Personalized treatment in NSCLC: fact or fiction?

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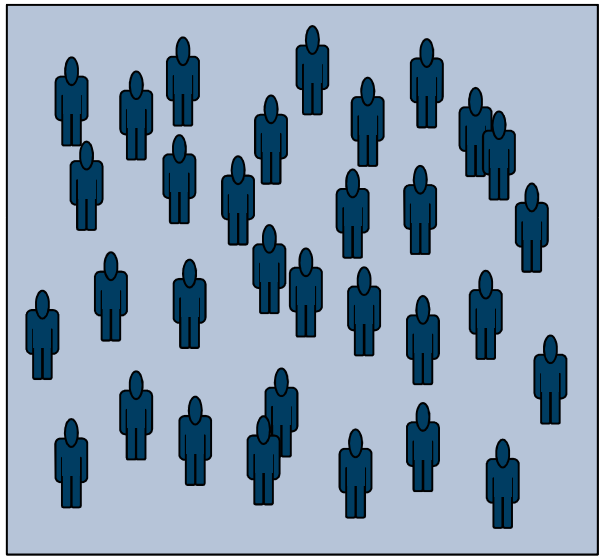
Personalized treatment in NSCLC

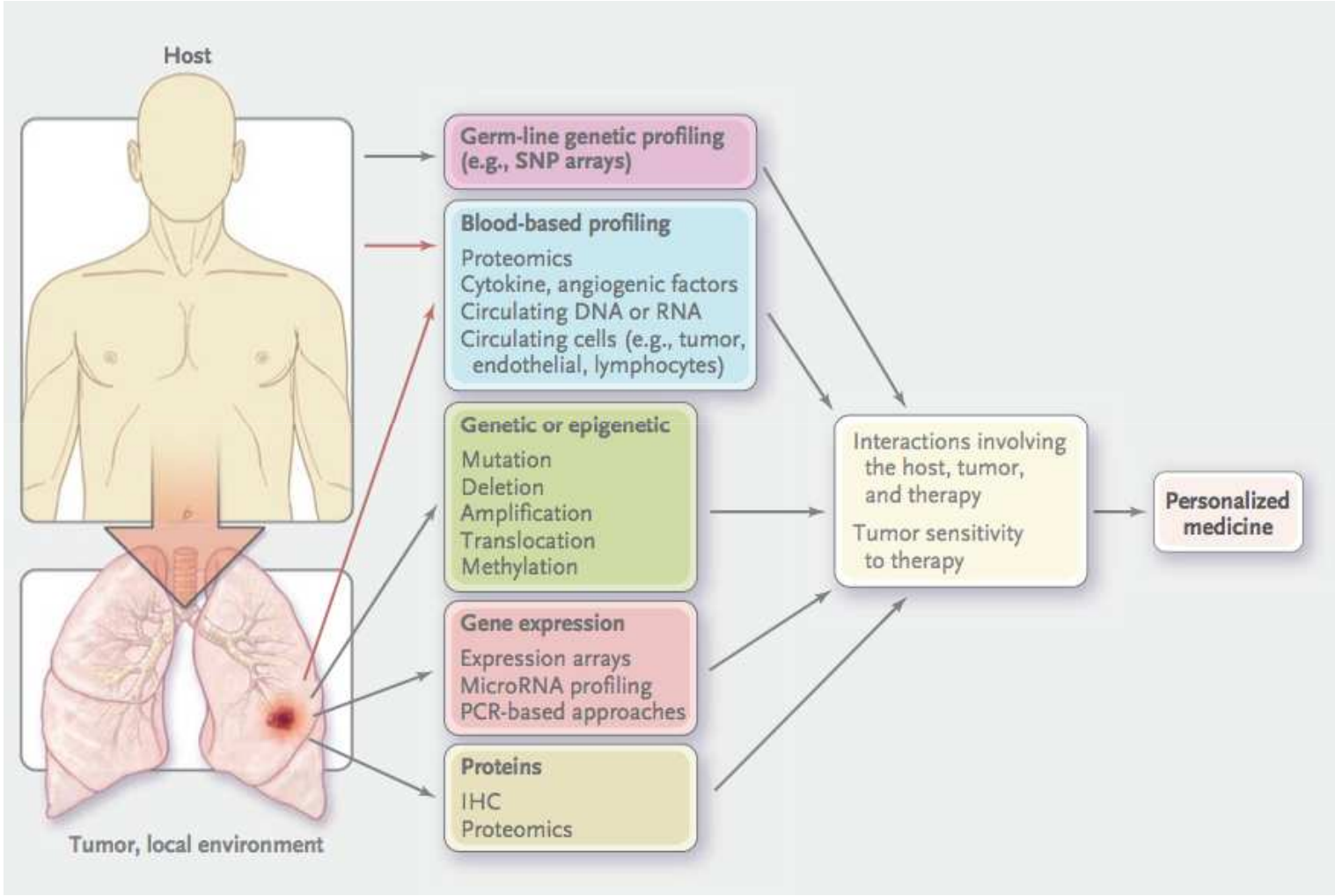
- Aims and challenges of biomarker driven treatment
- Treatment customized on histology or tumor biomarkers
  - Targeted therapies:
    - EGFR-TKIs
    - Anti-VEGF
  - Chemotherapy:
    - Pemetrexed
    - Cisplatin-based chemotherapy
- Treatment customized on patient genotype markers
    - Gemcitabine
    - Paclitaxel

Treatment selection in NSCLC

Tumor characteristics	• TNM-stage
Patient characteristics	• Performance status • Age and comorbidities
Patient preference	• Toxicities • Treatment administration
Doctor preference	• Experience with drug



Development of Personalized Therapy for NSCLC



Herbst RS et al. *NEJM*. 2008; 359:1367-80.

Aims of personalized cancer care

- Individual patient level
  - selection of treatment based on the biology and molecular characteristics of the patient as well as the tumor in order to:
    - improve the efficacy of the treatment and/or
    - avoid life threatening toxicity
- Society level
  - reduction of the cost of cancer care by
    - restricting the treatment to the patients most likely to benefit
    - avoiding ineffective treatments
    - reducing morbidity and complications

Prognostic versus predicitive markers

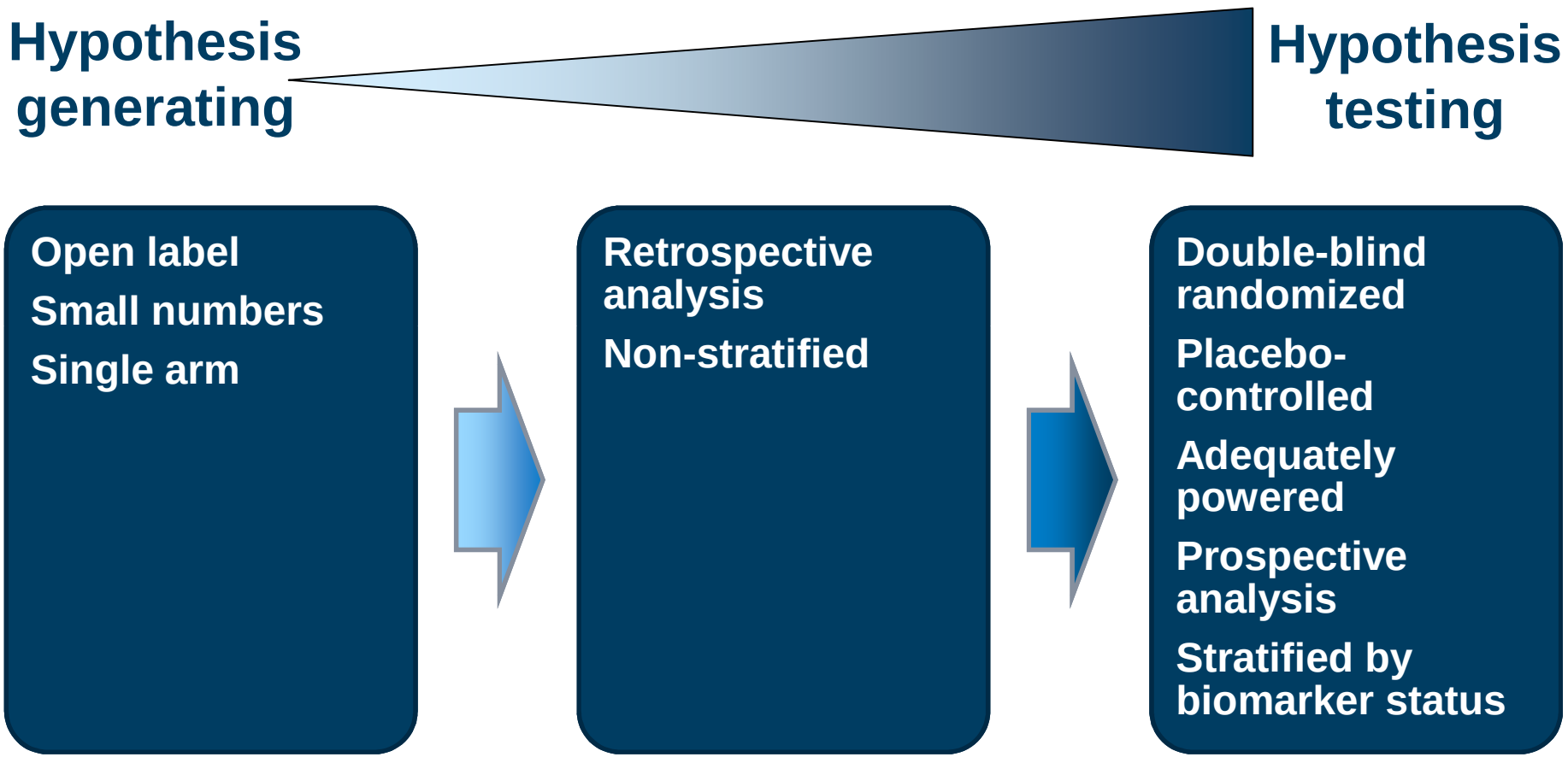
Prognostic
Provides information on outcome, regardless of of treatment

Predictive
Provides information on outcome with regards to a specific therapy

Many biomarkers have both prognostic and predicitive value

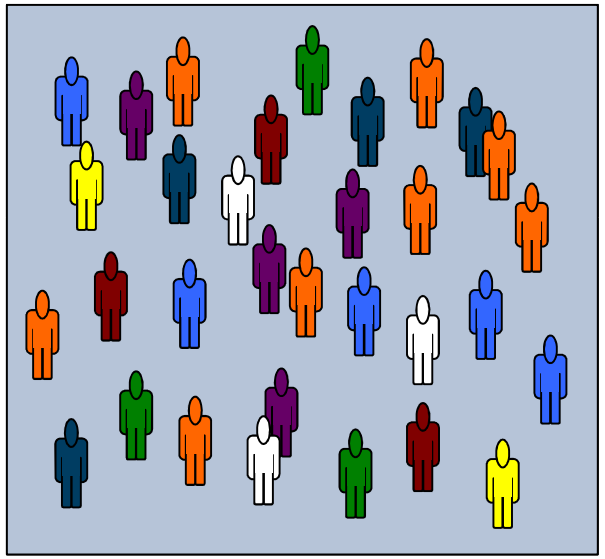
Controlled trials or meta-analyses are required to determine the prognostic and predictive contributions made by a particular marker

Requirements on the trial design for identifying a predictive biomarker



Moving towards customized treatment

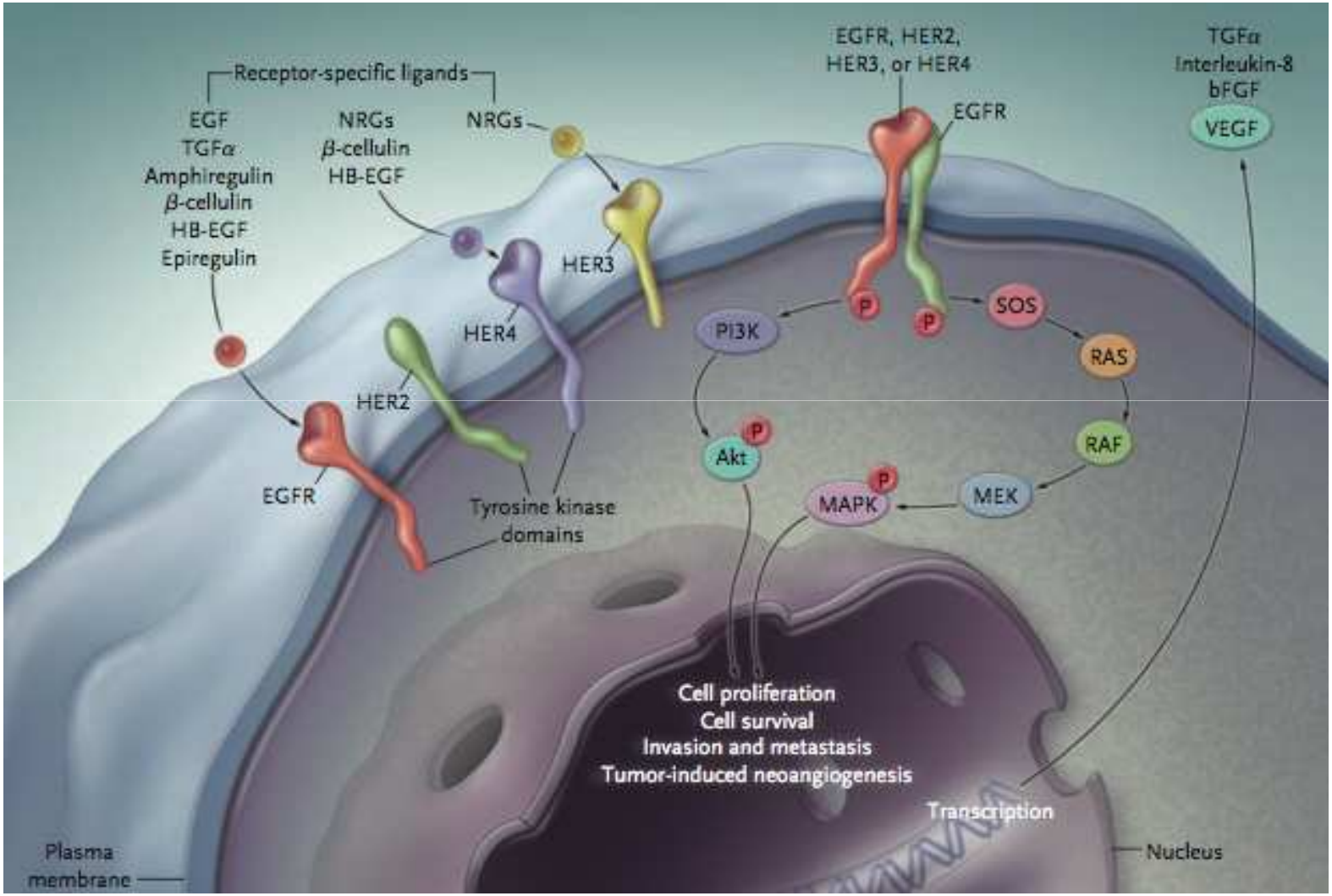
Tumor characteristics	• TNM-stage • **Tumor biomarkers**
Patient characteristics	• Performance status • Age and comorbidities • **Patient biomarkers**
Patient preference	• Toxicities • Treatment administration
Doctor preference	• Experience with drug



Personalized treatment in NSCLC

- Aims and challenges of biomarker driven treatment
- Treatment customized on histology or tumor biomarkers
  - Targeted therapies:
    - EGFR-TKIs
    - Anti-VEGF
  - Chemotherapy:
    - Pemetrexed
    - Cisplatin-based chemotherapy
- Treatment customized on patient genotype markers
    - Gemcitabine
    - Paclitaxel

Signal Transduction Pathways Controlled by the Activation of EGFR



Ciardiello and Tortora. *NEJM*. 2008; 358:1160-74.

