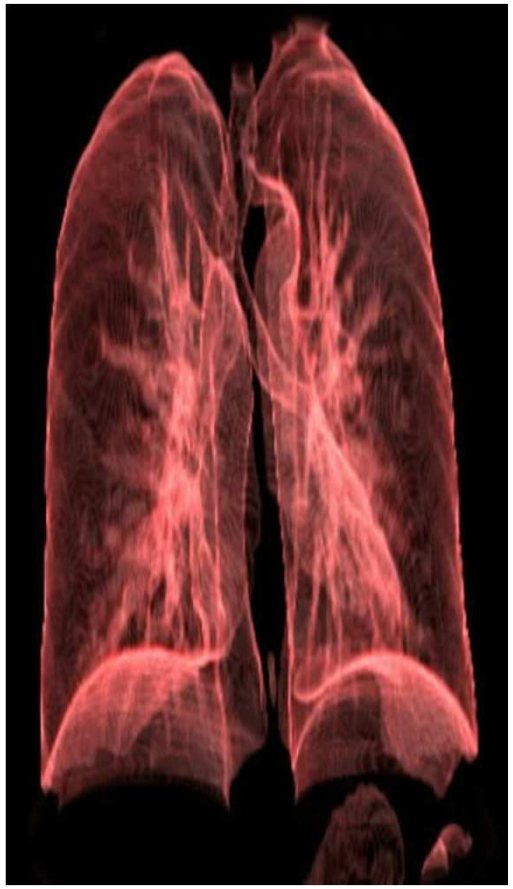
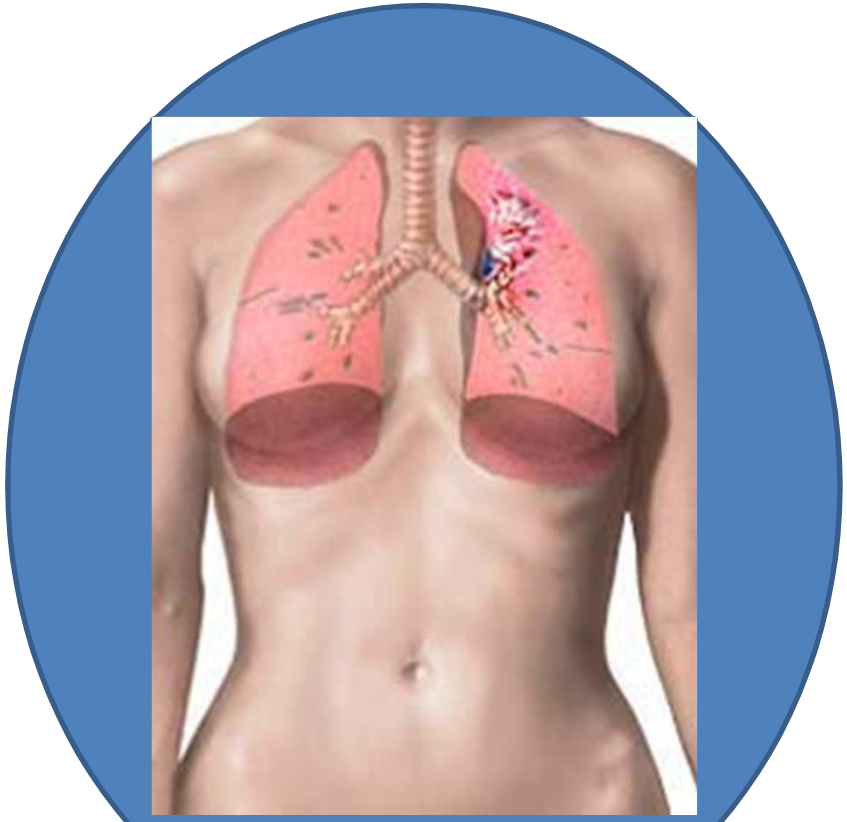
ARE ALL LUNG & BREAST CANCERS SAME ??

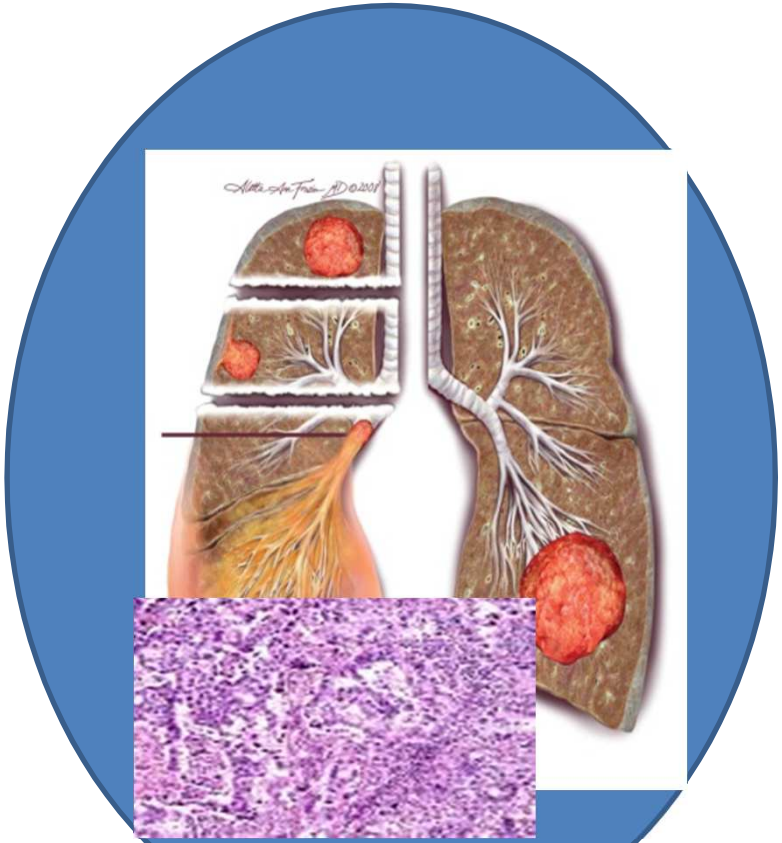


Dr.DIPTI RANI SAMANTA
ASST PROF,
DEPT OF MEDICAL ONCOLOGY,
A.H.REGIONAL CANCER CENTRE

TREATMENT OF NSCLC BASED ON



PATIENT FACTOR



TUMOR FACTORS

PT FACTOR

AGE

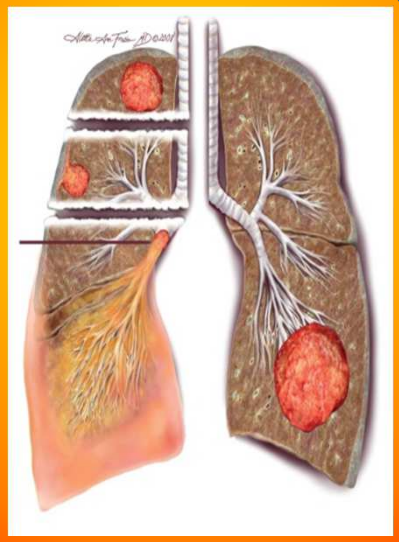
SEX

PERFORMANCE STATUS

HISTORY OF SMOKING

ETHNICITY

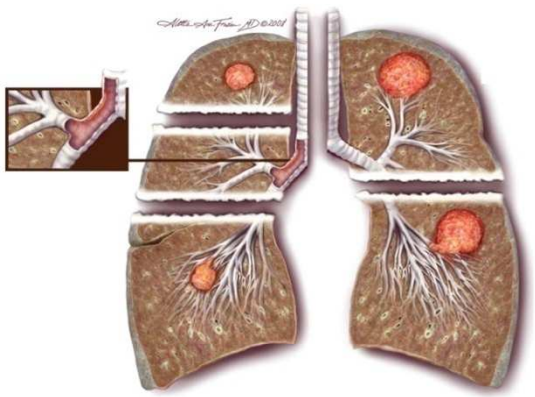
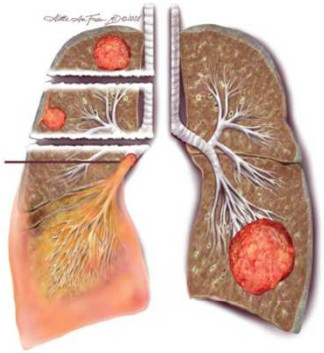
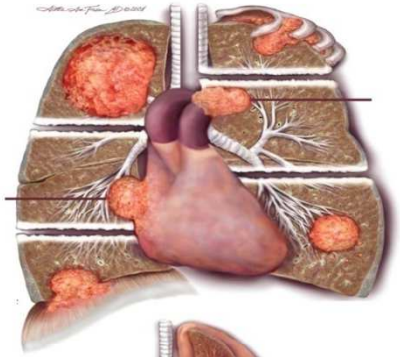
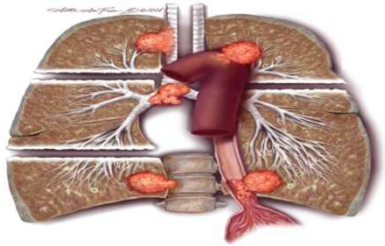
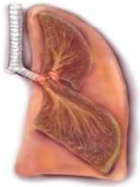
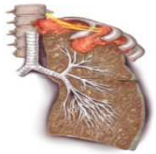
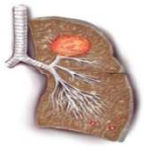
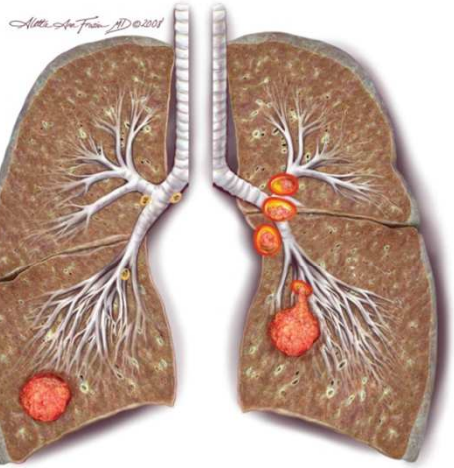
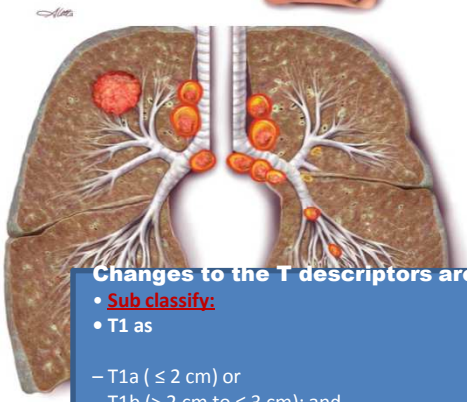
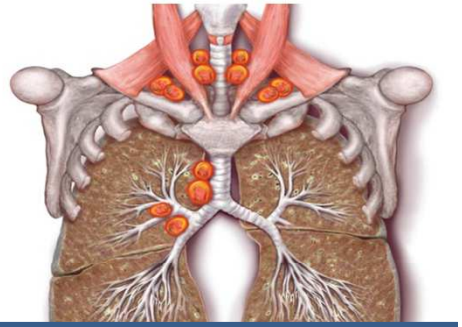
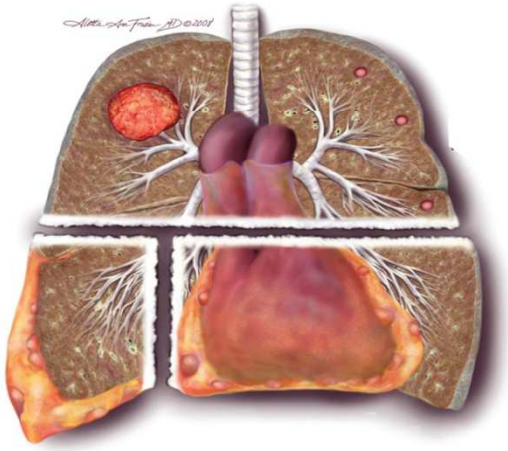
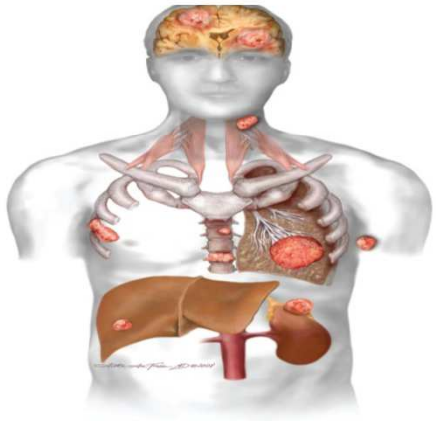
STAGE OF THE DISEASE



TUMOR FACTORS

HISTOLOGY

????

Changes to the T descriptors are:

- **Sub classify:**
- **T1 as**

– T1a (≤ 2 cm) or
– T1b (> 2 cm to ≤ 3 cm); and

- **T2 as**

– T2a (>3 to ≤ 5 cm or T2 by other factor and ≤ 5 cm) or
– T2b (>5 to ≤ 7 cm).

- **Reclassify:**

- T2 tumors > 7 cm as T3.

- T4 tumors by additional nodule/s in the lung (primary lobe) as T3.

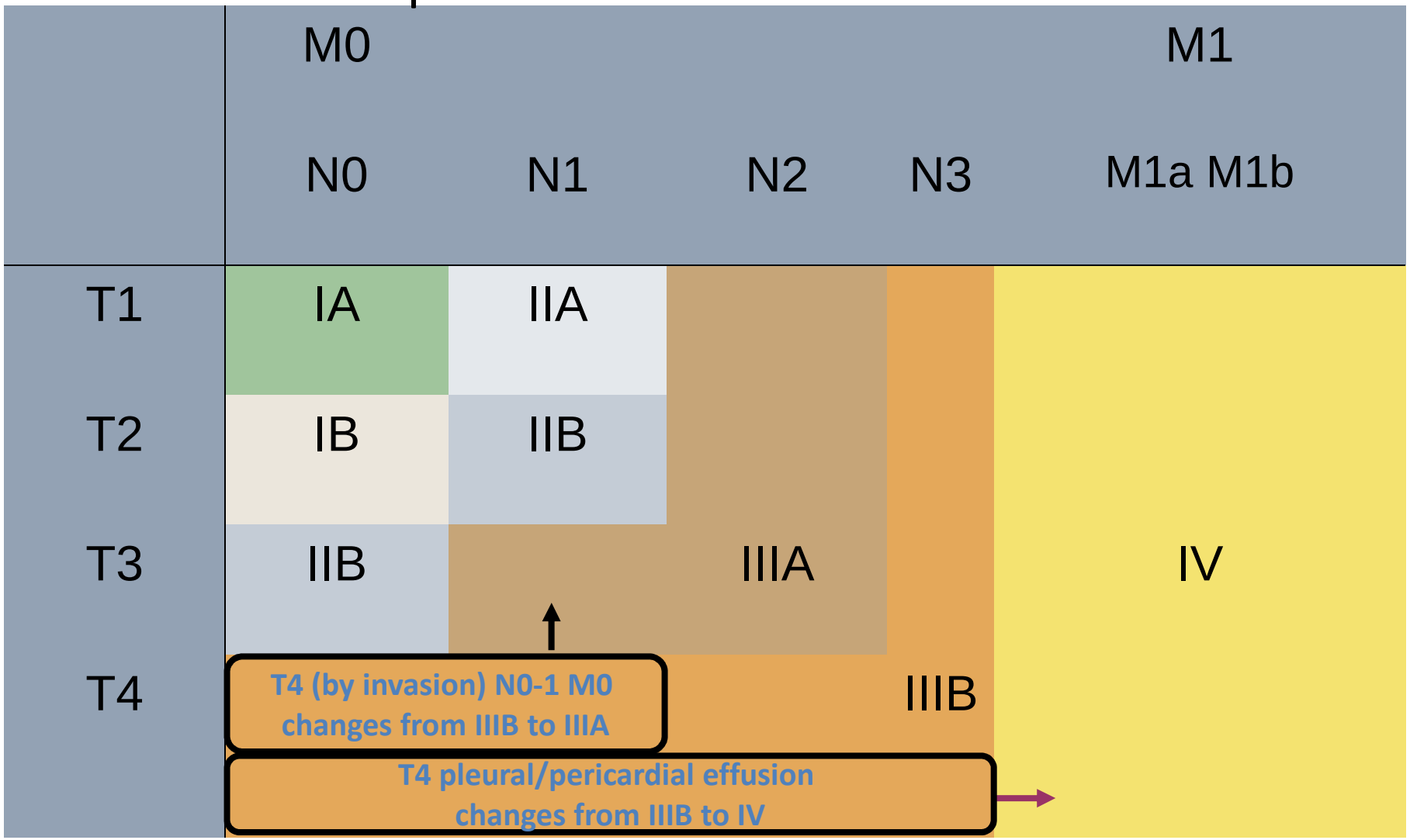
- M1 by additional nodule/s in the ipsilateral lung (different lobe) as T4.

- Pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) as M1.

Changes to the M descriptors are:

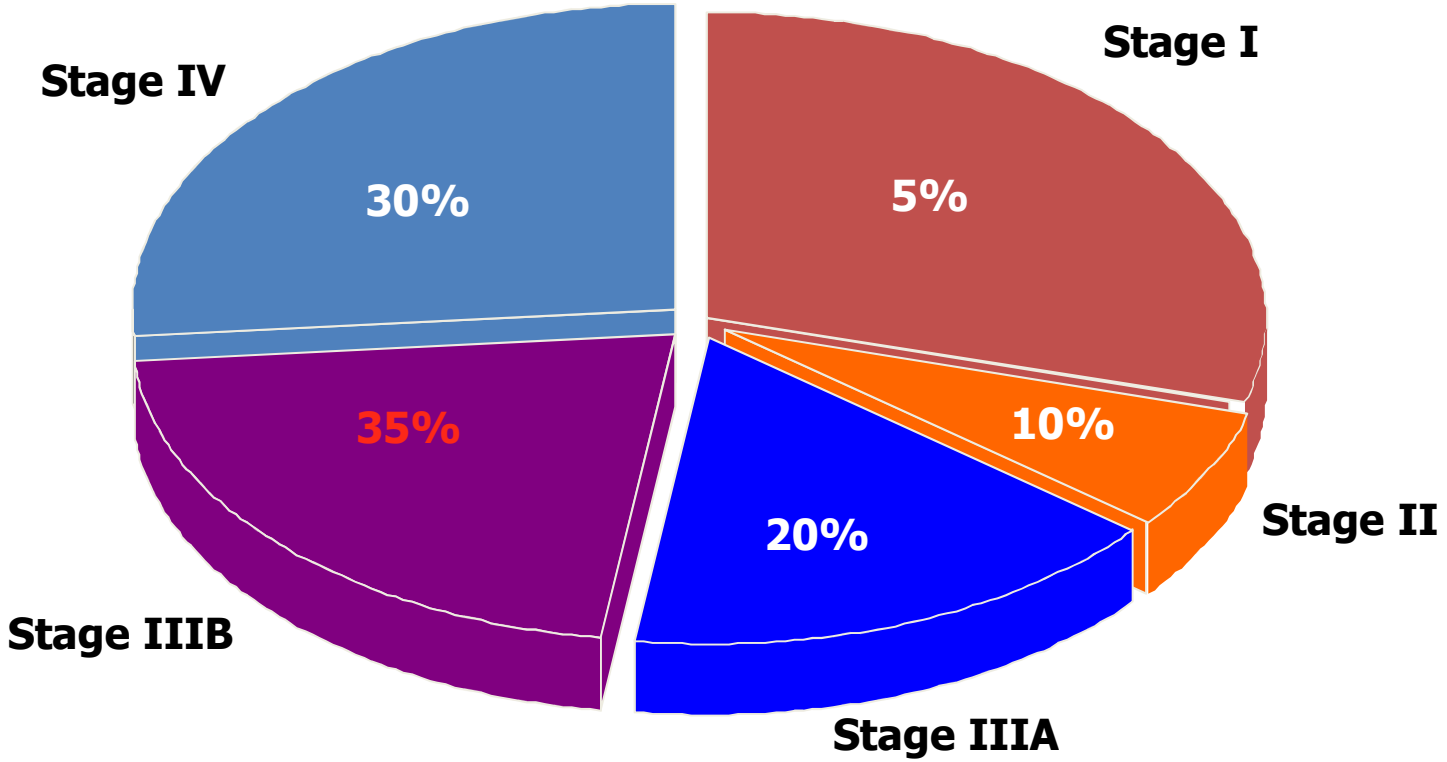
- Reclassify pleural dissemination (malignant pleural effusions, pleural nodules) from T4 to M1a.
- Sub classify M1 by additional nodules in the contra lateral lung as M1a.
- Sub classify M1 by distant metastases (outside the lung/pleura) as M1b

Current International Staging System with treatment implications for advanced NSCLC



1. Pujol JL, Chakra M. J Thorac Oncol. 2007;2:679-681. 2. Goldstraw P, et al. J Thorac Oncol. 2007;2:706-714.
3. Silvestri GA. J Thorac Oncol. 2007;2:682-683, 4. Mountain CF. Semin Surg Oncol. 2000; 18:106-115.

Indian Incidence of NSCLC by Stage appox.

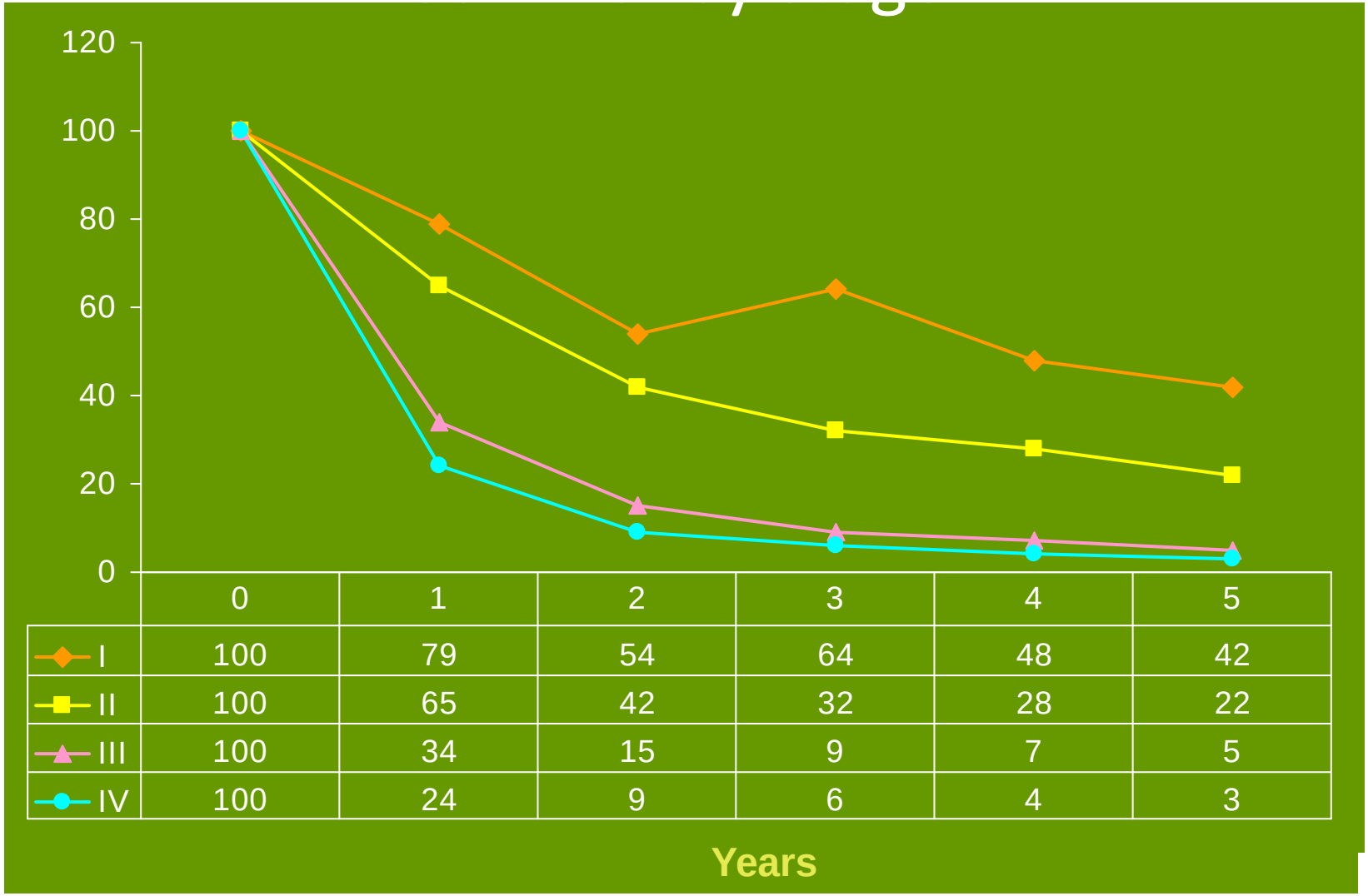


NSCLC distribution by stage and associated survival rates

NSCLC Stage	Distribution[1]	NSCLC Stage	1-Year Survival[2]	5-Year Survival[3]
I	13%–24%	IA IB	91% 72%	50% 43%
II	5%–10%	IIA IIB	79% 59%	36% 25%
III	31%–44%	IIIA IIIB	50% 37%(T4/N0-2/M0) 32%(anyT/N3/M0)	19% 7%
IV	32%–39%	IV	20%	2%

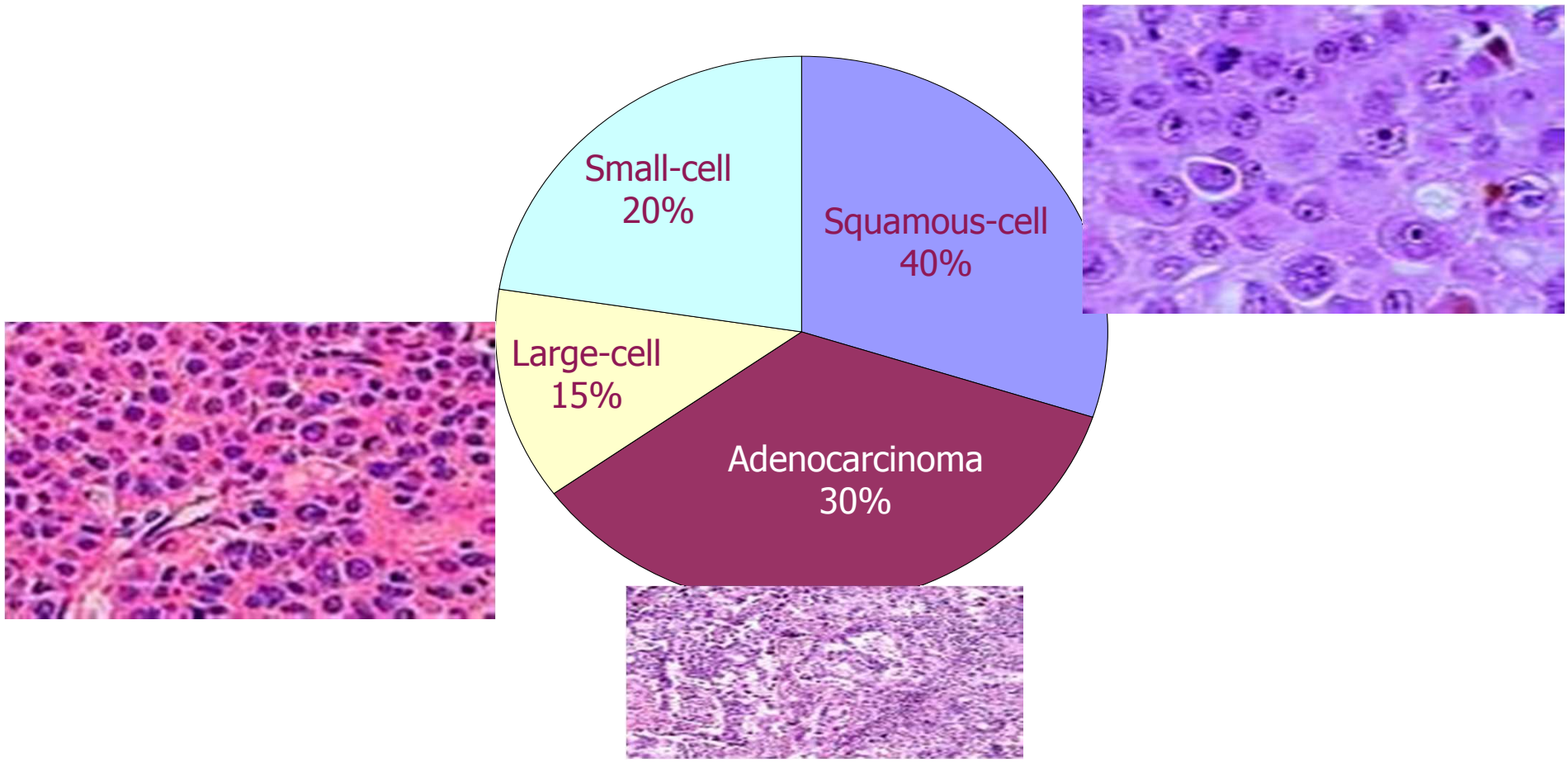
1. Bulzebruck H, et al. Cancer. 1992;70:1102-1110. 2.Mountain CF. Chest. 1997:111;1710-1717.
3. Goldstraw P. Presented at the 12th World Conference on Lung Cancer; September 5, 2007; Seoul, Korea.

