El oncólogo y los biomarcadores en cáncer de pulmón

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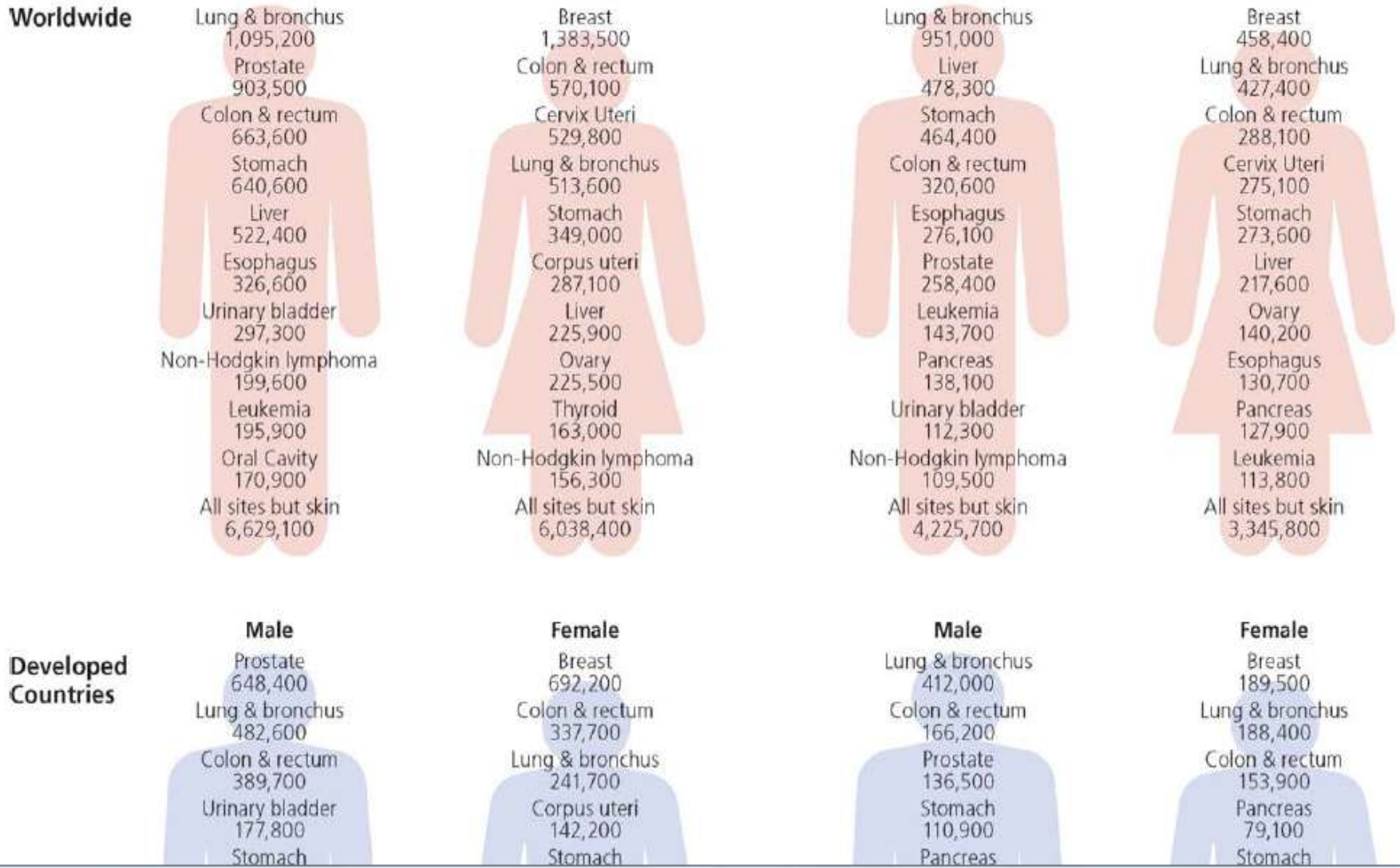
CA CANCER J CLIN 2011;61:69-90

Global Cancer Statistics

Ahmedin Jemal, DVM, PhD[1]; Freddie Bray, PhD[2]; Melissa M. Center, MPH[3]; Jacques Ferlay, ME[4]; Elizabeth Ward, PhD[5]; David Forman, PhD[6]



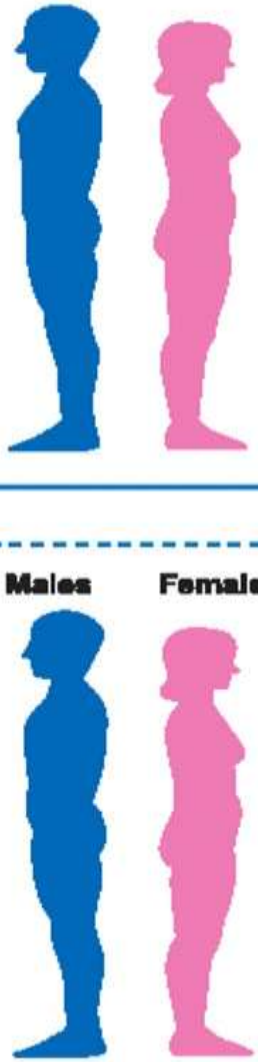
Ten Leading Cancer Types for Estimated New Cancer Cases and Deaths United States, 2009

Estimated New Cases*

Males				Females		
Prostate	192,280	25%		Breast	192,370	27%
Lung & bronchus	116,090	15%		Lung & bronchus	103,350	14%
Colon & rectum	75,590	10%		Colon & rectum	71,380	10%
Urinary bladder	52,810	7%		Uterine corpus	42,160	6%
Melanoma of the skin	39,080	5%		Non-Hodgkin lymphoma	29,990	4%
Non-Hodgkin lymphoma	35,990	5%		Melanoma of the skin	29,640	4%
Kidney & renal pelvis	35,430	5%		Thyroid	27,200	4%
Leukemia	25,630	3%		Kidney & renal pelvis	22,330	3%
Oral cavity & pharynx	25,240	3%		Ovary	21,550	3%
Pancreas	21,050	3%		Pancreas	21,420	3%
All Sites	**766,130**	**100%**		**All Sites**	**713,220**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	88,900	30%		Lung & bronchus	70,490	26%
Prostate	27,360	9%		Breast	40,170	15%
Colon & rectum	25,240	9%		Colon & rectum	24,680	9%
Pancreas	18,030	6%		Pancreas	17,210	6%
Leukemia	12,590	4%		Ovary	14,600	5%
Liver & intrahepatic bile duct	12,090	4%		Non-Hodgkin lymphoma	9,670	4%
Esophagus	11,490	4%		Leukemia	9,280	3%
Urinary bladder	10,180	3%		Uterine Corpus	7,780	3%
Non-Hodgkin lymphoma	9,830	3%		Liver & intrahepatic bile duct	6,070	2%
Kidney & renal pelvis	8,160	3%		Brain & other nervous system	5,590	2%
All Sites	**292,540**	**100%**		**All Sites**	**269,800**	**100%**



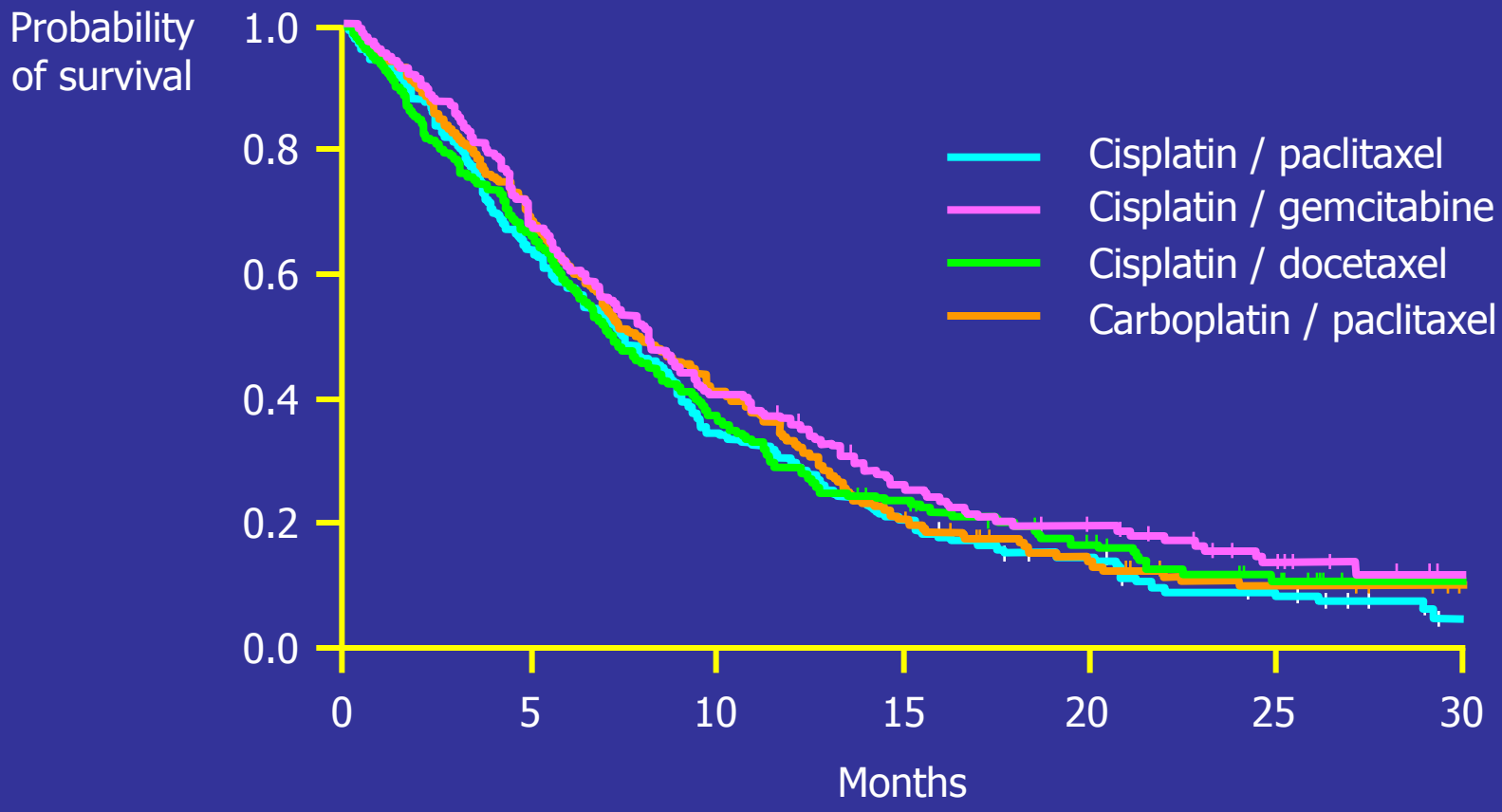
Jemal, A. et al. CA Cancer J Clin 2009

Cáncer de pulmón: cifras

- CP de célula pequeña: 15%
- CP no célula pequeña: 85%
  - 85-90% fumadores
  - 40 % diagnosticados estadio IV
  - Supervivencia en enfermedad avanzada a 5 años: <5%
  - Tratamiento estándar: quimioterapia basada en platino

Jemal. CA Cancer J Clin 2011

A ceiling has been reached in the efficacy of 1st-line chemotherapy for advanced NSCLC



ECOG trial 1594
ECOG = Eastern Cooperative Oncology Group

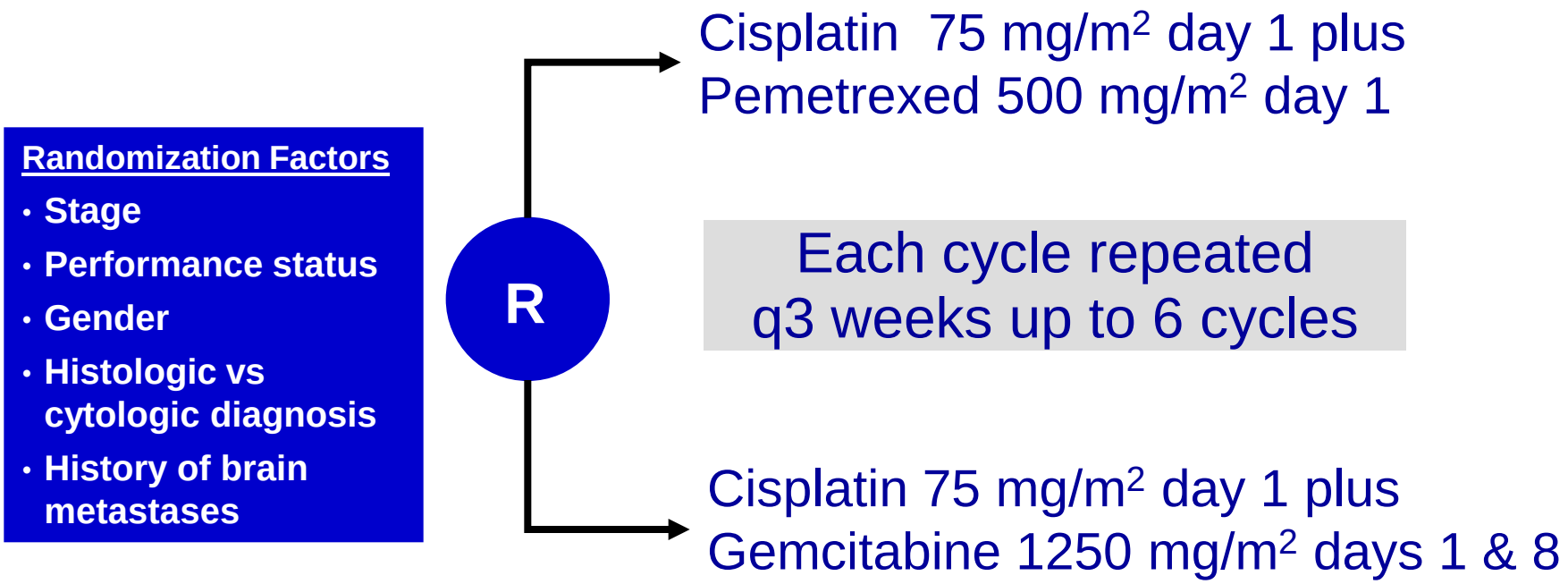
Schiller JH, et al. NEJM 2002;346:92-8

Regimen de elección en primera línea

- En ausencia de diferencias clínicamente relevantes en cuanto a eficacia, DEPENDE DE:

  - Perfil de toxicidad
  - Características del paciente (co-morbilidad, PS)
  - Conveniencia (paciente, sistema sanitario)
  - Costes (paciente, hospital, patentes)
  - Experiencia

