

LUNG CANCER: ASCO 2010

- **Small cell lung cancer**
- **Adjuvant gefitinib**
- **Erlotinib as first-line therapy**
- **Chemotherapy in elderly patients**
- **New agents**

DISCLOSURES

- **Stock:**

AMGEN, Glaxo, Biogenidec

- **Scientific Advisory Board:**

Celgene and Ziopharm

SMALL CELL LUNG CANCER

- 17 oral and 40 poster discussion abstracts
- Only 1 SCLC abstract, giving new meaning to the word “small” ($p < 0.00000001$)

PICOPLATIN VERSUS BSC IN SCLC*

- **Picoplatin, a new generation IV platinum, designed to overcome drug resistance**
- **401 patients with progression within 6 months of platinum-based therapy randomized 2:1**
- **Study conducted in 15 countries in Central and Eastern Europe and S. America**
- **Objective response rate 4%**
- **PFS 9 versus 6.6 weeks (HR 0.78; p = 0.03)**
- **MST 21 weeks vs. 20 weeks (p = 0.09)**
- **“The study supports the use of picoplatin in the second-line therapy of SCLC after platinum-based chemotherapy”**

***Ciuleanu T, et al.: Proc ASCO 28:515, 2010**

ADJUVANT GEFITINIB IN RESECTED NSCLC

- **Between September 2002 and April 2005, 503 patients with resected stage IB-IIIa NSCLC randomized to gefitinib for 2 years versus placebo; after January 2003, adjuvant chemotherapy also allowed**
- **Study closed prematurely in April 2005**
- **Only 17% received adjuvant chemotherapy**
- **MFU 4.7 years**

BR.19 - Schema

Pts with completely resected stage IB,II, and IIIA NSCLC

Stratified by

- stage
- histology
- post-op RT
- sex
- adjuvant chemotherapy*

Randomized 1:1

**Gefitinib
250 mg po
daily x 2 yrs**

**Placebo
0 mg po
daily x 2 yrs**

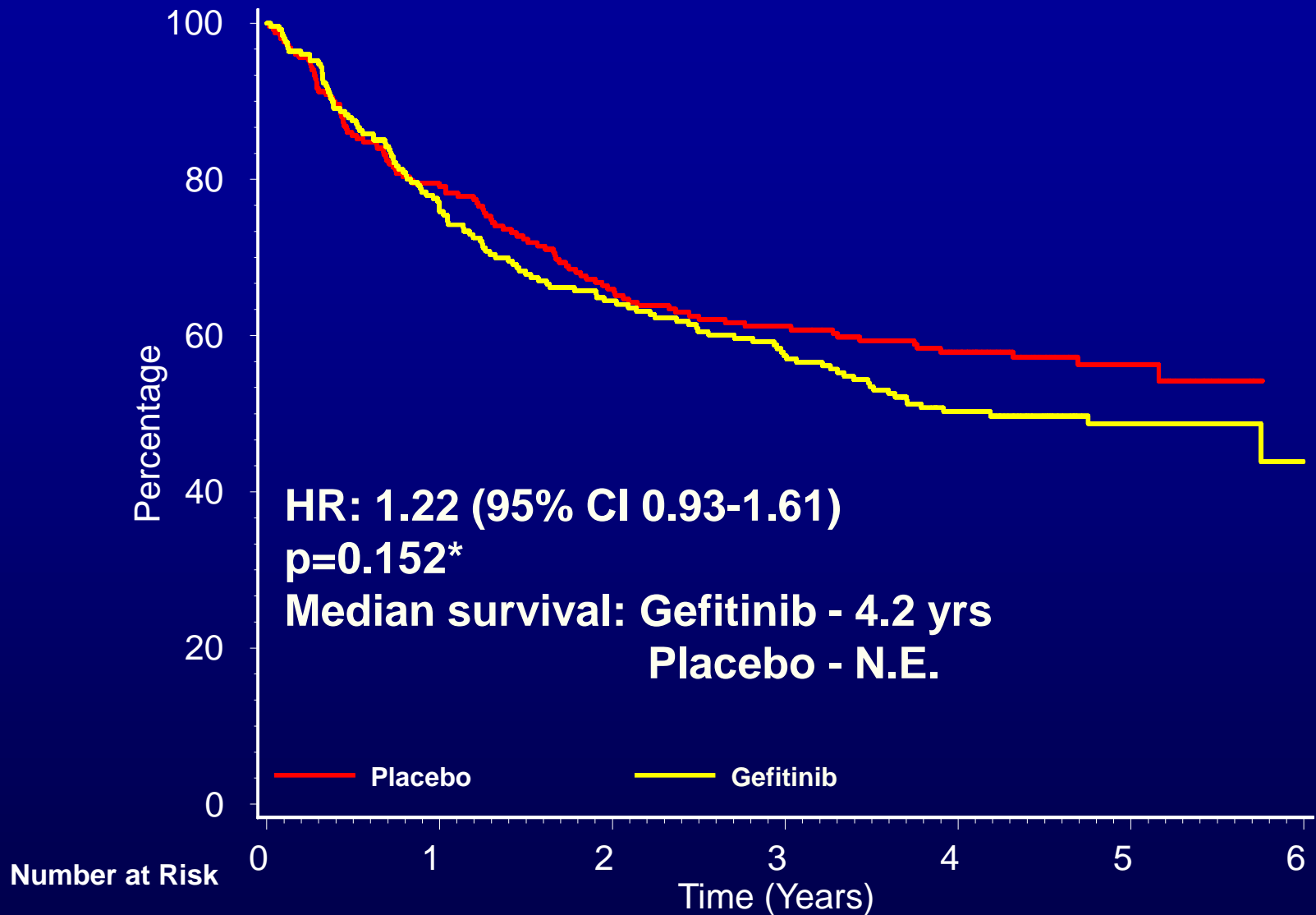
***Protocol amended January 2003 to allow adjuvant chemotherapy which became a stratification factor**

ADJUVANT GEFITINIB: RESULTS*

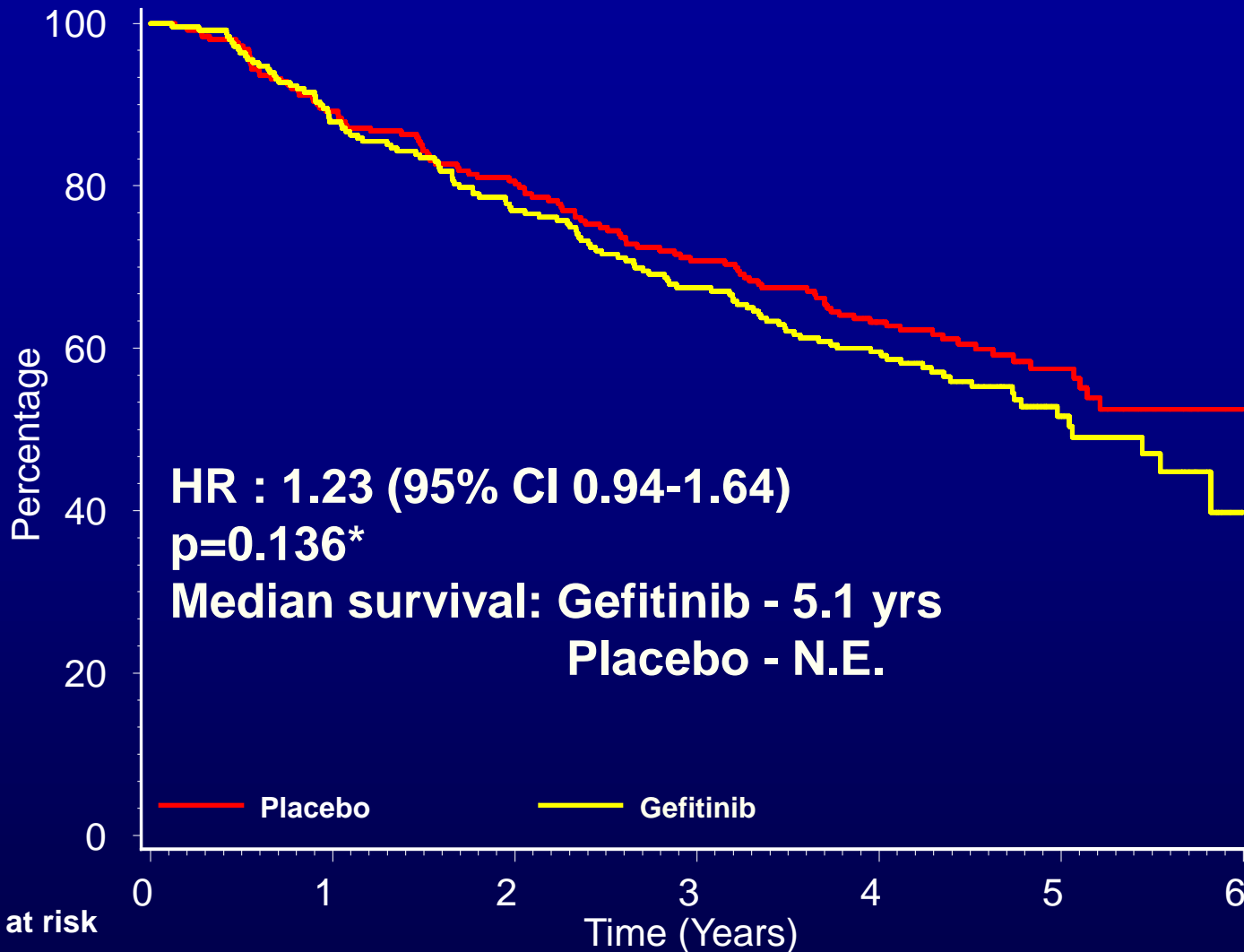
- Median DFS is 4.2 years for gefitinib and not reached yet for placebo (HR 1.22; $p = 0.09$ favoring placebo)
- Median O.S. 5.1 years for gefitinib versus not reached yet for placebo ($p = 0.14$ favoring placebo)
- 75 patients had EGFR mutations – no difference in DFS or OS

