ESMO 2012 Vienna discussion of abstracts : 12270, 12280, LBA30

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Disclosure slide - WEE Eberhardt

1. CEO function or other direct job relationships

none

2. Advisor function

advisory board function	Astra Zeneca, Roche, Eli Lilly, Novartis, Pfizer, BayerSchering, Sanofiaventis, Boehringer Ingelheim, BMS, GSK, Amgen, Novocure

3. stocks

none

4. honoraria

for lectures	Pierre Fabre, MerckSerono, Astra Zeneca, Roche, Eli Lilly, Novartis, Pfizer, BayerSchering, SanofiAventis, OSI, BMS, GSK, Boehringer Ingelheim, Synthon

5. research funding

none

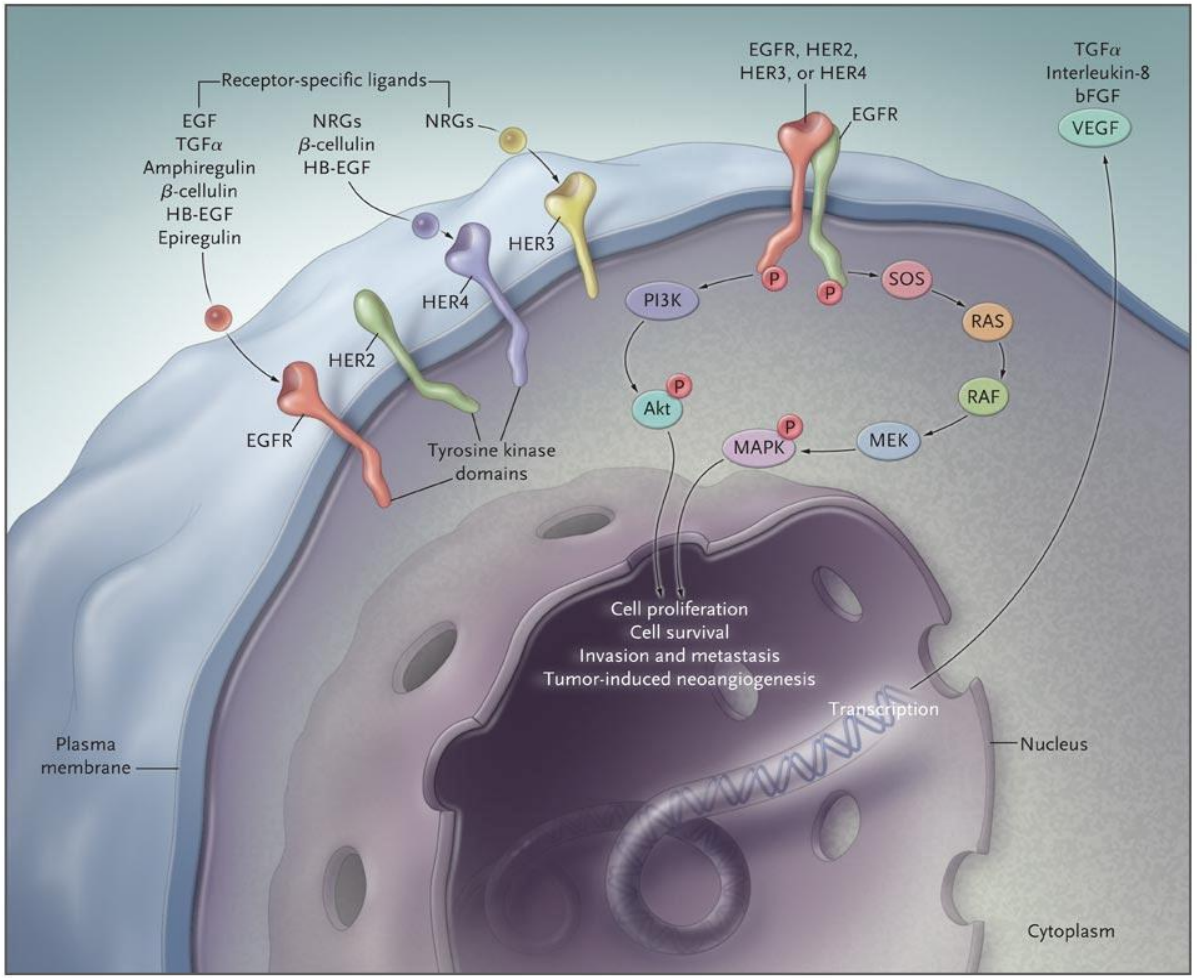
6. scientific evidence

none

7. other financial relations

none

“Her”story in advanced NSCLC : mutation, overexpression and resistance…… - act 1 -



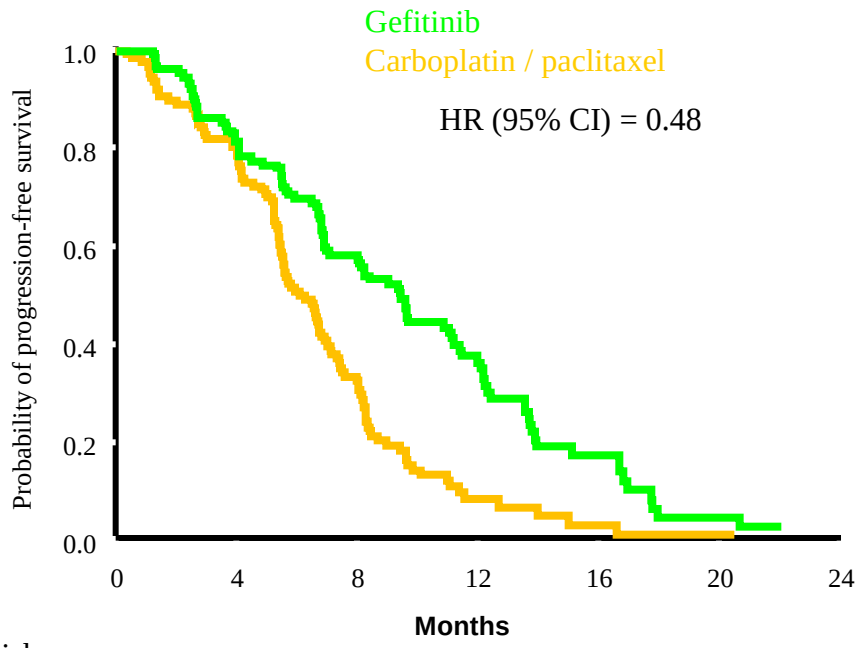
Ciardiello F, Tortora G. N Engl J Med 2008;358:1160-1174.

“Her”story in advanced NSCLC : mutation, overexpression and resistance…….

