ASSOCIAZIONE CULTURALE
"GIUSEPPE DOSSETTI"

THE PARADIGM OF PERSONALIZED THERAPY IN ONCOLOGY

Giampietro Gasparini

Oncology - San Filippo Neri Hospital
Rome, Italy

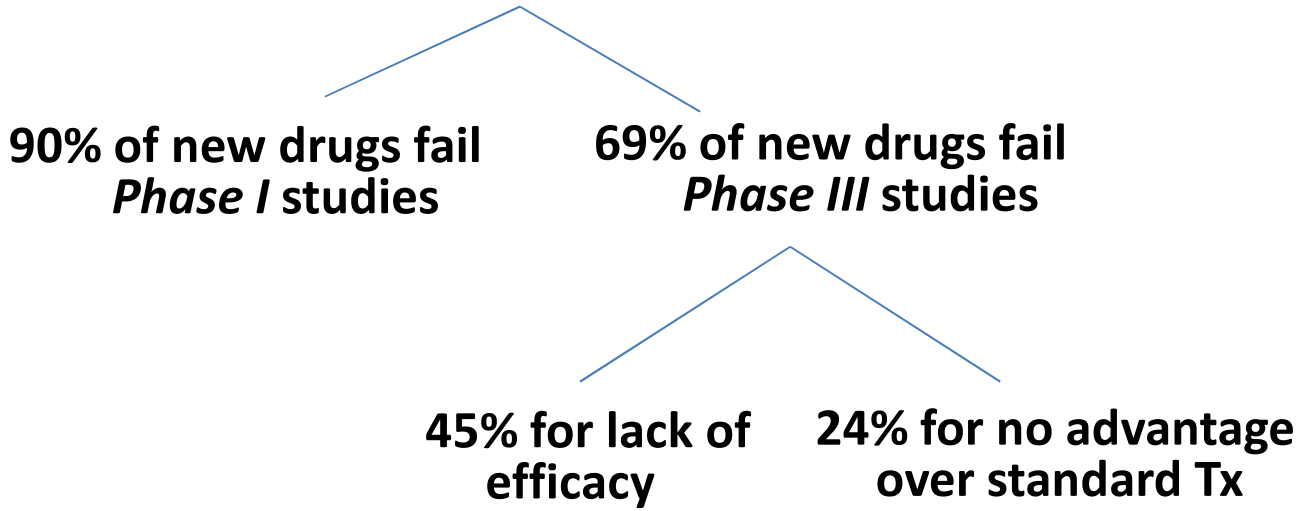
Roma, 26 October 2011

www.professorgasparini.com

THE NEED FOR NEW ANTICANCER STRATEGIES

Mortality rates X 100.000

	Heart Diseases	*Cancer*
1950	**586**	**194**
2005	**211**	**184**



CANCER THERAPY ERAS

- Locoregional treatments — **yrs ’40 -’50**
- Chemotherapeutic- based systemic treatments — **yrs ’60 -’80**
- Targeted treatments — **current yrs**
- Genomic-based treatments — **the era is beginning**

UNRESOLVED BIOLOGICAL QUESTIONS

- ***Driver vs Passenger genetic alterations***

  (Pancreatic cancer genome : a single tumor has a median of 63 *mutated* genes*)*

- ***The identification of the core pathway in each single tumor***

- ***Site heterogeneity***

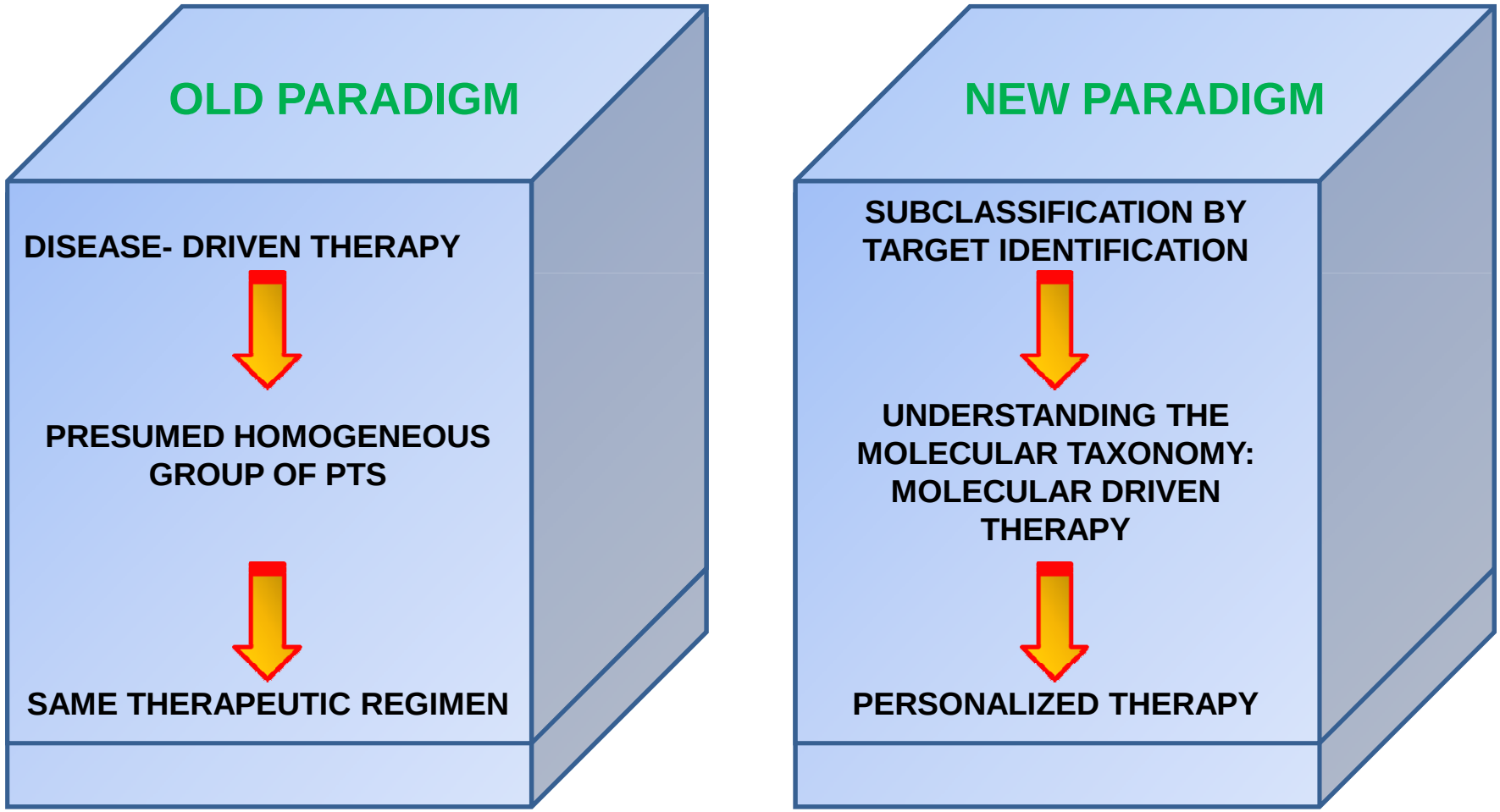
  (Primary *vs* metastasis *vs* ≠ metastatic organs)

- ***Factors modifying the response to targeted therapy (Theranosis)***

  (Pharmacogenomics, Pharmacogenetics)

- ***Comprehensive knowledge of the mechanisms of acquired resistance***

THE SWITCH FROM HISTOLOGIC TYPE TO MOLECULAR CLINICAL ONCOLOGY: *THERAPEUTIC IMPLICATIONS*



THE TUMOR OF EACH SINGLE PATIENT IS UNIQUE BECAUSE THE GENOME OF HIS/HER CANCER IS UNIQUE

KOCH'S POSTULATES FOR INFECTIVE DISEASES : SIMILARITIES WITH ANTICANCER PERSONALIZED THERAPY

INFECTION	TUMOR
Pathogenesis of the infective disease	Driver target mutation/s
Identification of the microorganism	Identification of the predictive tool
Therapy with the selective antimicrobic drug/s	Anticancer therapy with the targeted agent/s

PERSONALIZED CANCER CARE: WHAT DOES IT MEAN?

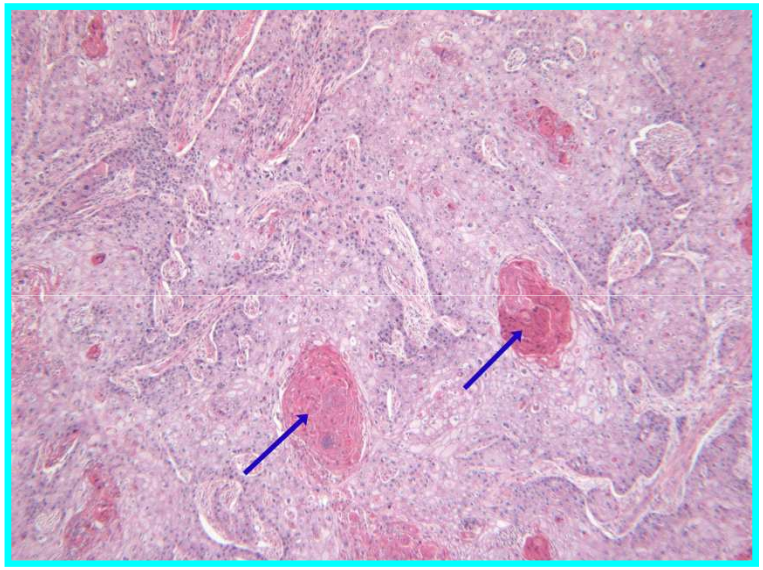
THE ASPIRATION TO BASE A TREATMENT ON THE UNIQUE BIOLOGICAL FEATURES OF A PATIENT'S DISEASE THROUGH THE IDENTIFICATION OF VALIDATED TOOLS OF RESPONSE/RESISTANCE TO THERAPY

AIMS

- ***TO IMPROVE DRUG EFFICACY***
- ***TO AVOID INAPPROPRIATE DRUG EXPOSURE (PRIMARY RESISTANT TUMORS)***
- ***TO MAXIMIZE QUALITY OF LIFE***
- ***TO SPARE UNNECESSARY COSTS***

NSCLC

Different histotypes: Different treatments



Squamous cell

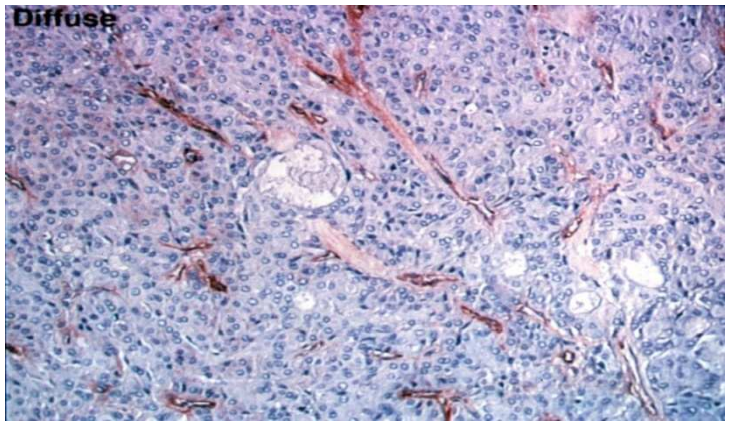
(Bevacizumab)