Cis/Pem vs Cis/Gem in First-line NSCLC Study Design

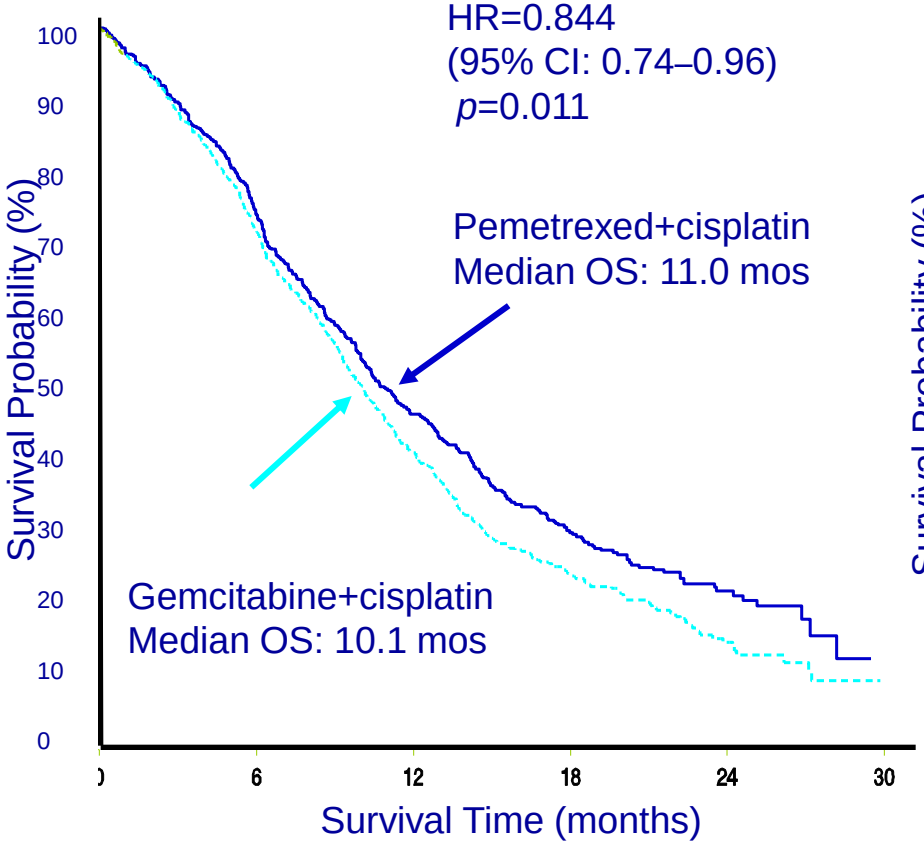


Vitamin B_{12}, folate, and dexamethasone given in both arms

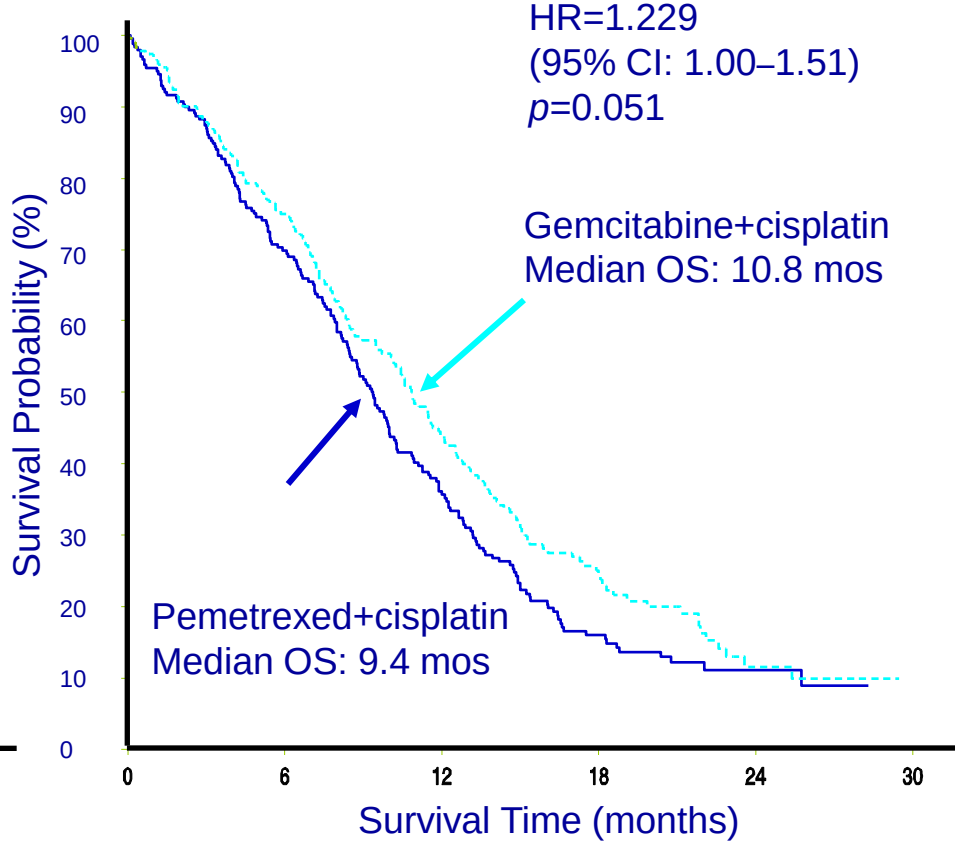
Scagliotti GV et al, Presented at 12th World Conference on Lung Cancer: Sept 5, 2007; Seoul, Korea.

Pemetrexed/Cis vs Gem/Cis in1st-line NSCLC: Prospective Analysis of Histology and OS

Nonsquamous* (n=1252)



Squamous (n=473)



* Nonsquamous=adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

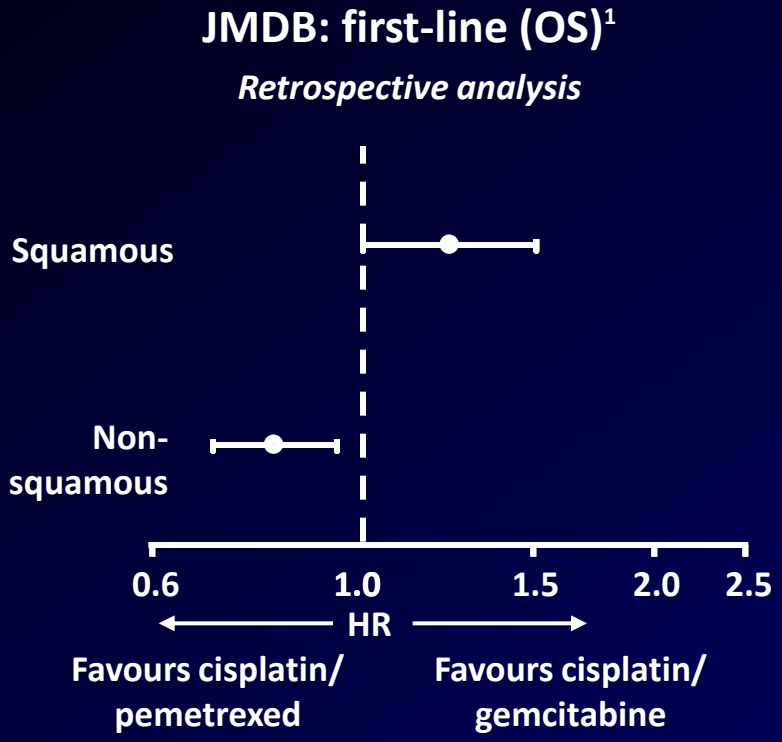
EDITORIAL

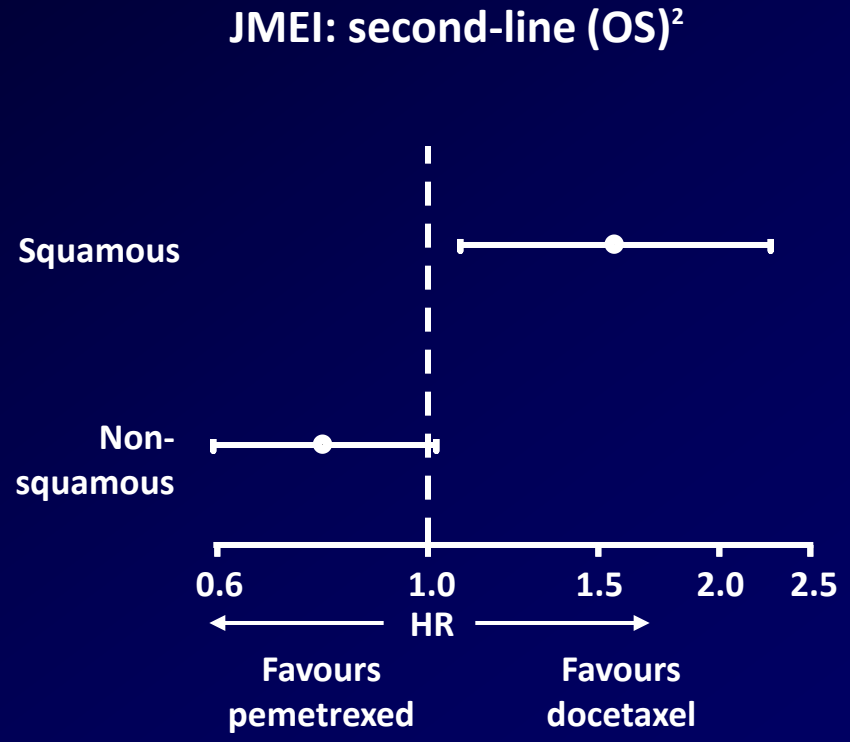
First-Line Chemotherapy for Non–Small-Cell Lung Cancer: Is There a Superior Regimen Based on Histology?

Lawrence H. Einhorn, *Division of Hematology-Oncology, Indiana University Department of Medicine, Indianapolis, IN*

The question posed by this editorial was whether there is a superior regimen based on histology. Is cisplatin plus pemetrexed a superior regimen for adenocarcinoma? Is it inferior in squamous cell carcinoma? These questions will continue to be debated. However, I

Pemetrexed: three phase III trials show lack of efficacy in squamous histology



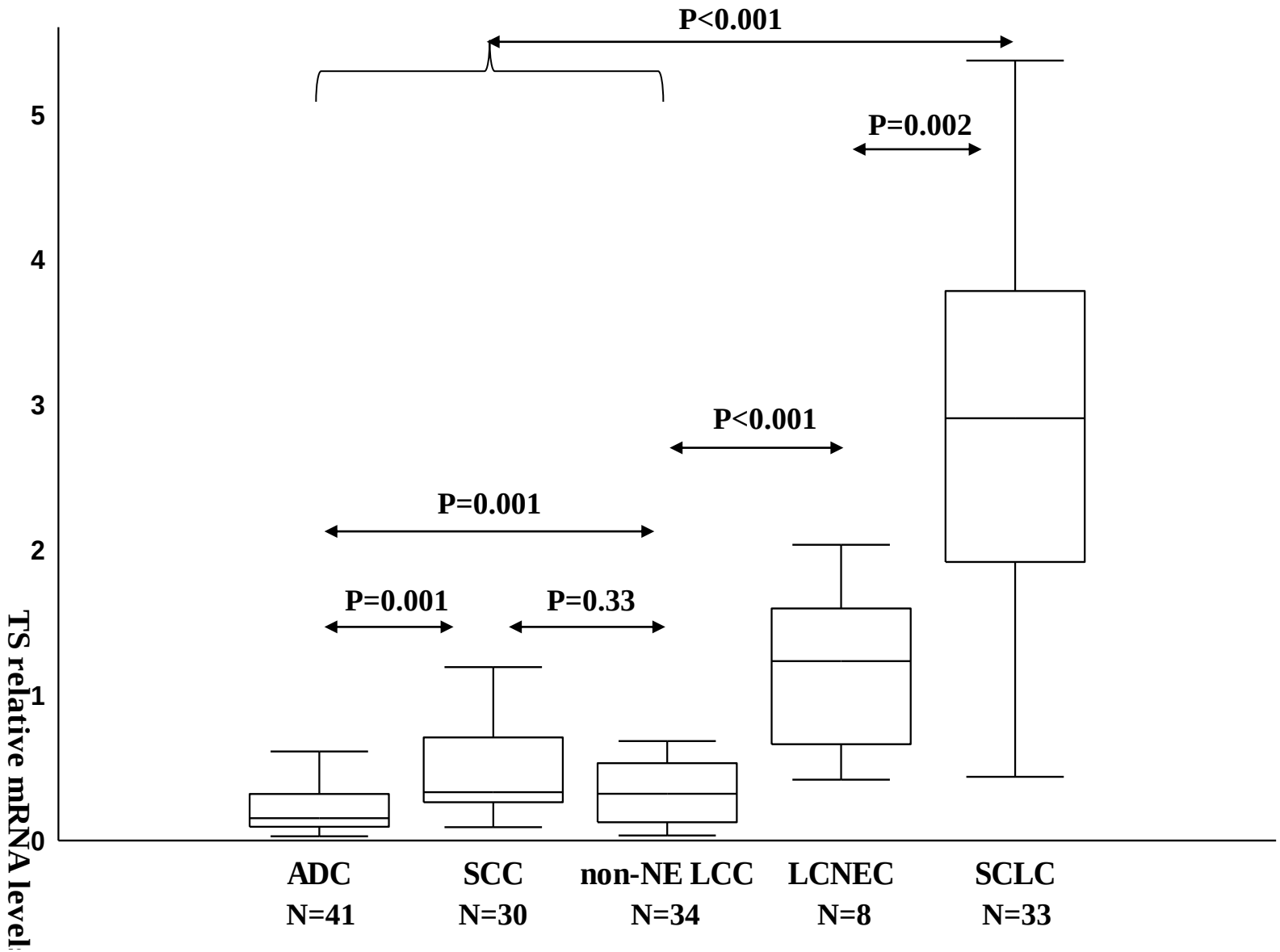


JMEN: maintenance[3]

Median PFS: pemetrexed 2.43 months vs placebo 2.50 months

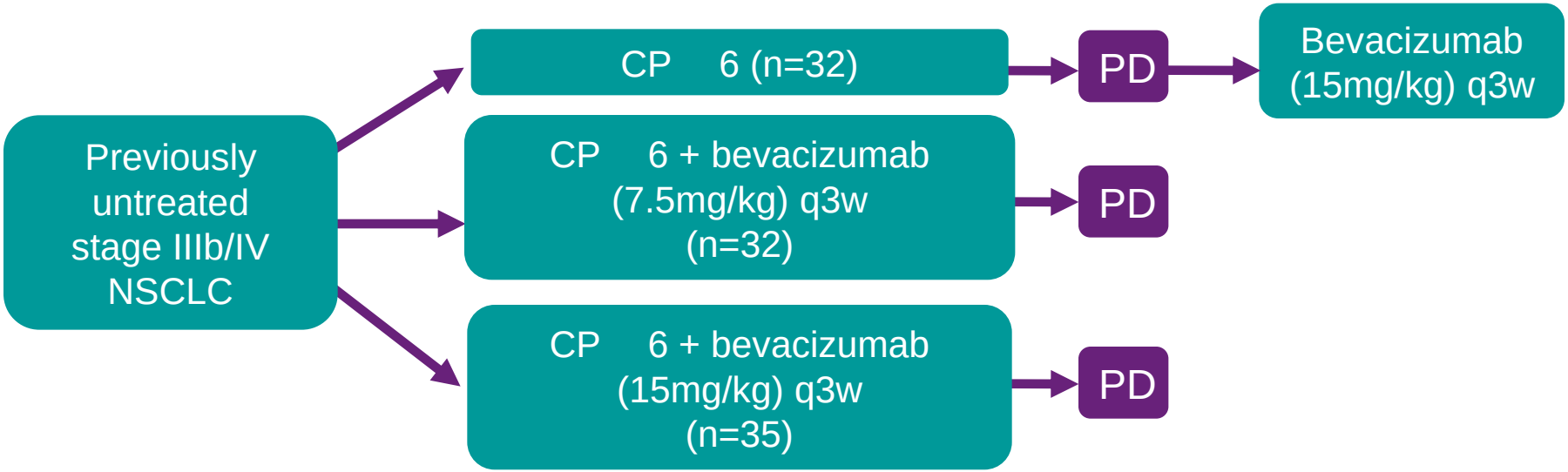
[1]Scagliotti, et al. JCO 2008; [2]Peterson, et al. EJC Suppl. 2007
[3]Ciuleanu, et al. ASCO 2008

TS mRNA Expression in Lung Cancer (n=146)



Monica V. et al. Clin. Cancer Res. 2009

Phase II trial of bevacizumab in NSCLC



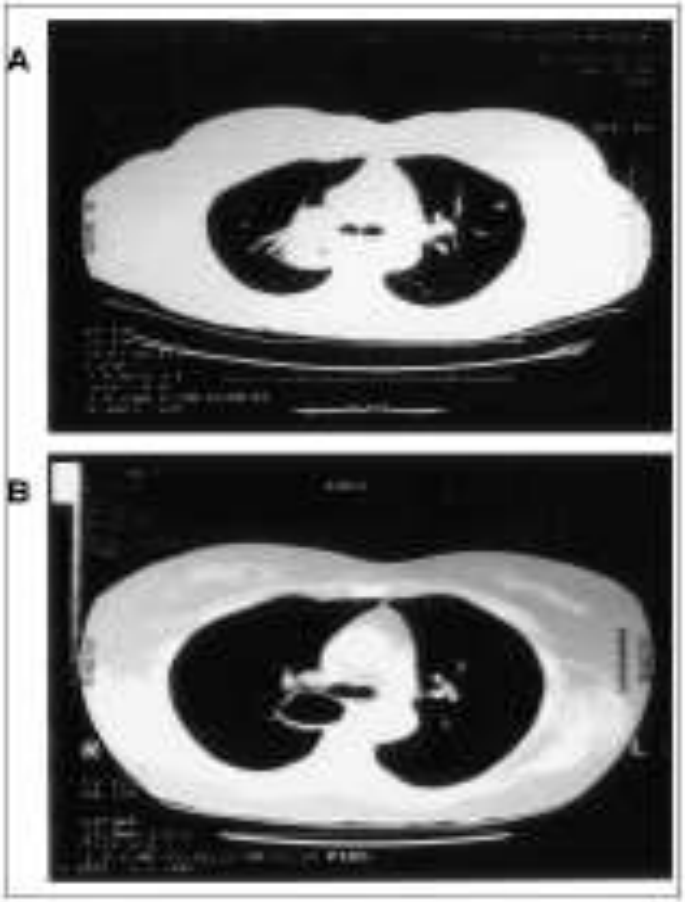
- End points include time to progression, duration of response and survival
- Bevacizumab administered every 3 weeks
- Chemotherapy administration
  - paclitaxel 200mg/m^2 iv every 3 weeks
  - carboplatin iv to AUC 6 every 3 weeks following paclitaxel infusion