NON-SMALL CELL LUNG CANCER



	0	1	2	3	4	5
I	100	79	54	64	48	42
II	100	65	42	32	28	22
III	100	34	15	9	7	5
IV	100	24	9	6	4	3

Lung Cancer TYPES



Therapeutic Classification of NSCLC

Resectable NSCLC

Stage I, II, IIIA

Unresectable NSCLC

Stage ?III A/III B

Advanced/metastatic NSCLC

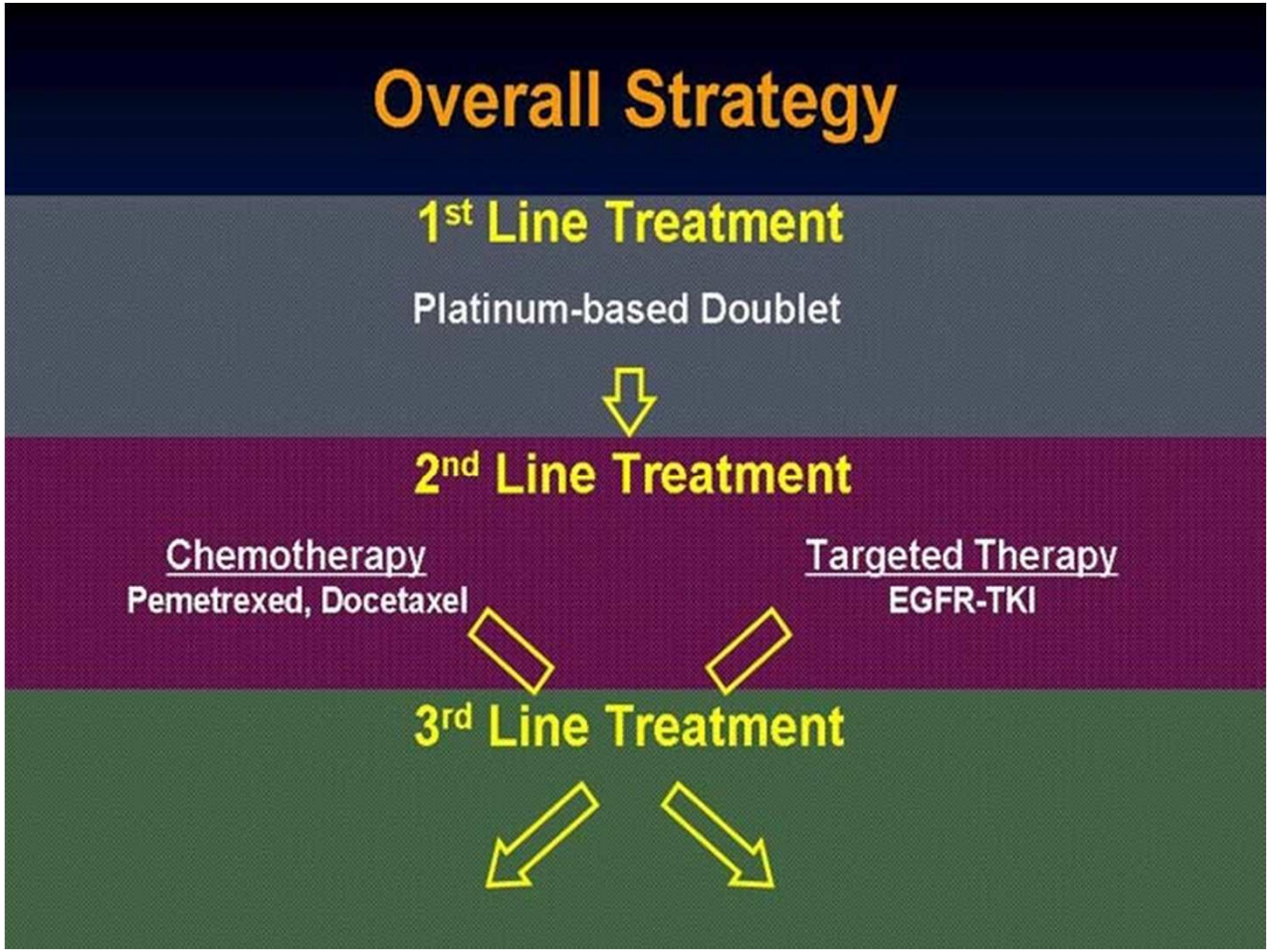
T4 any N, N3 any M

NSCLC: Treatment by Stage

Stage	Description	Treatment Options
Stage I a/b	Tumor of any size is found only in the lung	Surgery
Stage II a/b	Tumor has spread to lymph nodes associated with the lung	Surgery
Stage III a	Tumor has spread to the lymph nodes in the tracheal area, including chest wall and diaphragm	Chemotherapy followed by radiation or surgery
Stage III b	Tumor has spread to the lymph nodes on the opposite lung or in the neck	Combination of chemotherapy and radiation
Stage IV	Tumor has spread beyond the chest	Chemotherapy and/or palliative (maintenance) care

Survival in advanced NSCLC

Therapy	Median Survival (months)
Best Supportive Care	4 months
Cisplatin	6 months
Platinum-based doublet	8-10 months
Chemotherapy + Targeted Therapy	12 months


Overall Strategy
1st Line Treatment
Platinum-based Doublet
2nd Line Treatment
Chemotherapy
Pemetrexed, Docetaxel
Targeted Therapy
EGFR-TKI
3rd Line Treatment

Where We Were With Chemotherapy Before ASCO 2004

Study	Drugs	# Pts	%, St. IV	%,ORR	MST	%, 1-YS
Kelly,2001	Vnr/Cis	202	88	28	8	33
SWOG 9503	Tax225/Cb	208	89	25	8	36
Schiller,2002	Tax135/Cis	292	89	21.3	8.1	31
ECOG 1594	Gem/Cis	288	86	21	8.1	36
	Txt/Cis	293	86	17.3	7.4	31
	Tax225/Cb	290	86	15.3	8.3	35
Scagliotti,2002	Vnr/Cis	201	81	30	9.5	37
ILCP	Gem/Cis	205	81	30	9.8	37
	Tax225/Cb	201	82	32	9.9	43
Belani,2002	Vnr/Cis	404	67	25	10.1	41
TAX 326	Txt/Cis	408	67	32	11.3	46
	TxT/Cb	402	67	24	9.4	38

Summary: Outcome

	IP	TC	GP	NP
MST (months)	14.2	12.3	14.8	11.4
1 year survival (□)	59	51	60	48
TTP (months)	4.7	4.5	4.0	4.1
Response Rate (□)	31	32	30	33

Kubota K. et al. Proc. ASCO 2004

Results: Overall Survival

Result	Overall Survival
Median, mos	
Gem/platinum	9
Platinum comparators	8.2
Hazard ratio	**0.90 (0.84-0.96)***
	P<0.001
Absolute benefit	**3.9% (year 1)**

***Statistically significant reduction in favor of gem-based arms**

Overall Strategy

1st Line Treatment

Platinum-based Doublet

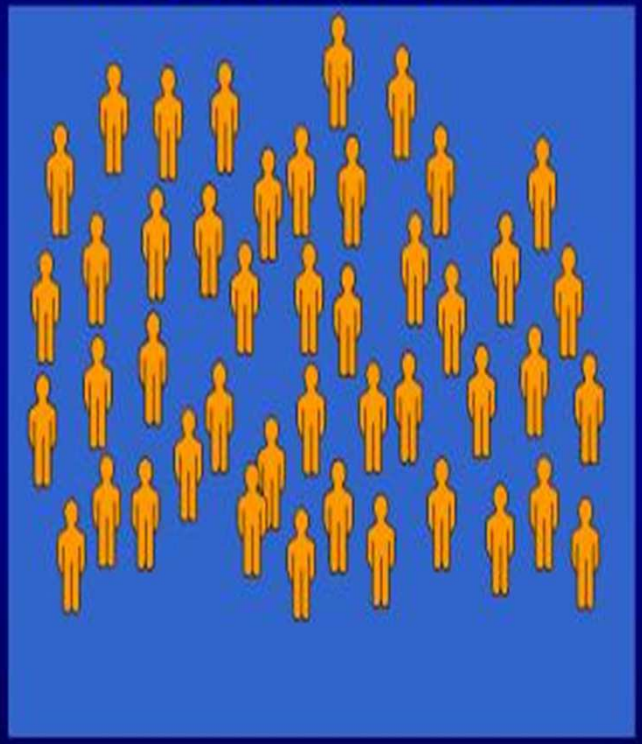
Gemzar + platinum may be the best 1st line treatment.

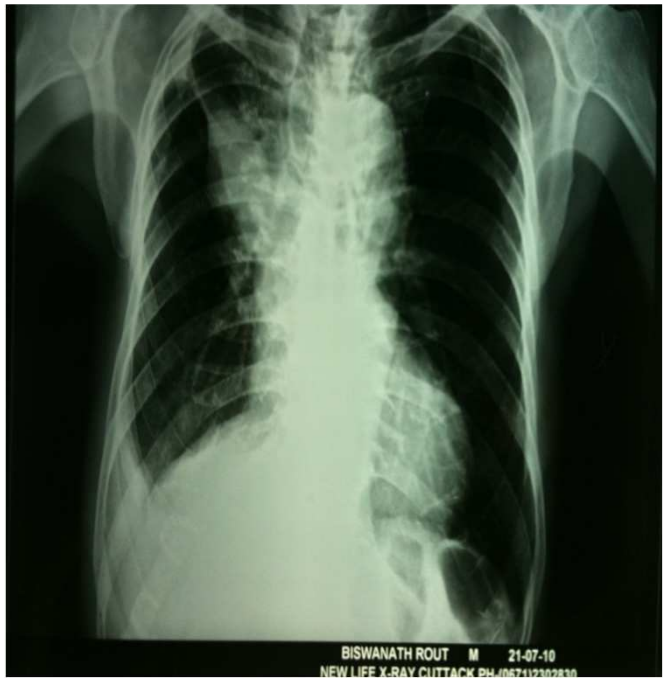
- It is the most widely and extensively tested regimen in the world….treatment outcomes have been universally consistent.
- A meta-analysis of 13 randomized clinical trials indicate a statistically significant ↑PFS and a slightly ↑OS.
- Side effects among the best tolerated of any 1st line regimen.
- 1st line treatment may affect 2nd line efficacy

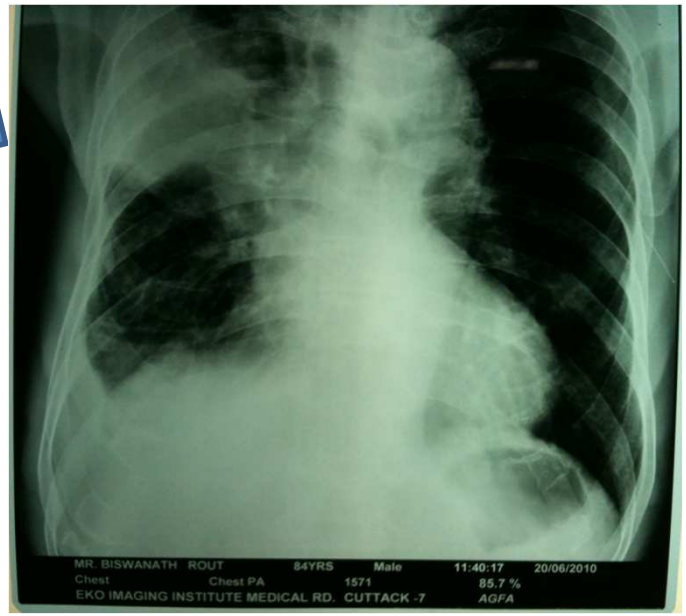
Exploiting the Tumor Molecular Profile of Individual Patients for Selection of Therapy

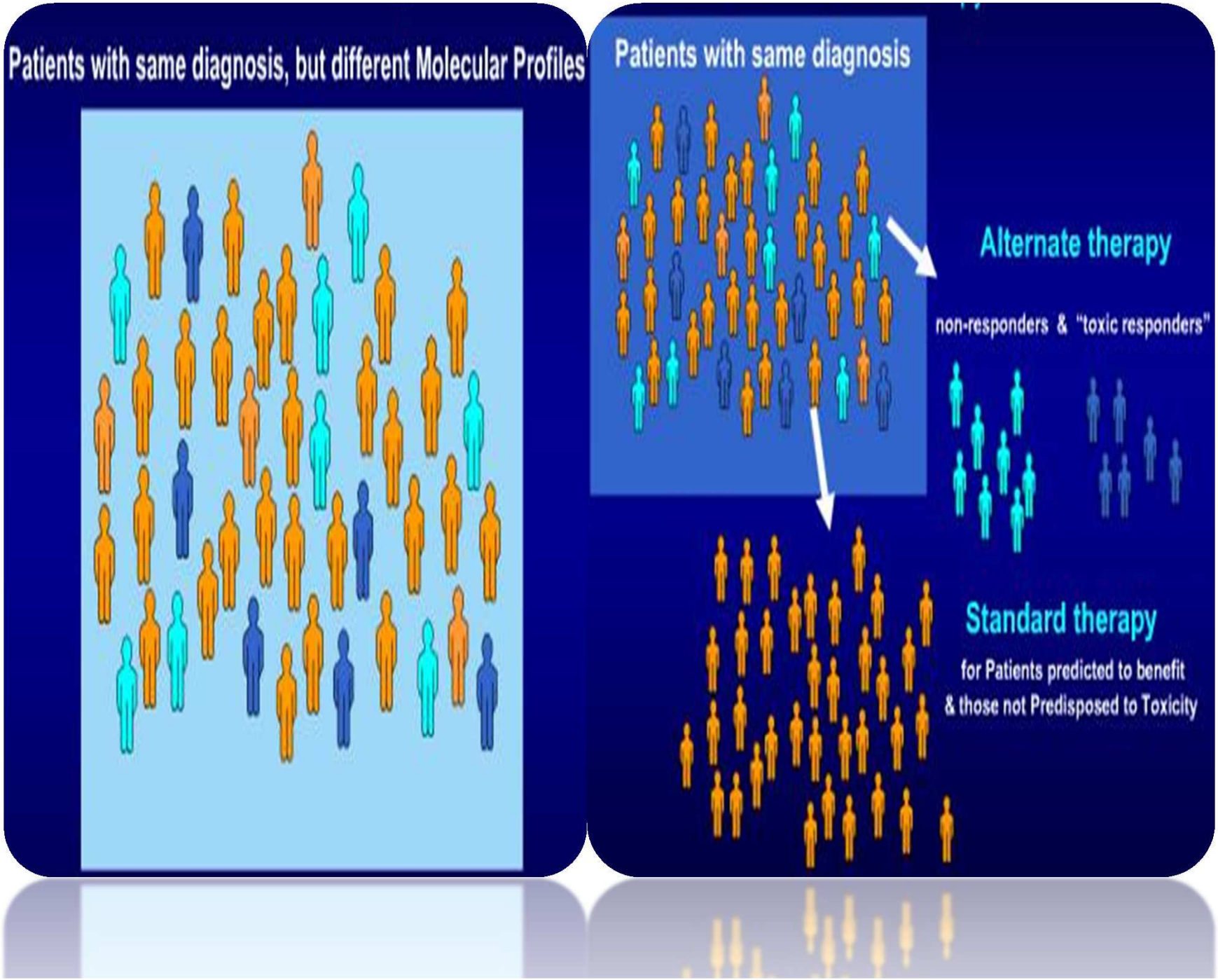
Patients with the same Diagnosis &Clinical Features

(Stage IV Non-small Cell Lung Cancer)








Patients with same diagnosis, but different Molecular Profiles
Patients with same diagnosis
Alternate therapy
non-responders & "toxic responders"
Standard therapy
for Patients predicted to benefit
& those not Predisposed to Toxicity

Main Molecular Markers in Lung Cancer

MARKERS OF CARCINOGENESIS

- Growth-Regulating Proteins (K-ras, EGFR, HER2/neu)
- Cell-Cycle Specific Proteins (p53,bcl2, RB, p16, FHIT)

MARKERS OF TUMOR INVASION

- Angiogenesis
- Invasion/extracellular Matrix Degradation

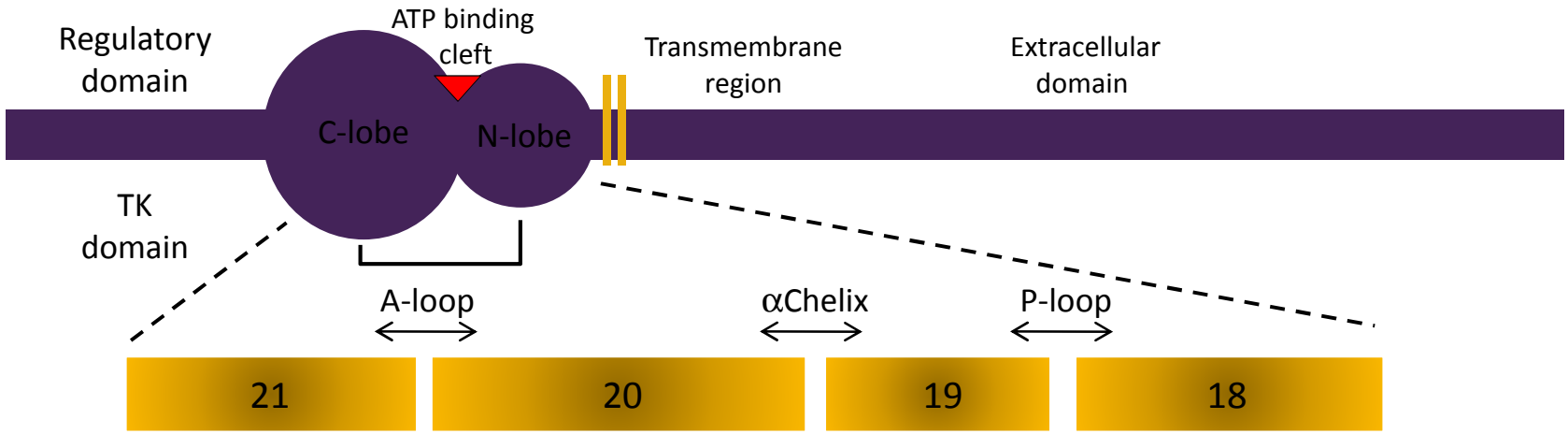
MARKERS OF METASTASES

- Adhesion Molecules
- Blood Group Antigens & Precursors

MARKERS OF PROLIFERATION

- Mitotic Index/Ploidy, PCNA, KI67

The distribution of activating mutations among EGFR mutation positive patients is similar in Asian and non-Asian studies

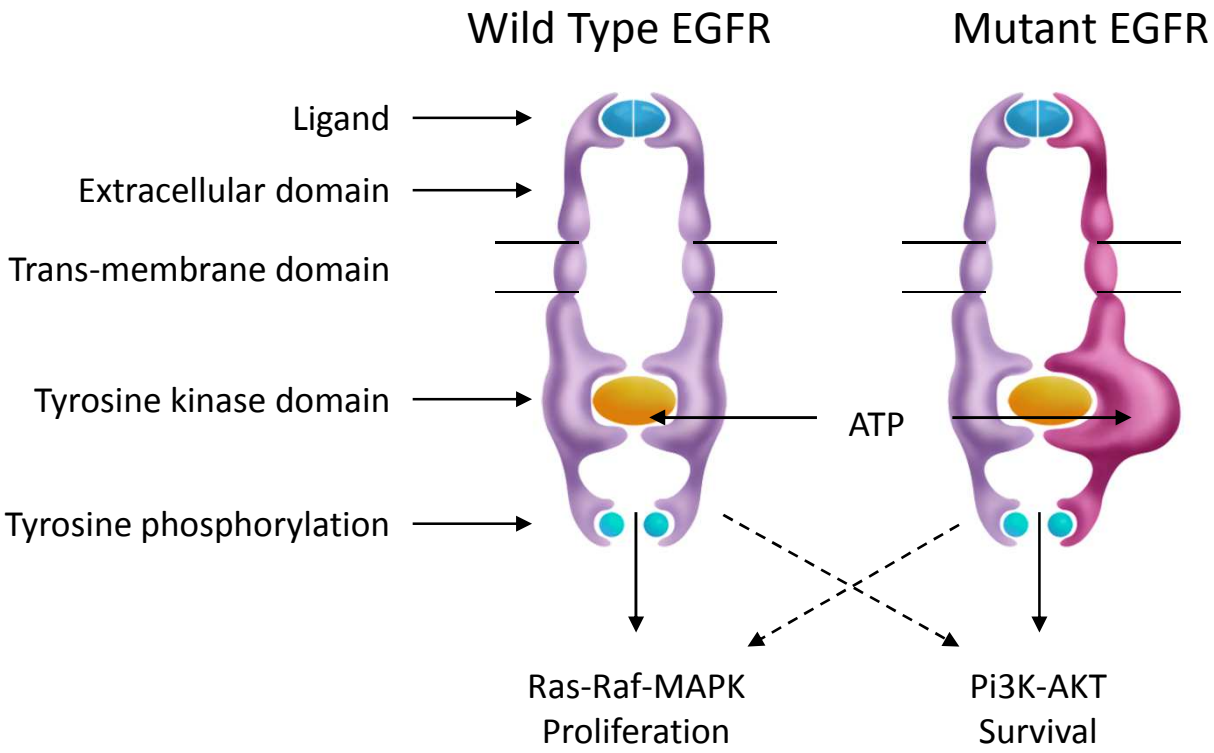


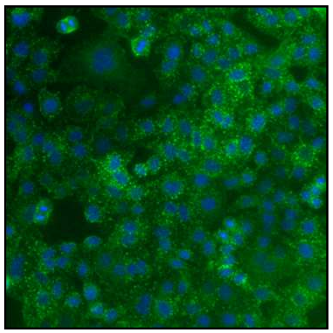
Distribution of mutation types (% of mutations)		
Literature review	Asian studies	Non-Asian studies
Most prevalent mutation types	Literature (n=1523)	Literature (n=583)
Exon 19 deletion	51%	58%
Exon 21 point mutation L858R	42%	32%
Exon 20	2%	6%
Exon 18 G719A/C	3%	2%
Exon 21 L861Q	1%	1%