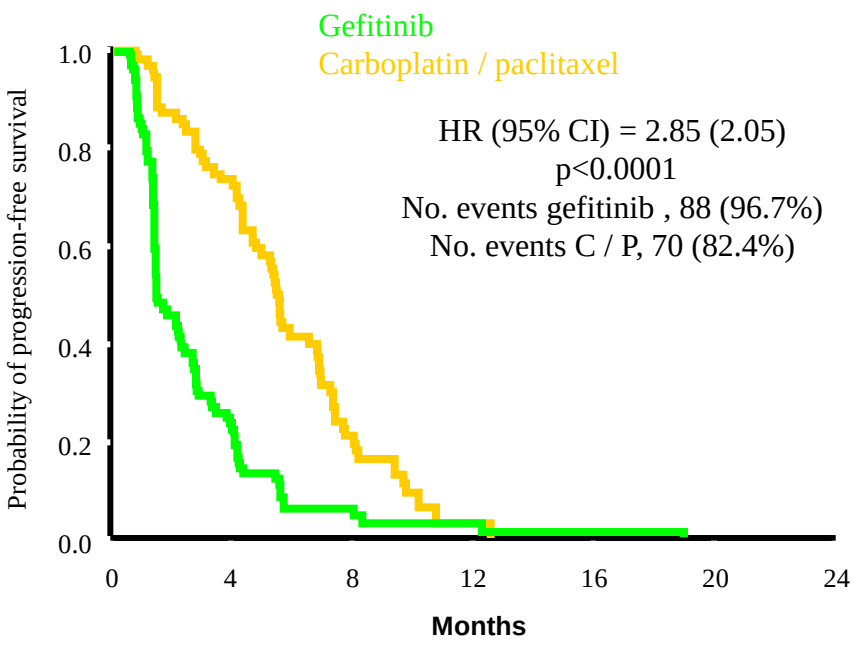
- patients with EGF-R mutations as a cancer driver in advanced NSCLC derive a substantial and relevant benefit from treatment with EGF-R TKI (Mok et al NEJM 2008)
- patients with EGF-R overexpression (IHC: H-score > 200) have a reported benefit from treatment with an EGF-R targeting monoclonal antibody (Pirker et al, Lancet Oncol 2011)

Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive



EGFR mutation negative



At risk :							
Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

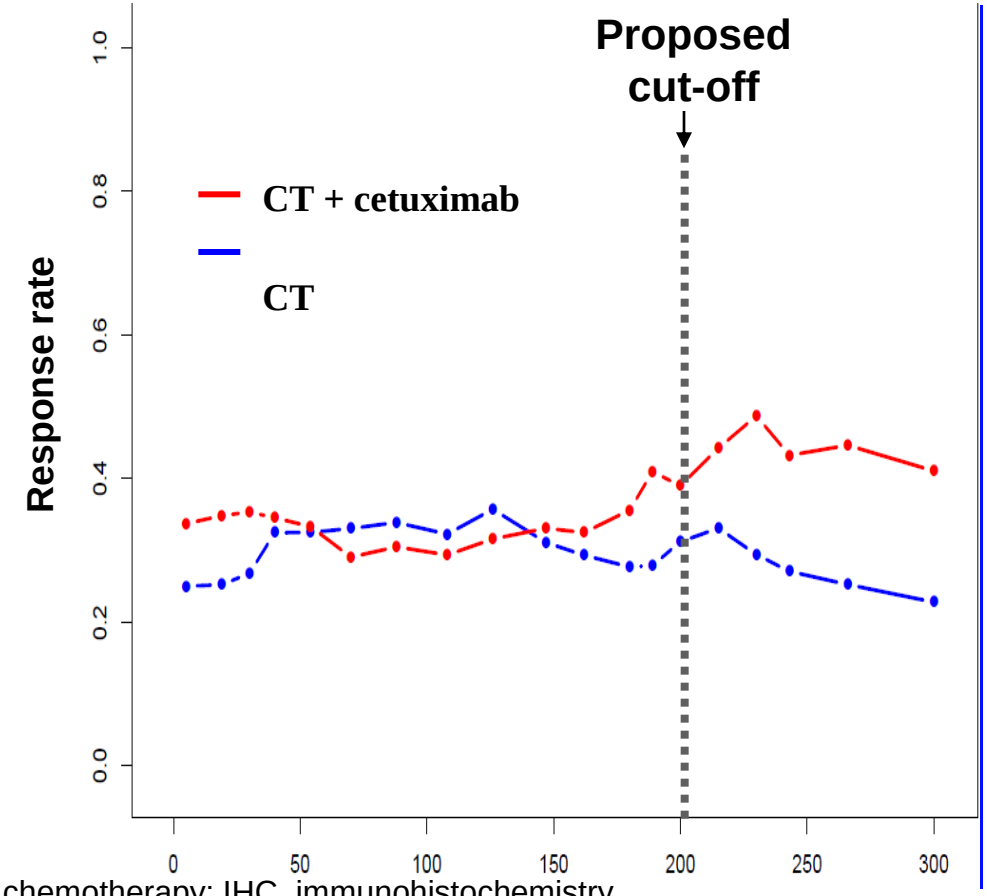
91	21	4	2	1	0	0
85	58	14	1	0	0	0

ITT population
Cox analysis with covariates

Treatment by subgroup interaction test, p<0.0001

Mok et al ESMO 2008 / NEJM 2008

Identification of discriminating EGFR IHC score threshold for increased cetuximab efficacy by response rate



Increased tumor response
for CT + cetuximab
with EGFR IHC score ≥200

CT, chemotherapy; IHC, immunohistochemistry

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o´Byrne/Pirker et al CMSTO 2010 / Lancet Oncol 2011

Presentation 1: Abstract 12270

Activity of afatinib/cetuximab in patients with *EGFR* mutant non-small cell lung cancer and acquired resistance to EGFR inhibitors

Yelena Y. Janjigian, Egbert F. Smit, Leora Horn, Harry J.M. Groen, D. Ross Camidge, Scott Gettinger, Yali Fu, Louis Denis, Vincent A. Miller, William Pao

Presented by Yelena Y. Janjigian

Memorial Sloan-Kettering Cancer Center, New York, USA; VU University Medical Centre, Amsterdam, The Netherlands; Vanderbilt University, Nashville, USA; University Medical Center Groningen, Groningen, The Netherlands; University of Colorado Cancer Center, Aurora, Colorado, USA; Yale University School of Medicine, New Haven, USA; Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; Foundation Medicine, Cambridge, MA, USA