BR.21: predictors of response

		Erlotinib Patients (%) (n=427)	p*
Gender	Female (146)	14.4	0.006
	Male (281)	6.1	
Histology	Adenocarcinoma (209)	13.9	<0.001
	Other (218)	4.1	
Ethnicity	Asian (53)	18.9	0.02
	Other (374)	7.5	
Ever smoked	Yes (311)	3.8	<0.001
	No (93)	24.7	
	Unknown (23)	13.0	

*Significance between subgroups

Shepherd et al. *NEJM* 2005, 353:123-32.

BR.21: overall survival ~ clinical predictors for response (EGFR mutation)

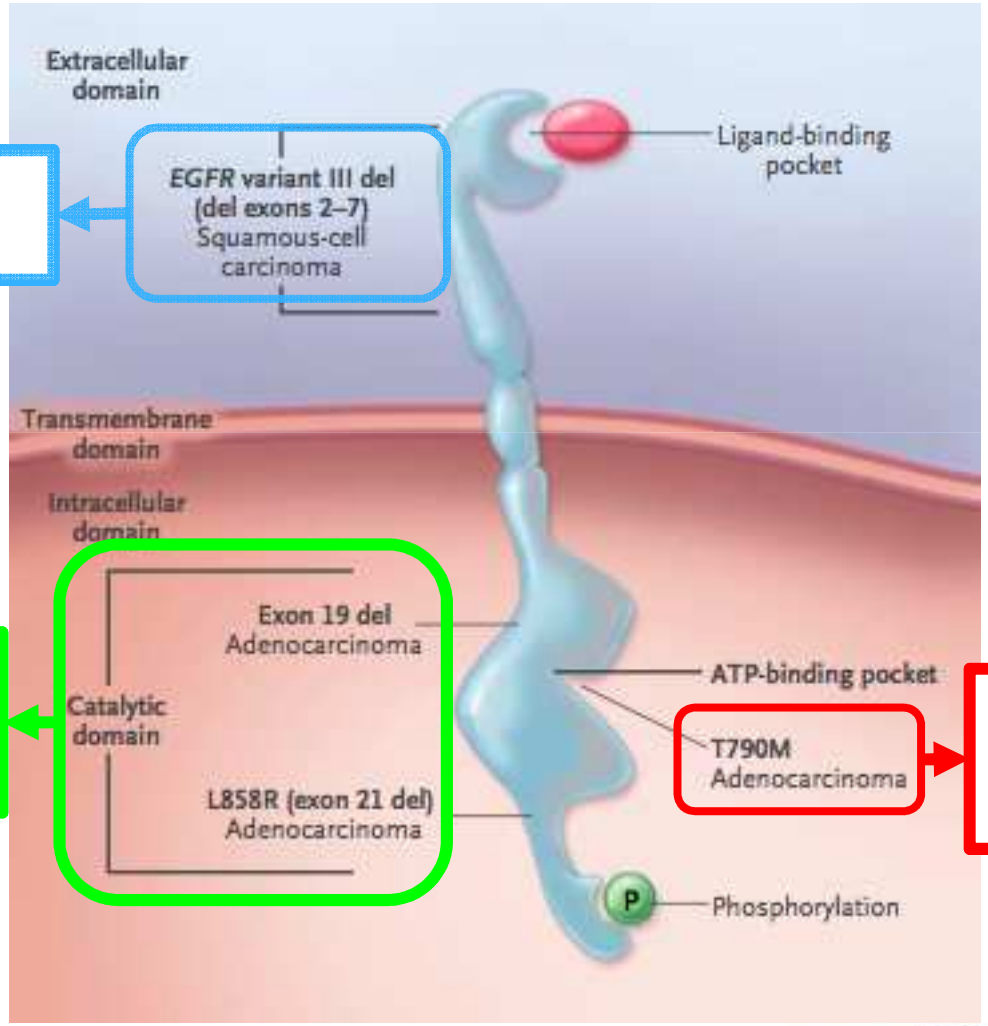
		HR	CI	p*
Gender	Male (475)	0.8	0.6–0.9	0.76
	Female (256)	0.8	0.6–1.1	
Histology	Adenocarcinoma (365)	0.7	0.6–0.9	0.37
	Other (366)	0.8	0.6–1.0	
Ethnicity	Asian (91)	0.6	0.4–1.0	0.44
	Other (640)	0.8	0.7–0.9	
Smoking history	Ever (545)	0.9	0.7–1.0	0.02
	Never (146)	0.4	0.3–0.6	
	Unknown (40)	1.1	0.5–2.6	

*p value for interaction between erlotinib and clinical variables

Shepherd et al. *NEJM* 2005, 353:123-32.

Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

Constitutively active TK (ligand independent)



>80% of EGFR mutations; results in constitutive EGFR **activation**

associated with aquired **resistance** to EGFR-TKI

IPASS : 1st line EGFR-TKI *vs* chemotherapy

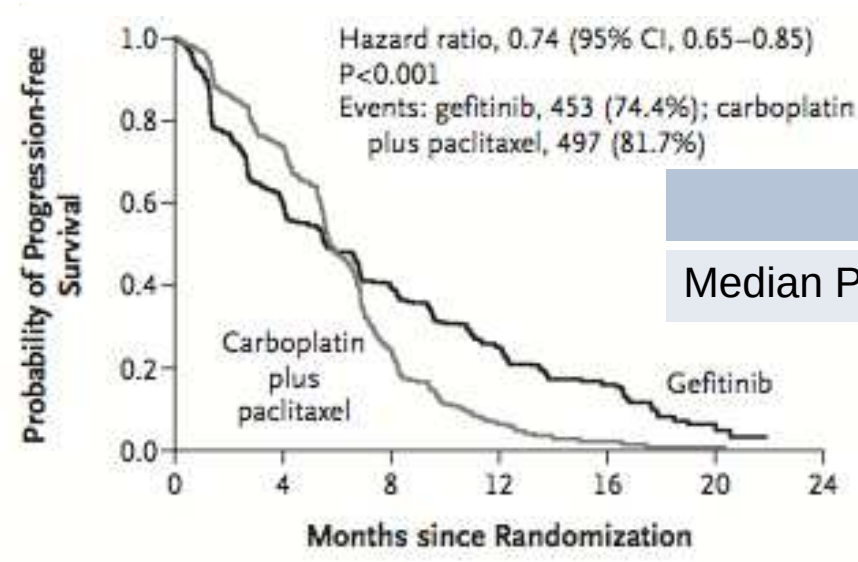
Inclusion criteria:
- Chemonaive Asian pts
- Adenocarcinoma
- Never or light ex-smokers

R

Gefitinib arm:
Gefitinib 250 mg/d until PD

Chemotherapy arm:
Carboplatin + Paclitaxel (6 cycles)

Statistics : PFS as primary endpoint

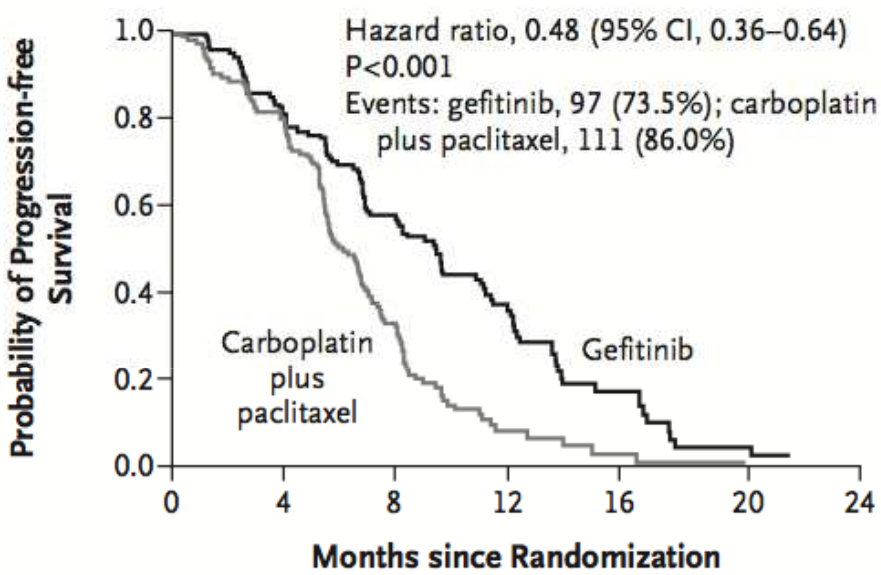


	Gefit	Chemo
Median PFS	5.7 m	5.8 m

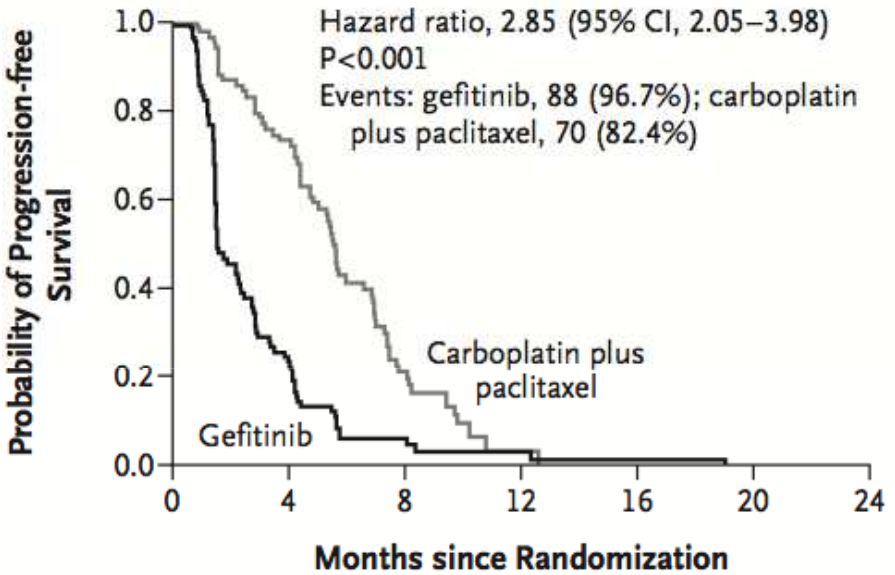
Mok et al. *NEJM* 2009; 361:947-57.

IPASS: Progresion-free survival

EGFR-mutation positive



EGFR-mutation negative



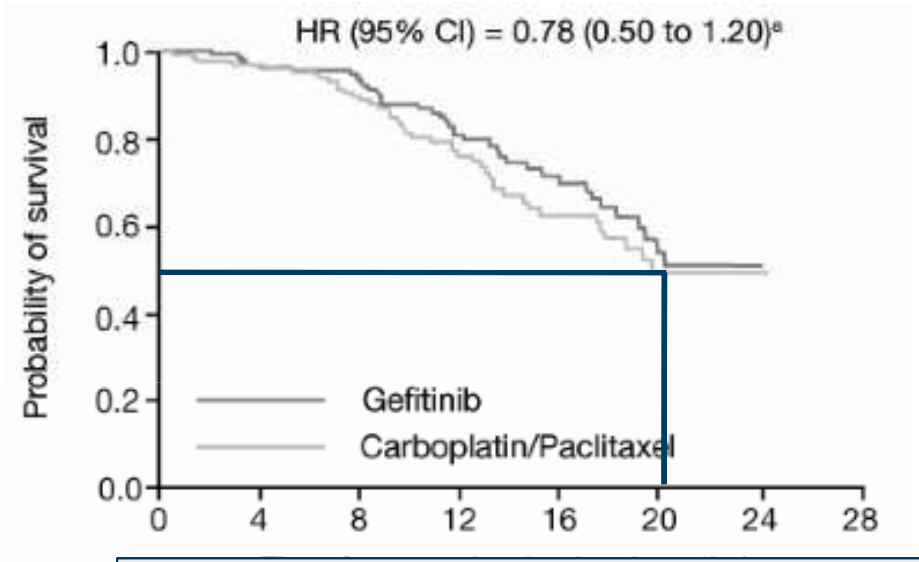
	EGFR-mutation pos.		EGFR-mutation neg.	
	Gefitinib	Carbo/Pacli	Gefitinib	Carbo/Pacli
Respose rate	71% *	47%	1%	23% *
Median PFS	9.6 m *	6.3 m	1.5 m	5.5 m *

* $P < 0.05$

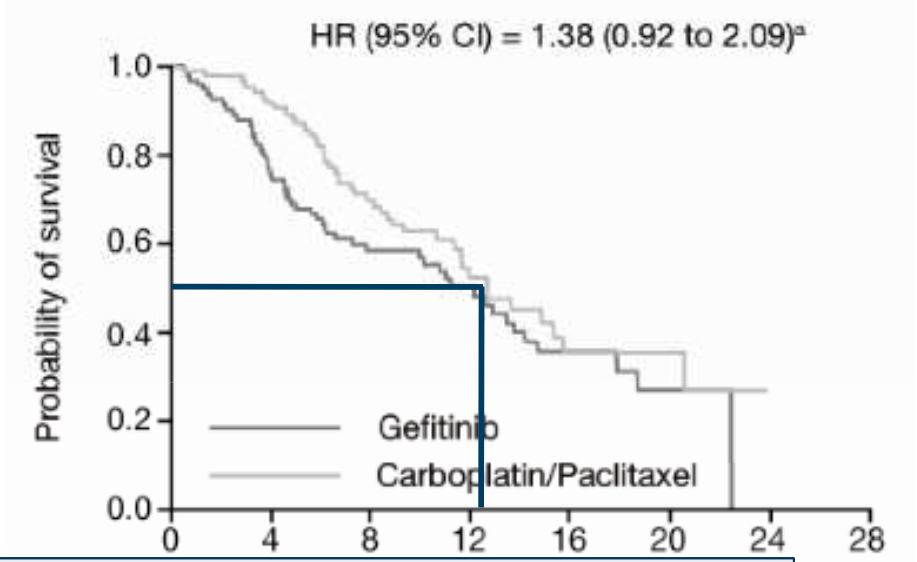
Mok et al. *NEJM* 2009; 361:947-57.