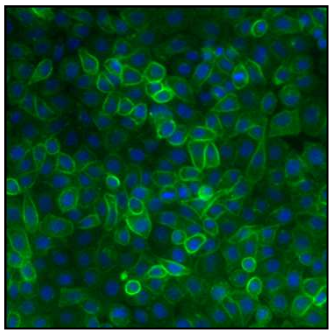
Some patients had more than one mutation type

AstraZeneca data on file 2009

EGFR mutation causes conformational change and increased activation







EGFR internalisation
Degradation/recycling

EGFR signals for longer
at the cell membrane

Arteaga 2006, Gadzar et al 2004, Hendricks et al 2006, Sordella et al 2004

Recommendations for tumour samples for EGFR mutation analysis

- **Tumour biopsy from primary tumour or metastases is the "gold standard" for mutation analysis**
  - **It is recommended that DNA samples are extracted from formalin-fixed, paraffin-embedded tumour biopsy diagnostic samples**
  - **Robust well validated DNA extraction methodologies are recommended to avoid assay failures and false negative results**
  - **Mutation testing in surrogate tissues such as serum/plasma, bronchoalveolar lavage fluid or cytology specimens is not currently recommended**

Eberhard et al 2008, Kimura et al 2006

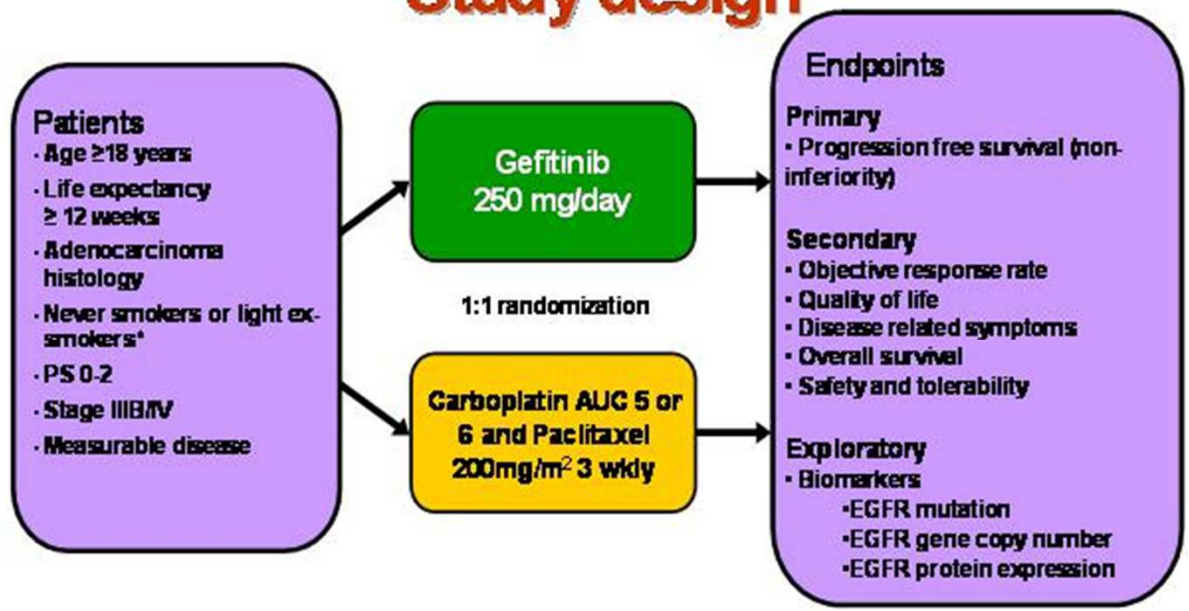
EGFR mutation positive status and clinical characteristics

Overall EGFR mutation positive rate = 59.7% (261 / 437)

Mok T, ESMO 2008

IPASS (Iressa Pan Asia Study)

Study design



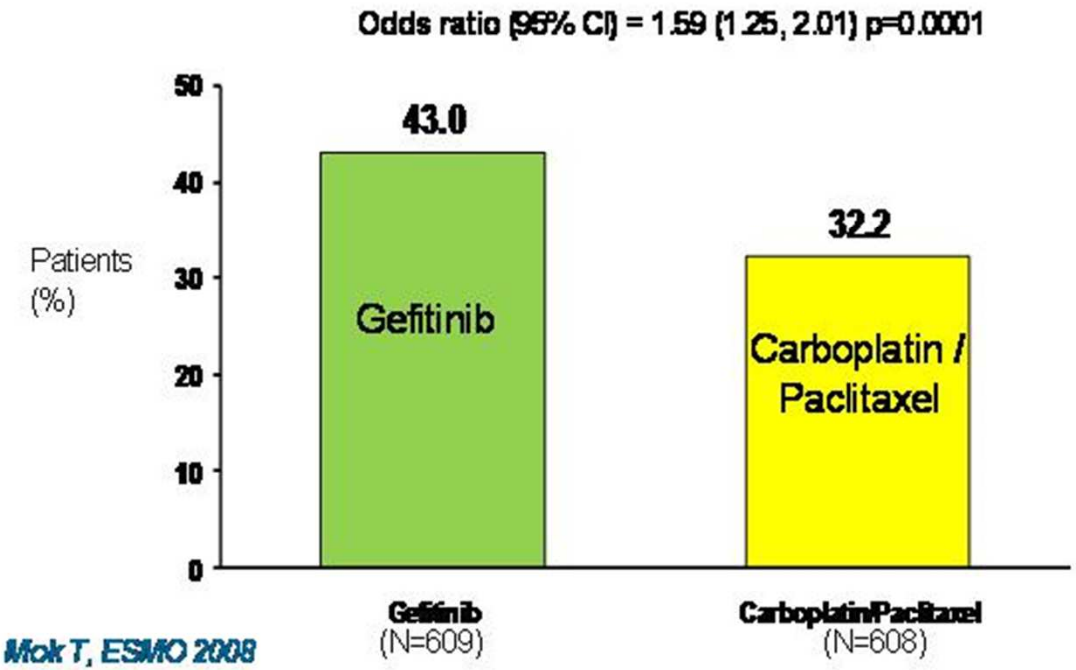
*Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ≥15 years ago and smoked ≤10 pack yrs

Carboplatin/paclitaxel was offered to gefitinib patients upon progression

PS, performance status; EGFR, epidermal growth factor receptor

IST

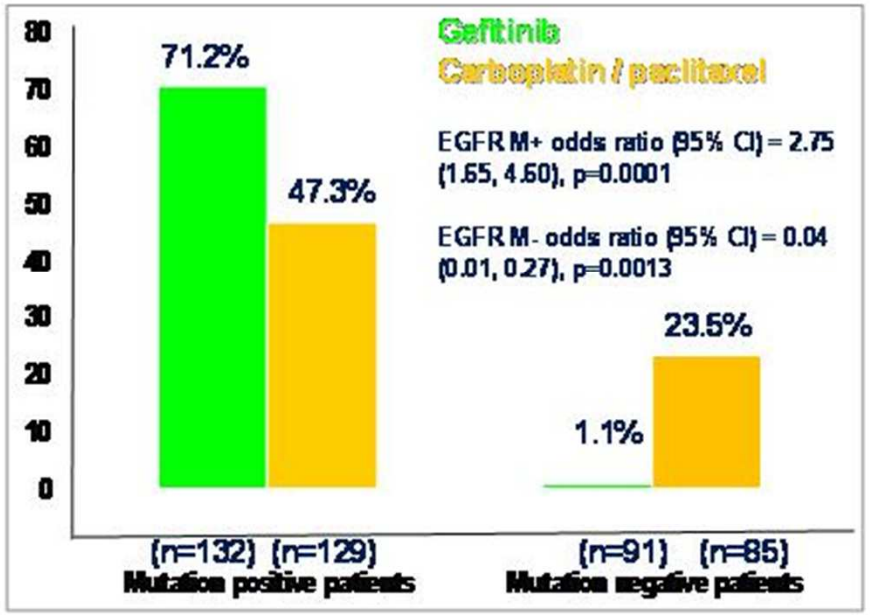
Objective tumour response (RECIST) (ITT population)



Mok T, ESMO 2008

IST

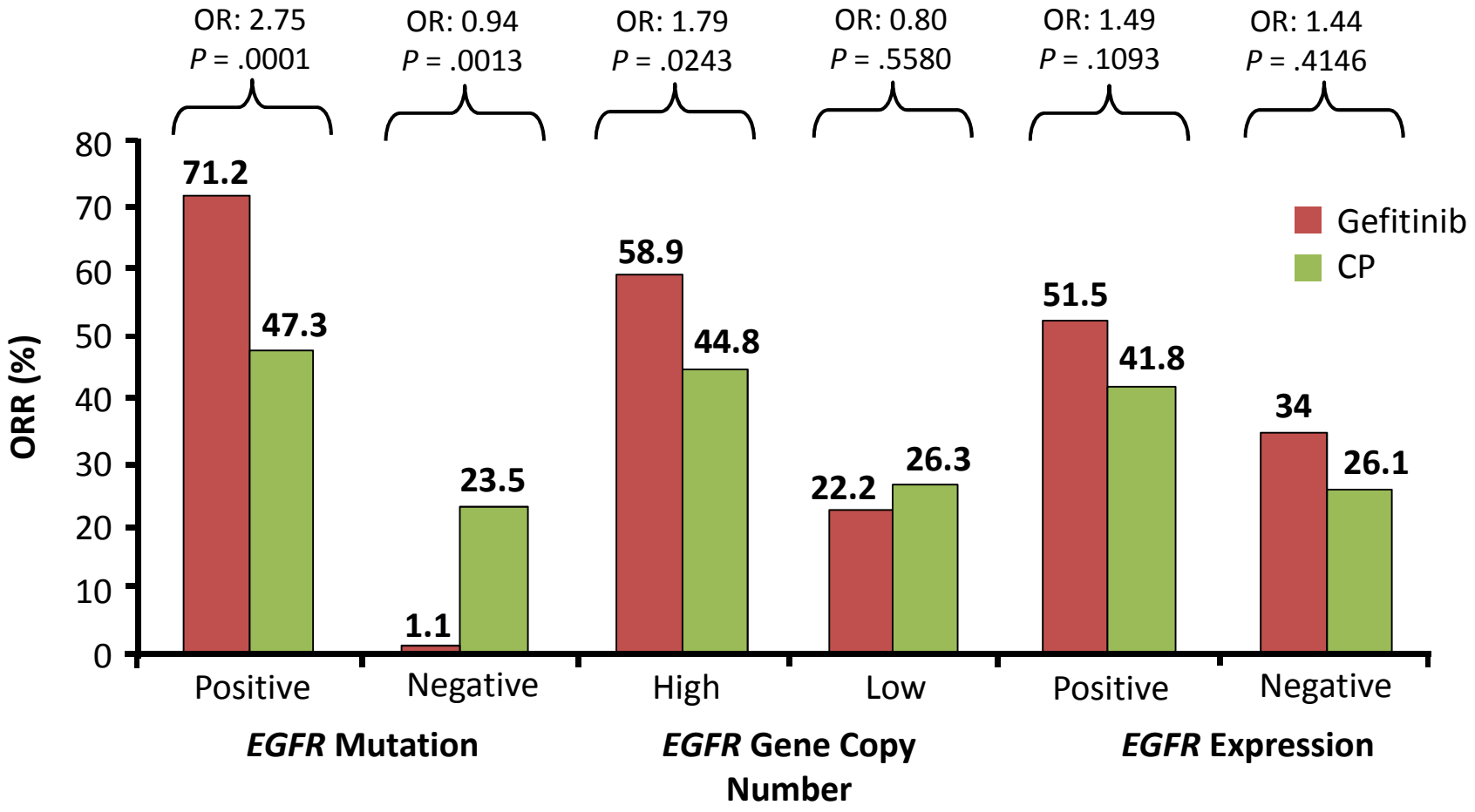
IPASS trial: EGFR mutation is a prognostic factor for response to CT



Odds ratio >1 implies greater chance of response on gefitinib

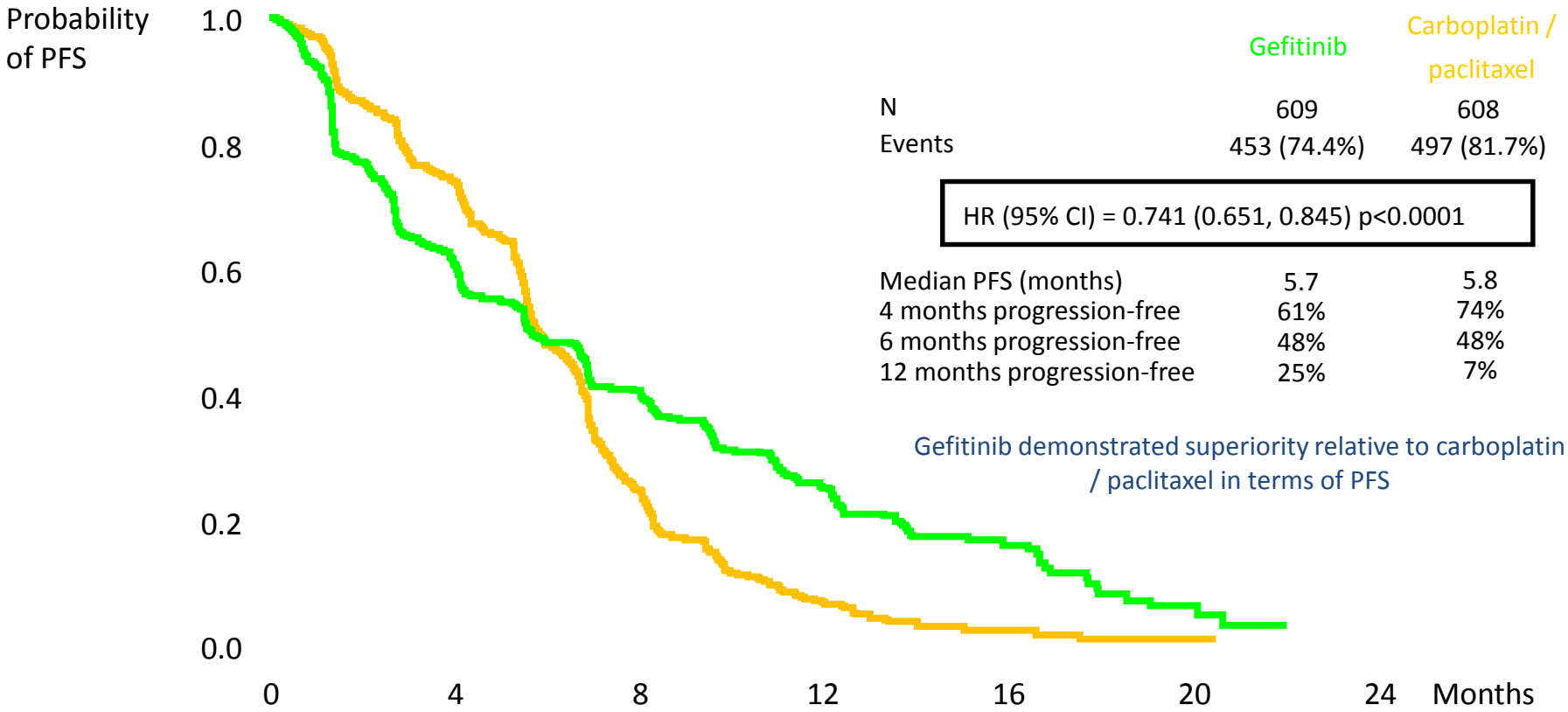
Mok T, ESMO 2008

IPASS Ph III Study: First-Line Gefitinib vs CP in Advanced NSCLC: ORR



Fukuoka M, et al. ASCO 2009. Abstract 8006.

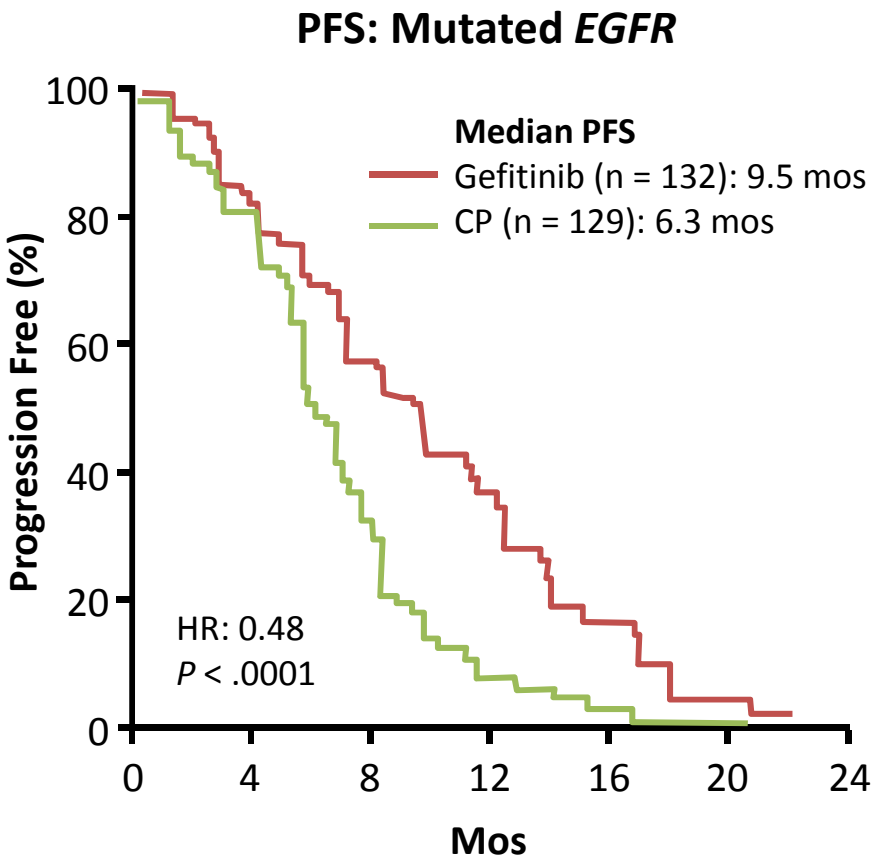
IPASS: Progression-free survival in ITT population

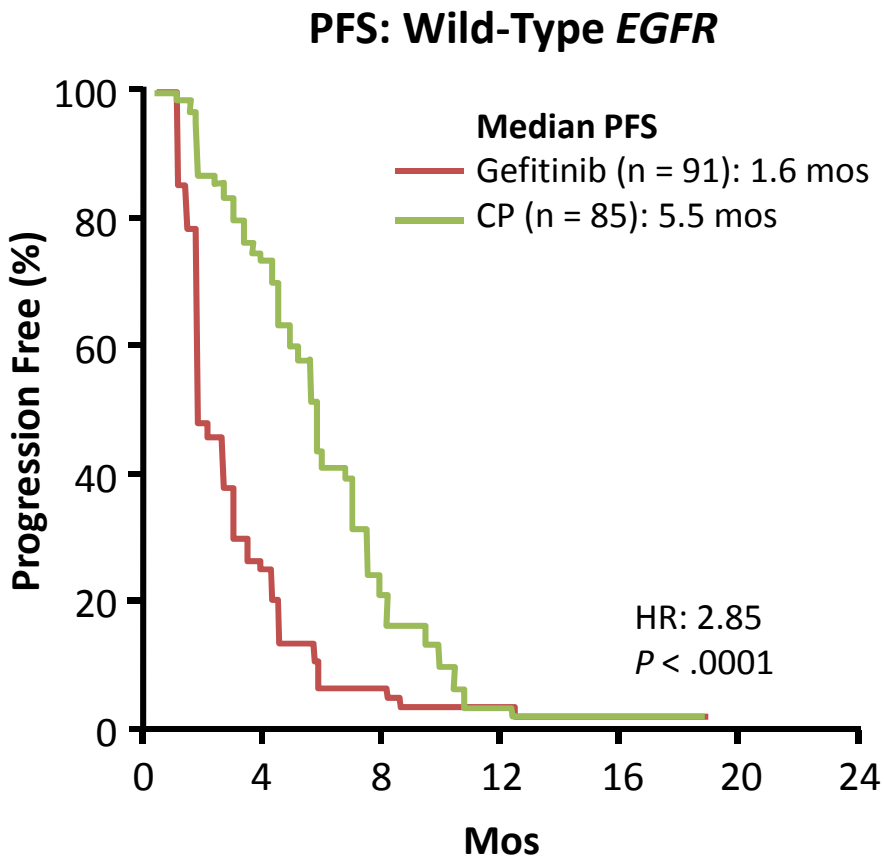


Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

Mok et al ESMO LBA 2, 2008

IPASS: First-line Gefitinib vs CP in Advanced NSCLC: PFS





Treatment by EGFR mutation status interaction test, *P* < .0001

Fukuoka M, et al. ASCO 2009. Abstract 8006.

Progression-Free Survival by Biomarker Status

	N	PFS Hazard Ratio*	P-value	PFS Interaction by Subgroup**
EGFR mutation status				
M+	261	**0.48**	<0.0001	
M-	176	**2.85**	<0.0001	<0.0001
M-unknown	780	0.68	<0.0001	
EGFR-gene-copy number				
FISH+	249	0.66	0.0050	
M+	190	**0.48**	--	
M-	55	**3.85**	--	
FISH-	157	1.24	0.2368	0.0437
FISH-unknown	811	0.70	<0.0001	
EGFR protein expression				
PE+	266	0.73	0.0243	
PE-	99	0.97	0.8932	0.2135
PE-unknown	852	0.73	<0.0001	

*HR < 1.0 favors gefitinib; **HR in biomarker-positive vs HR in biomarker-negative

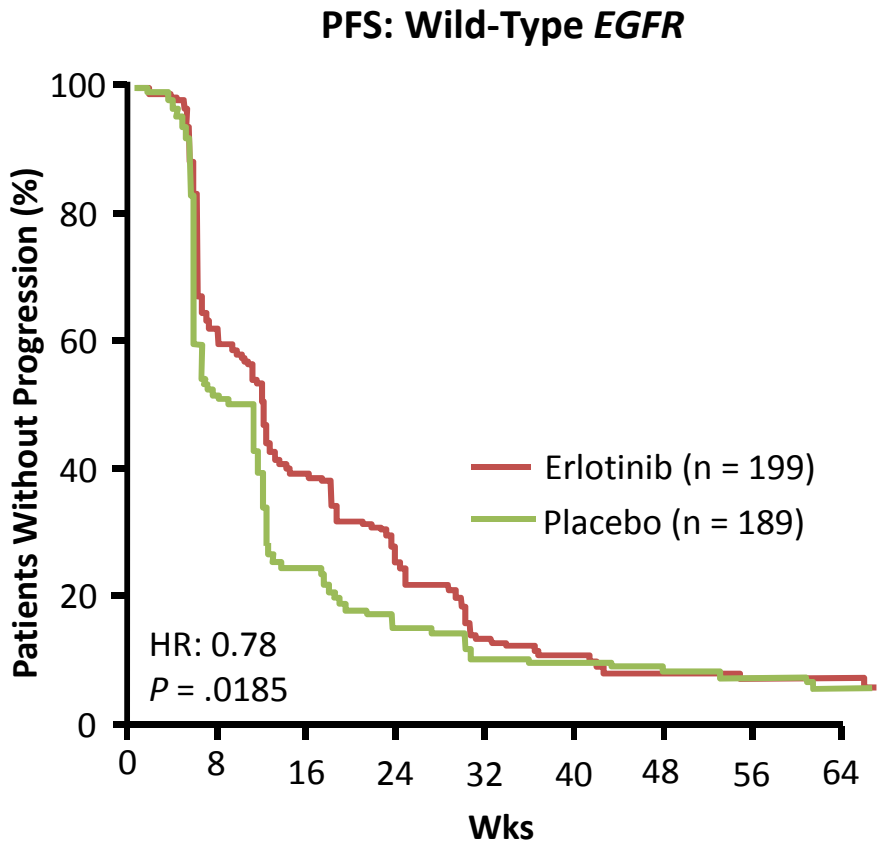
Source: Fukuoka M et al. *ASCO* 2009; Abstract 8006.