*Goss GD, et al.: Proc ASCO 28: No. 185 953s, 2010

BR.19 - Disease Free Survival



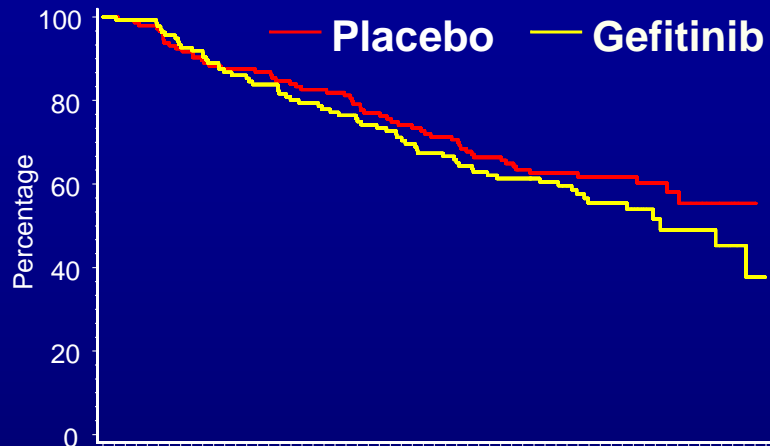
BR.19 - Overall Survival



Number at risk	0	1	2	3	4	5	6
Gefitinib	251	217	188	163	133	42	2
Placebo	252	219	198	171	138	56	4

Overall Survival by *EGFR* Mutation Status and Treatment

Wild type



# at Risk	0	1	2	3	4	5	6
Placebo	145	126	118	101	77	34	2
Gefitinib	136	121	105	89	74	21	2

HR (95% C.I.)

Gefitinib/Placebo: 1.21 (0.84, 1.73)

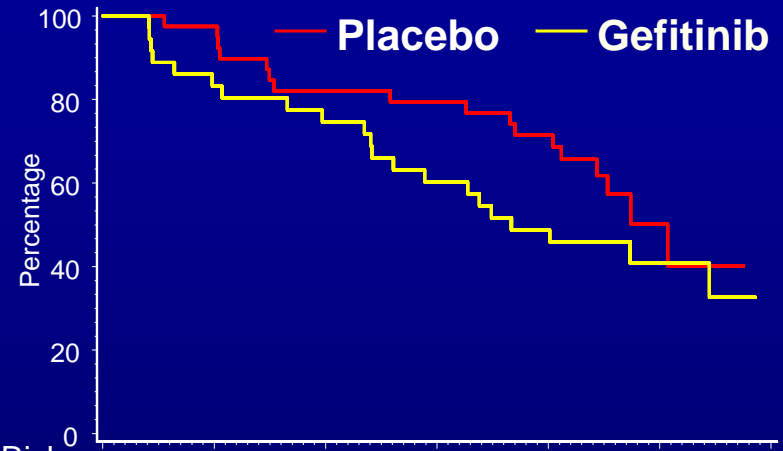
Log Rank: p=0.301

Median (95% C.I.)

-Placebo: Not reached (5.1, inf.)

-Gefitinib: 5.0 (4.3, inf.)

Sensitizing mutation



# at Risk	0	1	2	3	4	5	6
Placebo	40	38	32	30	26	6	1
Gefitinib	36	29	26	21	17	7	0

HR (95% C.I.)

Gefitinib/Placebo: 1.58 (0.83, 3.00)

Log Rank: p=0.160

Median (95% C.I.)

- Placebo: 5.1 (4.4, inf.)

- Gefitinib: 3.7 (2.6, inf.)

ADJUVANT GEFITINIB OR ERLOTINIB: COMMENTS

- **NCI-C study started prior to positive adjuvant chemotherapy trials**

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- **Similar study with adjuvant erlotinib (RADIANT) recently completed**
- **No current indication for adjuvant gefitinib or erlotinib**

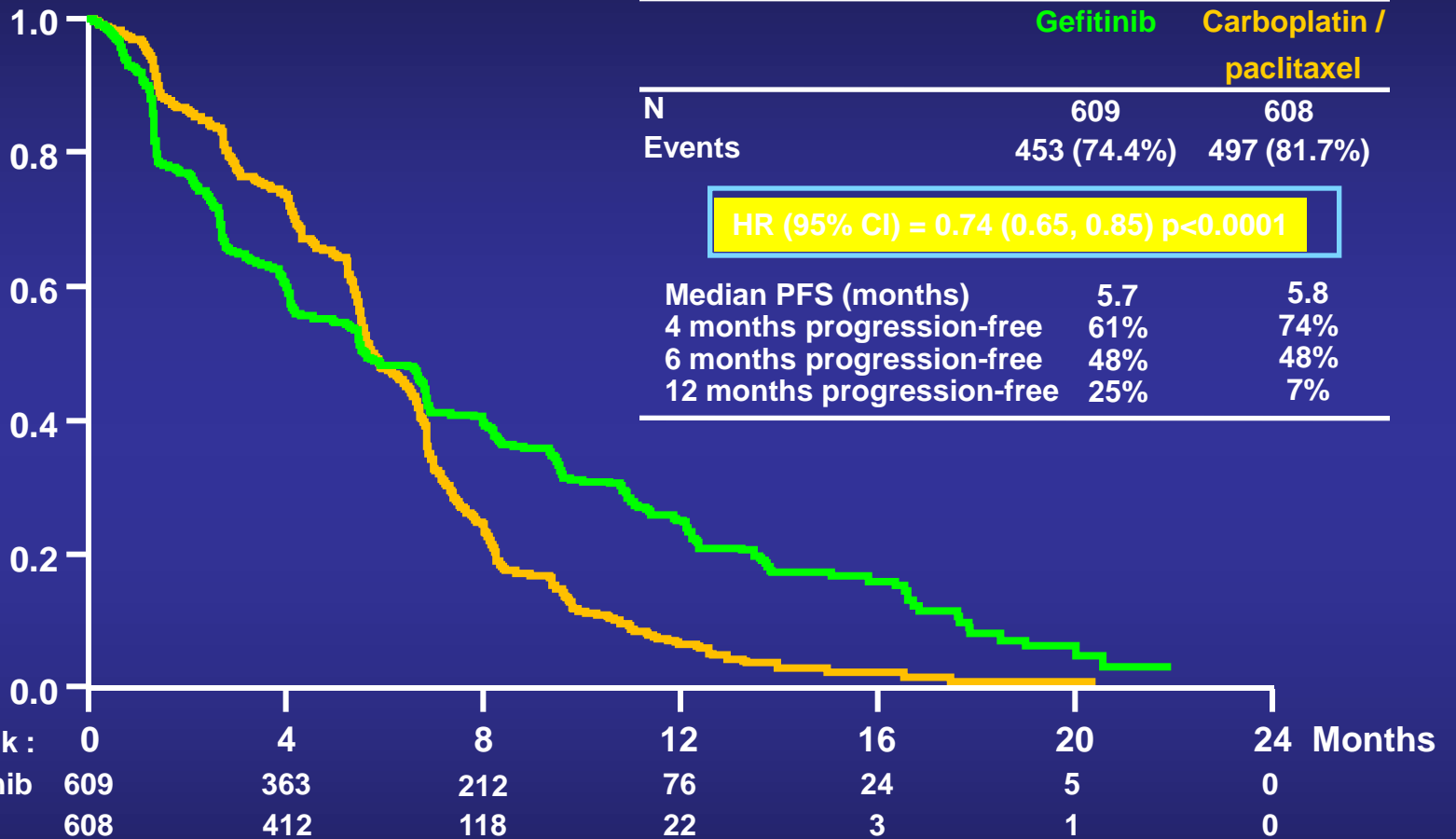
IPASS PHASE III STUDY*

- **First-line therapy randomized to carboplatin (AUC 6) + paclitaxel (200 mg/M²) versus gefitinib 250 mg**
- **Study conducted in Asia; 96% adenoCA; nonsmokers or minimal smoking history (enriched population)**
- **EGFR mutations – 71% (gefitinib) versus 47% response rate**
- **Improved PFS with gefitinib (H.R. 0.74); H.R. 0.48 if mutation positive, but carboplatin + paclitaxel superior if mutation negative (H.R. 2.85)**