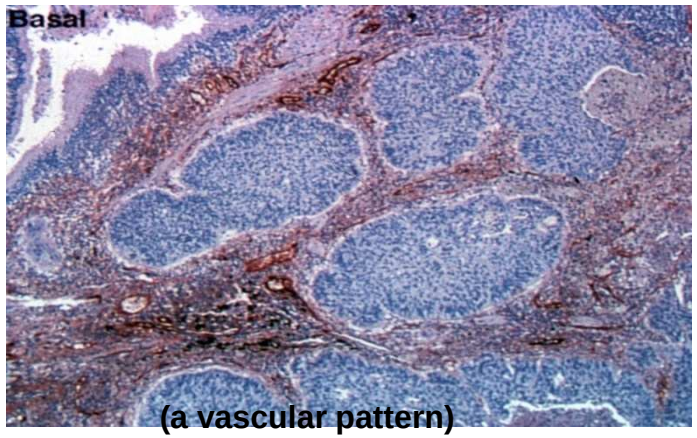


Non Squamous cell

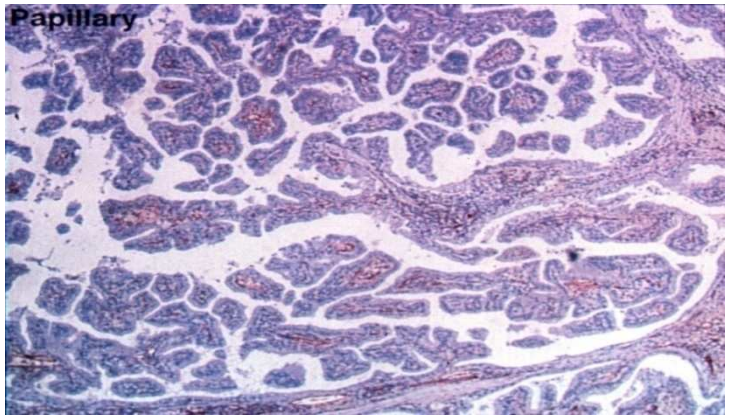
(Pemetrexed)

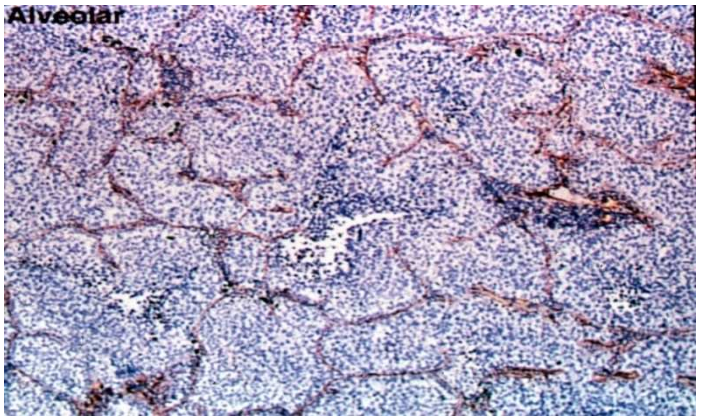
CHARACTERISTICS OF THE NSCLC TUMORS ACCORDING TO THE VASCULAR PATTERNS





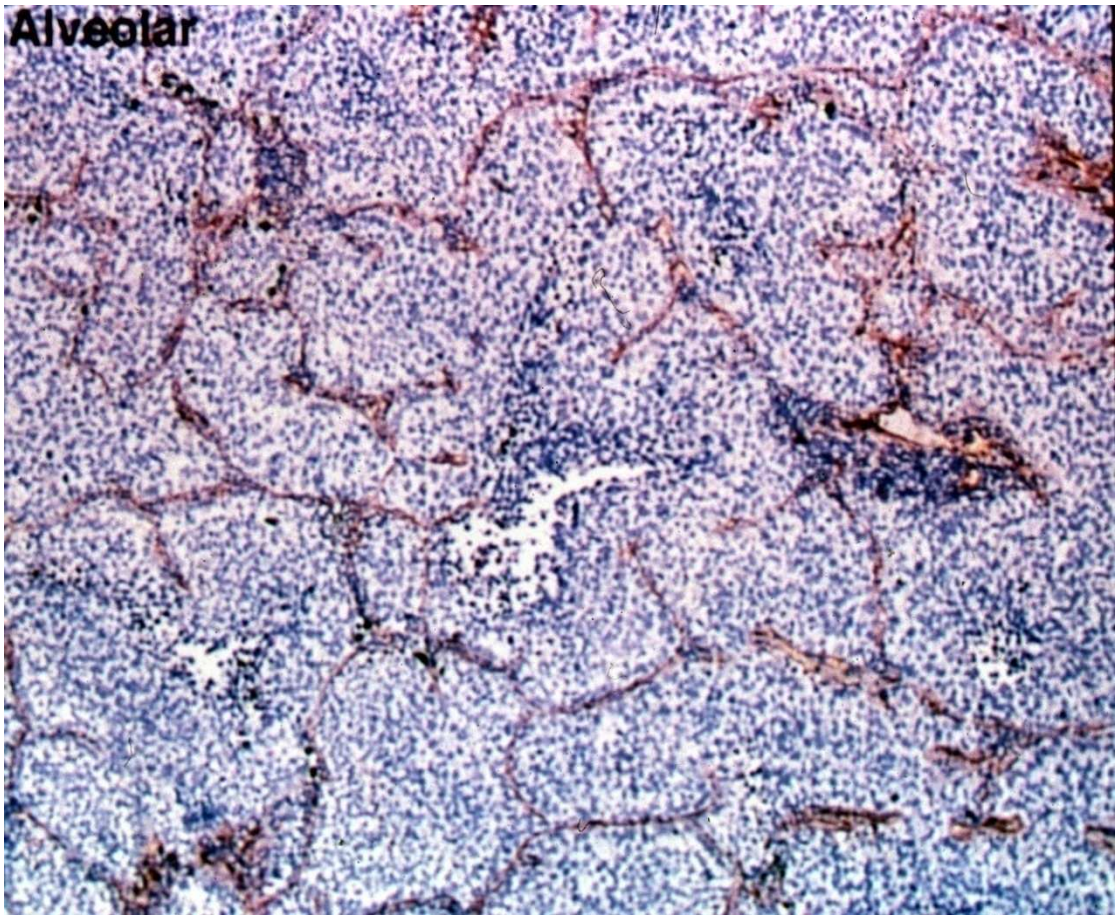
(a vascular pattern)





ALVEOLAR PATTERN

The only vessels evident in this pattern arise from the alveolar septa

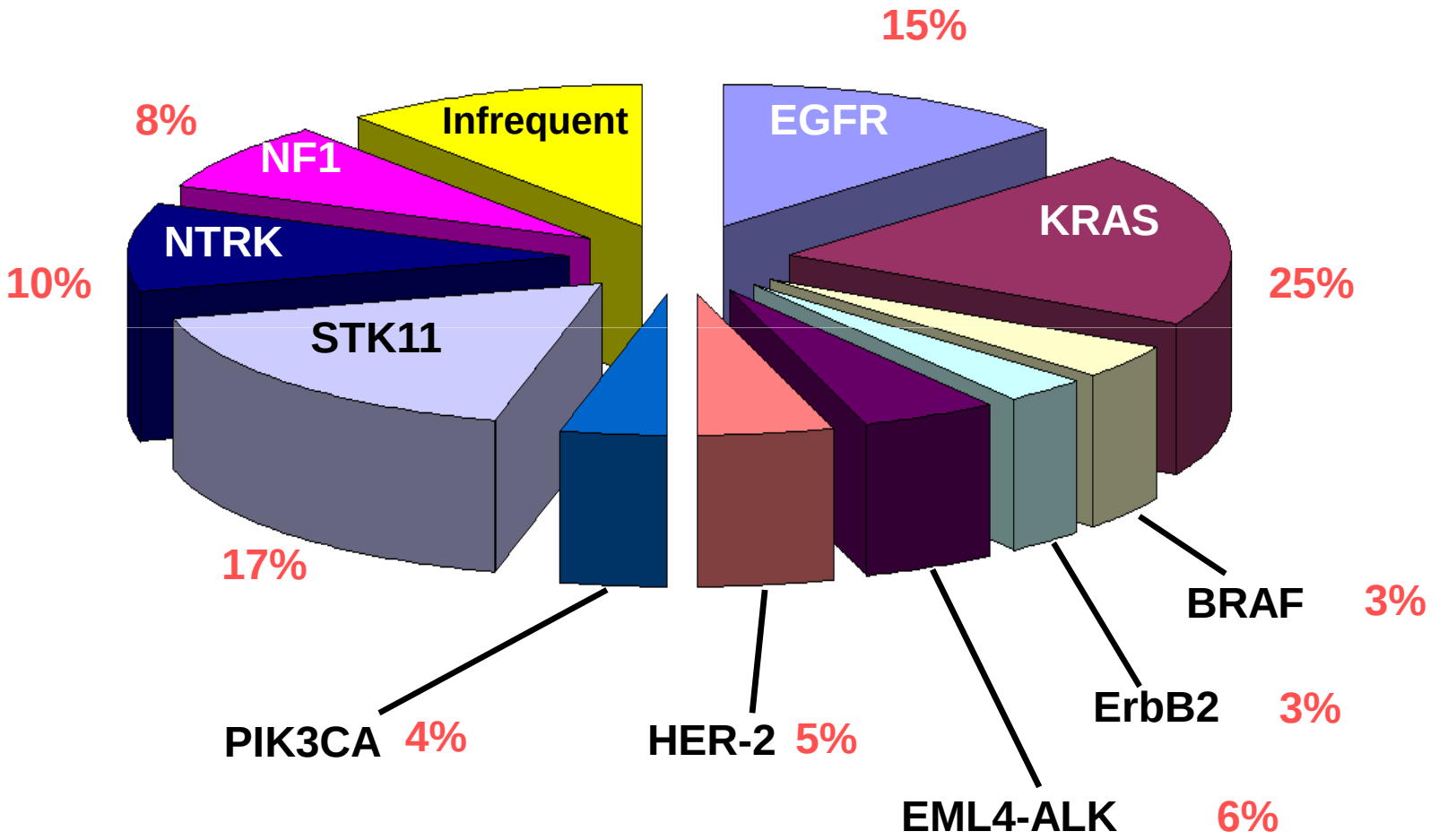


NSCLC MAIN FEATURES ACCORDING TO THE VASCULAR PATTERNS

	ANGIOGENESIS PATTERNS			
	BASAL	PAPILLARY	DIFFUSE	ALVEOLAR
MUCOSA ARCHITECTURE	Reproduced	Reproduced	Absent	Absent
NORMAL LUNG	Destroyed	Destroyed	Destroyed	Preserved
NEW VESSELS	Present	Present	Present	Absent
TUMOR STROMA	Present	Present	Present	Absent
NON-SMOKER PATIENTS	Lower incidence	Higher incidence	Expected incidence	Expected incidence
PREVALENT HISTOTYPE	Squamous	Adenocarcinoma	None	None
PREVALENT GRADING	None	Well differentiated	Poorly differentiated	Poorly differentiated
HIGHER THAN EXPECTED	BCL-2, laminin receptor	-	-	BCL-2
LOWER THAN EXPECTED	-	BCL-2, p53, EGFR	BCL-2, laminin receptor	-

Pezzella, Gasparini et al Am J Pathol 151: 1417, 1997

Driver mutations in lung adenocarcinoma



Paik et Al,JCO 29: 2046. 2011

ROAD MAP FOR SUCCESS IN LUNG CANCER THERAPY

- Understanding the complexity of biology
  - Histology subtypes
  - Molecular heterogeneity-NSCLCs as the sum of rare diseases
- Molecular target identification
- Inhibiting target using selective agents

