UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

Poster Discussion session NSCLC, metastatic

Silvia Novello

silvia.novello@unito.it

University of Turin - Italy

Disclosures

- Honoraria from Eli Lilly, Pfizer, Roche, Daiichi-Sankyo.

- 1229PD; LUX-Lung 3: Symptom and health-related quality of life results from a randomized phase III study in 1st-line advanced NSCLC patients harbouring EGFR mutations. *Sequist L. et al*
- 1230PD; Updated Results of a Global Phase II Study with Crizotinib in Advanced ALK-positive Non-Small Cell Lung Cancer (NSCLC). *Kim DW et al.*
- 1231PD; Impact of crizotinib treatment on patient-reported symptoms and quality of life (QOL) in advanced ALK-positive non-small cell lung cancer (NSCLC). *Blackhall F et al*.

- Irreversible EGFR Tkis as first line treatment in advanced NSCLC
- QoL data in enriched patient populations treated with targeted therapies
- More data on crizotinib in advanced NSCLC

- Irreversible EGFR Tkis as first line treatment in advanced NSCLC
- QoL data in enriched patient populations treated with targeted therapies
- More data on crizotinib in advanced NSCLC

LUX-Lung 3: Symptom and Health-related Quality of Life Results from a Randomized Phase III Study in First-line Advanced NSCLC Patients Harbouring EGFR Mutations

L. V. Sequist; M. Schuler; N. Yamamoto; K. O'Byrne; V. Hirsh; T. Mok; J. Lungershausen; M. Shahidi; M. Palmer; J. C.-H. Yang

EGFR-TKIs: Front - Line Studies

Study	Entry Criteria	HR for PFS (EGFR mut +)	HR for OS (EGFR mut +)
IPASS Mok NEJM 2009	Asiatic, never- & light – smokers, adenocarcinoma (EGFR mut + 59.7%)	0.48 (0.36-0.66)	0.91 * (0.76-1.10) *overall population
First – SIGNAL Proc. IASLC 2009	Adenocarcinoma, Never-smokers (EGFR mut + 44%)	0.61 (0.30-1.22)	0.82 (0.35-1.92)
NEJ002 NEJM 2010 Proc. ASCO 2011	EGFR Mutation + (all)	0.35 (0.25-0.50)	0.887 (0.634-1.241)
WJTOG3405 Lancet Onc. 2010	EGFR Mutation + (all)	0.520 (0.378-0.715)	1.185 (0.767-1.829)
EURTAC (EU)	EGFR Mutation + (all)	0.42 (0.27-0.64)	?
OPTIMAL (China)	EGFR Mutation + (all)	0.16 (0.10-0.26)	1.04 (0.69–1.58)
LUX-LUNG3	EGFR Mutation + (all)	**0.58** (0.43–0.78) **0.47** (0.34–0.65)*	-

***common mutations**

Lux Lung 3

- Data availables in other terapeutic lines/setting
- vanced
  ients
  ed)
- : asiatic
  ether
- comparator arm: a mor
  adeguate doublet chem
- Competitive drugs already available
- T

	IPASS		EURTAC		Lux-Lung 3	
	Gefitinib	Carbo/Paclitaxel	Erlotinib	Chemotherapy	Afatinib	Cis/Pem
AEs all grades	95.6%	98.6%	96%	99%	100%	98.2%
Treatment related AEs	88.6%	96.6%	92%	95%	99.6%	95.5%
Grade 3,4 AEs	17%	56.7%	45%	81%	60.7%	56.8%
SAE	3.5%	9.0%	7%	16%	22.8%	22.5%
AE leading to discontinuation	4%	11.4%	5%	14%	10%	14.4%

AEs CTC 3,4	IPASS		EURTAC		Lux-Lung 3	
	Gefitinib	Carbo/Paclitaxel	Erlotinib	Chemotherapy	Afatinib	Cis/Pem
Rash	3.1%	0.8%	9%	0%	16.2%	0
Diarrhea	3.8%	1.4%	4%	0%	14.4%	0
Neutropenia	3.7%	67.1%	0	22%	0.4	18%
Febr. Neutrop.	0.2%	2.9%	0	4%	nr	nr
Anemia	2.2%	10.6%	1%	4%	0.4	6.3%
ILD	2.6%	1.4%	1%	1%	nr	nr
Paronychia	0.3%	0	nr	nr	11.4%	0

T. Mok et al, NEJM 2009; R. Rosell et al, Lancet Oncol 2012; J.C.-H. Yang et al, ASCO 2012

Lux Lung 3

IN FAVOUR

- Data availables in other terapeutic lines/setting
- Largest trial in advanced NSCLC EGFRm patients

  (N=345 randomized)
- Unique in etnicity: asiatic and caucasian together
- Unique in the comparator arm: a more adeguate doublet chemo
- Competitive drugs already available
- Toxicity profile
- Comparator arm already “outdated” and not properely adeguate (maintenance?)
- Unsatisfactory data about rare mutations