*Mok, et al.: NEJM 361:947, 2009

Progression-free Survival

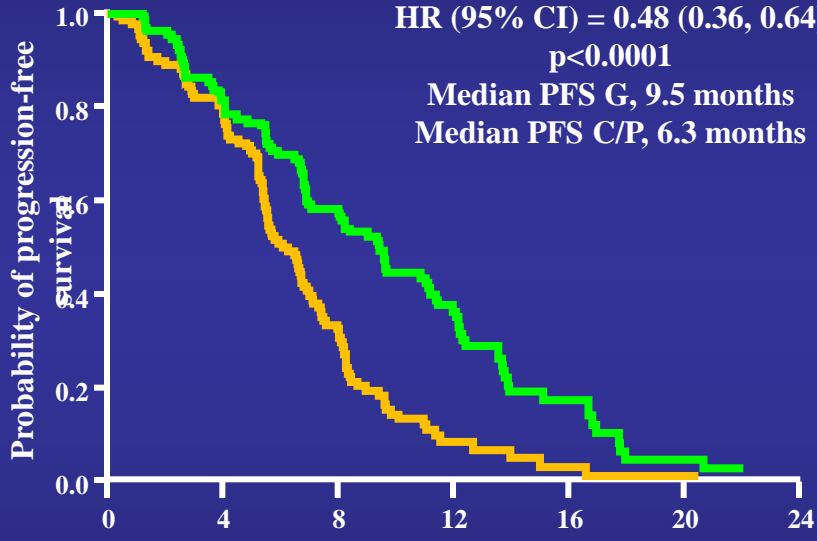
Probability of PFS



Progression-free Survival in EGFR Mutation Positive and Negative Patients

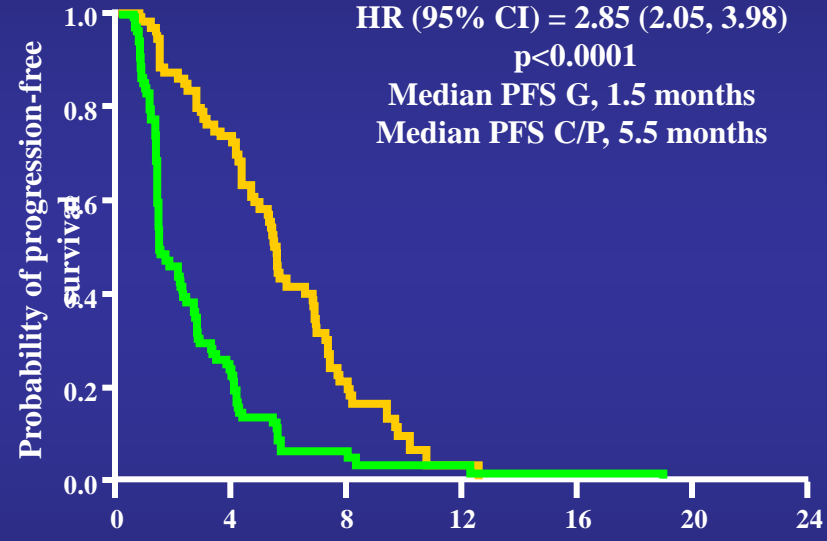
EGFR mutation positive

Gefitinib (n=132)
Carboplatin/paclitaxel (n=129)
 HR (95% CI) = 0.48 (0.36, 0.64)
 p<0.0001
 Median PFS G, 9.5 months
 Median PFS C/P, 6.3 months



EGFR mutation negative

Gefitinib (n=91)
Carboplatin/paclitaxel (n=85)
 HR (95% CI) = 2.85 (2.05, 3.98)
 p<0.0001
 Median PFS G, 1.5 months
 Median PFS C/P, 5.5 months



Patients at risk :

	0	4	8	12	16	20	24
Gefitinib	132	108	71	31	11	3	0
C/P	129	103	37	7	2	1	0

	0	4	8	12	16	20	24
Gefitinib	91	21	4	2	1	0	0
C/P	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

TORCH Trial

Unselected Population



Patient population

- NSCLC
- Age >18 and <70
- PS 0-1
- Stage IIIb-IV

Stratification

- histology
- smoking status
- gender
- centre
- PS
- stage

R
A
N
D
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M

*Phase II analysis
of activity: after XX
patients have been
assigned Erlotinib*

*900 patients planned as
phase III sample size: 669
events required to demonstrate
non-inferiority in survival*

Erlotinib

Chemotherapy

Chemotherapy

Erlotinib

*First-line
treatment*

*Second-line
treatment (after PD)*

Chemotherapy

- Cisplatin, 80 mg/m², day 1
- Gemcitabine, 1200 mg/m², day 1 and 8
- every 3 weeks, for 6 cycles

Erlotinib

- 150 mg/die p.o.
- until progression

PHASE III TRIAL OF ERLOTINIB VERSUS CISPLATIN + GEMCITABINE AS INITIAL THERAPY IN NSCLC*

- **TORCH trial randomized 760 patients from December 2006 to November 2009 in Italian and Canadian Cancer Centers**
- **Crossover to alternative arm after progression**
- **Primary endpoint overall survival**
- **PFS 5.7 months (chemotherapy) vs. 2.2 months**
- **MST 12 months (chemotherapy) vs. 8.5 months (erlotinib) with HR 1.36 (1.12-1.65) and p value 0.02**
- **Response rates 28% (chemotherapy) versus 10% erlotinib with p = 0.001; 10% response rate with cisplatin + gemcitabine as second-line therapy and 6% with second-line erlotinib**

***Gridelli C, et al.: Proc ASCO 28:540, 2010**

ELVIS STUDY*

- **Elderly Lung Vinorelbine Italian Study**
- **Eligible patient age 70 or older, ECOG PS 0-2 and stage IIIB or IV NSCLC**
- **Vinorelbine 30 mg/M² days 1 and 8 every 3 weeks versus BSC**
- **161 patients randomized**
- **Response rate 20% and MST 28 versus 21 weeks and 1 year survival 32% versus 14% (p = 0.03)**
- **Subsequent Italian study achieved comparable results with gemcitabine**

*JNCI 91:66-72, 1999

PHASE III TRIAL OF CARBOPLATIN + PACLITAXEL VERSUS SINGLE AGENT CHEMOTHERAPY IN ELDERLY PATIENTS WITH ADVANCED NSCLC

- **Worldwide, 35-50% of lung cancer pts. > 70**
- **French multicenter study randomized patients age 70-89 to single agent therapy (gemcitabine or vinorelbine) or carboplatin AUC 6 + paclitaxel 90 mg/M² days 1, 8, and 15 every 4 weeks for 4 cycles**
- **Study conducted April 2006 – December 2009 with MFU 21 mos.**
- **Erlotinib given in both arms after progression**
- **Median age 77; 26.4% ECOG PS 2**
- **451 patients randomized out of 522 initially planned; stopped early due to survival difference**

ELDERLY NSCLC: RESULTS*

	<u>C + P</u>	<u>Single agent</u>	<u>p value</u>
PFS (months)	6.1	3	0.00001
O.S. (months)	10.3	6.2	0.00004
1 year surv.	45%	27%	HR 0.63

*Quoix E, et al.: Proc ASCO 28: No. 185, 946s, 2010

Overall Survival (ITT)