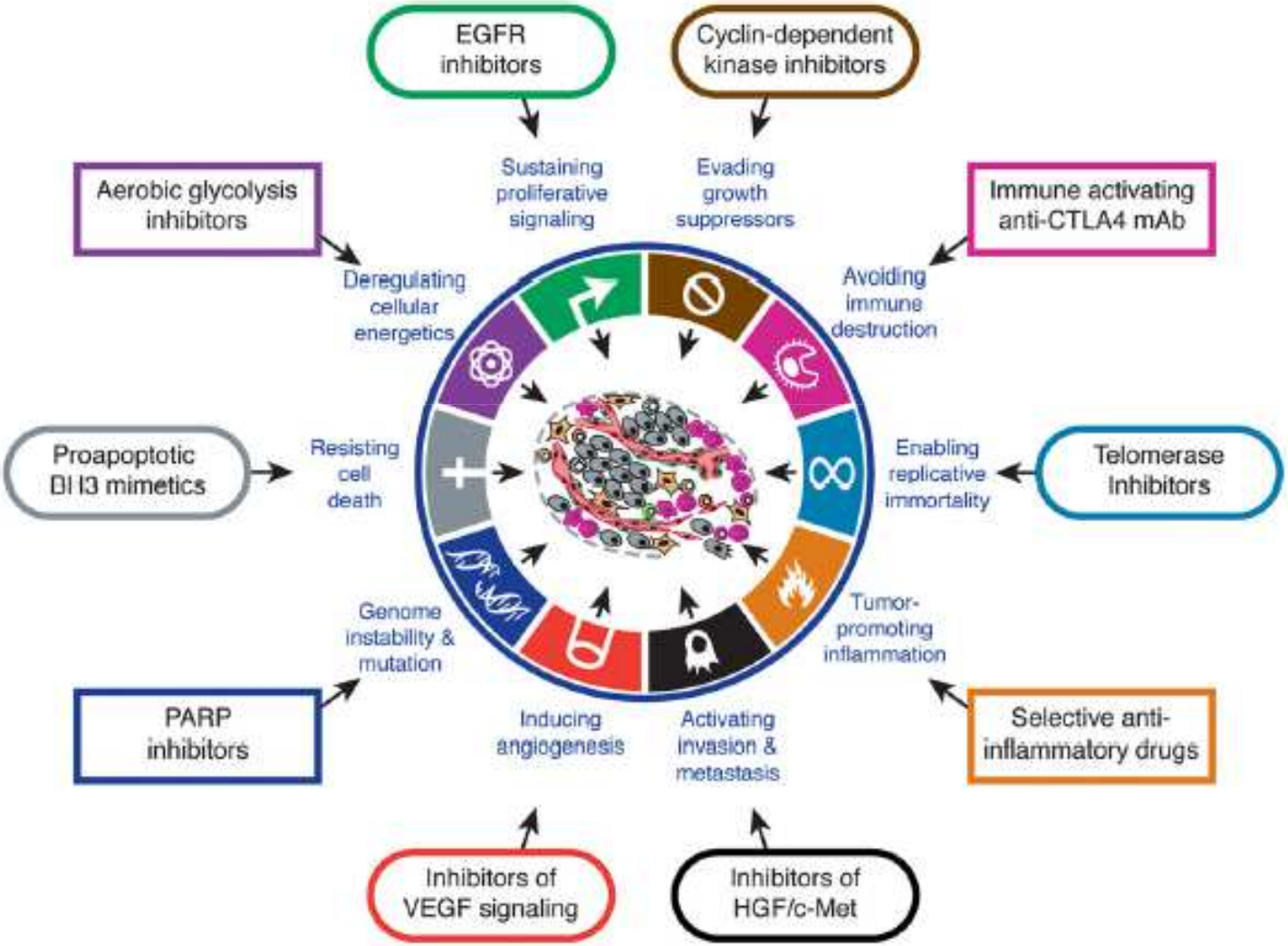
ARE SOLID TUMORS TO BE TREATED AS A NUMBER OF DISTINCT RARE DISEASES?

STATE OF THE ART OF PERSONALIZED THERAPY : DO WE HAVE A “MAGIC PILL”?

800 new targeted agents under development

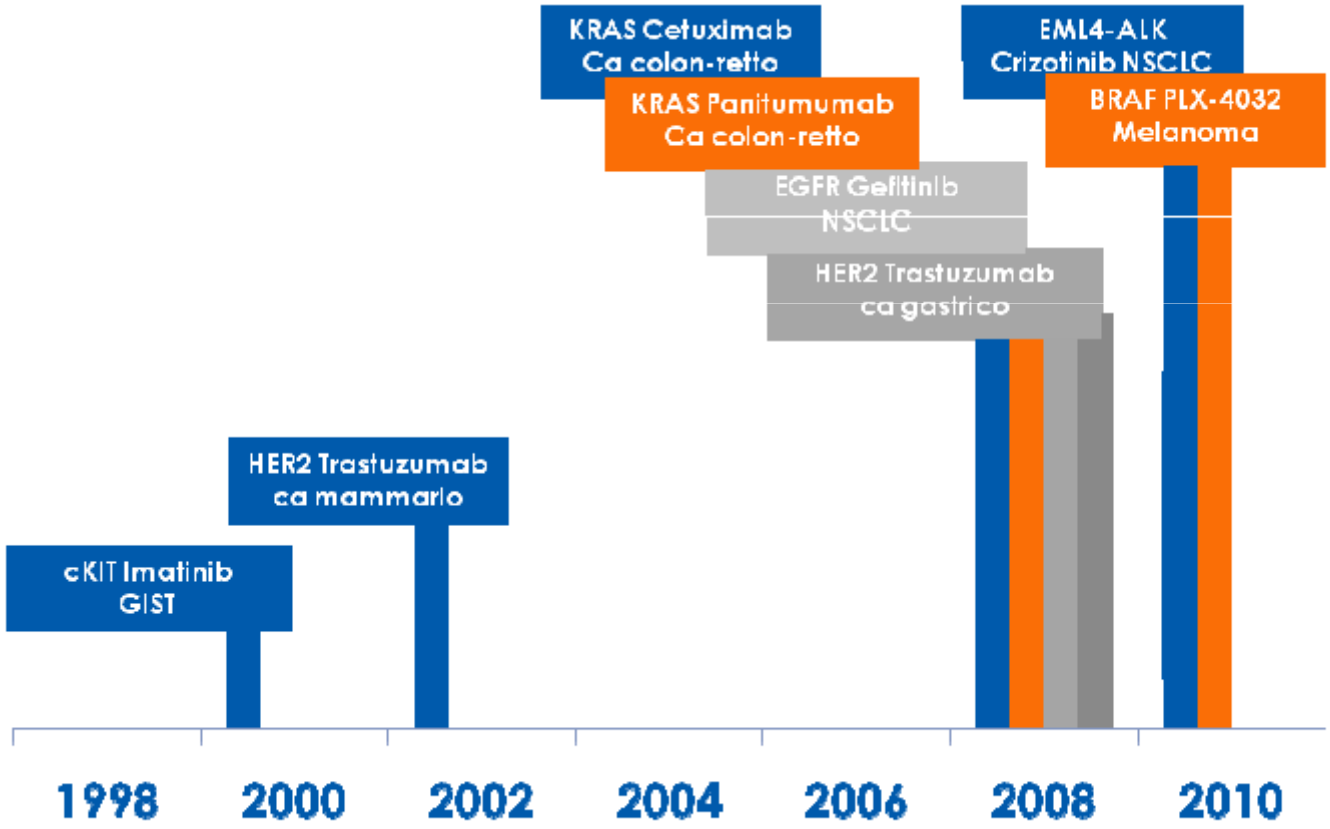
140 targeted agents in Phase I-II trials

THERAPEUTIC TARGETING OF THE HALLMARKS OF CANCER



Hanahan & Weinberg, Cell, 144:646, 2011

TIMING OF PERSONALIZED THERAPY



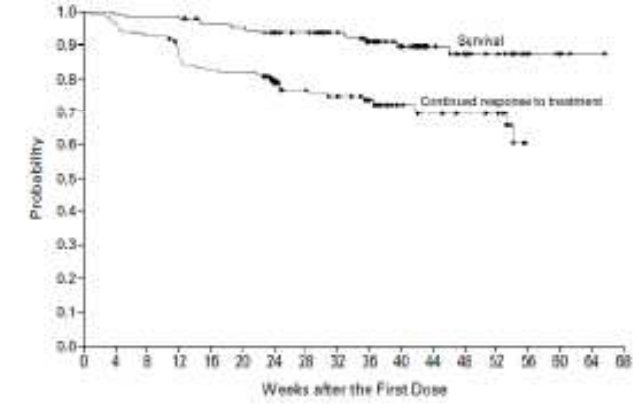
PERSONALIZED THERAPY: C-kit GIST

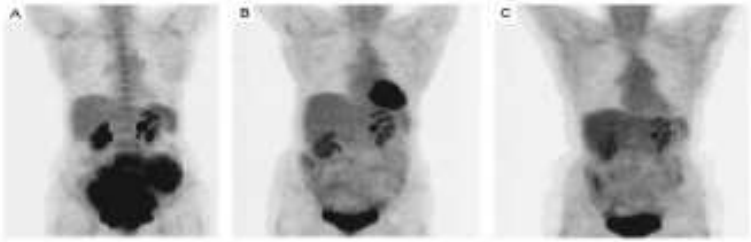
N Engl J Med, Vol. 347, No. 7 · August 15, 2002 · www.nejm.org

The New England Journal of Medicine

EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

George D. Demetri, M.D., Margaret von Mehren, M.D., Charles D. Blanke, M.D., Aaron D. Van den Abbeele, M.D., Burton Eisenberg, M.D., Peter J. Roberts, M.D., Michael C. Heinrich, M.D., David A. Tuveson, M.D., Ph.D., Samuel Singer, M.D., Milos Janicek, M.D., Ph.D., Jonathan A. Fletcher, M.D., Stuart G. Silverman, M.D., Sandra L. Silberman, M.D., Ph.D., Ronald Capdeville, M.D., Beate Kiese, M.Sc., Bin Peng, M.D., Ph.D., Saša Dimitrijevic, Ph.D., Brian J. Druker, M.D., Christopher Corless, M.D., Christopher D.M. Fletcher, M.D., and Heiko Joensuu, M.D.

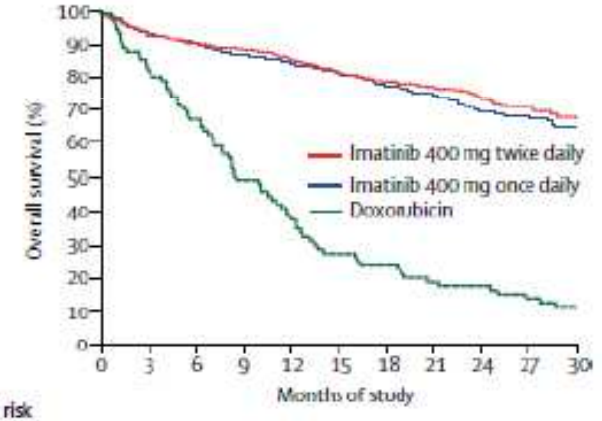




www.thelancet.com Vol 364 September 25, 2004

Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

Jaap Verweij, Pedro G Casali, John Zalcberg, Axel Le Cesne, Peter Reichardt, Jean-Yves Blay, Rolf Issels, Alban van Oosterom, Patrick C W Hogendoorn, Martine Van Glabbeke, Rosalba Bertulli, Ian Judson, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group*



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	10	14	8

PERSONALIZED THERAPY: HER-2 BREAST

The New England
Journal of Medicine

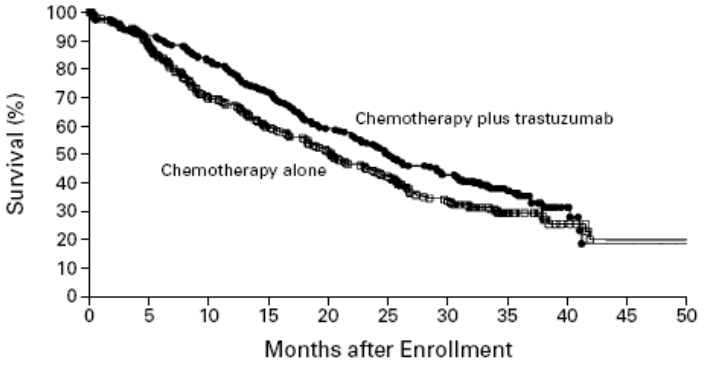
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VOLUME 344 MARCH 15, 2001 NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

