ESMO Personalised Medicine Symposium
Sitges, March 5th 2016

Unraveling signal escape through maintained receptor activation: New treatment options

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GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

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Thank you

- **Jean-Charles SORIA**
- **David PLANCHARD**
- **Jordi REMON MASIP**

Outline

- **Why should we maintain EGFR inhibition?**
- **‘NGI’ Next Generation EGFR Inhibitors**
- **Keep EGFR inhibition, and…Add…**
  - **1) Chemotherapy**
  - **2) Other EGFR inhibitors**
  - **3) Immunotherapy**
- **One patient, one disease: Personalised Medecine is not dead**

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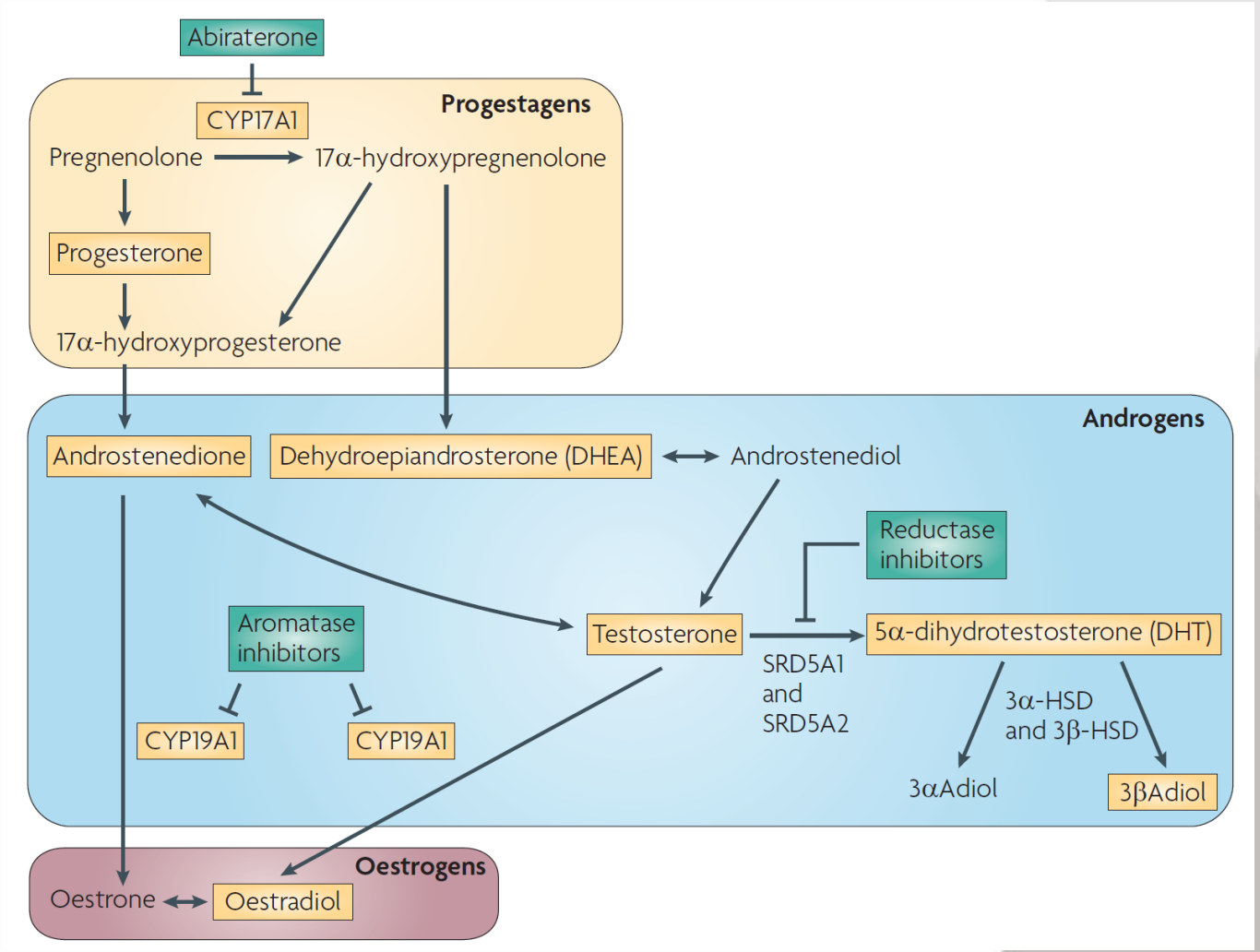
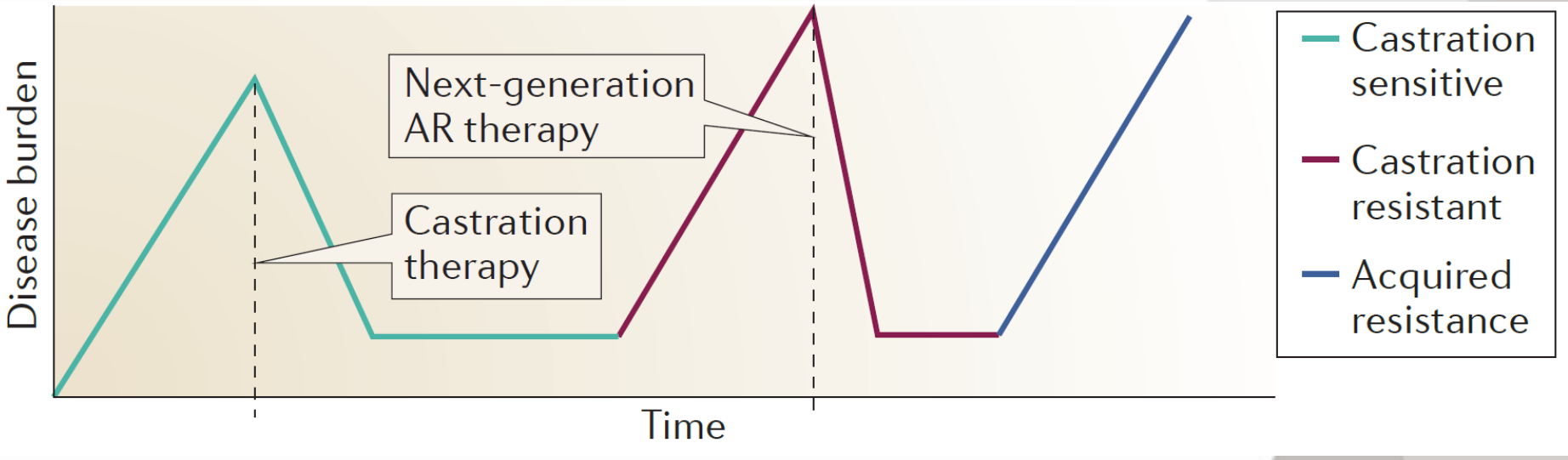
Personalised Medecine