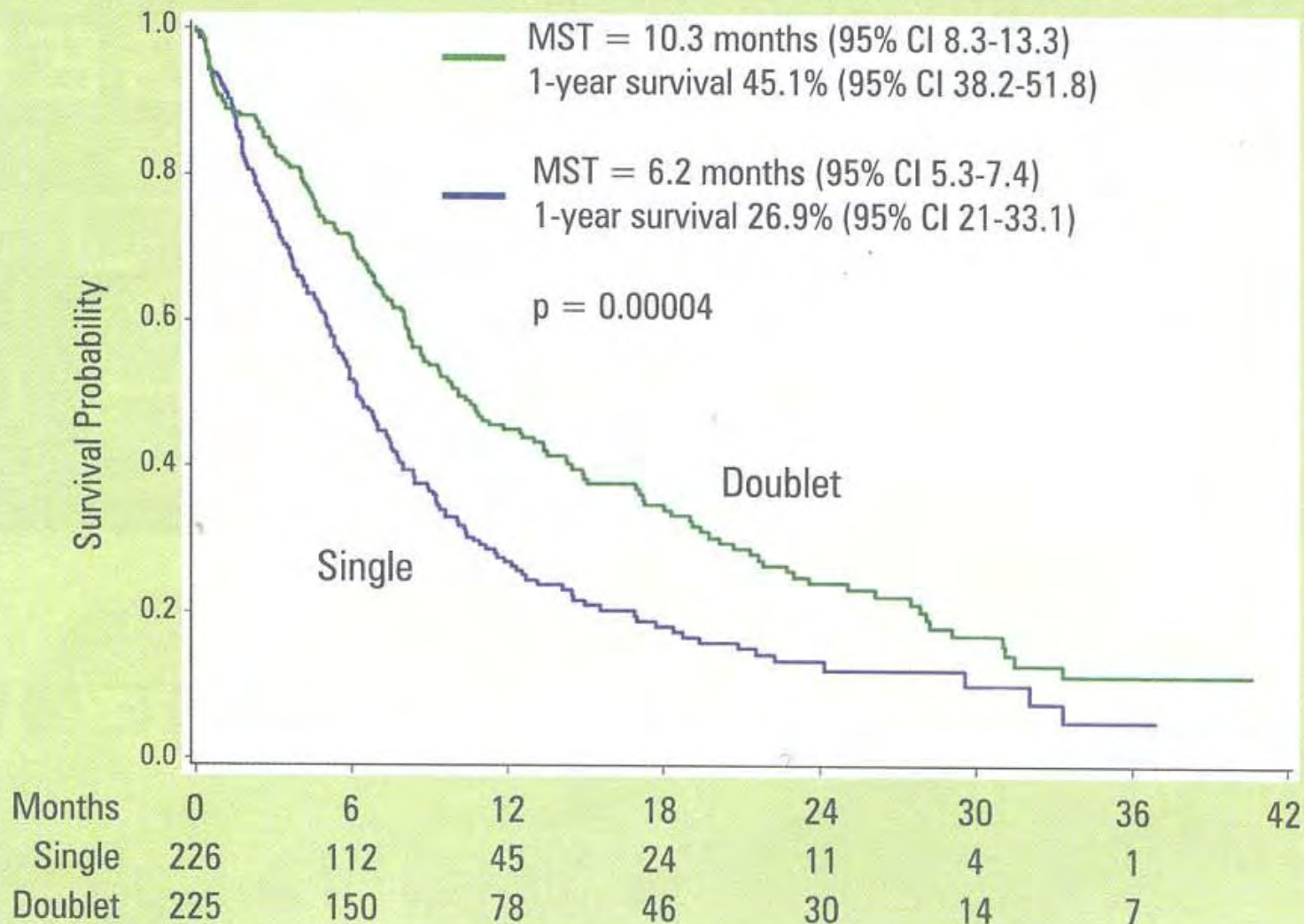


Figure 1. Abbreviations: CI, confidence interval; MST, median survival time.

CARBOPLATIN + PACLITAXEL VERSUS PACLITAXEL*

- CALGB 9720 – plenary session 2002;
no age requirement**
- 561 patients randomized; 18% PS 2**
- Response rate 17% versus 29% (p = 0.001)**
- MST 6.7 versus 8.8 months (p = 0.01)**

***Lillenbaum R, et al.: Proc ASCO 21:1, 2002**

PHASE III TRIAL OF CARBOPLATIN + GEMCITABINE VERSUS GEMCITABINE ALONE: SWEDISH LUNG CA STUDY*

- 334 patients randomized to gemcitabine 1,250 mg/M² days 1 and 8 alone or with carboplatin (AUC 5 day 1) every 3 weeks

	<u>Results</u>		
	<u>Gem</u>	<u>Gem + Carbo</u>	<u>p value</u>
Resp. rate	11.3%	29.6%	< 0.0001
T.T.P.	3.9 mos.	5.7 mos.	0.0001
M.S.T.	8.6 mos.	10.0 mos.	0.02
1 yr. surv.	32%	40%	
2 yr. surv.	5%	15%	0.009

PLATINUM DOUBLET VERSUS SINGLE AGENT

	<u>Carbo</u> <u>+ Pac</u>	<u>Pac</u>	<u>Carbo</u> <u>+ Paclitaxel*</u>	<u>VNR*</u>	<u>Carbo + Gem</u>	<u>Gem</u>
Number	280	281	225	226	170	174
Overall						
Surv. (mos.)	8.8	6.7	10.3	6.2	10.0	8.6

***Age 70 or older**

ELDERLY NSCLC: CRITICISMS

- **Best platinum doublet ? Study utilized monthly carboplatin AUC 6 + weekly paclitaxel**
- **> 5% wt. loss a prognostic factor for survival; 48.7% wt. loss with platinum doublet versus single agents 64% and 59%**
- **Greater survival benefit (4.1 months) than earlier studies of platinum doublets versus single agents (cisplatin or non-platinum compound) in younger patient populations**
- **More toxicity, including 6.6% versus 1.8% treatment related mortality (p = 0.035)**
- **26% ECOG PS 2**

PERFORMANCE STATUS 2 PATIENTS IN E1594

- E1594 randomized 1,207 patients to 1 of 4 platinum chemotherapy regimens**
- This included 68 patients with PS 2 before entry was closed due to excessive toxicity and poor survival**
- Overall response rate 14% with T.T.P. 1.7 months, median survival 4.1 months and 1 year survival 19.1%**

***Sweeney CJ, et al.: Cancer 92:2639-2647, 2001**

ELDERLY NSCLC: RECOMMENDATIONS

- **Erlotinib should be first-line therapy for elderly (or younger) patients with EGFR mutations**
- **Consider carboplatin + pemetrexed for non-squamous cell lung cancer**
- **Future recommendations:**
 - **Crizotinib for ALK mutations**
 - **Genomic analysis to exclude platinum-based chemotherapy (e.g., ERCC-1, KRAS, etc.)**
- **“New treatment paradigm for PS 0-2 patients”**

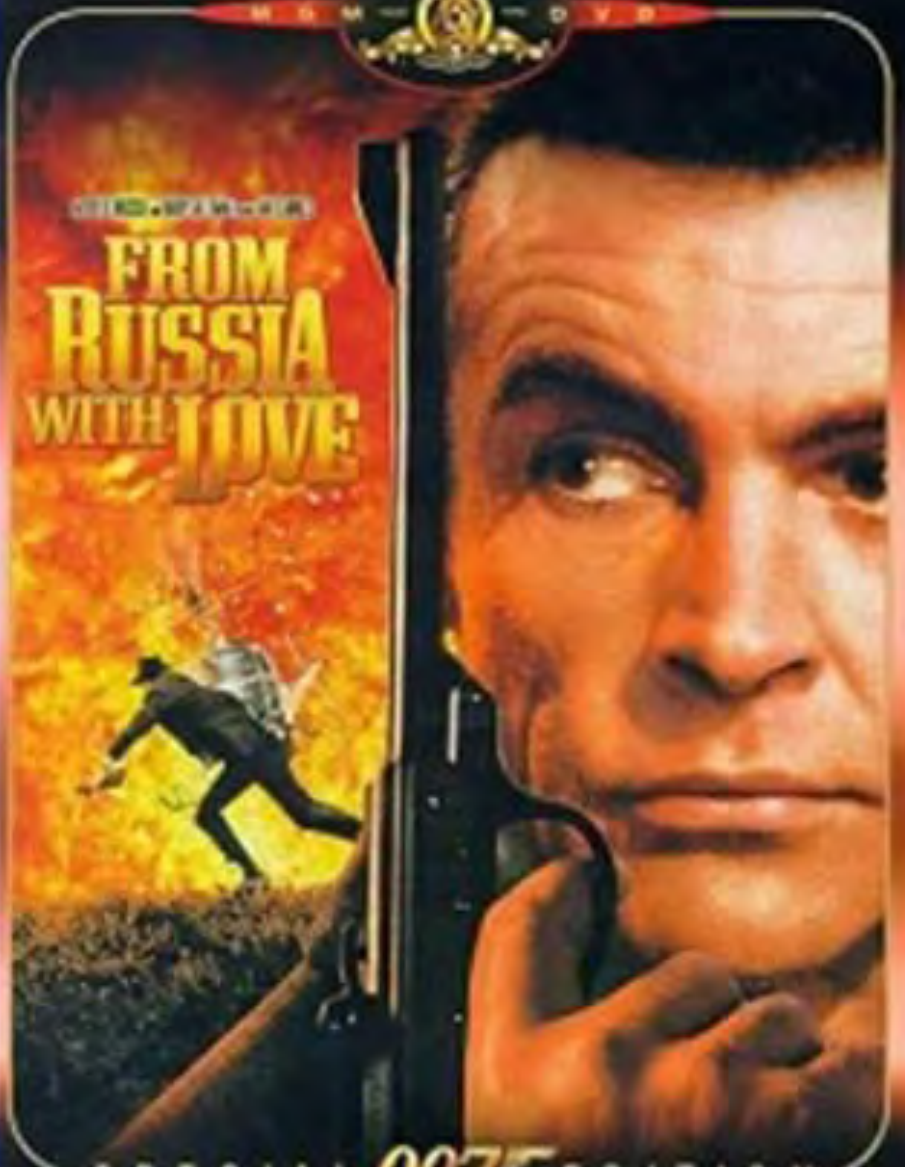
**Ladies and Gentlemen,
ELVIS has left the building**