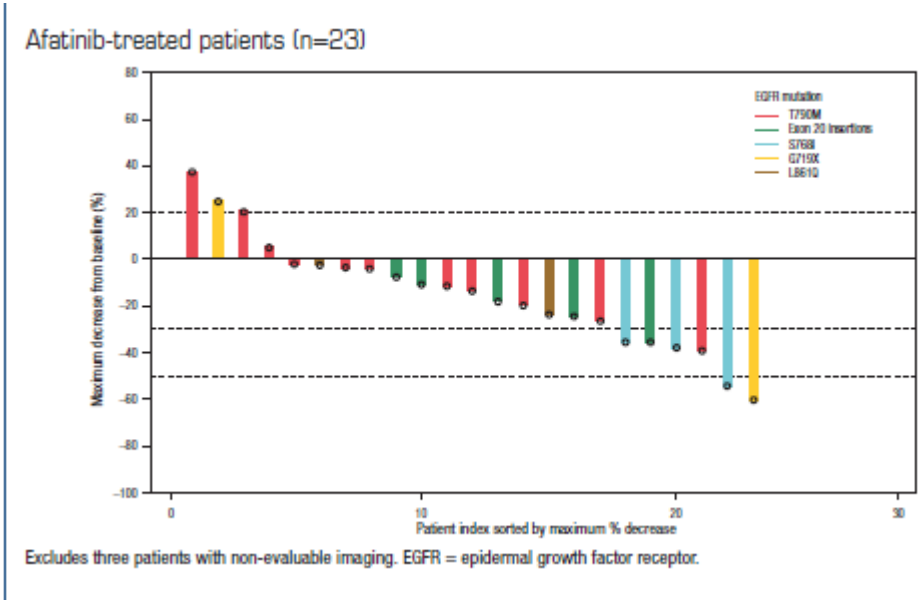
J.C.-H. Yang et al, ASCO 2012

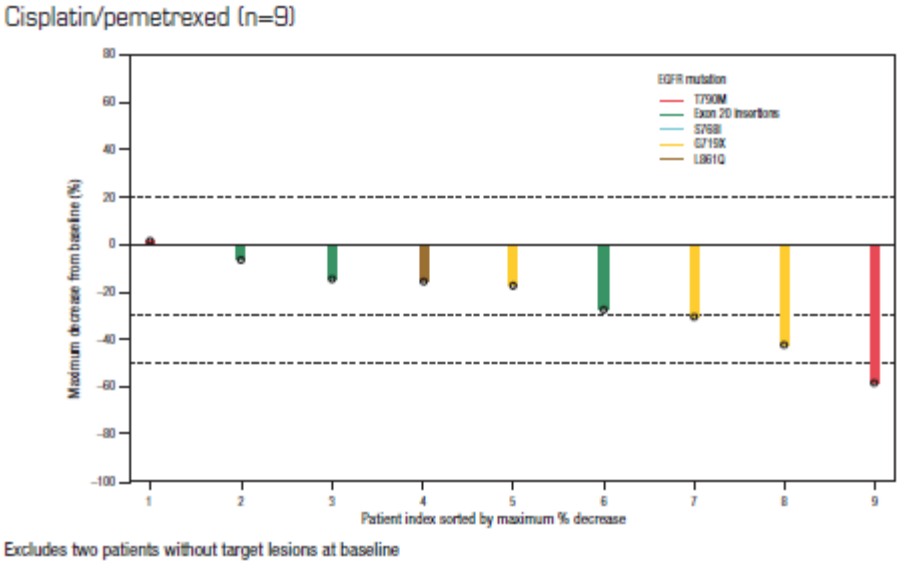
Activity of Afatinib in uncommon EGFR mutations in Lux-Lung 3

	Afatinib (n=26)	Cisplatin/ pemetrexed (n=11)	Total (n=37)
Gender, n (%)			
Male	11 (42)	6 (55)	17 (46)
Female	15 (58)	5 (46)	20 (54)
Age, years, median (range)	58 (42–82)	66 (41–73)	61 (41–82)
Race, n (%)			
Caucasian	8 (31)	3 (27)	11 (30)
Eastern Asian	17 (65)	8 (73)	25 (68)
Other	1 (4)	0	1 (3)
Smoking status, n (%)			
Never smoked	17 (65)	9 (82)	26 (70)
Ex-smoker	7 (27)	2 (18)	9 (24)
Current smoker	2 (8)	0	2 (5)
Stage (AJCC 6.0), n (%)			
IIIB (wet)	1 (4)	1 (9)	2 (5)
IV	25 (96)	10 (91)	35 (95)
ECOG PS, n (%)			
0	13 (50)	5 (46)	18 (49)
1	13 (50)	6 (55)	19 (51)
Liver metastases, n (%)	7 (27)	0 (0)	7 (19)
Brain metastases, n (%)	7 (27)	2 (18)	9 (78)
EGFR mutation, n (%)			
T790M*	11 (42)	2 (18)	13 (35)
Exon 20 insertions	6 (23)	3 (27)	9 (24)
S768I†	3 (12)	0	3 (8)
G719X‡	3 (12)	3 (27)	6 (16)
L861Q	3 (12)	3 (27)	6 (16)

J.C.-H. Yang et al, ESMO 2012

Activity of Afatinib in uncommon EGFR mutations in Lux-Lung 3





- EGFR common mutations (Del19/L858R; n=308)
- EGFR uncommon mutations n=37
- Of 32 pts with evaluable lesions 19 out of 23 afatinib treated and 8 out of 9 cisplatin-pemetrexed treated pts had measurable shrinkage
- The small size of the uncommon mutation cohort, its molecular heterogeneity and numeric imbalances within genetic subgroups limited formal statistical analyses

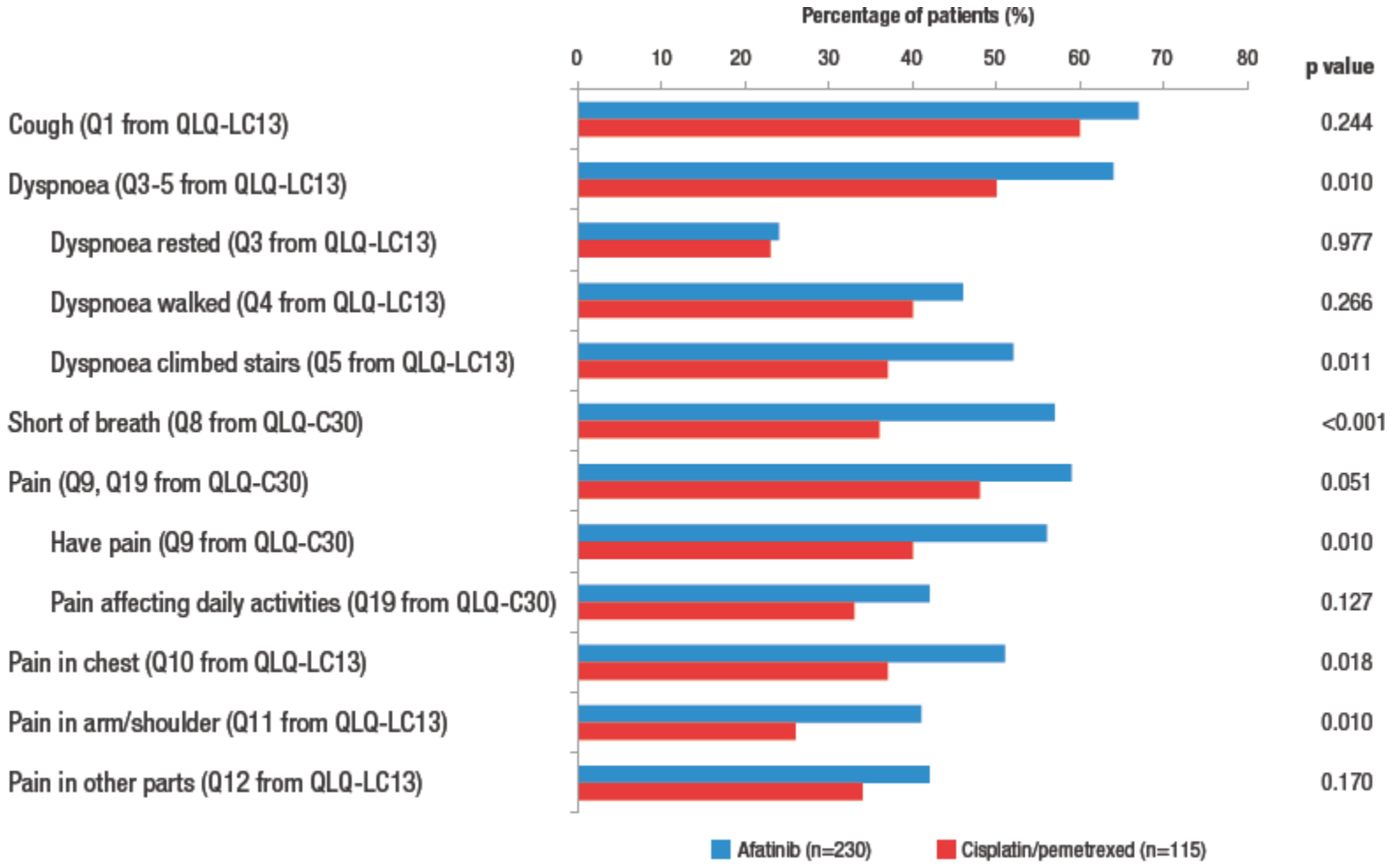
J.C.-H. Yang et al, ESMO 2012

- Irreversible EGFR Tkis as first line treatment in advanced NSCLC
- QoL data in enriched patient populations treated with targeted therapies
- More data on crizotinib in advanced NSCLC

Lux Lung3. Patient Reported Outcomes were assessed using multidimensional cancer-specific questionnaires at baseline and every 3 weeks until disease progression

Results

Improvement in cough, dyspnoea and pain



European Organization for Research and Treatment of Cancer scores improved by ≥10 points.