IPASS: Overall survival

EGFR-mutation positive



EGFR-mutation negative



At progression ~40% of patients in each arm crossed over to other treatment modality

The presence of an EGFR mutation:

- is a strong predictive biomarker for ↗response rate (both to chemotherapy and EGFR-TKI)
- is a strong predictive biomarker for ↗ PFS with EGFR-TKI *versus* chemotherapy
- is a favourable prognsotic factor

WJTOG3405 : 1st line gefitinib *vs* chemotherapy

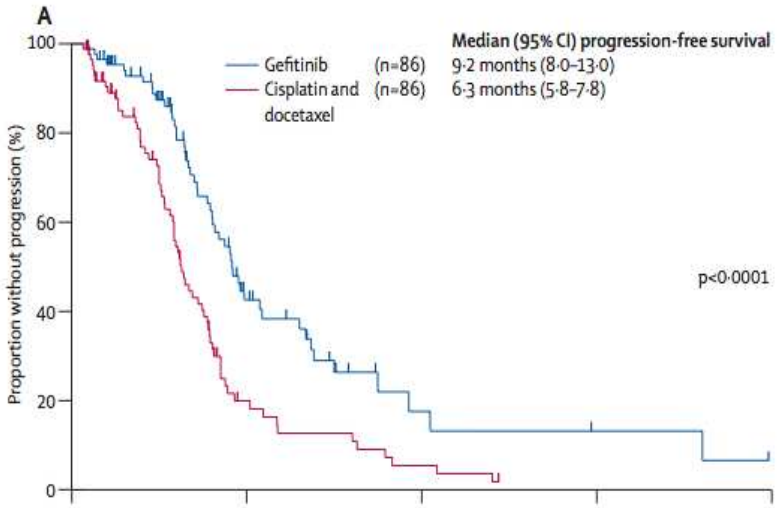
Inclusion criteria:
- Chemonaive Asian pts
- EGFR activating mutation

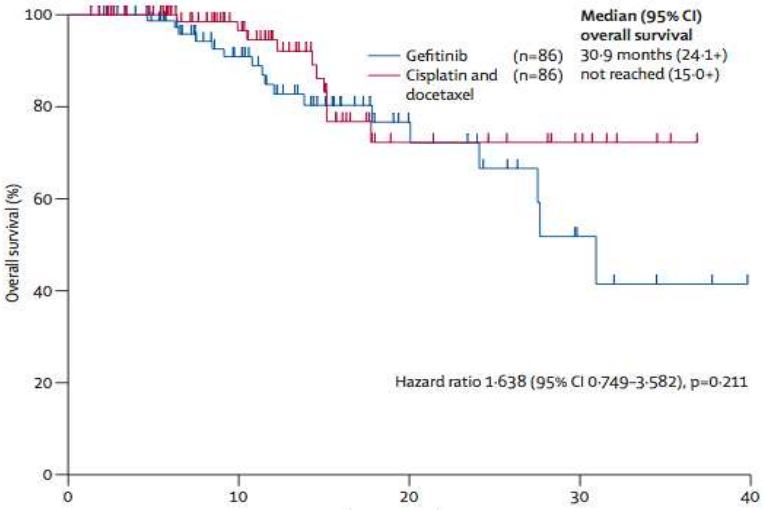
R

Gefitinib arm:
Gefitinib 250 mg/d until PD

Chemotherapy arm:
Cisplatin + Docetaxel (6 cycles)

Statistics : PFS as primary endpoint





Mitsudomi et al. *Lancet: DOI:10.1016/S1470-2045(09)70364-X.*

SATURN: erlotinib as maintenance in 1st-line treatment of advanced NSCLC

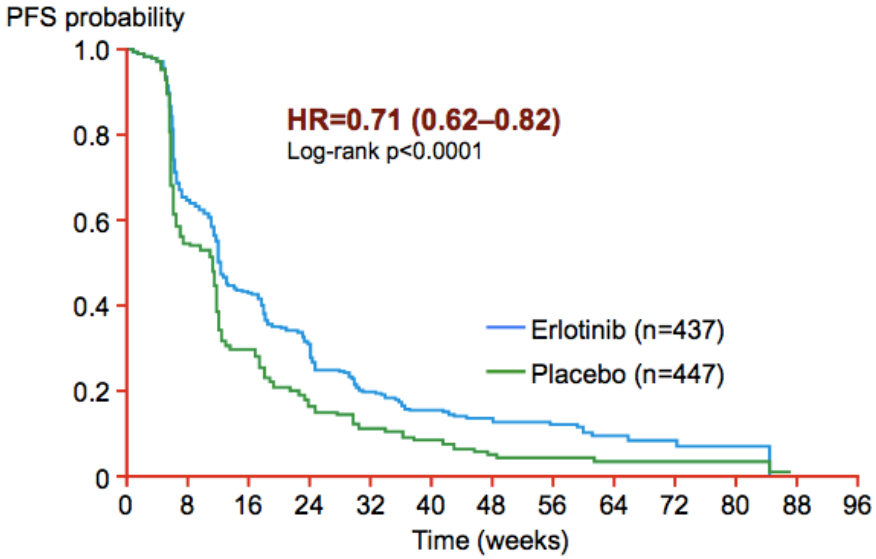
Inclusion criteria:
- Stage IIIB/IV NSCLC
- PS 0-1
- Non-PD following 4 cycles of platinum-based chemotherapy*

R 1:1

Maintenance arm (n=438):
Erlotinib 150 mg/d until PD

Control arm (n=451):
Placebo 1x/d until PD

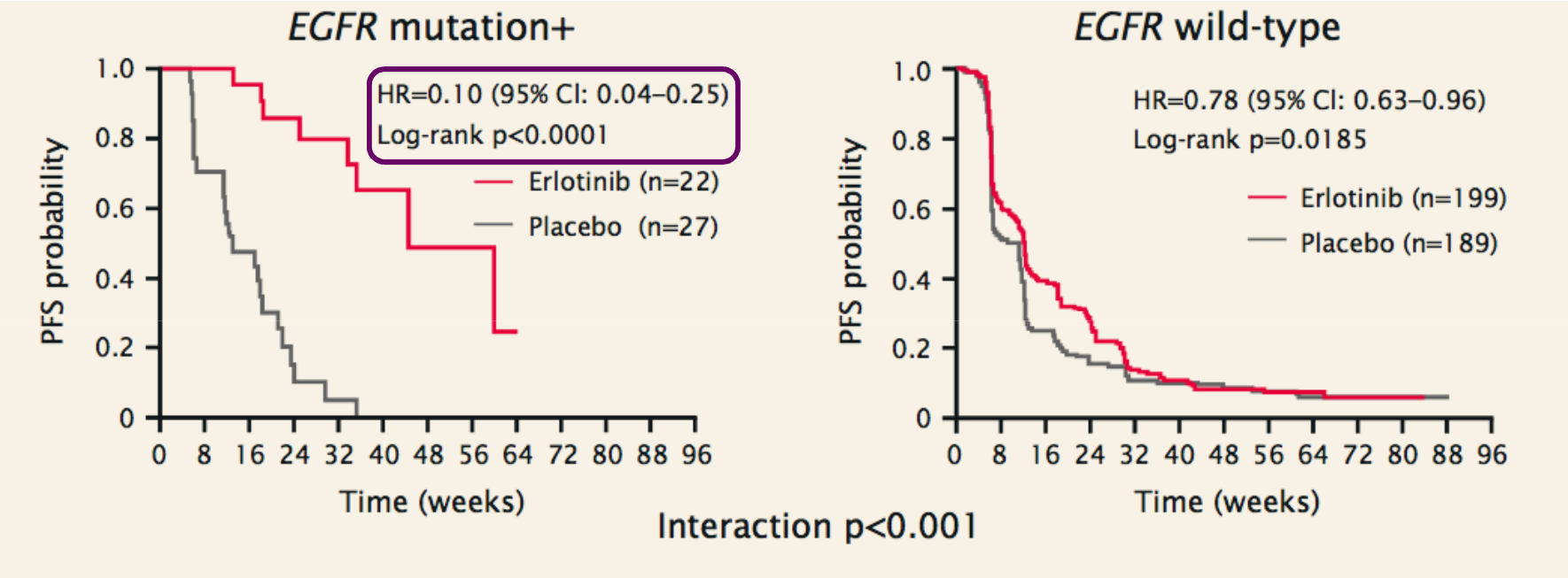
Statistics : PFS as primary endpoint



* 1st line chemotherapy: Cisplatin/Carboplatin + Docetaxel/Paclitaxel/Gemcitabine/Vinorelbine

Cappuzzo et al. *ASCO 2009*: abstract 8001.

SATURN: PFS by biomarkers

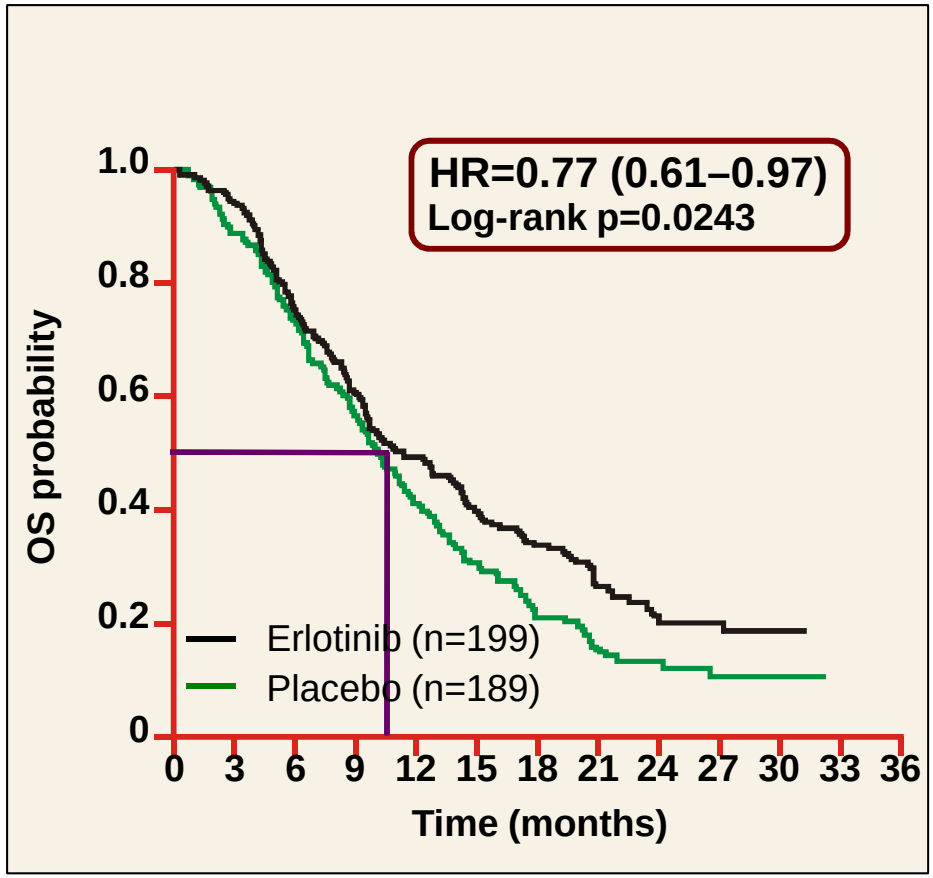


EGFR mutations identify patients who derive a great PFS-benefit from erlotinib maintenance (median PFS 45 wks *vs* 13 wks).

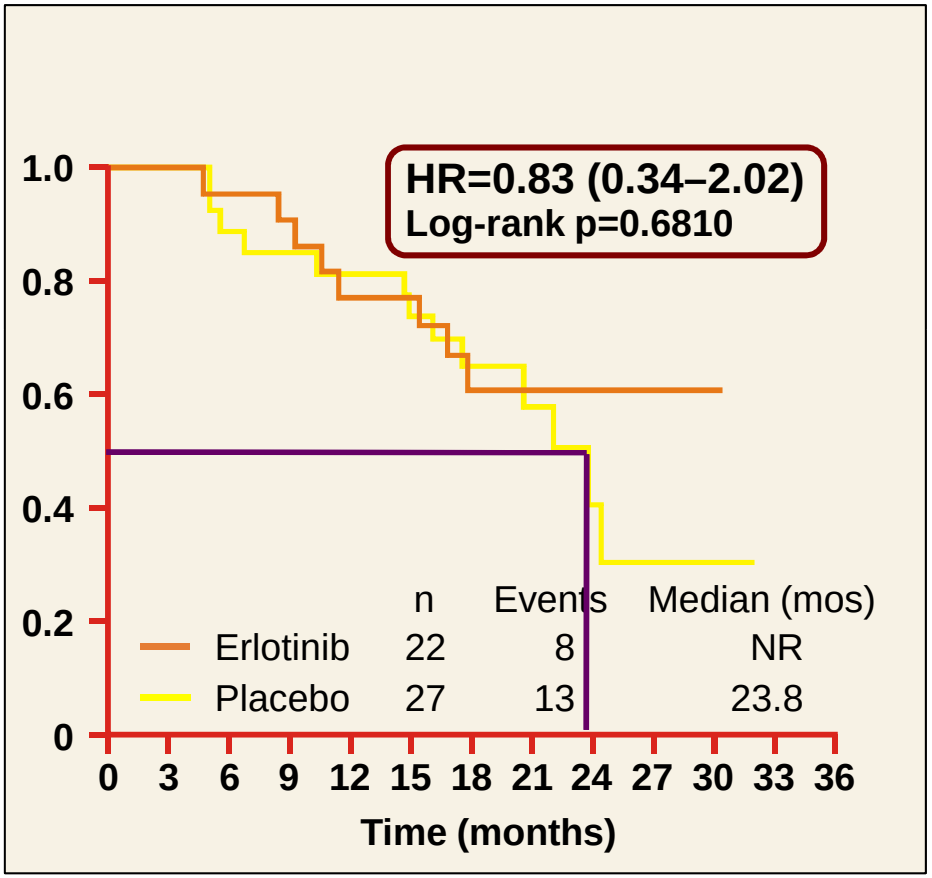
Brugger et al. *ASCO 2009*: abstract 8020.

