5 Minute JournalClub

Key ASCO Presentations

Issue 7, 2010

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CME Information

LEARNING OBJECTIVES

- Recall the clinical activity and adverse event profile of the ALK inhibitor crizotinib in patients with ALK-positive NSCLC.
- Compare and contrast the value of EGFR mutation status versus former smoking status in the accurate identification of patients likely to benefit from first-line EGFR tyrosine kinase inhibitor therapy, with or without concurrent chemotherapy.
- Evaluate the efficacy and tolerability of gefitinib monotherapy in patients with completely resected Stage IB to IIIA NSCLC.
- Describe the relationship between K-ras or EGFR mutation status and overall survival following post-operative treatment with gefitinib or placebo.
- Identify end-of-life outcomes significantly affected by early palliative care for patients with Stage IV NSCLC.
- Integrate new clinical trial evidence demonstrating the efficacy and safety of combination chemotherapy with paclitaxel/carboplatin into the therapeutic algorithm for elderly patients with advanced NSCLC.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
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Clinical Activity of the Oral ALK Inhibitor, Crizotinib (PF-02341066), in Patients with ALK-Positive Non-Small Cell Lung Cancer

Bang Y et al.

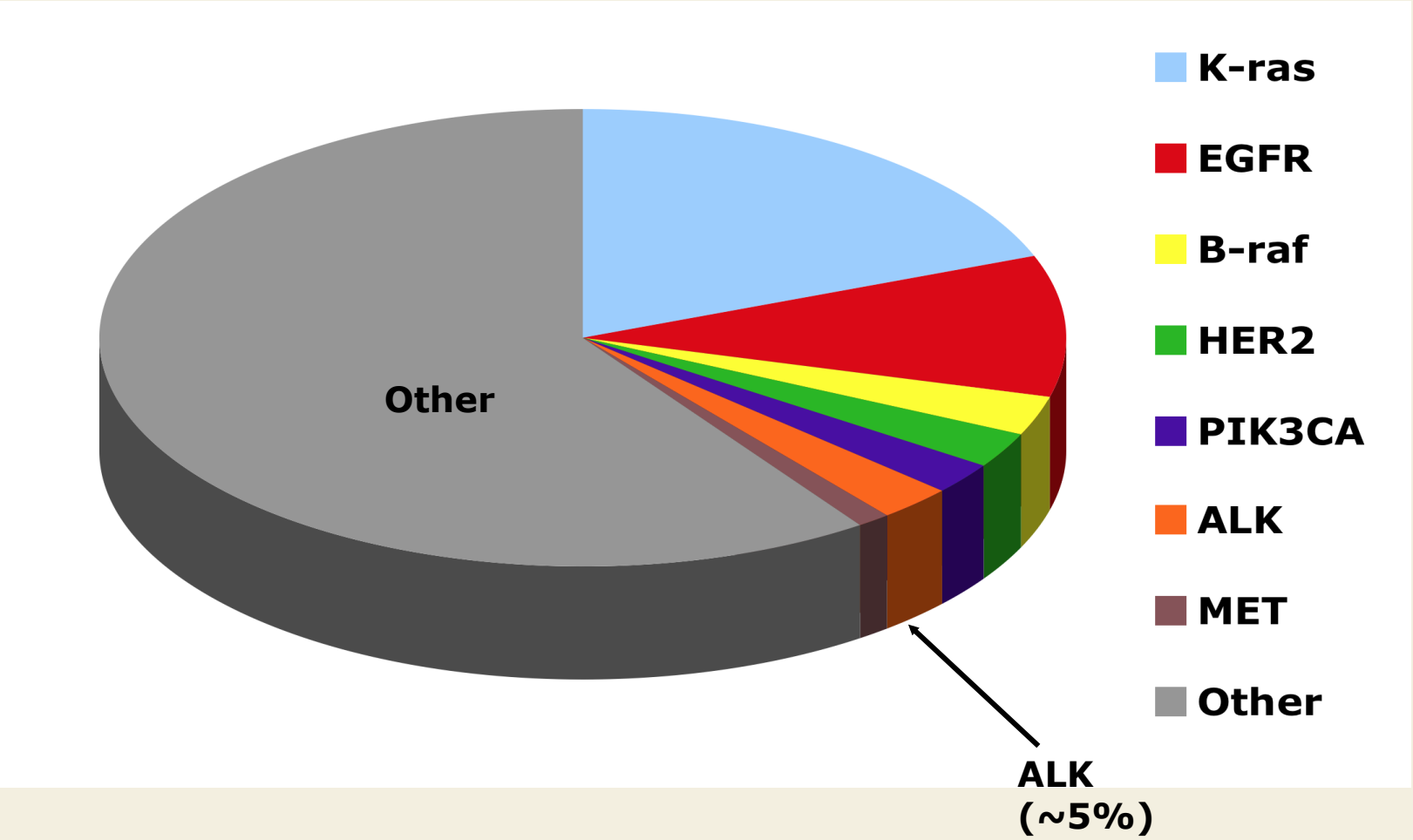
Proc ASCO 2010;Abstract 3.

Introduction

- Crizotinib is an orally bioavailable inhibitor of anaplastic lymphoma kinase (ALK) and select tyrosine kinase receptors.
- In non-small cell lung carcinoma (NSCLC), EML4-ALK has been identified as a unique tumor specific fusion gene present in approximately 4% of patients (*Nature* 2007;148:561).
- **Current study objective:**
  - Investigate the safety and clinical activity of crizotinib in patients with ALK-positive non-small cell lung carcinoma.

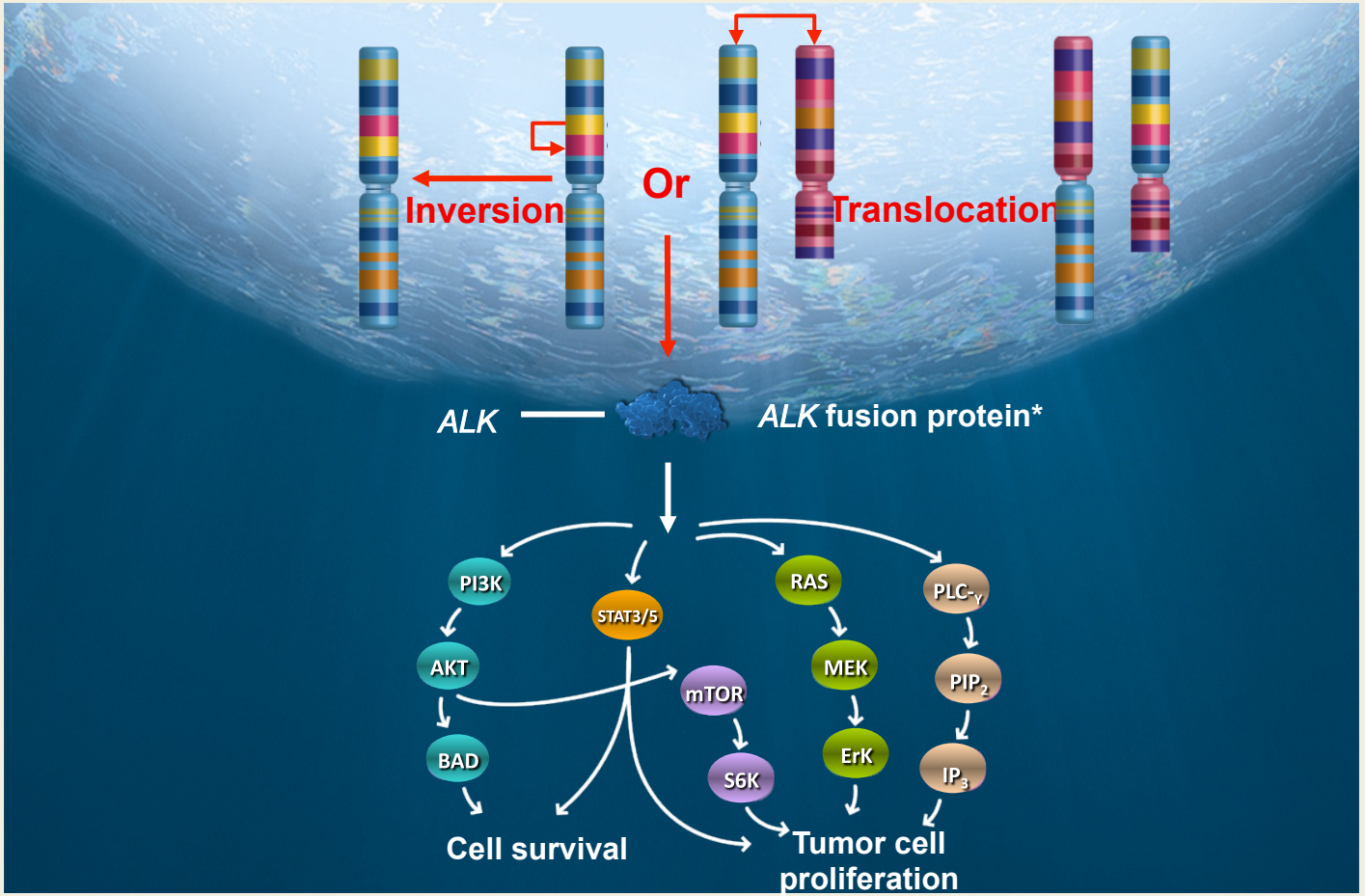
Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Potential Oncogenic Drivers in NSCLC Adenocarcinoma