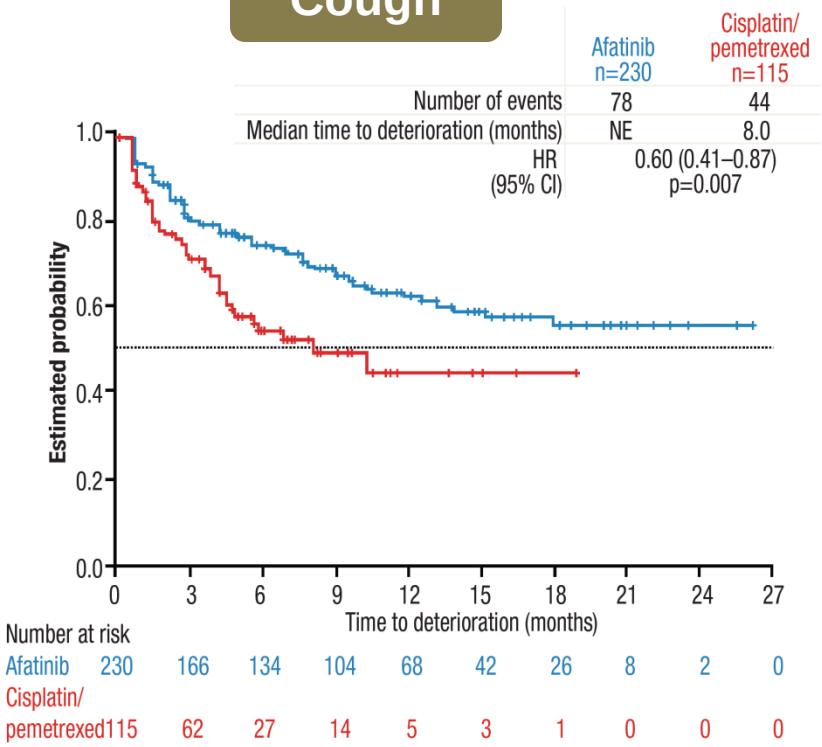
Sequist LV et al, ESMO 2012, 1229 PD

Results

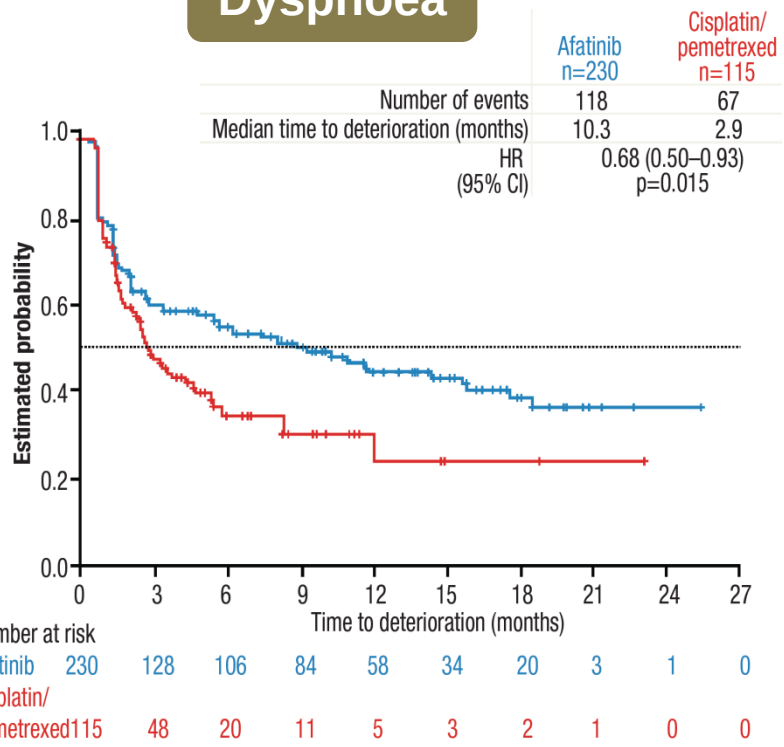
Time to symptom deterioration

First-line afatinib significantly delayed time to deterioration for:

Cough



Dyspnoea

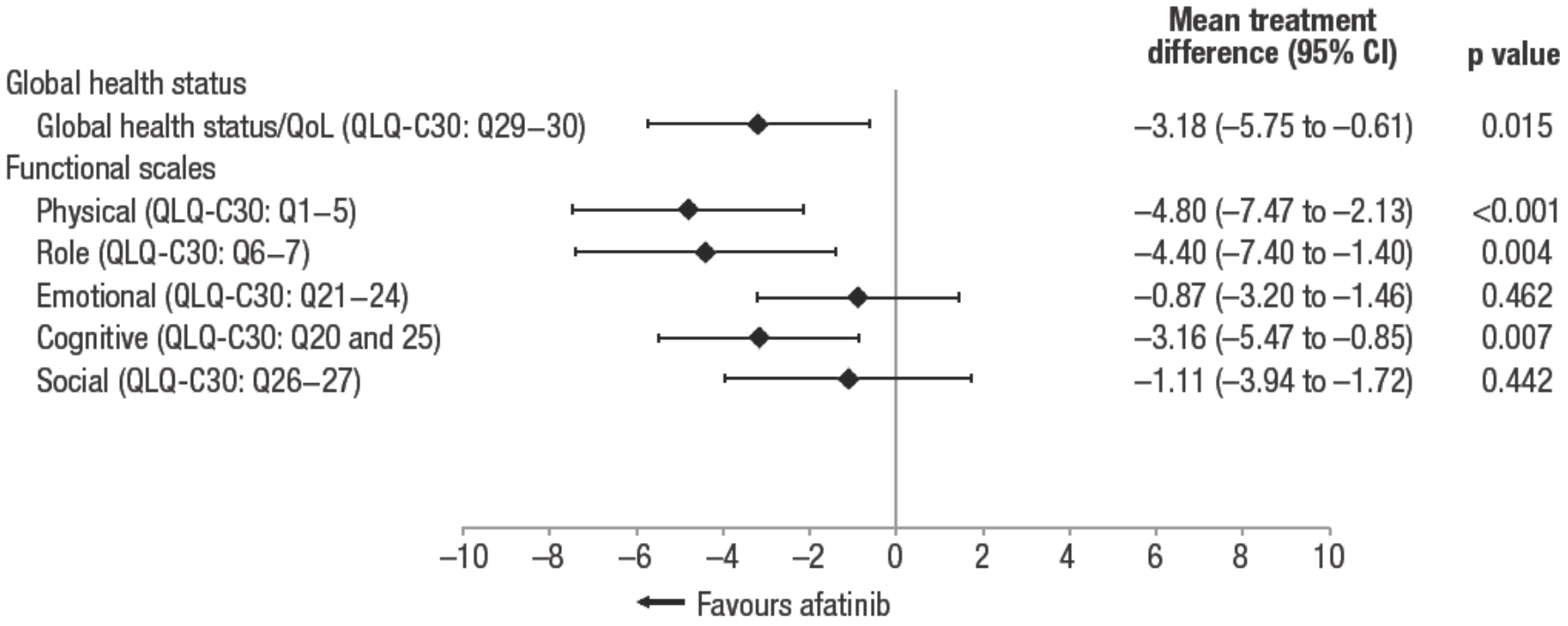


Time to deterioration for pain favoured afatinib (HR=0.83; p=0.1913)