SATURN: overall survival

EGFR-wild type

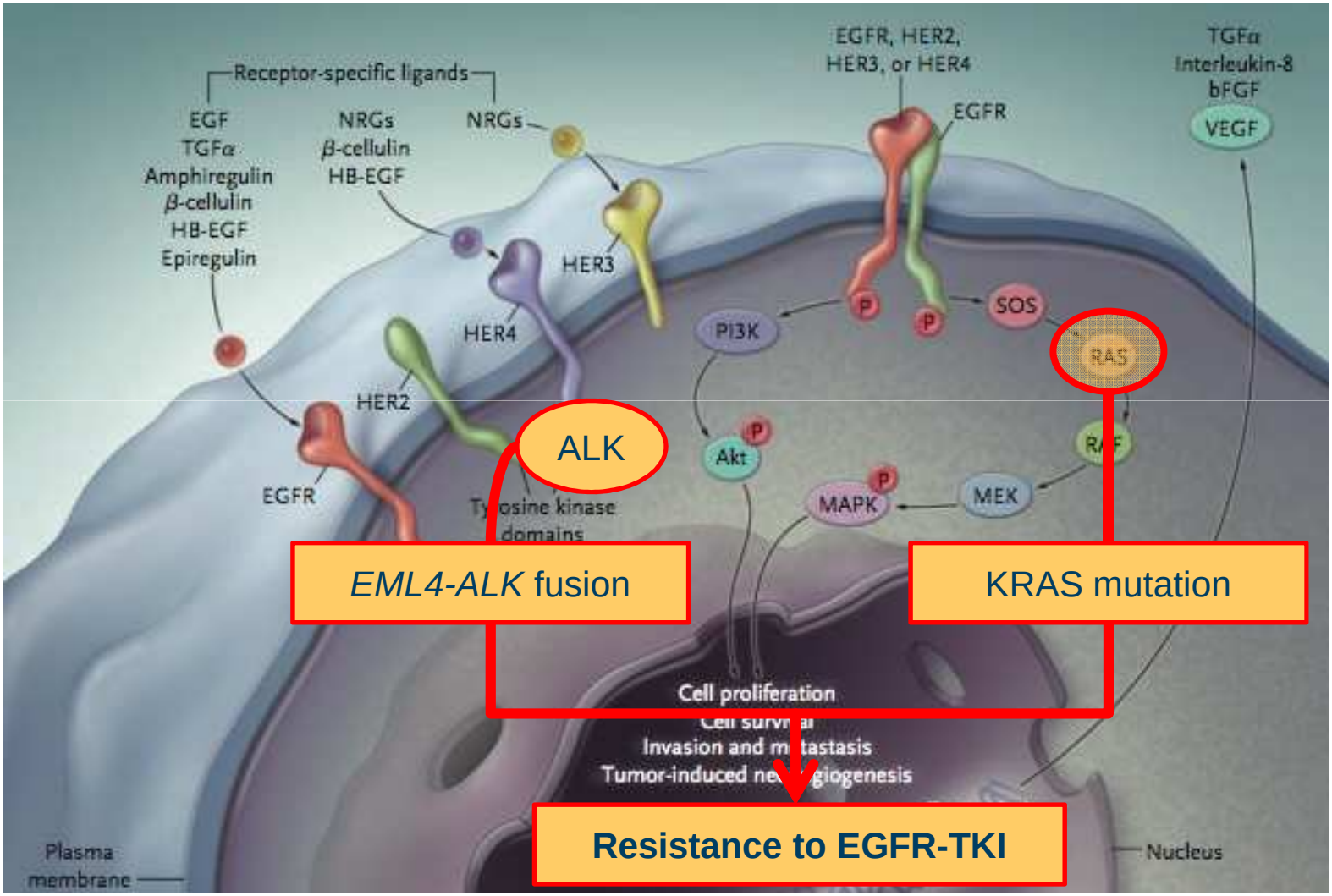


EGFR-mutation positive *



*67% of patients with *EGFR* mutation+ disease in the placebo arm received a second-line EGFR TKI

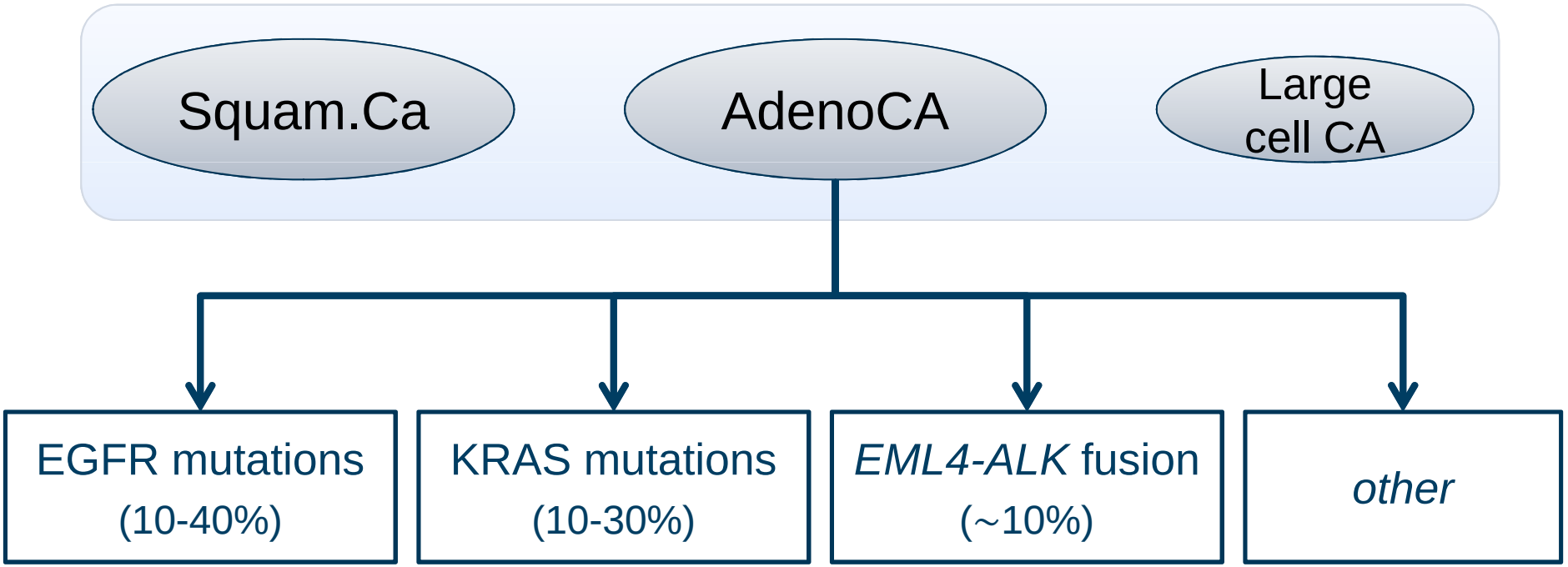
Signal Transduction Pathways Controlled by the Activation of EGFR



Ciardiello and Tortora. NEJM. 2008; 358:1160-74.

NSCLC: driver mutations

Genetic alterations responsible for initiating and maintaining lung cancer:



ALK gene rearrangements and crizotinib in NSCLC

- ALK gene rearrangements:
  - occur in 3-5% of unselected NSCLC
  - higher frequency in adenoCA in light or never smokers
- Crizotinib (PF-02341066):
  - potent oral inhibitor of ALK and MET
- Phase I-II trial of crizotinib :
  - heavily pre-treated NSCLC with proven FISH-positive ALK rearrangement
  - symptomatic improvements occur within 3 days
  - in 50 evaluable pts:
    - objective response rate 64%
    - disease control rate 90%

→ Phase III initiated

Camidge et al. *TAT2010*: O33.

Bevacizumab and NSCLC

- Randomized phase 2 trial of carbo-pacli ± bevacizumab:
  - incidence of life-threatening pulmonary hemorrhage:
    - 9% in all bevacizumab-treated patients
    - 31% in pts with squamous cell cancer
    - 4% in pts with adenocarconima

  →the phase 3 studies enrolled only **non-squamous-cell** NSCLC.

- EMEA label:
  bevacizumab, in addition to platinum-based chemotherapy, is indicated for 1st-line treatment of patients with unresectable advanced, metastatic or recurrent **NSCLC other than predominantly squamous cell histology**.

Johnson et al. *JCO* 2004; 22:2184-2191..

Personalized treatment in NSCLC

- Aims and challenges of biomarker driven treatment
- Treatment customized on histology or tumor biomarkers
  - Targeted therapies:
    - EGFR-TKIs
    - Anti-VEGF
  - Chemotherapy:
    - Pemetrexed
    - Cisplatin-based chemotherapy
- Treatment customized on patient genotype markers
    - Gemcitabine
    - Paclitaxel

Cisplatin+Pemetrexed *vs* Cisplatin+Gemcitabine in 1st-line treatment of advanced NSCLC

Inclusion criteria:

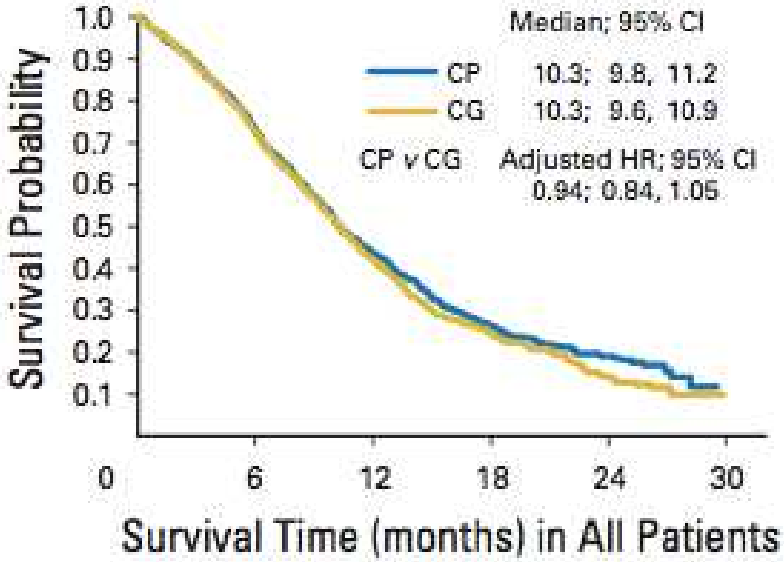
- Chemo-naïve advanced NSCLC
- PS 0-2
- No CNS metastasis

R 2:1

Cis-Pem arm *
Cisplatin 75 mg/m2 d1
Pemetrexed 500 mg/m2 d1

Cis-Gem arm *
Cisplatin 75 mg/m2 d1
Gemcitabine 1250 mg/m2 d1,8

* every 3 weeks for 6 cycles

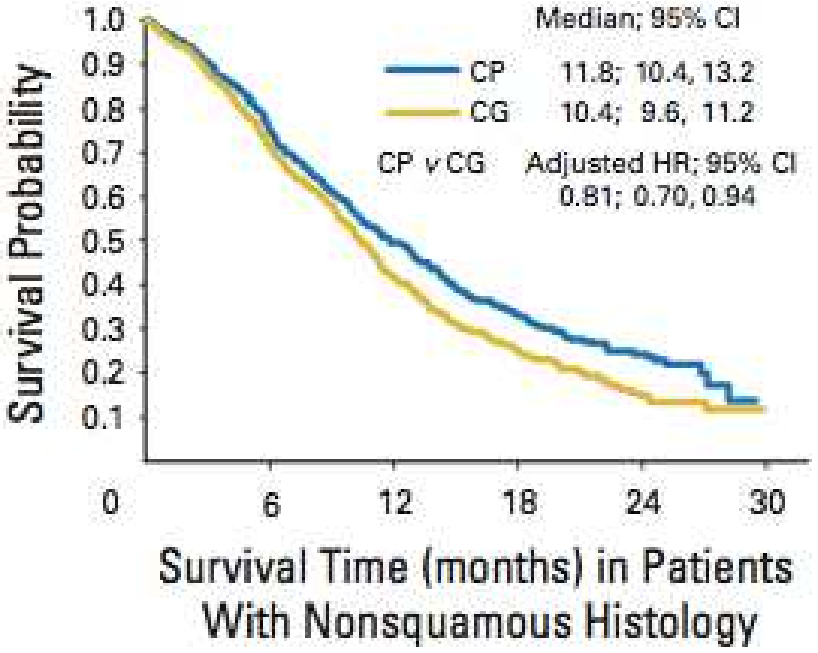


ITT population	C-P	C-G	HR
Median OS (m)	**10.3**	**10.3**	**0.94**

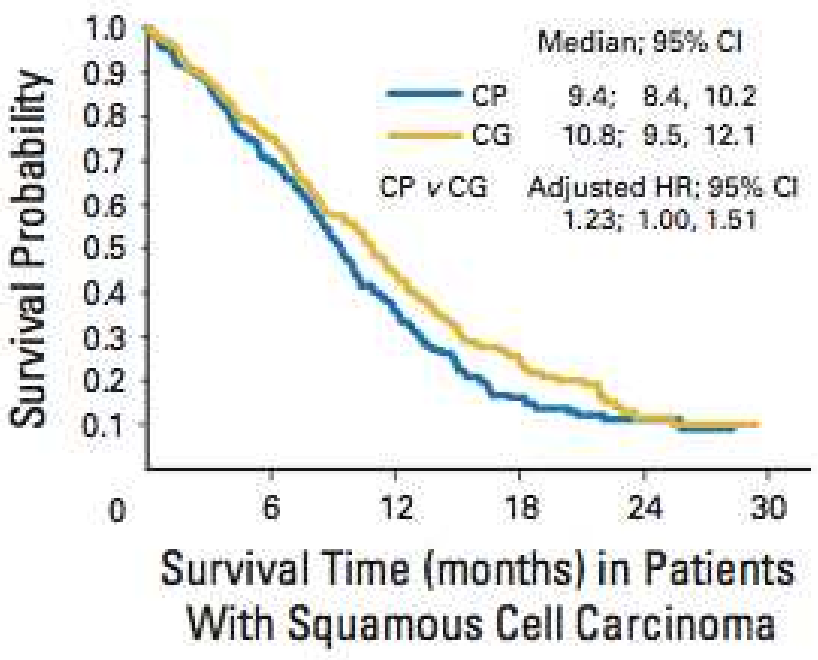
Scagliotti *ea*. JCO 2008; 26: 3543–51.

Cisplatin+Pemetrexed *vs* Cisplatin+Gemcitabine in 1st-line treatment of advanced NSCLC

Non-squamous patients



Squamous patients



Scagliotti *ea*. JCO 2008; 26: 3543–51.