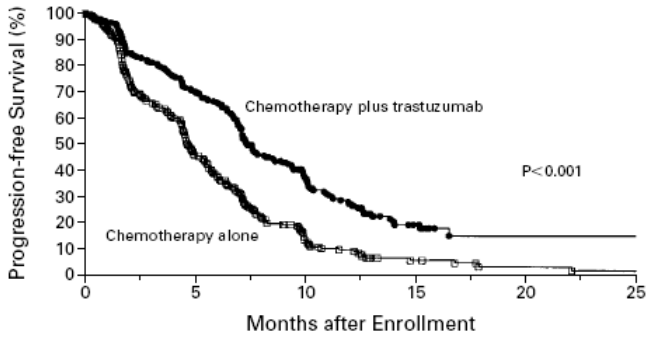
DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

A



No. at Risk									
Chemotherapy plus trastuzumab	235	214	192	165	134	114	96	47	11
Chemotherapy alone	234	205	160	136	116	97	76	37	13

A



No. at Risk				
Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

TABLE 3. RATES AND DURATIONS OF RESPONSES.*

VARIABLE	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Complete response — no. (%)	18 (8)	8 (3)	11 (8)	6 (4)	7 (8)	2 (2)
Partial response — no. (%)	100 (43)	66 (28)	69 (48)	52 (38)	31 (34)	14 (15)
Complete and partial responses — no. (% [95% CI])	118 (50 [44–57])	74 (32 [26–38])	80 (56 [48–64])	58 (42 [34–50])	38 (41 [31–51])	16 (17 [9–24])
P value	<0.001		0.02		<0.001	
Median duration of response — mo	9.1	6.1	9.1	6.7	10.5	4.5
P value	<0.001		0.005		<0.01	

*The analysis included all 469 patients. A complete response was defined as the disappearance of all tumors on the basis of radiographic evidence, visual inspection, or both. A partial response was defined as a decrease in the dimensions of all measurable lesions of more than 50 percent. The duration of response was defined as the time from the first response to disease progression or death. The response-evaluation committee assessed the tumor response in 446 patients: 99 percent of the 452 patients who had an assessment after the base-line evaluation and 95 percent of the 469 patients who enrolled in the study. In the group given paclitaxel and trastuzumab, the response rate was higher among patients who had a Karnofsky score of 90 to 100 at base line. CI denotes confidence interval.

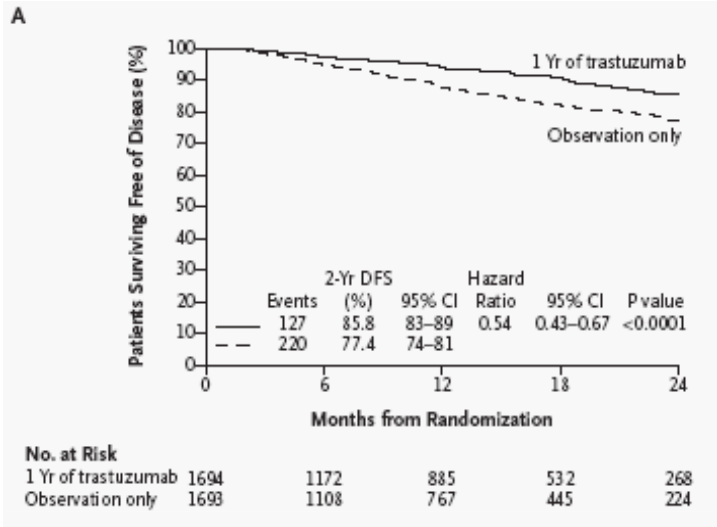
PERSONALIZED THERAPY: HER-2 BREAST

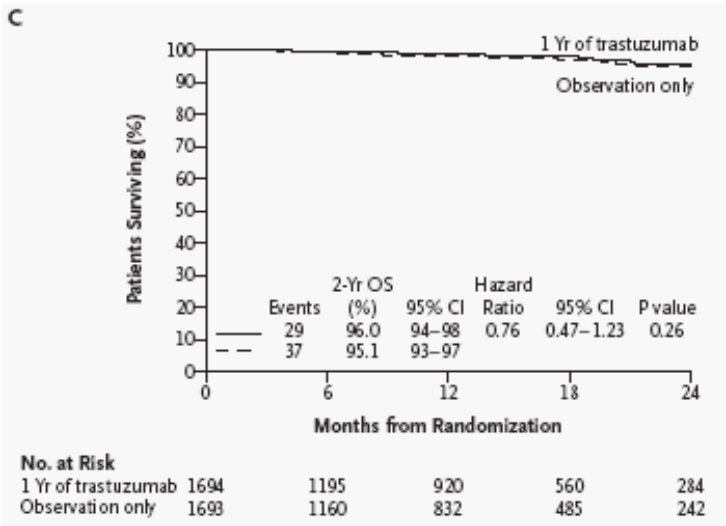
The NEW ENGLAND JOURNAL of MEDICINE

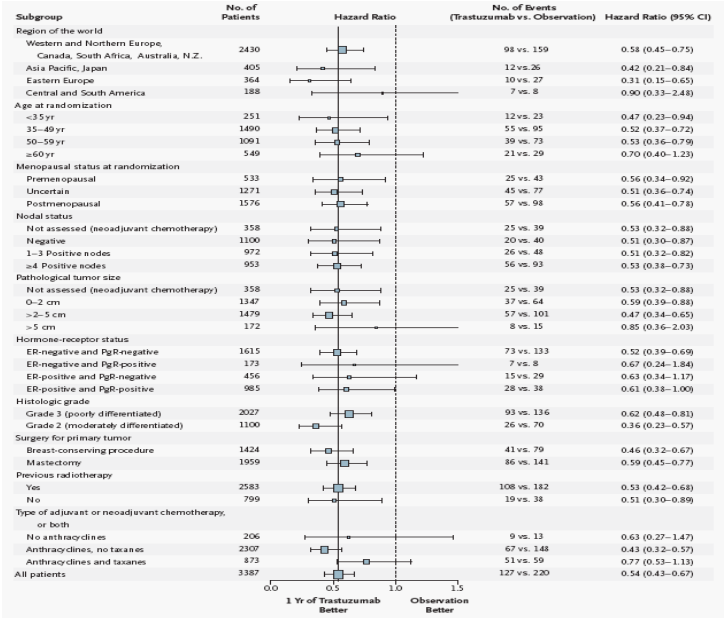
ESTABLISHED IN 1812 OCTOBER 20, 2005 VOL. 353 NO. 16

Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Martine J. Piccart-Gebhart, M.D., Ph.D., Marion Procter, M.Sci., Brian Leyland-Jones, M.D., Ph.D., Aron Goldhirsch, M.D., Michael Untch, M.D., Ian Smith, M.D., Luca Gianni, M.D., Jose Baselga, M.D., Richard Bell, M.D., Christian Jackisch, M.D., David Cameron, M.D., Mitch Dowsett, Ph.D., Carlos H. Barrios, M.D., Günther Steger, M.D., Chiun-Shen Huang, M.D., Ph.D., M.P.H., Michael Andersson, M.D., Dr.Med.Sci., Moshe Inbar, M.D., Mikhail Lichinitser, M.D., István Láng, M.D., Ulrike Nitz, M.D., Hiroji Iwata, M.D., Christoph Thomssen, M.D., Caroline Lohrisch, M.D., Thomas M. Suter, M.D., Josef Rüschoff, M.D., Tamás Sütő, M.D., Ph.D., Victoria Greatorex, M.Sc., Carol Ward, M.Sc., Carolyn Straehle, Ph.D., Eleanor McFadden, M.A., M. Stella Dolci, and Richard D. Gelber, Ph.D., for the Herceptin Adjuvant (HERA) Trial Study Team

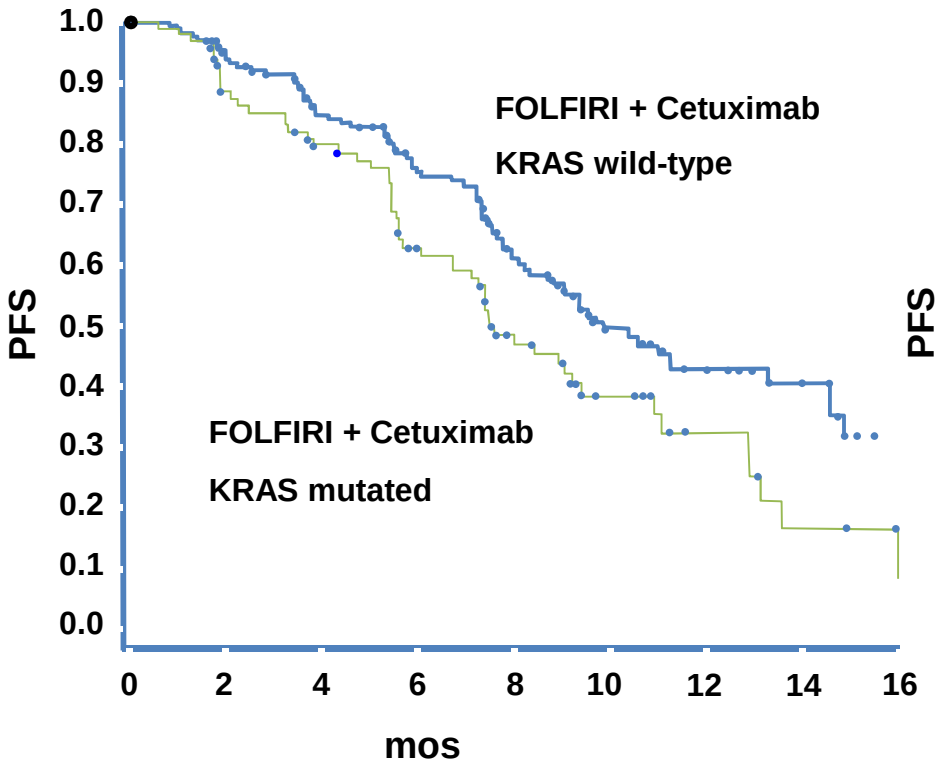




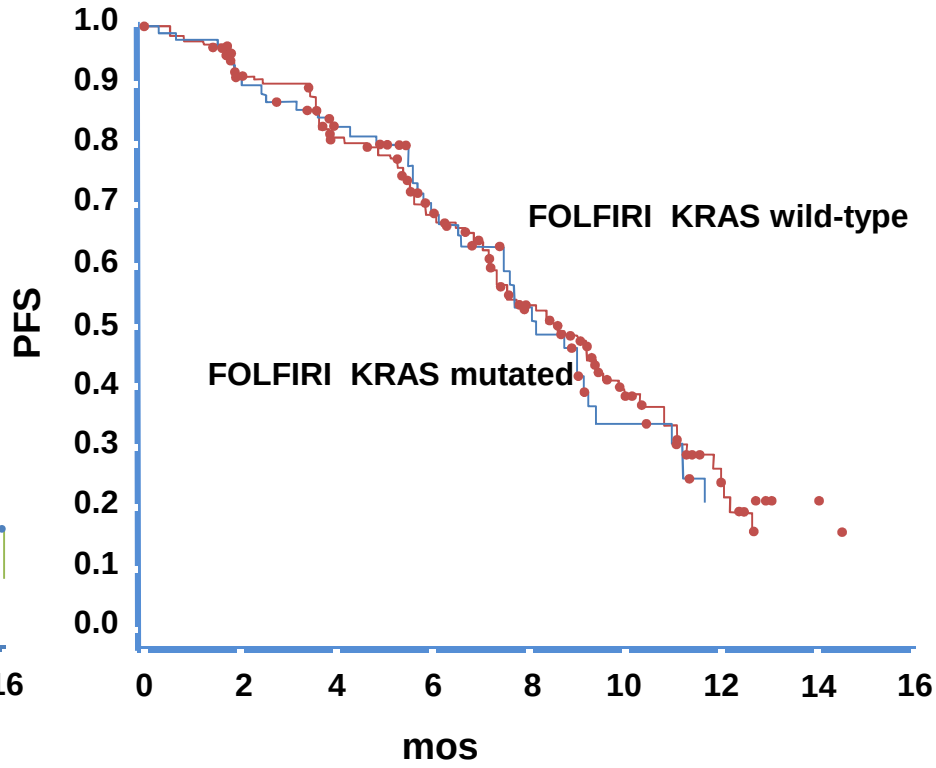


KRAS WILD-TYPE:PREDICTIVE VALUE FOR CETUXIMAB

FOLFIRI + Cetuximab HR=0.63 (p=0.007)
mPFS: Wild-type (n=172) 9.9 mos
vs mutated (n=105) 7.6 mos