With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

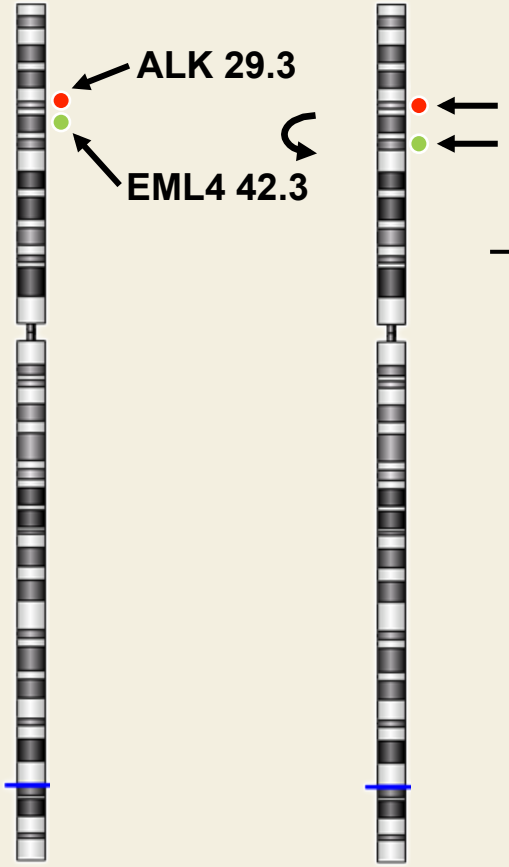
ALK Pathway

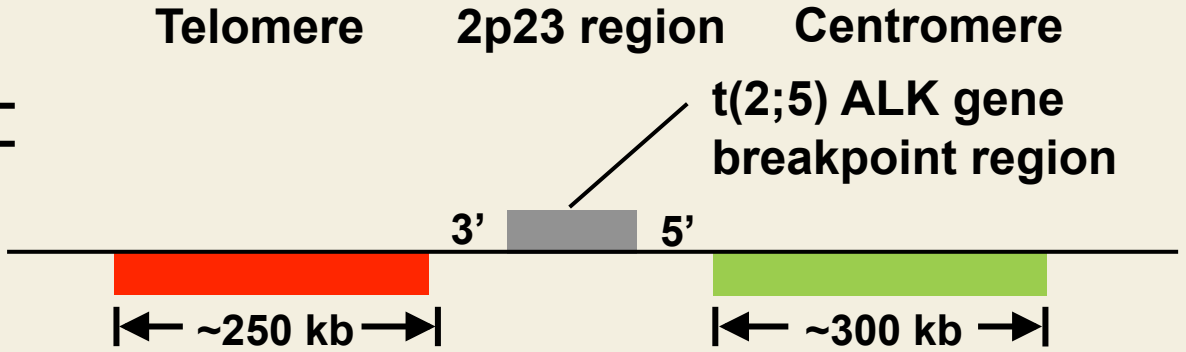


*Subcellular localization of the ALK fusion protein is thought to occur in the cytoplasm, but it is not confirmed.

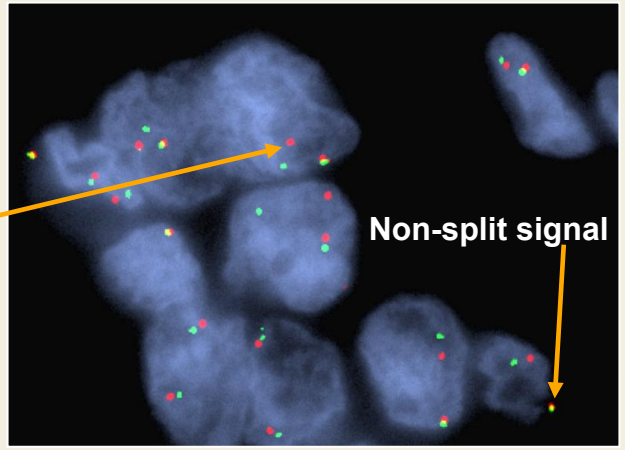
With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

FISH Assay for ALK Rearrangement*





Break-apart FISH assay for *ALK*-fusion genes



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

***Assay is positive if rearrangements can be detected in ≥15% of cells**

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Crizotinib First-in-Human Study Design

Accrual: 82 (Open)

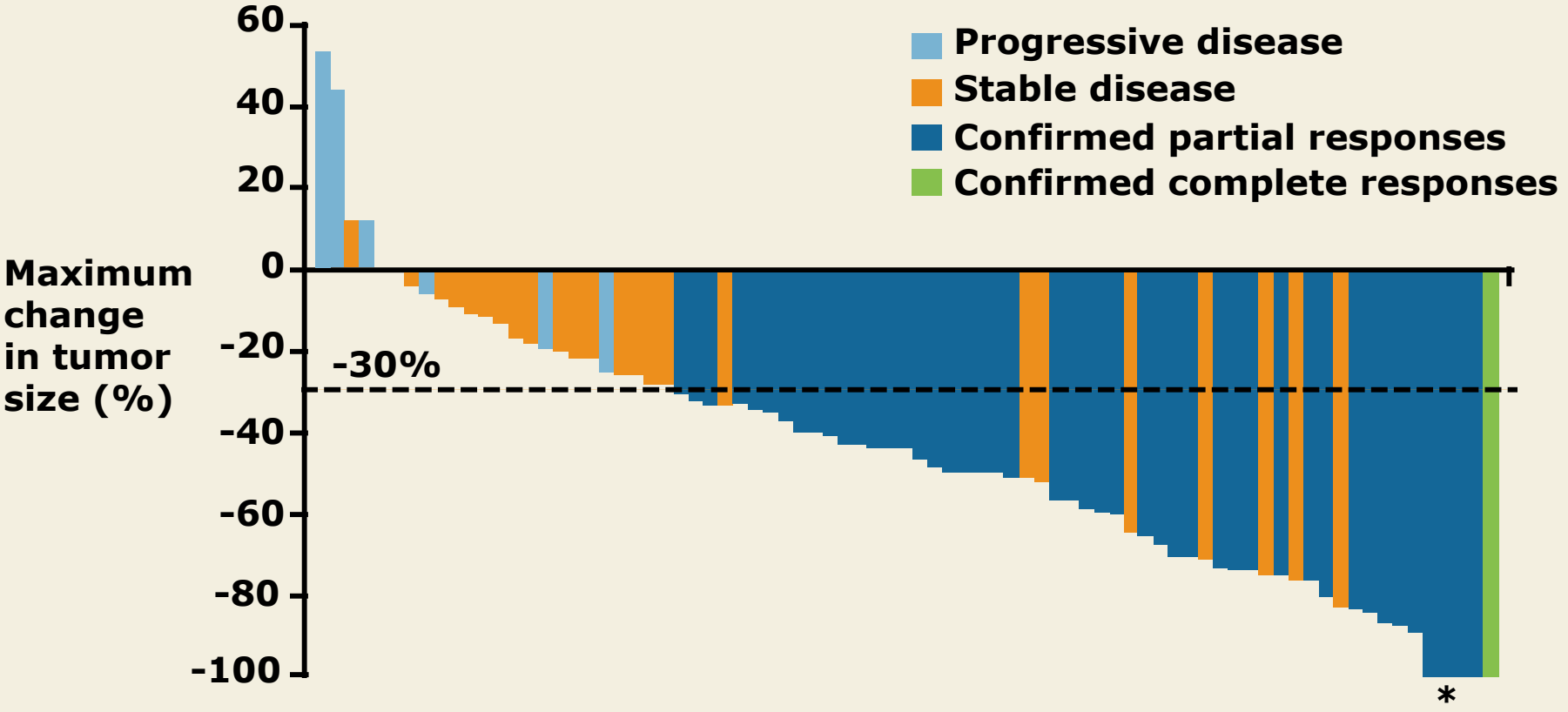
Eligibility
Advanced NSCLC harboring ALK fusion (determined by FISH assay)
Prior therapy allowed
Treated brain metastases allowed

→ **Crizotinib 250 mg/d PO BID***

***Maximum tolerated dose of 250 mg/d BID was established in the dose escalation phase of the study.**

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Tumor Responses to Crizotinib for Patients with ALK-Positive NSCLC