Risbridger – Nature Rev Can 2010

Example of prostate cancer

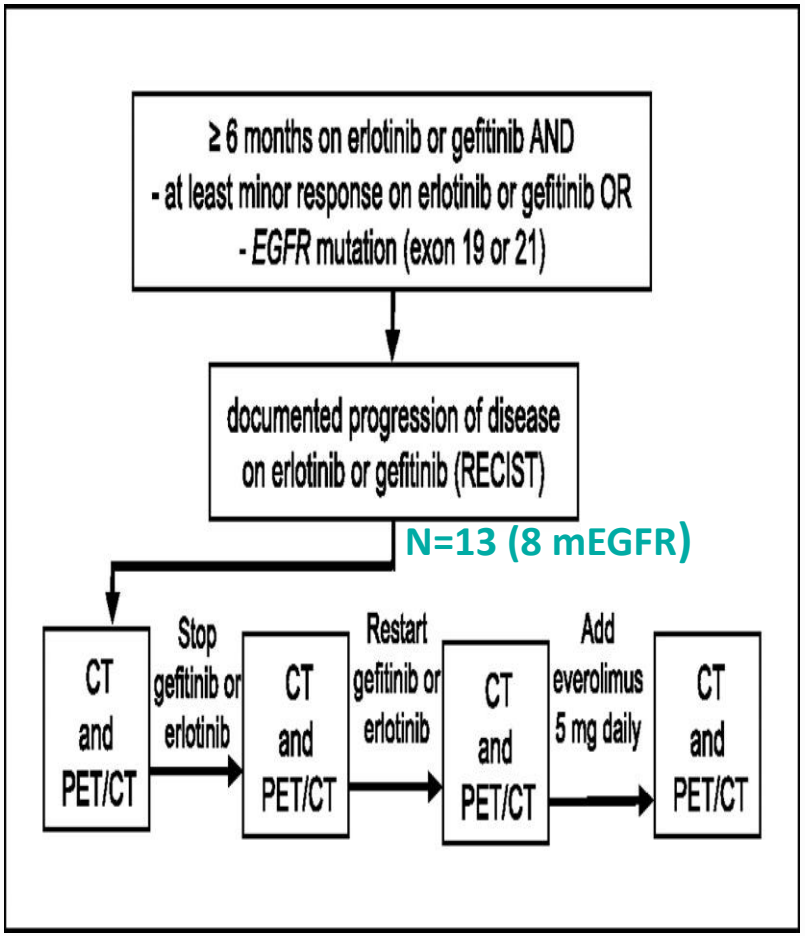


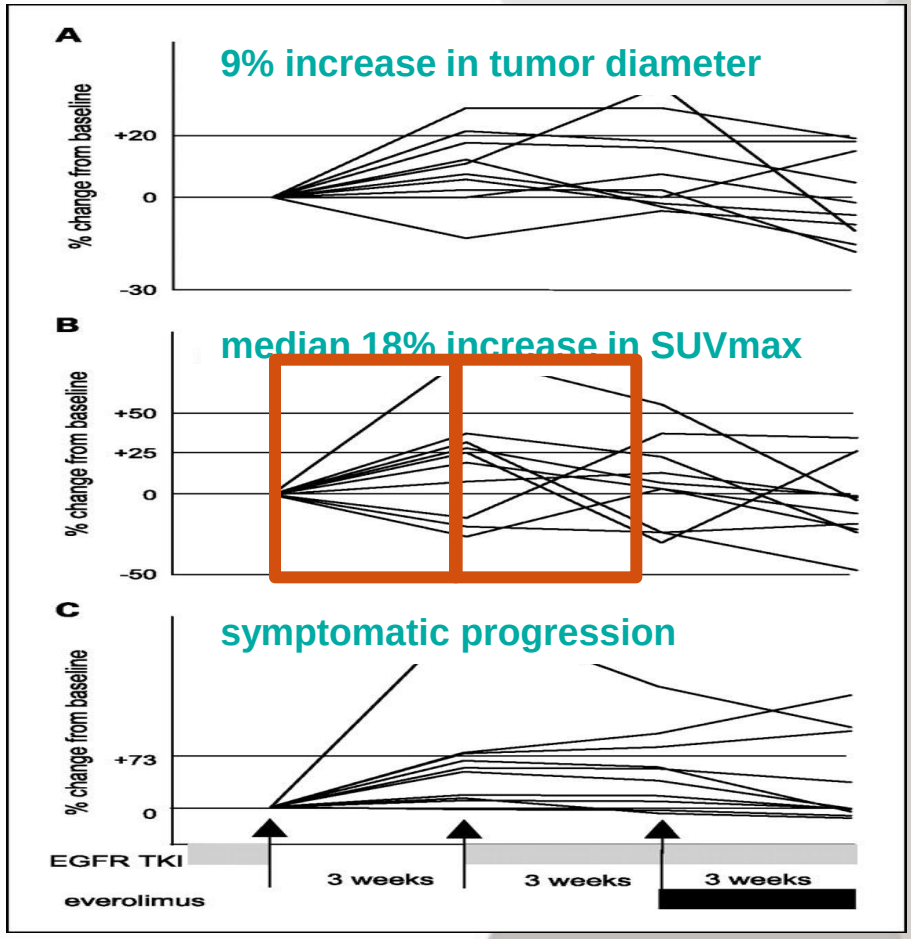
Castration therapy

Next Generation Therapy

Watson – Nature Rev Can 2015

Oncogene addiction even in acquired resistant EGFRm tumors