NEW AGENTS



007
**FROM
RUSSIA
WITH LOVE**



SPECIAL **007th** EDITION

FROM RUSSIA WITH LOVE

- **Novelos compound from Russia causes “pleiotropic molecular effects”**
 - **positive 68 patient trial in NSCLC in Russia – already approved and sold**
- **Positive small trial in U.S. (44 patients)**
- **Phase III randomized study of carboplatin + paclitaxel +/- Nov-002**
 - **907 patients, 12 countries (25% from U.S.)**
 - **Primary endpoint of improved survival not met**

CARBOPLATIN + PACLITAXEL

+/- NOV-002

- **MST 10.2 versus 10.8 months (p = 0.375)**
- **Median PFS 5.3 versus 5.6 months**
- **Response rate 26.6 versus 26%**
- **Angry Russian came to microphone during discussion**

***Fidias P, et al.: Proc ASCO 28:953s, 2010**

PHASE III TRIAL OF CARBOPLATIN + PACLITAXEL WITH OR WITHOUT FIGITMUMAB IN NSCLC*

- **Figitumumab (CP-75187) is a MoAb targeting IGF-I receptor**
- **Promising randomized phase II study, including 78% response rate in squamous cell cancer**
- **820 pts. were to be randomized, but permanently discontinued due to treatment related mortality (8 versus 0) and HR crossed the pre-specified futility boundary; 681 patients randomized**
- **O.S. 10.3 months versus 8.5 months (HR 1.23; $p = 0.051$); no benefit in any subset including squamous cell cancer**

***Jassem J, et al.: Proc ASCO 28:539, 2010**

PHASE III TARGETED THERAPY

<u>Agent</u>	<u>Tumor</u>	<u>No. Pts.</u>	<u>Results</u>
Bexarotene	NSCLC	1200 ⁺	Neg
MMPIs	NSCLC	2000 ⁺	Neg
Erlotinib	NSCLC	2000 ⁺	Neg
Gefitinib	NSCLC	2000 ⁺	Neg
PKC inhibitor	NSCLC	1000 ⁺	Neg
Lonafarnib (FTI)	NSCLC	700	Neg
Thalidomide	NSCLC	700	Neg
Sorafenib	NSCLC	1100	Neg
PF-3512676	NSCLC	<u>1667</u>	Neg
TOTAL		12,367	

CARBOPLATIN + PACLITAXEL +/- NEW TARGETED AGENT

- 1. AZD 2171 (Recentin)-closed**
- 2. Toll 39 (immunomodulatory agent)-closed**
- 3. ASA 404(tumor vasc. disrupting agent)- (Figitmumab) negative**
- 4. CP-751,871-IGF-1R inhibitor-negative**
- 5. Novelos compound – negative**
- 6. Sunitinib – CALGB study as maintenance**
- 7. Talactoferrin (immunomodulatory agent)**
- 8. TGF beta vaccine**
- 9. Cedaraniib**
- 10. Vorinostat (HDAC) – randomized phase II**

Clint Eastwood
is Dirty Harry in
Magnum Force



**ARE YOU
FEELING
LUCKY ?**

PREDICTIVE FACTORS FOR EGFR INHIBITORS

Sensitive

EGFR mutation

Never smoker

Female, adenoCA,

Asian

Resistant

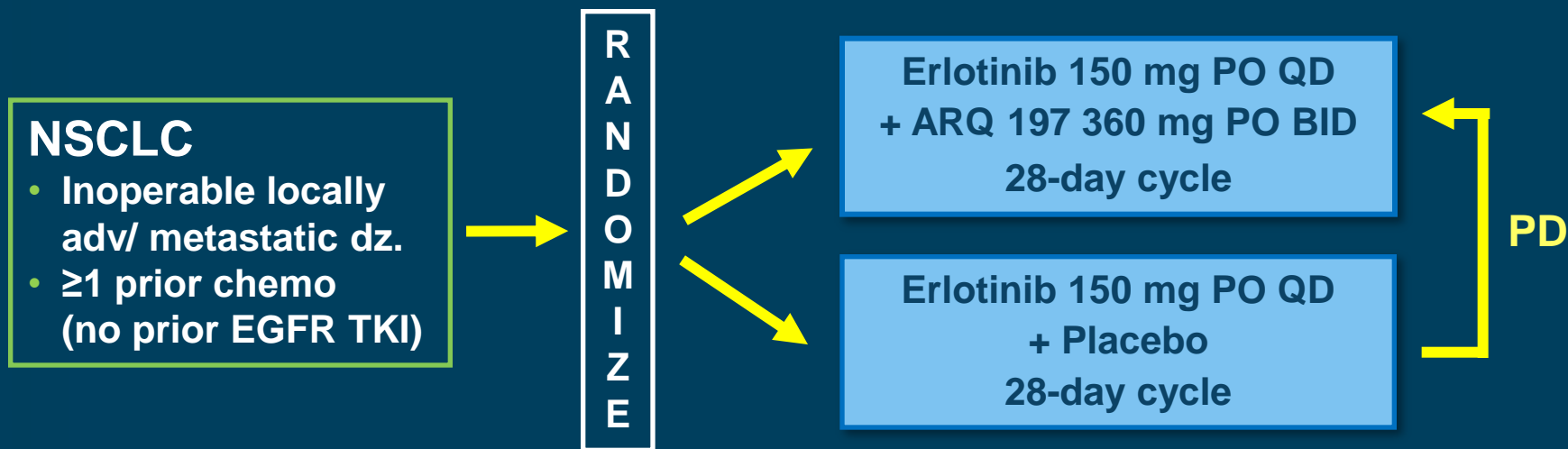
T790M

KRAS

met amplification

ARQ 197-209: Study Design

Randomized, placebo-controlled, double-blind clinical trial



- Endpoints**
- 1° PFS
 - 2° ORR, OS
 - Subset analyses
 - Crossover: ORR

- 33 sites in 6 countries
- Study accrual over 11 months (10/08-9/09)
- Randomization stratified by prognostic factors incl. sex, age, smoking, histology, performance status, prior therapy and best response, and geography (U.S. vs. ex-U.S.)

RANDOMIZED PHASE II STUDY OF ERLOTINIB + ARQ-197 OR PLACEBO

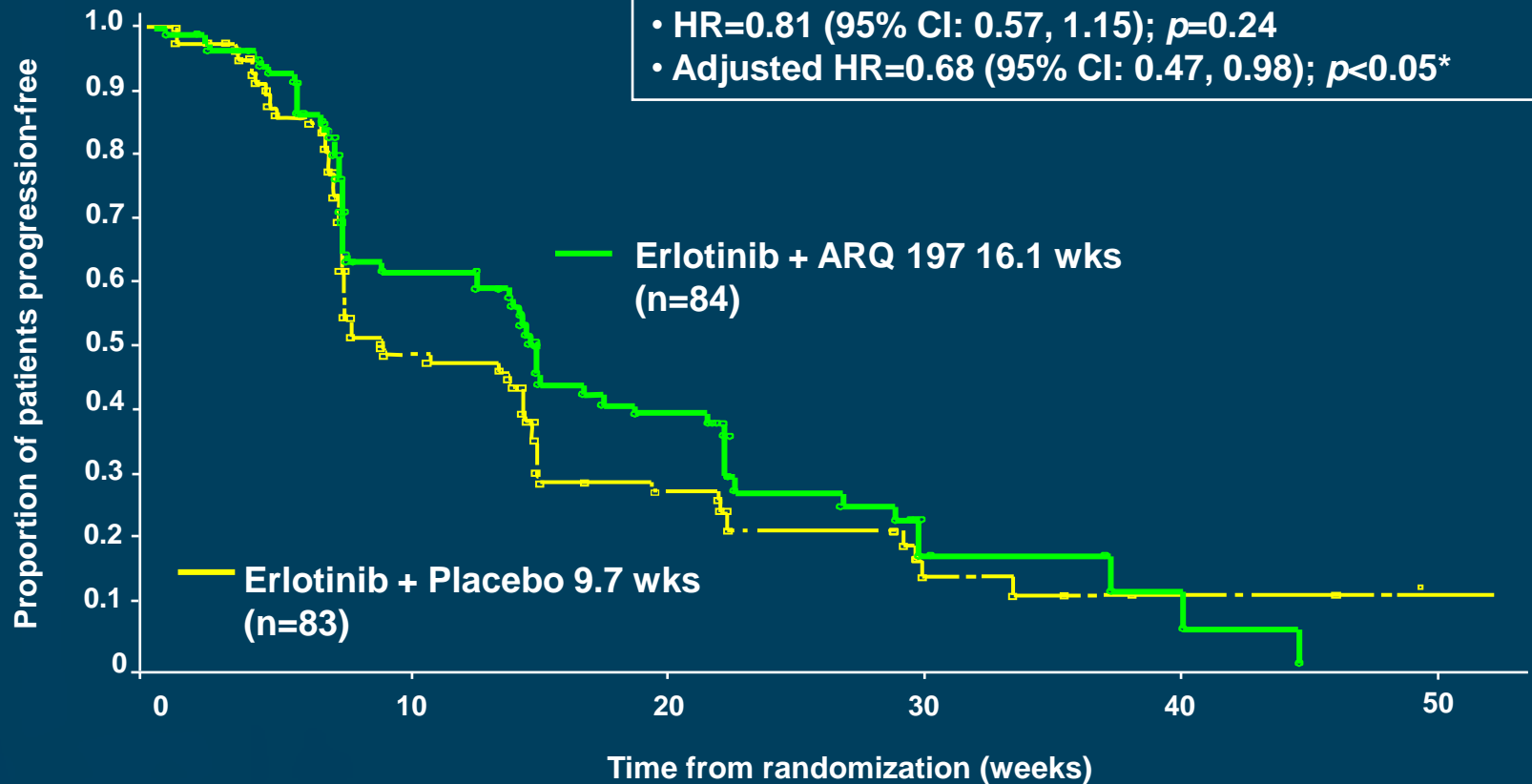
- **True randomization as ARQ-197 has virtually no toxicity**
- **Erlotinib 150 mg + placebo or ARQ-197 360 mg p.o. bid**
- **ARQ-197 is an oral c-met inhibitor**
- **Dual EGFR-MET inhibition is a promising strategy for overcoming MET-mediated resistance to EGFR inhibitors**
- **167 patients with prior chemotherapy randomized in 33 sites in 6 countries over 11 months**
- **Archival tissue collected for K-RAS, EGFR and MET**
- **Primary objective PFS**