FOLFIRI HR=0.97 (p=0.87)
mPFS: Wild-type (n=176) 8.7 mos
vs mutated (n=87) 8.1 mos

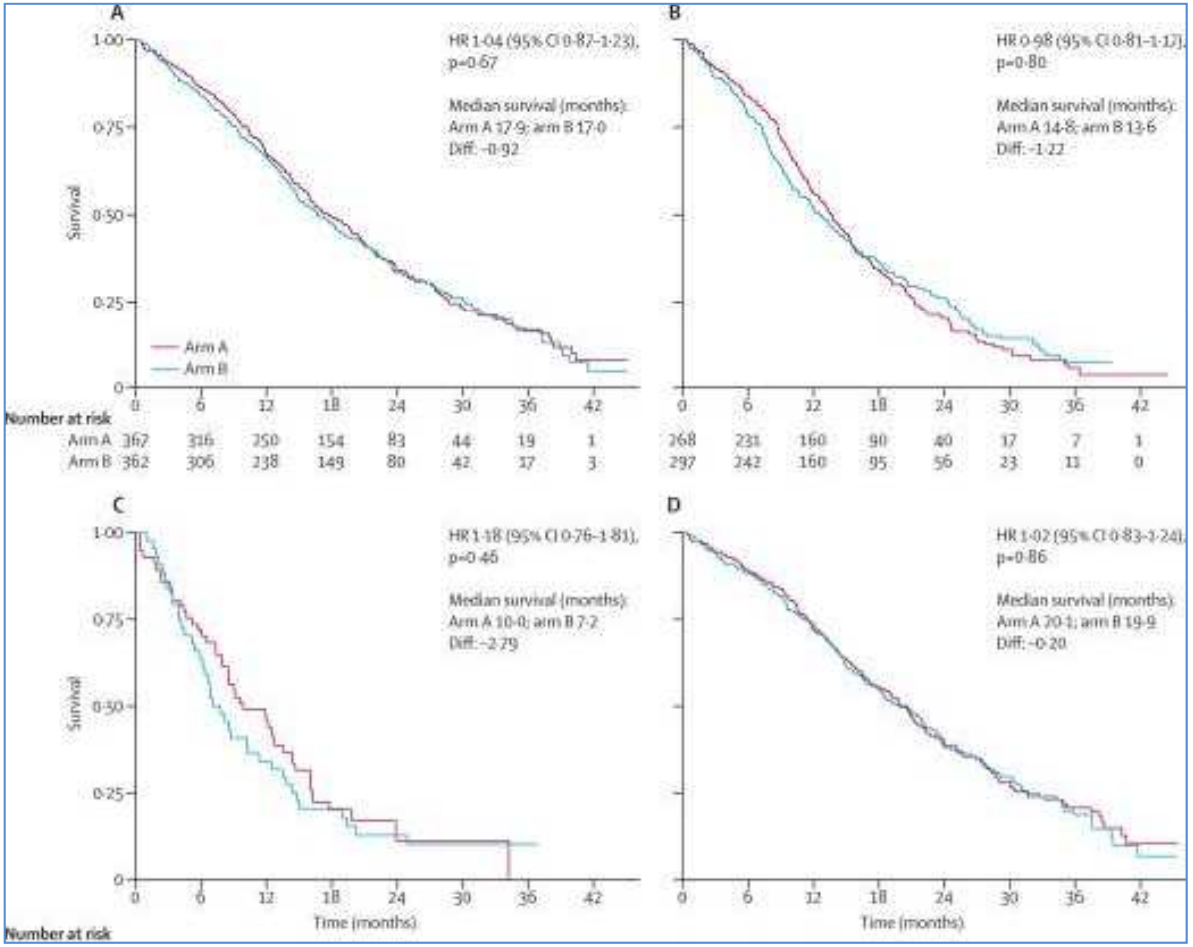


CRYSTAL Trial, Van Cutsem E, et al. J Clin Oncol 2008;26 (Suppl. abstract 2)

KRAS WT: NO PREDICTIVE VALUE FOR CETUXIMAB

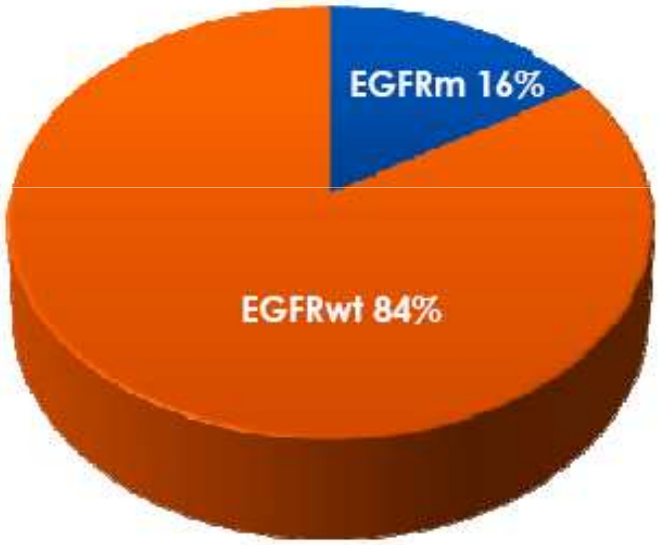
FOLFOX +/- Cetuximab HR=1.04 (p=0.67)

OS: (n=729) 17.9 mos vs 17.0 mos



MRC COIN Trial, Maughan TS, et al. Lancet 2011;377:2103

PERSONALIZED THERAPY: EGFR NSCLC



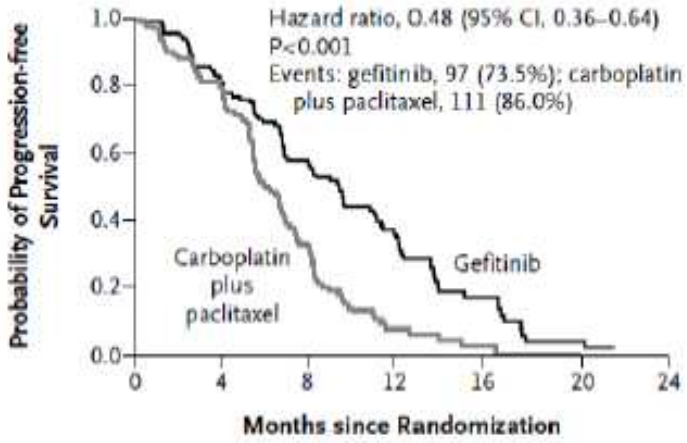
The NEW ENGLAND JOURNAL of MEDICINE

SEPTEMBER 3, 2009

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

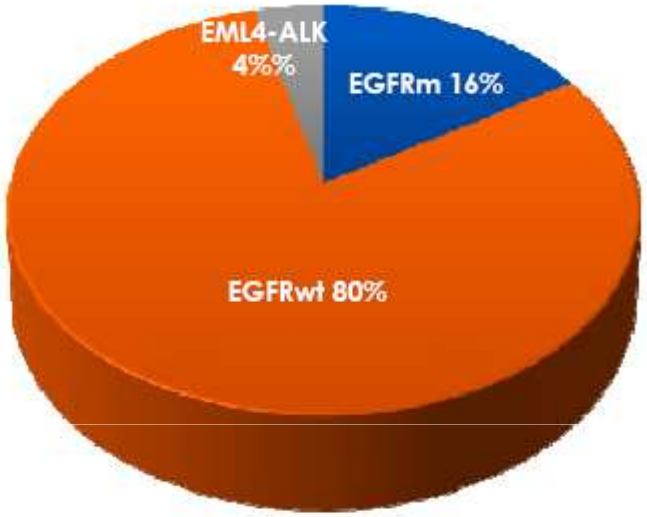
Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.P., and Masahiro Fukuoka, M.D., Ph.D.

B *EGFR*-Mutation–Positive



No. at Risk							
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

PERSONALIZED THERAPY: EML4-AKT NSCLC

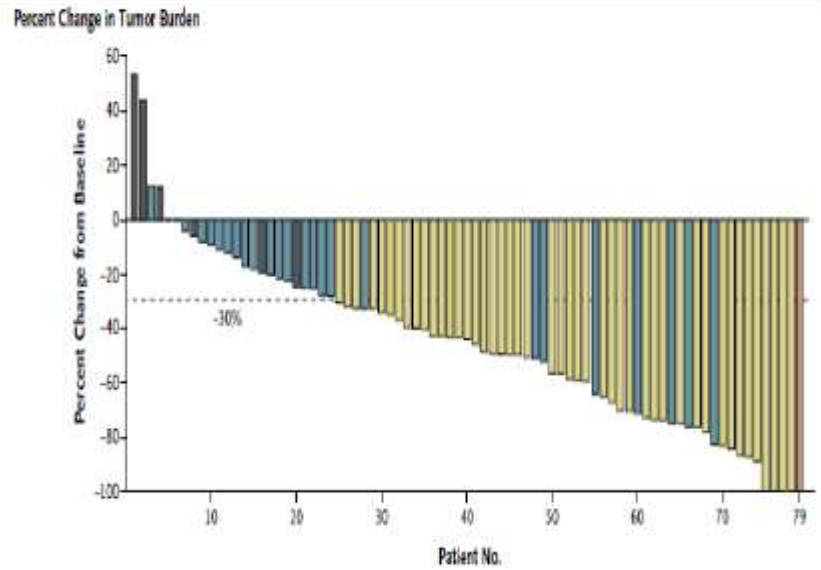


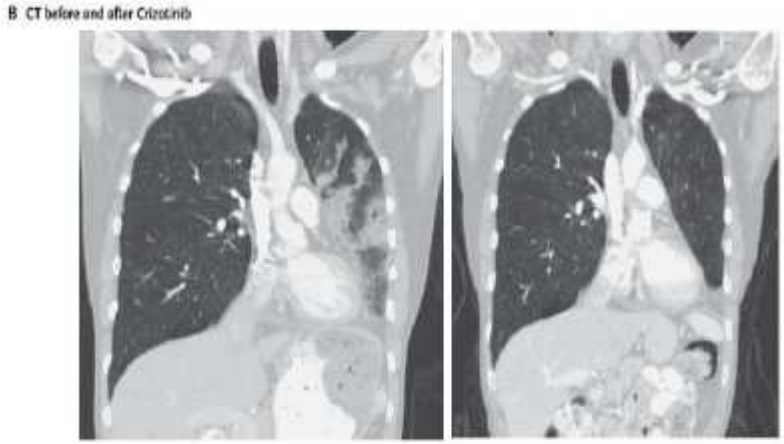

The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 28, 2010

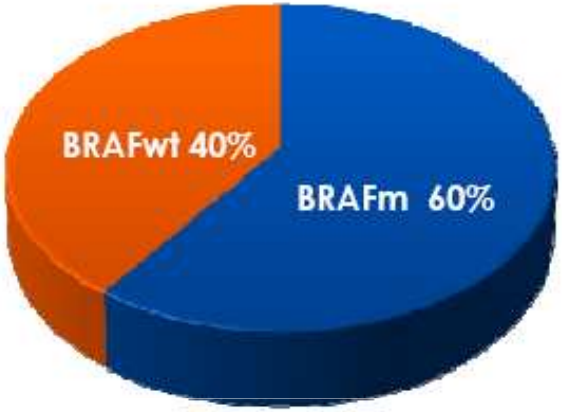
Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