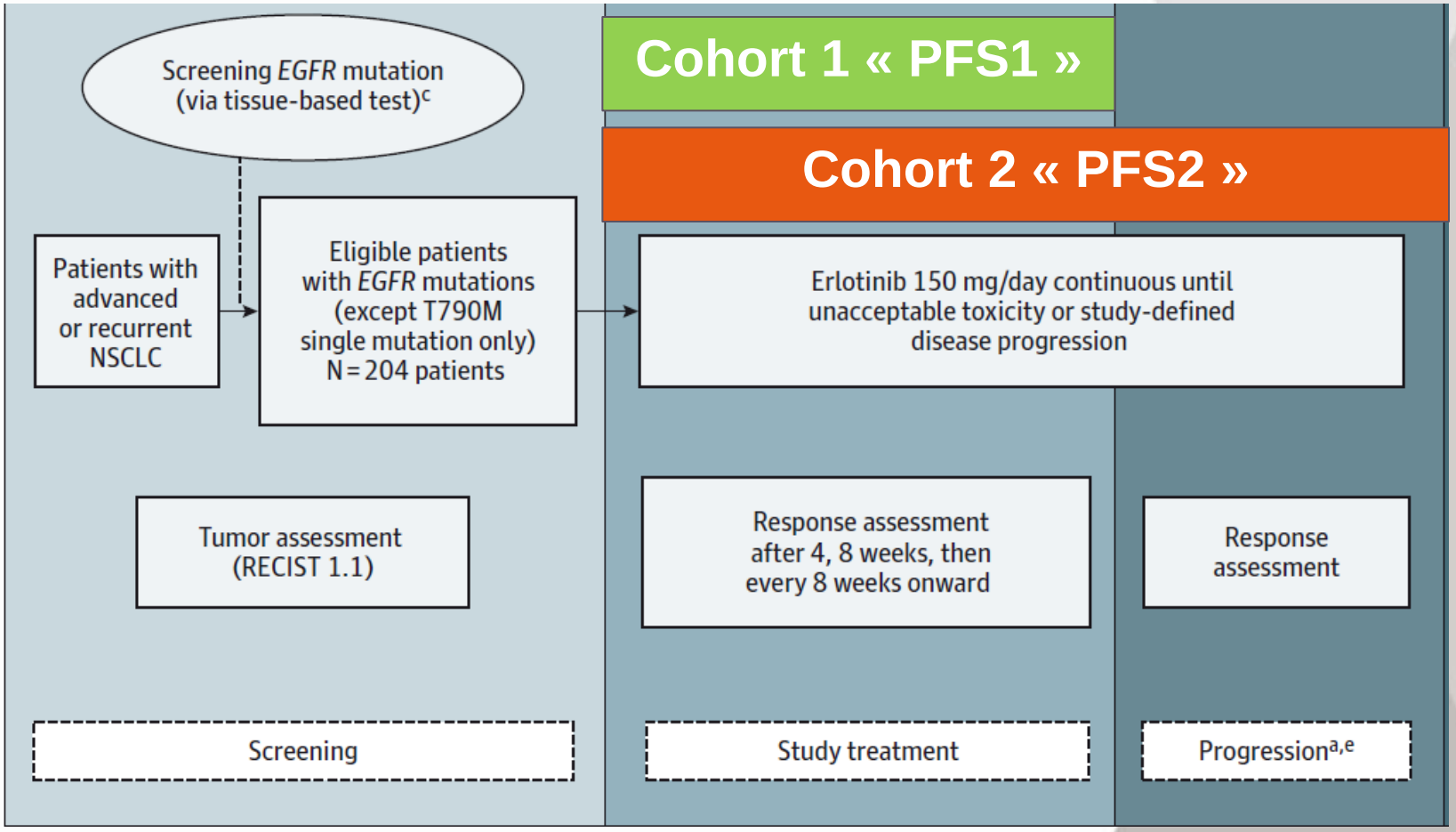




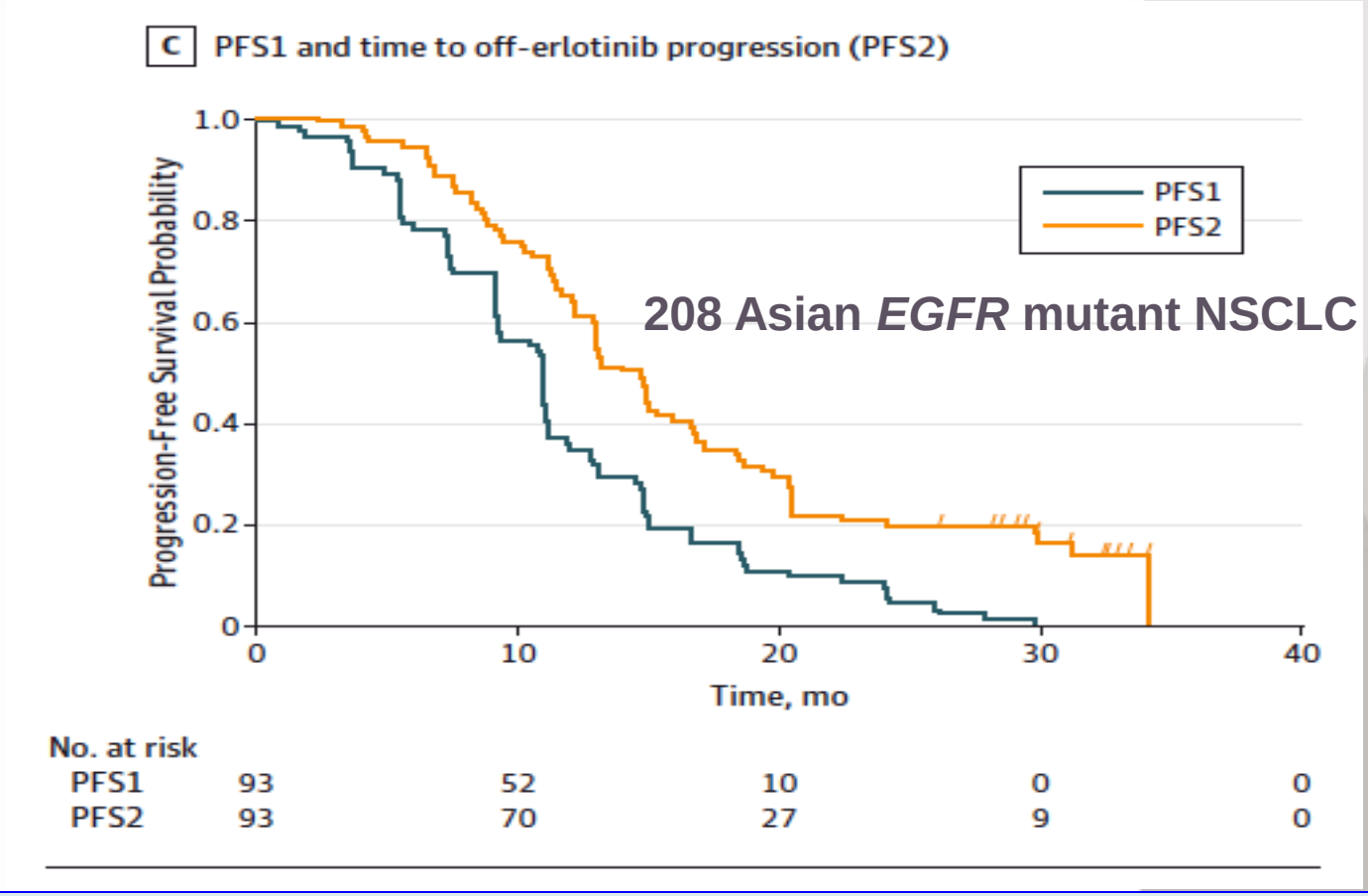
Indication show that EGFR mutant lung cancer maintain a degree of sensitivity to TKI despite development of acquired resistance (AR)