AUC = area under the curve
PD = progression of disease

Johnson DH, et al. J Clin Oncol 2004;22:2184-91

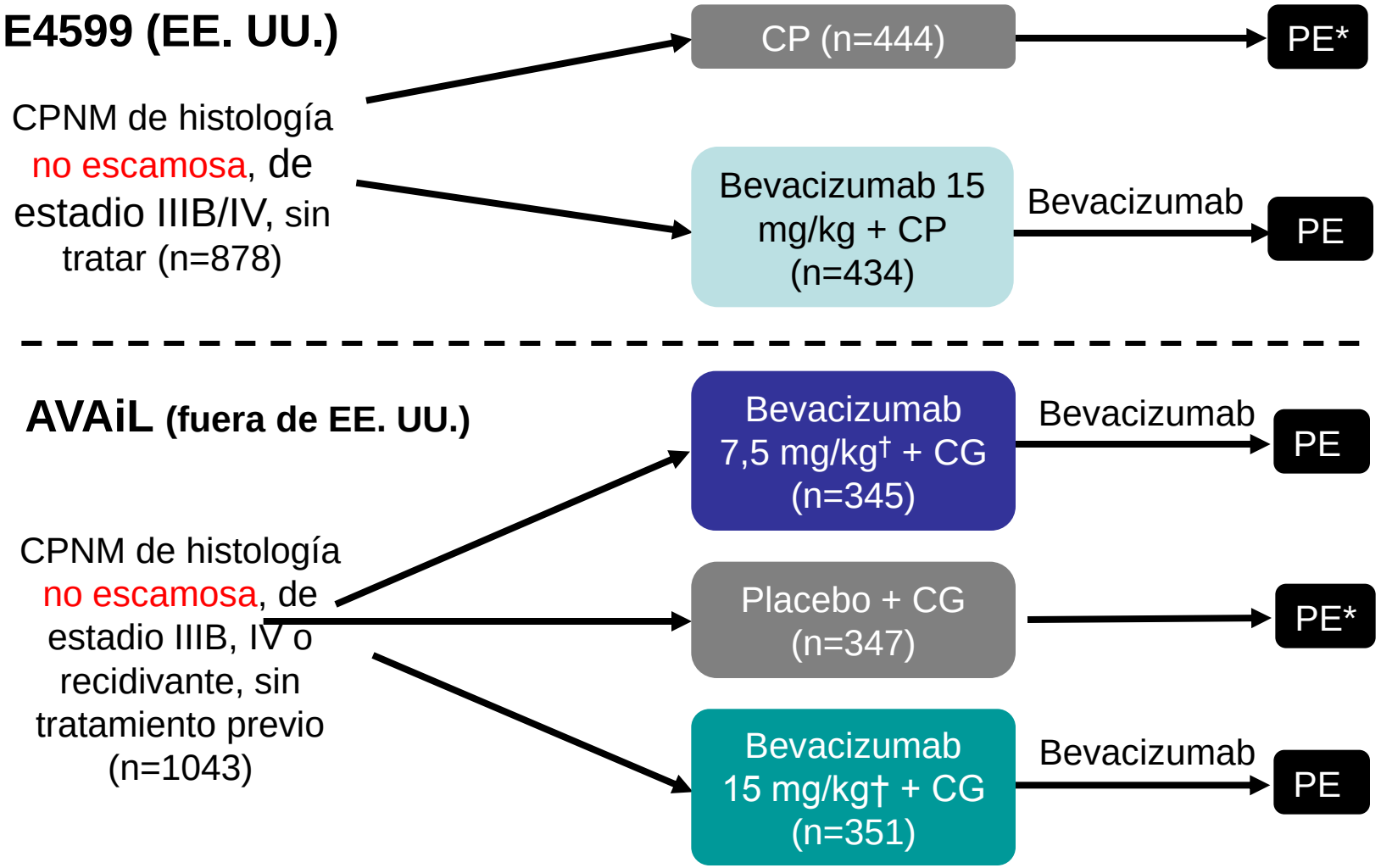
Phase II trial of bevacizumab plus CP in NSCLC (AVF0757): summary

- This 'proof of principal' trial demonstrated that bevacizumab therapy is feasible and effective in patients with NSCLC
- The addition of bevacizumab to CP was generally well tolerated
- Severe, pulmonary haemorrhage was a concern in 6/66 (9%) patients receiving bevacizumab
  - apparent risk factors
    - squamous-cell histology (4/6)
    - centrally located cavitary or necrotic tumours (5/6)
- Based on these observations, patients with predominantly squamous-cell carcinoma were excluded from future trials



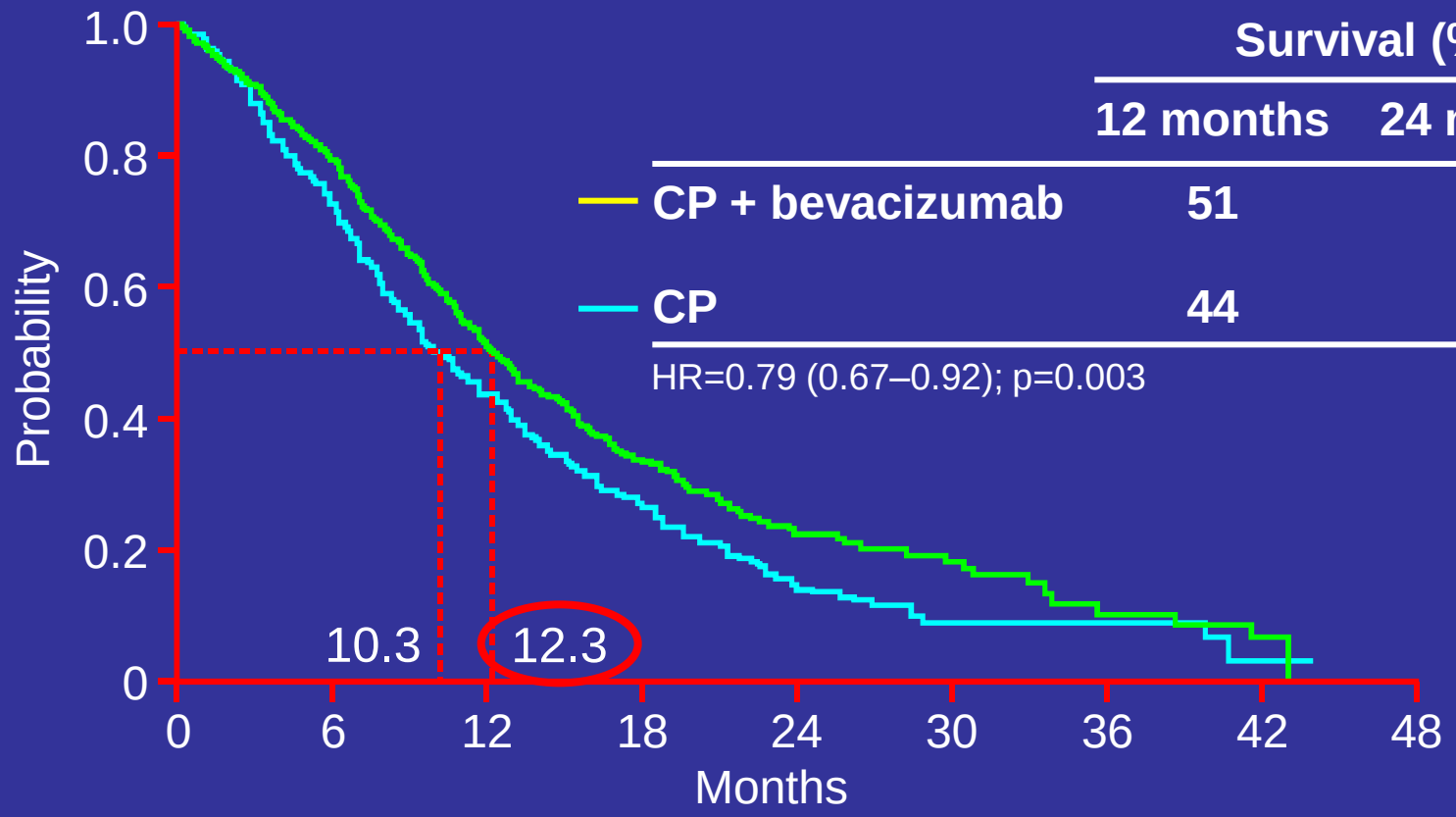
Johnson, et al. JCO 2004

Estudios pivotales de bevacizumab combinado con quimioterapia con platino para el CPNM



*No se permitió el cruce de tratamientos; †Dosis de Avastin cada 3 semanas
CG = cisplatino/gemcitabina; CP = carboplatino/paclitaxel; PE = progresión de la enfermedad

E4599 trial: improvement in overall survival when bevacizumab is added to standard first-line therapy



	Survival (%)	
	12 months	24 months
CP + bevacizumab	51	23
CP	44	15

HR=0.79 (0.67–0.92); p=0.003

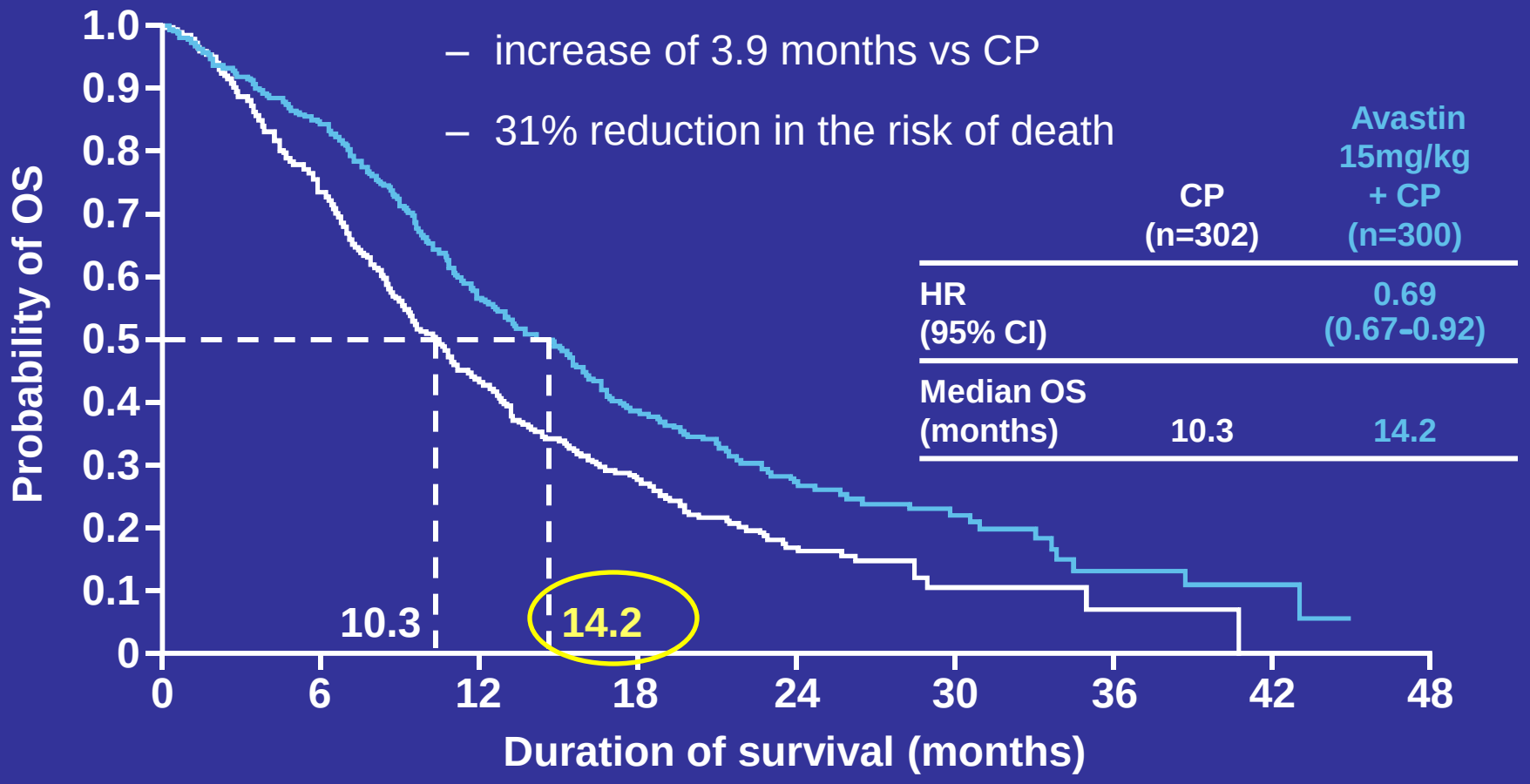
In this milestone trial, bevacizumab-based therapy extended median overall survival beyond 1 year

HR = hazard ratio

Sandler A, et al. N Engl J Med 2006

E4599: unprecedented OS benefit in Avastin-treated patients with *adenocarcinoma* histology

- Avastin-based therapy extends OS to 14.2 months
  - increase of 3.9 months vs CP
  - 31% reduction in the risk of death



	CP (n=302)	Avastin 15mg/kg + CP (n=300)
HR (95% CI)		0.69 (0.67–0.92)
Median OS (months)	10.3	14.2

Note: preplanned subgroup analysis in E4599

Sandler, et al. JTO 2008;3(Suppl. 4):S283 (Abs. 133)

Cell Adhesion Molecules, Vascular Endothelial Growth Factor, and Basic Fibroblast Growth Factor in Patients with Non – Small Cell Lung Cancer Treated with Chemotherapy with or without Bevacizumab—an Eastern Cooperative Oncology Group Study

Afshin Dowlati,[1] Robert Gray,[3] Alan B. Sandler,[2] Joan H. Schiller,[4] and David H. Johnson[2]

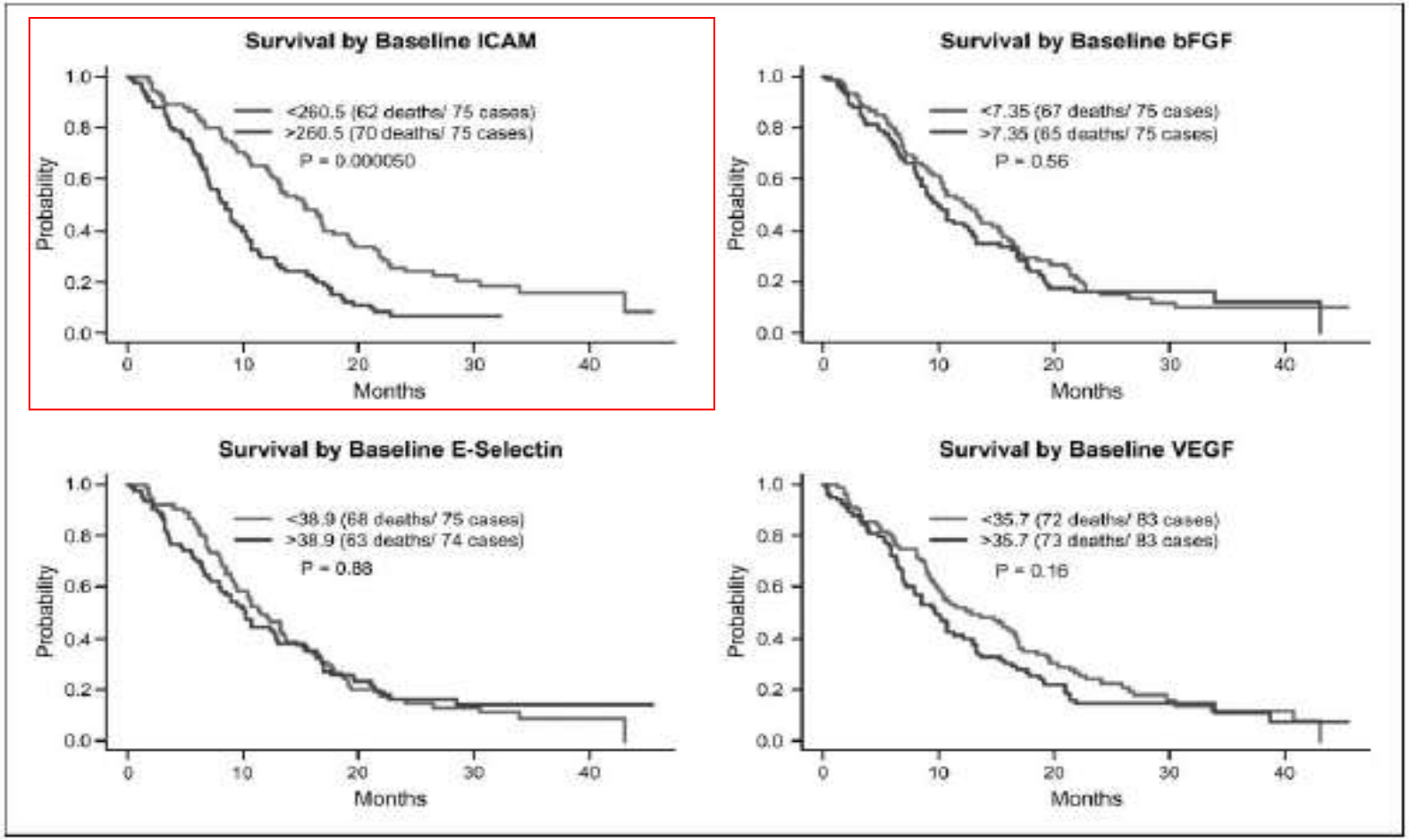


Fig. 1. Survival based on baseline factor levels.