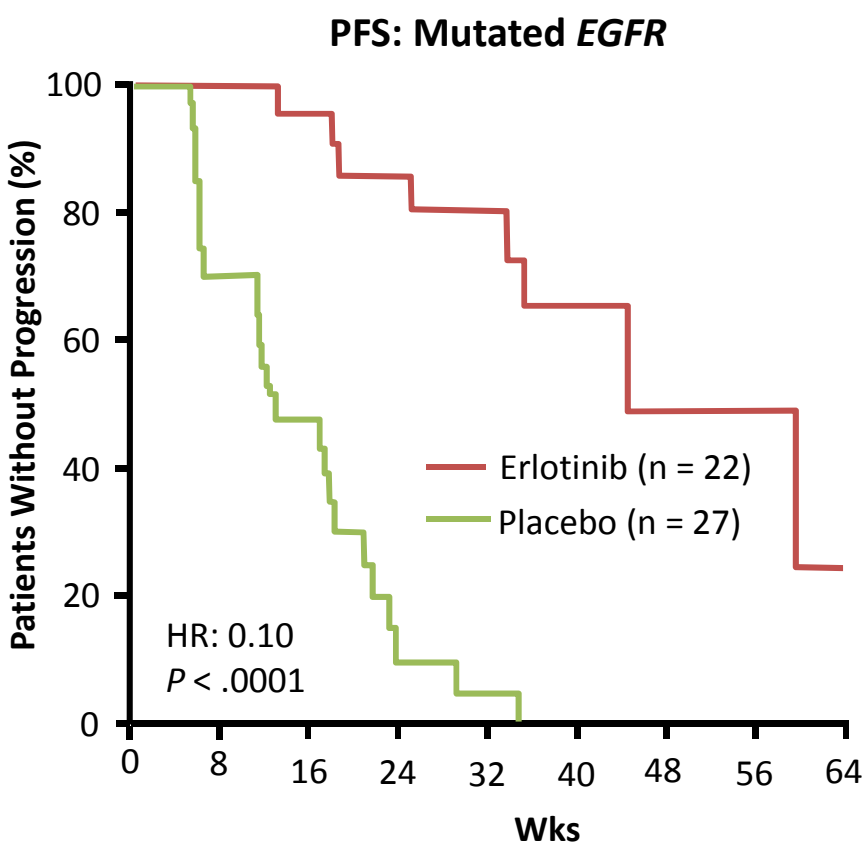
Summary and Conclusions

- **EGFR mutation status:** a strong predictive biomarker for a differential PFS and ORR benefit with first-line G versus C/P in clinically selected patients (Interaction by subgroup, $p < 0.0001$)
  - PFS: (M+ HR = 0.48, $p < 0.0001$, M- HR = 2.85, $p < 0.0001$)
  - ORR: (M + OR = 2.75, $p = 0.0001$, M- OR = 0.04, $p = 0.0013$)
- **EGFR-gene-copy number:** trended toward being predictive of a differential PFS (Interaction by subgroup, $p = 0.0437$)
  - Post hoc explorations suggest that the PFS benefit to gefitinib was driven by the overlap of high EGFR-gene-copy number with a positive EGFR mutation status
  - PFS: High EGFR-gene-copy, M+ HR = 0.48
  - PFS: High EGFR-gene-copy, M- HR = 3.85
- **EGFR protein expression:** least differentially predictive

Source: Fukuoka M et al. *ASCO* 2009; Abstract 8006.

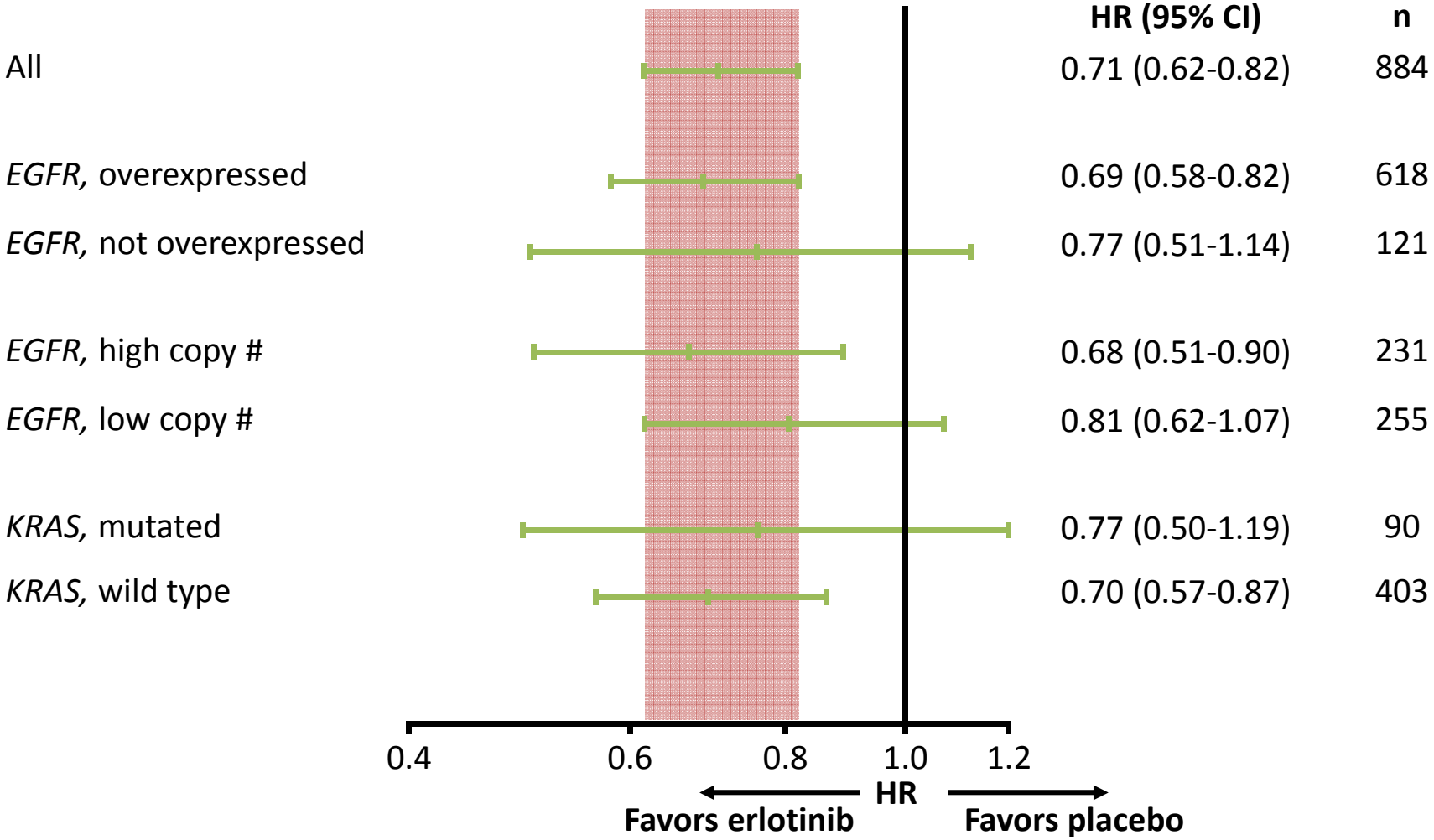
SATURN Ph III: Strong PFS Benefit for Erlotinib Maintenance With Mut *EGFR*





Cappuzzo F, et al. ASCO 2009. Abstract 8001. Brugger W, et al. ASCO 2009. Abstract 8020.

SATURN Phase III Study: PFS by Biomarker Status



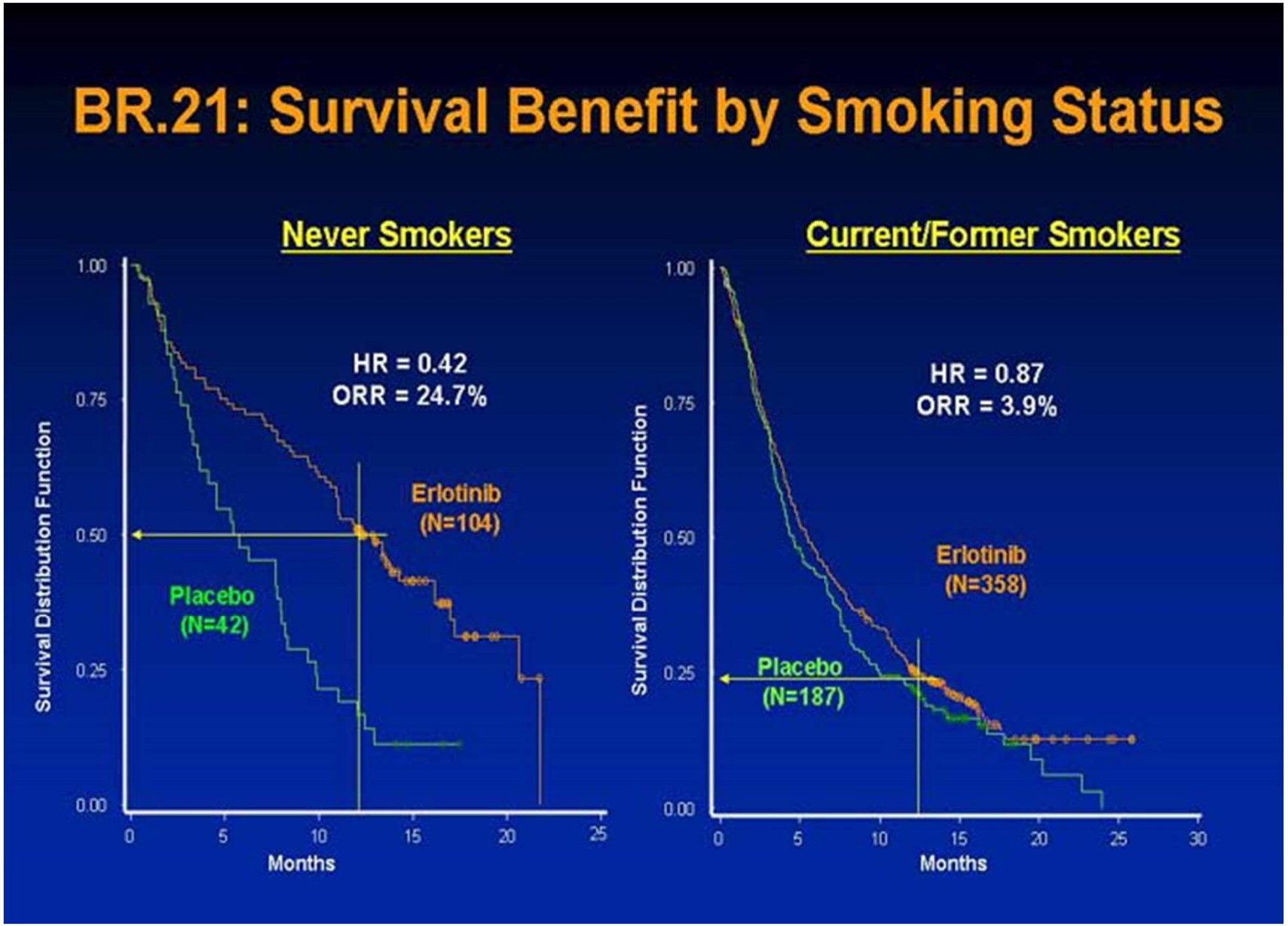
Brugger W, et al. ASCO 2009. Abstract 8020.

SATURN Study: Biomarker Analysis Conclusions

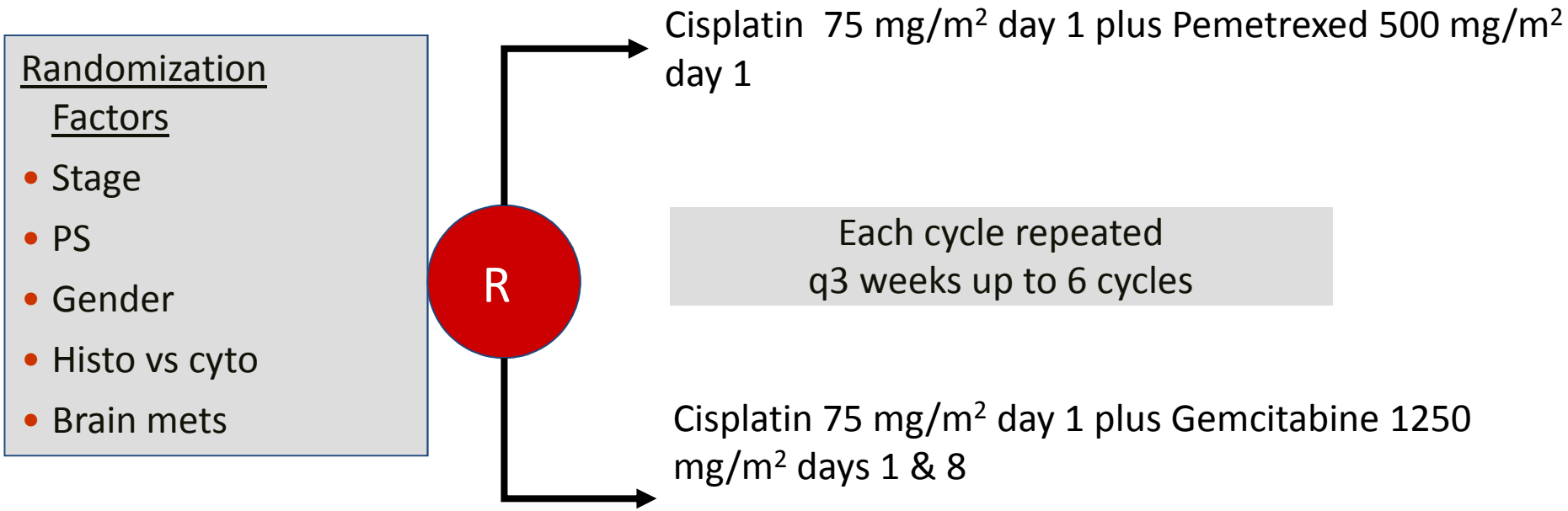
- ***EGFR* overexpression and *EGFR* gene copy number do not have adequate predictive power to guide selection of NSCLC patients for erlotinib maintenance therapy**
- **Erlotinib significantly improves PFS in NSCLC patients with mutated *EGFR***
  - **Patients with wild-type *EGFR* benefited to a much lesser degree**
- ***KRAS* mutations not predictive for erlotinib outcomes**
  - **Strong negative prognostic factor**

Brugger W, et al. ASCO 2009. Abstract 8020.

BR.21: Survival Benefit by Smoking Status



JMDB: Pemetrexed vs Gemcitabine in advanced NSCLC (Phase III, first line)

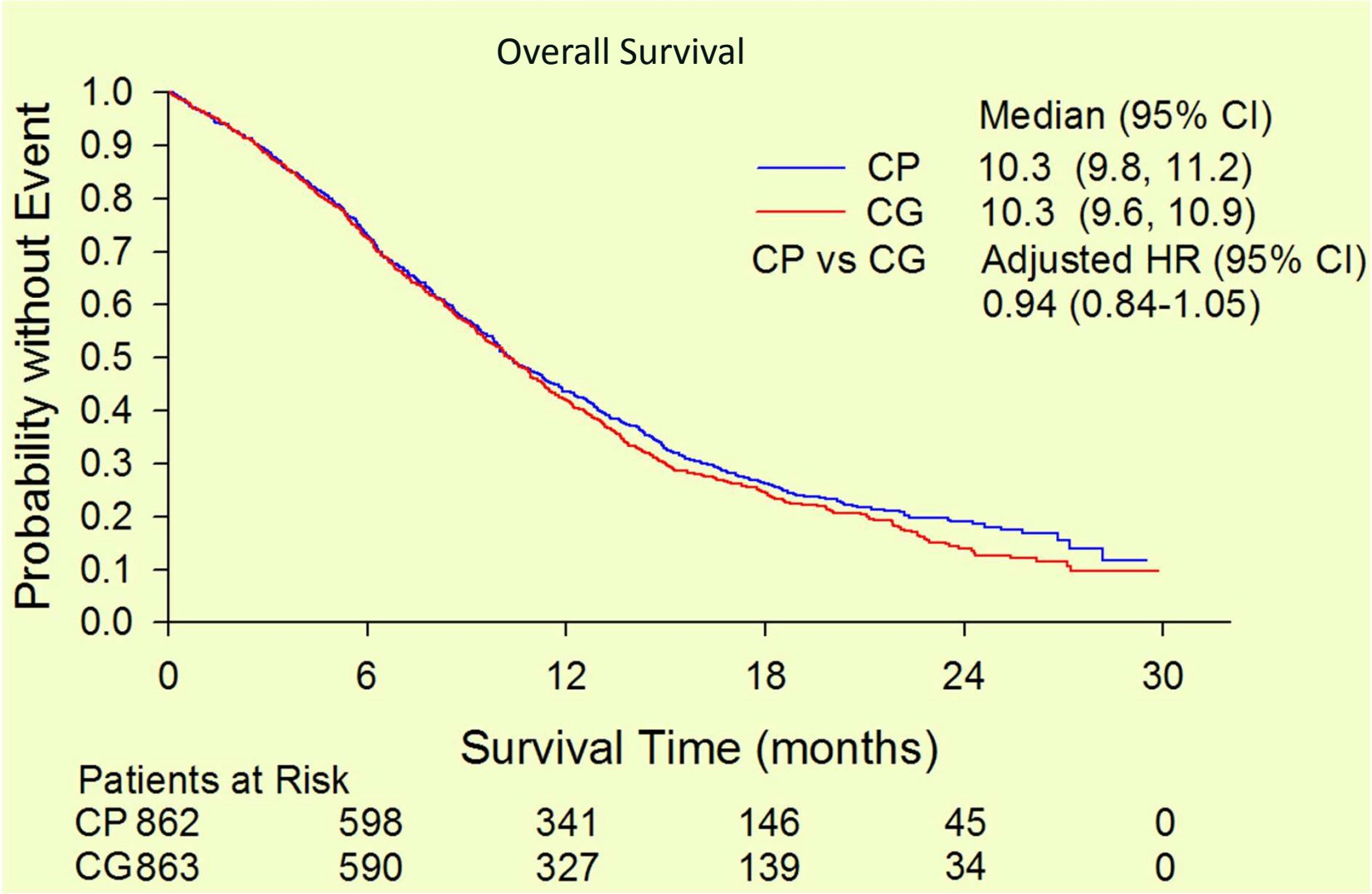


Vitamin B_{12}, folate, and dexamethasone given in both arms

Primary endpoint: survival; non-inferiority design

Scagliotti et al J Clin Oncol, 26, 3543-3551, 2008

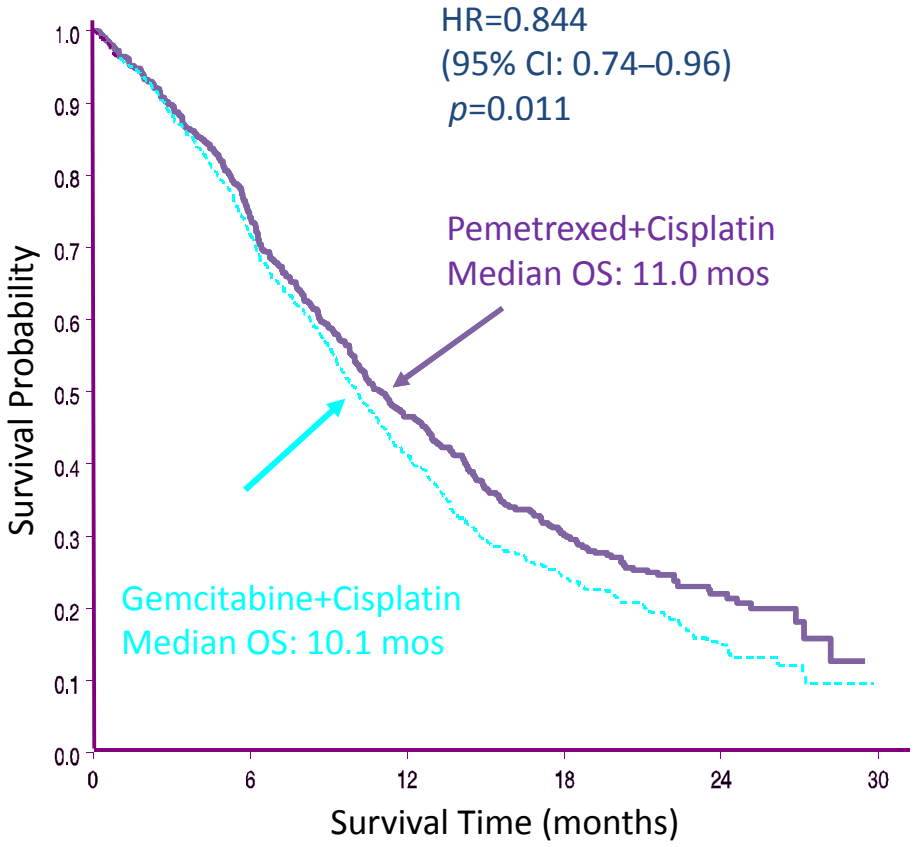
JMDB: Pemetrexed vs Gemcitabine in advanced NSCLC (Phase III, first line)



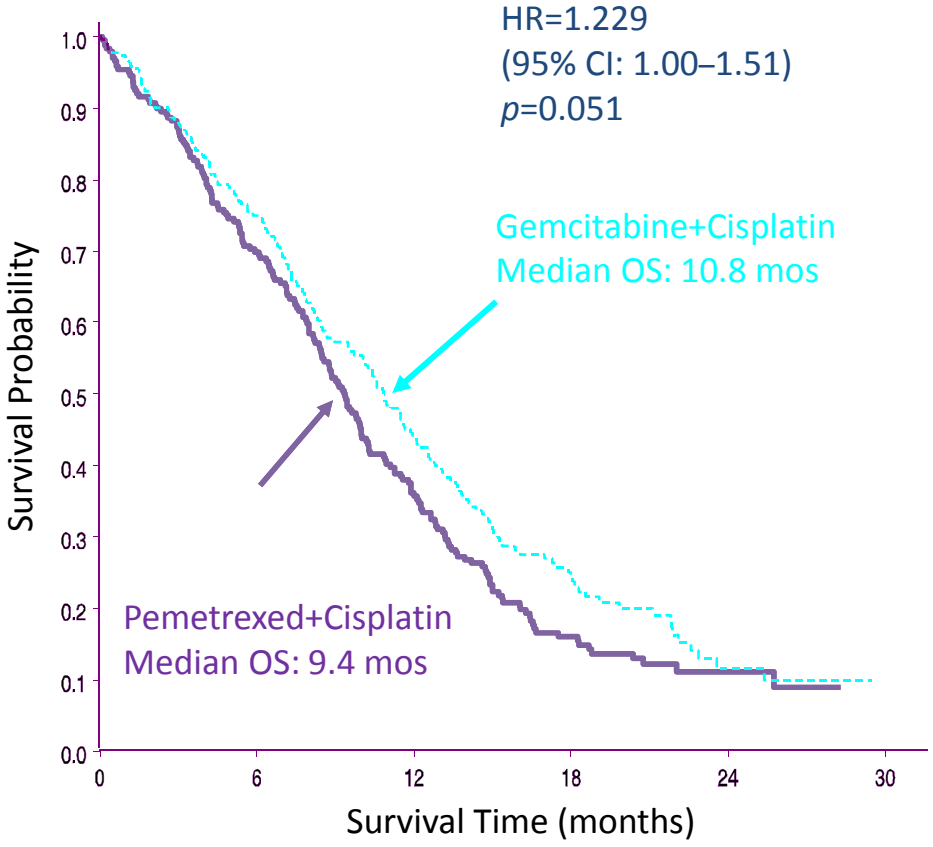
Scagliotti et al J Clin Oncol 26, 3543-3551, 2008

JMDB: Pemetrexed vs Gemcitabine in advanced NSCLC (Phase III, first line)

Nonsquamous* (n=1252)



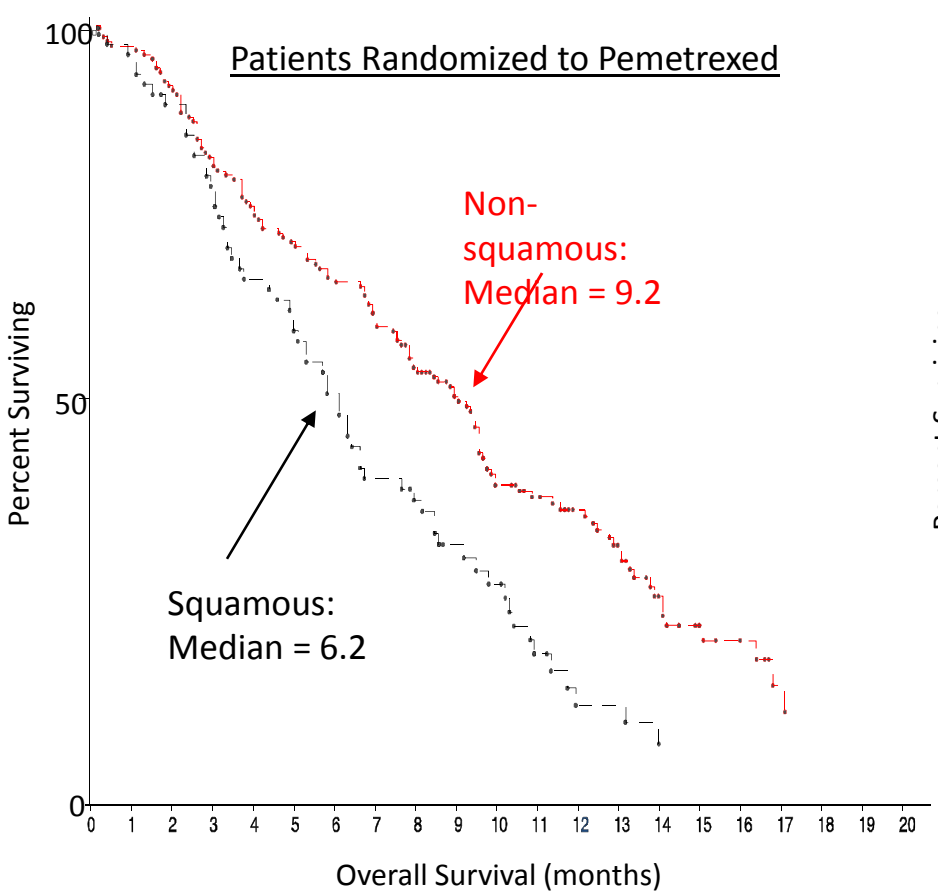
Squamous (n=473)