Riely – Clin Cancer Res 2007

The ASPIRATION Study

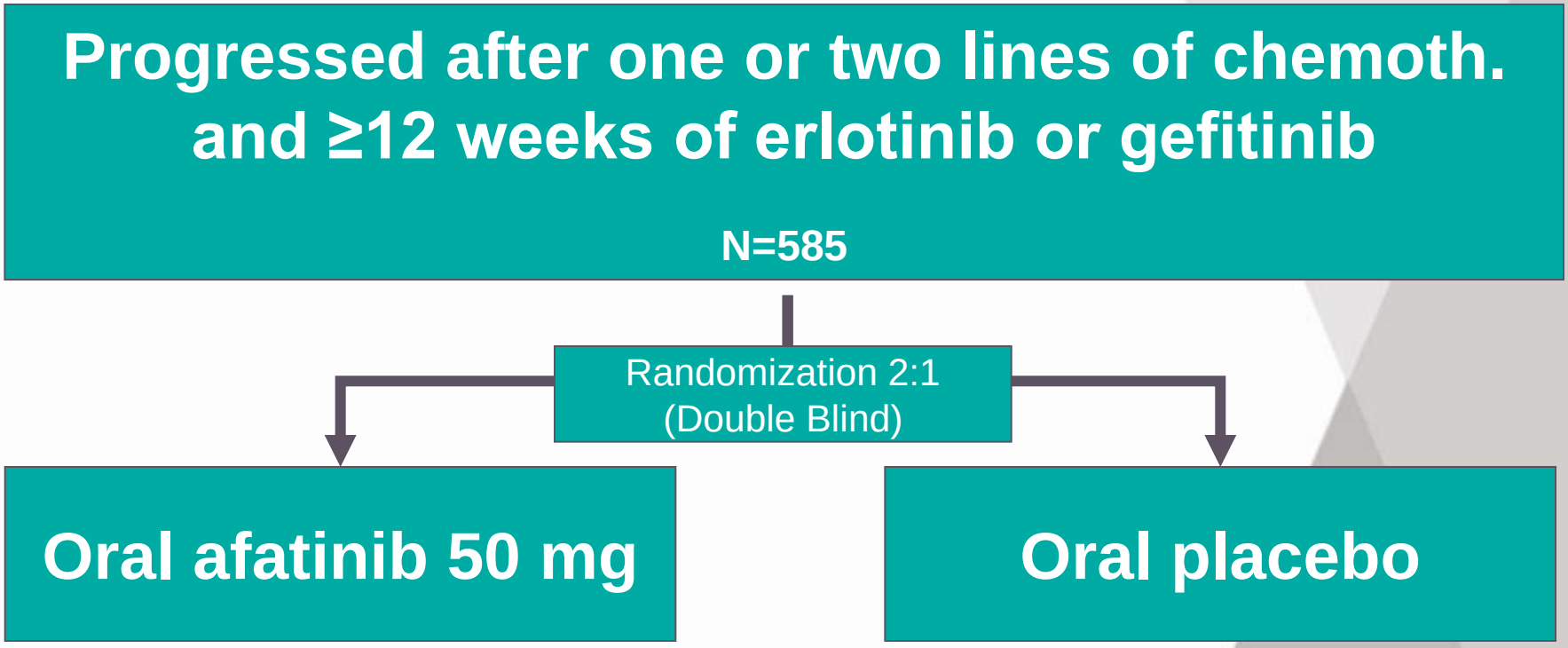


The ASPIRATION Study



Continuation of erlotinib beyond RECIST PD improved 3.9 months the PFS (from 11 months to 14.9 months) for tumours with common *EGFR* mutations