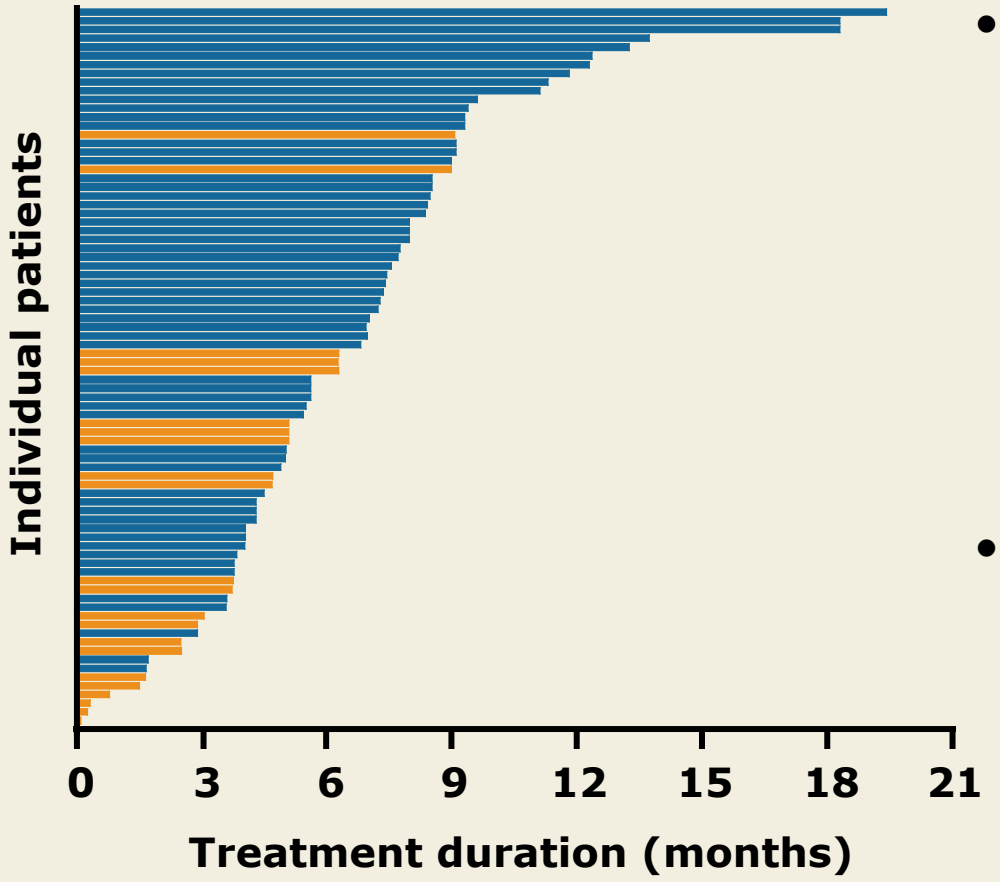


A change of ≥30% is defined as a partial response by RECIST.

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

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

77% of Patients with ALK-Positive NSCLC Remain on Treatment



- **Duration of treatment**
  (median: 5.7 months)

0-3 mo	13 pts
>3-6 mo	29 pts
>6-9 mo	24 pts
>9-12 mo	9 pts
>12-18 mo	4 pts
>18 mo	3 pts

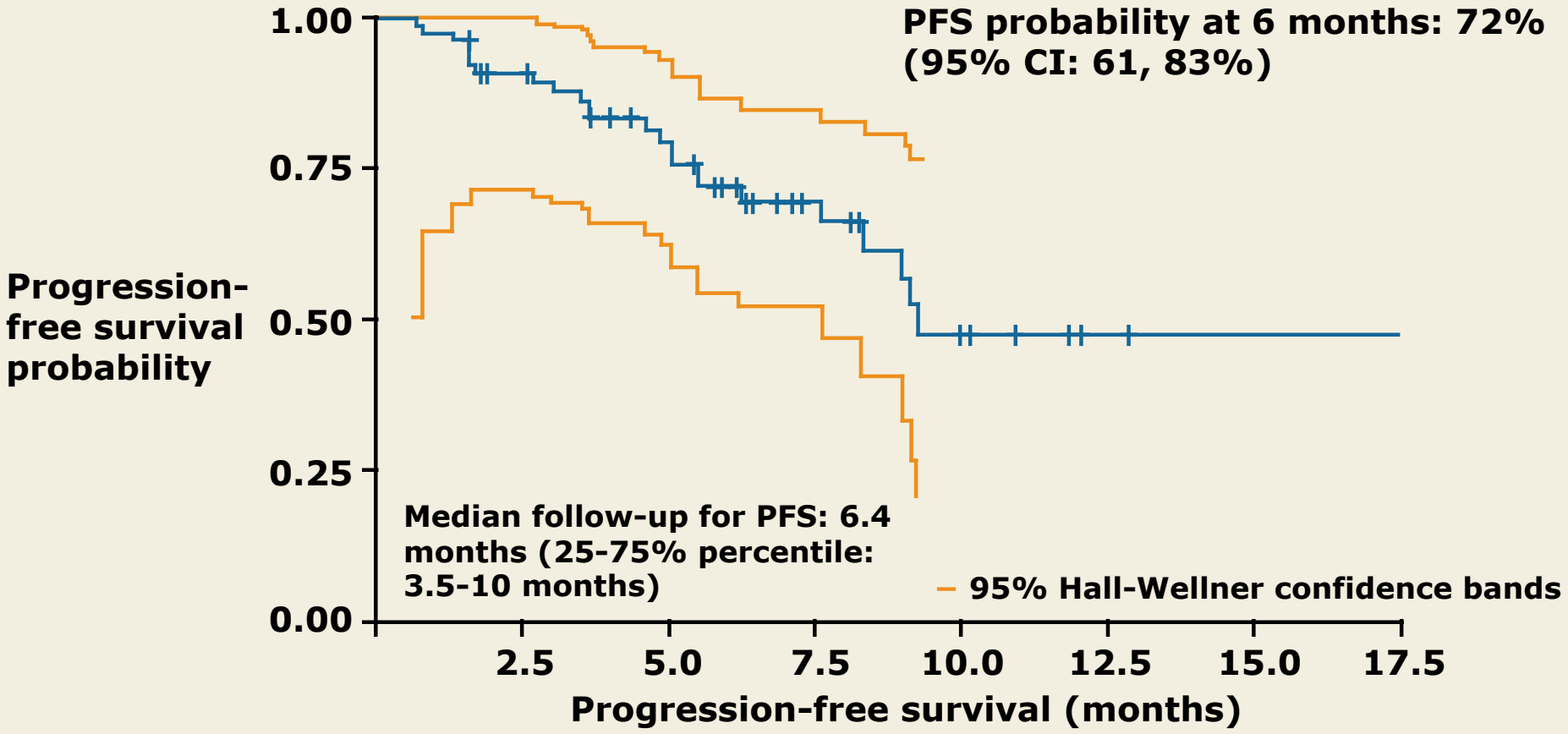
- **Reasons for discontinuation**

- Related AEs	1
- Non-related AEs	1
- Unrelated death	2
- Other	2
- Progression	13

N = 82; orange bars represent discontinued patients

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Progression-Free Survival



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Select Grade 3/4 Adverse Events

Adverse Event (AE)	Grade 3 n (%)	Grade 4 n (%)
Any adverse event	10 (12)	1 (1)
ALT elevation	4 (5)	1 (1)
AST elevation	5 (6)	0
Lymphopenia	2 (2)	0
Dyspnea	1 (1)	0
Pulmonary embolism	1 (1)	0
Hypoxia	1 (1)	0

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Conclusion

- Crizotinib resulted in impressive clinical activity in patients with ALK-positive advanced NSCLC, with:
  - Objective response rate: 57%
  - Disease control rate at eight weeks: 87%
  - Progression-free survival probability at six months: 72%
- The most frequent AEs were mild and moderate gastrointestinal events and mild visual disturbances.
- The data also support molecular profiling of patients as a personalized approach to NSCLC treatment.
- Overall, crizotinib was well tolerated and may offer a potentially new standard of care in the treatment of NSCLC.

Bang Y et al. *Proc ASCO* 2010;Abstract 3.

Investigator comment on the results of a study evaluating crizotinib in ALK-positive NSCLC

This was clearly the "big bang" of ASCO, and it speaks to the fact that targeted therapy works in patients who have the target. This is a newly identified target — an EML4-ALK translocation, which occurs in approximately four to five percent of patients, but that's four to five percent of 200,000 patients in the United States and several million around the world.

Crizotinib is an oral agent that targets the ALK tyrosine kinase. The bottom line of this report is that in a group of 82 patients treated, nearly 75 had some tumor shrinkage. Approximately 60 percent had a response as defined by RECIST and about 90 percent had at least stable disease. Most of these patients had received prior therapy. The objective response rate was 80 percent for patients who had no prior regimens, but even for patients with three or more prior regimens the response rate was 56 percent. This is an extraordinary result for a drug that is so well tolerated. The adverse events were quite mild — some nausea, diarrhea and vomiting — and consistent with what's been observed with oral tyrosine kinase inhibitors (TKIs).

Interview with Roy S Herbst, MD, PhD, June 23, 2010

Investigator comment on the results of a study evaluating crizotinib in ALK-positive NSCLC

This is a paradigm-shifting study for a smaller population of patients. The four to five percent of patients with advanced NSCLC who have the EML4-ALK translocation derive tremendous benefit from crizotinib.