Regimen de elección en primera línea

- En ausencia de diferencias clínicamente relevantes en cuanto a eficacia, DEPENDE DE:
  - ***Histología***
  - Perfil de toxicidad
  - Características del paciente (co-morbilidad, PS)
  - Conveniencia (paciente, sistema sanitario)
  - Costes (paciente, hospital, patentes)
  - Experiencia

You Just Can't Call it Lung Cancer Anymore

George R. Simon, MD, and Gerard A. Silvestri, MD, MS†*

We envision a future in which patients are diagnosed and staged for their lung cancer using a much more rigorous approach. Rather than prescribing treatment for a patient with "stage IV NSCLC," clinicians should move toward describing the same patient as T2N2M1a, stage IV, invasive mucinous adenocarcinoma, epidermal growth factor receptor+, and *Kras*−. The new classification system for adenocarcinoma described herein provides one of the missing pieces needed to accomplish that goal and allows for the personalized treatment of lung cancer. We applaud this effort because you just cannot call it lung cancer anymore.

REFERENCES

1. Travis W. IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma. *J Thorac Onc* 2011;6:244–285.

"Here's my tumor profile..."

The New Yorker

BR.21 Study Design - 2

Stratified by:
Centre
PS, 0/1 *vs* 2/3
Response to prior Rx
(CR/PR:SD:PD)
Prior regimens,
(1 *vs* 2)
Prior platinum,
(Yes *vs* no)

RANDOMISE

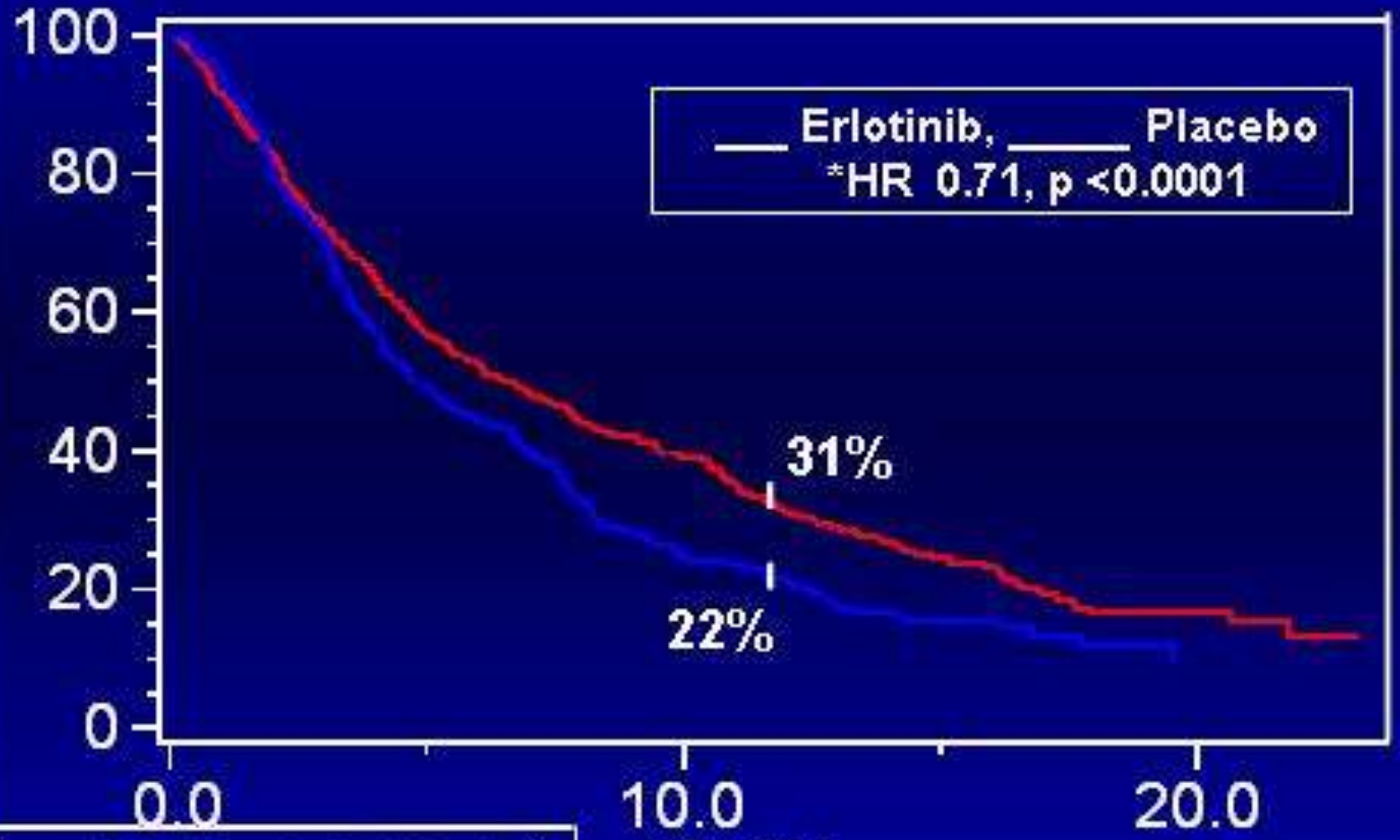
Erlotinib*
150 mg daily

Placebo
"150 mg" daily

*2:1
Randomization

National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

BR.21 Overall Survival



National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

*Adjusted for stratification factors (except centre) AND EGFR status

Clinical characteristics and response to EGFR TKIs

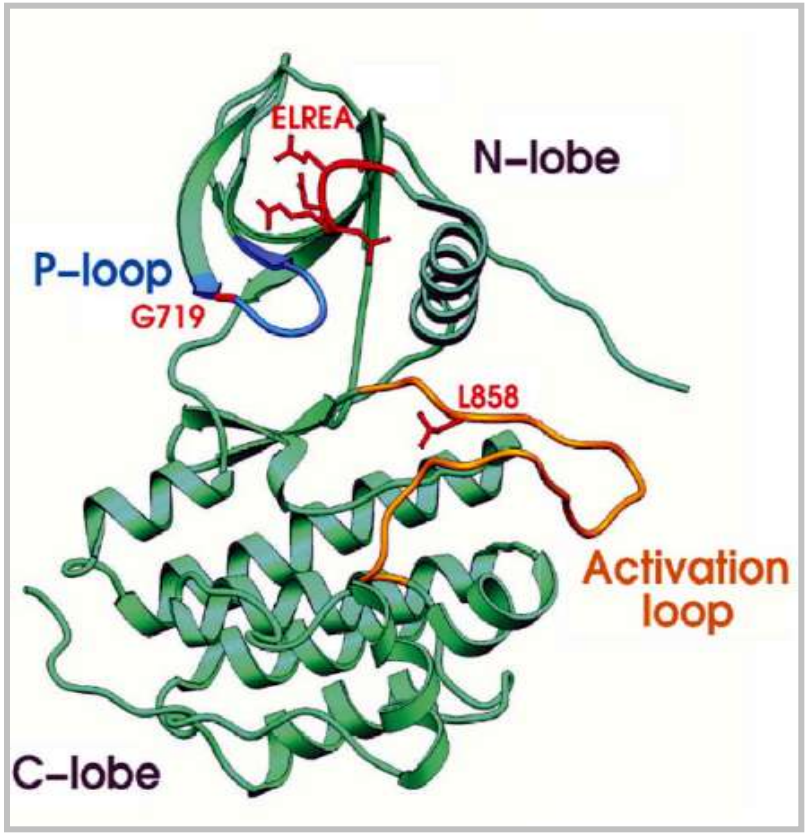
Clinical factors: Never-smoked, BAC features, female	Overall Response Rate (%)	Median Survival (months)
3 of 3	56%	14 + m
2 of 3	30%	12 m
1 of 3	9%	5 m
0 of 3	3%	3 m

Shah JCO 2005

2004 Spring
Activating mutations of the EGFR genes・・・

Lynch et al., NEJM, Paez et al., Science

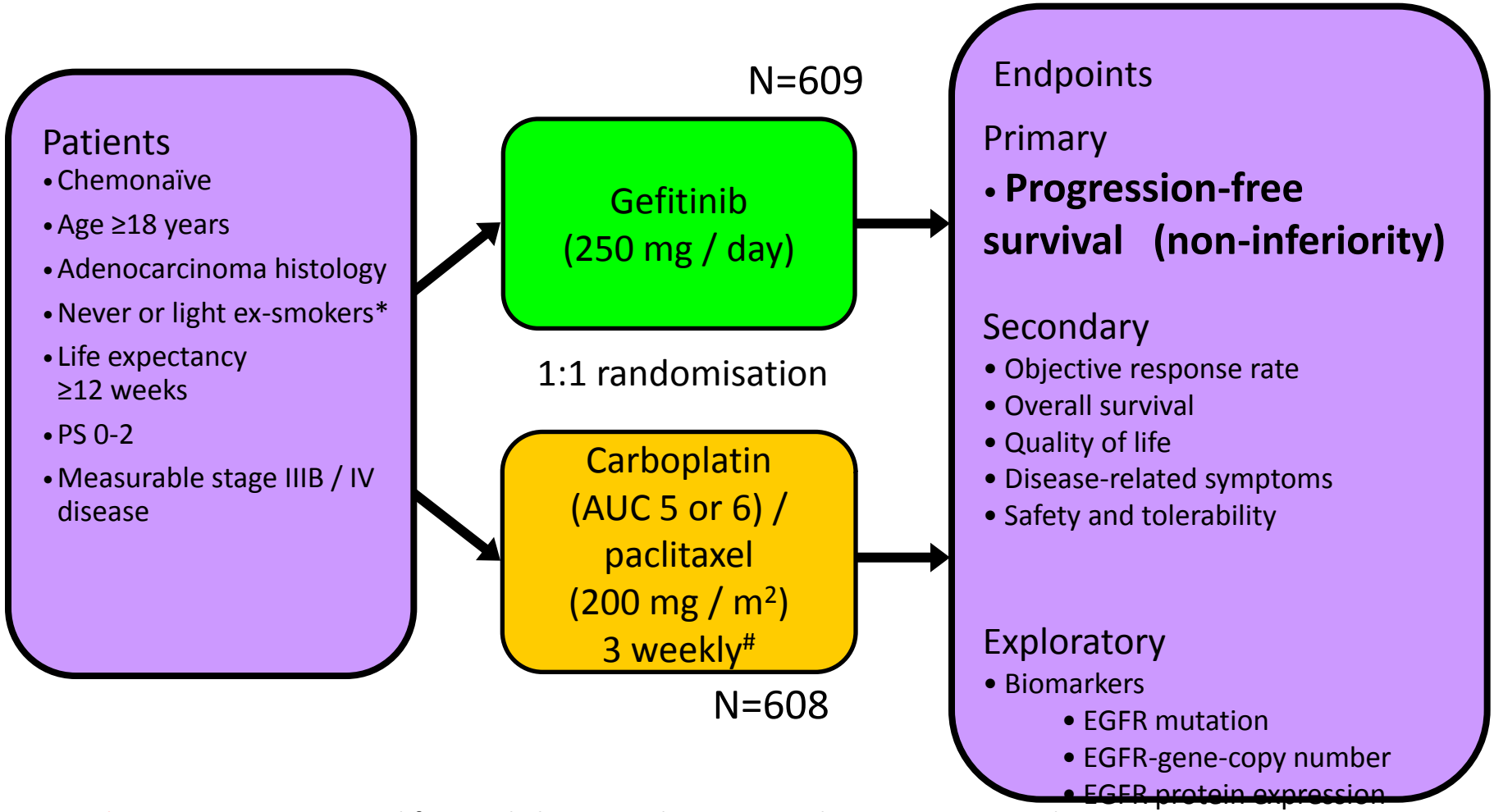
- Lung cancer specific
- In distinct subsets of patients
  - Adeno, Non smokers, Asians, Females
- Tyrosine kinase domain of the EGFR
  - Exon 19 deletion
  - L858R
  - G719, Exon 20 insertion, others
- Striking correlation with EGFR-TKI response



IPASS

Phase III, randomized, open-label, first-line study of gefitinib vs. carboplatin / paclitaxel in clinically selected patients with advanced non-small cell lung cancer