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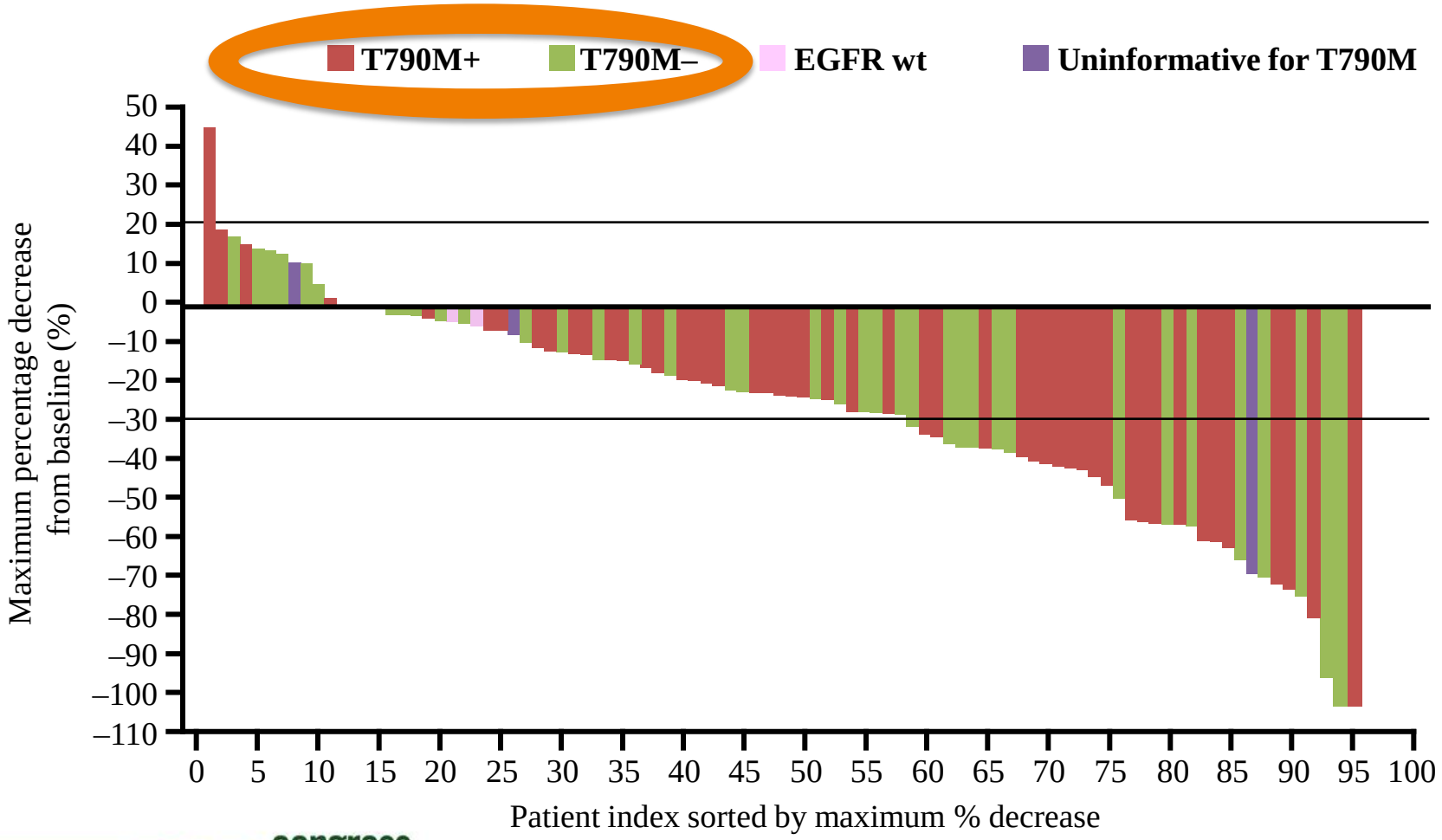
Baseline patient characteristics

	T790M mutation status*		Total†*
	T790M+	T790M–	
n	53	42	100
Median age, years (range)	57 (31 to 82)	60 (43 to 79)	59 (31 to 82)
Women, n (%)	40 (76)	29 (69)	72 (72)
Ethnicity, Asian/non-Asian, %	19/81	17/83	17/83
Baseline ECOG, 0/1/2, %	24/74/2	21/67/12	22/72/6
Time since diagnosis (*years*), median (range)	2.2 (0.4 to 10.5)	2.4 (0.6 to 6.6)	2.3 (0.4 to 10.5)
Time on prior erlotinib/gefitinib (*years*), median (range)	1.6 (0.2 to 6.8)	1.5	1.6 (0.2 to 6.8)
Prior chemotherapy, n (%)	41 (77)	30 (71)	75 (75)
EGFR mutation			
Del 19, n (%)	33 (62)	30 (71)	63 (63)
L858R, n (%)	18 (34)	12 (29)	32 (32)
Other,‡ n (%)	2 (4)	–	2 (2)

*Five patients not classified: Two with uninformative biopsy for T790M, two EGFR wild type (WT) and one whose EGFR mutation was untested;
†This study is ongoing: 100 eligible patients who have initiated treatment for at least 6 months are reported here;
‡EGFR exon 18 mutation and exon 18-insertion.