The responses are impressive, with an objective response rate close to 60 percent, and several of the patients who were clearly starting to respond weren't included in that group because they hadn't received their second or third assessments. The results are as good, if not better, than we observed with erlotinib in patients with the EGFR mutation. The median overall survival endpoint has not yet been reached. These results are particularly impressive because the majority of patients had received two or more prior regimens and were essentially refractory or only marginally responsive to standard treatment. In general, these patients don't respond to EGFR inhibitors.

We are now routinely screening for EGFR, K-ras and EML4-ALK in all patients with adenocarcinoma of the lung. Phase II and III clinical trials are ongoing, and I don't believe we can deny crizotinib to any patient who harbors this translocation.

Interview with Corey J Langer, MD, July 2, 2010

Investigator comment on the results of a study evaluating crizotinib in ALK-positive NSCLC

One of the most important take-home messages from ASCO this year was for personalized targeted therapy in lung cancer. For several years we have been hearing the EGFR story, and now a parallel story is emerging with the EML4-ALK translocation.

An exciting Phase I study was presented at the ASCO plenary session this year that evaluated an oral TKI — crizotinib — that specifically blocks the ALK receptor. The side effects were very mild, especially when compared to those of chemotherapy, and were distinct from the side effects of EGFR TKIs. Crizotinib does not cause a lot of diarrhea or rash. The main side effects are lower extremity edema, reversible vision changes and some liver function test abnormalities. The response rate was approximately 60 percent by RECIST, and other patients had very durable stable disease. The overall clinical benefit rate was approximately 90 percent.

Currently, EGFR and K-ras genotyping are widely available nationally. ALK testing is not yet as accessible but it will be soon. This study is exciting and provides a paradigm that will be repeated again and again in lung cancer.

Interview with Lecia V Sequist, MD, MPH, June 18, 2010

Randomized Phase II Trial of Erlotinib (E) Alone or in Combination with Carboplatin/ Paclitaxel (CP) in Never or Light Former Smokers with Advanced Lung Adenocarcinoma: CALGB 30406

Jänne PA et al.

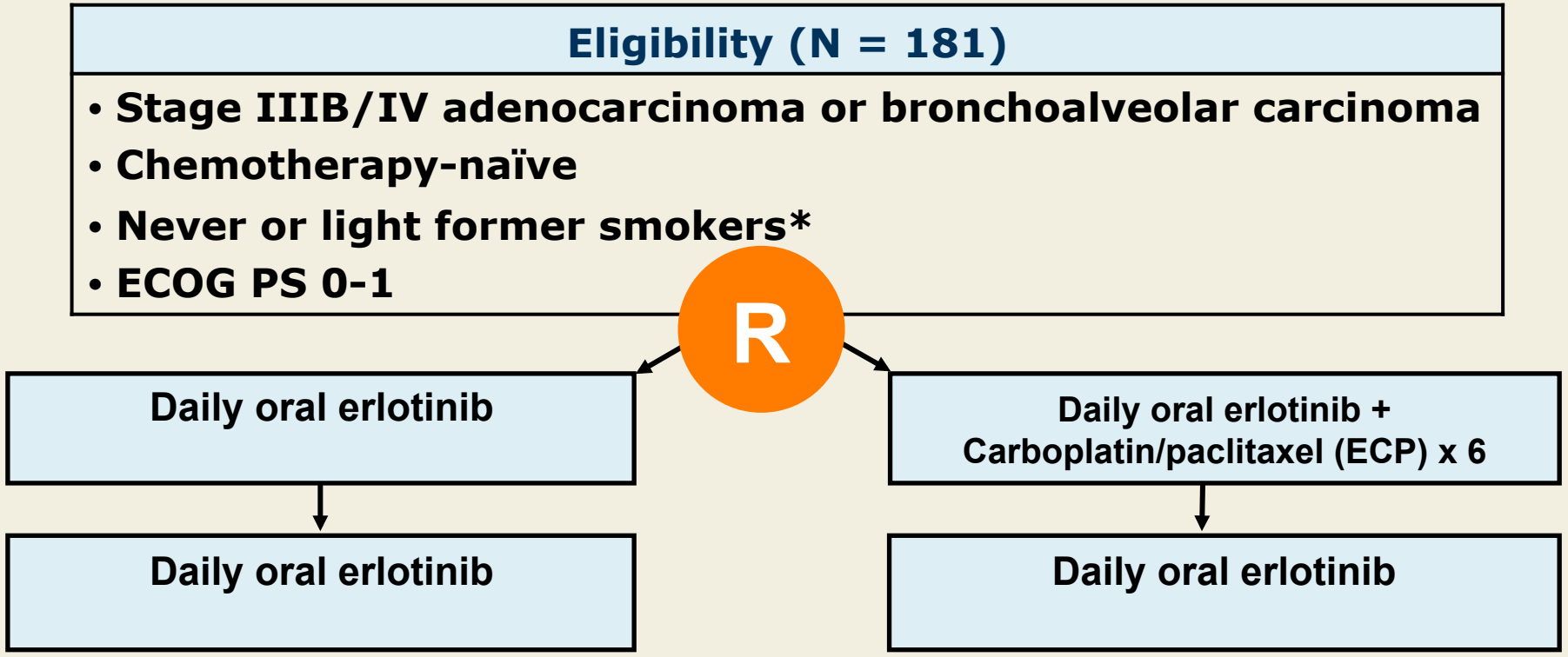
Proc ASCO 2010;Abstract 7503.

Introduction

- The efficacy of EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) is greatest in patients with EGFR mutations.
- Single-agent activity of EGFR TKIs in EGFR mutation-positive NSCLC (*NEJM* 2009;361:947; *NEJM* 2009;361:958)
  - 1st-line response rate (RR): 60-80%
  - 1st-line progression-free survival (PFS): 10-14 months
- Gefitinib is superior to 1st-line chemotherapy in nonsmokers or former light smokers in East Asia (*NEJM* 2009;361:947).
- In never smokers, the addition of erlotinib (E) to chemotherapy resulted in improvement in survival, time to progression and RR in advanced NSCLC (*JCO* 2005;23:5892).
- **Current study objective:**
  - Evaluate erlotinib alone or in combination with chemotherapy as first-line therapy for never or former light smokers with advanced adenocarcinoma of the lung.

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

Study Design

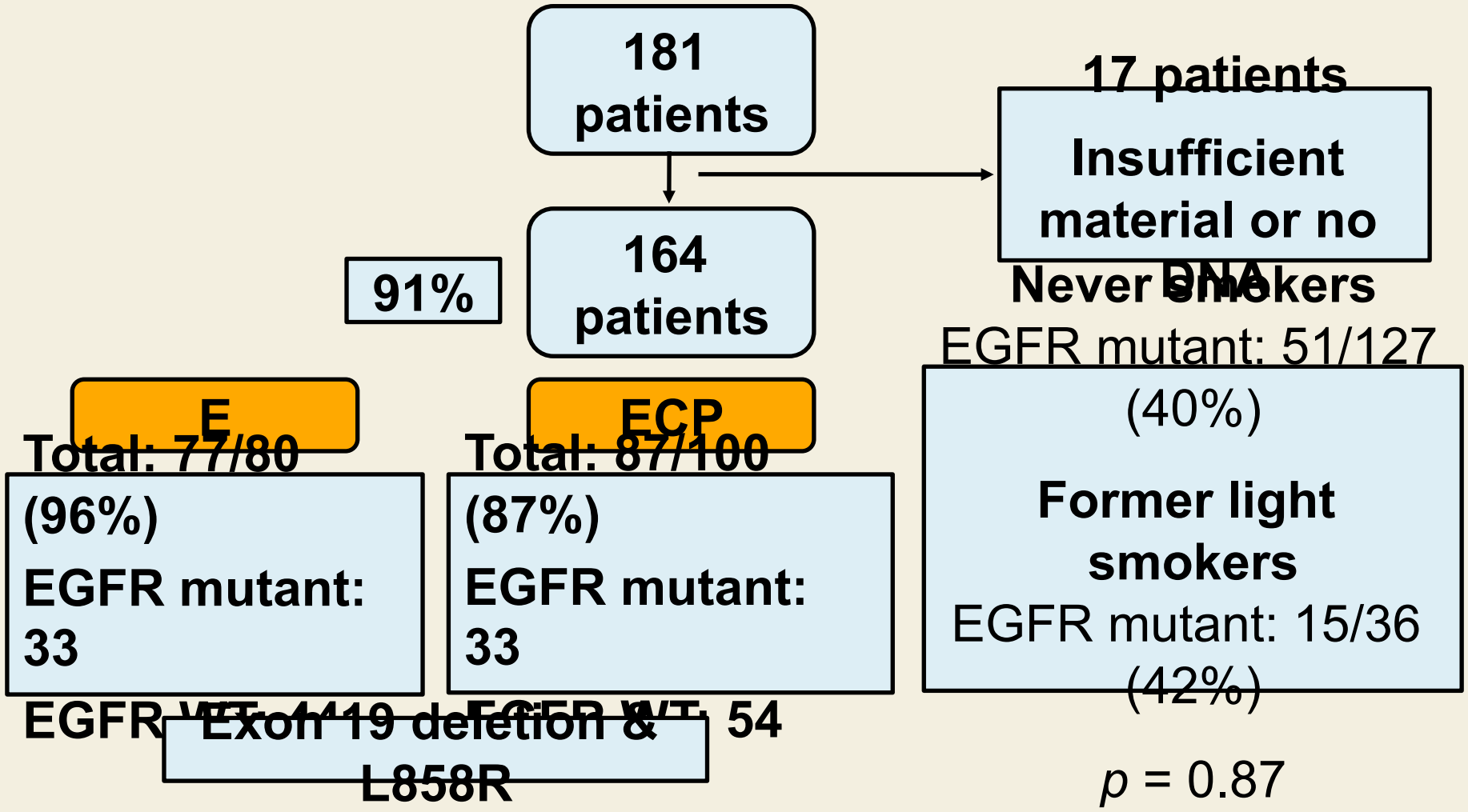


Therapy continues until disease progression or toxicity

* Never smoker: <100 cigarettes/lifetime; light former smoker: quit >1 year ago and smoked <10 pack years