LUX-Lung 1: Trial design

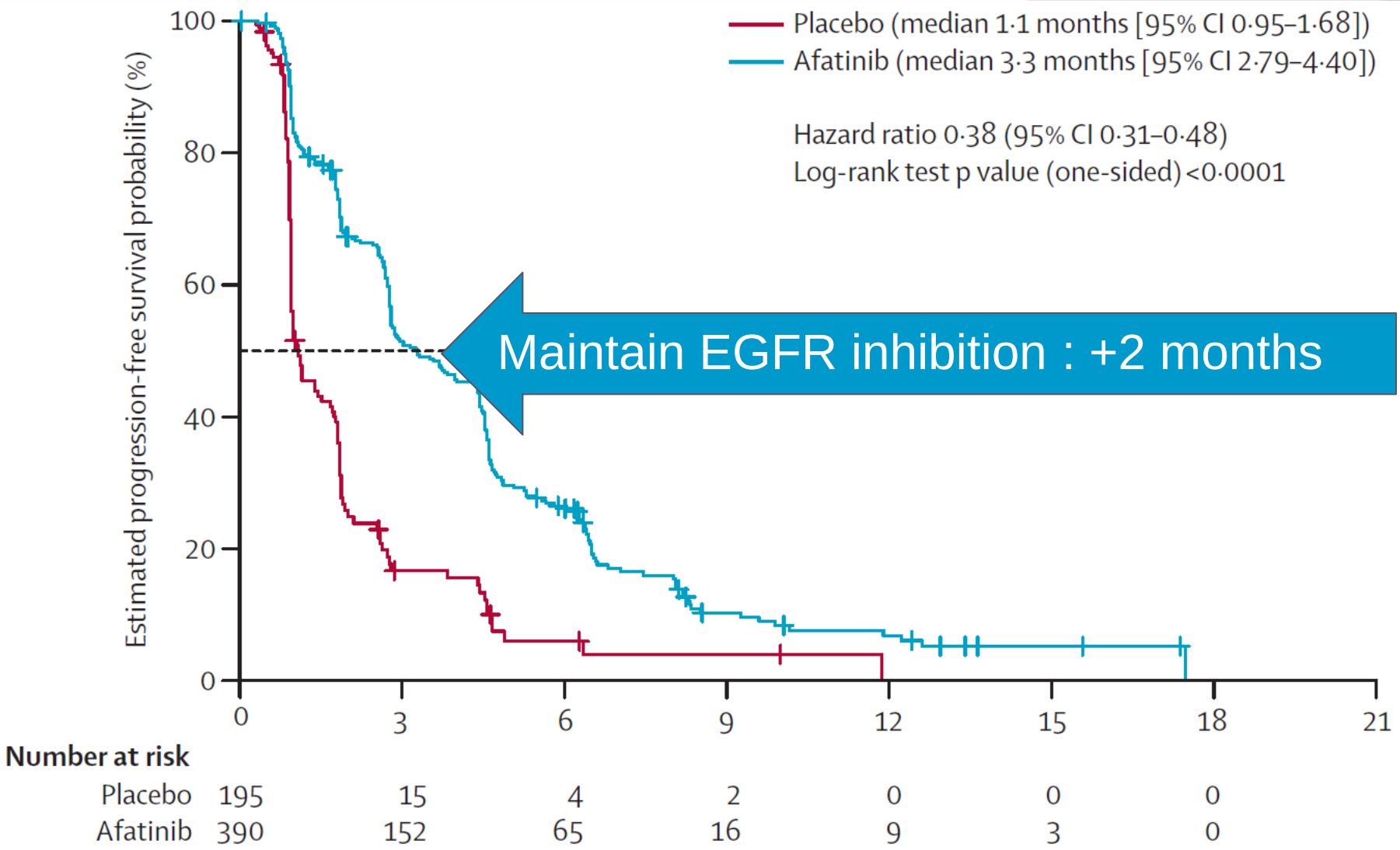


Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

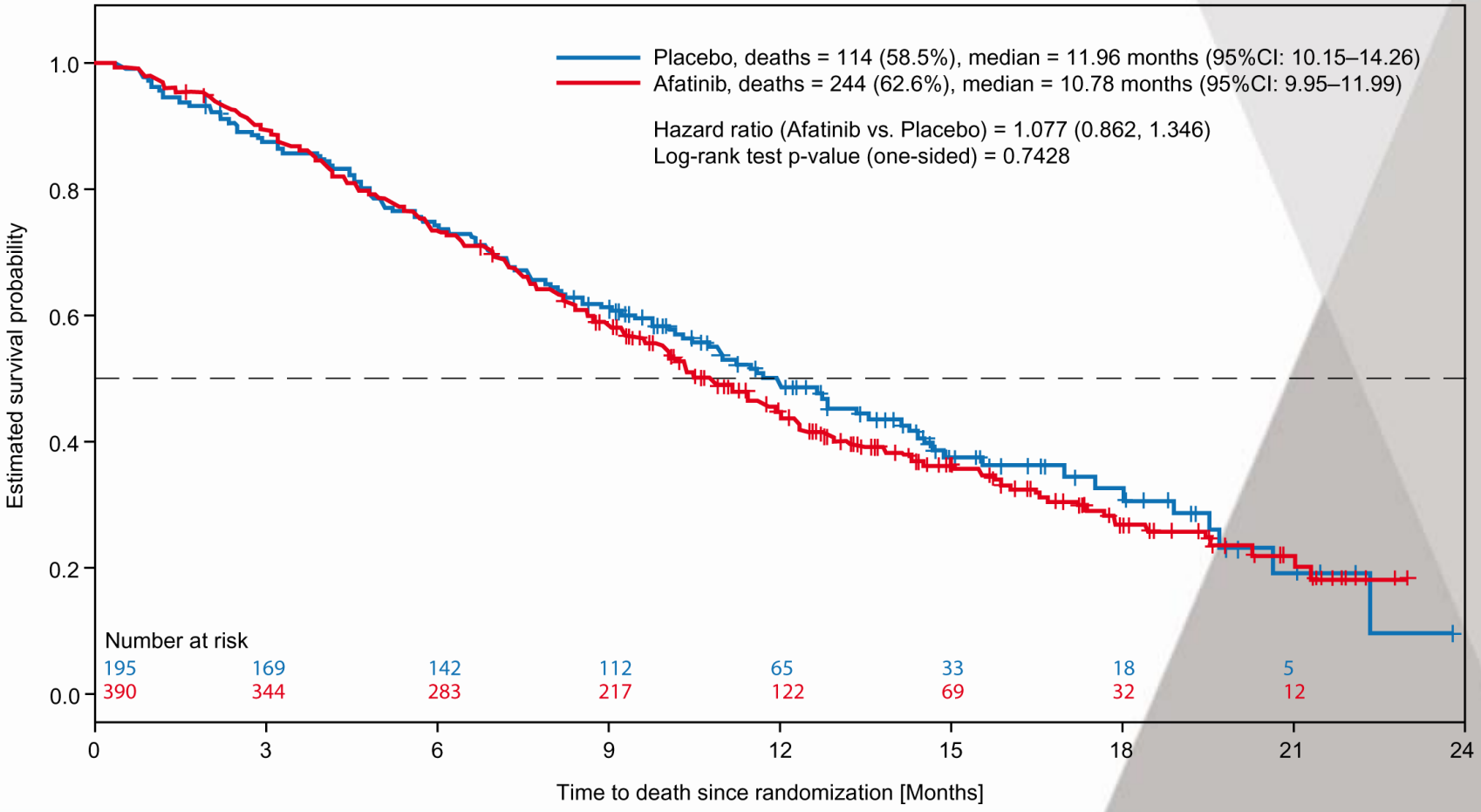
Miller – Lancet Oncol 2012

LUX-Lung 1



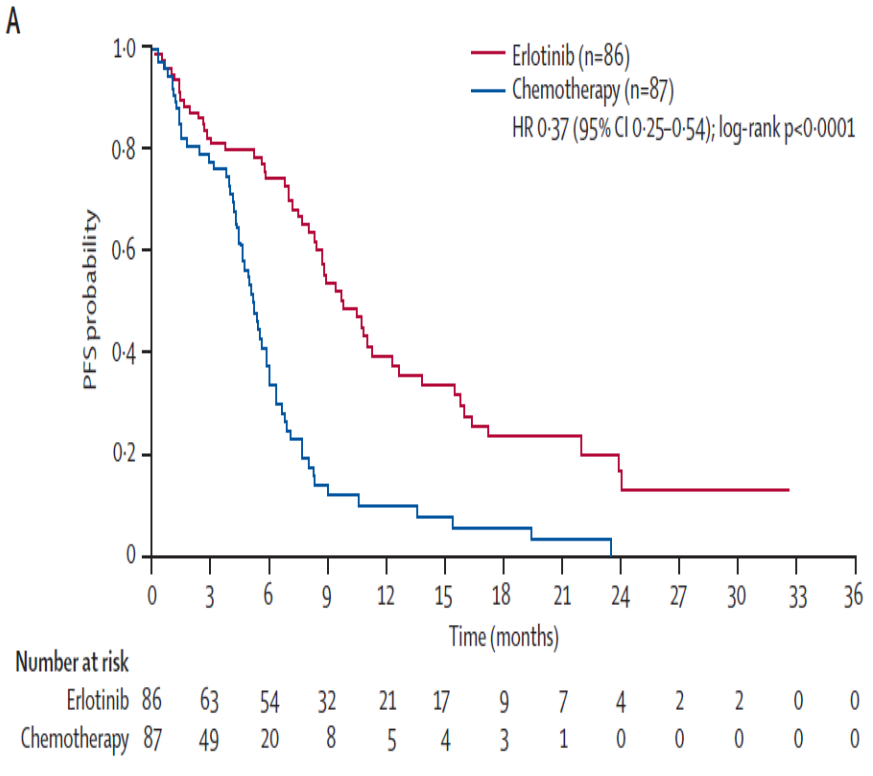
Miller – Lancet Oncol 2012

Afatinib vs placebo in 3rd/4th line

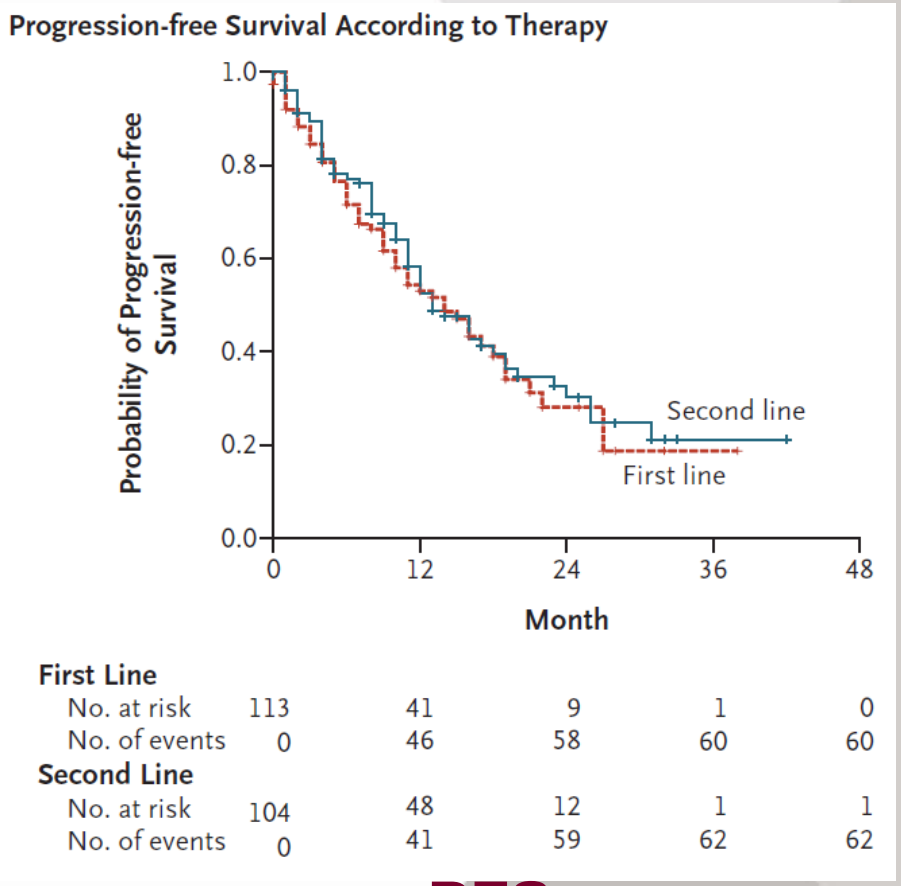


Miller – Lancet Oncol 2012

We don’t use RECIST to treat



PFS
~9 months



PFS
~14 months

Rosell et al, NEJM 2009

Rosell Lancet Oncol 12

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EGFR mutant NSCLC and EGFR TKI

