analysis (**Table 2**)
  - Objective response rate in this subgroup was 22.5%
- Significant association was observed between the identified gene signatures and best overall response and PFS (**Table 3**)
- At the Youden index–derived cutoff, the IFN-γ signature is able to maintain a very high negative predictive value (NPV) of 95% while still providing meaningful enrichment of response rates (**Figure 2**)
  - Positive predictive value (PPV): 40%

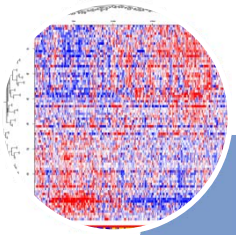
Common structures for clinical dvlpmt?

- Big data (transversal)
- Decrease trial cost, common platforms
- Increase transparency
- Neutrally held biobanks
- Biomarker devlpmt
- Adequate design (learning obj vs market acces)
- Performance (control)

Clinical implications/applications



Testable hypothesis
Outcomes confrontation

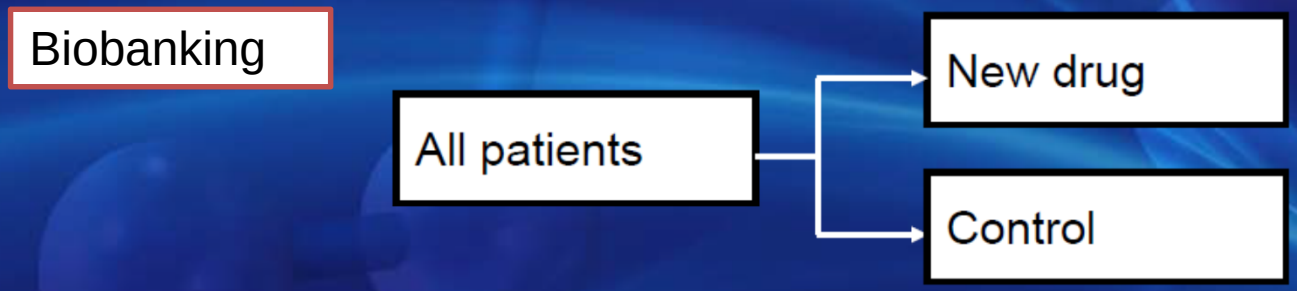


Markers of underlying Biology

Predictive Marker Study Design

Completely Randomized Design

Marker tested on all patients, but result not used for randomization



Randomized Block Design

Marker tested pre-randomization, stratification by marker

Common structures for clinical dvlpmt?

- Big data (transversal)
- Decrease trial cost, common platforms
- Increase transparency
- Neutrally held biobanks
- Biomarker devlpmt
- Adequate design (learning obj)
- Performance (control)

NCI-MATCH: A National Precision Medicine Trial Conception, Development and Adjustment