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

Tumor Genotyping Analyses



Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

Efficacy Analyses by Treatment and EGFR Mutation Status

Endpoint	E	ECP
Progression-free survival (n = 81, 100)	6.7 mo	6.6 mo
EGFR mutant vs wild type*	15.7 vs 2.7 mo $p < 0.0001$	17.2 vs 4.8 mo $p < 0.0001$
Overall survival (n = 81, 100)	24.3 mo	19.6 mo
EGFR mutant vs wild type*	31.3 vs 18.1 mo $p = 0.0093$	39.0 vs 13.7 mo $p = 0.0012$
Response rate (n = 81, 100)	35%	48%
EGFR mutant vs wild type*	67% vs 9% $p < 0.0001$	73% vs 33% $p = 0.0004$

* E arm: n = 33 EGFR mutant, n = 44 EGFR wild type; ECP arm: n = 33 EGFR mutant, n = 54 EGFR wild type

Response evaluation every 2 cycles (6 weeks)

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

Grade 3/4 Adverse Events

Adverse Event (AE)	E (n = 81)	ECP (n = 100)
Hematologic - any	1/0	29/20
Anemia Neutropenia Febrile neutropenia Thrombocytopenia	0/0 0/0 0/0 0/0	6/0 24/17 7/3 1/4
Non-hematologic - any	18/2	38/12
Rash Diarrhea Fatigue Nausea/vomiting	6/0 4/0 1/0 1/0	10/0 6/0 16/1 7/0
Dose reductions	23%	27%
Death on study	3 (4%)	2 (2%)

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

Conclusions

- E and ECP yield similar outcomes in a predominantly Caucasian never smoker population of patients with NSCLC.
  - PFS = 6.6 and 6.7 mo, respectively
  - OS = 24.3 and 19.6 mo, respectively
- EGFR mutations identify patients most likely to benefit (PFS, OS, RR) from E or ECP.
- E is better tolerated than ECP.
- EGFR TKIs alone remain an acceptable first-line therapy for patients with advanced EGFR mutant NSCLC.

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

Investigator comment on the results of CALGB-30406: Erlotinib versus erlotinib/carboplatin/paclitaxel in never or light smokers with advanced NSCLC

As enthusiastic as we were about the IPASS data, I believe the average community oncologist wondered whether that study in an Asian population applied to US patients. Our CALGB data with mostly Caucasian, US patients largely mirrors the IPASS experience.

The rate of EGFR mutations in IPASS was 60 percent, and in the CALGB study it was 40 percent for never smokers, so a little less. However, when a molecular marker predicts for very high response and survival rates in 40 percent of your patients, then it's worth looking for that marker. These study results reinforce the concept that we should be carefully considering whom we need to test for the EGFR mutation and whether we have enough tissue or whether we should rebiopsy the tumor. The impact of this once-a-day oral EGFR TKI can be fantastic in the right patients.

Interview with Mark A Socinski, MD, June 4, 2010

Investigator comment on the results of CALGB-30406: Erlotinib versus erlotinib/carboplatin/paclitaxel in never or light smokers with advanced NSCLC

This study was actually derived from my own work with the TRIBUTE trial, which demonstrated no improvement from adding an EGFR inhibitor to carboplatin/paclitaxel in unselected patients. However, for never smokers the median survival improved from 10.1 to 22.5 months. Today we realize that those were patients with EGFR mutations, which had not been identified when we reported.

In the current study never or former light smokers received erlotinib with or without chemotherapy. There was no difference in progression-free or overall survival in patients overall who received erlotinib alone versus the combination. The same appears to be true for patients with EGFR mutations, although those groups cannot be compared directly.

Patients who received chemotherapy and erlotinib obviously experienced more toxicity, especially anemia, neutropenia, febrile neutropenia and thrombocytopenia. So for light or never smokers, used as a surrogate for EGFR mutations, one would probably use erlotinib alone because there is no additional benefit from the addition of chemotherapy.

Interview with Roy S Herbst, MD, PhD, June 23, 2010

Investigator comment on the results of CALGB-30406: Erlotinib versus erlotinib/carboplatin/paclitaxel in never or light smokers with advanced NSCLC

This study was based on the post hoc observation from the TRIBUTE trial, in which a subgroup of never smokers who were about 22 percent of the total population had a marvelous survival benefit, on the order of 22.5 months with the addition of the EGFR inhibitor to chemotherapy versus 10.1 months with placebo.

My one quibble with the CALGB study is that they didn't have a true control arm. Everybody received erlotinib, either alone or combined with chemotherapy. Nevertheless, patients with an EGFR mutation and advanced NSCLC who received chemotherapy with erlotinib fared quite well, with a median overall survival of 39 months. For those who received single-agent erlotinib, it was approximately 31 months. Dr Pasi Janne glossed over this difference, and the question remains: Should we administer erlotinib alone to patients with an EGFR mutation or should we interdigitate it with standard chemotherapy? Certainly the trial did not address this issue, because it made no direct comparison of outcome in patients with EGFR mutations who received erlotinib alone versus chemotherapy/erlotinib. Nonetheless, this was an excellent study, which actually mandated tissue collection.

Interview with Corey J Langer, MD, July 2, 2010

A Phase III Randomized, Double-Blind, Placebo-Controlled Trial of the Epidermal Growth Factor Receptor Inhibitor Gefitinb in Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC): NCIC CTG BR.19

Goss GD et al.

Proc ASCO 2010;Abstract LBA7005.

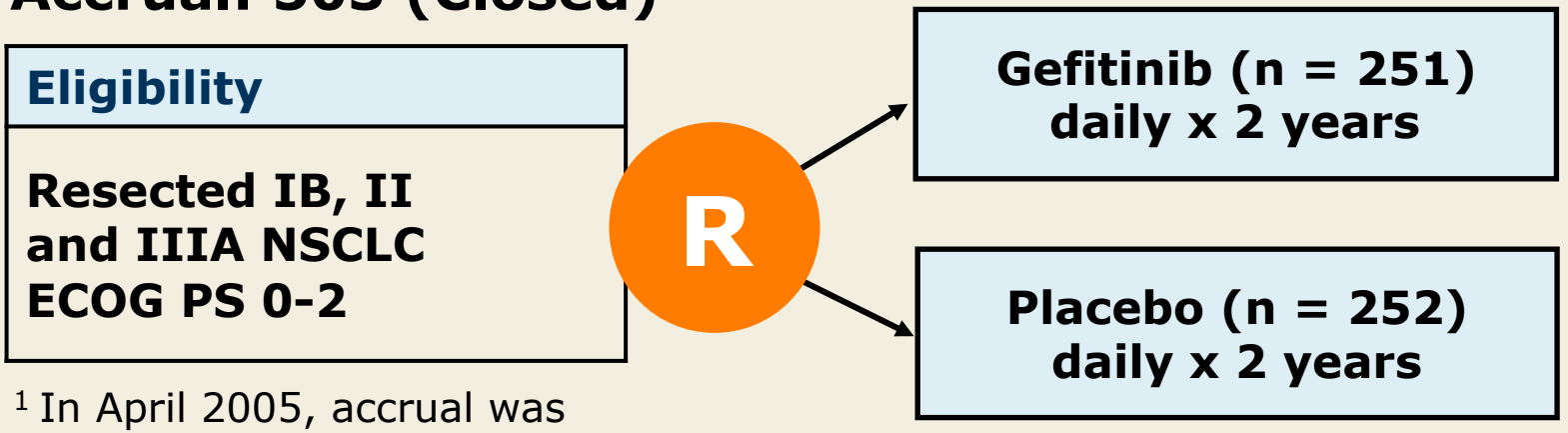
Introduction

- A 2002 meta-analysis from 52 randomized trials revealed a five percent improvement in survival at five years with adjuvant chemotherapy for patients with completely resected NSCLC (*BMJ* 1995;311:899).
- Gefitinib, an EGFR tyrosine kinase inhibitor, demonstrated activity in monotherapy trials for patients with advanced NSCLC (*Proc Am Assoc Cancer Res* 2001;42:630A).
- **Current study objectives:**
  - To investigate the efficacy and tolerability of oral gefitinib in patients with completely resected NSCLC.
  - To confirm the prognostic and predictive significance of KRAS mutation, EGFR gene expression and EGFR mutation.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

Trial Schema

Accrual: 503 (Closed)[1]



[1] In April 2005, accrual was closed early due to the inferiority of gefitinib arm.