Pemetrexed as maintenance in 1st-line treatment of advanced NSCLC

Inclusion criteria:

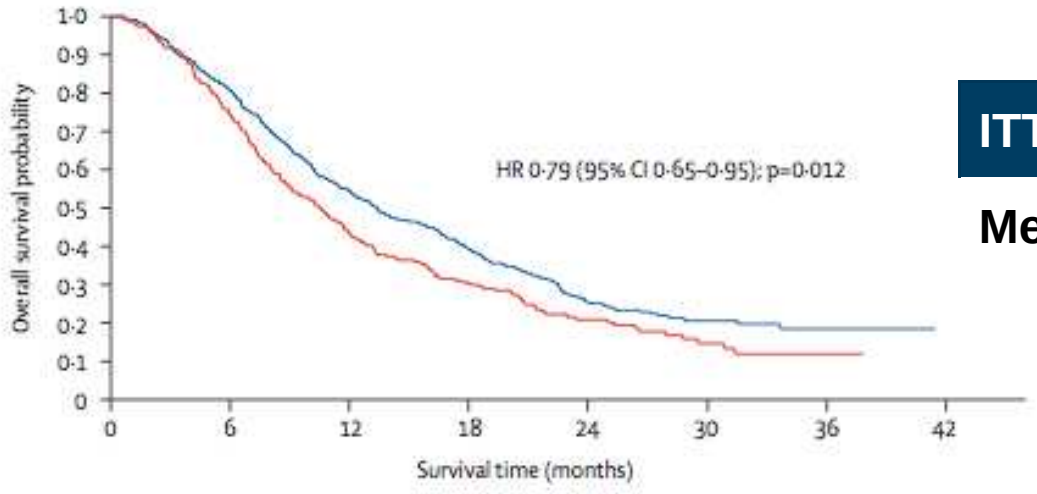
- PS 0-1
- Non-progressing following 4 cycles of platinum + gemci, doc or pacli

R 2:1

Maintenance arm:
Pemetrexed 500 mg/m^2 Q3wks* until PD (n=441)

Control arm:
Placebo d1 Q3wks* until PD (n=222)

*Vitamin B12, folate and dexamethasone given in both arms

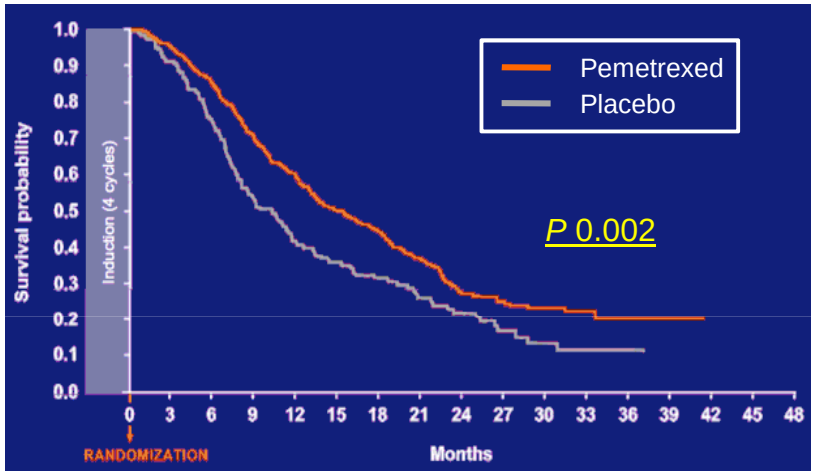


ITT population	Pem	Plac	*P*
Median OS (m)	**15.5**	**10.3**	***.012***

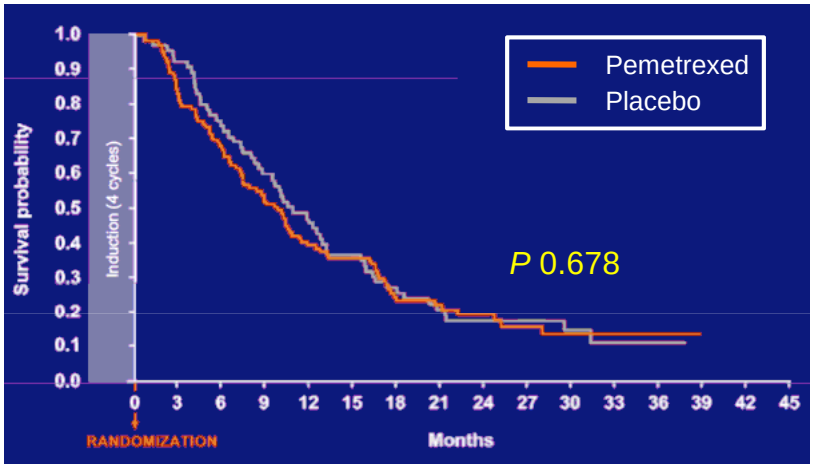
Ciuleanu *ea*. Lancet 2009; 374: 1432-40.

Pemetrexed maintenance trial: preplanned analysis of OS by histology

Non-squamous patients



Squamous patients



	Median OS (months)		
	Pem	Plac	HR
Nonsquamous	**15.5**	**10.3**	**0.70**
Squamous	9.9	10.8	1.07

Ciuleanu *ea*. Lancet 2009; 374: 1432-40.

Pemetrexed and NSCLC hisotology: hazard ratios for overall survival

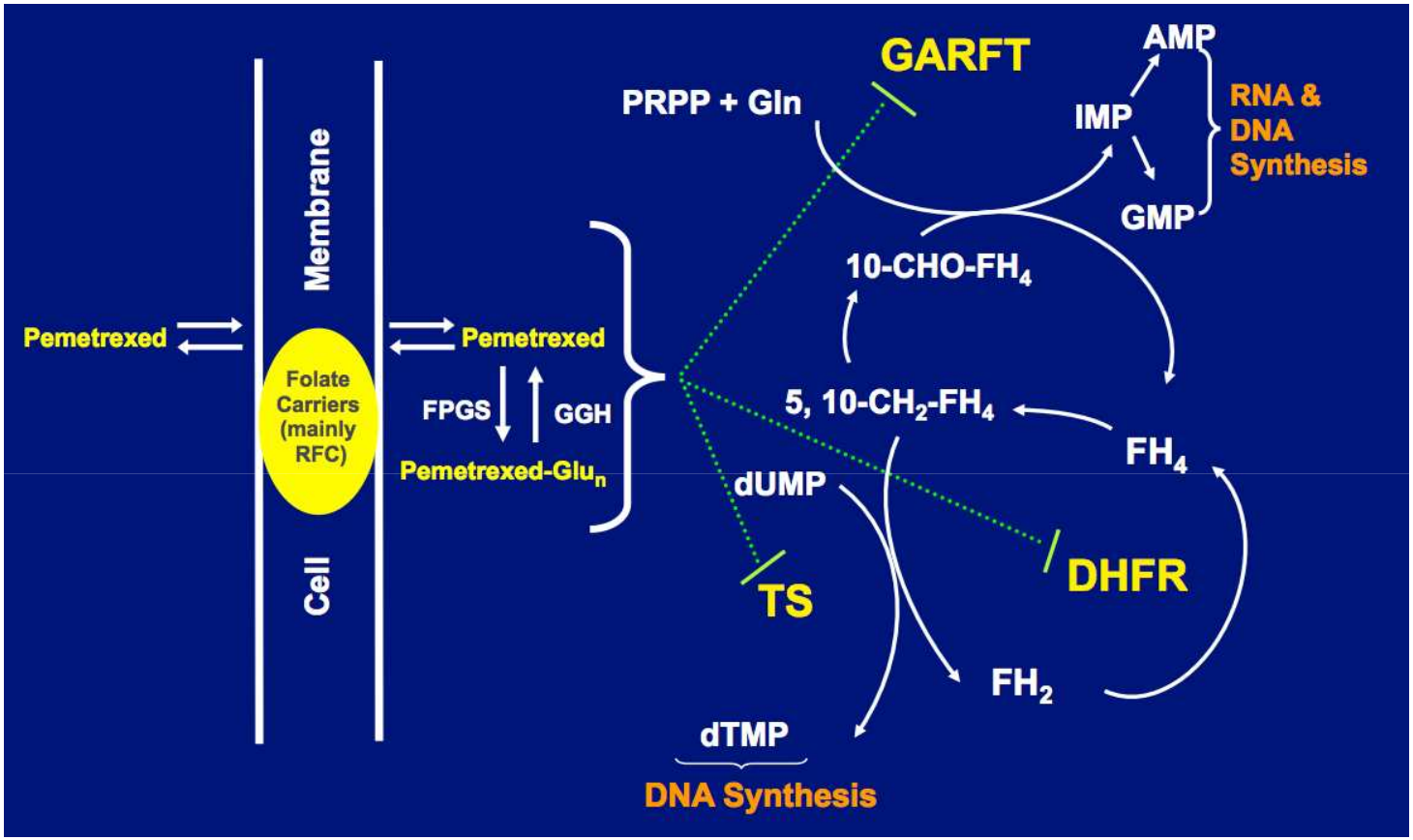
Histology	1st line: Cis-Pem *vs* Cis-Gem	2nd line: Pem *vs* Doc	Maintenance: Pem *vs* Plac
Non-squamous	**0.81** *	**0.78** *	**0.70** *
Squamous	**1.23**	**1.56** *	**1.07**

Conclusion:

- Pemetrexed is superior compared to gemcitabine (and placebo) in patients with non-squamous NSCLC and/or
- Pemetrexed has no anti-tumoral acitivty in squamous cell NSCLC

Peterson *ea*. JTO 2007; 2: S851.
Scagliotti *ea*. JCO 2008; 26: 3543–51.
Ciuleanu *ea*. Lancet 2009; 374: 1432-40.

Pemetrexed: mechanism of action



Resistance to pemetrexed in cancer cell line is solely due to upregulation of thymidylate synthase (TS)

Sigmond et al. *Biochem Phamacol* 2003.

Thymidylate expression in lung cancer

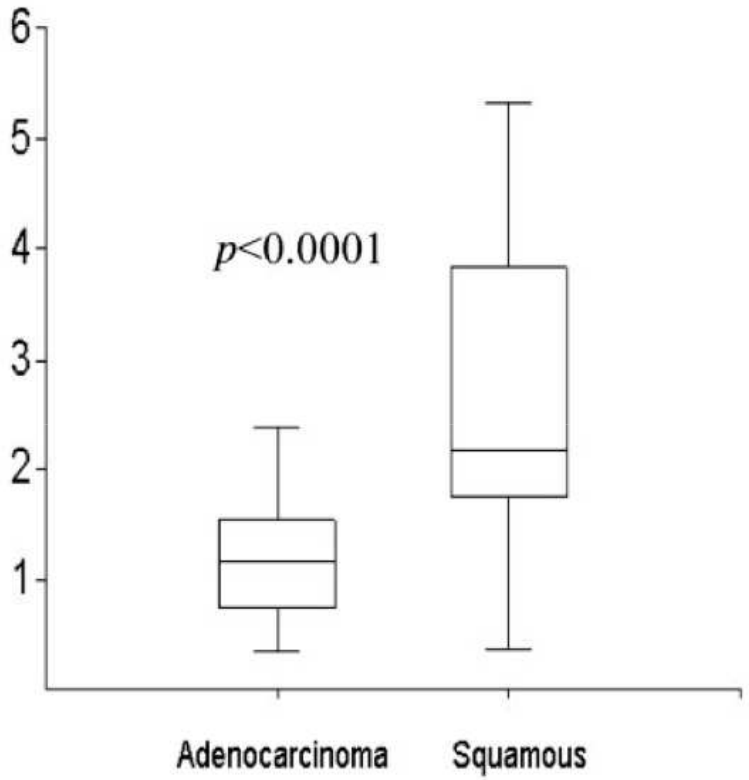
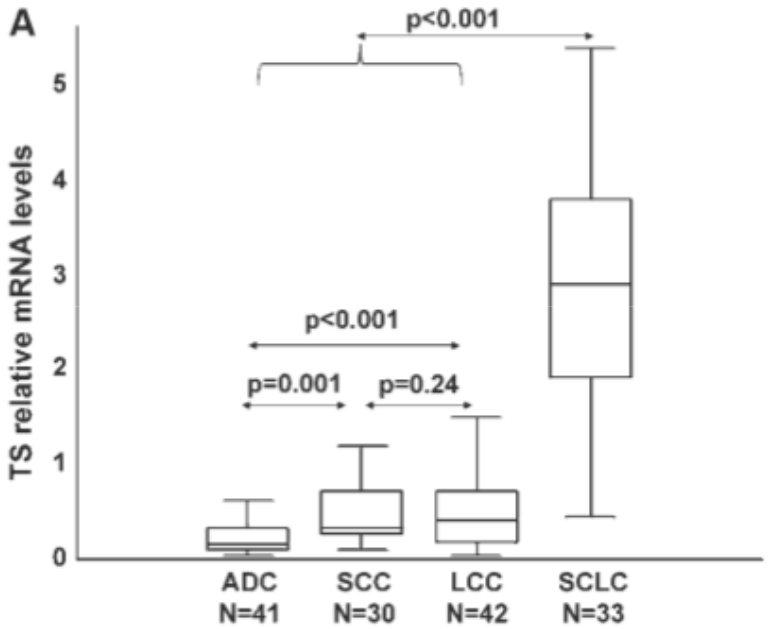


FIGURE 1. Thymidylate synthase messenger RNA levels are illustrated in adenocarcinoma compared with squamous cell carcinoma. Horizontal lines in the middle represent median values, and upper and lower bars represent the distance from the 10th to 90th percentile from the median, respectively.

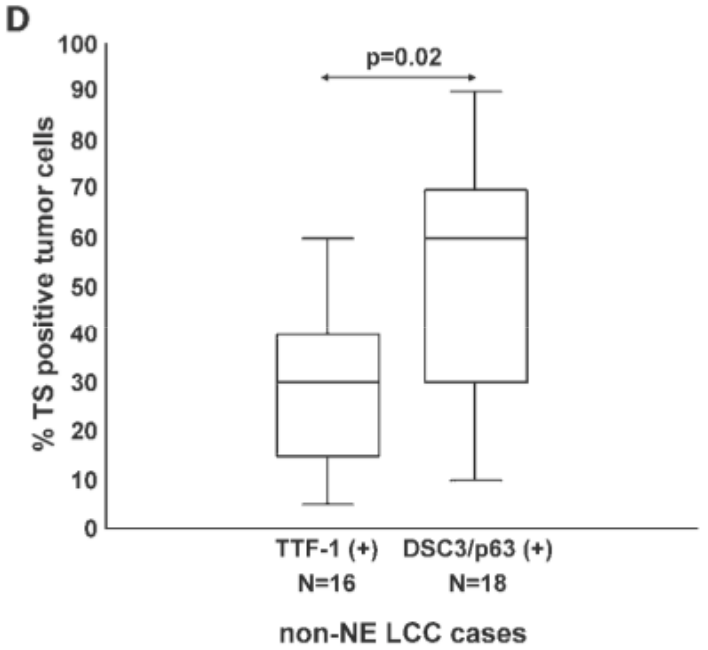
Ceppi et al. *Cancer* 2006; 107:1589-96.

Thymidylate expression in lung cancer

TS mRNA expression



TS protein expression



- The LCC immunoprofile may resemble that of SCCs or ADCs.
- This immunoprofile is associated with differential TS expression levels

LCC: large cell carcinoma
SCLC: small cell lung cancer

Monica et al. *Clin Cancer Care* 2009; 15:7547-52.

Pemetrexed and NSCLC hisotology: hazard ratios for overall survival

Histology	1st line: Cis-Pem *vs* Cis-Gem	2nd line: Pem *vs* Doc	Maintenance: Pem *vs* Plac
Non-squamous	**0.81 ***	**0.78 ***	**0.70 ***
Adenocarcinoma	***0.84 ****	***0.92***	***0.73 ****
Large cell	***0.67***	***0.27 ****	***0.98***
NOS	***1.08***	***0.57***	***0.61 ****
Squamous	**1.23**	**1.56 ***	**1.07**

Peterson *ea*. JTO 2007; 2: S851.
Scagliotti *ea*. JCO 2008; 26: 3543–51.
Ciuleanu *ea*. Lancet 2009; 374: 1432-40.