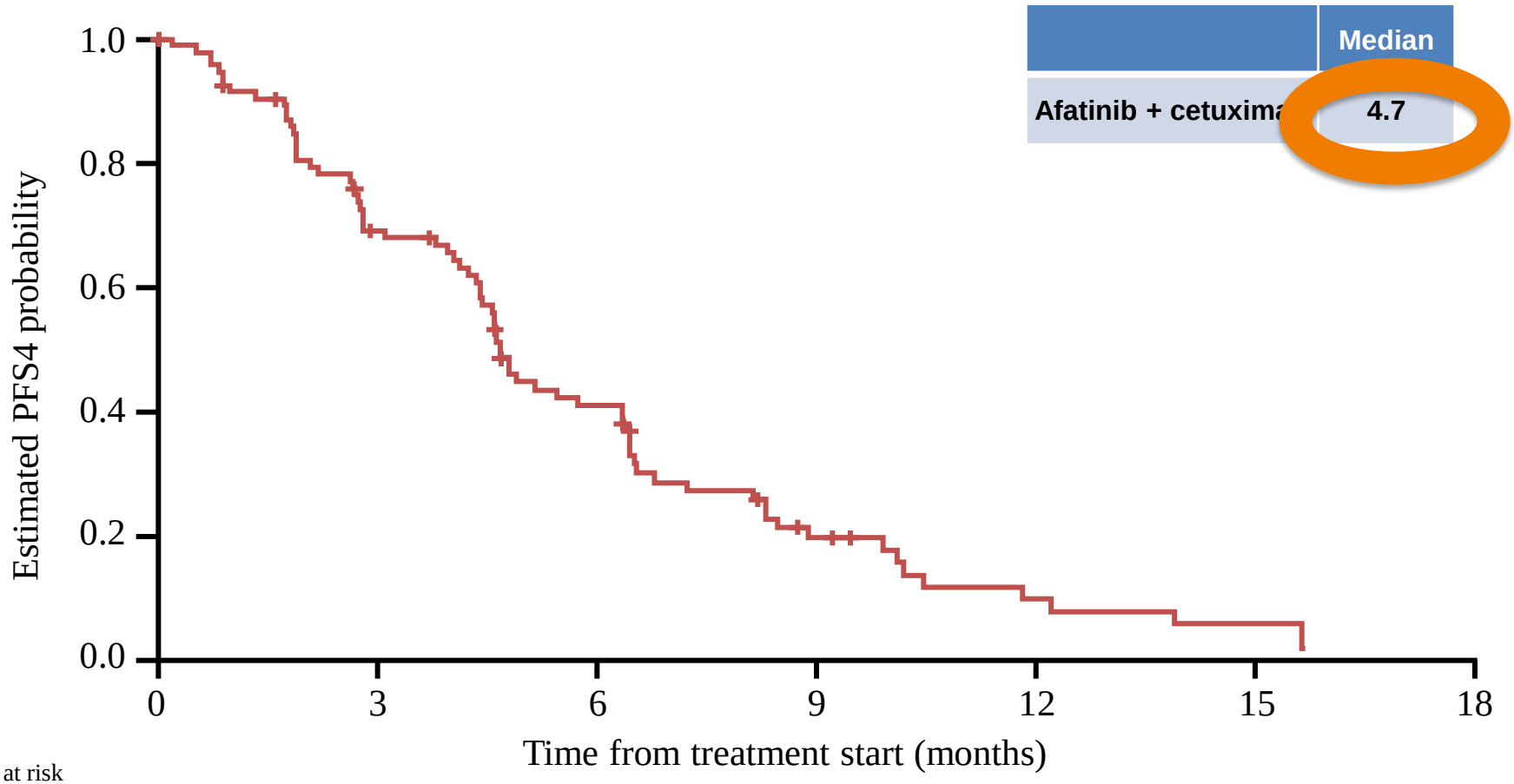
Janjigian et al ESMO 2012 abstr 12270

Afatinib + cetuximab at MTD: Responses by T790M mutation



Janjigian et al ESMO 2012 abstr 12270

PFS at MTD



MTD: Afatinib 40 mg daily + cetuximab 500 mg/m^2 every 2 weeks

MTD = maximum tolerated dose; PSF4 = progression-free survival at 4 months.

Janjigian et al ESMO 2012 abstr 12270

“Her”story in advanced NSCLC : mutation, overexpression and resistance…….

- patients with EGF-R Mutation and prior EGF-R TKI (>70%) as well as CTx (>75%) show a high response rate to combined application of **afatinib** (irreversible pan-Her TKI) and **cetuximab** (MoAb against EGF-R)
- **median PFS of 4.7 months with this combination in 2+ line treatment is absolutely promising and comparable to second-line docetaxel at the time of its registration……..**

Presentation 2: Abstract 12280

Dacomitinib (PF-00299804), an Irreversible pan-HER Tyrosine Kinase Inhibitor, for First-Line Treatment of *EGFR*-Mutant or *HER2*-Mutant or -Amplified Lung Cancers

Mark G Kris,[1] Tony Mok,[2] Sai-Hong Ignatius Ou,[3] Renato G. Martins,[4] Dong-Wan Kim,[5] Zelanna Goldberg,[6] Hui Zhang,[7] Ian Taylor,[8] Joseph O'Connell,[9] and Pasi A. Jänne[10]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY, US; [2]The Chinese University of Hong Kong, Shatin, Hong Kong; [3]School of Medicine, University of California at Irvine, Irvine, CA, US; [4]University of Washington, Seattle, WA, US; [5]Seoul National University Hospital, Seoul, Republic of Korea; [6]Pfizer Oncology, La Jolla, CA, US; [7]Pfizer (China) Research & Development Co. Ltd, Shanghai, China; [8]Pfizer Oncology, Groton, CT, US; [9]Pfizer Oncology, New York, NY, US; [10]Dana-Farber Cancer Institute, Boston, MA, US.

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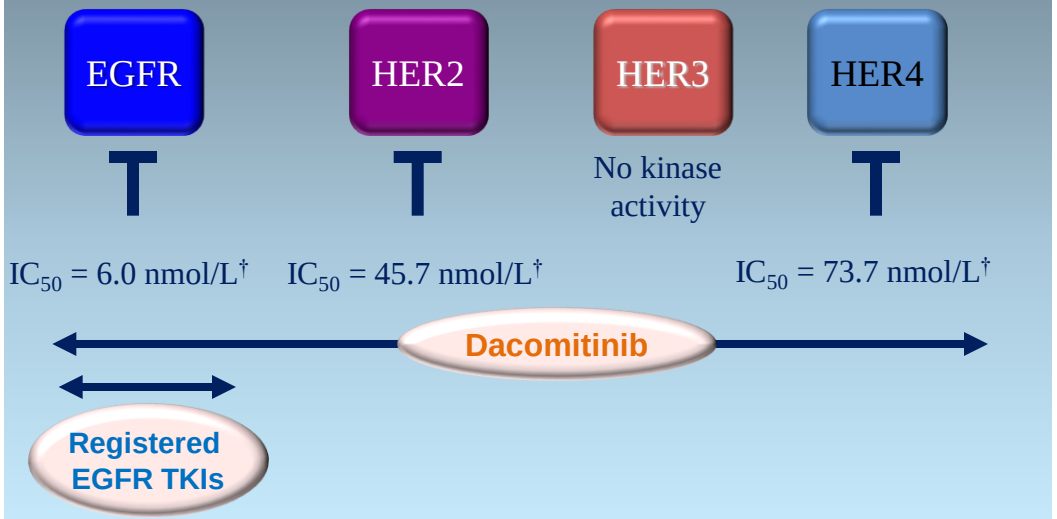
Dacomitinib

Pan–HER inhibition



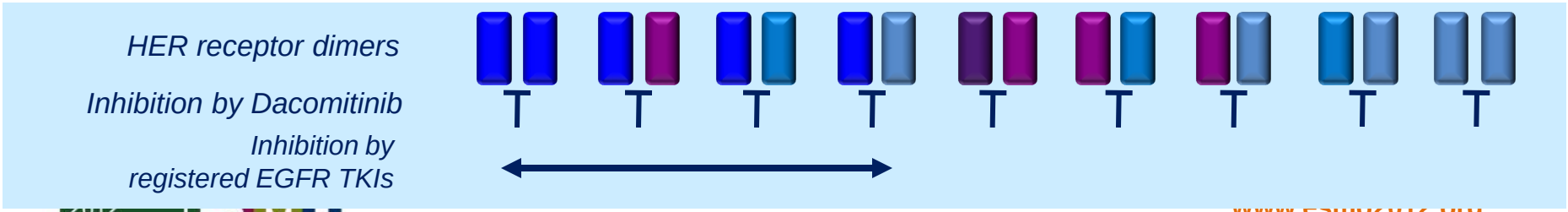
Irreversible inhibition‡

- Permanent blockade of catalytic activity
- Non-competitive inhibition
- Higher specificity and selectivity
- Low intracellular levels capable of inhibiting TK activity