Sequist LV et al, ESMO 2012, 1229 PD

Results

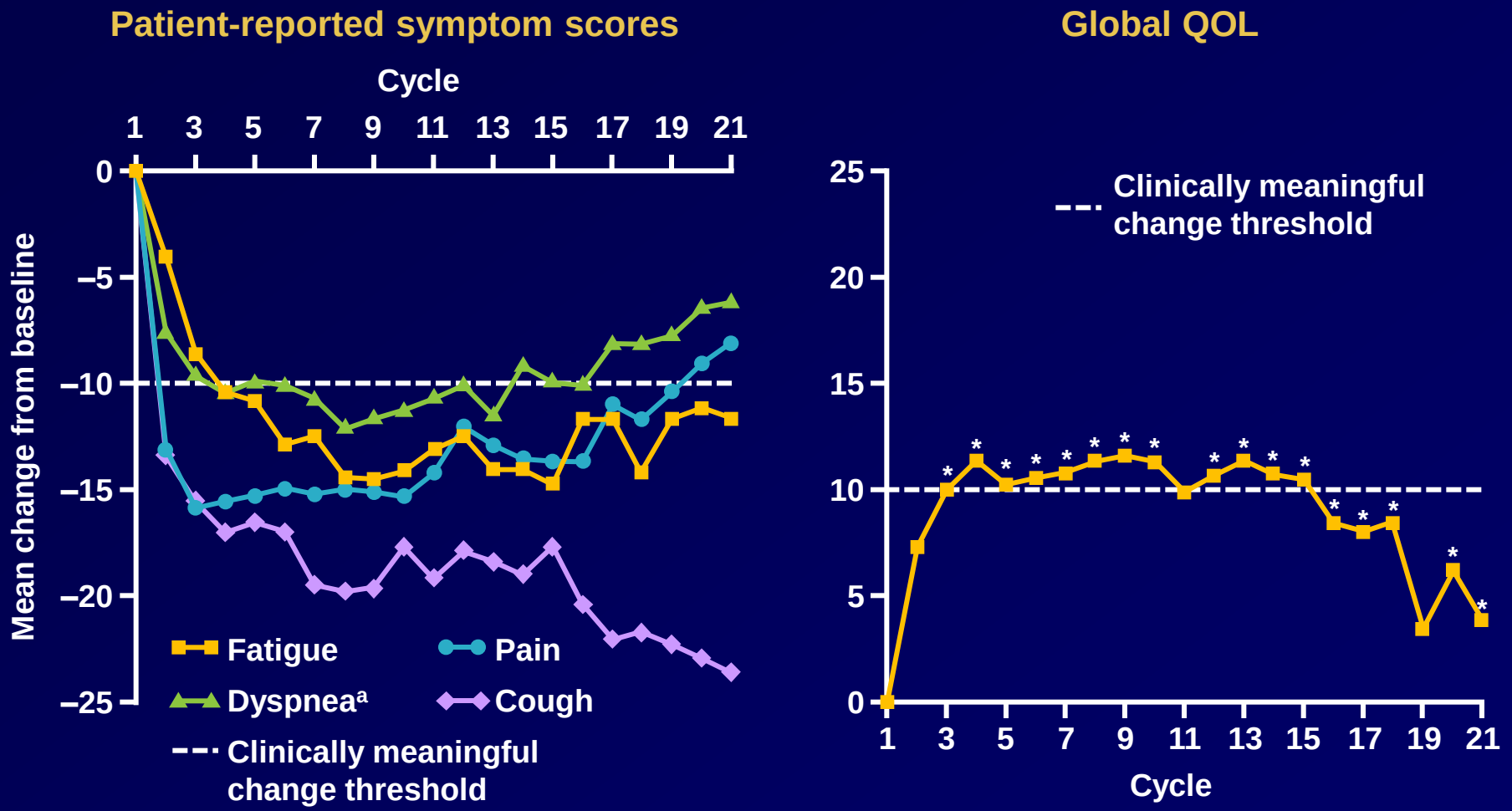
Global health status and functional scale domains



Afatinib significantly improved **global health status/quality of life** and **physical, role and cognitive functioning** compared with cisplatin/pemetrexed

EORTC QLQ-C30 and lung cancer-specific module (QLQ-LC13): baseline, day 1 of each subsequent cycle, and end of treatment

Mean Change from Baseline Measured Using QLQ-C30 – Selected Results



[a]QLQ-LC13
*P≤0.05

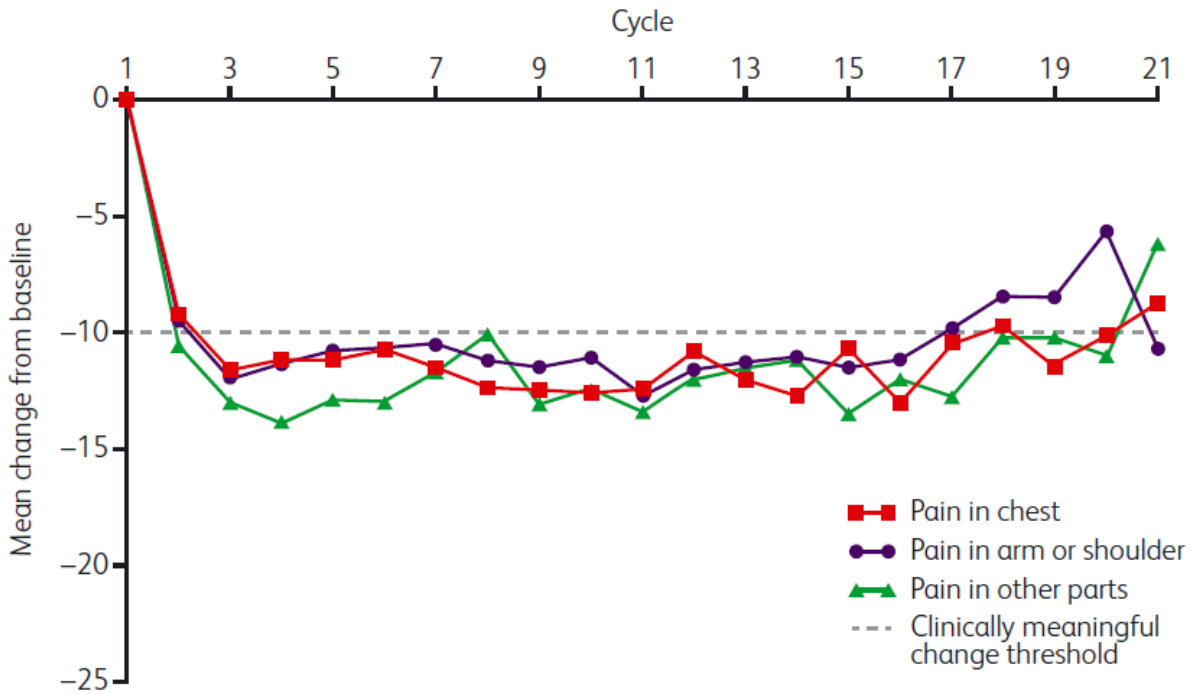
Blackhall et al. Impact of Crizotinib Treatment on Patient-reported Symptoms and QOL in Advanced ALK-positive NSCLC. Abstract 1231PD

Impact of Crizotinib Treatment on Patient-reported Symptoms and Quality of Life in Advanced *ALK*-positive Non-small Cell Lung Cancer