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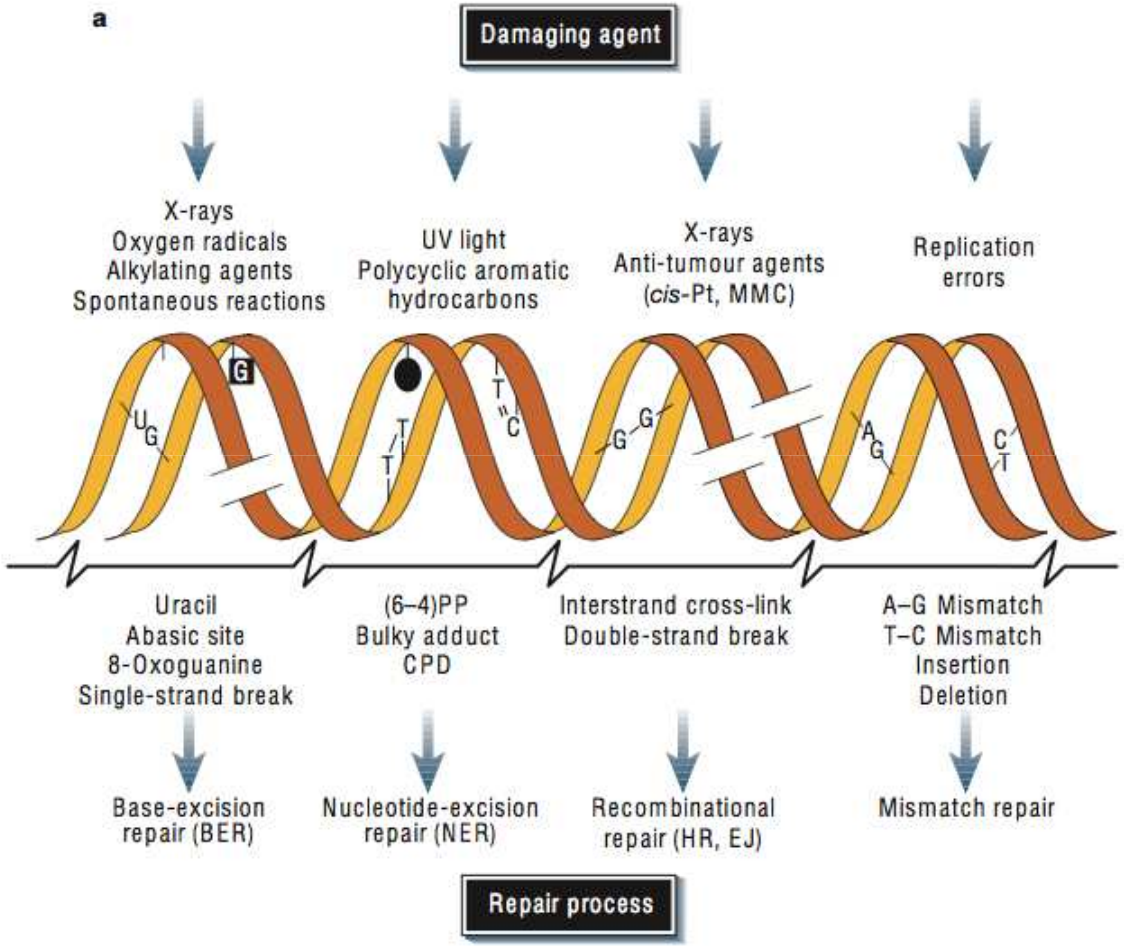
DNA Damage and DNA repair mechanisms



Hoeijmakers JHJ. *Nature* 2001; 411:366-374.

Cisplatin-based chemotherapy and DNA repair mechanisms

Excision repair cross-complementation group 1 (ERCC1)

- ERCC1 is a rate-limiting protein in the NER and ICL-R pathways, which works by recognising and removing platinum adducts and by repairing interstrand DNA cross-links

Ribonucleotide reductase messenger 1 (RRM1)

- RRM1 is the regulatory component of ribonucleotide reductase, which assists with DNA synthesis and repair.
- RRM1 is the predominant target of the nucleoside analogue gemcitabine.
- RRM1 mediates suppression of cell migration and tumour metastasis by inducing *PTEN*, a prominent tumour-suppressor gene responsible for attenuation of growth-factor pathway signalling.

NER: nucleoside excission repair
ICL-R: interstrand cross-link repair

Cisplatin-based chemotherapy and DNA repair mechanisms

Breast cancer type 1 susceptibility protein (BRCA1)

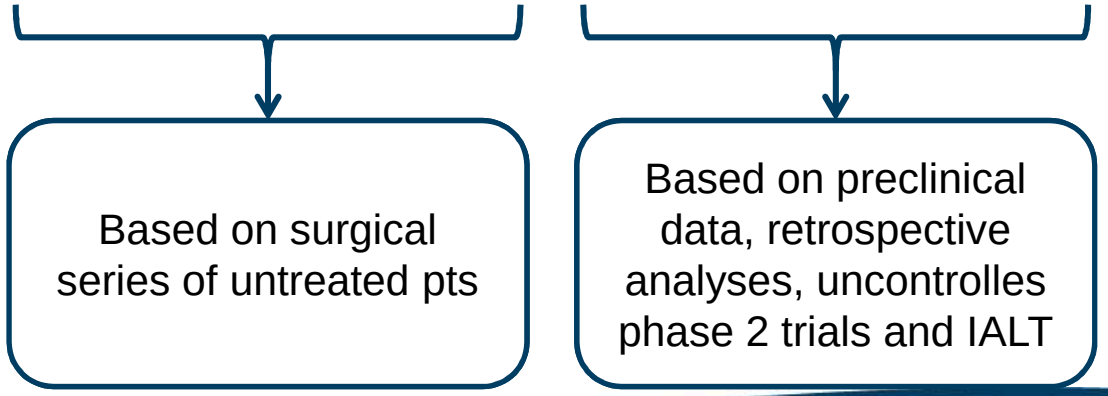
- BRCA1 is a component of multiple repair pathways and plays a central role in DNA repair:
  - is involved in the repair of double-strand DNA breaks by the HR and NH-EJ pathways
  - is implicated in the transcription-coupled NER and the ICL-R pathway.
  - is a component of the BRCA1-associated genome surveillance complex, suggesting a role for BRCA1 in mismatch repair
- BRCA1 and β-tubulin co-localise to the microtubules of the mitotic spindle → potential regulator of mitotic spindle assembly.
- BRCA1 has been implicated BRCA1 in apoptosis via the c-Jun N-terminal kinase pathway.

HR: homologous repair NH-EJ: nonhomologous end joining
NER: nucleoside excission repair
ICL-R: interstrand cross-link repair

Coate et al. *Lancet Oncol* 2009; 10: 1001-10.

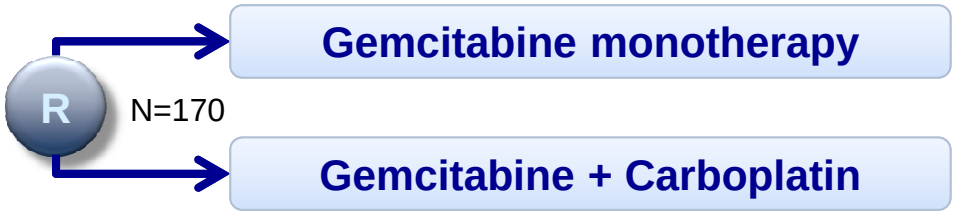
Biomarkers and cisplatin-based chemotherapy in NSCLC

	Prognostic significance	Predictive significance
ERCC1 overexpression	conflicting results	resistance to cisplatin
RRM1overexpression	better prognosis	resistance to cisplatin
BRCA1 overexpression	worse prognosis	resistance to cisplatin sensitivity taxane/vinca

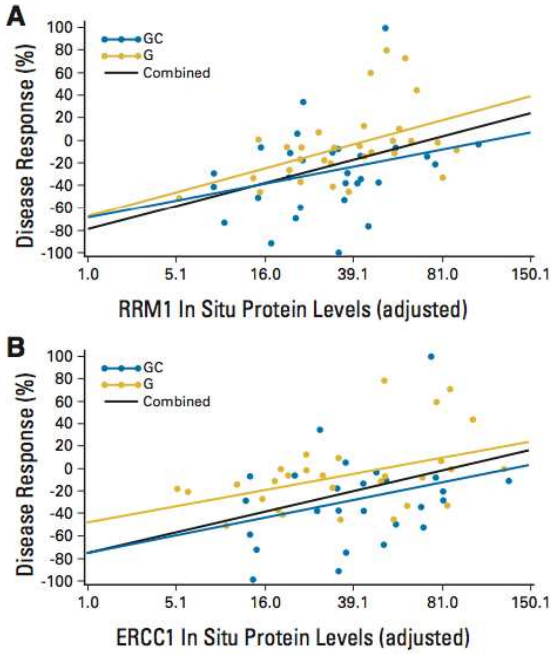


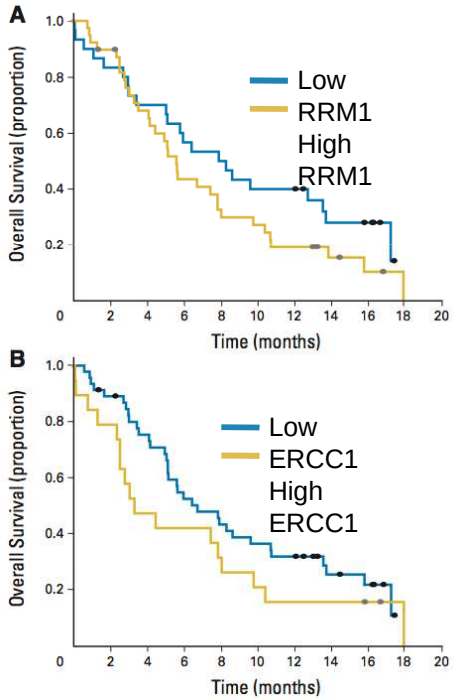
Coate et al. *Lancet Oncol* 2009; 10: 1001-10.

RRM1 and ERCC1 in Gemitabine treated NSCLC



	G	G+C
Median OS	5.1 m	6.7 m

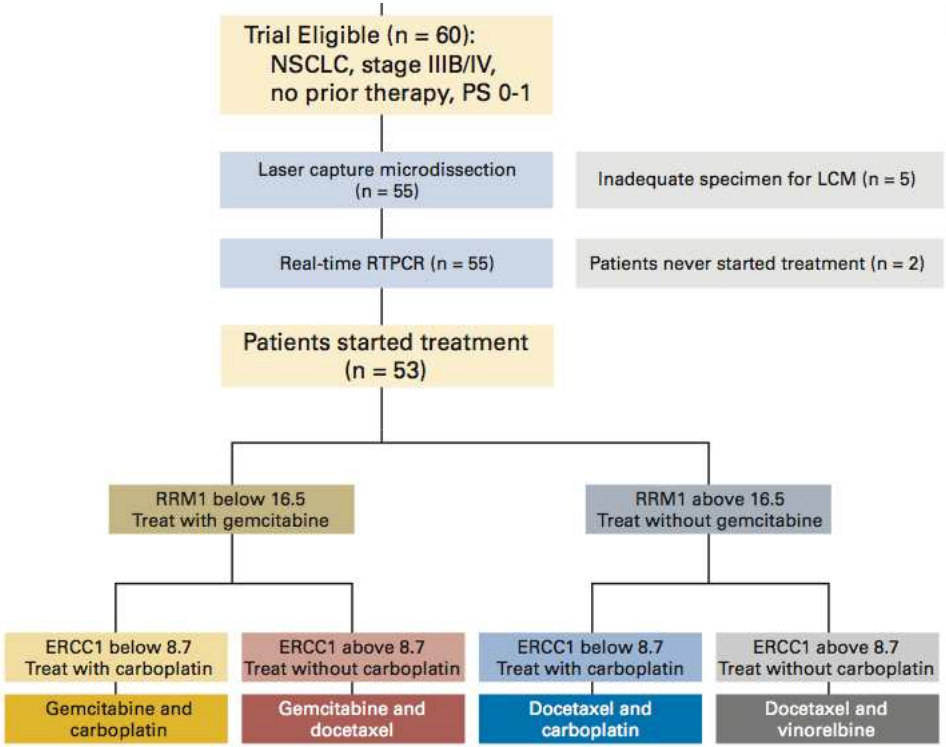




RRM1 (and ERCC1) overexpression is correlated with resistance to gemcitabine (and carboplatin) chemotherapy in NSCLC

Reynolds et al. *JCO* 2009; 27: 5808-15.

Molecular Analysis-Directed Therapy in NSCLC



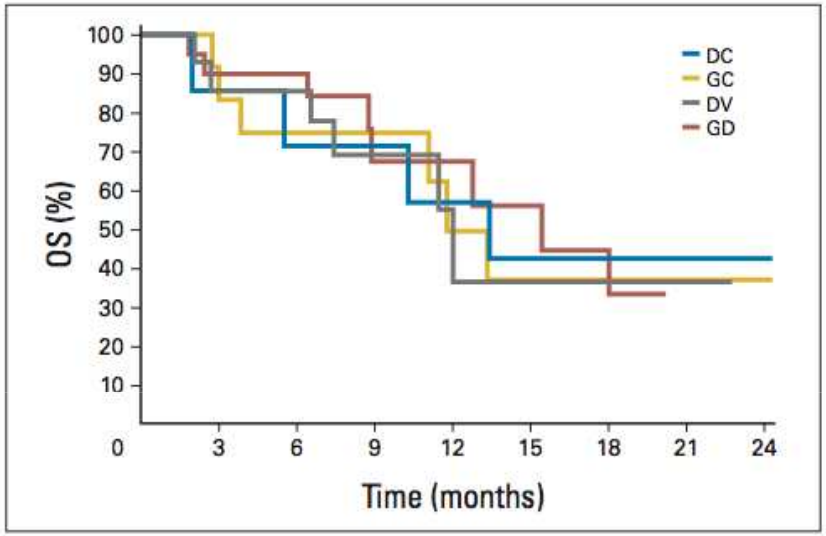
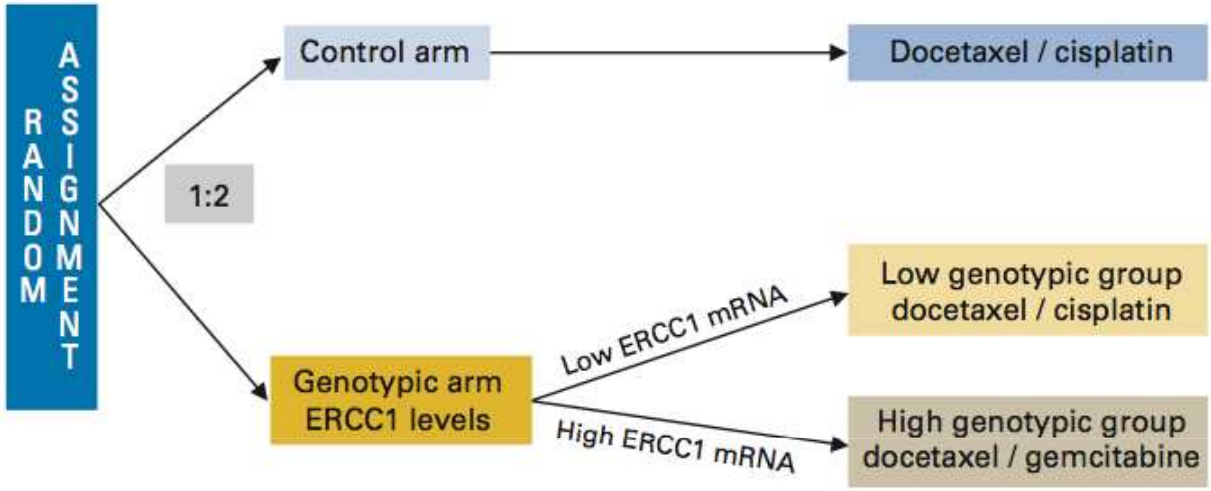


Fig 3. Overall survival (OS) by assigned chemotherapy. DC, docetaxel and carboplatin; GC, gemcitabine and carboplatin; DV, docetaxel and vinorelbine; GD, gemcitabine and docetaxel.