†*In vitro* kinase assay against WT receptor ;↑[ATP] = high concentrations of ATP (e.g. intracellular concentrations)

‡ Potential benefits – based on preclinical data

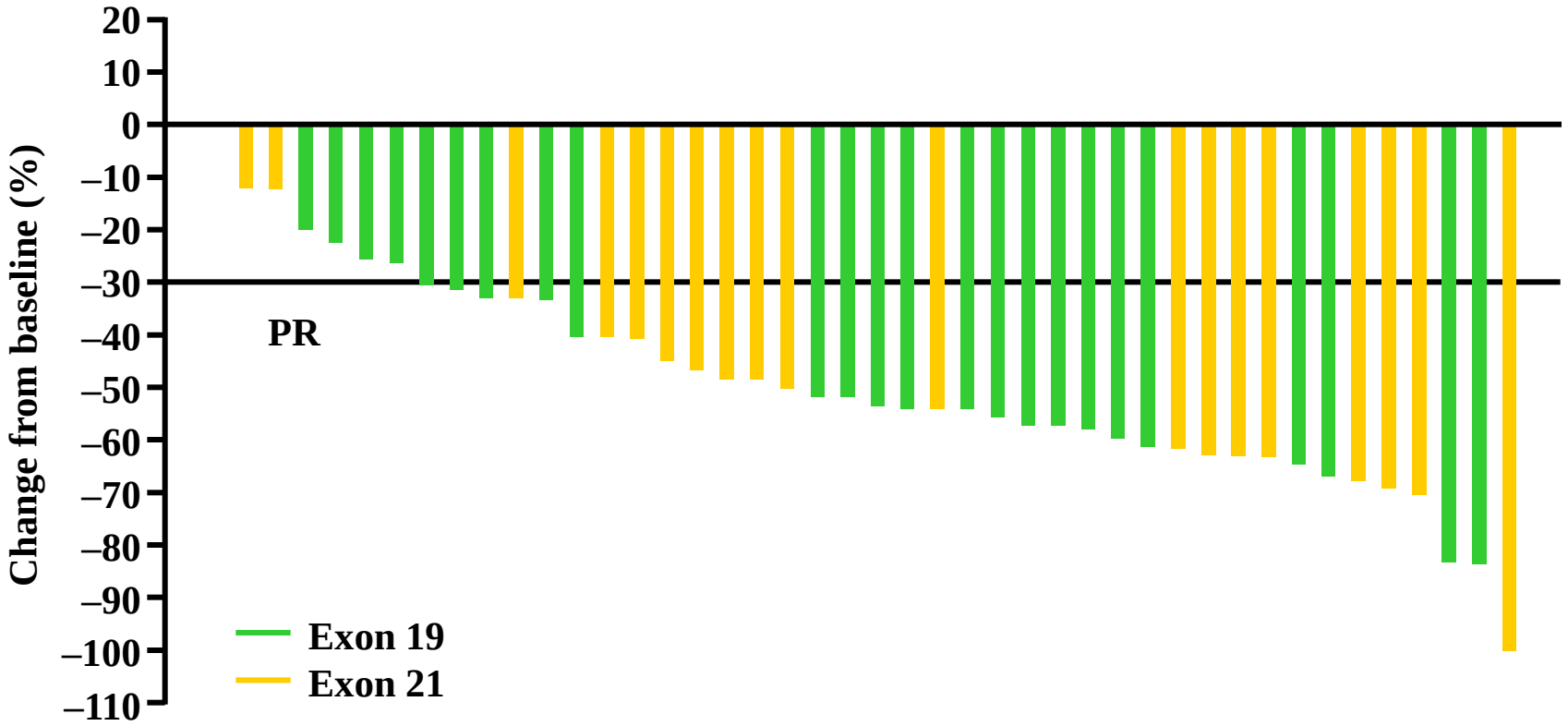
Inhibition of all kinase-active HER receptors offers potential for a more complete inhibition of HER signaling: receptor dimerization is key to HER-family signaling