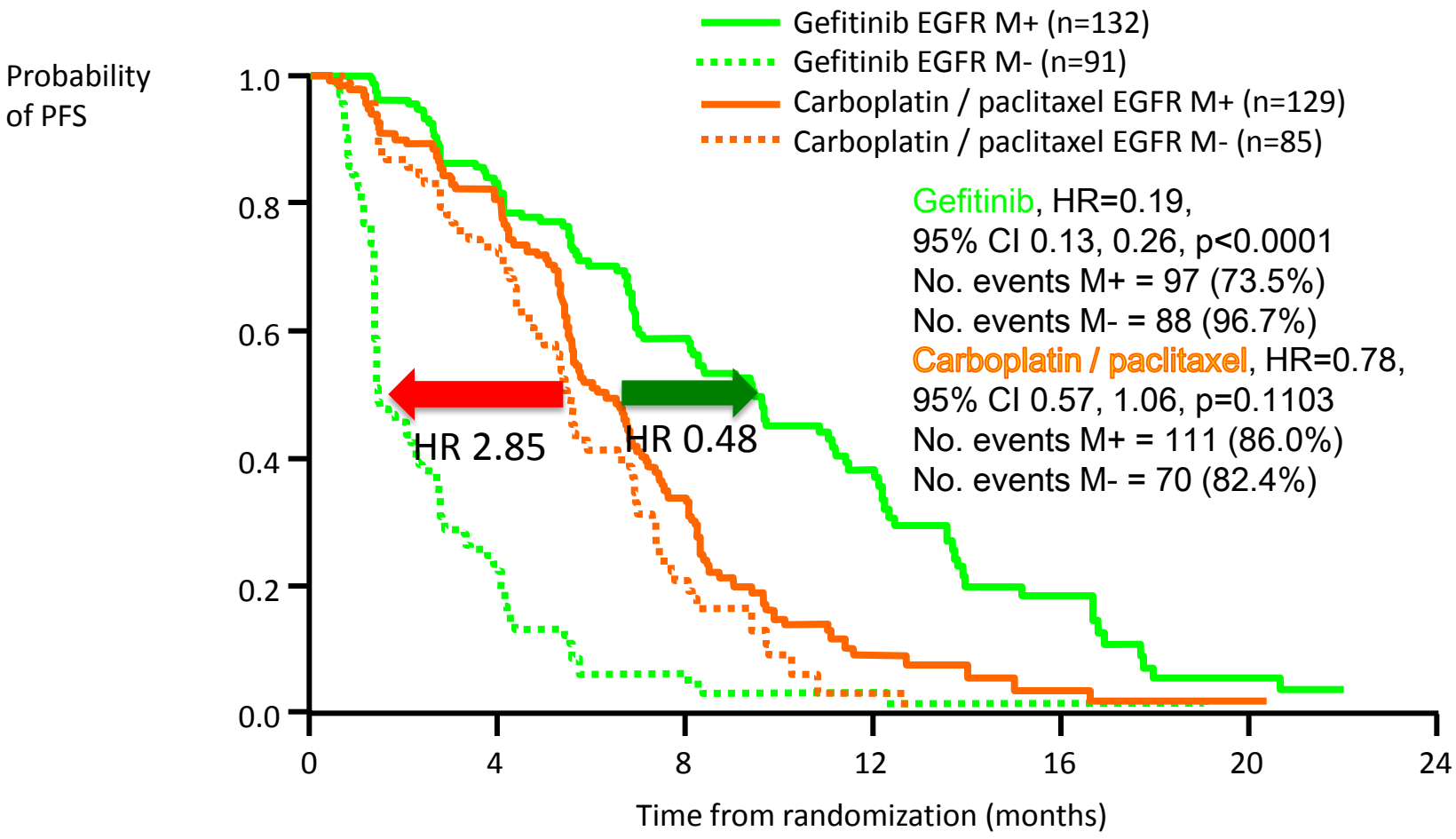
Mok et al. NEJM 2009



*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles

Carboplatin / paclitaxel was offered to gefitinib patients upon progression

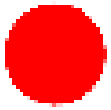
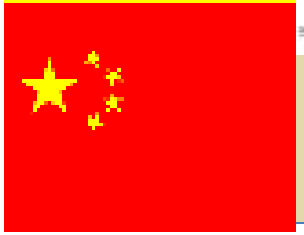
IPASS: Comparison of PFS by mutation status within treatment arms



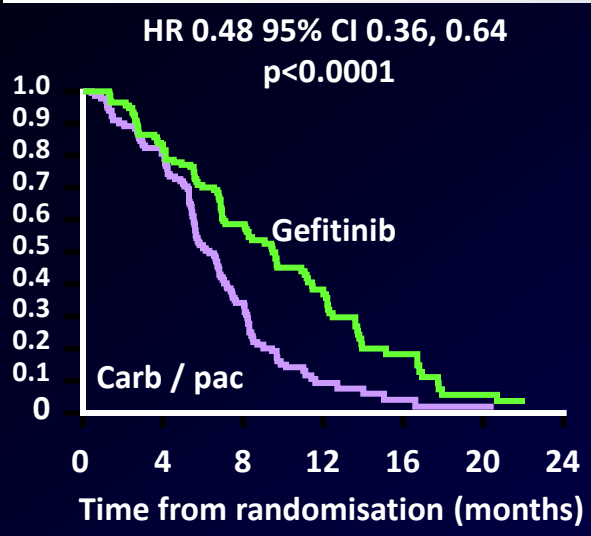
Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M- group

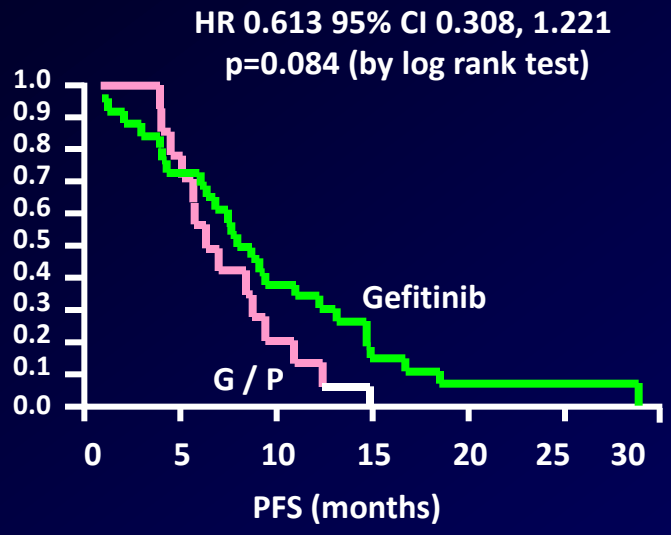
M+, mutation positive; M-, mutation negative

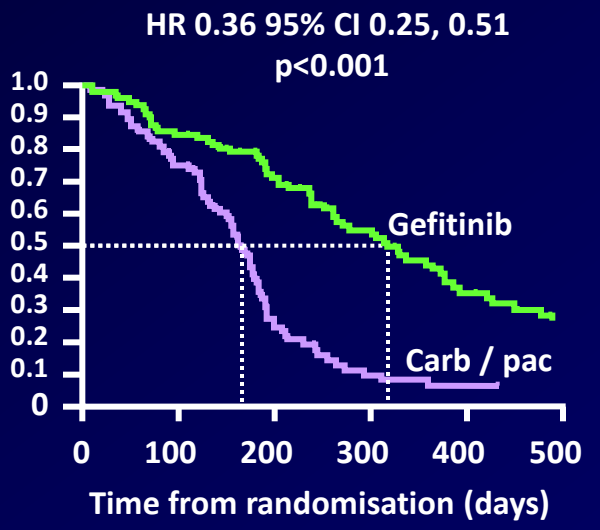
Phase III studies comparing EGFR-TKI with platinum doublet in patients selected by EGFR mutational status

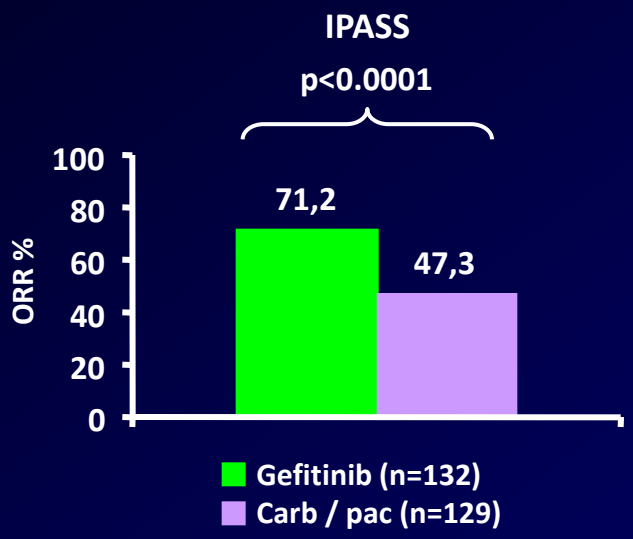
Group	Study	EGFR mutation	N	Primary endpoint	TKI	Control
	3405	X19, L858R	200 (HR=0.56)	PFS	G	CDDP+DOC
		X19, L858R, G719X, L861Q	300 (HR=0.69)	PFS	G	CBDCA+PAC
	EURTARC	X19, L858R	130	PFS	E	Pt doublet
	ML20981	EGFR mutation	150	PFS	E	CBDCA+GEM

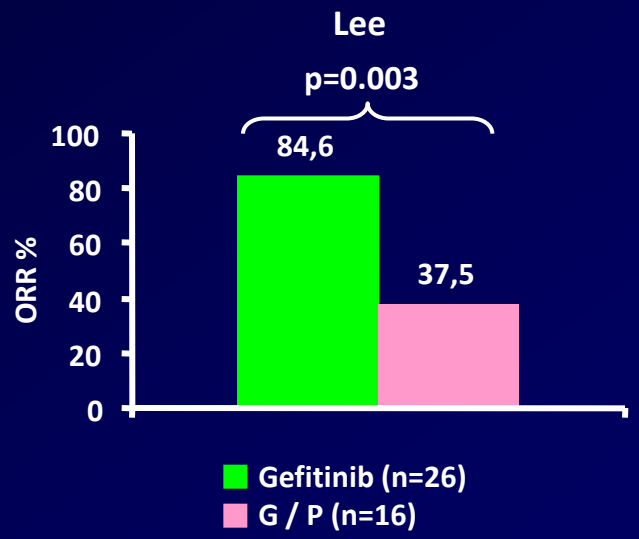
Gefitinib standard of care in first-line EGFR mut+ NSCLC: Phase III Asiatic study results

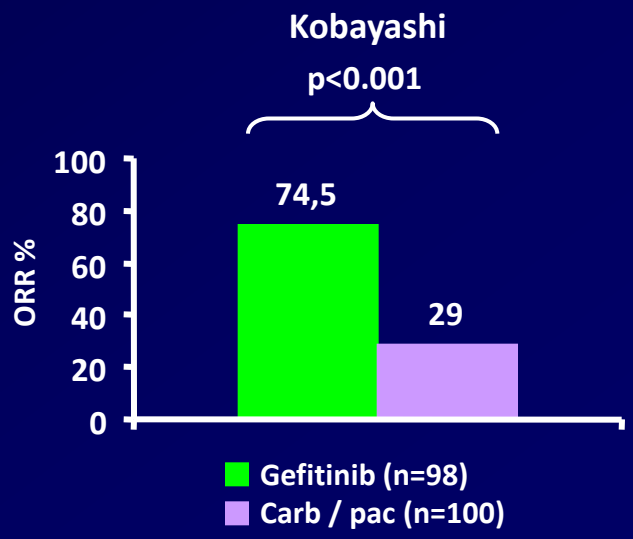








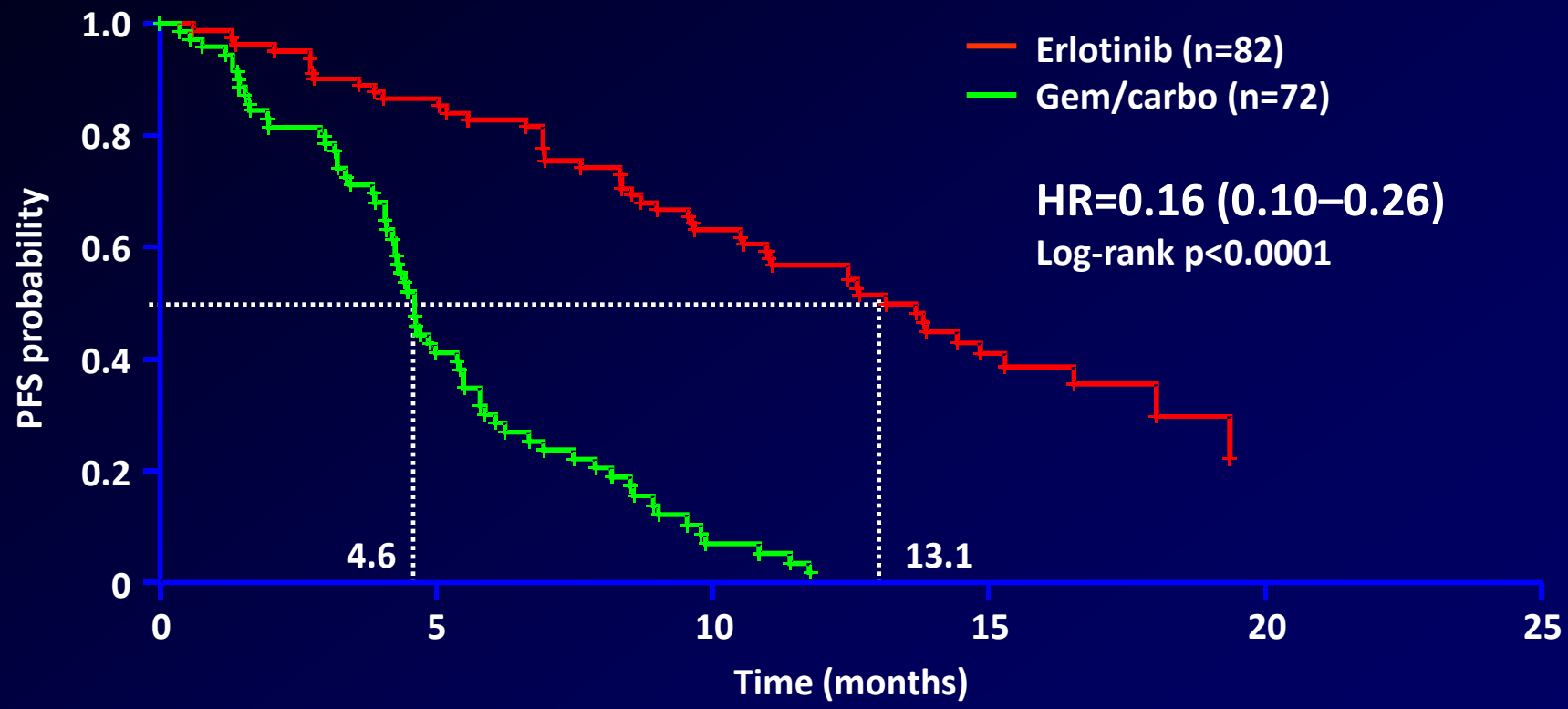




ORR, objective response rate

Mok et al 2008, Lee et al 2009, Kobayashi et al 2009

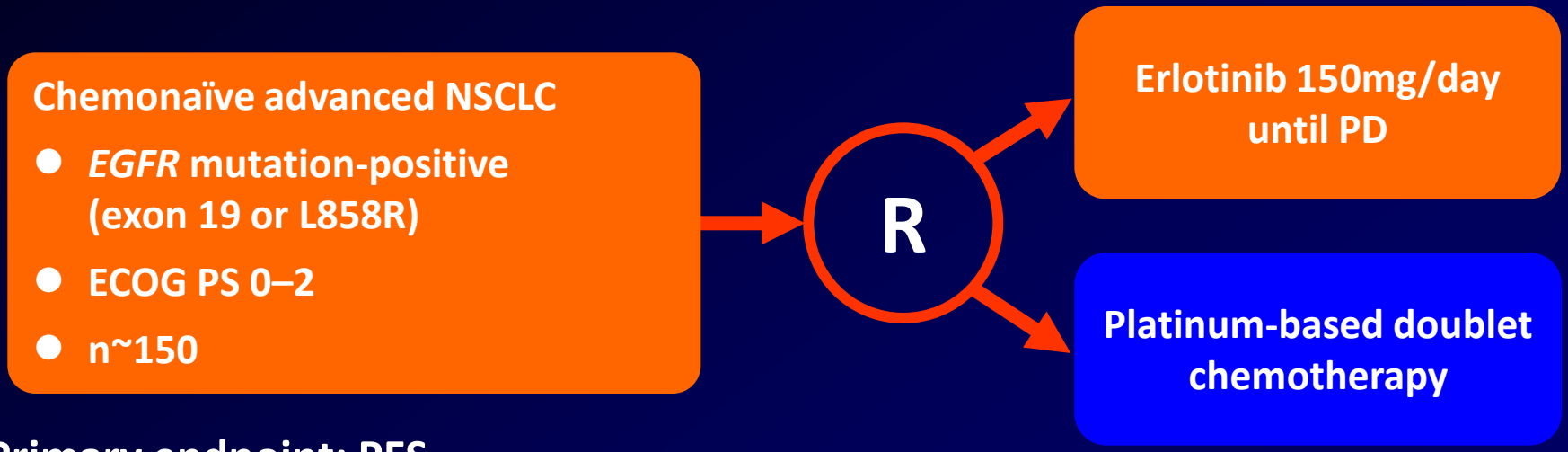
OPTIMAL: Progression-free survival



Patients at risk						
Erlotinib	82	70	51	20	2	0
GC	72	26	4	0	0	0

EURTAC: erlotinib first-line in *EGFR* mutation+ NSCLC

- Phase III study initiated by the Spanish Lung Cancer Group (GECP)
- Recruitment ongoing in Spain, Italy and France