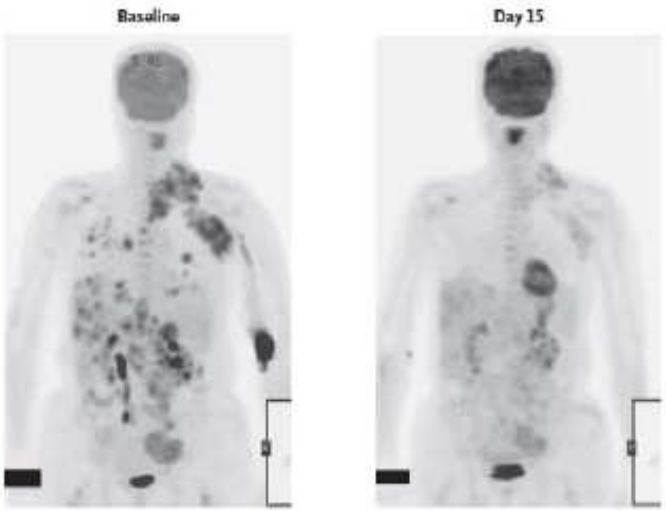






PERSONALIZED THERAPY:
BRAF MELANOMA

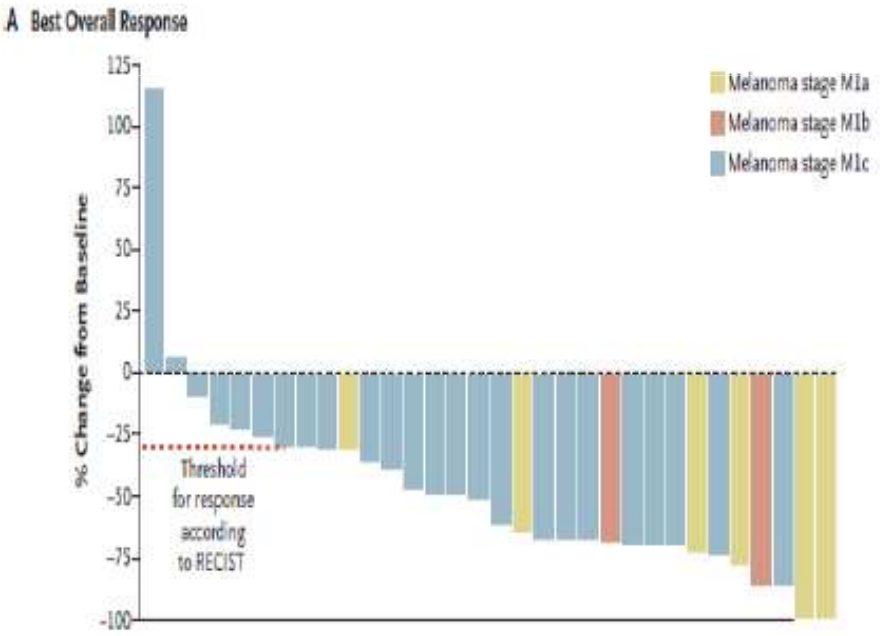






Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

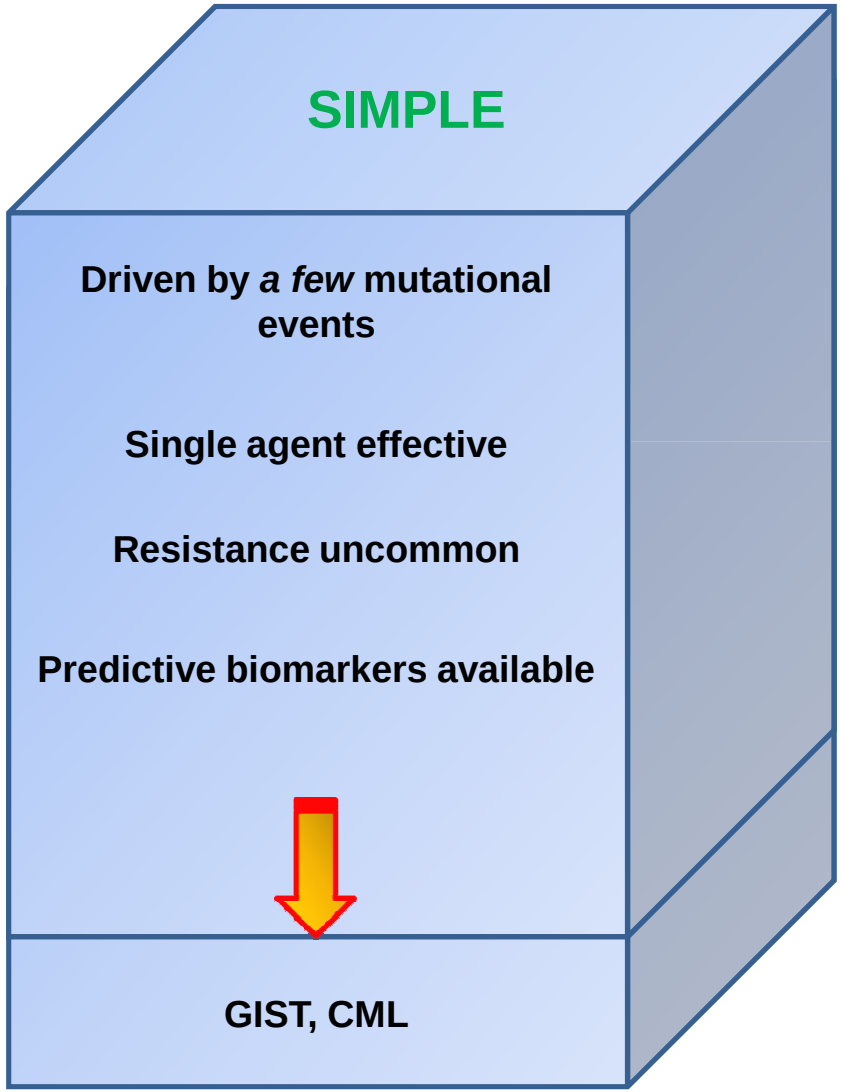
Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

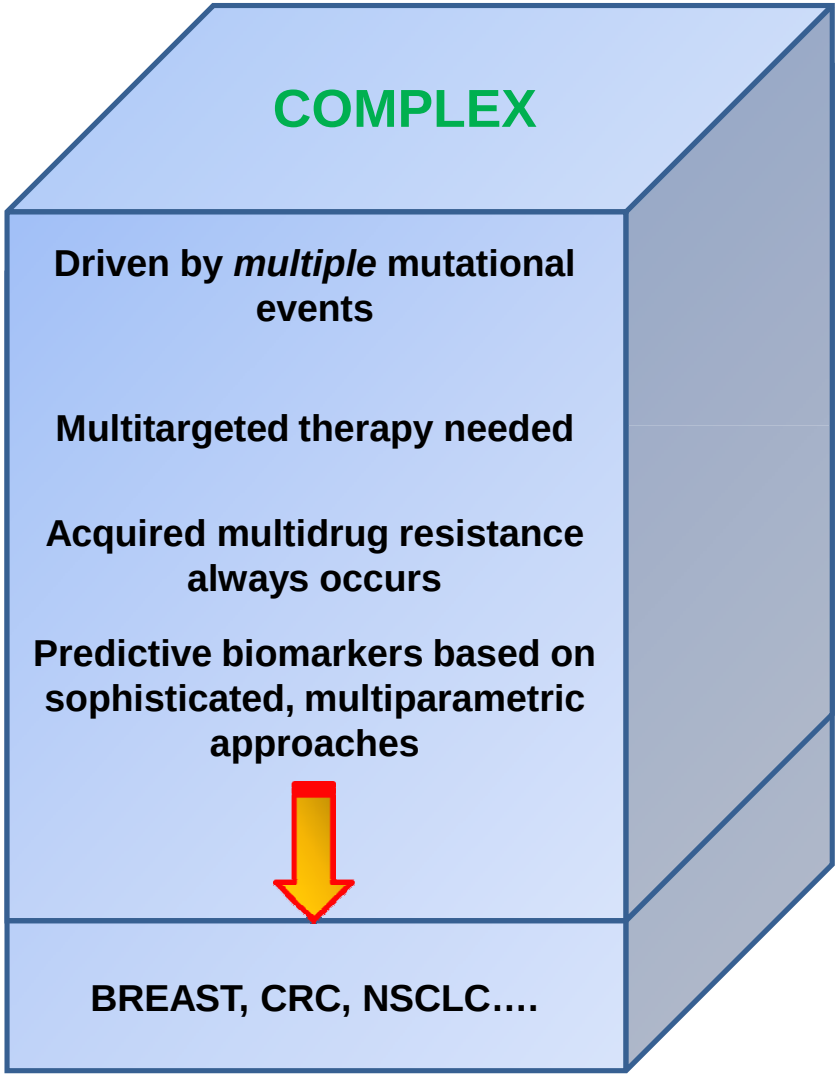


OVERALL CLINICAL EFFICACY OF AVAILABLE TARGETED AGENTS IN SOLID TUMORS

	DRUG	*TUMOR*
• **DRUGS IMPROVING OS**	Imatinib	GIST
	Gefitinib	NSCLC
	Trastuzumab	Breast
• **DRUGS IMPROVING ONLY RR & TTP**	Cetuximab,Panitumumab	CRC
	Erlotinib	NSCLC
	Crizotinib	NSCLC
	Lapatinib	Breast
	PLX 4032	Melanoma

SIMPLE (*STUPID*) *VS* COMPLEX (*SMART*) TUMOR GENOMICS





POSSIBLE DETRIMENTAL EFFECTS OF THE INAPPROPRIATE USE OF TARGETED AGENTS

Anti-EGFR-TKIs in *EGFR wt* NSCLCs (Gefitinib)



Lower efficacy vs **Platinum-based Tx**

Anti – VEGF MoAb in unselected *Squamous* NSCLCs (Bev)



Enhanced coagulatory complications

Anti – MET MoAb in *MET negative* NSCLCs (OAM-45588)



Lower efficacy vs **single agent Erlotinib**

Anti – VEGFR-2 TKIs in H & N cancers *after RT*



Enhanced coagulatory complications

RECENT "STATISTICALLY SIGNIFICANT ADVANCES" IN CANCER PATIENTS WHO HAD *NOT BEEN SELECTED* ON THE BASIS OF BIOMARKERS

Drug	Tumor	OS Gain (ms)	Cost per QALY ($)
Bevacizumab	Colon	2.2	603.000
Erlotinib	Pancreas	0.4	659.772
Bevacizumab	NSCLC	2.0	1.206.000
Erlotinib	NSCLC	2.0	659.772
Cetuximab	NSCLC	1.2	401.760
Bevacizumab	Breast	1.5	496.072
Cetuximab *	Colon	1.5	283.595