F Blackhall,[1] TL Evans,[2] J-Y Han,[3] R Salgia,[4] D Moro-Sibilot,[5] SN Gettinger,[6] L Crinò,[7] K Wilner,[8] A Reisman,[9] S Iyer[9]

[1]Christie Hospital NHS Foundation Trust, Manchester, UK; [2]University of Pennsylvania, Philadelphia, PA, USA; [3]National Cancer Center, Goyang, South Korea; [4]University of Chicago, Chicago, IL, USA; [5]Hôpital Universitaire, Grenoble, France; [6]Yale University School of Medicine, New Haven, CT, USA; [7]Ospedale Santa Maria della Misericordia, Perugia, Italy; [8]Pfizer Oncology, La Jolla, CA, USA; [9]Pfizer Inc, New York, NY, USA

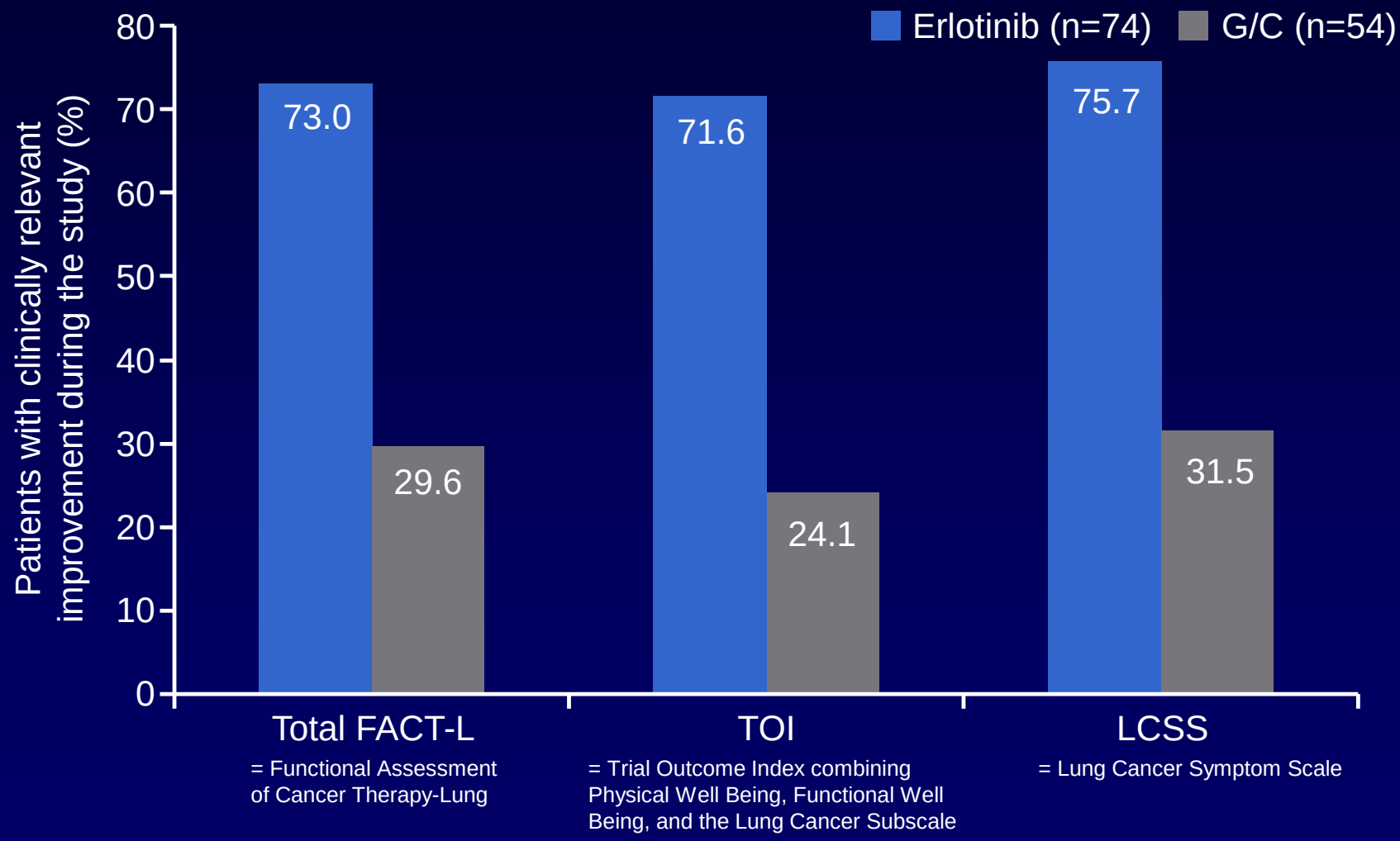
Figure 4. Mean change from baseline in patient-reported pain symptoms measured using QLQ-LC13.[a]



[a]Reductions in scores reflect less symptom severity, hence showing improvement.

Blackhall et al. Impact of Crizotinib Treatment on Patient-reported Symptoms and QOL in Advanced ALK-positive NSCLC. Abstract 1231PD

OPTIMAL Quality-of-life-Analysis: Patients' QoL was significantly improved



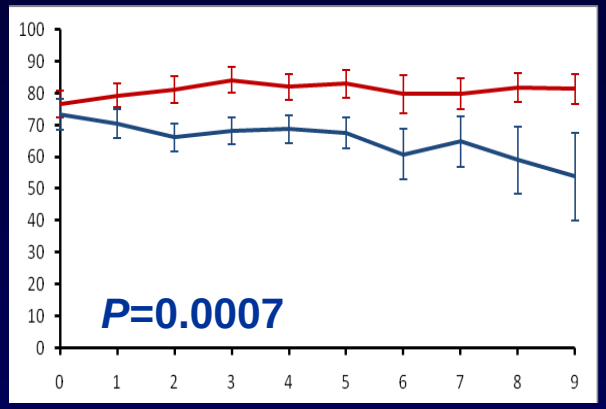
Includes all patients with a baseline and ≥1 post-baseline QoL assessment

Zhou C et al., ASCO 2011, #7520

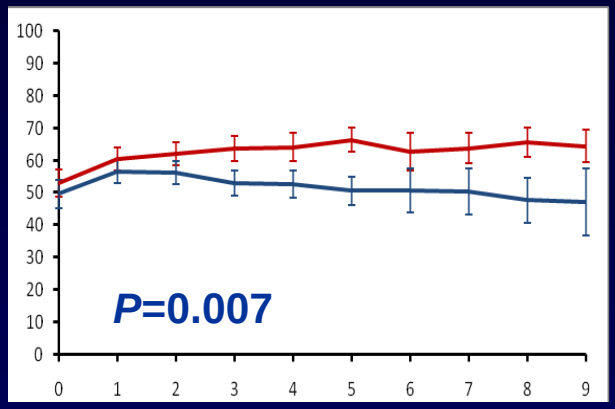
First-SIGNAL: Improved Quality of Life EORTC QLQ-C30 and QLQ-LC13