Barbara A. Conley MD

Associate Director, Cancer Diagnosis Program, DCTD, NCI, NIH

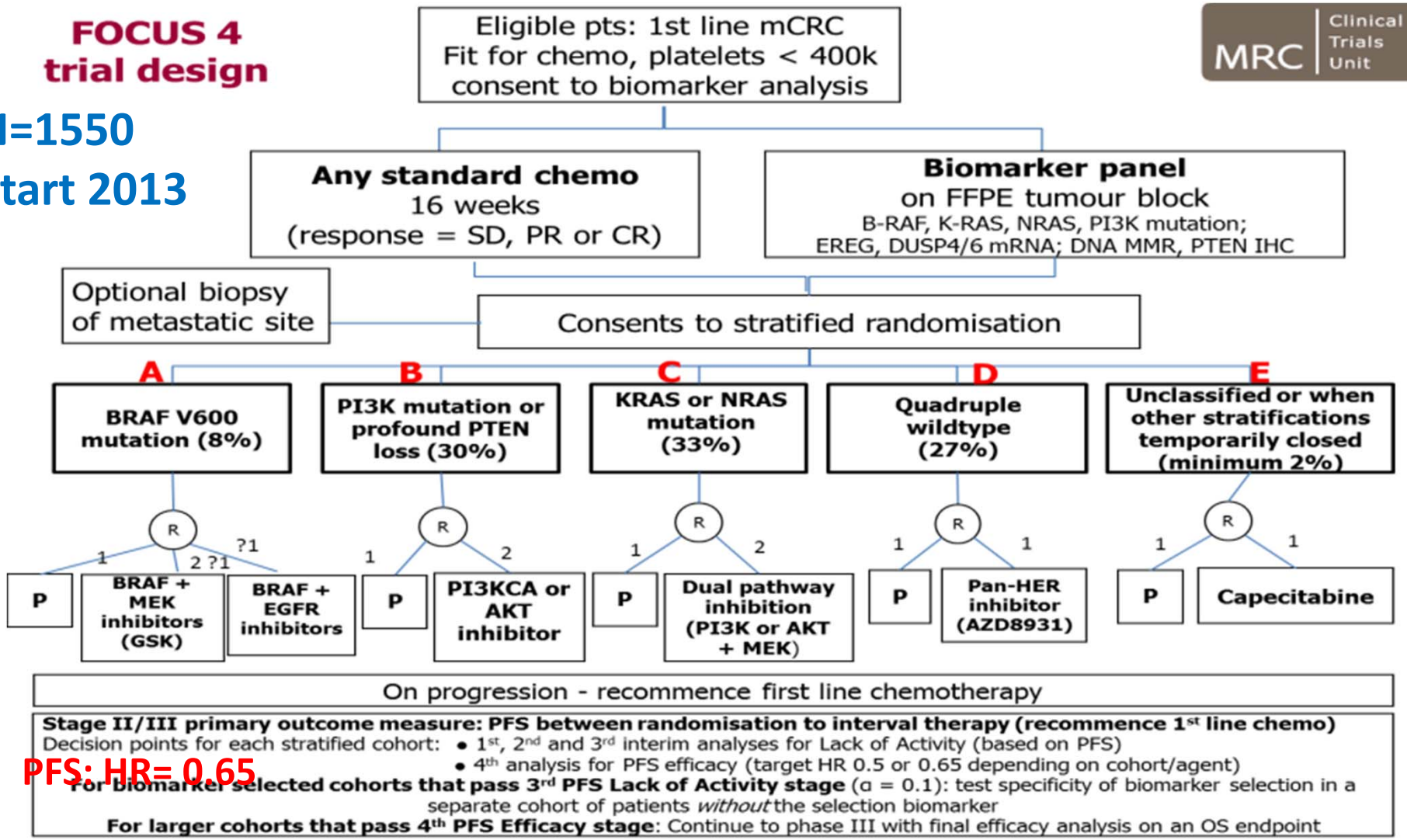
NIH NATIONAL CANCER INSTITUTE

November 16, 2015

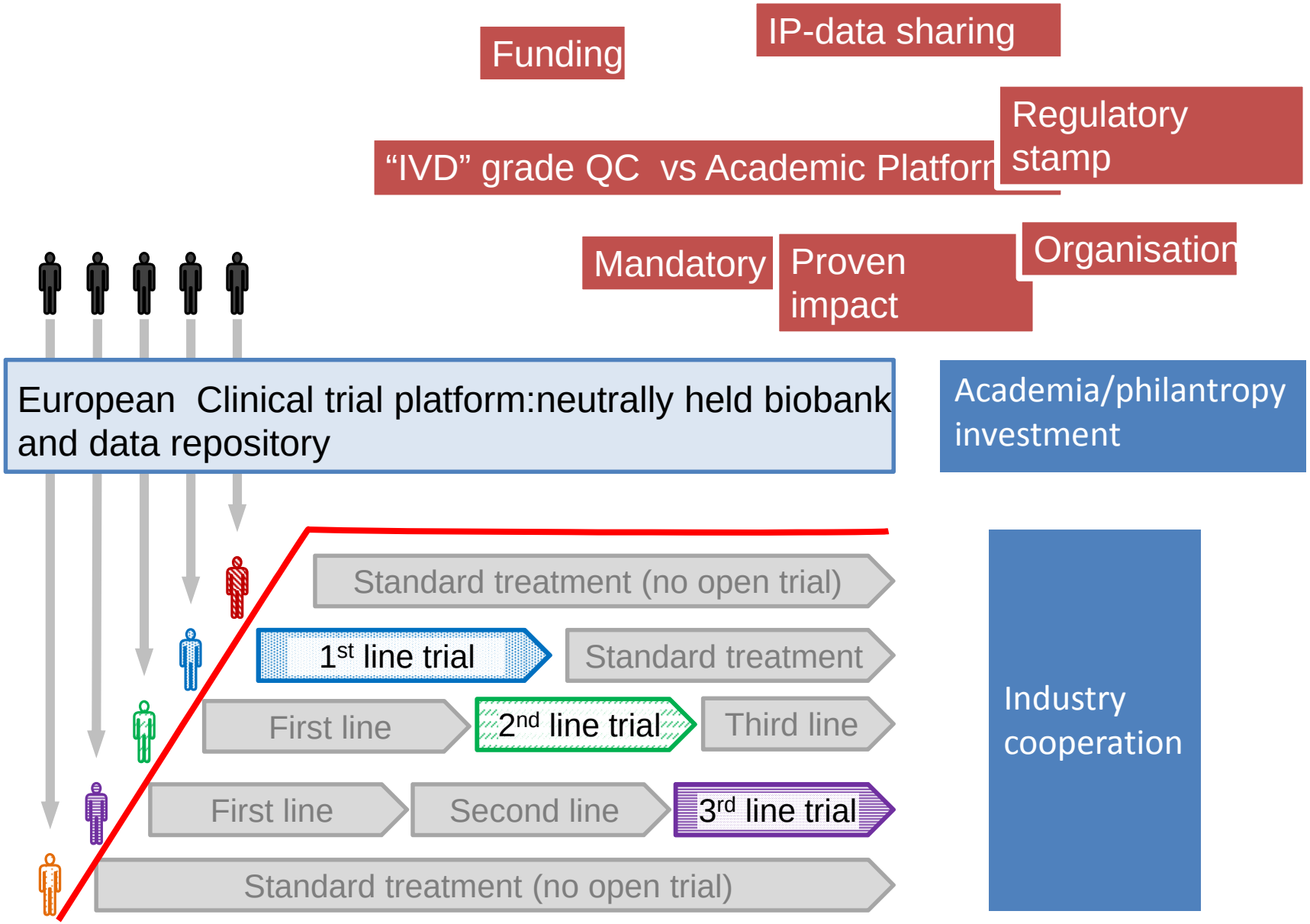
FOCUS 4 trial design

N=1550

Start 2013



PFS: HR= 0.65


Funding
IP-data sharing
Regulatory stamp
"IVD" grade QC vs Academic Platform
Mandatory
Proven impact
Organisation
European Clinical trial platform:neutrally held biobank and data repository
Academia/philantropy investment
Standard treatment (no open trial)
1st line trial
Standard treatment
First line
2nd line trial
Third line
First line
Second line
3rd line trial
Standard treatment (no open trial)
Industry cooperation

EMA, EFPIA, Payers, EC, IMI, EORTC, academics ……..????
Rest of the world?