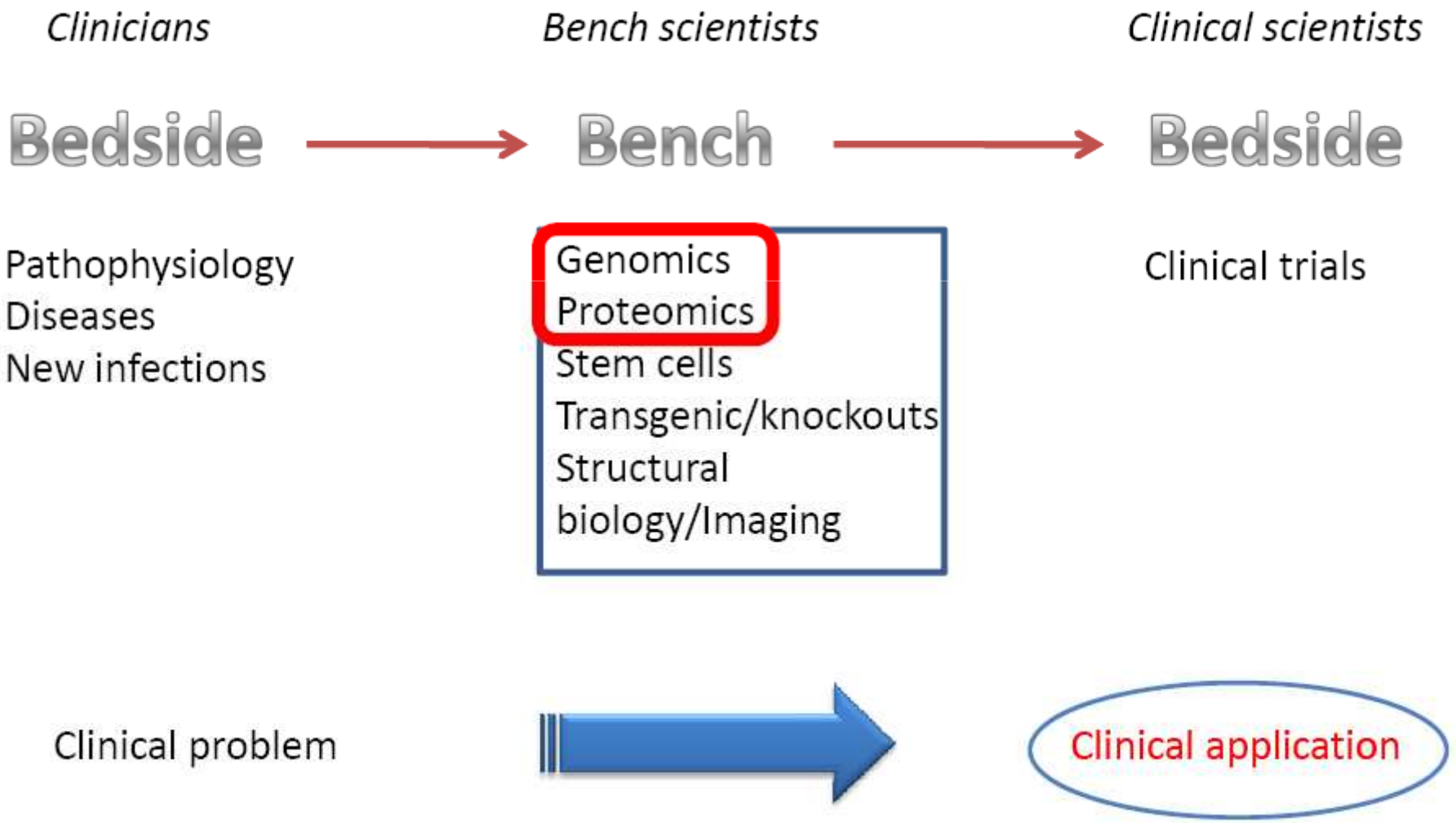
QALY: A measure of the impact of a treatment intervention. If an action gives a person an extra yr of helthy life, that counts as 1 QUALY

* Before K-Ras determination

TARGETED THERAPY IN ADVANCED DISEASE: WHY IS IT NOT CURATIVE?

- ***Acquired resistance*** **to single agent Tx**
- ***Wrong target*** **: Passenger *vs* driver genetic alterations**
- ***Wrong predictive test :*** **i.e. methodological problems**
- ***Wrong patient :*** **pharmacogenetics, SNPs alterations**
- ***Core pathway :*** **not completely blocked**
- ***Cross-pathways escape***

TRANSLATIONAL RESEARCH: THE CENTRAL ROLE OF BIOTECHNOLOGIES



BIOMARKERS CLASSIFICATION

- For Targeting = **drug target receptors**
- For Pathway = **enabling/inhibiting pathways**
- For Efficacy = **response/resistance targets**



THERANOSTIC INTEGRATED BIOMARKERS

BIOMARKERS AS PREDICTORS OF TIME-DEPENDING ACTIVITY

- **SUPERSTARS** c Kit mutations (imatinib)

  BCR – ABL (imatinib)

- **INCREMENTALISTS** EGFR mutations (erlotinib; gefinitib)

  EGFR polymorphisms (cetuximab)

  PgR expression (tamoxifen)

  VEGF polymorphisms (bevacizumab)

  BRAF mutations (PLX4032)

  EML4-AKT mutations (crizotinib)

BIOMARKERS AS PREDICTORS OF PRIMARY RESISTANCE

• **SUPERSTARS**	ER negativity	(tamoxifen; aromatase inhibitors)
	HER-2 negativity	(trastuzumab; lapatinib)
	K-RAS mutations ?	(cetuximab; panitumumab)
• **INCREMENTALISTS**	B-RAF mutations	(cetuximab; panitumumab)
	PTEN expression	(cetuximab; panitumumab)
	PIK3CA mutations	(cetuximab; panitumumab)
	CYP2C19 SNPs	(tamoxifen)

- ***Predictor of activity >50% of responsive patients***
- ***Predictor of resistance < 10% of responsive patients***

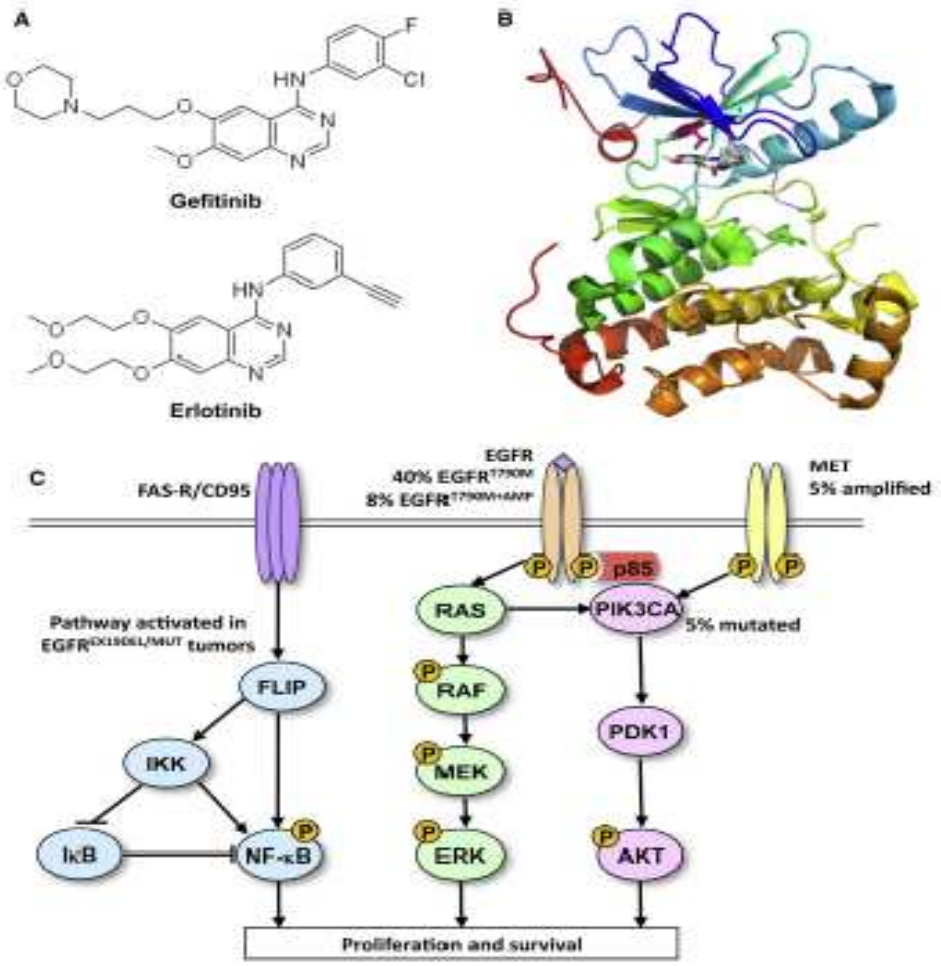
THE KEY PROBLEMS : CANCER CELLS HETEROGENEITY AND ACQUIRED RESISTANCE

THERAPEUTIC RESISTANCE TO KINASE INHIBITORS

- Gatekeeper mutations near to kinase active site
- Additional mutations in the target oncogene
- Gene amplification
- Upstream mutations activating the target oncoproteins
- Bypass mechanisms involving alterations that dysregulate a cellular effector acting in parallel to the drug target

Wagle et al, JCO;29:3085, 2011

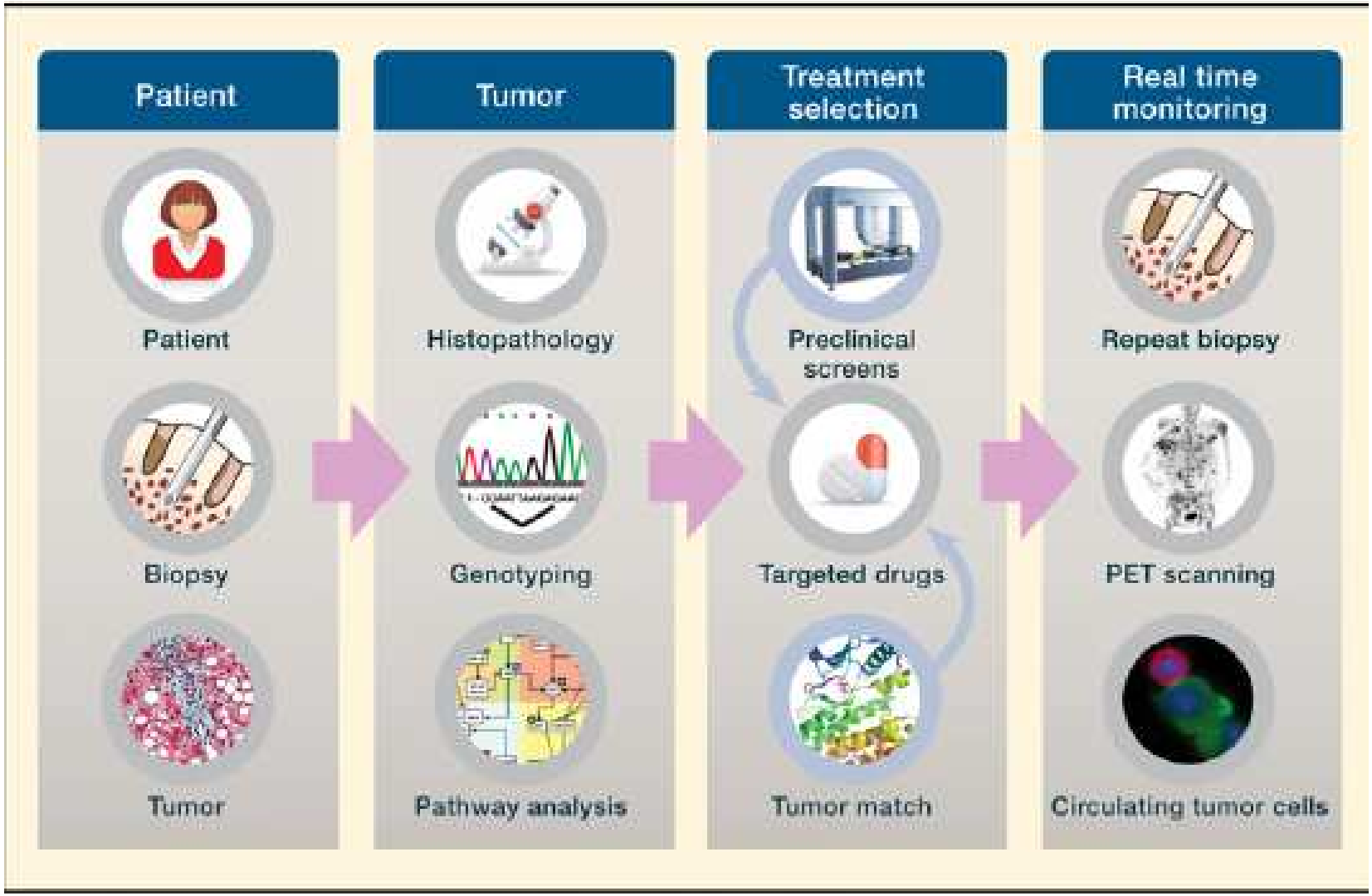
POSSIBLE PATHWAYS OF RESISTANCE TO ANTI-EGFR TKIs