Gefitinib — GP chemotherapy

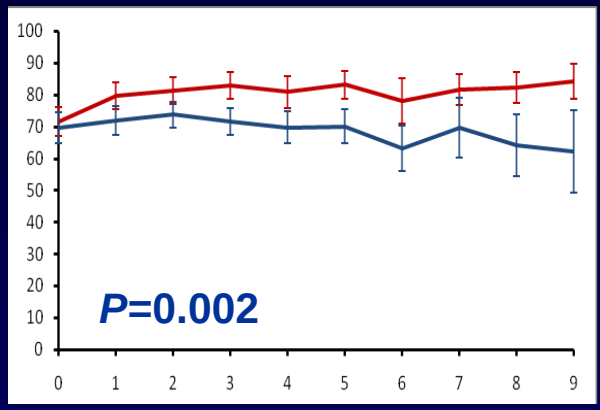
Global health status



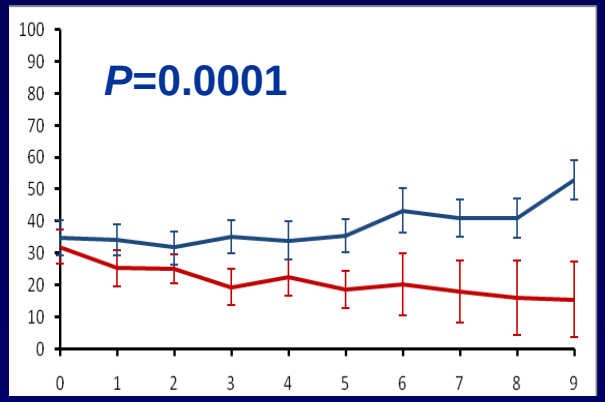
Role function



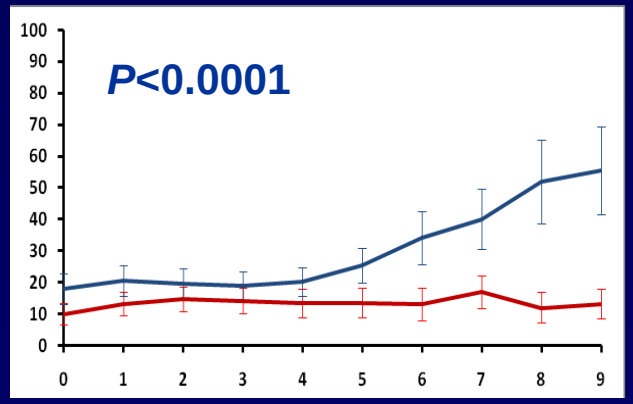
Social function



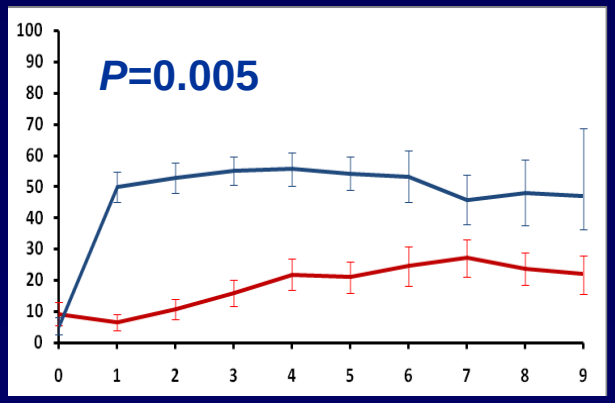
Appetite loss



Peripheral Neuropathy

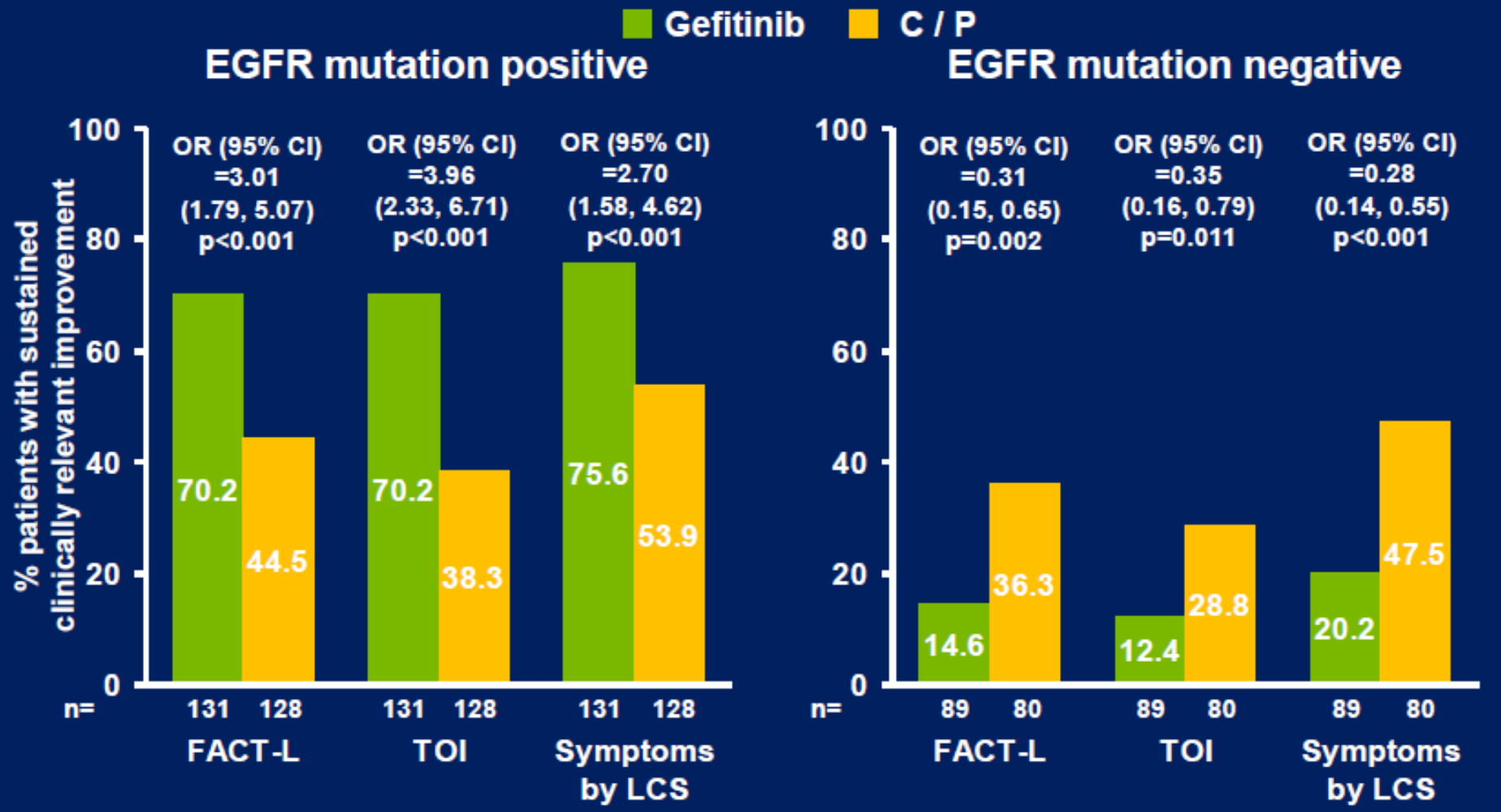


Alopecia



Courtesy of Keunchil Park

IPASS: HRQoL and symptom improvement by EGFR mutation status



Post hoc analyses, evaluable for quality-of-life population
p-values are derived from logistic regression analysis with covariates WHO PS, smoking history and gender
HRQoL=health-related quality-of-life, EFQ=evaluable for quality-of-life, FACT-L=functional assessment of cancer therapy - lung, TOI=trial outcome index, LCS=lung cancer subscale

Thongprasert et al 2011

Analysis and Interpretation of health-related quality of life data from phase III trials