ARQ-197 + ERLLOTINIB: RESULTS*

- PFS prolonged with ARQ-197 from 9.7 weeks to 16.1 weeks (HR 0.81 and $p < 0.05$ when adjusted for key prognostic factors in Cox regression analysis)
- Overall survival 36.4 (ARQ-197) versus 29.4 weeks ($p = 0.52$)
- For non-squamous, PFS 18.9 versus 9.7 weeks (HR 0.61) and overall survival 41 vs. 29 weeks ($p < 0.05$)
- Response rates 10% vs. 7% and stable disease 56% vs. 47%
- Crossover allowed – 23 evaluable with 2 P.R. and 9 stable

*Schiller J, et al.: Proc ASCO 28:954s, 2010

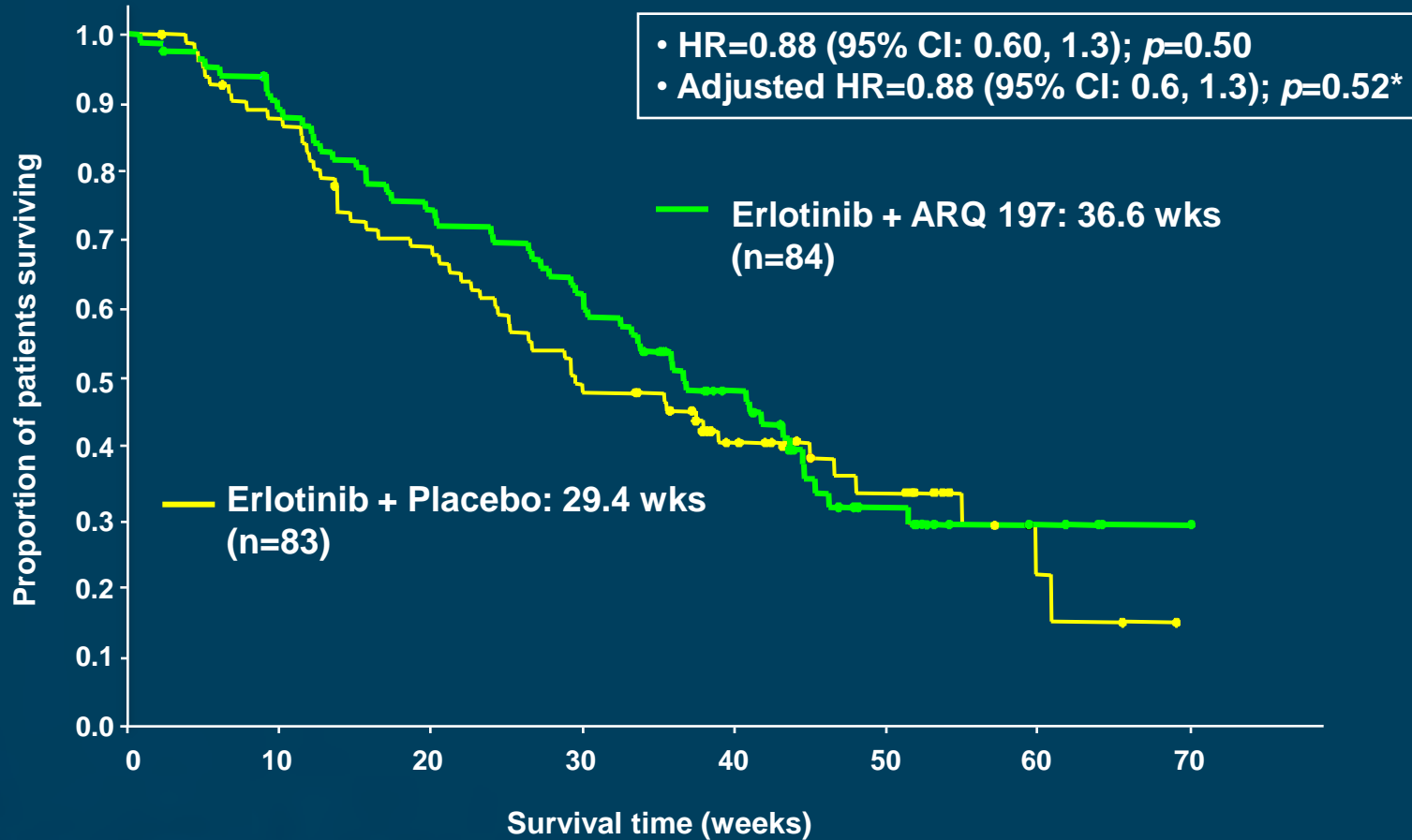
ARQ 197-209: Progression-Free Survival (ITT Population)



* Cox regression model

- PFS also measured by independent radiographic review:
 - median 15.6 vs. 8.4 wks
 - unadjusted/adjusted HR= 0.74/0.51

ARQ 197-209: Overall Survival (ITT Population)

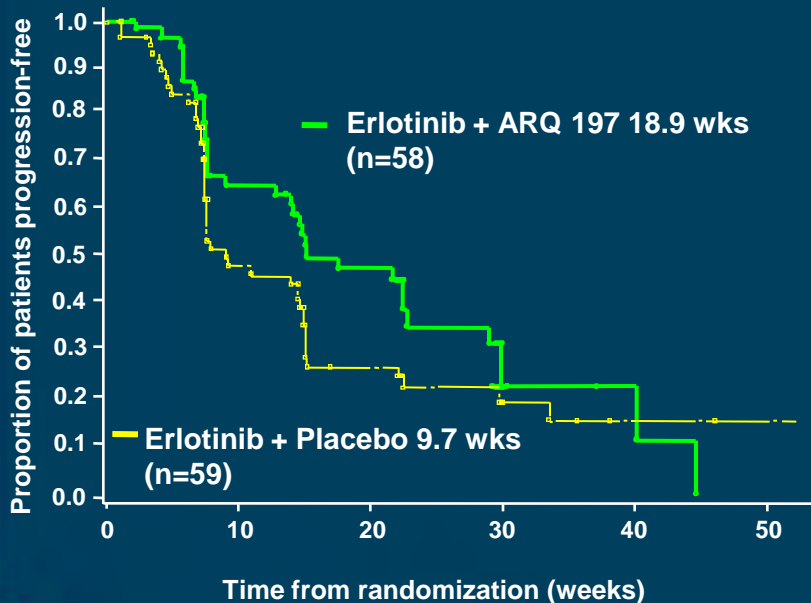


* Cox regression model

ARQ 197-209: PFS and OS in Non-Squamous Cell Histology Patients (n=117)