	RR	MST	1-yr OS
Individualized chemo	44 %	13.3 m	59%

Reynolds et al. *JCO* 2009; 27: 5808-15.

Customizing Cisplatin-chemotherapy based on ERCC1 mRNA expression in NSCLC



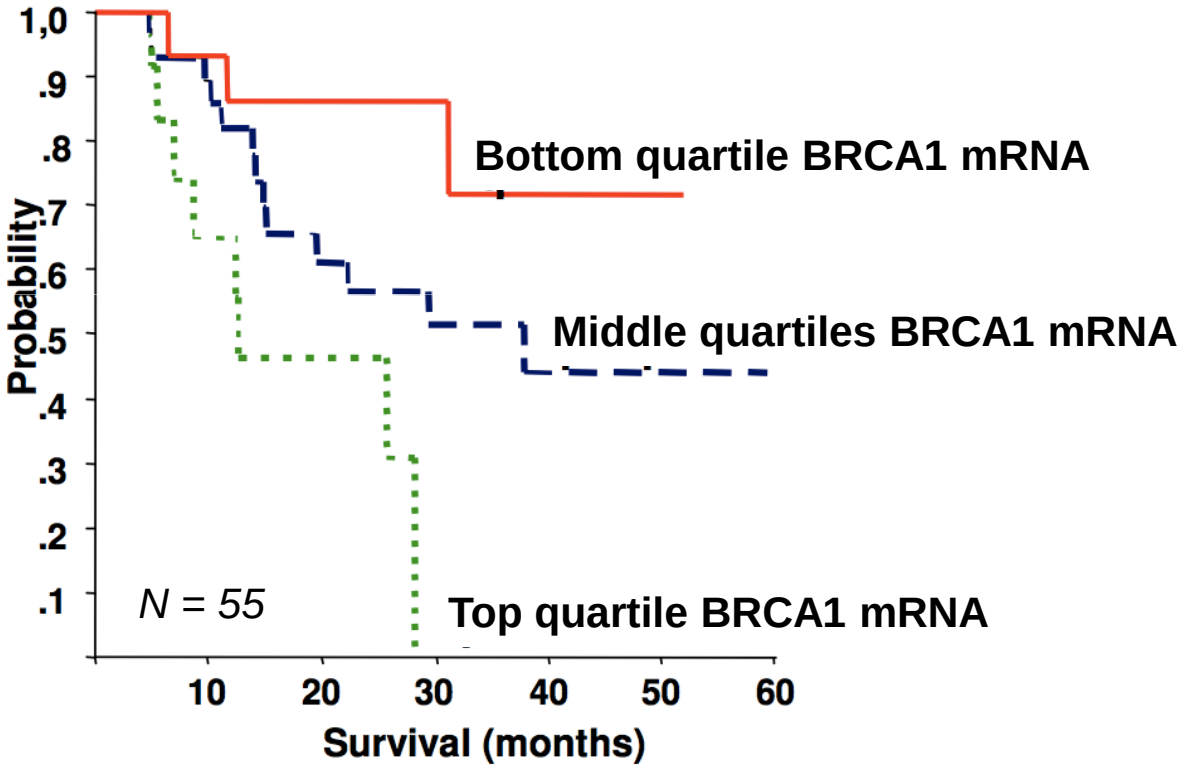
	RR	PFS	MST	1-yr OS	2-yr OS
Control arm	40%	5.2 m	9.8 m	39%	19%
Genotypic arm	51%	6.1 m	9.9 m	41%	20%

Customizing chemo based on tumor ERCC1 mRNA expression:

- is feasible in the clinical setting
- improves response rate (but not overall survival)

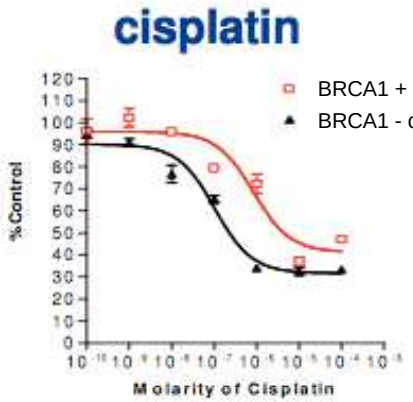
Cobo et al. *JCO* 2007; 27: 2747-54.

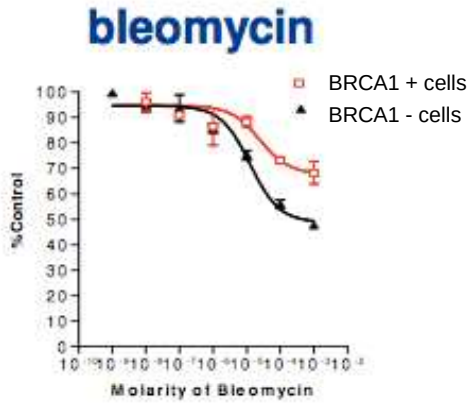
BRCA1 as preditor of survival in patients with resected NSCLC treated with induction cis + gemci

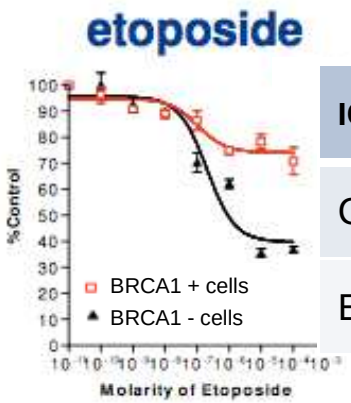


Taron et al. *Human Mol Genet* 2004

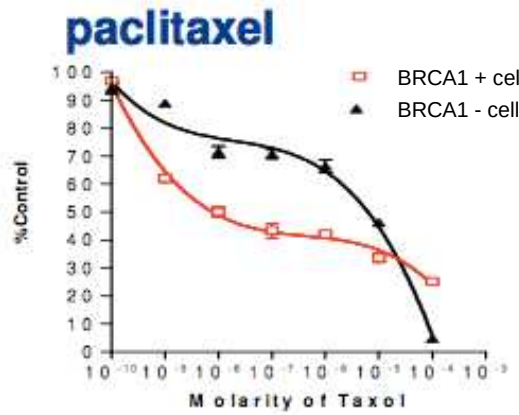
BRCA1 has differential modulating effect on chemotherapy

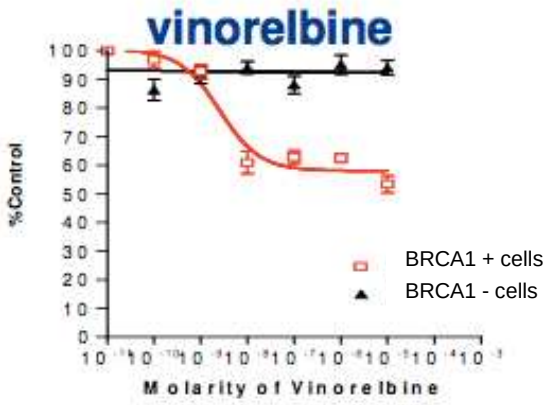






IC 50	BRCA1 -	BRCA1 +
Cispl	0,2 µM	4,1 µM
Etop	0,9 µM	>100 µM



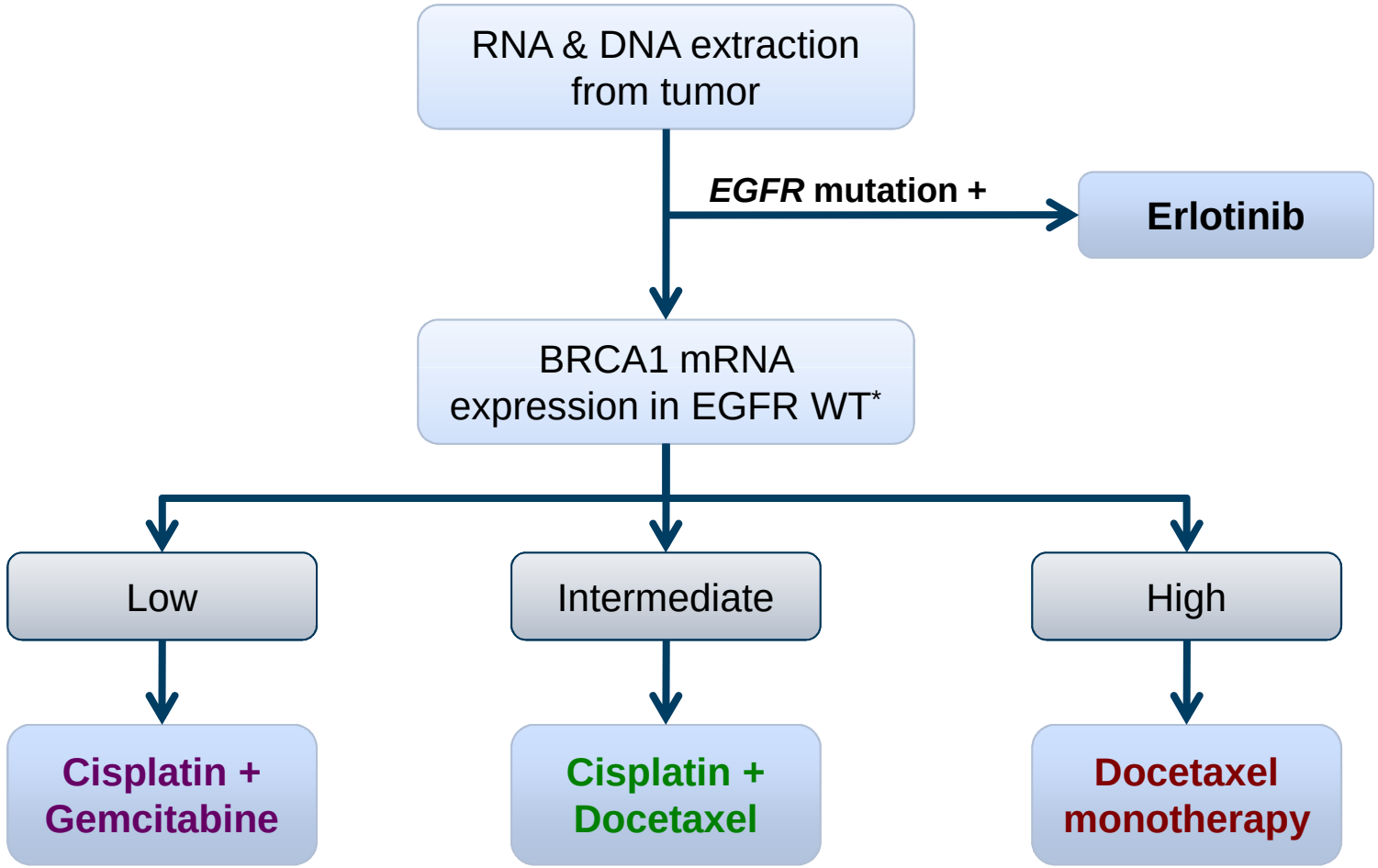


IC 50	BRCA1 -	BRCA1 +
Pacli	6,2 µM	7,2 nM
VRB	17 µM	1,9 nM

BRCA1 expression induces resistance to cisplatin and sensitivity to paclitaxel and vinorelbine.

Quinn et al. *Cancer Res* 2003; 63:6221-28.

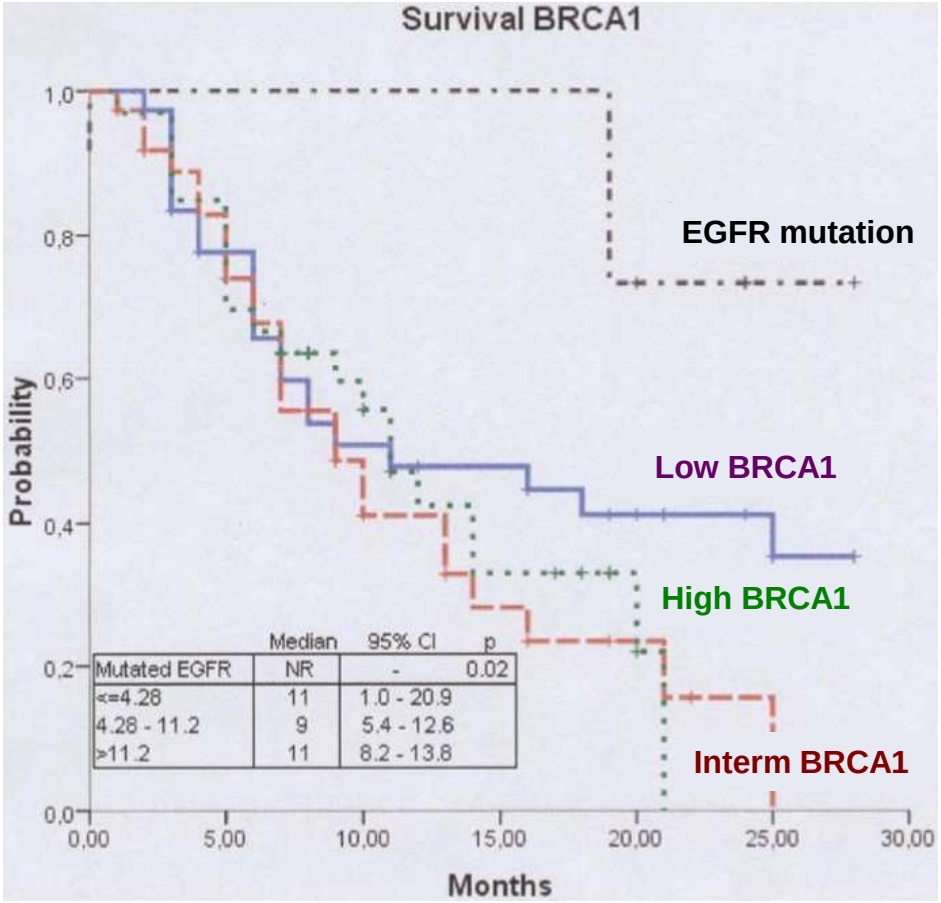
Customized treatment of NSCLC based on EGFR mutations and BRCA1 mRNA expression



* exploratory analysis of RAP80 and Abraxas expression

Rosell et al. *PLoS ONE* 2009; 4: e5133.