- In consideration of the number of trials including QoL data, the heterogeneous way to present these results and the different relevance given to these data across studies…….just a summary of steps to approach this issue

A special thank to M. Di Maio

Osoba D., et al. EJC 2005: 280-287

Analysis and Interpretation of health-related quality of life data from phase III trials

- Calculating Completion Rates
  - N of pts completing the baseline over the total N of elegible pts entered
  - N of pts completing the assessments at designated time points over the total N (the “intent to treat” population”)
  - N of pts completing the assessments at designated time points over the total N completing the assessment at baseline (“efficacy population”)
  - N of pts completing the assessments at designated time points over the total N of pts still on study and expected to fill (the “number expected” population)

Osoba D., et al. EJC 2005: 280-287

Analysis and Interpretation of health-related quality of life data from phase III trials

- Comparing Baseline Scores between Groups
  - N of pts providing responses
  - Mean score and SD (or range) for each QoL component

Osoba D., et al. EJC 2005: 280-287

Analysis and Interpretation of health-related quality of life data from phase III trials

- Comparing the change scores between and within treatment groups
  - Means for the differences (and SD) at each designated time point
  - Test for statistically significant differences in the mean change score between tratment groups
  - Test for statistically significant differences between baseline scores and scores from designated time points within each treatment group

Osoba D., et al. EJC 2005: 280-287

Analysis and Interpretation of health-related quality of life data from phase III trials

- Determining the proportions of patients with improved, stable and worsened scores

DECIDE A PRIORI THE MAGNITUDE OF CHANGE

  - N of pts who reported the preset magnitude of change for each domain during the study in each treatment arm
  - Calculate the prportion of pts who reported improvement or worsening in each intent to treat group
  - Calculate the median duration of improvement (or stable) QoL status
  - Test for statistically significant differences between the three categories of response

Osoba D., et al. EJC 2005: 280-287

- Irreversible EGFR Tkis as first line treatment in advanced NSCLC
- QoL data in enriched patient populations treated with targeted therapies
- More data on crizotinib in advanced NSCLC

Abstract #1230PD

Updated Results of a Global Phase II Study with Crizotinib in Advanced *ALK*-positive Non-small Cell Lung Cancer

D-W Kim[1], M-J Ahn[2], Y. Shi[3], P-C Yang[4], X. Liu[5], T.M. De Pas[6], L. Crinò[7], S. Lanzalone[8], A. Polli[8], A. T. Shaw[9]

[1]Seoul National University Hospital, Seoul, South Korea; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3]Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [4]National Taiwan University Hospital, College of Medicine, Taipei, Taiwan; [5]307 Hospital of the Academy of Military Medical Sciences, Cancer Center, Beijing, China; [6]European Institute of Oncology, Milan, Italy; [7]Ospedale Santa Maria della Misericordia, Perugia, Italy; [8]Pfizer Italy Srl, Milan, Italy; [9]Massachusetts General Hospital Cancer Center, Boston, MA

Presented at the Congress of the European Society for Medical Oncology (ESMO), Vienna, Austria, September 28–October 2, 2012

What we add to our knowledges about Crizotinib in NSCLC with this data

- Age

	PROFILE 1001[1]	PROFILE 1005[2]	PROFILE 1005[3]	
			N=261	N=901
Age, Yrs (median range)	51 (21-79)	52 (29-82)	52 (24-82)	53.0 (>18.0–83.0)

1. Camidge et al., ASCO 2011; Abs #2501
2. Riely et al., IASLC 2011; Abs #O31.05

3. Kim D, et al., ESMO 2012; Abs #1230PD

What we add to our knowledges about Crizotinib in NSCLC with this data

- Age
- Gender

	PROFILE 1001[1]	PROFILE 1005[2]	PROFILE 1005[3]	
Gender, % Male/Female	50/50	47/53	N=261	N=901
			45.6/54.4	43/57

3. Bang Y, et al., ASCO 2010; Abst 3

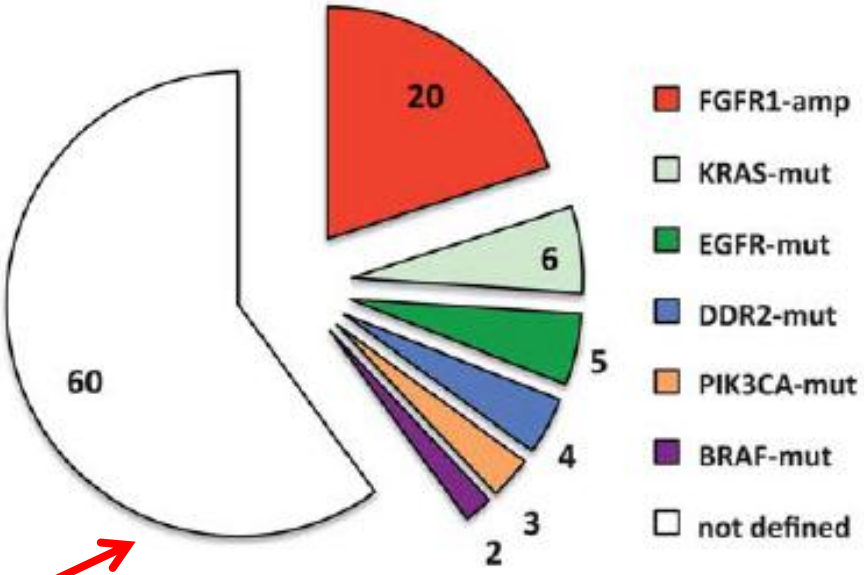
1. Camidge et al., ASCO 2011; Abs #2501
2. Riely et al., IASLC 2011; Abs #O31.05