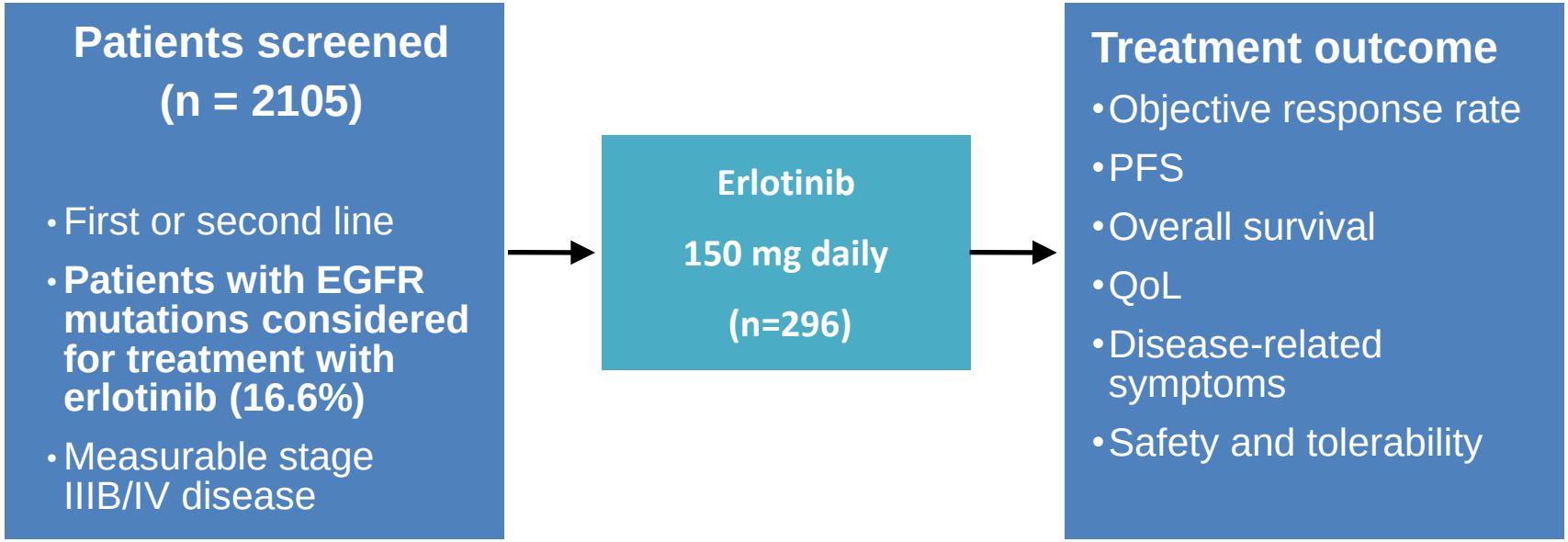


- Primary endpoint: PFS
- Secondary endpoints: ORR, 1-year survival, OS, safety, QoL, localisation of PD

ORR = objective response rate; QoL = quality of life

Prospective screening for EGFR mutations

Evaluation of feasibility and effect on clinical outcome

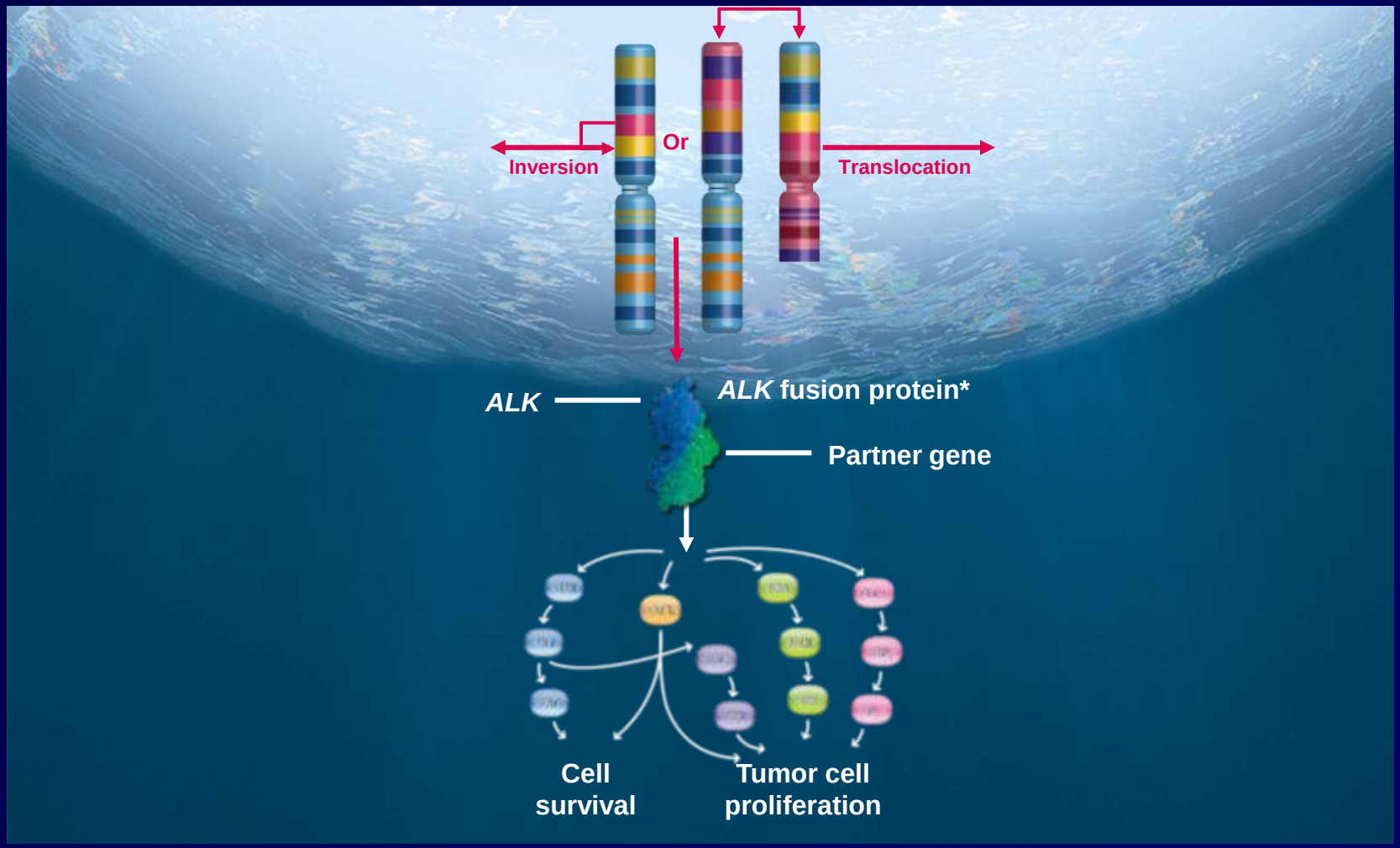


Assessment of EGFR mutations:

- Samples from pre-treatment biopsy
- 2060 paraffin-embedded tissues and 45 fresh specimens
- L858R (Cycleave method) or exon 19 deletion (fragment analysis)
- Confirmation by direct sequencing

Rosell R, et al. *N Engl J Med* 2009;361:958–67

Formation of the *ALK* fusion gene



***Subcellular localization of the ALK fusion gene, while likely to occur in the cytoplasm, is not confirmed.[1,2]**

1. Inamura K et al. J Thorac Oncol 2008;3:13-17
2. Soda M et al. Proc Natl Acad Sci U S A 2008;105:19893-19897
Figure based on: Chiarle R et al. Nat Rev Cancer 2008;8(1):11-23
Mossé YP et al. Clin Cancer Res 2009;15(18):5609-5614; and Data on file. Pfizer Inc.

ALK fusion gene

- **Originally discovered in lymphomas, alterations in the anaplastic lymphoma kinase (*ALK*) gene have been identified as an direct driver of oncogenesis [1,2,3]**
- **The EML4-ALK fusion gene was identified in 2007 by Soda *et al* in NSCLC[4]**
- **Preliminary epidemiology suggests approximately 3-5% of patients have NSCLC tumors have the ALK fusion gene[5]**
- **Crizotinib is an oral, potent and selective small-molecule ATP-competitive inhibitor of ALK and its oncogenic variants[6,7]**

1. Chiarle R, et al. Natl Rev Cancer. 2008;8:11-23
2. Shaw AT, et al. J Clin Oncol. 2009;27:4247-4253.
3. Mossé YP, et al. Clin Cancer Res. 2009;15(18):5609-5614.
4. Soda M, et al. Nature 2007;448:5616
5. Garber K. JNCI. 2010;102:672–675
6. Zou HY, et al. Cancer Res 2007;67:440817
7. Christensen JG, et al. Mol Cancer Ther 2007;6:331422

ALK FISH Analytical Parameters

Well Defined

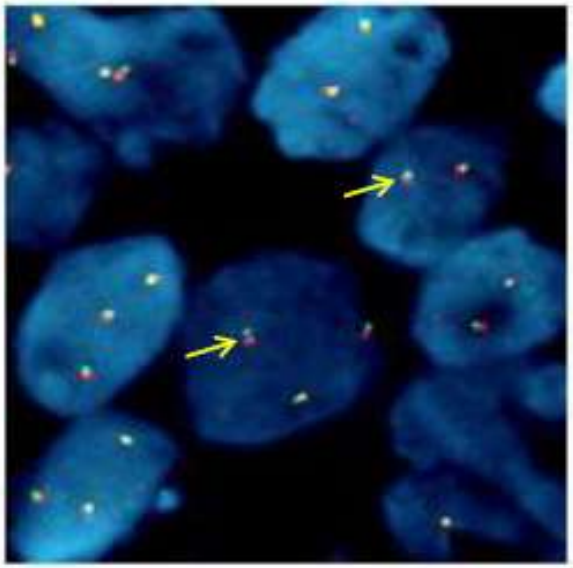
- The 3'ALK/5'ALK is split when red and green signals are separated by a gap >2 signal diameters

- A specimen is positive for ALK rearrangement when showing split signals or single ALK3' signals in >15% of tumor cells

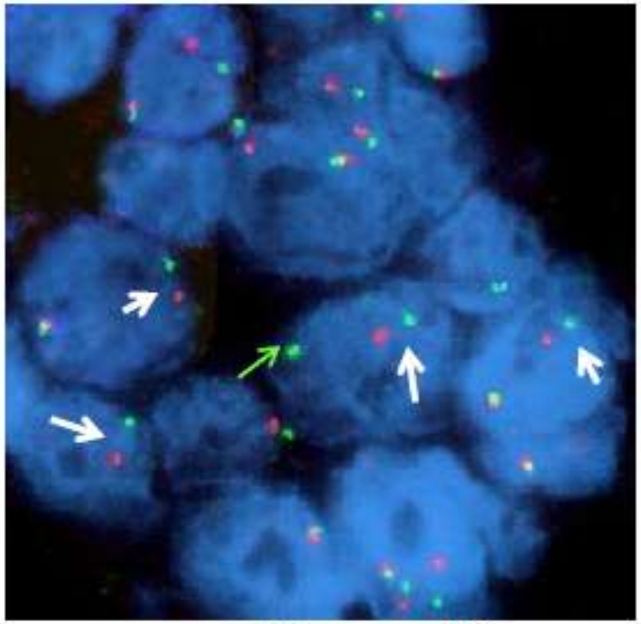
- Minimum of 50 tumor cells

- Validated in clinical trial

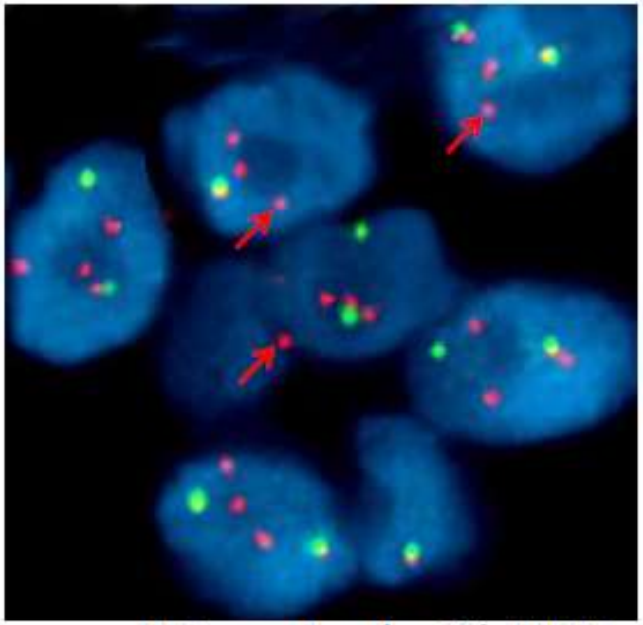
ALK Break Apart FISH Patterns in NSCLC



Negative for rearrangement



positive split



positive single 3’ ALK

Challenges in Analysis and Interpretation

a. **Selection of nuclei to score: Requires experience**
   - Must choose tumor nuclei
   - Inclusion of macrophages and other non-tumor cells will dilute the positivity

b. **Definition of "2-diameter gap":** Requires practice

c. **Low frequency of positive cells (<30%)**
   - Requires independent confirmation

d. **Rare atypical features**
   - Have unknown significance
     - additional studies are necessary
     - independent testing is recommended

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

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

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

EL Kwak et al. NEJM 2010

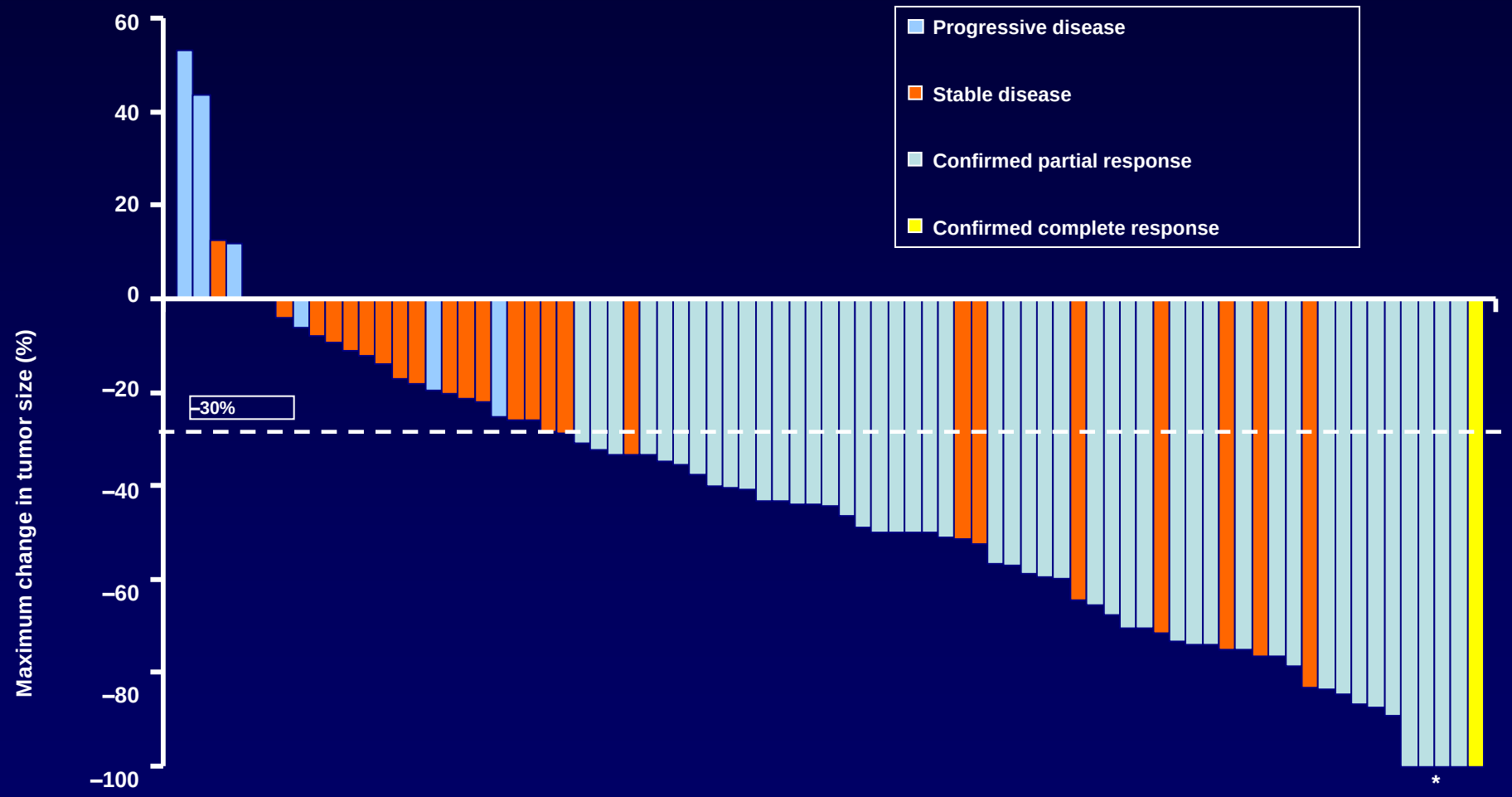
Clinical and Demographic Features of Patients with *ALK*-positive NSCLC