Engelman JA, *et al.* Cancer Res 2008;67:11924–32

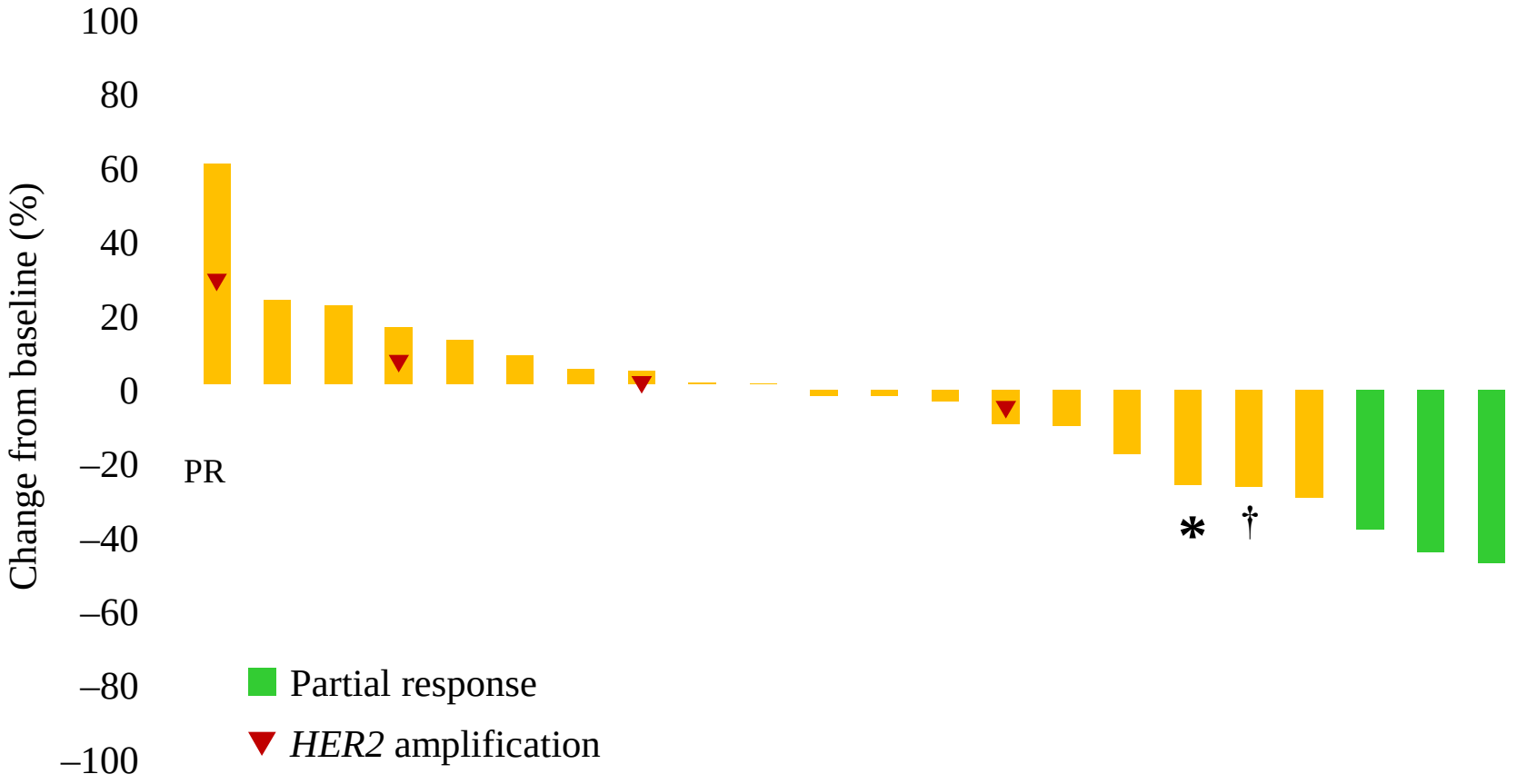
Kris et al ESMO 2012 abstr 12280

Waterfall Plot for Patients with *EGFR*-mutant Lung Cancers with Exon 19 and Exon 21 Mutations (N=45)



Kris et al ESMO 2012 abstr 12280

Waterfall Plot: *HER2* Cohort (n=22)

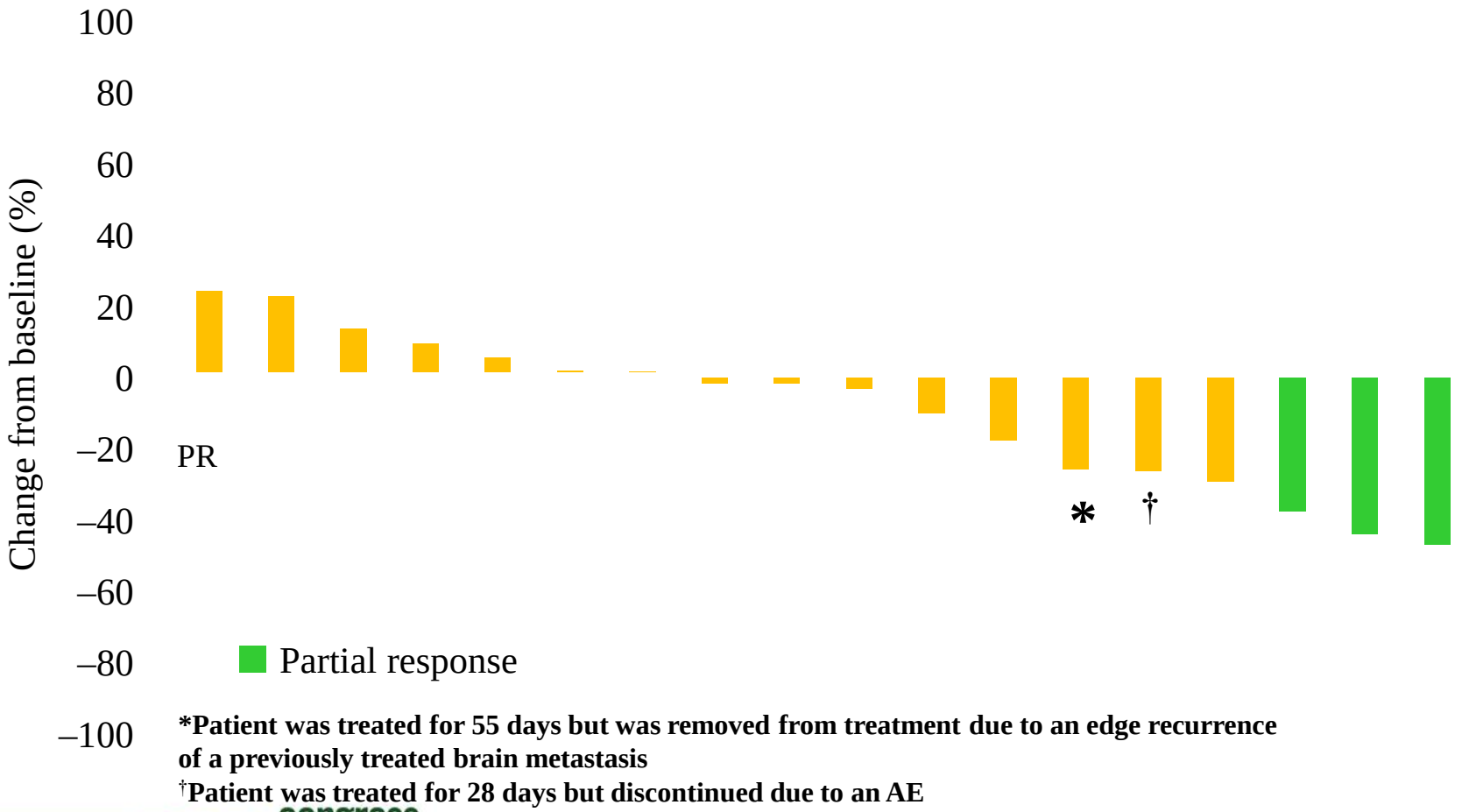


***Patient was treated for 55 days but was removed from treatment due to an edge recurrence of a previously treated brain metastasis**

†Patient was treated for 28 days but discontinued due to an AE

Kris et al ESMO 2012 abstr 12280

Waterfall Plot for Patients with *HER2*-Mutant Lung Cancers (n=18)



***Patient was treated for 55 days but was removed from treatment due to an edge recurrence of a previously treated brain metastasis**

†Patient was treated for 28 days but discontinued due to an AE

Kris et al ESMO 2012 abstr 12280

“Her”story in advanced NSCLC : mutation, overexpression and resistance…….