Patients were stratified by stage, histology, post-operative radiation, sex and adjuvant chemotherapy.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

Overall Survival and Disease-Free Survival

	Gefitinib (n = 251)	Placebo (n = 252)	Hazard Ratio	*p*-value
Median overall survival (OS)	5.1 years	Not reached	1.23	0.136
Median disease-free survival (DFS)	4.2 years	Not reached	1.22	0.152

Multivariate analysis

- **Age ≥65 years and tumor size ≥4 cm (p = 0.0003) were significantly associated with shorter survival.**
- **Gefitinib remained not significant, but there was a trend suggesting it may be harmful (p = 0.097).**

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

Exploratory Biomarker Analyses: Overall Survival (Placebo Arm)

Patient Group (n)	Hazard Ratio	*p*-value
KRAS mutant vs wild-type (n = 53, 128)	1.12	0.662
EGFR mutant vs wild-type (n = 40, 145)	1.06	0.830
EGFR FISH High polysomy vs low copy (n = 59, 104) Amplified vs low copy (n = 15, 104)	 0.94 1.26	0.77

KRAS and EGFR mutation status and EGFR copy number are not prognostic for overall survival.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

Exploratory Biomarker Analyses: Overall Survival (Gefitinib vs Placebo Arm)

Patient Group (n)	Hazard Ratio	*p*-value
KRAS		
Wild-type (n = 254)	1.13	0.512
Mutant (n = 96)	1.51	0.163
EGFR		
Wild-type (n = 281)	1.21	0.301
Mutant (n = 76)	1.58	0.160
EGFR FISH		
Low copy (n = 205)	1.38	0.13
High copy (n = 134)	1.25	0.38
Amplified only	1.22	0.69

KRAS and EGFR mutations and EGFR copy number are not predictive for a trend towards improvement in survival nor an overall survival benefit in response to gefitinib.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

Selected Grade 3/4 Adverse Events

	Gefitinib (n = 249)		Placebo (n = 243)	
Adverse Event	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Dehydration	2 (<1)	0	1 (<1)	0
Diarrhea	3 (2)	0	2 (<1)	0
Dyspnea	7 (3)	3 (2)	9 (4)	1 (<1)
Infection - Other	4 (2)	0	3 (1)	0
Nausea	2 (<1)	0	0	0
Pneumonitis	1 (<1)	2 (<1)	3 (1)	0

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

Conclusions

- Gefitinib was well tolerated.
- Gefitinib did not improve DFS and OS in patients with completely resected early stage NSCLC in this underpowered study.
- KRAS mutation status, EGFR by FISH or EGFR sensitizing mutation status were neither prognostic nor predictive of survival in exploratory analysis.
- A targeted agent that improves OS in NSCLC in the adjuvant setting has yet to be demonstrated.
- Currently, the treatment of choice for patients in good performance is chemotherapy.
- The results of the RADIANT trial of adjuvant erlotinib are awaited (NCT00373425).

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005; www.clinicaltrials.gov.

Investigator comment on the results of NCIC-CTG BR.19: A Phase III study of adjuvant gefitinib in NSCLC

SWOG-S0023 evaluated chemoradiation therapy followed by maintenance gefitinib versus placebo, and that study was halted because patients who received maintenance gefitinib actually fared worse than those who received placebo.

This is a similar study in earlier, Stage I to IIIA disease, in which patients received adjuvant chemotherapy and then either gefitinib or placebo. They had enrolled about 500 patients when SWOG-S0023 was completed, and this study was stopped because of that negative result. It was the right decision because, for whatever reason, the patients who received gefitinib fared no better and actually are trending a little worse in terms of overall survival.

Even though gefitinib was well tolerated, there is no benefit from gefitinib in patients with resected lung cancer. In exploratory analyses of K-ras and EGFR mutations and EGFR FISH, none were predictive for outcome.

Another ongoing study, RADIANT, is evaluating adjuvant erlotinib. Based on these results, I would not bet the house on the outcomes of that study. For whatever reason, adjuvant EGFR TKIs will not be beneficial in unselected patients.

Interview with Roy S Herbst, MD, PhD, June 23, 2010

Investigator comment on the results of NCIC-CTG BR.19: A Phase III study of adjuvant gefitinib in NSCLC

Nobody quite knows what to make of the results from this study. In 2005, the ISEL study of second- and third-line gefitinib versus placebo and the SWOG study of maintenance gefitinib versus placebo were negative, and the BR.19 investigators decided to shut their trial down before completing the planned accrual.

After several years of follow-up, BR.19 was presented, but it was difficult to discern how many patients received gefitinib and the duration of treatment. The bottom line was that no survival difference was evident between those who received adjuvant gefitinib and those who received placebo. Of most concern, there was a trend toward possible harm from gefitinib, which was observed to be consistent across different subgroups, including those with an EGFR mutation. It's not entirely clear what might cause this apparent detriment, but it's consistent with the SWOG study.

We are now awaiting the results of the RADIANT trial, which is evaluating adjuvant erlotinib versus placebo, but instead of taking "all-comers," it requires patients to be positive for EGFR overexpression by either immunohistochemistry or FISH. So hopefully in two years we will have an answer, but I would be especially interested to see the results in patients with EGFR mutations.

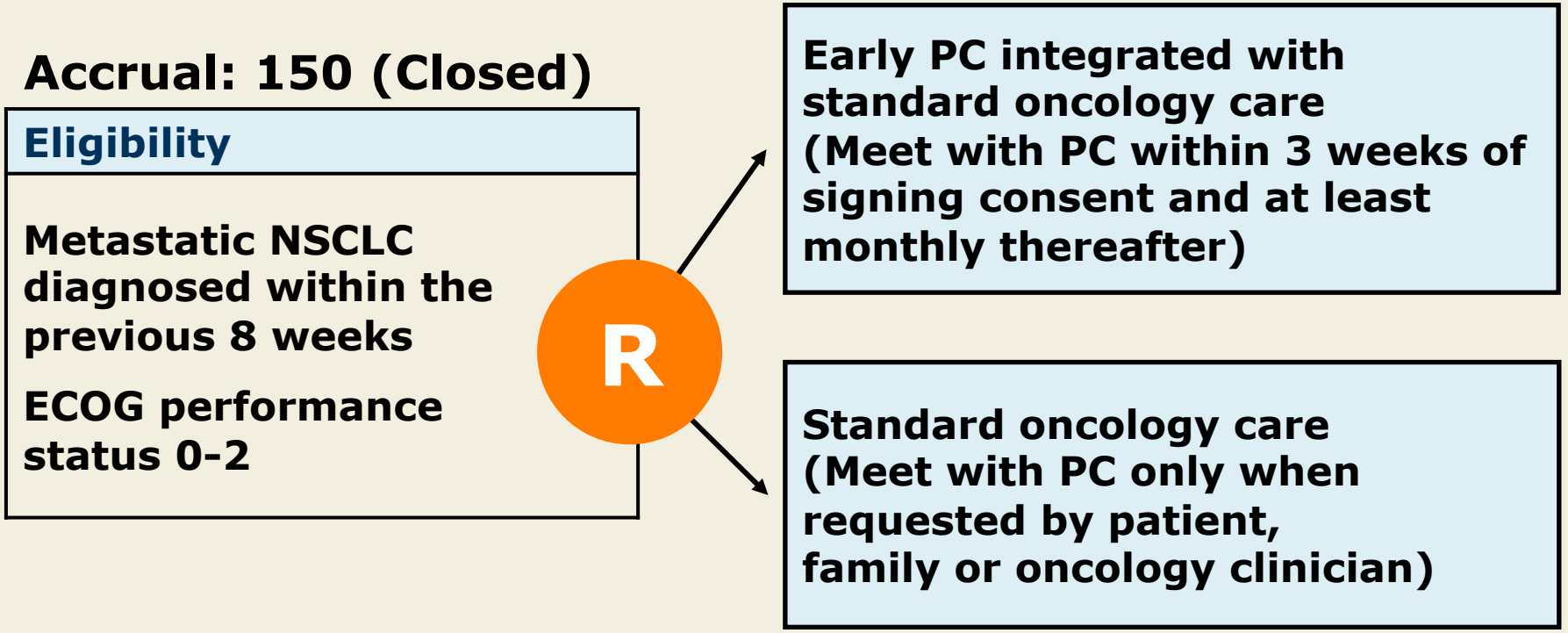
Interview with Lecia V Sequist, MD, MPH, June 18, 2010

Effect of Early Palliative Care (PC) on Quality of Life (QOL), Aggressive Care at the End-of-Life (EOL), and Survival in Stage IV NSCLC Patients: Results of a Phase III Randomized Trial

Temel JS et al.

Proc ASCO 2010;Abstract 7509.

Trial Schema



Prior to randomization, patients completed baseline measures of QOL (FACT-Lung) and mood (HADS and PHQ-9).

Temel JS et al. *Proc ASCO* 2010;Abstract 7509.