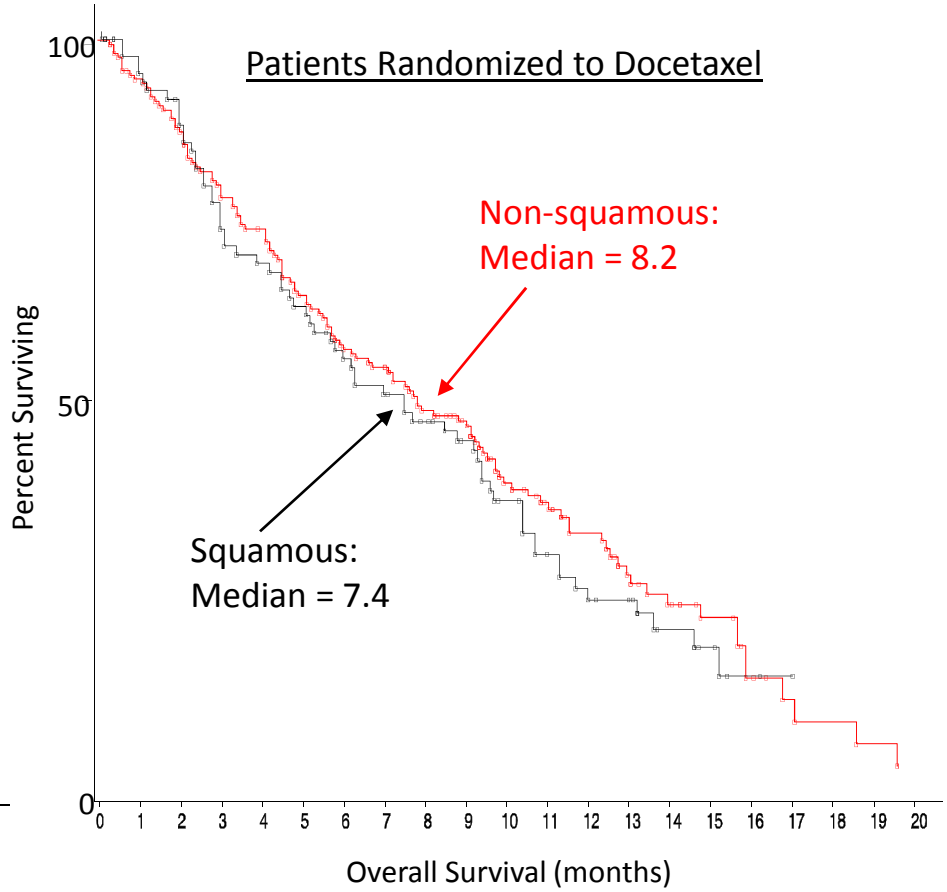


Scagliotti et al J Clin Oncol, 26, 3543-3551, 2008

NSCLC: Pemetrexed is more effective in patients with non-squamous tumors

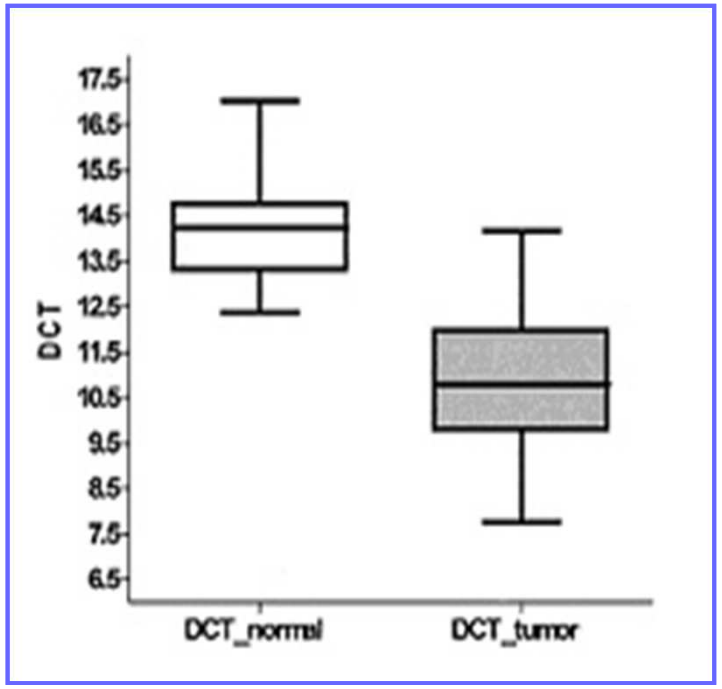
(retrospective analysis of Pem vs Doc)

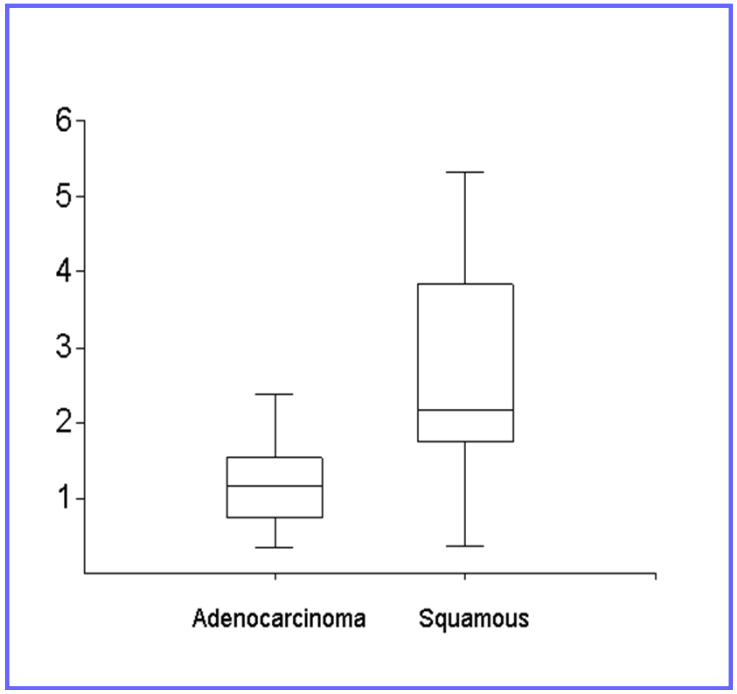




Peterson et al., JTO 2, 8 (suppl4), 851 (Abstr. P2-328), 2007

Thymidilate Synthase Expression in Normal Lung Tissue & Lung Cancer





Clinically relevant survival advantage favoring PEMETREXED/cisplatin in adenocarcinoma and large cell carcinoma

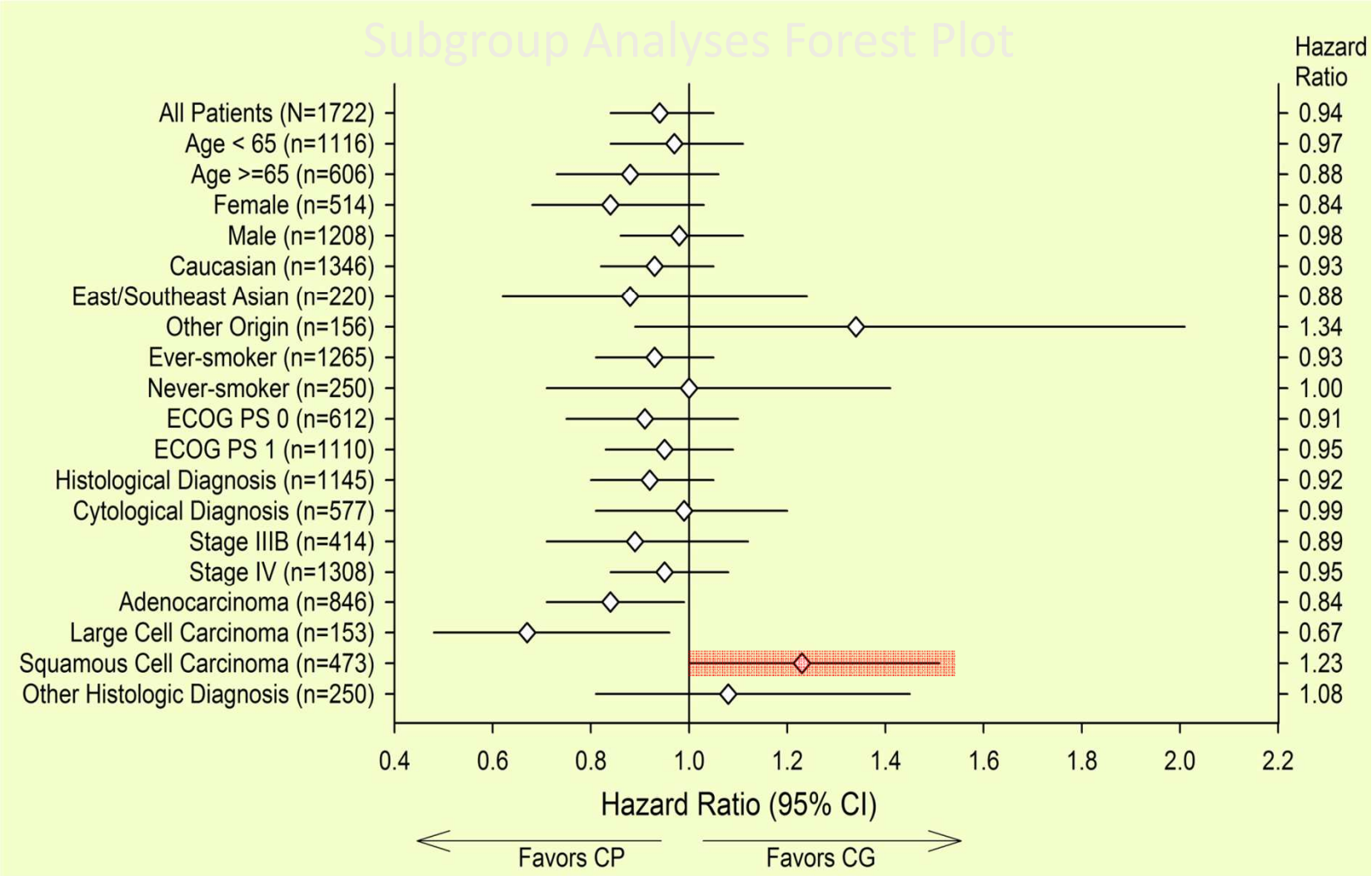
Median overall survival by histologic group (months)	PEMETREXED/CIS (N=862)	GEMCITABINE/CIS (N=863)	Adjusted Hazard ratio (95% CI)	p-Value[a]
Adenocarcinoma (N=847)	12.6	10.9	0.84 (0.71, 0.99)	0.033
Large cell carcinoma (N=153)	10.4	6.7	0.67 (0.48, 0.96)	0.027
Other[b] (N=252)	8.6	9.2	1.08 (0.81, 1.45)	0.586
Squamous cell carcinoma (N=473)	9.4	10.8	1.23 (1.00, 1.51)	0.050

[a]Superiority p-values.
[b]Patients whose histologic diagnosis did not clearly qualify as adenocarcinoma, large cell carcinoma, or squamous cell carcinoma.

Abbreviations: CIS=cisplatin; CI=confidence interval

Scagliotti et al J Clin Oncol, 26, 3543-3551, 2008

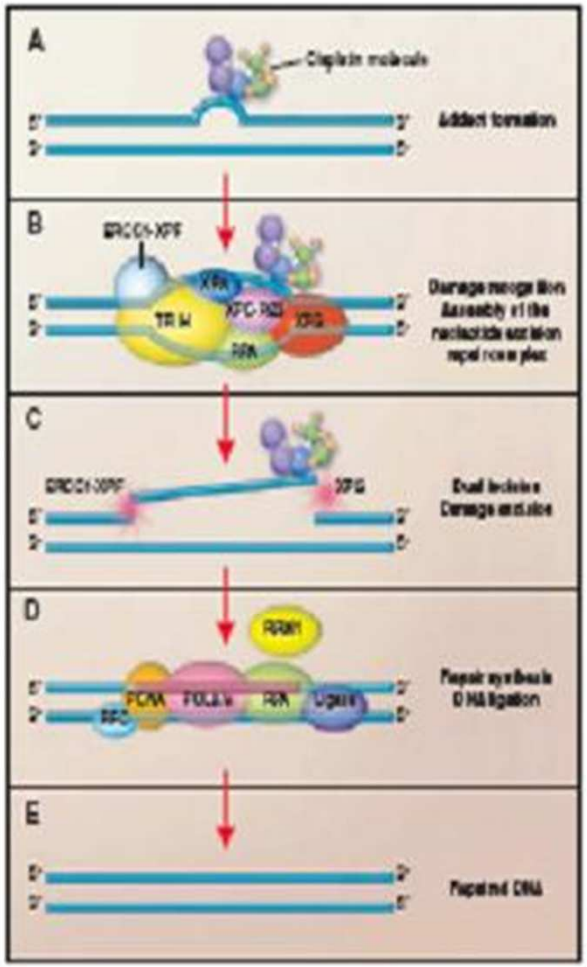
JMDB: in squamous cell carcinoma Cis/Gem had a better overall survival



Scagliotti et al J Clin Oncol 26, 3543-3551, 2008

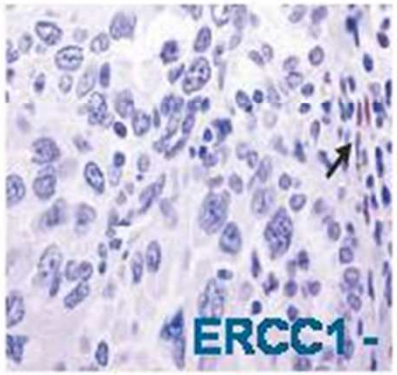
ERCC1 and RRM1 in DNA damage repair

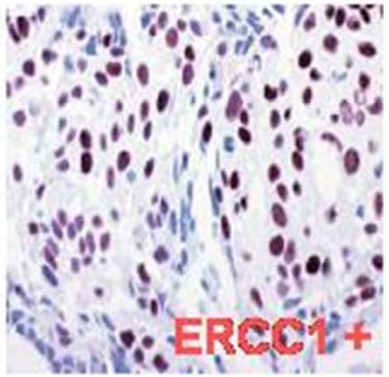
- Nucleotide excision repair (NER) plays a central role in DNA repair pathways
- ERCC1 enzyme plays a rate-limiting role in the NER pathway
- Overexpression of the excision repair cross complementing 1 (ERCC1) gene, which is crucial in the repair of cisplatin (CDDP)-DNA adducts
- Ribonucleotide reductase, although not an integral part of the repair complex, catalyzes the biosynthesis of deoxyribonucleotides from the corresponding ribonucleotides, providing the building blocks for reconstitution of the excised oligonucleotide.

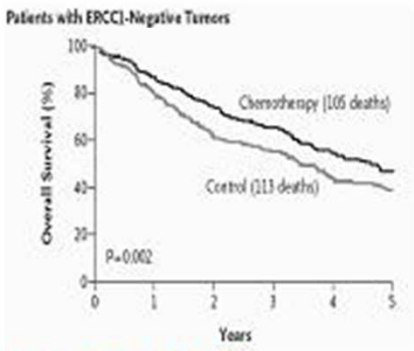


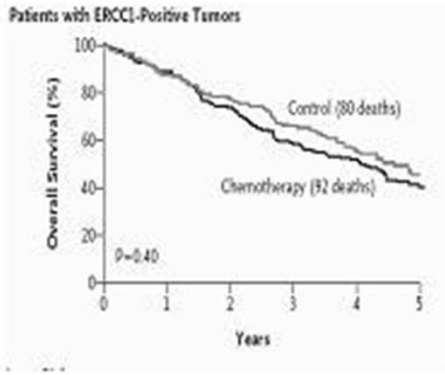
Friedberg EC, Nat Rev Cancer 2001

ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based CT







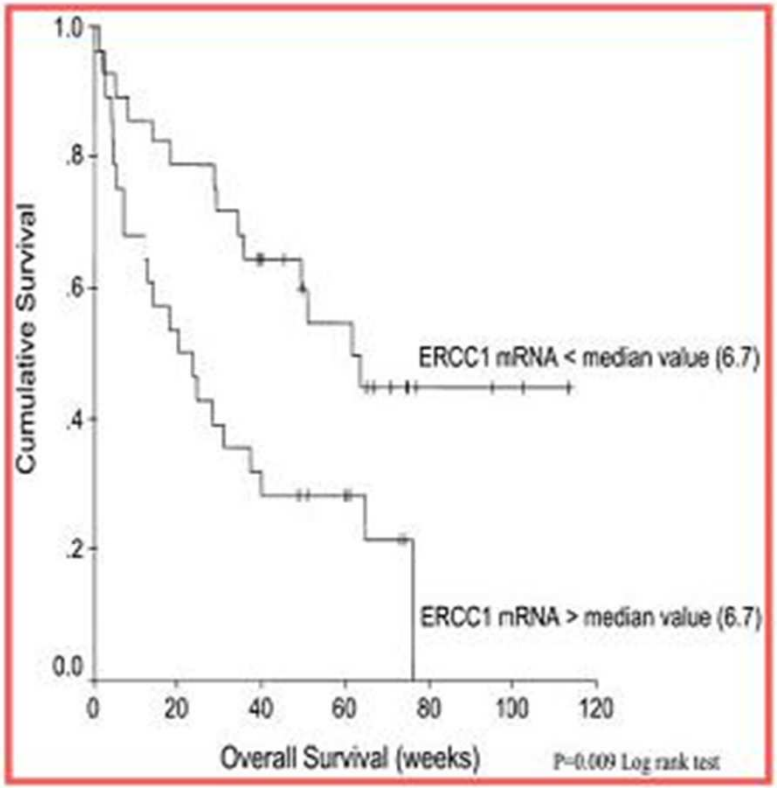


Olaussen KA, NEJM 2006

IST

Low ERCC1 expression correlates with prolonged Survival after Cisplatin + Gemcitabine CT in NSCLC

- ERCC1 expression is a predictive factor for survival after CDDP/Gem therapy in advanced NSCLC.
- Although there was a trend toward decreased response with high ERCC1 mRNA levels, this difference failed to reach statistical significance.

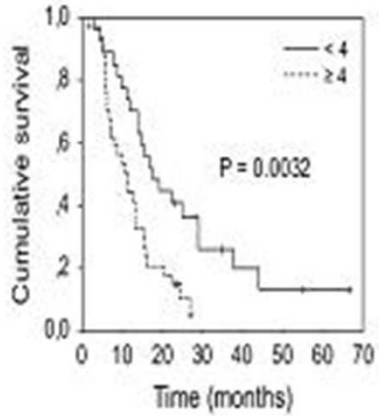


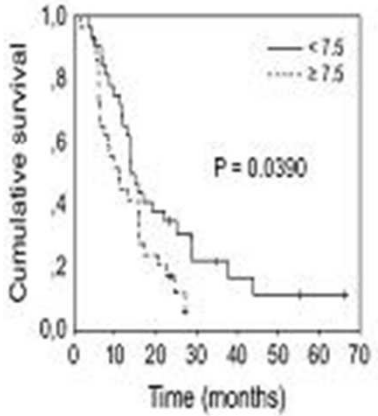
Lord RVN, CCR 2002

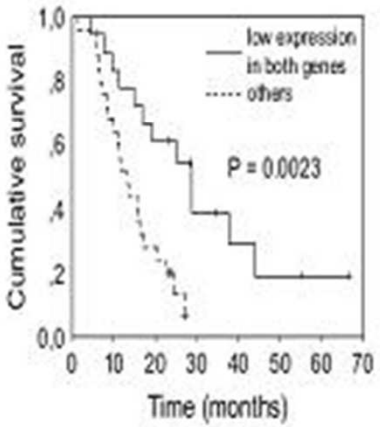
IST

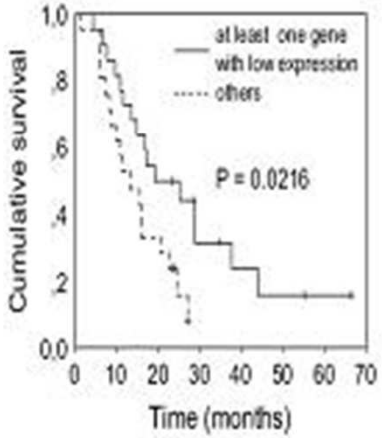
Survival for ERCC1, RRM1 & for the combination of both in CDDP-treated pts

- Median survival time in patients with low ERCC1 was significantly longer (17.3 versus 10.9, p= 0.0032) as well as in patients with low RRM1 (13.9 versus 10.9, p= 0.039).
- Concomitant low expression levels of ERCC1 and RRM1 were predictive of a better outcome (14.9 versus 10.0, p= 0.0345).
- Among cisplatin treated patients, a low ERCC1 level was highly predictive of a longer survival (23.0 versus 12.4, p= 0.0001).







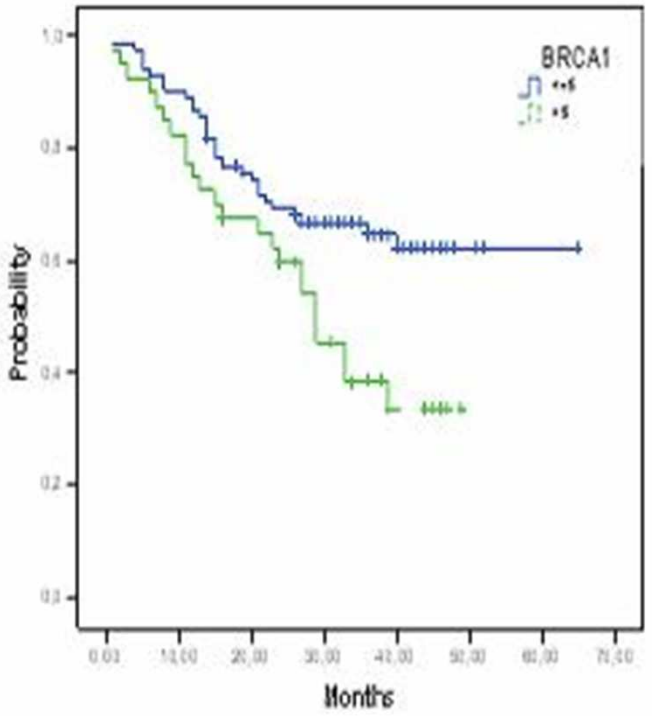


Ceppi P, Ann Oncol 2006

IST

Overexpression of BRCA1 mRNA was strongly associated with poor survival

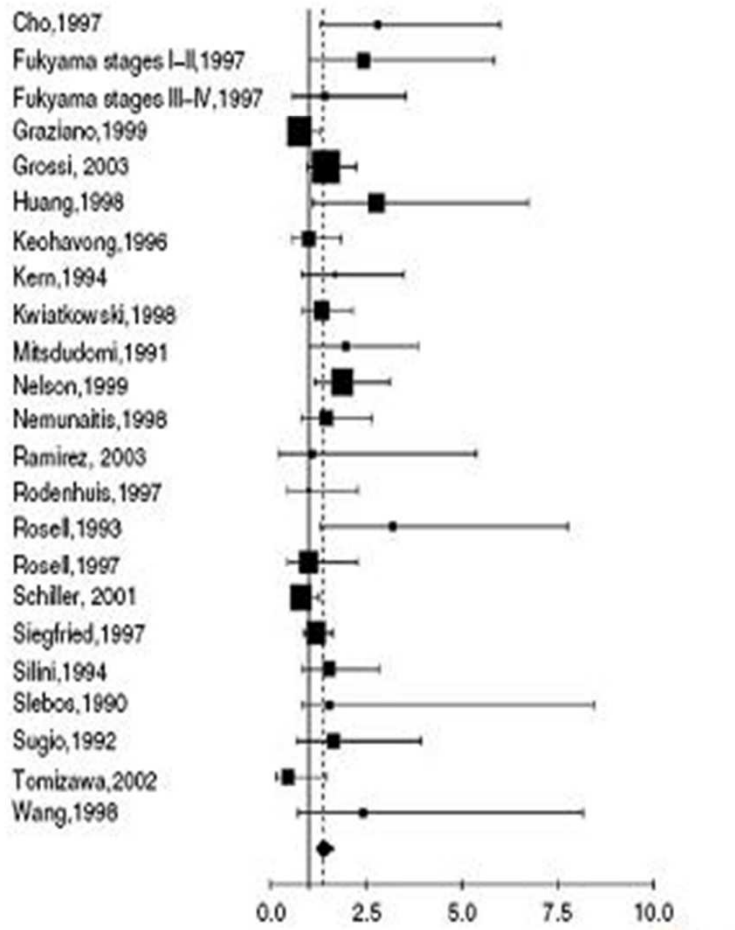
- Patients whose tumors had high BRCA1 expression had significantly worse survival and should be candidates for adjuvant chemotherapy.
- Patients with high BRCA1 levels will benefit from antimicrotubule-based but not cisplatin-based CT.



Rosell R, PLoS ONE 2007

Prognostic significance of Ras in NSCLC

- The combined HR was 1.35 (95% CI: 1.16–1.56), showing a worse survival for NSCLC with KRAS2 mutations or p21 overexpression and, particularly, in adenocarcinomas and in studies using PCR but not in studies using IHC.
- RAS appears to be a pejorative prognostic factor in terms of survival in NSCLC globally, in adenocarcinoma and when it is studied by PCR.