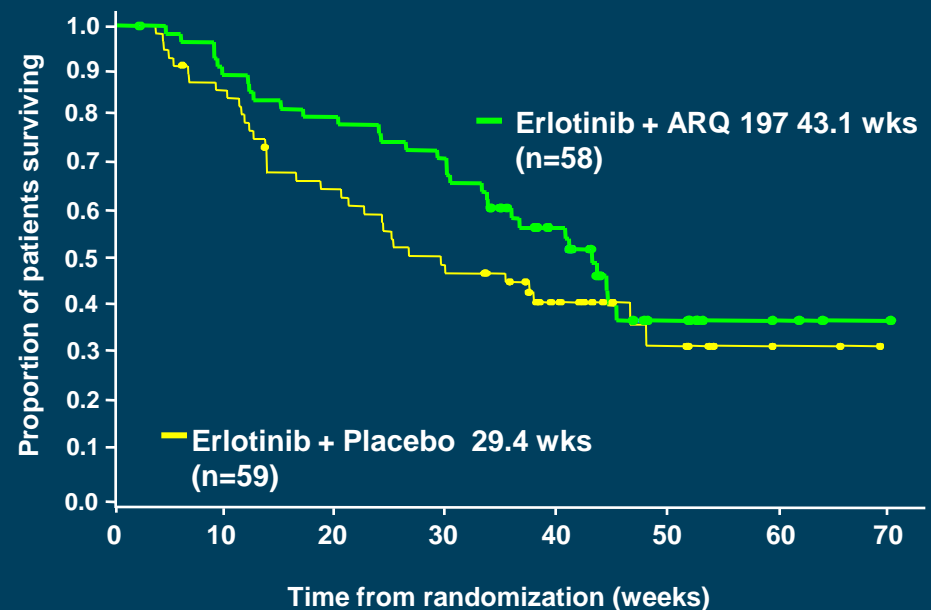
PFS (Investigator Assessed)

- HR=0.71 (95% CI: 0.46, 1.10) $P=0.12$
- Adjusted HR=0.61 (95% CI: 0.47, 0.98) $P<0.05^*$



Overall survival

- HR=0.72 (95% CI: 0.6, 1.3) $P=0.18$
- Adjusted HR=0.58 (95% CI: 0.34, 0.99) $P<0.05^*$



ARQ-197 COMMENTS

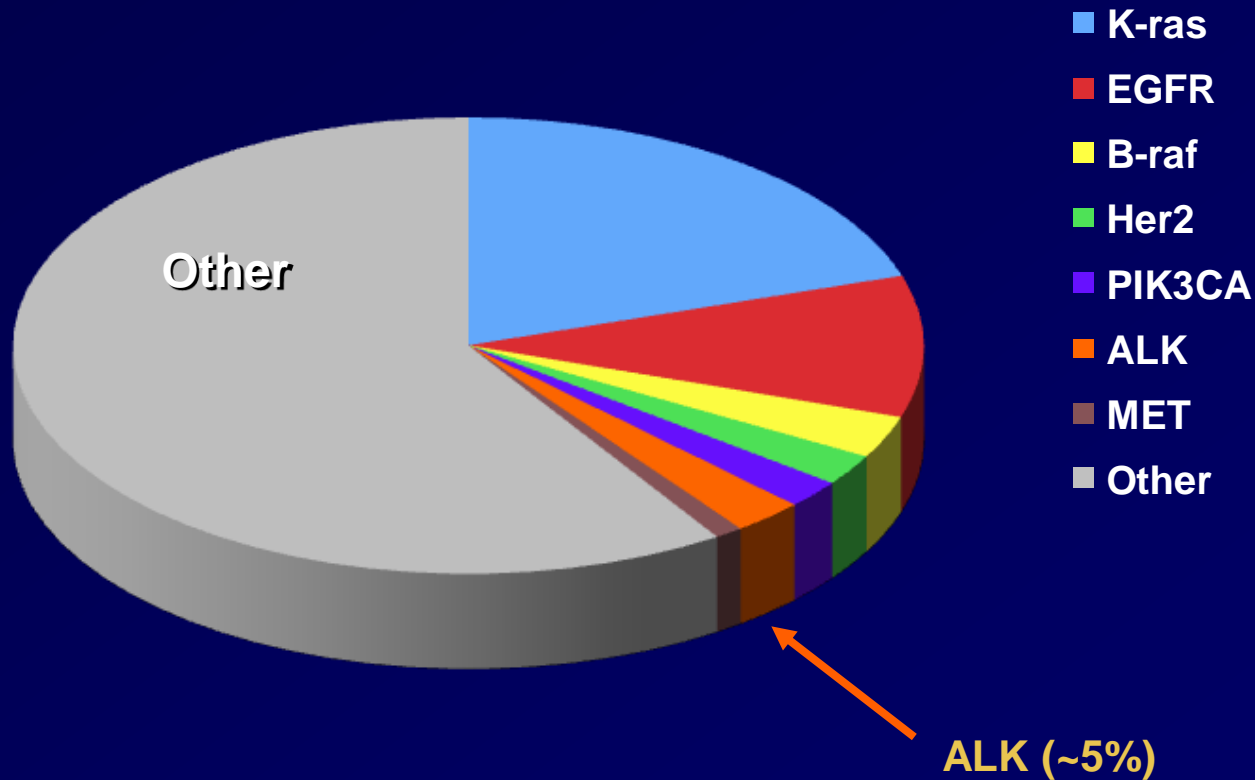
- **Drug is devoid of any meaningful toxicity**
- **Excellent investigators from U.S. and Europe**
- **Logical combination, rather than simply combining 2 molecular targeted agents from the same company**
- **Are there predictive biomarkers for MET-I?**

MET-INHIBITORS

<u>Compound</u>	<u>Company</u>	<u>Mechanism</u>
ARQ 197	Arqule	MET
PF 02341066	Pfizer	MET/ALK
PF 4217903	Pfizer	MET
AMG 102	AMGEN	Anti HGF Ab
BMS—777607	Bristol	MET
XL – 184	Exelis/Bristol	MET/VEGF R2/REG
XL – 880	Exelis/Glaxo	MET/VEGFR R2
MK 2461	Merck	MET
MET MAb	Genentech	Anti-Met Ab
JNJ – 38877605	Johnson & Johnson	MET
INCB – 28060	Incyte	MET

Potential Oncogenic “Drivers” in Non-small Cell Lung Cancer (NSCLC)

Adenocarcinoma



ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; Her2 = human epidermal growth factor receptor 2; PIK3CA = phosphoinositide-3-kinase, catalytic, alpha polypeptide

Massachusetts General Hospital, data on file.
[AT Shaw, personal communication]

MOUSE MODEL FOR EML-4-ALK POSITIVE LUNG CANCER*

- **Transgenic mouse lines established that express EML 4-ALK specifically in lung alveolar cells**
- **All of the transgenic mice examined developed hundreds of adenocarcinoma nodules in both lungs within a few weeks after birth, confirming the potent oncogenic activity of EML-4 ALK**
- **Oral administration of an inhibitor of the Kinase activity of ALK resulted in their rapid disappearance**

***Soda M, et al.: PNAS 105:19893-19897, 2008**

Clinical Activity of the Oral ALK Inhibitor, Crizotinib (PF-02341066), in Patients with *ALK*-positive Non-small Cell Lung Cancer

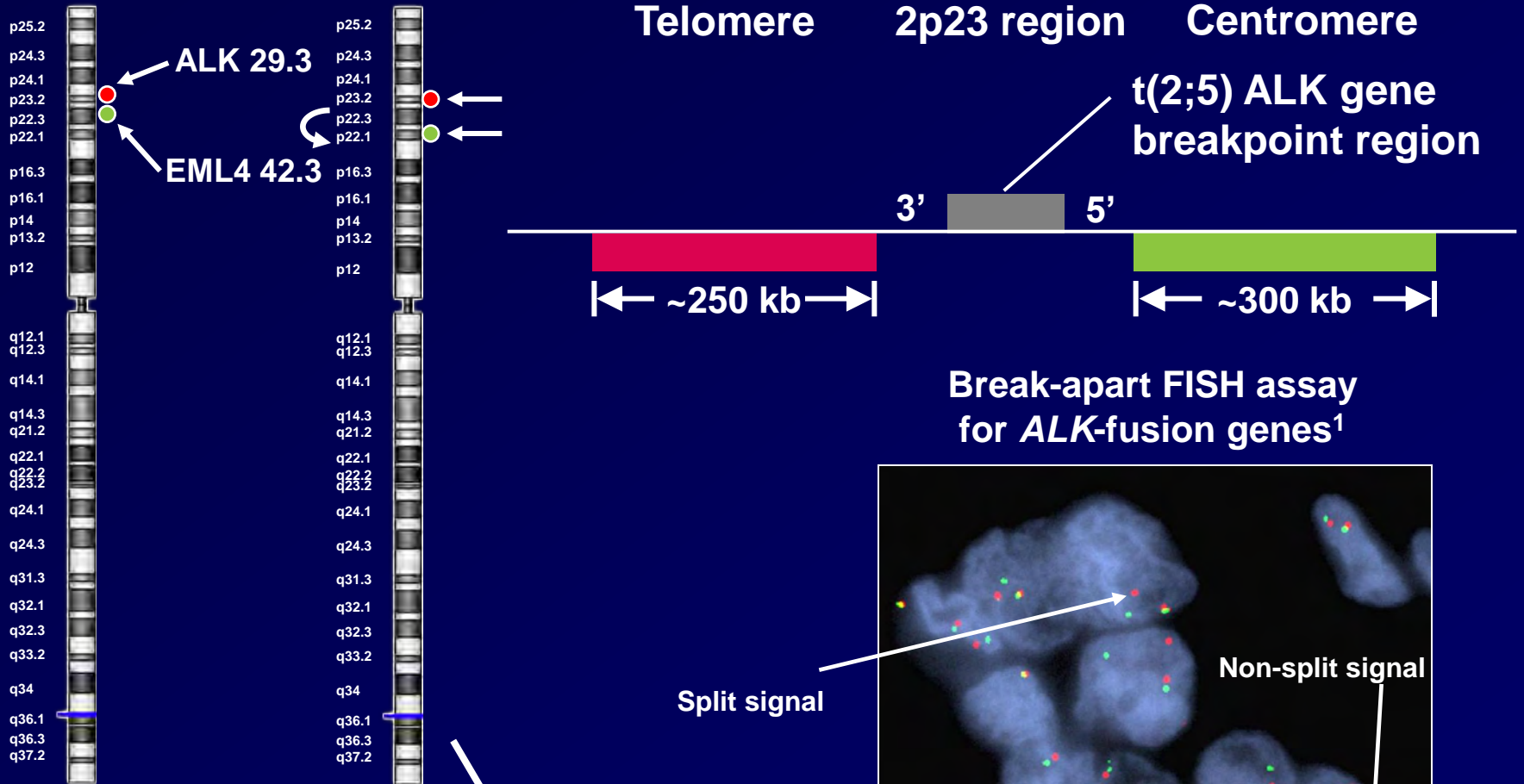
Bang Y,¹ Kwak EL,² Shaw A,² Camidge DR,³ Iafrate AJ,² Maki RG,⁴ Solomon B,⁵ Ou SI,⁶ Salgia R,⁷ Clark J²