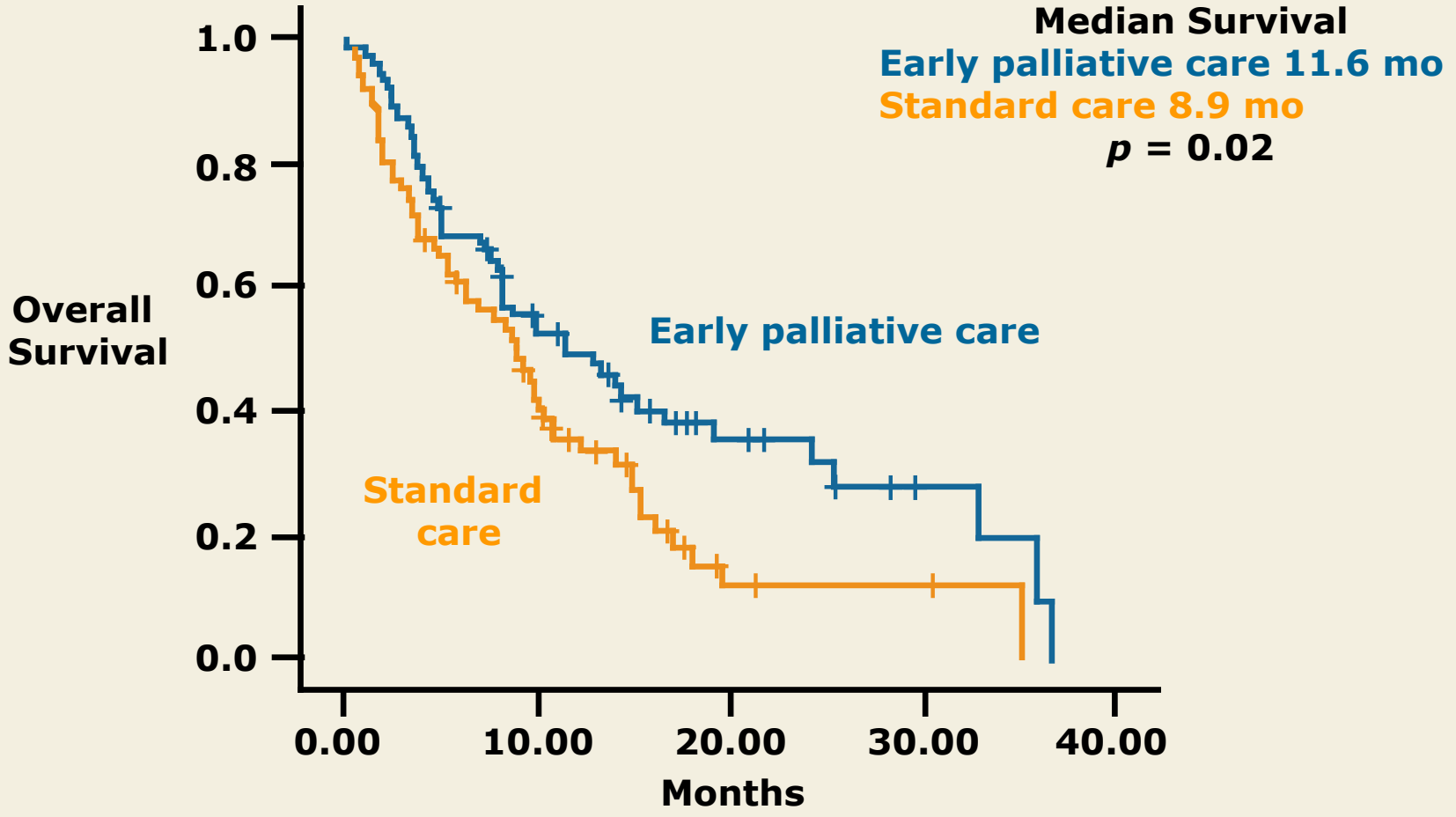
Quality of Life (QOL) Measures at 12 Weeks

	Standard care Mean score	Early PC Mean score	*p*-value
FACT-Lung*	91.5	98.0	0.03
Lung Cancer Symptoms (LCS)*	19.3	21.0	0.04
Trial Outcome Index (TOI)*	53.0	59.0	0.009
Change in QOL from baseline to week 12	**Standard care Mean change**	**Early PC Mean change**	***p*-value**
FACT-Lung	-0.4	+4.2	0.09
FACT-Lung TOI	-2.3	+2.3	0.04

* Lower scores indicative of greater symptom burden

Temel JS et al. *Proc ASCO* 2010;Abstract 7509.

Survival Analysis



Controlling for age, gender and PS, adjusted HR = 0.59 (0.40-0.88), p = 0.01

With permission from Temel JS et al. *Proc ASCO* 2010;Abstract 7509.

ASCO Quality Measures

Measure	Standard care - Median	Early PC - Median	*p*-value
Aggressive EOL care	54%	33%	0.05
No hospice	39%	31%	
Hospice <3 days	15%	3%	
Chemo within 14 days of death	24%	18%	
Documented resuscitation preferences	28%	53%	0.05

Temel JS et al. *Proc ASCO* 2010;Abstract 7509.

Conclusions

- Compared to standard oncology care, integrated PC led to:
  1) Improvement in QOL
     - May be due to improved symptom management
  2) Lower rates of depression
     - May be due to improved symptom management and illness acceptance
  3) Less aggressive care at EOL
  4) Greater documentation of resuscitation preferences
  5) Higher survival rates. Survival was not a pre-specified study endpoint. Prolonged survival possibly related to:
     - Earlier recognition and management of medical issues; improved QOL and mood; less chemotherapy at the EOL; longer hospice admissions

Temel JS et al. *Proc ASCO* 2010;Abstract 7509.

Investigator comment on the results of a study evaluating the effects of early palliative care on quality of life, aggressive care at the end of life and survival

This was a "sleeper abstract," and in the long run this study may change how we approach lung cancer. The trial met every endpoint: Quality of life, pain and depression scores were all improved. The patients who received early palliative care had fewer days in the hospital at the end of life and were more likely to be enrolled in hospice. Despite this and perhaps surprisingly, median survival was improved by 2.7 months, which is the outcome we seek with newer targeted agents. This is a very important paper and certainly merited its placement in the lung plenary session.

This study underscores the need to intervene early with palliative care issues. We tend to take a "go-stop" approach. We go full force with chemotherapy or various other interventions while we still think it's worthwhile. Then patients enroll in hospice and we shut the door and suddenly our whole approach shifts. We focus on managing symptoms. The emphasis here is that we have to do both in tandem and intervene early with palliative care. We have to discuss all the prognostic implications of the diagnosis and what long-range plans to implement.

Interview with Corey J Langer, MD, July 2, 2010

Investigator comment on the results of a study evaluating the effects of early palliative care on quality of life, aggressive care at the end of life and survival

Dr Temel hypothesized that integrating palliative care when patients begin receiving chemotherapy for advanced NSCLC might improve quality of life for patients with metastatic lung cancer, which was indeed shown in this study. However, the real "buzz" at ASCO was the improvement in survival, despite the fact that patients in both arms received an equal number of chemotherapy regimens and the palliative care patients received less aggressive care at the end of life. The Kaplan-Meier curves looked very similar to what was observed in the ECOG study E4599, which evaluated carboplatin/paclitaxel with or without bevacizumab.

A couple of factors may have contributed to the improvement in survival, including better treatment of depression, which we know occurs at a very high rate in lung cancer and is associated with shorter survival. Additionally, better symptom control and faster recognition and treatment of problems may have played a role. In the end, we can't say definitively what contributed to the survival improvement, but Dr Temel is planning a larger, more definitive study to determine whether these results can be replicated in a multicenter fashion.

Interview with Lecia V Sequist, MD, MPH, June 18, 2010

Weekly Paclitaxel Combined with Monthly Carboplatin versus Single-Agent Therapy in Patients Age 70 to 89: IFCT-0501 Randomized Phase III Study in Advanced Non-Small Cell Lung Cancer (NSCLC)

Quoix EA et al.