		N=82
Mean (range) age, years		51 (25–78)
Gender, male/female		43/39
Performance status,* n (%)	0	24 (29)
	1	44 (54)
	2	13 (16)
	3	1 (1)
Race, n (%)	Caucasian	46 (56)
	Asian	29 (35)
Smoking history, n (%)	Never smoker	62 (76)
	Former smoker	19 (23)
	Current smoker	1 (1)
Histology, n (%)	Adenocarcinoma	79 (96)
	Squamous	1 (1)
	Other	2 (2)
Prior treatment regimens, n (%)	0	5 (6)
	1	27 (33)
	2	15 (18)
	≥3	34 (41)
	Not reported	1 (1)

*Performance status = Eastern Cooperative Oncology Group

Bang et al. ASCO 2010; EL Kwak et al. NEJM 2010

Tumor Responses to Crizotinib for Patients with *ALK*-positive NSCLC



*Partial response patients with 100% change have non-target disease present

Bang et al. ASCO 2010; EL Kwak et al. NEJM 2010

Alto porcentaje de respuestas independiente de subgrupos clínicos de los pacientes (n=105)

	Objective Response Rate % (n/N)	
No. of prior regimens*		
0	50	(3/6)
1	60	(18/30)
2	56	(10/18)
3	62	(10/16)
> 3	53	(18/34)
Performance status		
0	50	(17/34)
1	54	(30/56)
2	80	(12/15)
Age		
< 65 years	59	(53/90)
≥ 65 years	40	(6/15)
Gender		
Male	60	(31/52)
Female	53	(28/53)

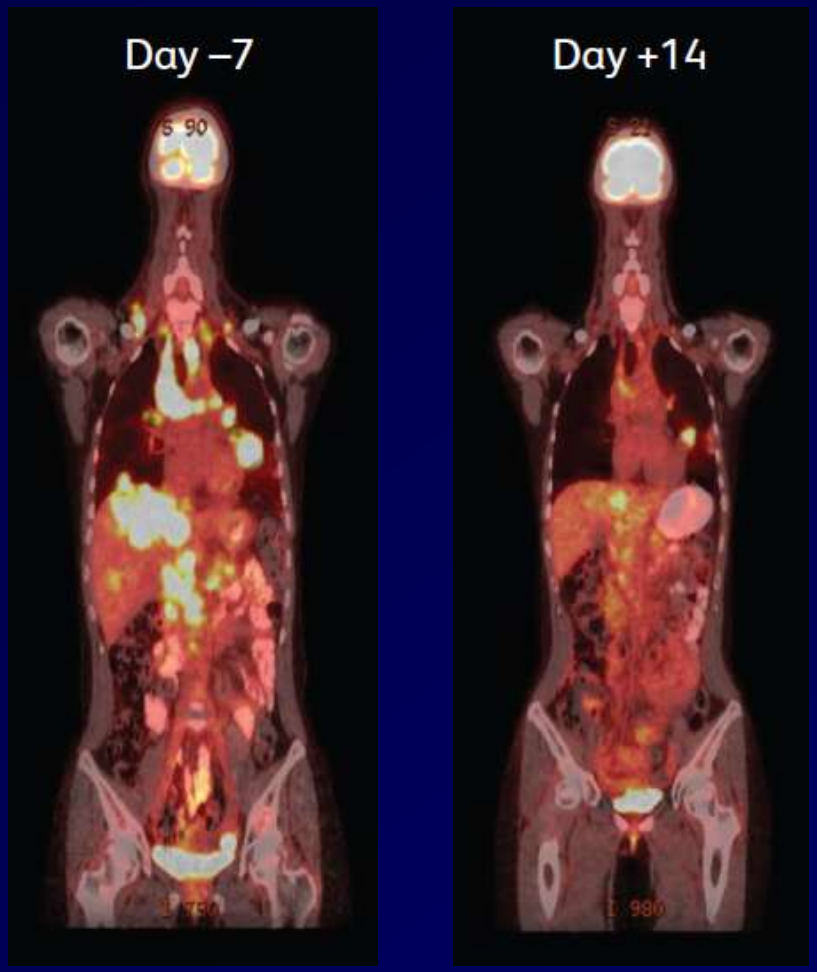
- Median response duration was 36.3 weeks (95% CI: 32.1, 72.9) in patients with an objective response (n=59)}

* Unknown for 1 patient

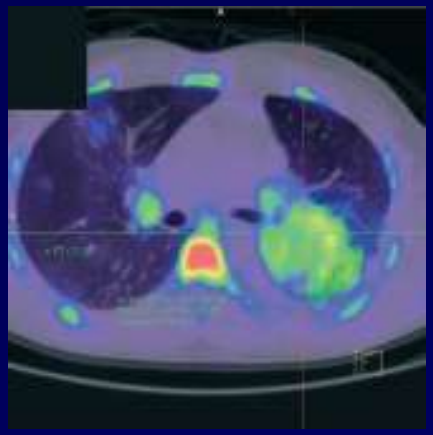
Camidge R et al. Poster 366 presented at the 35th ESMO, 2010

Response to Crizotinib Occurs Rapidly

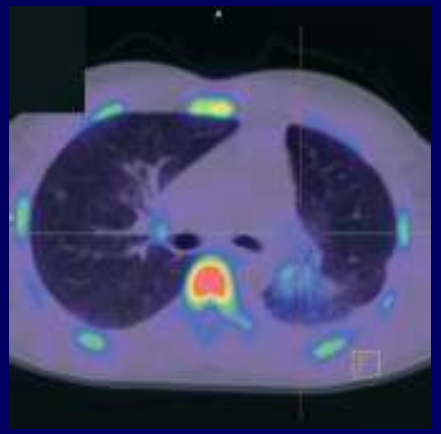
Case 1: Response within 14 days[1]



Case 2: Response within 28 days[2]



Baseline



End of cycle 1

1. Camidge R et al. Poster 366 presented at the 35th ESMO, 2010
2. Solomon B et al. Poster 369 presented at 22nd EORTC-NCI-AACR, 2010

Efectos adversos más frecuentes en CPNCP *ALK*-positivos

AE	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Nausea	58 (51)	1 (1)	0	0	59 (52)
Diarrhea	55 (49)	2 (2)	0	0	57 (50)
Visual impairment	51 (45)	0	0	0	51 (45)
Vomiting	46 (41)	1 (1)	0	0	47 (42)
Constipation	22 (19)	6 (5)	0	0	28 (25)
Peripheral edema	19 (17)	3 (3)	0	0	22 (20)
Decreased appetite	21 (19)	0	0	0	21 (19)
Dizziness	21 (19)	0	0	0	21 (19)
Fatigue	14 (12)	3 (3)	1 (1)	0	18 (16)
ALT increased	3 (3)	6 (5)	4 (4)	1 (1)	14 (12)

Phase III Trials with Crizotinib

PROFILE 1007 (ONGOING)

Key entry criteria (N=318)
- Positive for *ALK* by central laboratory
- 1 prior chemotherapy (platinum-based)

RANDOMIZE

Crizotinib 250 mg BID (n=159)
administered on a continuous dosing schedule

Pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 (n=159)
infused on Day 1 of a 21-day cycle

PROFILE 1014 (Ongoing)

Key entry criteria (N=334)
- *ALK*-positive locally adv./metastatic non-squamous NSCLC
- No prior treatment for advanced disease

RANDOMIZE

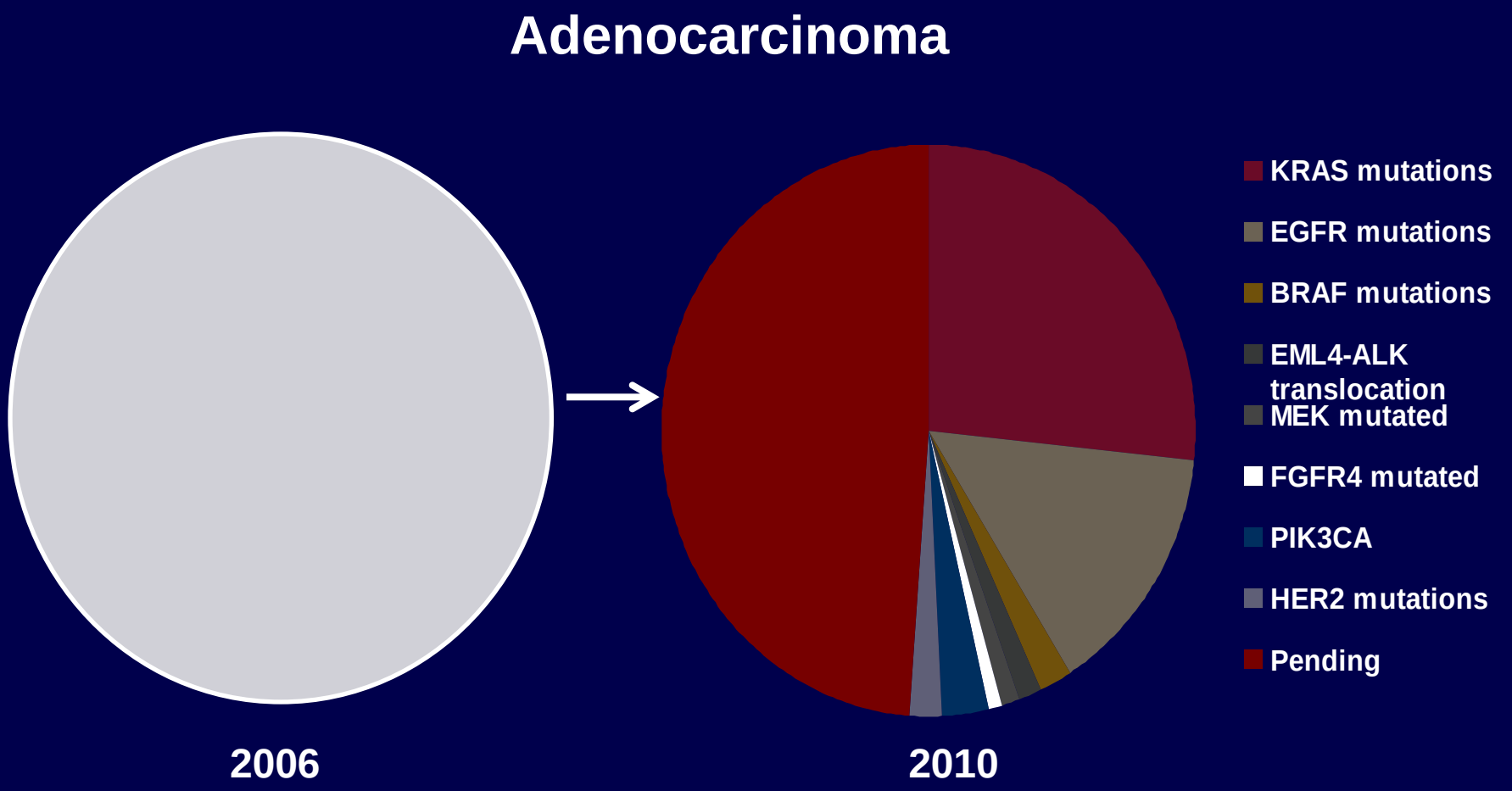
Crizotinib 250 mg BID (n=167)
administered on a continuous dosing schedule

Crossover on PD

Pemetrexed/cisplatin or pemetrexed/carboplatin (n=167)
infused on Day 1 of a 21-day cycle

PROFILE 1007: NCT00932893; PROFILE 1014: NCT01154140

Molecular Subtypes of Lung Adenocarcinoma

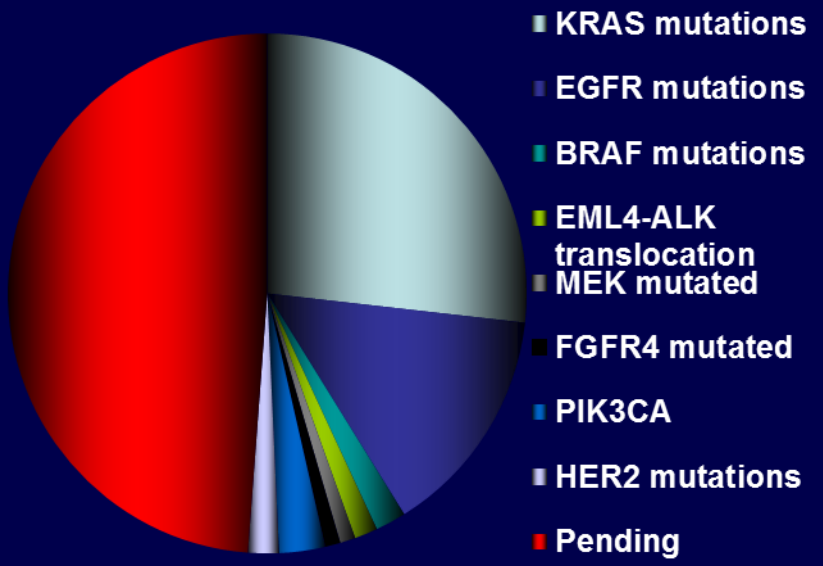


Ding L, et al. *Nature.* 2008;455:1069-1075.

Lung Cancer Mutation Consortium (LCMC)

- University of Colorado - Headquarters
- Executive Committee: Paul Bunn (PI), Bruce Johnson, Mark Kris, John Minna
- 14 Sites: SPORE, P01, NCI Intramural Programs
- Plan: Genotype 1000 patients with advanced lung adenocarcinoma, 2009-2011
- Determine Known Mutations in a CLIA-Certified Laboratory: *EGFR, KRAS, BRAF, HER2, ALK1, NRAS, PIK3CA, EML4-ALK, MET* Amplification
- Compare platforms (Sequenome, SNaPShot, Direct)
- Determine relationship of alterations with clinical features and with each other
- Enter patients on mutation specific clinical trial

Molecular Subtypes of Lung Adenocarcinoma



Mutated Gene	Frequency	Drugs Classes Under Study
KRAS/ NRAS	25% 1%	ARQ197+erlotinib GSK MEKi
EGFR	23%	OSI906+erlotinib MM121+erlotinib
NRAS	1%	GSK MEKi
HER2	2%	BIBW 2992
EML4/ALK	7%	PF-02341066 (crizotinib)
BRAF	6%	GSK1026 for V660E GSK MEKi for
PI3K/AKT	5%	BIM120
MET ampl	5%	Crizotinib

Ding L, et al. *Nature.* 2008;455:1069-1075.
Yamamoto H, et al. *Cancer Res.* 2008;68:6913-6921.

Published Ahead of Print on November 23, 2009 as 10.1200/JCO.2009.23.5622
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.23.5622

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

Christopher G. Azzoli, Sherman Baker Jr, Sarah Temin, William Pao, Timothy Aliff, Julie Brahmer, David H. Johnson, Janessa L. Laskin, Gregory Masters, Daniel Milton, Luke Nordquist, David G. Pfister, Steven Piantadosi, Joan H. Schiller, Reily Smith, Thomas J. Smith, John R. Strawn, David Trent, and Giuseppe Giaccone

Recommendation A7 supports the first-line use of gefitinib over carboplatin and paclitaxel in patients whose NSCLC tumors harbor *EGFR* mutation based on a clinically significant improvement in PFS, favorable toxicity profile, and improved quality of life. These data justify attempts to test NSCLC tumors for the presence of *EGFR* mutation. However, no study to date has demonstrated an improvement in OS when chemotherapy is selected on the basis of a molecular marker.