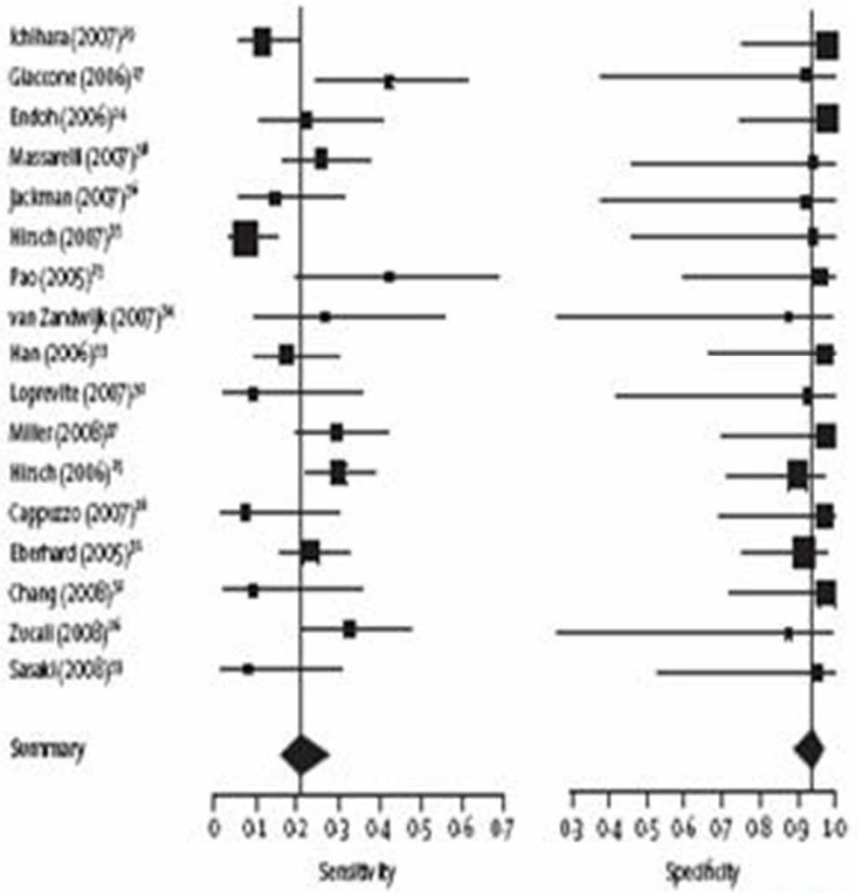


Mascaux C, BJC 2005

IST

K-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents

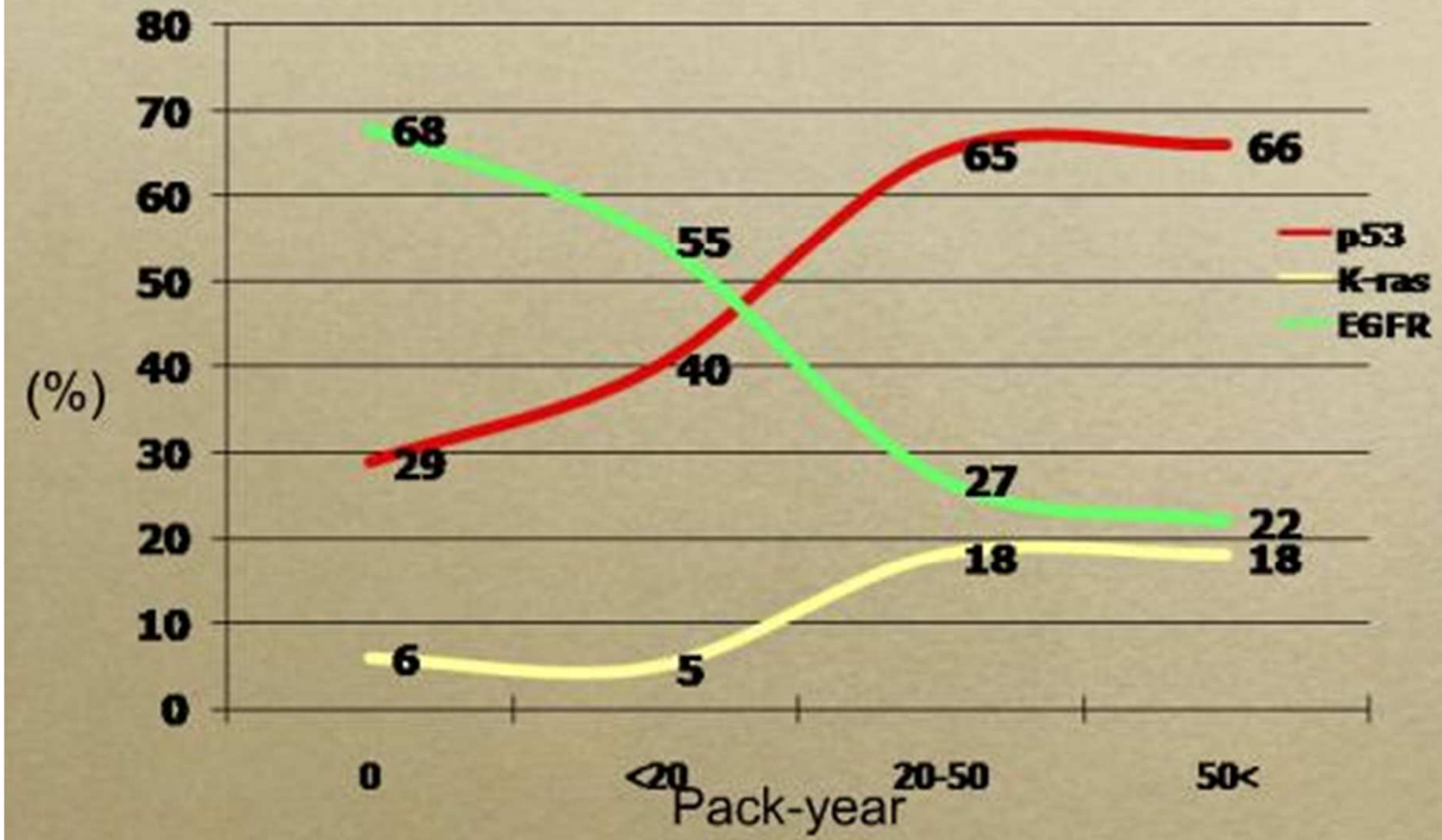
- K-RAS mutations was significantly associated with an absence of response to TKIs (sensitivity= 0.21 [95% CI 0.16–0.28], specificity= 0.94 [0.89–0.97]).
- This analysis provides empirical evidence that K-RAS mutations are highly specific negative predictors of response (de-novo resistance) to single-agent EGFR TKIs in advanced NSCLC.



Linardou H, Lancet Oncol 2008

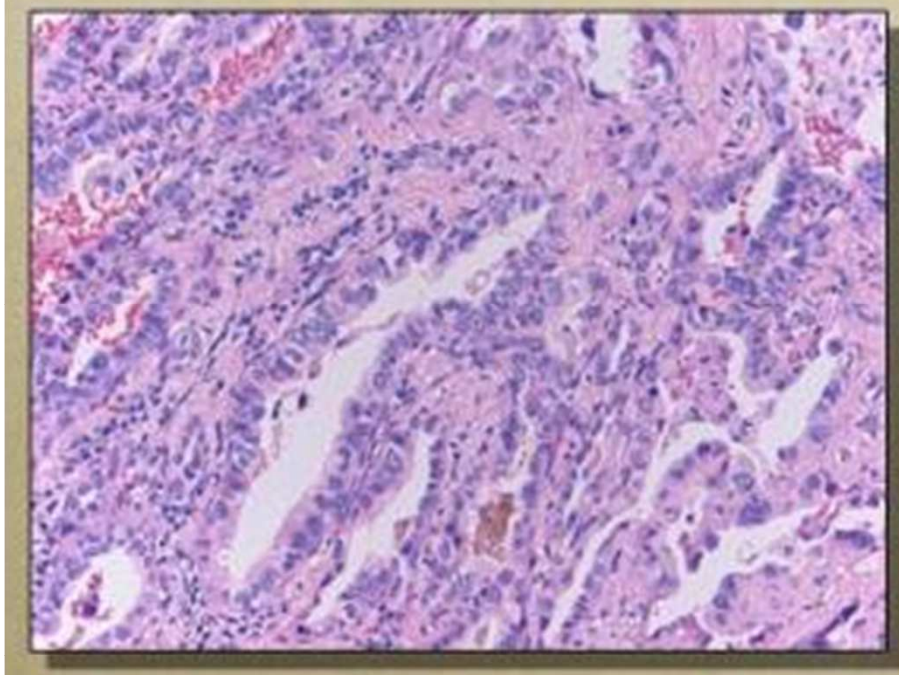
EGFR, TP53 and KRAS mutation and smoking dose in patients with adenocarcinoma

Kosaka et al., Cancer Res.64, 8919-8923, 2004

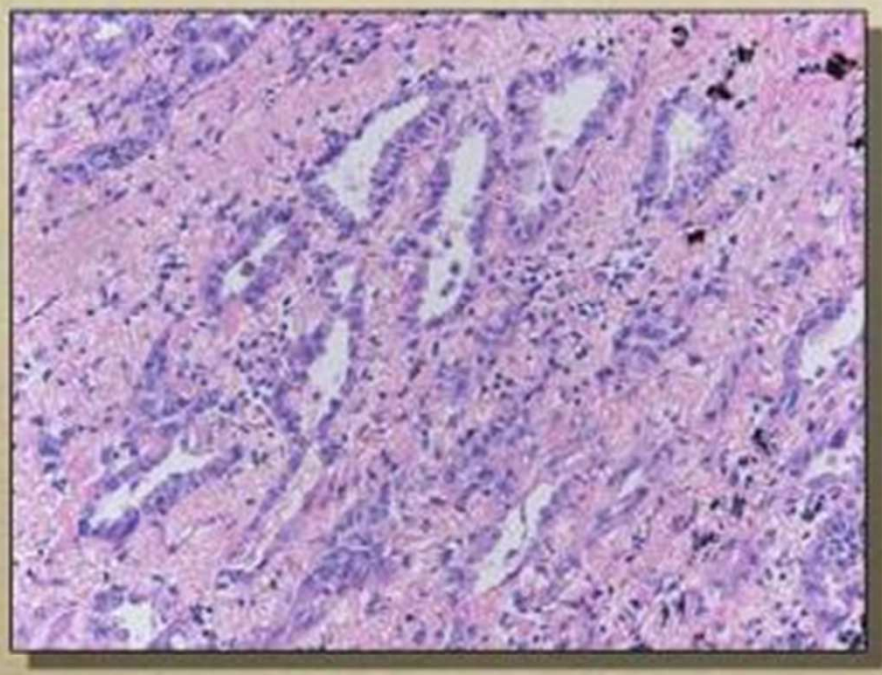


Note: Incidence of K-ras mutations: US(~30%) >> Japan

TRU-type adenocarcinoma with EGFR mutations and that with K-ras mutations



TRU type adeno
With K-ras mutation,
WT EGFR



TRU type adeno
With EGFR mutation,
WT K-ras

Two classes of genetic abnormalities found in human adenocarcinoma of the lung

Class I: Oncogenes/TSG whose mutations never occur in tumors that have EGFR mutations

KRAS

Class II: Oncogenes/TSG whose mutations may occur in tumors that have EGFR mutations

TP53

Mutations of EGFR, HER2 and KRAS gene in 200 adenocarcinomas (ACC)

Onozato et al., JCA, 2007

	No with mutations	(%)	Poorly diff.	Never-Smoker	Female	TP53 mut	TP53 G-T
EGFR	100	(50%)	17%	68%	64%	35%	1%
HER2	6	(3%)	17%	67%	83%	33%	0%
KRAS	28	(14%)	39%	25%	25%	46%	18%
unknown	66	(33%)	46%	35%	44%	44%	21%

Mutually exclusive

Is adenocarcinoma of the lung one disease

No!

can be classified according to;

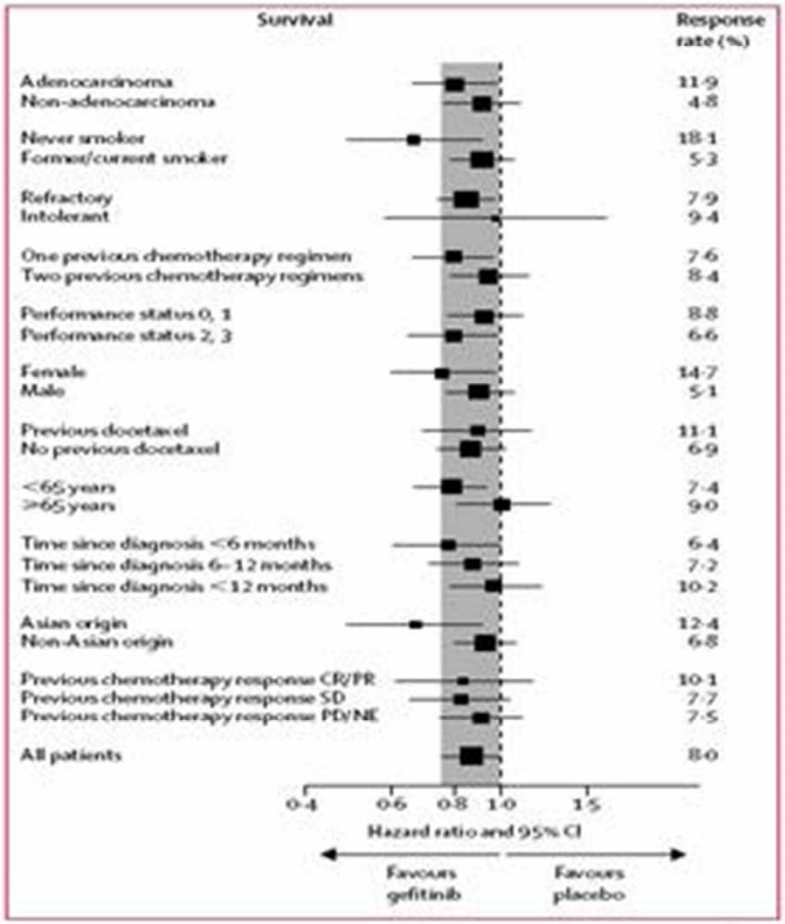
morphology

expression profile

altered oncogenes / tumor suppressor gen

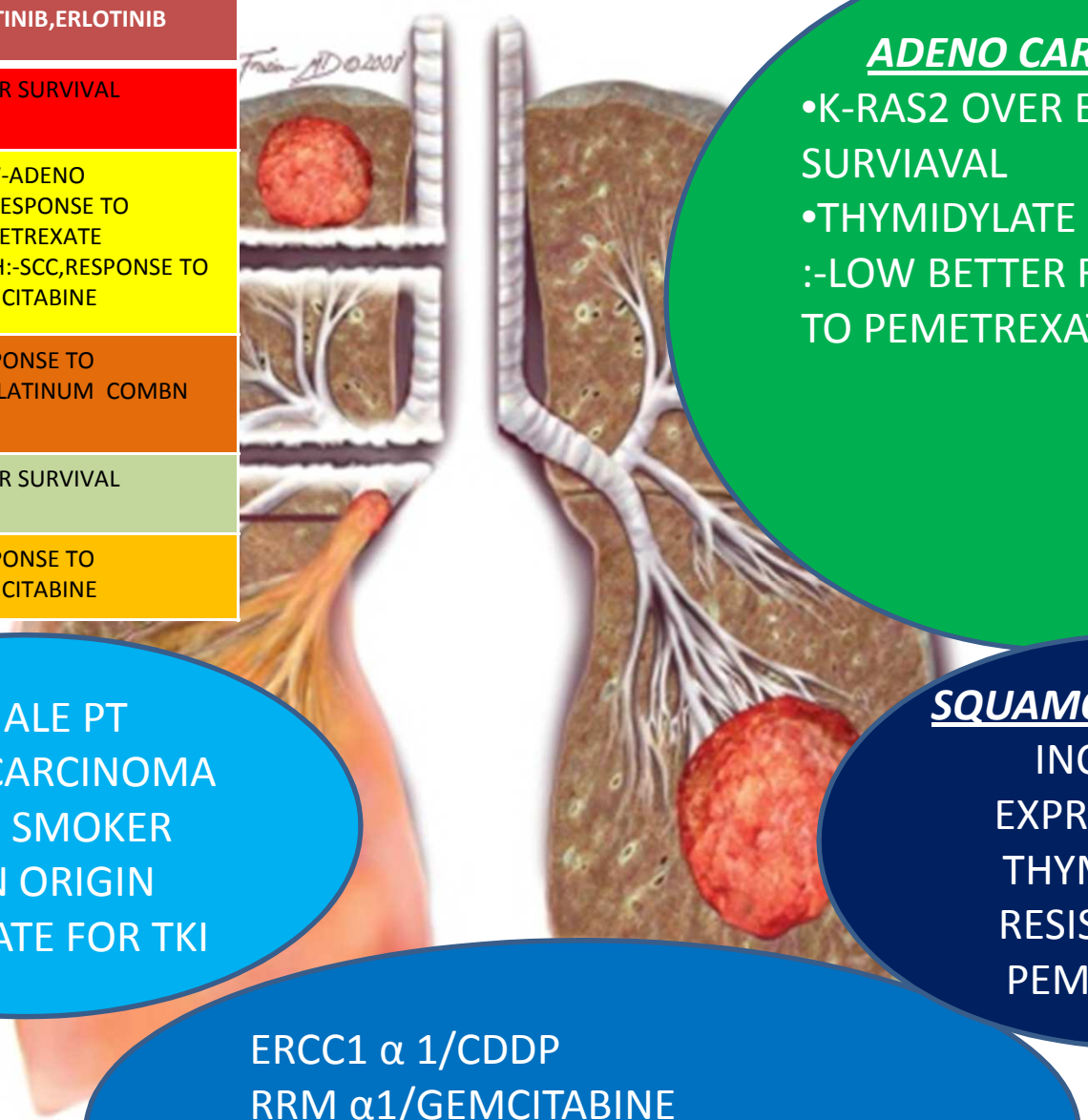
Survival and response rates by subgroup analysis in the overall population

- Survival was better in the gefitinib group than in the placebo group among never smokers (median 8.9 *vs* 6.1 months; HR 0.67 (p=0.012)
- Survival was better in the gefitinib group than in the placebo group among patients of Asian origin (median 9.5 *vs* 5.5 months; HR 0.66 (p=0.01)



Thatcher N, Lancet 2005

EGFR MUTATION	RESPONSE TO GEFTINIB,ERLOTINIB
KRAS2 MUTATION ,p21 OVER EXPN	POOR SURVIVAL
TS EXPRESSION	LOW-ADENO CA,RESPONSE TO PEMETREXATE HIGH:-SCC,RESPONSE TO GEMCITABINE
ERCC1-VE	RESPONSE TO CISPLATINUM COMBN
BRCA1 OVEREXPN	POOR SURVIVAL
RRM1 :- DECREASE	RESPONSE TO GEMCITABINE



ADENO CARCINOMA

- K-RAS2 OVER EXPN:-POOR SURVIAVAL
- THYMIDYLATE SYNTHETASE :-LOW BETTER RESPONSE TO PEMETREXATE

FEMALE PT
ADENO CARCINOMA
NEVER SMOKER
ASIAN ORIGIN
CANDIDATE FOR TKI

SQUAMOUS CELL CA

INCREASED EXPRESSION OF THYMIDYLATE-RESISTANCE TO PEMETREXATE

ERCC1 α 1/CDDP
RRM α1/GEMCITABINE
β TUBLIN α 1/TAXANE
THY.SYNTH. α 1/ PEMETRAXATE,

Take home messages

- Treatment by histology is the first step for tailored chemotherapy.
- A number of trials have suggested that pemetrexed may be particularly effective in first line nonsquamous NSCLC
- Gefitinib may be indicated in first line only in adenocarcinoma EGFR + patients
- In adenocarcinoma (mutation – or unknown mutational status) pemetrexed is a preferred regimen
- EGFR mutations are prognostic and predictive of response to EGFR inhibitors and prognostic for CT
- ERCC1/RRM1 could be useful as a prognostic factor in early stages and need further evaluations in prospective trials in advanced NSCLC