Study	Treatment randomization	n	RR (%)	PFS (mo)	OS (mo)
IPASS†	Gefitinib vs carboplatin/paclitaxel	261	71.2 vs 47.3 p < 0.001	9.5 vs 6.3 HR: 0.48; p < 0.001	21.6 vs 21.9 HR: 1.00; p = 0.99
First-SIGNAL‡	Gefitinib vs gemcitabine/cisplatin	42	84.6 vs 37.5 p = 0.002	8.0 vs 6.3 HR: 0.54; p = 0.086	27.2 vs 25.6 HR: 1.043
WJTOG 3405	Gefitinib vs cisplatin/docetaxel	177	62.1 vs 32.2 p < 0.001	9.2 vs 6.3 HR: 0.49; p < 0.001	36 vs 39 HR: 1.185
NEJ002	Ge				27.7 vs 26.6 HR: 0.887; p = 0.483
OPTIMAL	Erl car				22.6 vs 28.8 HR: 1.065; p = 0.685
EURTAC	Erl reg				19.3 vs 19.5 HR: 1.04; p = 0.87
ENSURE	Erlotinib vs gemcitabine/cisplatin	148	68.2 vs 39.3 p < 0.0001	11 vs 5.5 HR: 0.33; p < 0.0001	NR
LUX-Lung 3	Afatinib vs cisplatin/pemetrexed	345	56.0 vs 23.0 p = 0.001	13.6 vs 6.9§ HR: 0.47; p < 0.001	31.6 vs 28.2§ HR: 0.78; p = 0.1090
LUX-Lung 6	Afatinib vs cisplatin/gemcitabine	364	67.0 vs 23.0 p < 0.0001	11.0 vs 5.6§ HR: 0·25; p < 0·0001	23.6 vs 23.5§ HR: 0.83; p = 0.1756

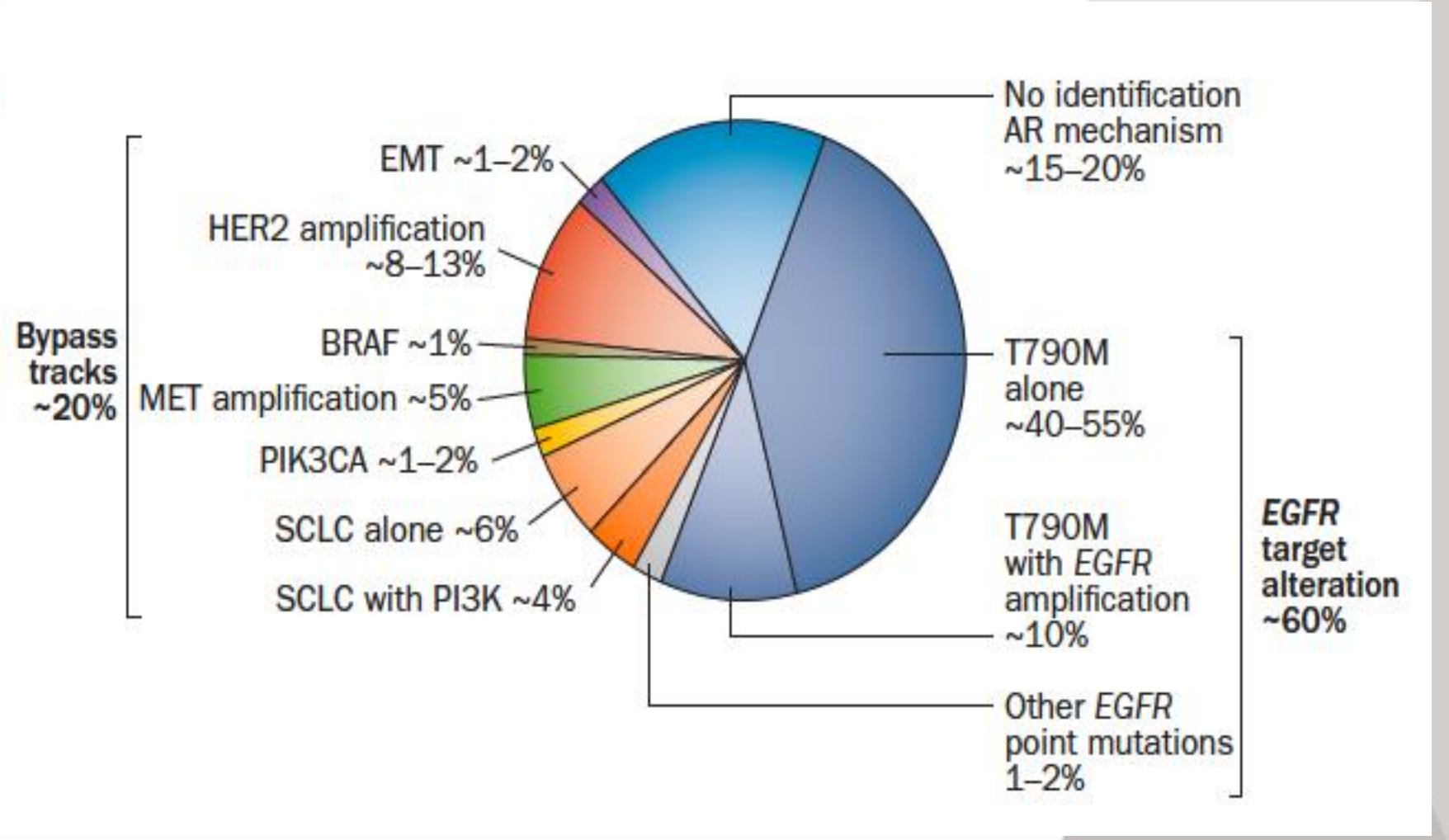
Erlotinib, Gefitinib, Afatinib, Same efficacy so far!