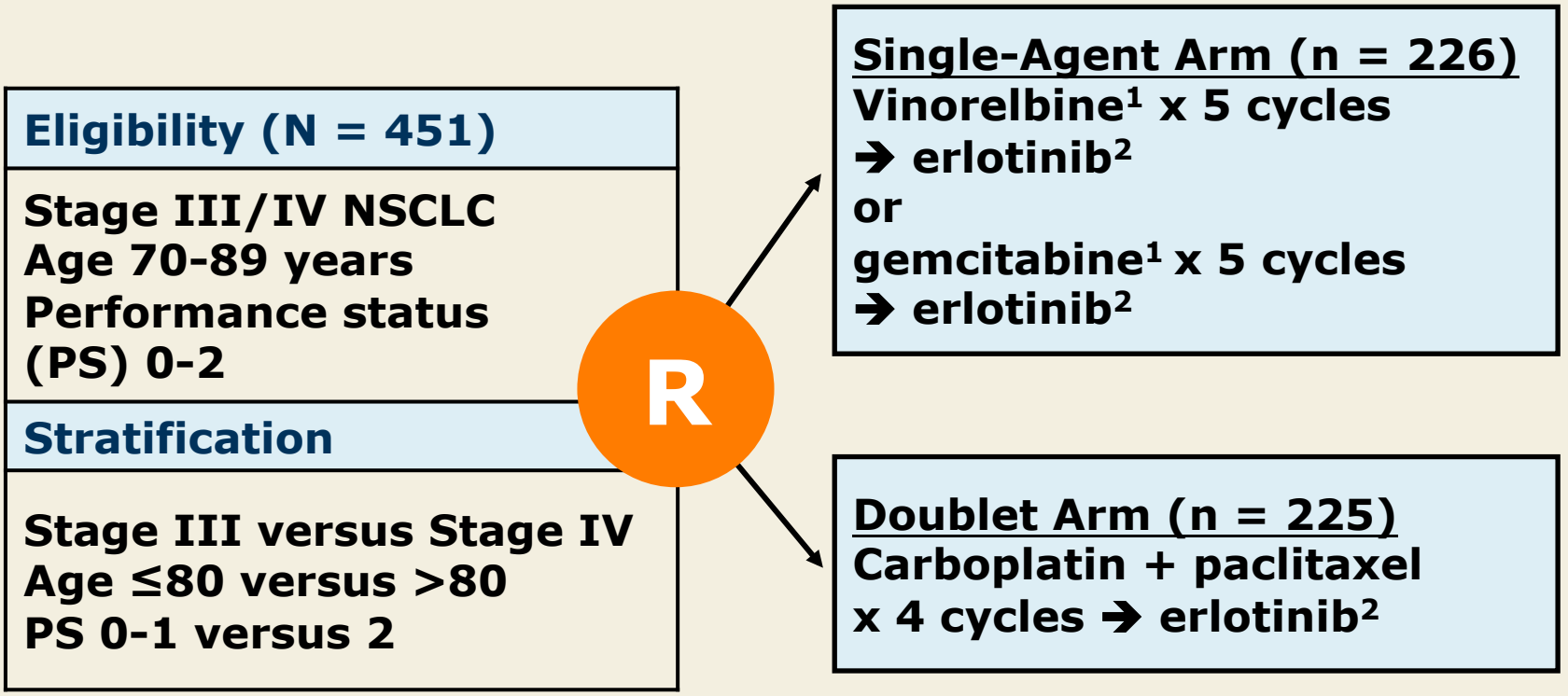
Proc ASCO 2010;Abstract 2.

Introduction

- Incidence of advanced NSCLC in the elderly is increasing, with increased life expectancy and increased incidence of cancers with aging.
- Phase II trial in elderly patients with advanced NSCLC showed gemcitabine to be effective (*Lung Cancer* 2005;47:405).
  - Objective response rate (ORR) was 28.2% and median survival was 6.83 mo.
- Phase II study in elderly patients with advanced NSCLC showed carboplatin plus paclitaxel to be effective (RR 43%, MST 13.6 months) and well tolerated (*J Thorac Oncol* 2006;1:328).
- **Current study objective:**
  - Phase III trial to compare efficacy and tolerability of gemcitabine (gem) or vinorelbine (vin) monotherapy to carboplatin/paclitaxel in elderly patients with advanced NSCLC.

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

Trial Schema



[1] Choice of vinorelbine or gemcitabine decided by center at the beginning of the study
[2] Erlotinib given in cases of progressive disease or excessive toxicity

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

Response Rate at Six Weeks (ITT)

	Single agent (n = 211)	Doublet (n = 210)	*p*-value
Partial response (PR)	10.90%	29.05%	$<10^{-5}$
Stable disease (SD)	45.50%	38.57%	0.18
Disease control rate (DCR) (PR + SD)	56.40%	67.62%	0.02
Progressive disease (PD)	21.80%	7.14%	$<10^{-4}$
Not reported	7.11%	9.53%	0.47
Withdrawal before first evaluation*	14.70%	15.70%	0.88

* Main causes: Deaths (20 in single-agent arm and 23 in doublet arm), reduced general condition (7 and 4, respectively), toxicity (0 and 4, respectively) and withdrawal of consent (6)

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

Survival Data (ITT)

	Single agent (n = 226)	Doublet (n = 225)	*p*-value
Progression-free survival (PFS) Median (95% CI) 1-year PFS rate (95% CI)	 3.0 months (2.6-3.9) 2.3% (0.8-5.3)	 6.1 months (5.5-8.7) 15.4% (10.8-20.8)	$<10^{-6}$
Overall survival (OS) Median (95% CI) 1-year OS rate (95% CI)	 6.2 months (5.3-7.4) 26.9% (21-33.1)	 10.3 months (8.3-13.3) 45.1% (38.2-51.8)	0.00004

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

Select Grade 3/4 Toxicities

	Gem (n = 149)	Vin (n = 61)	All single agent	Doublet (n = 208)	*p*-value
Neutropenia	4.70%	37.70%	14.30%	54.30%	$<10^{-5}$
Febrile neutropenia	0%	9.84%	2.90%	9.60%	0.004
Anemia	2.01%	9.84%	4.30%	7.70%	0.14
Thrombocytopenia	1.34%	0%	1.00%	6.30%	0.004
Neuropathy	0%	0%	0%	2.90%	0.015
Asthenia	6.04%	6.56%	6.20%	9.60%	0.19
Anorexia	1.34%	0%	1.00%	3.80%	0.061
Reduced general condition	0.67%	3.28%	1.50%	1.40%	1.0

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

Conclusions

- First study entirely devoted to elderly patients showing the superiority of a carboplatin doublet over single-agent therapy in advanced NSCLC.
  - Median PFS: 6.1 mo vs 3.0 mo ($p < 10^{-6}$)
  - Median OS: 10.3 mo vs 6.2 mo ($p = 0.00004$)
  - 1-yr OS rate: 45% vs 27%
- Doublet had a beneficial effect on survival in most of the subgroups tested, even those with worse prognosis (data not shown).
- Doublet regimen had acceptable toxicity.
- New paradigm for elderly patients with advanced NSCLC: Monthly carboplatin plus weekly paclitaxel.

Quoix EA et al. *Proc ASCO* 2010;Abstract 2.

Investigator comment on the results of IFCT 0501: A Phase III study of combination versus single-agent chemotherapy for elderly patients with advanced NSCLC

This plenary presentation focused on elderly patients who were 70 years or older with advanced NSCLC was notable and important. Whether these patients should receive single-agent or combination chemotherapy has been debatable because the results of previous studies have been mixed.

This was a large European study, which randomly assigned patients to weekly paclitaxel with carboplatin or single-agent therapy. Although we need better therapy than was utilized in either of these arms, the study clearly demonstrated superiority for the combination regimen. The combination was a little more toxic than the single agent, but overall the tolerability was good. I believe it's now clear that we should treat elderly patients without severe comorbidities as we treat younger patients. Many of us have believed for years that this was the appropriate way to treat older patients, and this study confirms it.

Interview with F Anthony Greco, MD, June 15, 2010

Investigator comment on the results of IFCT 0501: A Phase III study of combination versus single-agent chemotherapy for elderly patients with advanced NSCLC

This study met its primary endpoint in that the doublet chemotherapy was superior to the singlet, with median progression-free survival doubling from 3 to 6.1 months and the median overall survival improving from 6.2 to 10.3 months. This is quite significant.

Of course the question is, at what cost? In terms of nonhematologic toxicity, slightly more neuropathy was associated with the combination — 2.9 percent Grade 3 or 4 neuropathy — and possibly a trend for more anorexia. For hematologic toxicity, there was a little more neutropenia — 54.3 percent versus 37.7 percent Grade 3 or 4 neutropenia — which did translate to slightly more febrile neutropenia, and there was also more thrombocytopenia. Toxic deaths were also slightly more common with the combination regimen.

Clearly the benefit of the doublet versus single-agent therapy is significant, and one should consider using a platinum-based doublet for elderly patients with advanced NSCLC. The bottom line is that this study should cause us to revisit the standard approach for elderly patients with good performance statuses.

Interview with Roy S Herbst, MD, PhD, June 23, 2010

Investigator comment on the results of IFCT 0501: A Phase III study of combination versus single-agent chemotherapy for elderly patients with advanced NSCLC

This study for the elderly is near and dear to my heart because this has been an area of particular interest to me. I have done several retrospective analyses in patients 70 years of age or older and have consistently shown, at least in North America, that fit older patients fare as well or nearly as well as younger patients, but that mind-set is not universal. In Europe a single agent remains the standard for elderly patients with advanced NSCLC. In the NCCN and ASCO guidelines a single agent is certainly the preferred approach, although some allowance is made for combination therapy.

This study by Quoix and colleagues is paradigm shifting. They were able to accomplish what no other group has previously been able to do, which is to compare a platinum-based doublet to single-agent therapy, and they demonstrated convincingly and overwhelmingly that the doublet was superior in every imaginable way.

For myself, a platinum-based doublet, preferably carboplatin-based, is the standard, and I believe carboplatin and weekly paclitaxel will be the reference arm for future studies for the elderly.

Interview with Corey J Langer, MD, July 2, 2010