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Recent clinical trials have identified other tumor or patient characteristics that can have prognostic and/or predictive importance, including histology (squamous *v* nonsquamous),[27] molecular subgroups (*EGFR* mutation, *EGFR* amplification, EGFR expression, or *KRAS* mutation),[58,87,91,92,104,113] number of prior therapies (no, one, or ≥ two prior therapies),[72,74] time on prior therapy,[72] smoking status (including never smokers [< 100 cigarettes over lifetime],[55,74,140] former light smokers [< 15 pack-years], and heavy smokers [≥ 15 pack-years]),[55,74,140] and Asian ethnicity.[58,74] Future clinical trials should build on these discoveries, enrich for patients most likely to benefit, and stratify by prognostic factors, including PS, sex, smoking status, prior therapy, and molecular characteristics, whenever there is a potential for imbalance in enrollment. Techniques for molecular testing of tumor tissue should be optimized and standardized before being tested in prospective clinical trials. Ideally, new technologies should be refined so that they may be more readily adopted into the community practice setting.

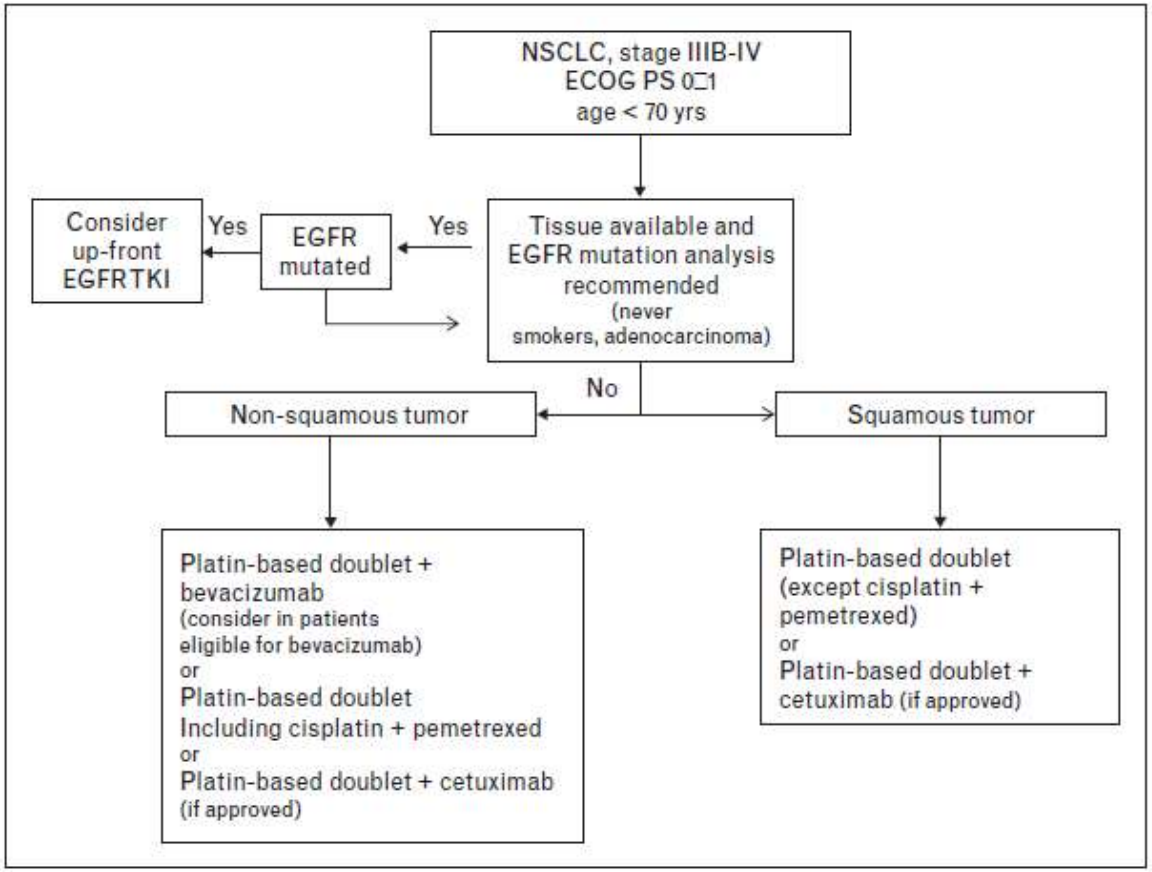
EDITORIAL

Can a decisional algorithm be used in first-line treatment of advanced nonsmall cell lung cancer?

Cesare Gridelli

Current Opinion in Oncology 2010, 22:77–78

Figure 1 Algorithm for front-line treatment decision



ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, nonsmall cell lung cancer.

Annals of Oncology Advance Access published May 2, 2011

special article

Annals of Oncology
doi:10.1093/annonc/mdr150

Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy
1st ESMO Consensus Conference in Lung Cancer; Lugano 2010

E. Felip[1], C. Gridelli[2], P. Baas[3], R. Rosell[4], R. Stahel[5*] & Panel Members[†]

Recommendation 1.1: EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs.

Strength of recommendation: A

Level of evidence: I

Recommendation 4: routine testing for EML4-ALK is not currently recommended outside of clinical trials. However, emerging data for ALK inhibition are promising and may lead to a clinical indication for routine testing.

Strength of recommendation: A

Level of evidence: V

Recommendation 5: routine testing for KRAS, BRAF, ERBB2 PIK3CA somatic gene mutations is not currently recommended outside of clinical trials.

Strength of recommendation: A

Level of evidence: V

Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy
1st ESMO Consensus Conference in Lung Cancer; Lugano 2010

E. Felip[1], C. Gridelli[2], P. Baas[3], R. Rosell[4], R. Stahel[5*] & Panel Members[†]

2. Guidance on tissue handling and reporting for EGFR somatic mutation testing

Handling of tumor specimens has yet to be standardized. In a previous workshop on EGFR mutation testing [8], the participants reached an agreement that 10% neutral-buffered formalin is the optimum fixative, whereas Bouin's fluid should not be used and other fixatives have yet to be validated against formalin. The fixation time should be optimal for tissue specimen and not prolonged, yet sufficient to permit diagnosis. Sections cut from the formalin-fixed paraffin-embedded tissue block are the standard resource used for DNA extraction. Between one and six sections of 5- to 10-μm thickness should be used. Laboratories that use laser capture microdissection will require thinner sections. Tissue fixation and processing have the

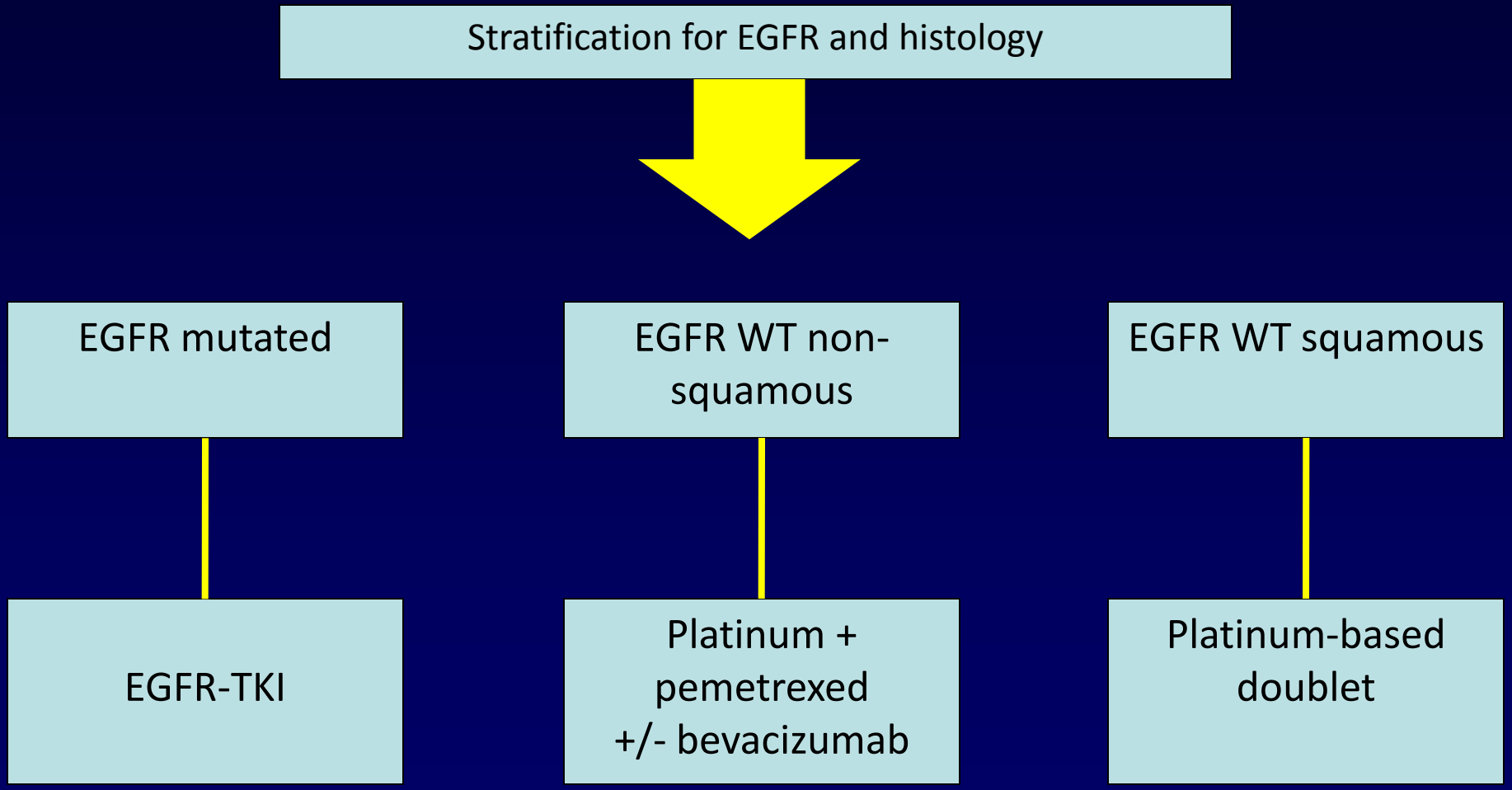
3. The relevance of participation in quality assurance programs for genetic testing

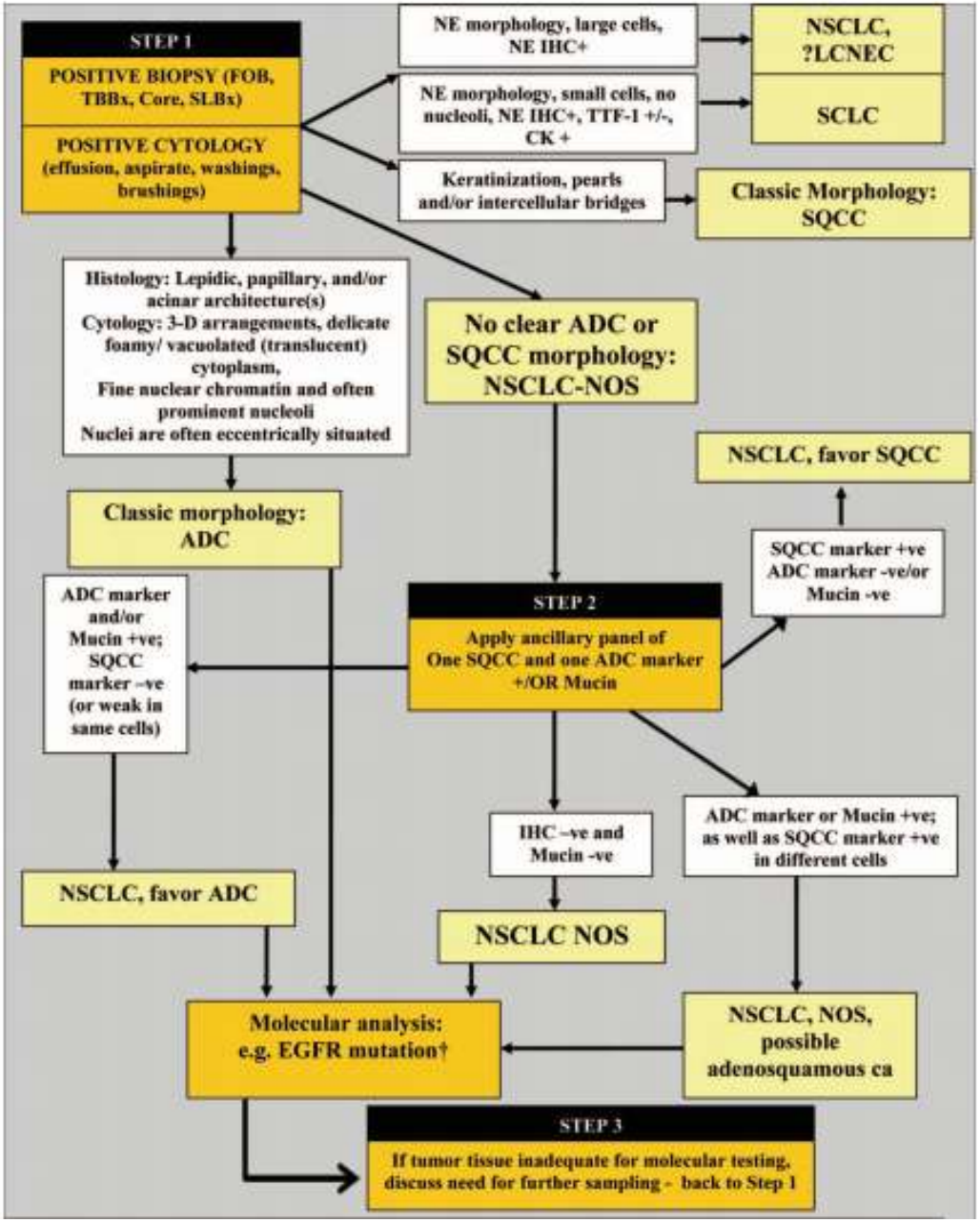
Molecular genetic techniques have been included in many areas of clinical practice. To maintain confidence in this technology, it is essential that the steps taken to ensure quality are clear and transparent to participants and public. External quality assessment schemes provide a mean of monitoring compliance with best practice procedures [22].

Recommendation 3: somatic mutation tests that are required for clinical decision making should be carried out in laboratories that are compliant with country-specific standards for clinical diagnostic testing (UK, Clinical Pathology Accredited Laboratories; USA, CLIA Laboratories). The laboratory should have accreditation to conduct the test and should participate in internal and external quality assurance to maintain accreditation (The European Molecular Genetics Quality Network, United Kingdom National External Quality Assessment Service).

Strength of recommendation: A

First-line therapy for metastatic NSCLC in 2011




STEP 1
POSITIVE BIOPSY (FOB, TBBx, Core, SLBx)
POSITIVE CYTOLOGY (effusion, aspirate, washings, brushings)
NE morphology, large cells, NE IHC+
NSCLC, ?LCNEC
NE morphology, small cells, no nucleoli, NE IHC+, TTF-1 +/-, CK +
SCLC
Keratinization, pearls and/or intercellular bridges
Classic Morphology: SQCC
Histology: Lepidic, papillary, and/or acinar architecture(s)
Cytology: 3-D arrangements, delicate foamy/ vacuolated (translucent) cytoplasm,
Fine nuclear chromatin and often prominent nucleoli
Nuclei are often eccentrically situated
No clear ADC or SQCC morphology: NSCLC-NOS
NSCLC, favor SQCC
Classic morphology: ADC
SQCC marker +ve ADC marker -ve/or Mucin -ve
ADC marker and/or Mucin +ve; SQCC marker –ve (or weak in same cells)
STEP 2
Apply ancillary panel of One SQCC and one ADC marker +/OR Mucin
IHC –ve and Mucin -ve
ADC marker or Mucin +ve; as well as SQCC marker +ve in different cells
NSCLC, favor ADC
NSCLC NOS
Molecular analysis: e.g. EGFR mutation†
NSCLC, NOS, possible adenosquamous ca
STEP 3
If tumor tissue inadequate for molecular testing, discuss need for further sampling - back to Step 1

Cambio de paradigma en el CPNCP: Implicaciones prácticas

- Necesidad de muestra de biopsia suficiente: implicación de **neumólogo o radiólogo**
- Necesidad de realizar las determinaciones básicas EGFR, ALK: implicación del **hospital- gerencia/dirección médica**
- Necesidad de NO retrasar el tratamiento en exceso a la espera de resultados: implicación del **patólogo.**

Consenso SEAP-SEOM

- Necesitamos biomarcadores para personalizar el tratamiento del cáncer.
- Importancia de las Sociedades Científicas para la estandarización de procesos e implantación asistencial.
- Primer consenso SEAP-SEOM sobre biomarcadores en cáncer de pulmón: 2011