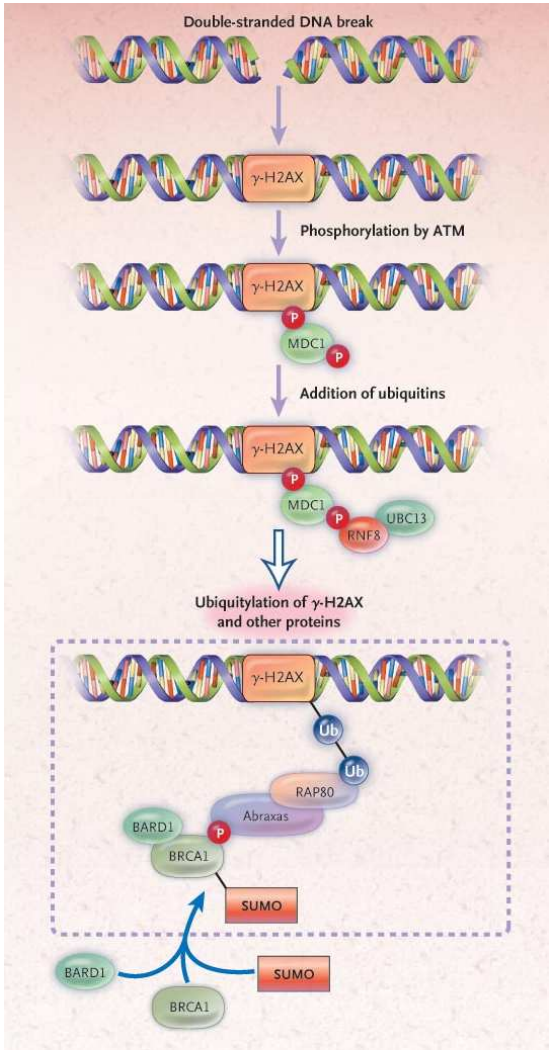
Customized treatment of NSCLC based on EGFR mutations and BRCA1 mRNA expression



	N	MST	1y OS	2y OS
EGFR mut +	12	NR	92%	73%
BRCA1 low	38	11m	48%	41%
BRCA1 inter	40	9m	41%	16%
BRCA1 high	33	11m	42%	0%

Rosell et al. *PLoS ONE* 2009; 4: e5133.

Bringing BRCA1 to Sites of DNA Damage



- Histone γ-H2AX and MDC1 are recruited to site of DNA damage

↓

- Ubiquilation of γ-H2AX and MDC1 complex occurs

↓

- RAP80 (and Abraxas) are attracted to the site

↓

- RAP80 transfers BRCA1 to the site of DNA-damage

MDC1: mediator of DNA-damage checkpoint 1
BRCA1: breast cancer suscpetibility gene 1
RAP80: receptor associated protein 80

RAP80 and DNA repair mechanisms

Receptor associated protein 80 (RAP80):

- acts upstream of BRCA1
- is required for accumulation of BRCA1 to sites of double strand DNA breaks
  → *RAP80 is required for DNA damage repair*
- is able to translocate to DNA-damage foci in cells which express a truncated BRCA1 that is unable to migrate to nuclear foci
  → *RAP 80 could replace the BRCA1 DNA repair function in cells lacking BRCA1*

Customized treatment of NSCLC based on EGFR mutations and BRCA1 mRNA expression

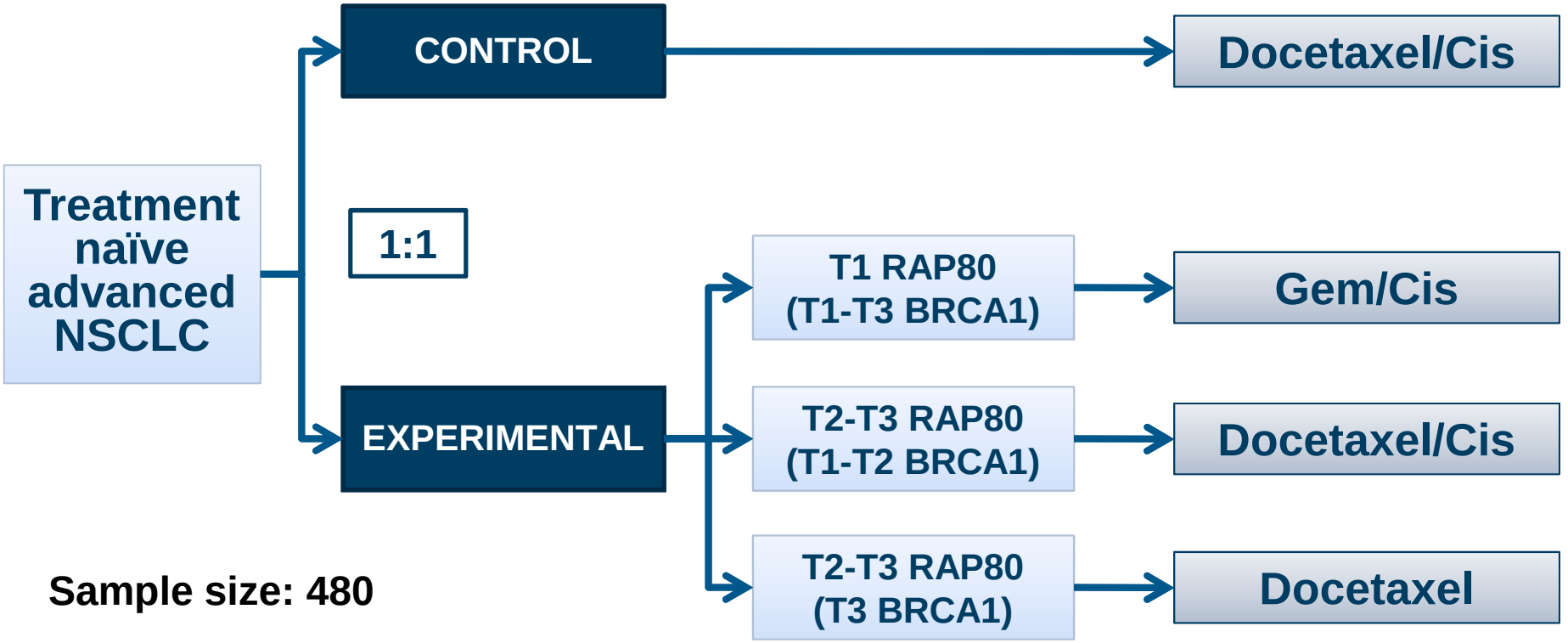
Median survival ~ BRCA1 and RAP80 expression

		RAP80 mRNA		
		Low	Intermediate	High
BRCA1 mRNA	Low	NR	8 m	7 m
	Intermediate	5 m	13 m	16 m
	High	6 m	12 m	11 m

Cisplatin + Gemcitabine
Cisplatin + Docetaxel
Docetaxel monotherapy

Rosell et al. *PLoS ONE* 2009; 4: e5133.

BREC trial: design



Sample size: 480

Primary endpoint:

- Time to progression between the standard non-customized first-line chemotherapy group and the 3 customized chemotherapy subgroups

Selection factors for customizing systemic treatment for NSCLC

Category	Drug	Selection factor	Effect
Tumor histology	EGFR-TKI	Adeno	Improved response rate
	Pemetrexed	**Non-Squamous**	**Exclusion non-benefiting pts**
	Bevacizumab	Non-Squamous	Safety
Molecular tumor biomarkers	**EGFR-TKI**	**EGFR-mutation**	**Improved PFS**
	Pemetrexed	Low TS expression	Selection benefiting pts
	Gemcitabine	Low RRM1	Selection benefiting pts
	Platinum	ERCC1, BRCA1 or RAP80 expression	Improved RR, PFS and/or OS

Data from adequately powered RCTs with prospective biomarker analysis

Personalized treatment in NSCLC

- Aims and challenges of biomarker driven treatment
- Treatment customized on histology or tumor biomarkers
  - Targeted therapies:
    - EGFR-TKIs
    - Anti-VEGF
  - Chemotherapy:
    - Pemetrexed
    - Cisplatin-based chemotherapy
- Treatment customized on patient genotype markers
    - Gemcitabine
    - Paclitaxel

Correlation of CDA Polymorphisms with Outcome in Gemcitabine/Cisplatin Treated NSCLC

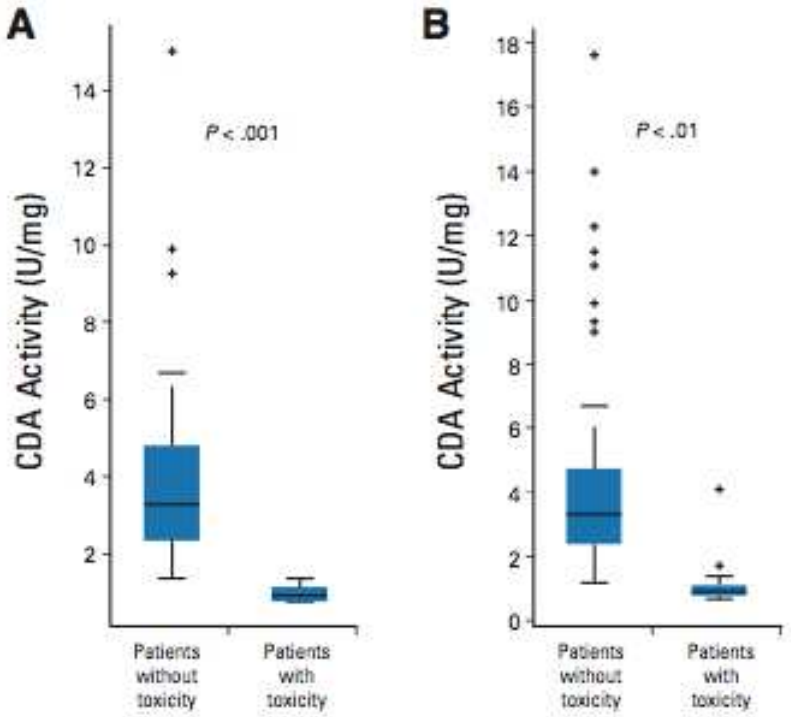
- The metabolic inactivation of gemcitabine is catalyzed by cytidine deaminase (CDA).
- *CDA* polymorphisms were analyszed in 65 chemonaive NSCLC pts treated with cisplatin + gemcitabine:
  - mean enzymatic activity in carriers of Lys/Gln and Gln/Gln genotypes was 1.7-fold higher compared to the wild-type CDA [27] Lys/Lys (P = 0.048)

CDA Lys[27]Gln	Incidence	RR	MST	Gr 3-4 Neutropenia	Gr 3-4 Thrombopenia
Lys/Lys	38%	52%	17 m	48%	33%
Lys/Gln	47%	31%	14 m	10%	7%
Gln/Gln	15%	11%	4 m	22%	11%

Tibaldi et al. *Clin Cancer Res* 2008; 14:1797-1803.

Cytidine deaminase (CDA) activity in serum and severe toxicities with gemcitabine

- Gemcitabine is primarily detoxified by cytidine deaminase



A. Gemcitabine monotherapy
B. Gemcitabine combinations

→ CDA deficiency is associated with a maximum risk of developing early severe toxicities with gemcitabine

Pharmacogenomic analysis of the common carboplatin-paclitaxel arm in US-Japanese trials

- Genomic DNA was prospectively collected in three phase III trials in advanced NSCLC, each with a common arm of paclitaxel plus carboplatin.
- Population-based pharmacogenomic analysis of genotypic variants of CYP3A4, CYP3A5, CYP2C8, NR1I2-206, ABCB1, ERCC1, and ERCC2 was performed.
- The CYP3A isozymes account for 45% to 60% of paclitaxel metabolism.
- An association was observed between occurrence of the CYP3A4*1B allele and PFS (P = .04)

  (*this association should be interpreted in the context that only African American patients harbored this allele)*

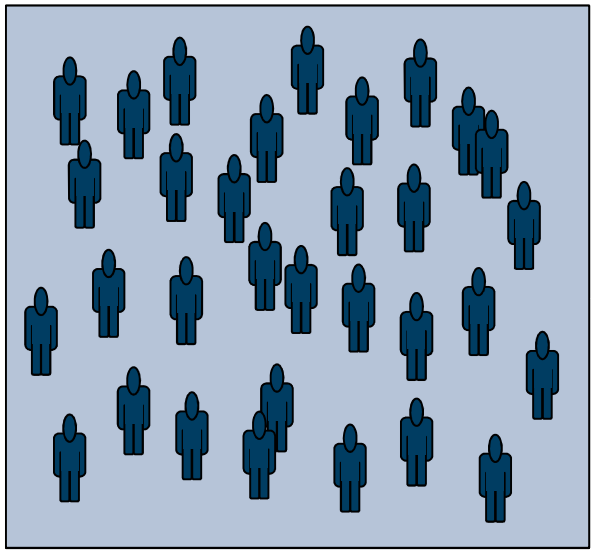
Gandara et al. *JCO* 2009; 27:3540-46.

Selection factors for customizing systemic treatment for NSCLC

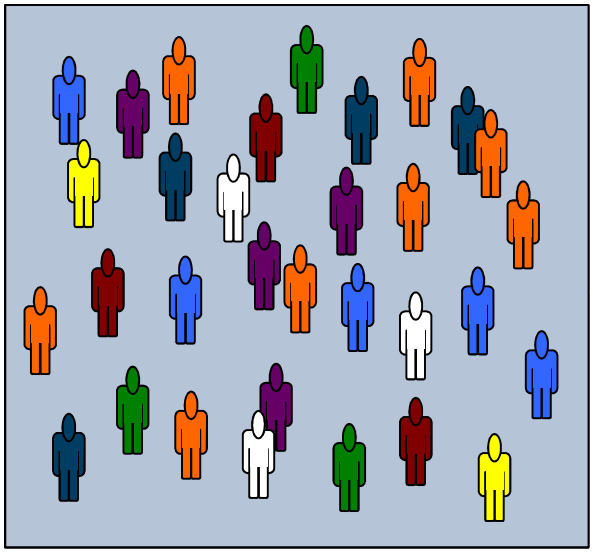
Category	Drug	Selection factor	Effect
Tumor histology	EGFR-TKI	Adeno	Improved response rate
	Pemetrexed	**Non-Squamous**	**Exclusion non-benefiting pts**
	Bevacizumab	Non-Squamous	Safety concerns in squamous
Molecular tumor biomarkers	**EGFR-TKI**	**EGFR-mutation**	**Improved PFS**
	Pemetrexed	Low TS expression	Selection of benefiting pts
	Gemcitabine	Low RRM1	Selection of benefiting pts
	Platinum	ERCC1, BRCA1, RAP80	Improved RR, PFS and/or OS
Patient genotype	Gemcitabine	CDA [27] Lys/Lys	Improved OS(worse toxicity)
	Paclitaxel	CYP3A4 SNP	Improved PFS

Data from adequately powered RCTs with prospective biomarker analysis

Personalized treatment of NSCLC



The future is now



“NSCLC is a common cancer”

“NSCLC is a collection of rare cancers”