- **dacomitinib** demonstrates high efficacy in patients with common EGF-R mutations (exon 19 or 21) !
- although targeting EGF-R, Her-2 and Her-4 this drug shows no clear signal in Her-2 overexpressed and Her-2 mutated patients with advanced NSCLC
- **beware:** mutation of a potential target does probably not always mean that this target is really the “driver” of the malignant phenotype in the disease

Presentation 2: Abstract LBA 30

eLung: A Multicenter, Randomized Phase IIb Trial of "Standard" Platinum Doublets plus Cetuximab (CET) as First-line Treatment of Recurrent or Advanced Non-Small Cell Lung Cancer (NSCLC)

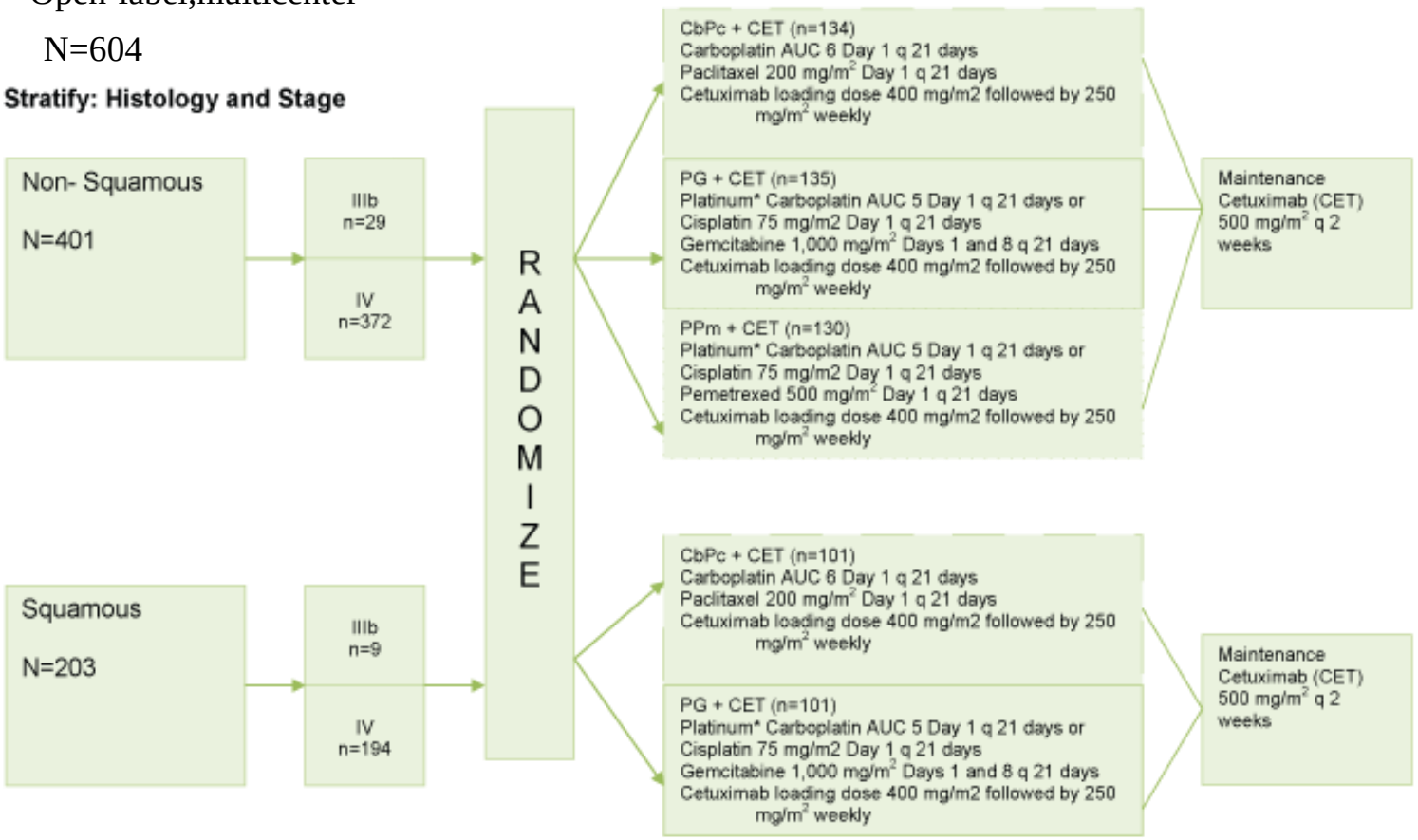
Lee S. Schwartzberg, Kurt Tauer, James Atkins, Kulumani Sivarajan, Vipul Patel, Bruno Bastos, Corey Langer, Mark Socinski, David Spigel