IST

ARE ALL BREAST CANCERS SAME

ER

HER

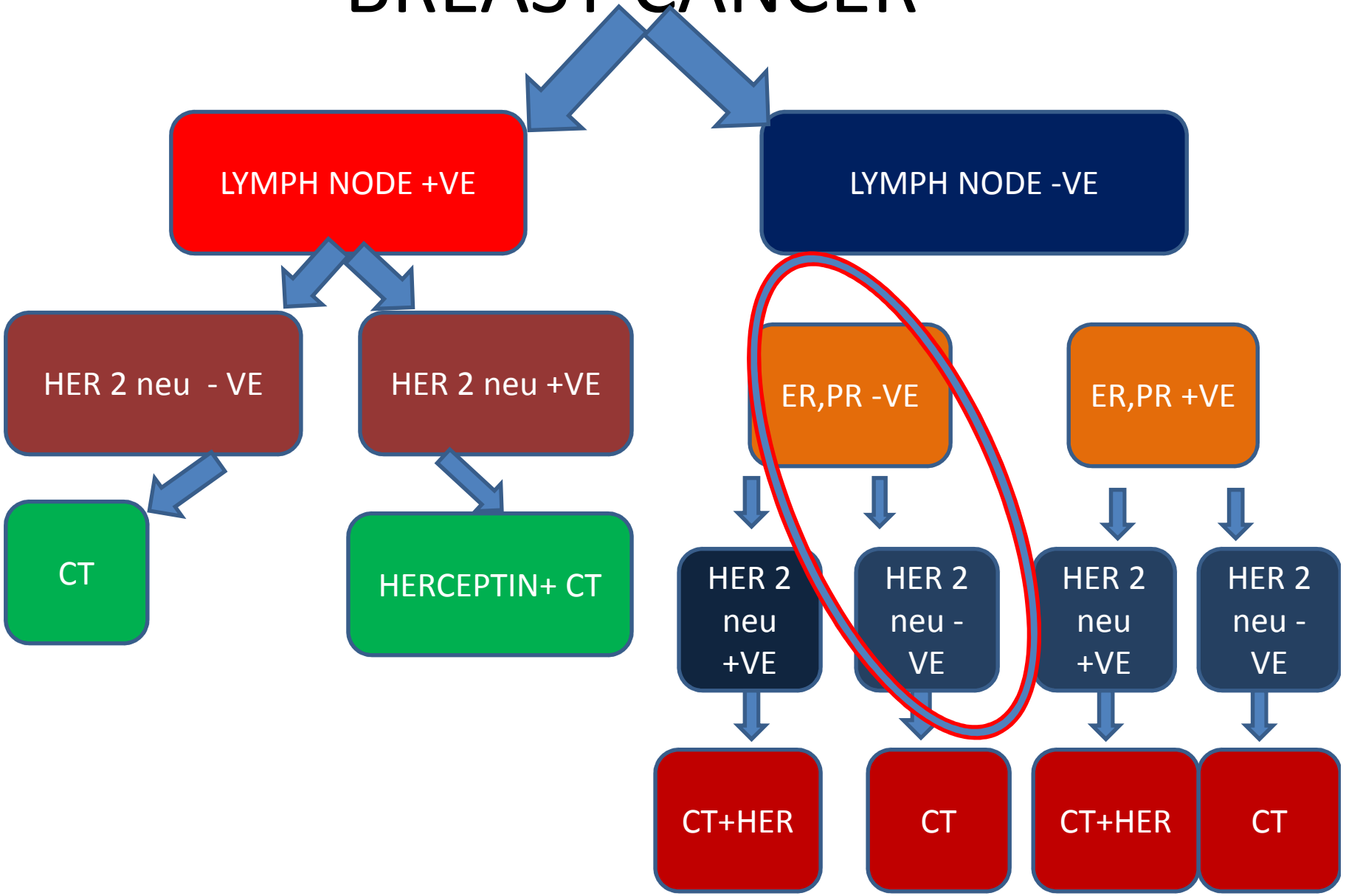
PR

OTHERS
TOP2A
Ki67
PTEN LOSS
PIK3CA
BRCA1
Upa &PAI1

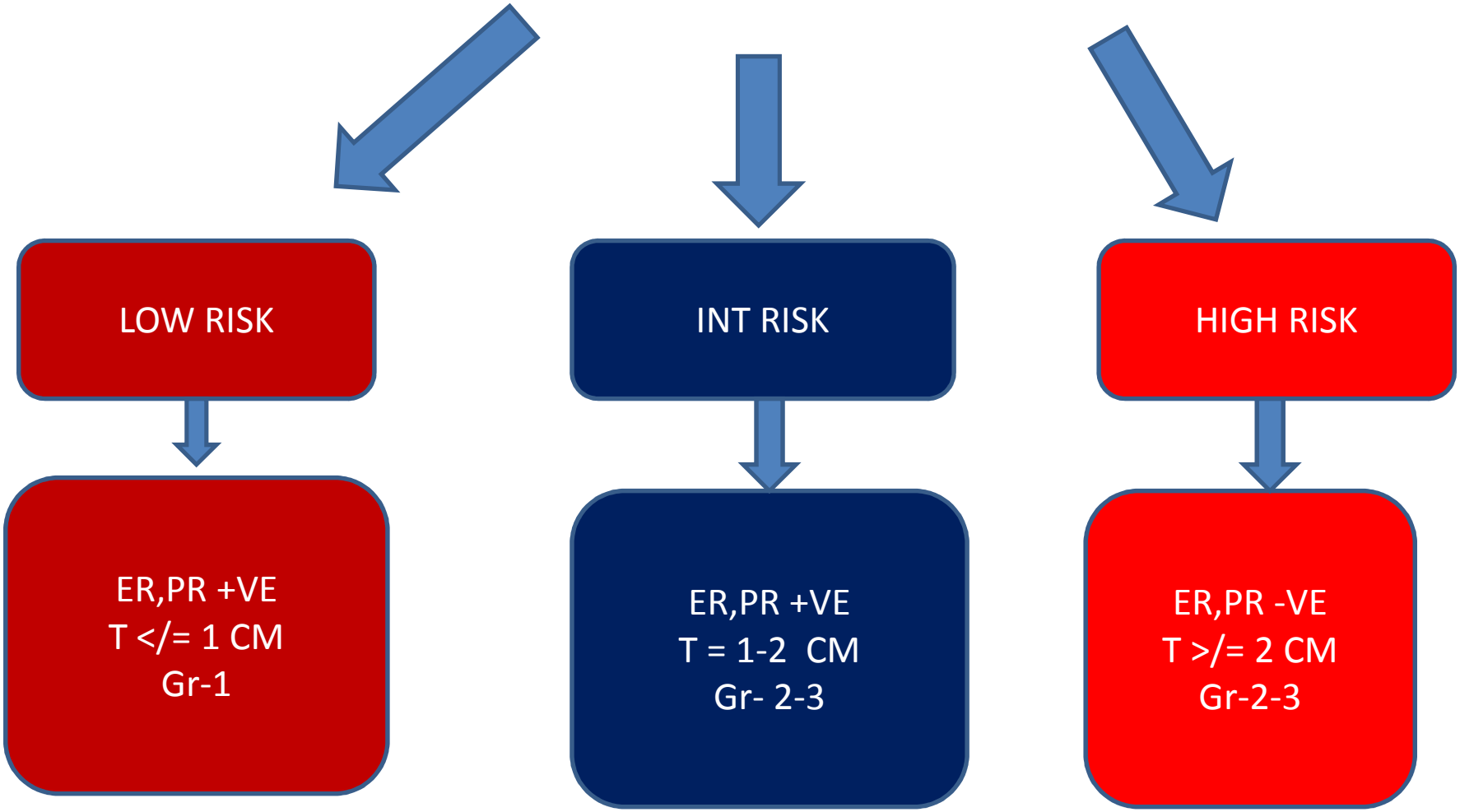
PROGNOSTIC FACTORS

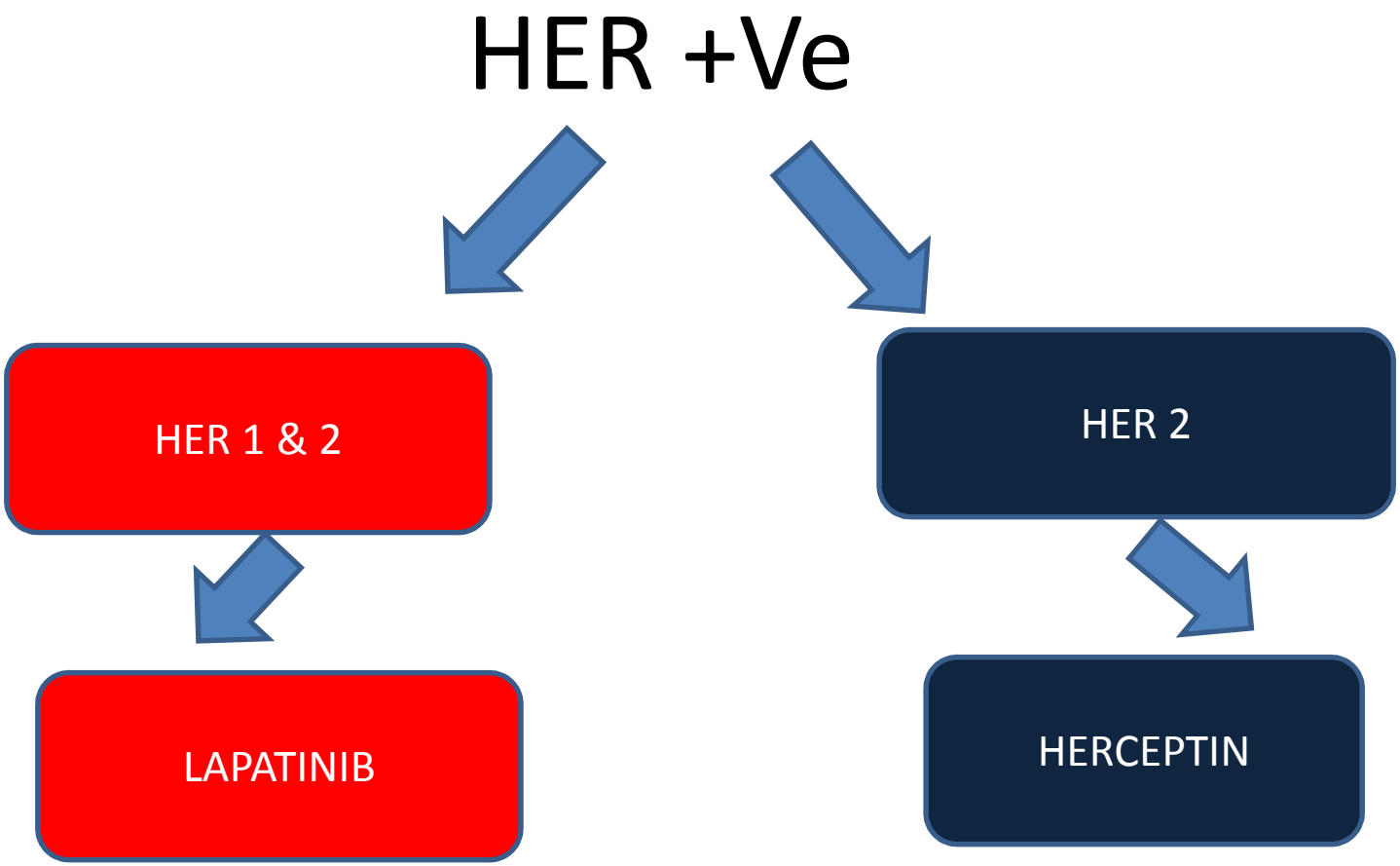
- AGE
- NODAL STATUS
- NUCLEAR GRADE
- RECEPTOR STATUS(ER,PR)

BREAST CANCER

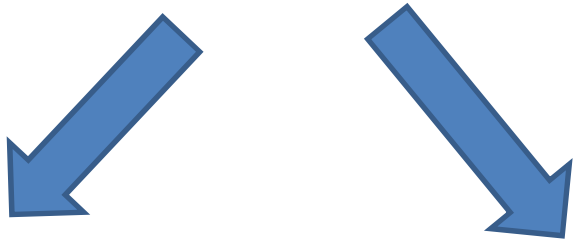


BREAST CANCER
NODE –VE




HER +Ve
HER 1 & 2
LAPATINIB
HER 2
HERCEPTIN

HER 2 +VE



HER 2 ECD +VE

- POOR PROGNOSIS
- RESISTANCE TO TAMOXIFEN & AROMATASE INHIBITOR
- BENEFIT FROM HERCEPTIN- CONTROVERSIAL

HER 2 ECD - Ve

SENSITIVE TO HERCEPTIN

HER 2 + Ve

P 95 HER 2+VE

P 95 HER 2 -Ve

NODE + Ve
POOR PROGNOSIS
LACKS HERCEPTIN /TRASTUZUMAB BINDING DOMAIN
RETAINS TYROSIN KINASE ACTIVITY.
LAPATINIB IS TREATMENT OF CHOICE

HERCEPTIN
LAPATINIB

PTEN LOSS,PIK3CA MUTATION
ACQUIRED RESISTANCE TO TRASTUZUMAB
REVERAL BY M-TOR INHIBITOR-EVORLIMUS

Table 1. Risik classification St. Gallen 2005/2007

Low risk	Intermediate risk	High risk
pN0 and all of the following criteria: size of tumor max. 2 cm G1 no vessel invasion ER-/PR-positive HER2-negative age ≥ 35 years	pN0 and at least 1 further criterion: size of tumor >2 cm G2 / G3 vessel invasion present HER2 overexpression age < 35 years or pN+ (N 1–3) and HER2-negative	pN+ (N1–3) and HER2 overexpression or pN+ (N ≥ 4)

Table 2. Therapy recommendations, St. Gallen Consensus 2005/2007

Low risk	Intermediate risk	High risk
endocrine therapy or no therapy	endocrine responsive endocrine therapy or chemotherapy then endocrine therapy trastuzumab where appropriate uncertain endocrine responsiveness chemotherapy then endocrine therapy trastuzumab where appropriate endocrine non-responsive chemotherapy trastuzumab where appropriate	endocrine responsive chemotherapy then endocrine therapy trastuzumab where appropriate endocrine non-responsive chemotherapy trastuzumab where appropriate

ROLE OF UROKINASE PLASMINOGEN ACTIVATOR & PLASMINOGEN ACTIVATOR INHIBITOR

- POOR PROGNOSIS
- NODE –VE WITH INCREASED LEVEL
- BENIFITED FROM CMF

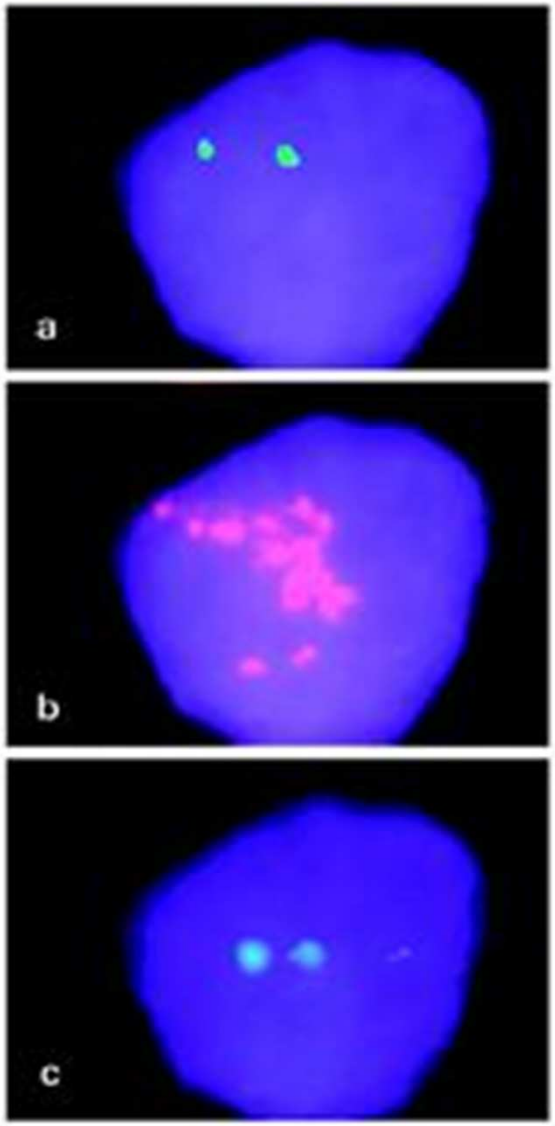
Amplification and Overexpression of Topoisomerase II Predict Response to Anthracycline-based Therapy in Locally Advanced Breast Cancer

FISH:

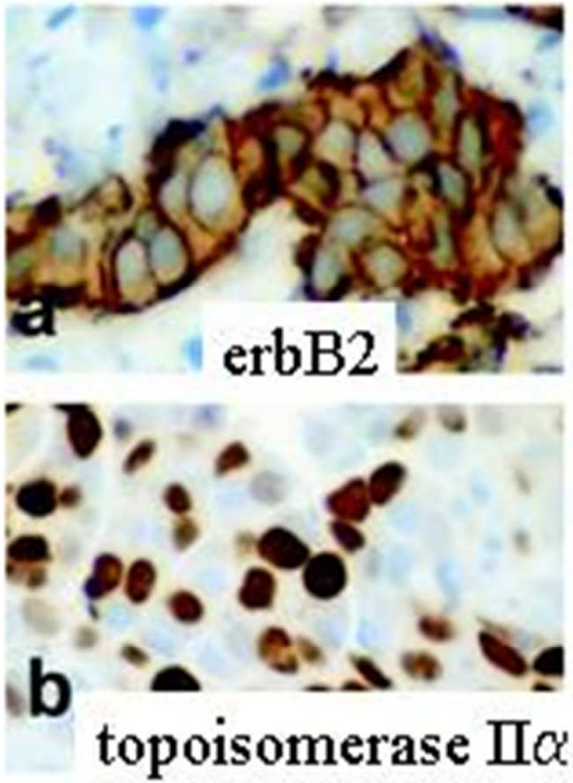
Topo IIα

c-erbB2

chr 17 centromere



IHC



Coon, et al., Clin Cancer Res 8: 1061-1067, 2002

Responses to doxorubicin preoperative chemotherapy according to HER2/topoisomerase II-α (topoII) amplification status (CISH)

	Response	Total
	n (%)	*n*
HER2-/topo II-	17 (47)	36
HER2+/topo II-	9 (75)	12
HER2+/topo II+	18 (95)	19

P=0.038.

Park, et al., Eur J Cancer 39: 631-34, 2003

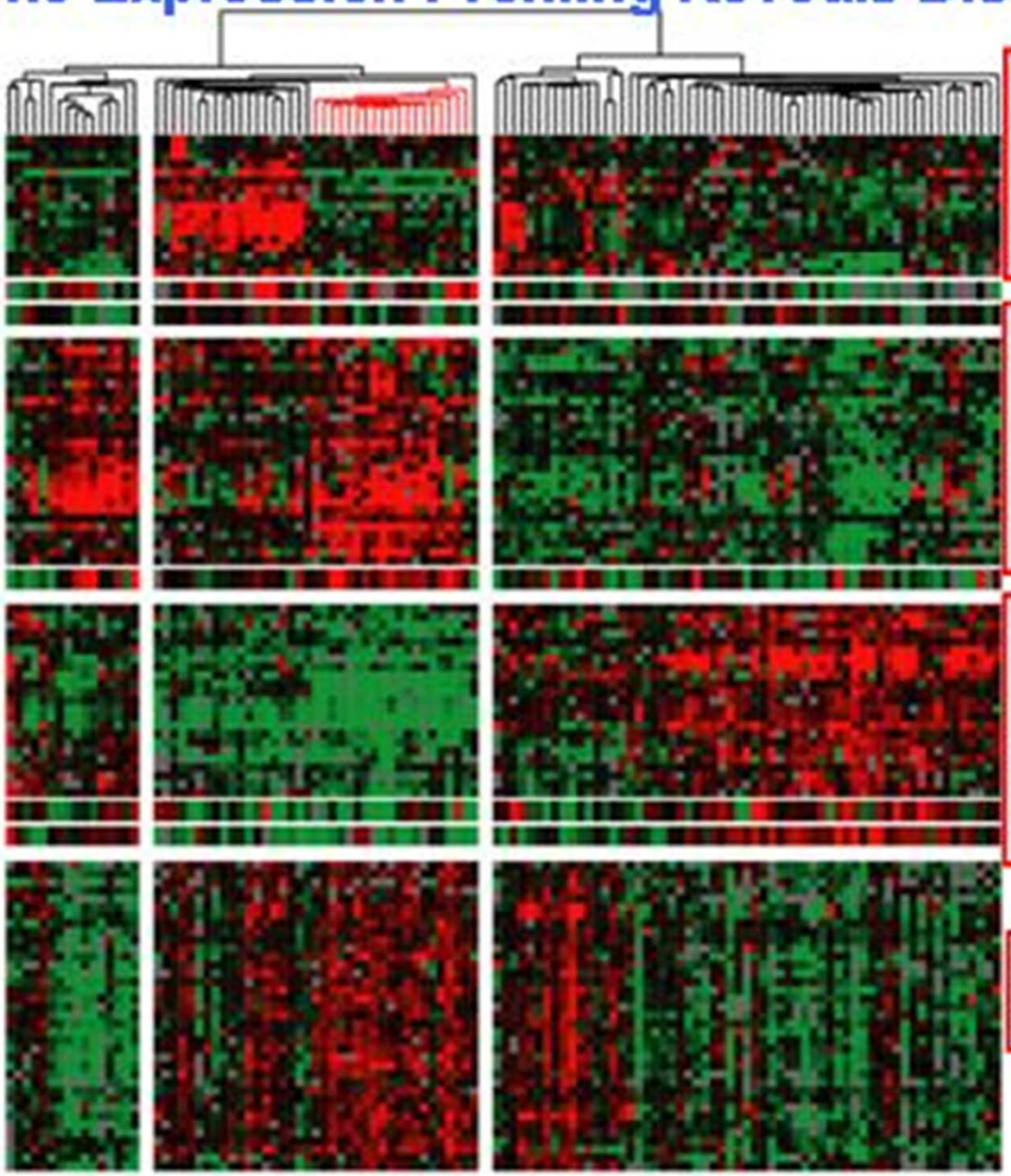
p53 Mutations Associated With Resistance to Doxorubicin (A)

- A-induced apoptosis is prevented
- p53 mutations could hamper response to A even in tumors carrying topo II α gene amplification

PerezASCO'03

Aas T et al. Nature Med 2:811-4, 1996

Gene Expression Profiling Reveals Distinct Clusters



HER2+ subtype
1. 15-20% of tumors
2. prognostic/predictive
2. proliferation
3. two types (ER -/+)

Basal subtype
1. 10-15% of tumors
2. ER/PR/HER2-negative
3. very proliferative
4. EGFR, c-kit, c-myc +
5. includes BRCA1 mutations

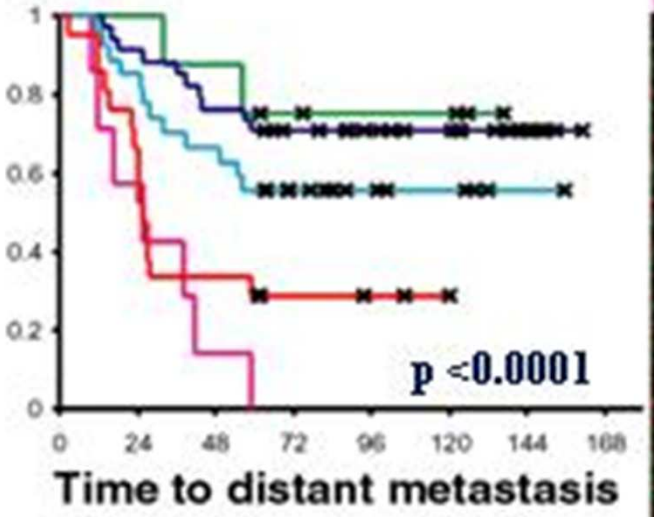
Luminal A and B (ER+)
1. continuum
2. prognostic/predictive
3. ER-GATA3-HNF3a-XBP1
4. proliferation (mutant p53)
5. cyclin D1 and BCL2 +

Ki-67, STK6, Survivin, Cyclin B1 and MYBL2

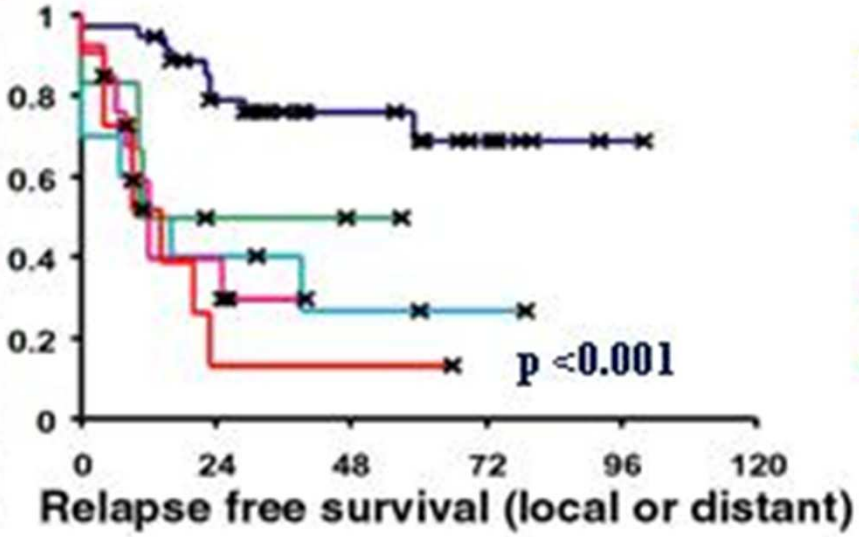
TripathyASCO'05

Sorlie T et al. PNAS 2003

tumor subtype predictions



No BRCA samples in relapse analysis

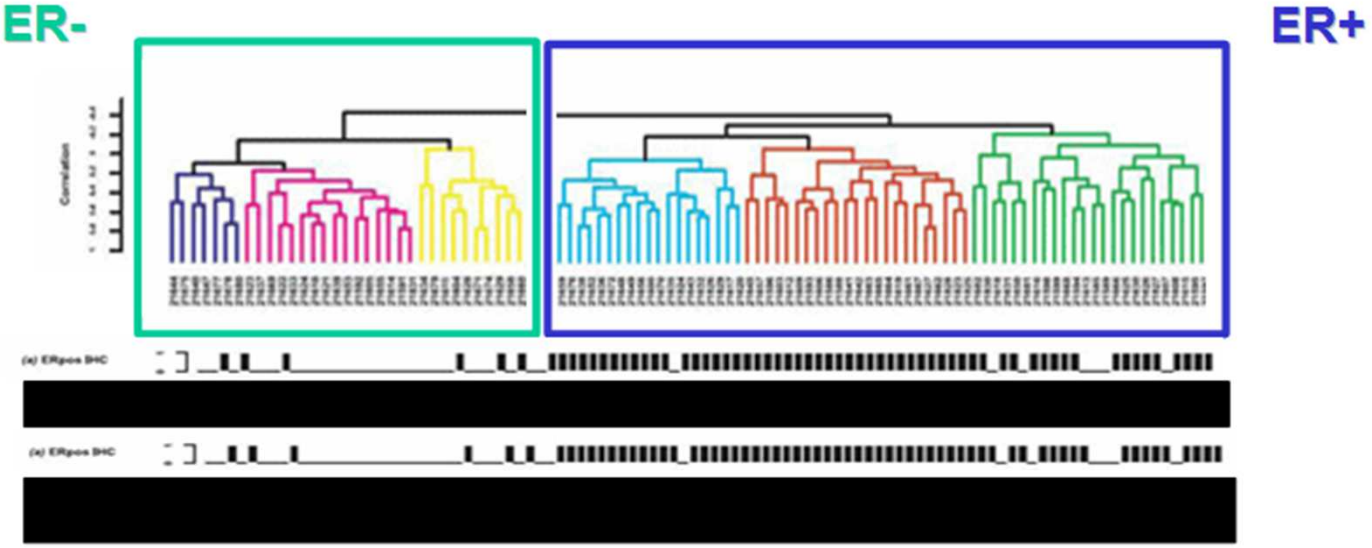


- Luminal A
- Luminal B
- Basal
- HER2+
- Normal breast-like

Sorlie T et al. PNAS 2003

TripathyASCO'05

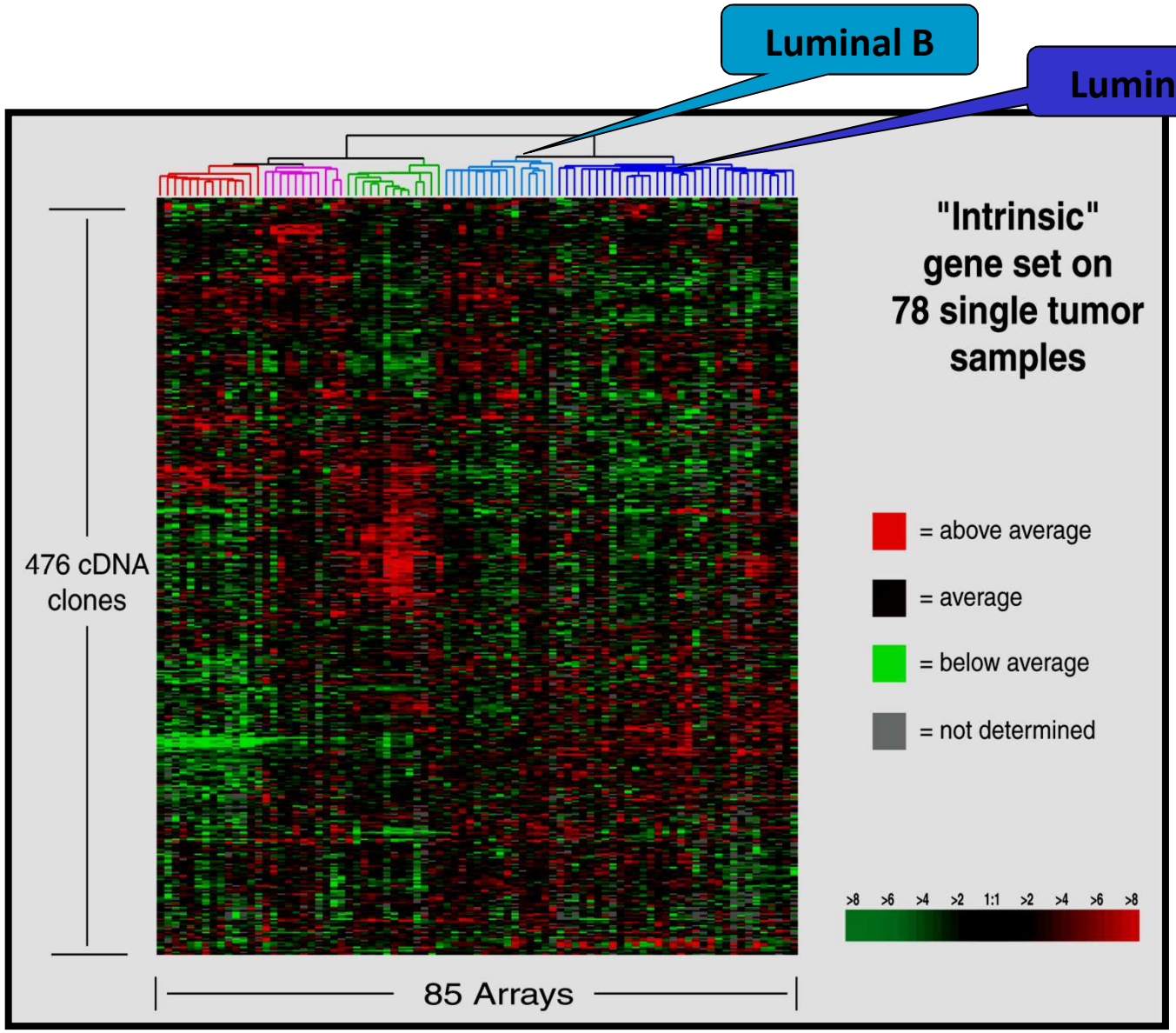
BREAST CANCER MOLECULAR CLASSIFICATION : ≥ 5 DISEASES ?