3. Kim D, et al., ESMO 2012; Abs #1230PD

What we add to our knowledges about Crizotinib in NSCLC with this data

- Age
- Gender
- Histology

%	PROFILE 1001[1]	PROFILE
Adenocarcinoma	97	
Other	3	



Bronchoalveolar Ca

Squamous Ca

Sos M. and Thomas R. Oncogene 2012

1. Camidge et al., ASCO 2011; Abs #2501
2. Riely et al., IASLC 2011; Abs #O31.05

3. Kim D, et al., ESMO 2012; Abs #1230PD

What we add to our knowledges about Crizotinib in NSCLC with this data

- Age
- Gender
- Histology
- Smoking Status

Smoking	PROFILE 1001[1]	PROFILE 1005[2]
Never Former/Current	72 27 / 1	68 29 / 4

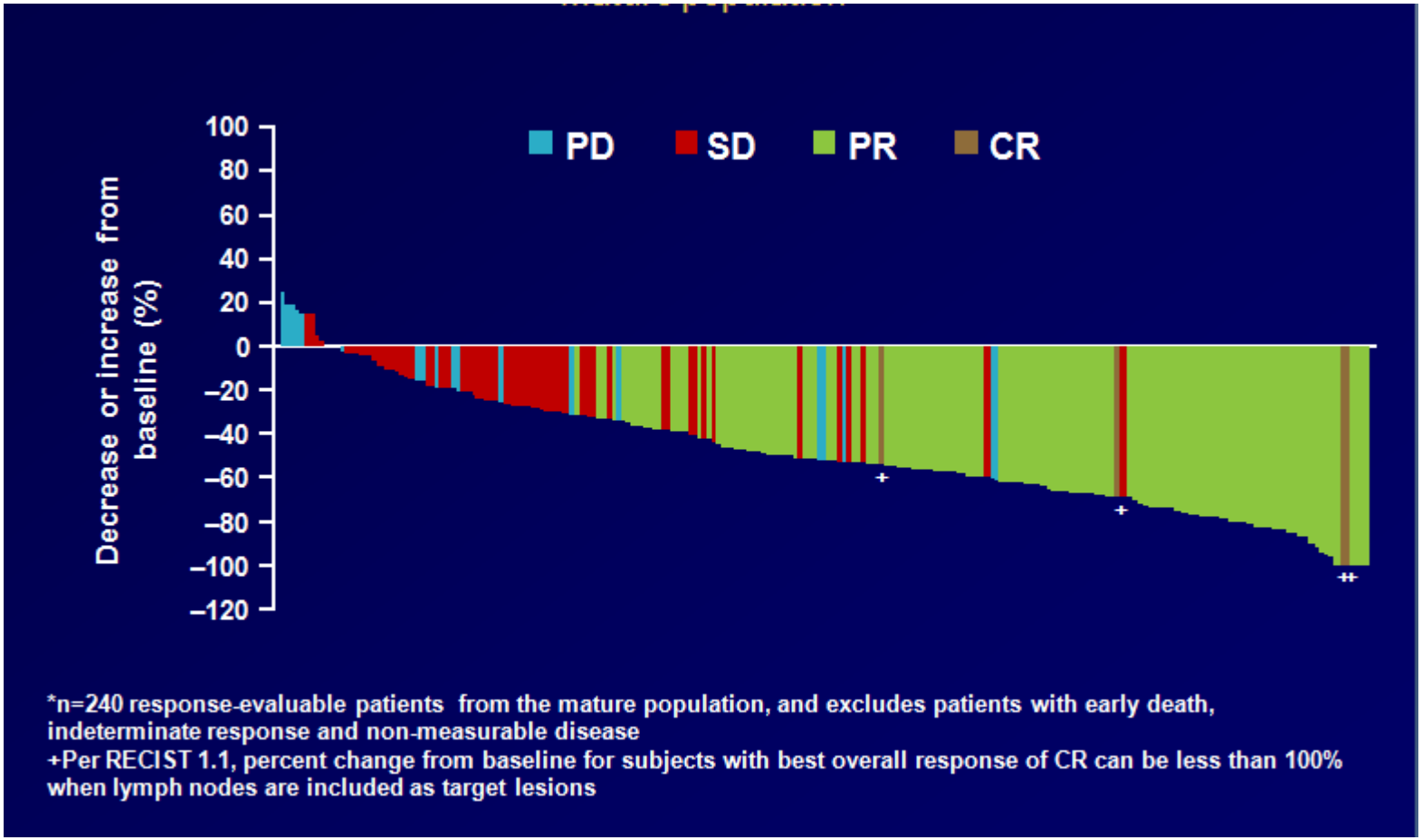
PROFILE 1005[3]	
N=261	N=901
67.4 28/4.6	65.7 38/4.2

1. Camidge et al., ASCO 2011; Abs #2501
2. Riely et al., IASLC 2011; Abs #O31.05

3. Kim D, et al., ESMO 2012; Abs #1230PD

What we add to our knowledges about Crizotinib in NSCLC with this data

- Efficacy is confirmed



Bang Y, et al., ASCO 2010; Abst 3
Kim D, et al., ESMO 2012; Abs #1230PD

What we still need to know about Crizotinib in NSCLC

Table 3. Treatment-related AEs in ≥10% of patients.

	Crizotinib (mature population) (n=261) n (%)		Crizotinib (overall population) (N=901) N (%)	
Adverse event	All grade	Grade 3/4	All grade	Grade 3/4
Any AE	245 (93.9)	76 (29.1)	827 (91.8)	220 (24.4)
Nausea	148 (56.7)	1 (0.4)	423 (46.9)	7 (0.8)
Vomiting	116 (44.4)	2 (0.8)	352 (39.1)	7 (0.8)
Vision disorder[a]	154 (59.0)	0 (0)	468 (51.9)	1 (0.1)
Diarrhea	106 (40.6)	2 (0.8)	369 (41.0)	9 (1.0)
Constipation	86 (33.0)	0 (0)	249 (27.6)	1 (0.1)
Peripheral edema	72 (27.6)	0 (0)	211 (23.4)	3 (0.3)
Fatigue				18 (1.9)
Decreased appetite				2 (0.2)
Alanine aminotransferase increased	45 (17.2)	19 (7.2)	146 (16.2)	36 (4.0)
Dysgeusia	43 (16.5)	0 (0)	149 (16.5)	0 (0)
Dizziness	40 (15.3)	0 (0)	95 (10.5)	0 (0)
Neutropenia	36 (13.8)	22 (8.4)	84 (9.3)	50 (5.5)
Aspartate aminotransferase increased	33 (12.6)	5 (1.9)	106 (11.8)	12 (1.3)

[a]Includes visual impairment, photopsia, vision blurred, vitreous floaters, photophobia and diplopia.

Salgia R, ASCO 2012

- Treatment-related grade **≥3 AEs** were reported in **25.6%** of patients, most frequently grade 3/4 neutropenia (n=50 [5.5%]), increased alanine aminotransferase (n=36 [4.0%]), and fatigue (n=18 [2.0%]).
- Eight (<1%) patients discontinued treatment due to **pneumonitis** and there was one instance of fatal pneumonitis.
- On 1,054 patients treated with crizotinib have been presented showing an high percentage of AST, ALT , AP and Bilirubin and AP. Most of these events were reported as grade 1-2 within the first 2 months
- Hypogonadism and crizotinib; testosterone levels significantly lower in crizotinib-treated patients

Kim D, et al., ESMO 2012; Abs #1230PD

SS Ramalingam, A Shaw, Cancer 2012

Schnell P et al, ASCO 2012

What we still need to know about Crizotinib in NSCLC

- Most common new lesions in single organ sites were brain and most common sites for single organ PD were brain

There were 18 patients with asymptomatic, non-irradiated brain metastases in the mature response-evaluable population who were evaluable for both brain and systemic disease

Brain Response	N=18
Complete Response	2 (11%)
Partial Response	2 (11%)
Stable Disease	12 (67%)
Progressive Disease	2 (11%)

- Media… 10 weeks

- Crizoti… barrier: …ured at 237 ng/mL (0.53mol/L), whereas the CSF concentration was 0.616 ng/mL (0.0014mol/L), with a CSF-to-plasma ratio of 0.0026.

Otterson GA et al, ASCO 2012
Costa DB et al, JCO 29: e443-e445

What we still need to know about Crizotinib in NSCLC

- Which is the optimal diagnostic test to identify the target

- Which is the best way to overcome drug resistance

International Association for the Study of Lung Cancer

IASLC

JOIN US FOR OUR UPCOMING MEETINGS

5th APLCC

Globalization of Standard and Targeted Therapy

5TH ASIA PACIFIC LUNG CANCER CONFERENCE
AND 3RD INTERNATIONAL THYMIC MALIGNANCY
INTEREST GROUP ANNUAL MEETING

NOVEMBER 25 – 28, 2012 | FUKUOKA, JAPAN

WWW.APLCC2012.ORG

15th World Conference on Lung Cancer

OCTOBER 27–30, 2013 | SYDNEY, AUSTRALIA

WCLC.IASLC.ORG

BECOME A MEMBER OF IASLC ▸ WWW.IASLC.ORG