eLung Study Design

Open-label,multicenter

N=604

Stratify: Histology and Stage

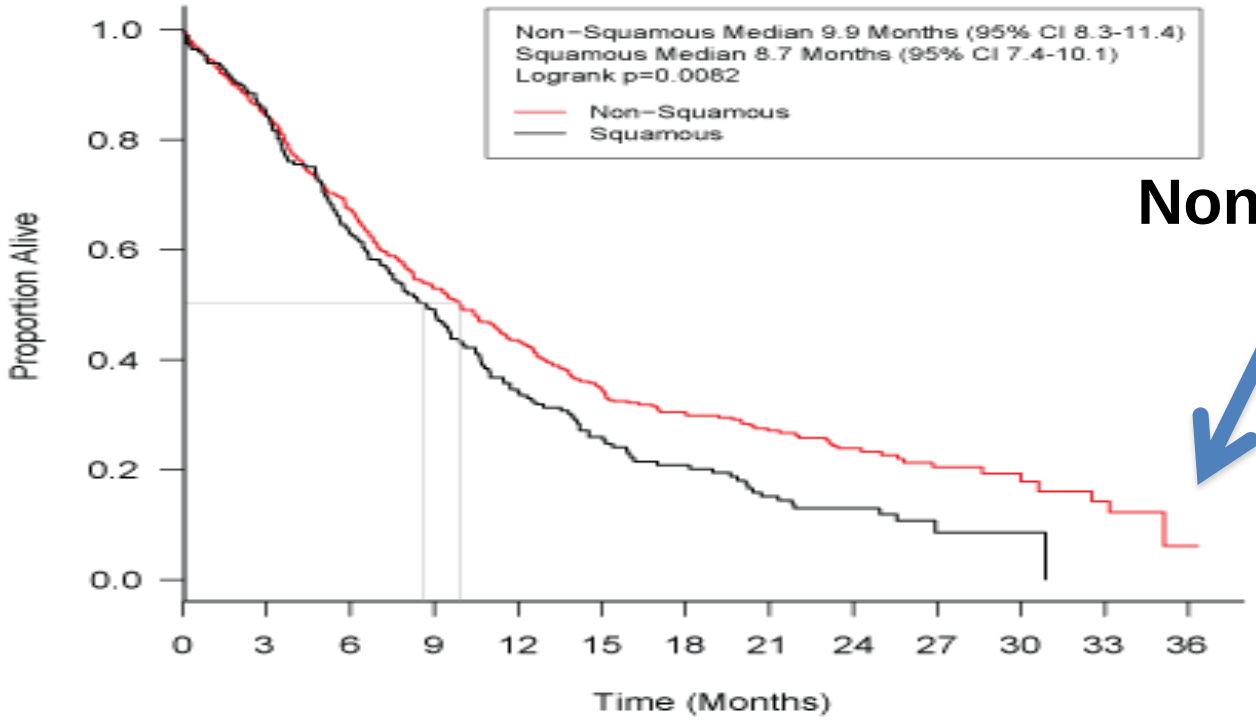


Chemo + CET = 4 to 6 cycles

*Physician and patient choice of cisplatin or carboplatin

Enrollment period:12/08-5/11

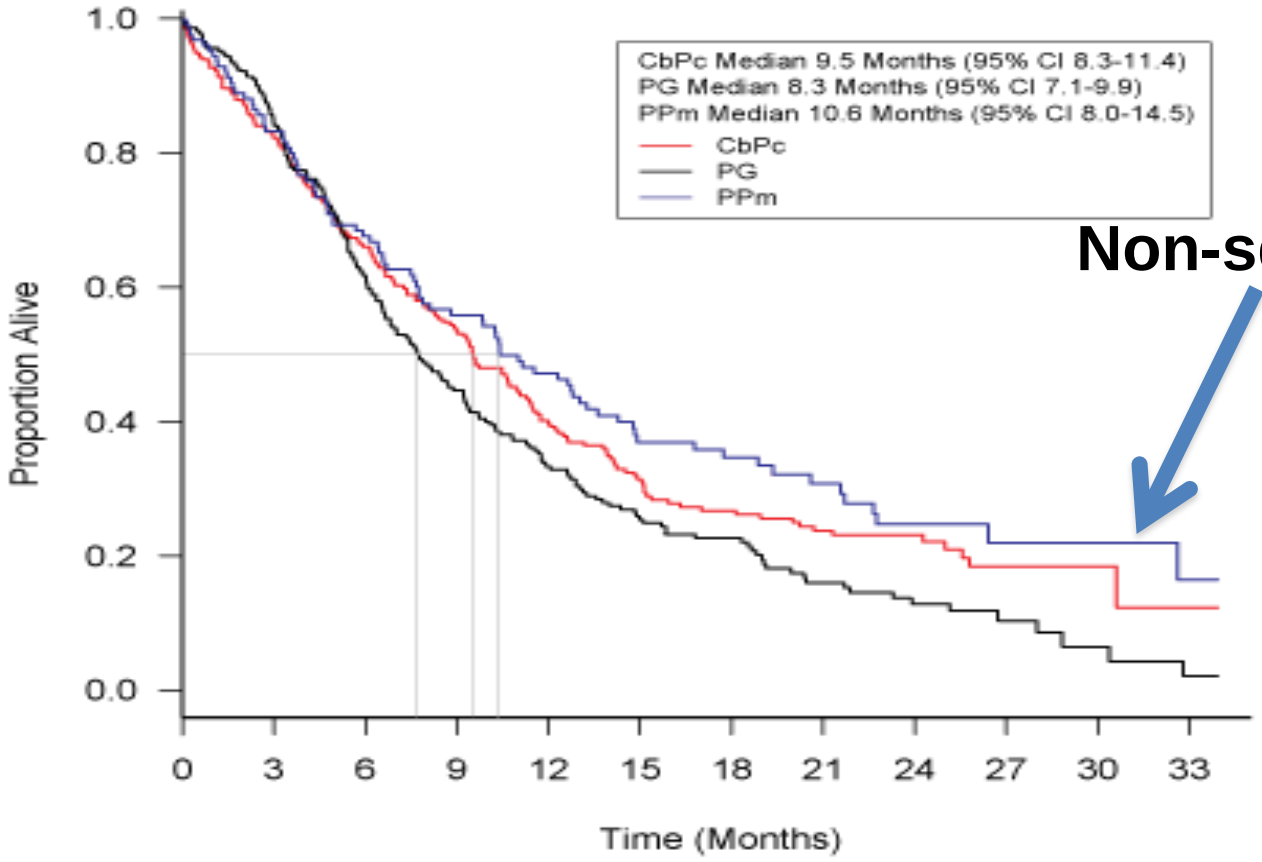
Overall Survival by Histology
ITT Analysis



Non-squamous

Schwartzberg et al ESMO 2012 LBA30

Overall Survival by Arm
ITT Analysis



Non-squamous

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“Her”story in advanced NSCLC : mutation, overexpression and resistance…….

- combining **cetuximab** with standard platinum-based combinations both in squamous-cell carcinoma as well as in non-squamous-cell carcinoma of the lung has demonstrated to be safe
- **no specific toxicity signals** were noted (eg. thrombotic events in combinations with cis/gem or cis/pem…….)
- in this **unselected patient population** with no pre-requisite of high expression of EGF-R (IHC H-score) **no clear survival signal** could be observed

“Her”story in advanced NSCLC : mutation, overexpression and resistance…… - act 2 -

“Her”story in advanced NSCLC : mutation, overexpression and resistance…….

CETUXIMAB - A DILEMMA :

- we do have a drug that is active in ≈ 30% of the advanced NSCLC population in combination with chemotherapy (Pirker et al, Lancet Oncol 2011)
- it shows a promising mechanism to restore sensitivity of patients with “acquired EGF-R resistance” when combined with a new effective irreversible EGF-R drug (afatinib, Janjigian, ESMO 2012)
- however, its clinical drug development in advanced NSCLC will be terminated due to high costs of further phase-III trials and the time schedule for running out of patent……

Press release 18th September 2012

FRANKFURT (Reuters) - German drugmaker Merck KGaA has withdrawn its second attempt to win European approval for use of its Erbitux drug against lung cancer, capping a string of setbacks in its drug development.

Merck said on Tuesday it gave up the new attempt it made in March to win EU approval for the use of its second best-selling drug Erbitux against lung cancer, which had targeted a quarter of the patients it had initially tried to address.

"The decision to withdraw the application was based on feedback from European regulatory authorities, indicating that further data would be required," Merck said in a statement.

Cited from : Reuters 18th September 2012

“Her”story in advanced NSCLC : mutation, overexpression and resistance…… Are there ways to solve this issue ?????

- **“revolutionary”:** development of alternative registration “mechanisms” and “tracks” for drugs already in use for a longer time period and coming near to the end of the patent lifecycle (we can forsee comparable problems) eg. via academia, foundations, charitable money, non-profit organizations……..
- **“economically orientated” :** simply try other EGF-R MoAbs (matuzumab, nimotuzumab, panitumomab, necitumomab etc……) – but this could fail……!?!?

"Her"story in advanced NSCLC : mutation, overexpression and resistance…… What did the story remind me of ????

- **cetuximab** restores sensitivity to **cisplatin** in **cisplatin-resistant head and neck cancer** (Baselga et al, J Clin Oncol 2005)
- **cetuximab** restores sensitivity to **irinotecan** in **irinotecan-resistant colorectal cancer** (Cunningham NEJM 2004)
- **ESMO 2012:** cetuximab restores sensitivity to **EGF-R TKI** in **EGF-R resistant NSCLC** in combination with the **potent second-generation pan-Her TKI afatinib ! (Janjigian et al, ESMO abstr 12270)**

International Association for the Study of Lung Cancer

IASLC

IASLC 15th World Conference on Lung Cancer

October 27 – October 31, 2013

Sydney, Australia

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Save the date!

October 27 - 31, 2013