Basal-like	HER-2 +++	Luminal A	Luminal B	Luminal C
Mostly grade 3		Mostly grade 1	Mostly grade 3	
Basal characteristics		Luminal characteristics		

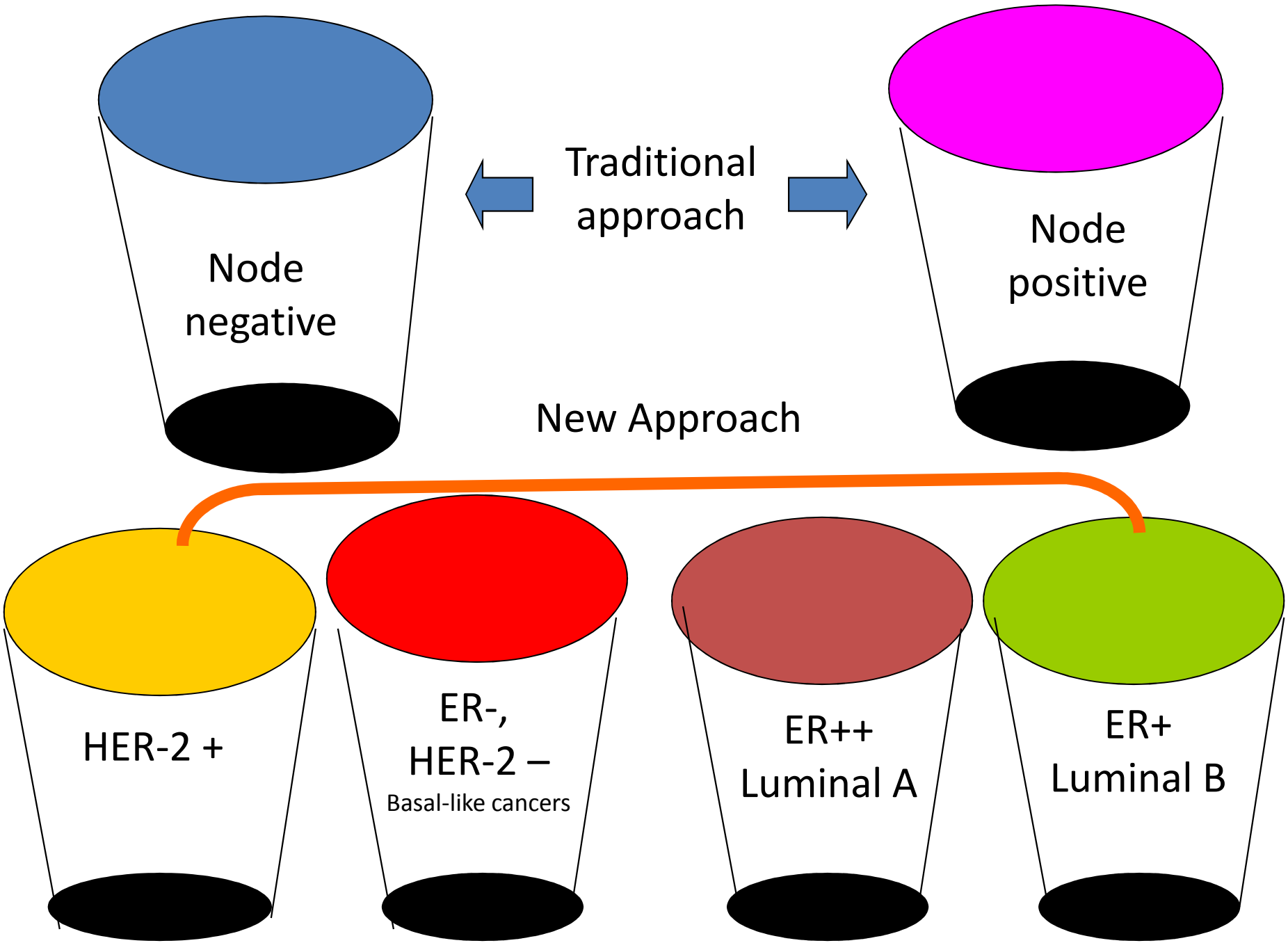
Courtesy of M Piccart

Molecular Portrait of Breast Cancers

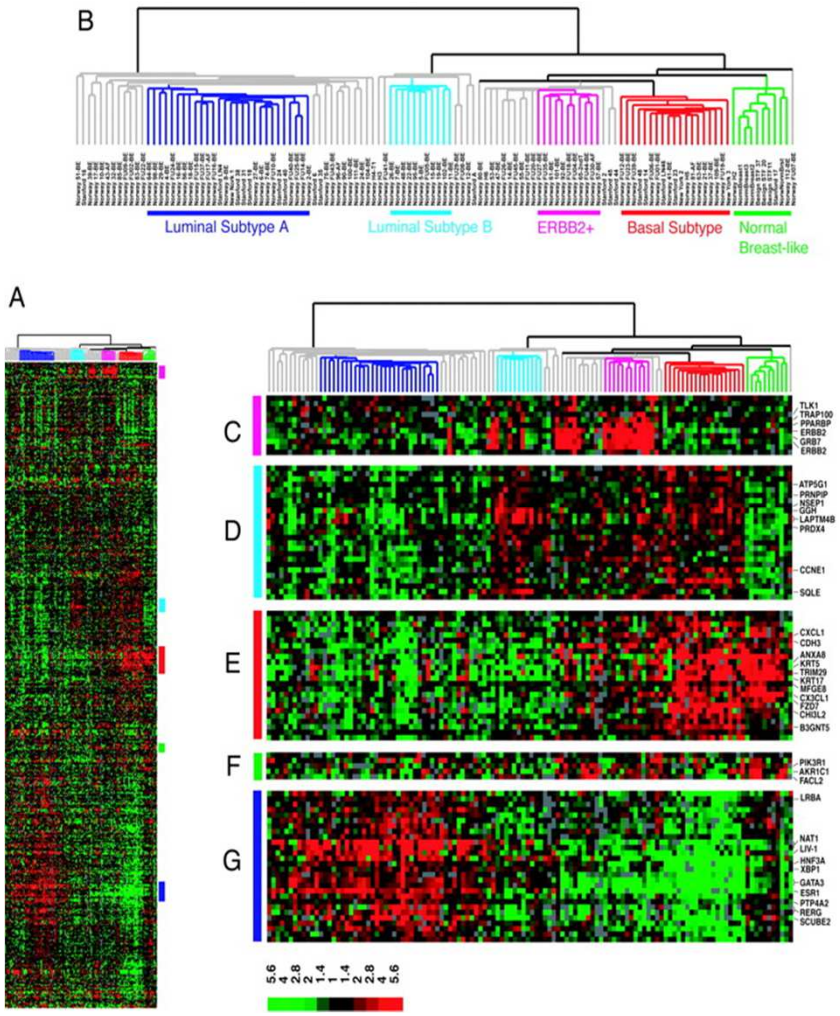


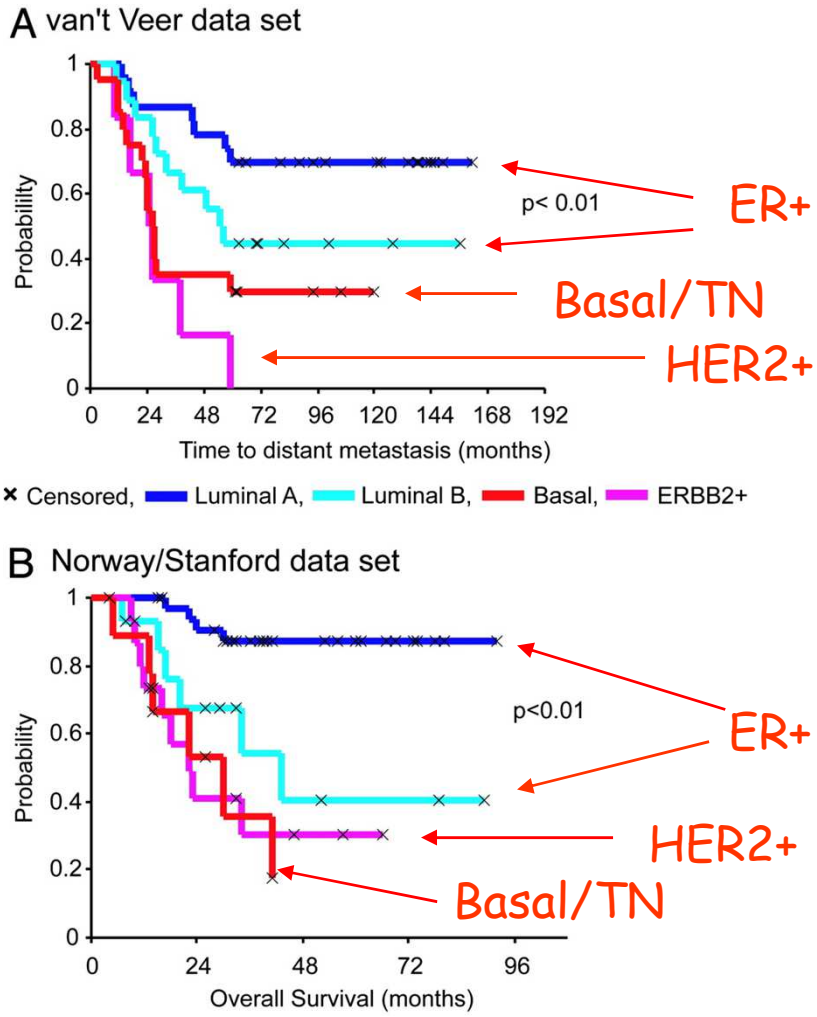
Both ER+, but different prognosis

Sorlie T et al, PNAS 2001


Node negative
Traditional approach
Node positive
New Approach
HER-2 +
ER-, HER-2 –
Basal-like cancers
ER++ Luminal A
ER+ Luminal B

Breast Cancer Subtypes based on Gene Expression Analysis





Sorlie et al *PNAS* 2003

TRIPLE –VE BREAST CANCER

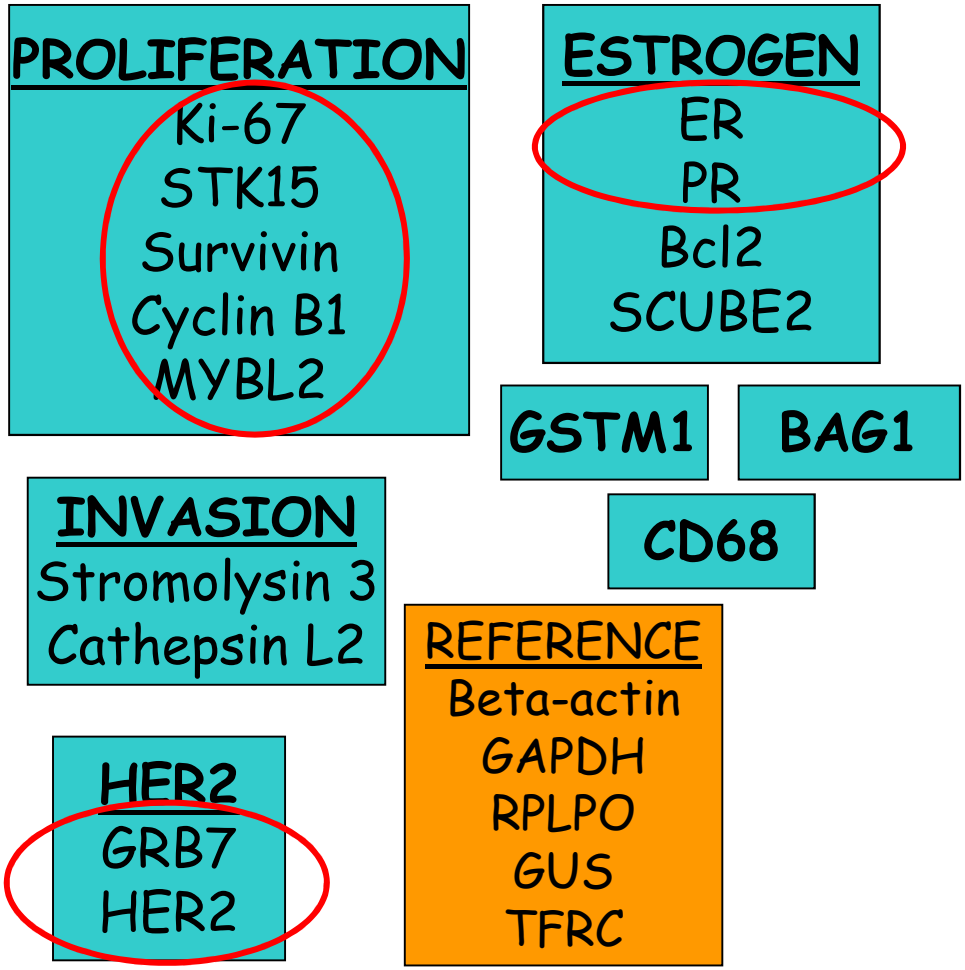
- YOUNG AGE
- HIGH HISTOLOGICAL GRADE
- BASAL LIKE HISTOPATHOLOGICAL PHENOTYPE
- TRIPLE –VE PHENOTYPE(ER-VE,PR-VE,HER 2 –VE)
- CARRIERS OF BRCA1 MUTATION
- HIGHLY SENSITIVE TO PLATINUM BASED CT
- PARP INHIBITORS(Poly ADP Ribose polymerase)

ONCOTYPE DX

- 21 GENE SIGNATURE
- ER,PR,HER 2,KI-67
- PREDICTOR OF TAMOXIFEN EFFICACY
- PREDICTS BENEFIT OF CMF ADJUVANT IN SAME PTS POPULATION.
- PROGNOSTIC AND PREDICTIVE VALUE IN NODE POSITIVE,ER POSITIVE POST MENOPAUSAL PTS RECEIVING CAF & TAMOXIFEN ADJUVANT.

Oncotype DX 21 Gene Recurrence Score (RS) Assay

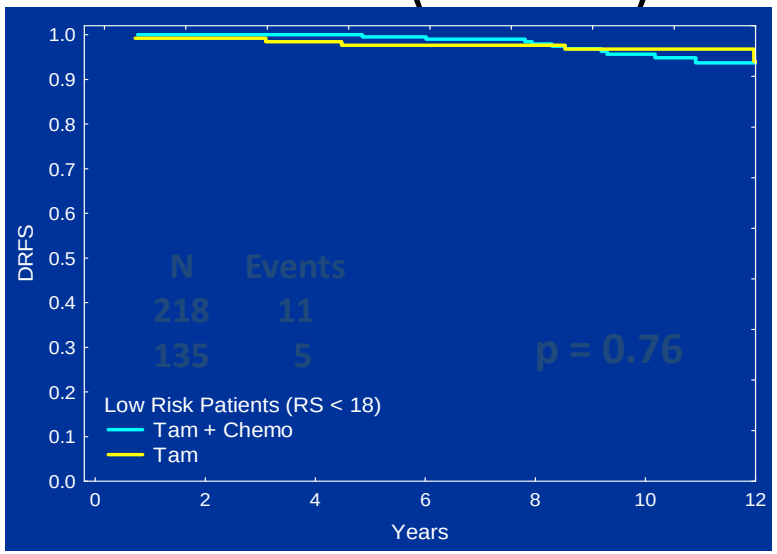
16 Cancer and 5 Reference Genes From 3 Studies



Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

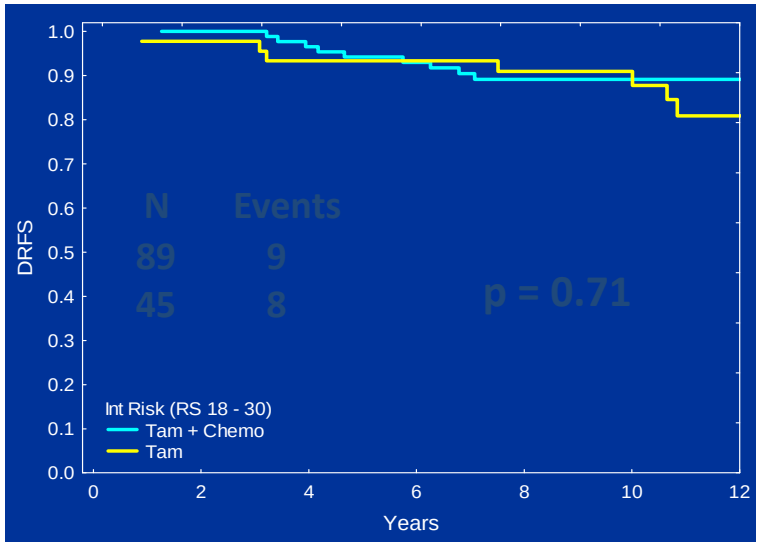
RS as a Predictor of C/MF Chemotherapy Benefit in Node (-), ER (+) Pts

Low Risk (RS < 18)



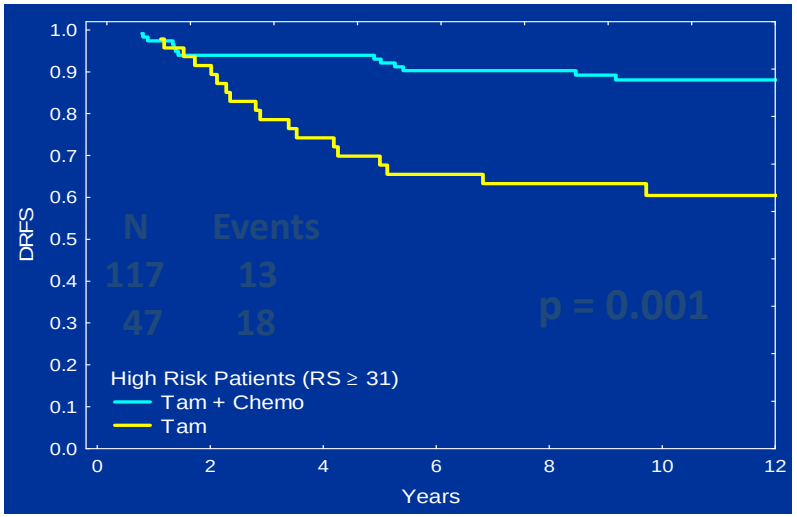
96%
95%

Interm. Risk (RS 18–30)



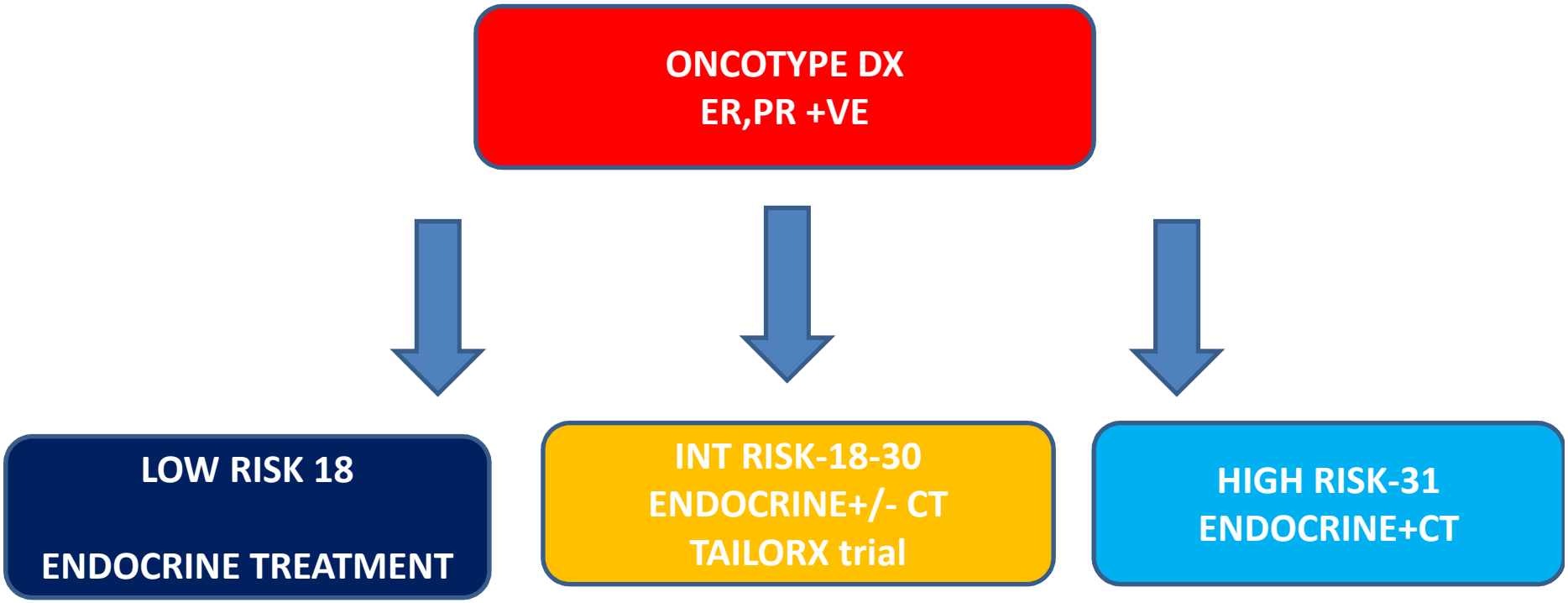
89%
90%

High Risk (RS ≥ 31)



88%
60%

Paik S, et al: SABCS 2004


ONCOTYPE DX
ER,PR +VE
LOW RISK 18
ENDOCRINE TREATMENT
INT RISK-18-30
ENDOCRINE+/- CT
TAILORX trial
HIGH RISK-31
ENDOCRINE+CT

MAMMAPRINT

- 70 GENE SIGNATURE
- YOUNG PATIENTS
- NODE –Ve
- EARLY STAGE I & II
- DNA MICRO ARRAY BASED DIAGNOSTIC TOOL REQUIRES FRESH FROZEN TISSUE.
- MINDACT
- LOW RISK MOLECULAR PROGNOSIS AND HIGH RISK CLINICAL PROGNOSIS

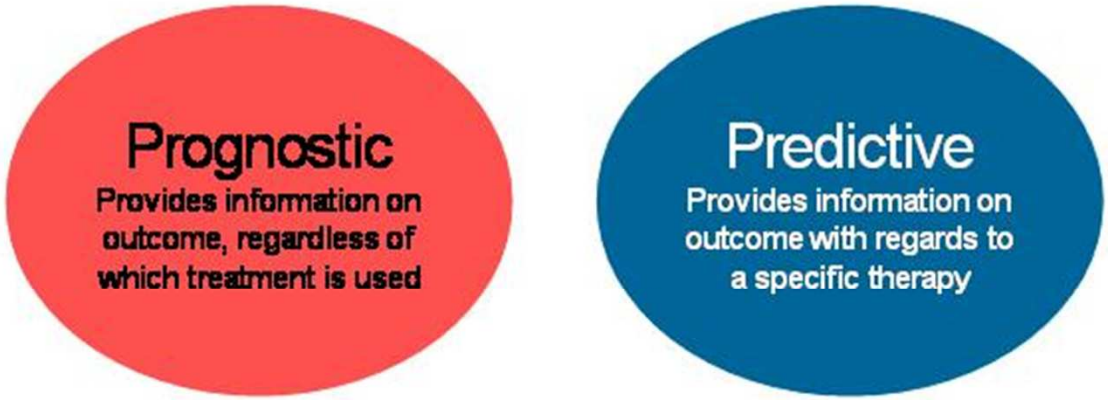
MAPQUANT DX

- A genomic grade Index
- RECLASSIFICATION GRADE 2 TUMORS IN TO HIGH RISK & LOW RISK RECURRENCE GROUP.

TAKE HOME MESSAGE

- BREAST CANCER IS HETEROGENOUS WITH RESPECT TO BIOLOGY AS WELL AS THERAPEUTIC APPROACH
- ONCOTYPE DX AND RECURRENT SCORE IN A SUBSET POPULATION GIVE A NEW INSIGHT FOR DECISSION MAKING REGARDING TREATMENT POLICY
- TRIPLE –VE BREAST CANCER IS A SEPARATE ENTITY CAN BE TREATED WITH PLATINUM BASED CT AND PARP INHIBITORS.

Prognostic versus predictive markers



Many biomarkers have both predictive and prognostic value

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

IST

Prognostic versus predictive markers

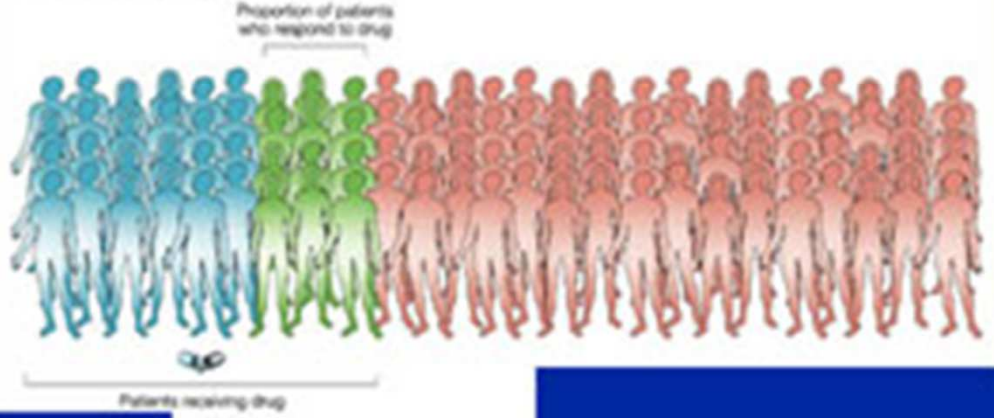
Prognostic factors
who to treat?

Predictive factors
how to treat?

Getting the right drug into the right patient

Pharmacogenomics will help explain why drugs work better in some patients than in others. It also presents numerous commercial opportunities for both startups and established biotechnology companies.

▲ **Current state of drug development research**



Cancer Treatment in the Future?

"Here's my sequence"

The New Yorker

THANK YOU