¹Seoul National University, Seoul, Korea; ²Massachusetts General Hospital, Boston, MA, USA;

³University of Colorado Cancer Center, Aurora, CO, USA; ⁴Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ⁵Peter MacCallum Cancer Centre, East Melbourne, Australia;

⁶University of California at Irvine, Irvine, CA, USA; ⁷University of Chicago Cancer Center, Chicago, IL, USA

FISH Assay for ALK Rearrangement*



ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]

***Assay is positive if rearrangements can be detected in ≥15% of cells**
FISH = fluorescence in situ hybridization

¹Shaw AT et al. J Clin Oncol
2009;27:4247-4253

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

Clinical Activity of Crizotinib in Patients with *ALK*-positive NSCLC

- **Objective response rate (ORR): 57% (95% CI: 46, 68%)**
 - 63% including 5 as yet unconfirmed PRs
 - 57% (8/14) for patients with performance status 2 or 3

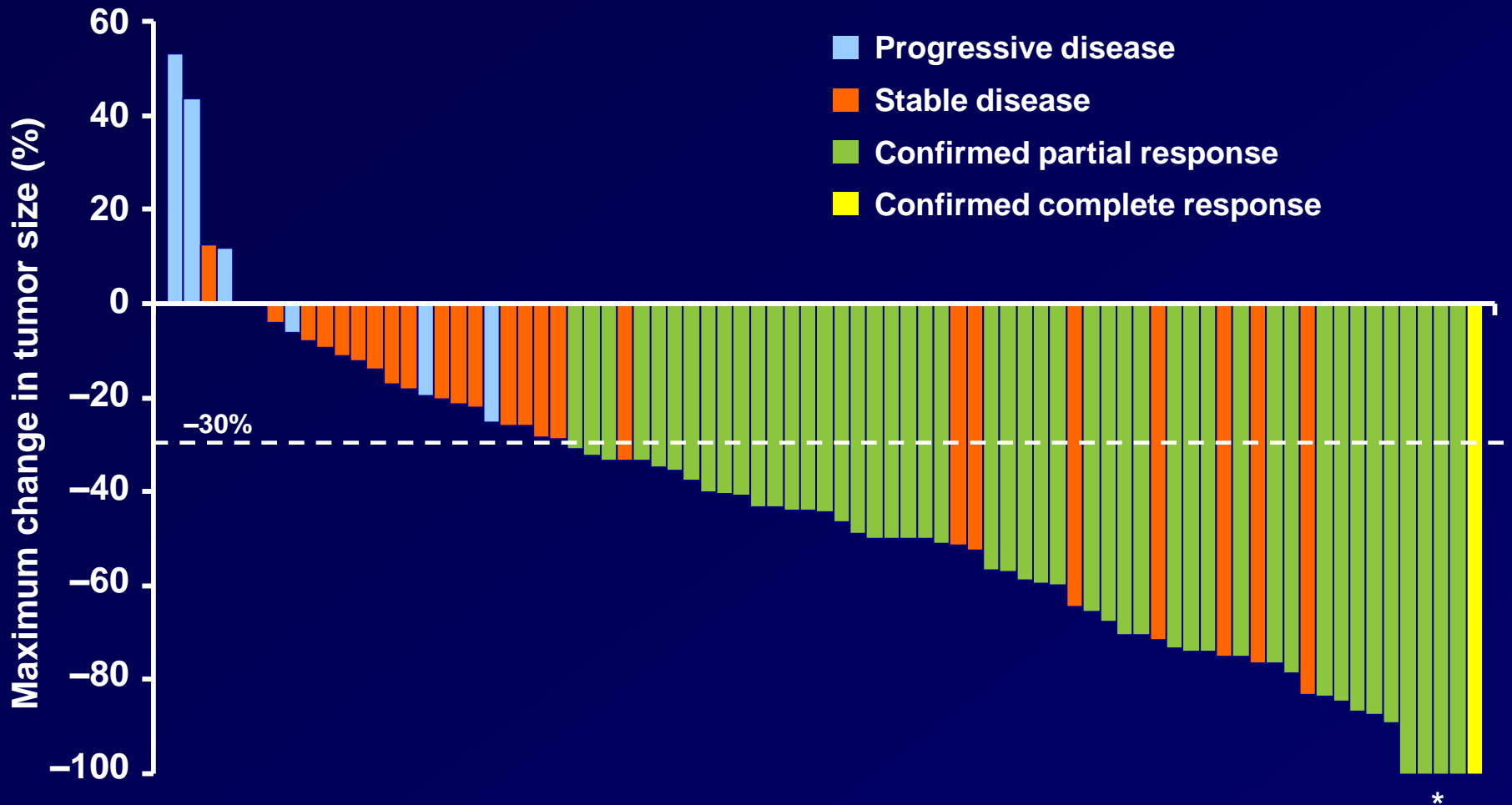
No. prior regimens*	ORR % (n/N)
0	80 (4/5)
1	52 (14/27)
2	67 (10/15)
≥3	56 (19/34)

* Unknown for 1 patient

- **Response duration: 1 to 15 months**
- **DCR[†] (CR/PR/SD at 8 weeks): 87% (95% CI: 77, 93%)**

[†]Disease control rate

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



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

Treatment-related Adverse Events in ALK-positive NSCLC ($\geq 10\%$)

Adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Nausea	43 (52)	1 (1)	0	0	44 (54)
Diarrhea	38 (46)	1 (1)	0	0	39 (48)
Vomiting	35 (43)	1 (1)	0	0	36 (44)
Visual disturbance*	34 (42)	0	0	0	34 (42)
Constipation	18 (22)	2 (2)	0	0	20 (24)
Peripheral edema	13 (16)	0	0	0	13 (16)
Dizziness	12 (15)	0	0	0	12 (15)
Decreased appetite	11 (13)	0	0	0	11 (13)
Fatigue	8 (10)	0	0	0	8 (10)

*Changes in light/dark accommodation (no abnormalities on ophthalmologic exam)

N=82

Conclusions

- **These results are an example of rapid clinical development from target identification, to clinical validation, and supports a personalized approach to NSCLC treatment**
- **For patients with *ALK*-positive NSCLC, crizotinib may offer a potential new standard of care**

Current Crizotinib Clinical Trials

PROFILE 1007

Key entry criteria

- Positive for ALK by central laboratory
- 1 prior chemotherapy (platinum-based)

R
A
N
D
O
M
I
Z
E

N=318

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

Pemetrexed 500 mg/m² or
docetaxel 75 mg/m² (n=159)
infused on day 1 of a 21-day cycle

PROFILE 1005

Key entry criteria

- Positive for ALK by central laboratory
- Progressive disease in Arm B of study A8081007
- >1 prior chemotherapy

N=250

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

LUNG CA ASCO 2010 SUMMARY

- **Small cell this year was so small, it was barely visible**
- **Adjuvant chemotherapy appropriate for resected stage IIA, IIB, and IIIA; no current role for adjuvant EGFR inhibitor**
- **Genomic analysis important as predictive and prognostic factor**
 - **Erlotinib appropriate first-line therapy only if EGFR activating mutation present**
- **Exciting and rational new drug development**