Workman P et al, Cancer Cell, 19: 437, 2011

WHICH STRATEGY FOR SEQUENTIAL TREATMENTS TO MAKE A TUMOR A CHRONIC DISEASE

STEPS FOR MATCHING EACH CANCER WITH INDIVIDUALLY TARGETED THERAPY



Haber et al, Cell, 145: 19, 2011

SEQUENTIAL THERAPY OF ADVANCED DISEASE

EMPIRIC APPROACH

Use **presumed non-cross resistant** cytotoxic agents

PHARMACOGENOMIC APPROACH

Biopsy-obtained **updated genomic characterization** (eg, secondary mutations, gene amplification, epigenetic alterations, …)

NSCLC

1st line Cisplatinum-based Therapy

2nd line Therapy

- **Docetaxel**
- **Pemetrexed**
- **Vinorelbine**

1st line Gefinitib/Erlotinib in EGFR m tumors

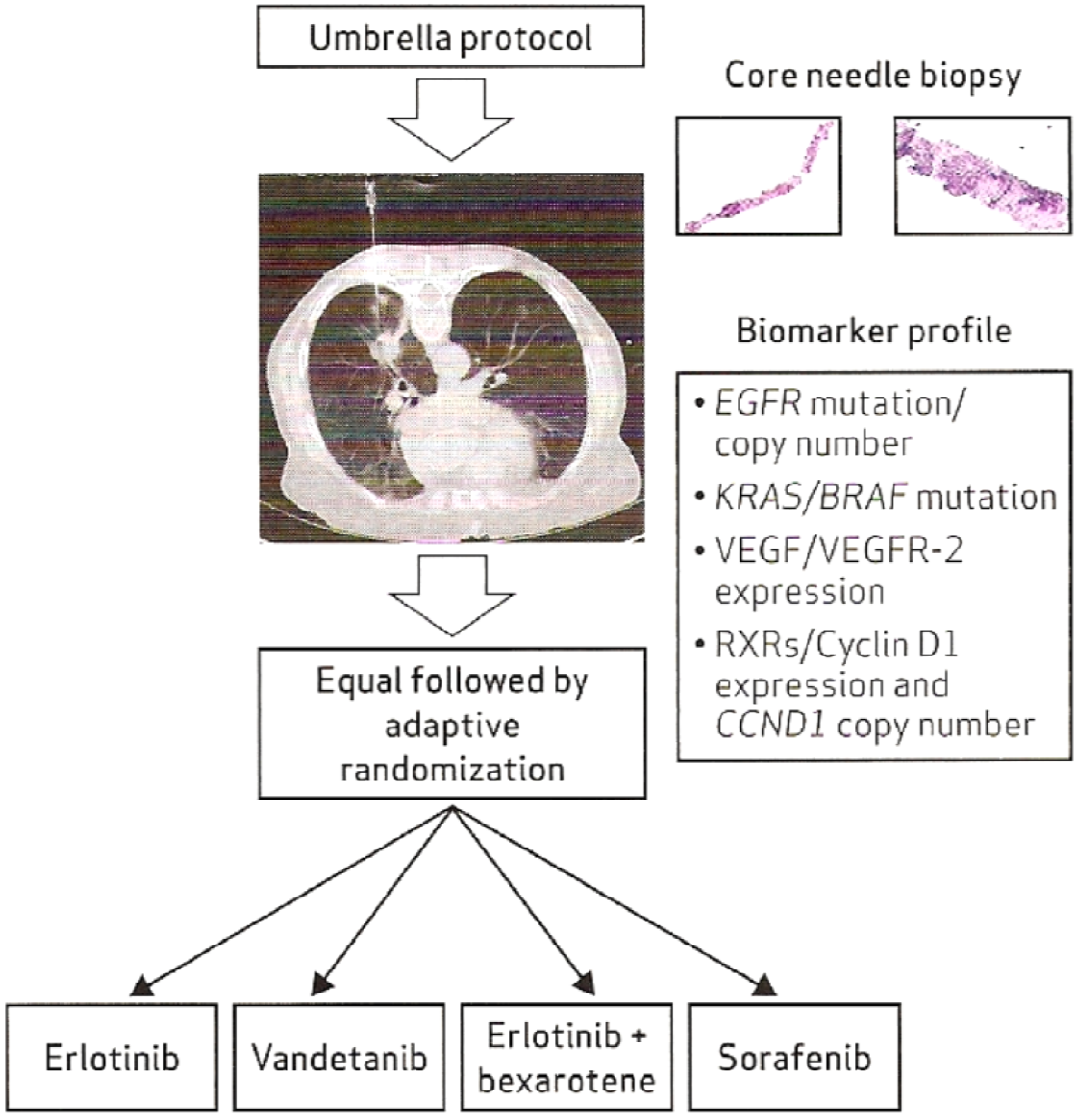
2nd line Therapy

Selective agents to T790 mutation-WZ4002

c-MET inhibitors

Irreversible anti-EGFR agents

THE BATTLE TRIAL: PERSONALIZING THERAPY FOR LUNG CANCER – STUDY DESIGN

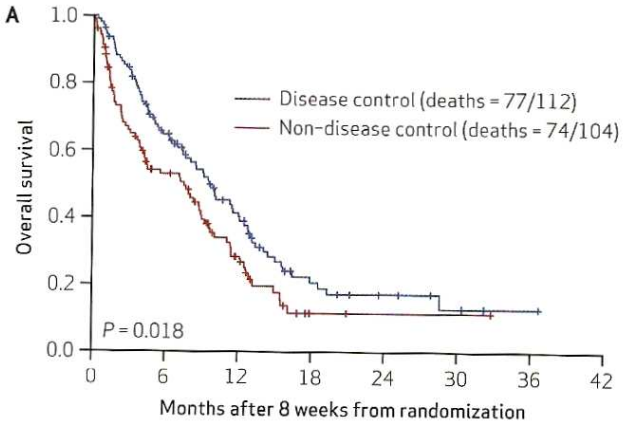


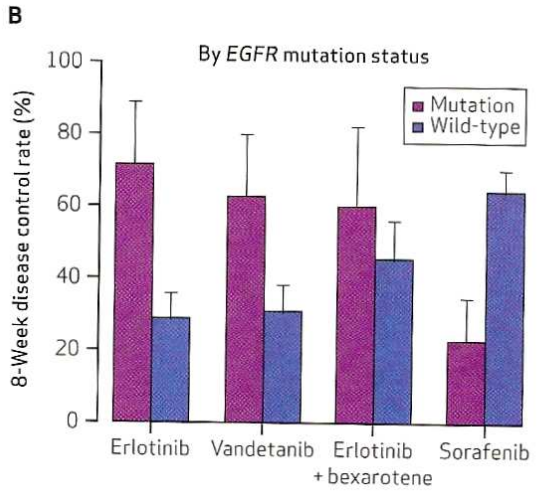
Kim et al, Cancer Discovery, 1:43, 2011

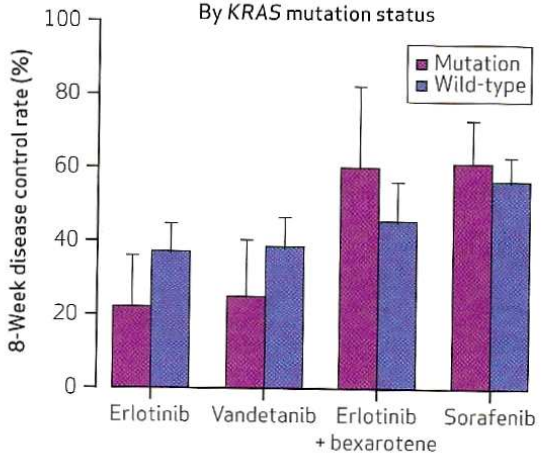
THE BATTLE TRIAL: PERSONALIZING THERAPY FOR LUNG CANCER – RESULTS

Number of patients with disease control / total number of patients (%)

Marker group	Treatment				Total
	Erlotinib	Vandetanib	Erlotinib + bexarotene	Sorafenib	
EGFR	6/17 (35%)	11/27 (41%)[a]	11/20 (55%)[a]	9/23 (39%)	37/87 (43%)
KRAS/BRAF	1/7 (14%)	0/3 (0%)	1/3 (33%)	11/14 (79%)[a]	13/27 (48%)
VEGF/VEGFR-2	10/25 (40%)[a]	6/16 (38%)	0/3 (0%)	25/39 (64%)[a]	41/83 (49%)
RXR/Cyclin D1	0/1 (0%)	0/0 (NA)	1/1 (100%)[a]	1/4 (25%)	2/6 (33%)
None	3/8 (38%)	0/6 (0%)	5/9 (56%)[a]	11/18 (61%)[a]	19/41 (46%)
Total	20/58 (34%)	17/52 (33%)	18/36 (50%)	57/98 (58%)	112/244 (46%)







BIOMEDICAL RESEARCH AND HEALTH ADVANCES BY INDIVIDUALIZED CARE -1

- ***Validation of predictive biomarkers*** **by standardized methods and development of trials as for new drugs in large research networks**

- ***Regulation experts*** **need to be involved in the design of biomarker validation trials**

- **Researchers must prove that the new diagnostic test is capable to *change clinical practice or reduce costs* by eliminating ineffective, expensive treatments**

BIOMEDICAL RESEARCH AND HEALTH ADVANCES BY INDIVIDUALIZED CARE - 2

- **The ability of biomarkers to improve cancer care and reduce health costs is potentially greater than in any other area of current medical research[1]**

- ***Academic centers must improve the ability to design proof-of-concept trials* by adopting realistic research goals (*we must not overpromise* !)**

- ***New integrated models for collaboration and financing* biomedical research on tailored therapy are needed by new non-profit, public-private partnerships - biomedical innovation trusts - [2]**

[1] Post , Nature: 469, 156, 2011

[2] Moses and Martin, NEJM: 364, 567, 2011

A FLIGHT ON FUTURE YEARS

- **NEW STRATEGIES FOR KILLING CANCER STEM CELLS (BC gene therapy vector with the *pro-apoptotic protein Bik* that overcomes the anti-apoptotic proteins highly expressed on CSC)- [1]**

- **INTERVENTION ON THE DYSREGULATION OF *ENDOGENOUS microRNA ACTIVITY* AFFECTING TUMOR-SUPPRESSIVE FUNCTIONS THROUGH THEIR ABILITY TO MODULATE *PTEN* AND *PI3K* SIGNALING IN GBM AND MELANOMA- [2,3]**

- **ULTRA-SELECTIVE ANTICANCER DRUG DELIVERY BY NANOTECHNOLOGIES (*Nanoporous particle-supported lipid bilayers*) - [4]**

[1] Lang, Cancer Cell, 20: 341,2011

[2] Tay, Cell, 147: 344,2011; [3] Karreth, Cell, 147: 382,2011

[4] Ashley, Nature Materials,10: 389, 2011

GENOMIC-BASED DRUG DEVELOPMENT : CONCLUSIONS AND CHELLANGES

- A NUMBER OF IDENTIFIED GENES OR DRIVER MUTATIONS ARE NOT DRUGGABLE
- LACK OF ROBUST PRECLINICAL TRANSLATIONAL INFRASTRUCTURE
- SOLID TUMORS ARE HETEROGENEOUS DISEASES: THERAPY WITH A SINGLE TARGETED DRUG IS NEVER ENOUGH
- ACQUIRED RESISTANCE REMAINS A KEY LIMIT
- LIMITED AVAILABILITY OF VALIDATED PREDICTIVE INDICATORS
- HIGH COSTS, SPECIFIC SIDE EFFECTS