No phase III 'TKI vs TKI'

ORR: ~ 70%, PFS: ~ 9-11 months, no OS benefit (cross-over)

Reguart – Future Oncol 2015

Acquired resistance to EGFR TKI

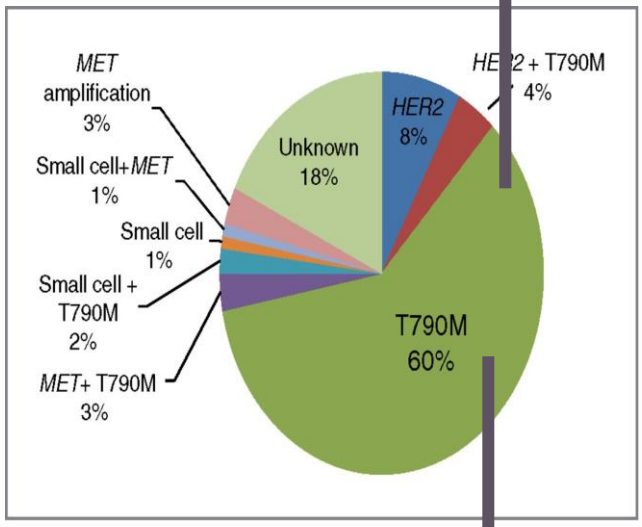


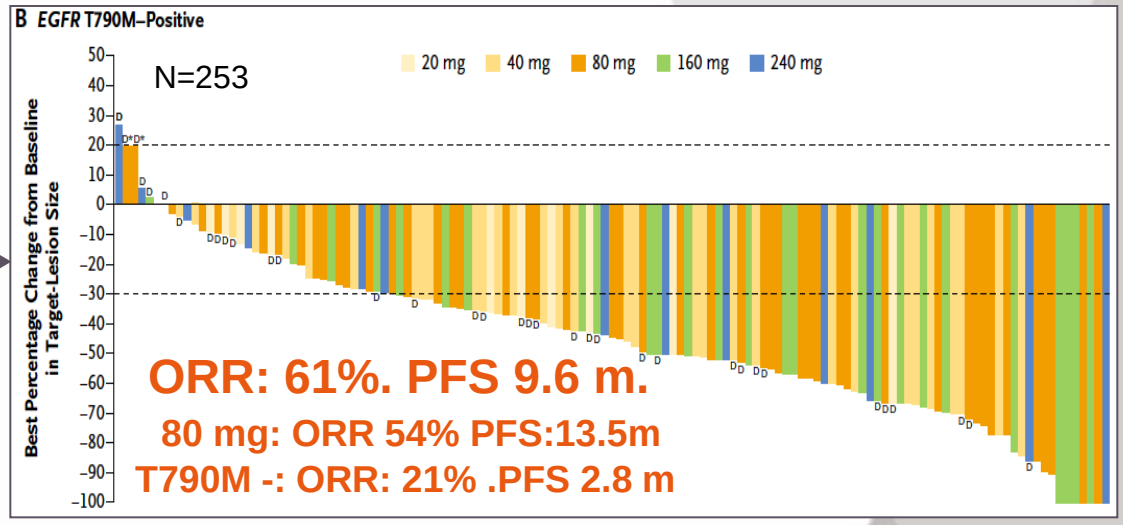
Acquired resistant to EGFR TKI. *T790M*

3rd GENERATION

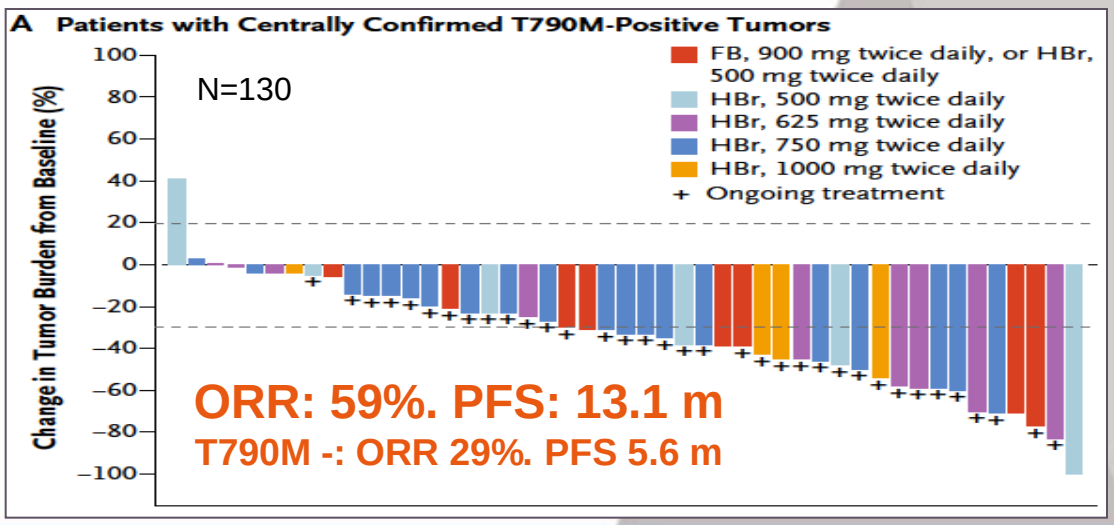
AZD9291

(Tagrisso ®. Approved by FDA)





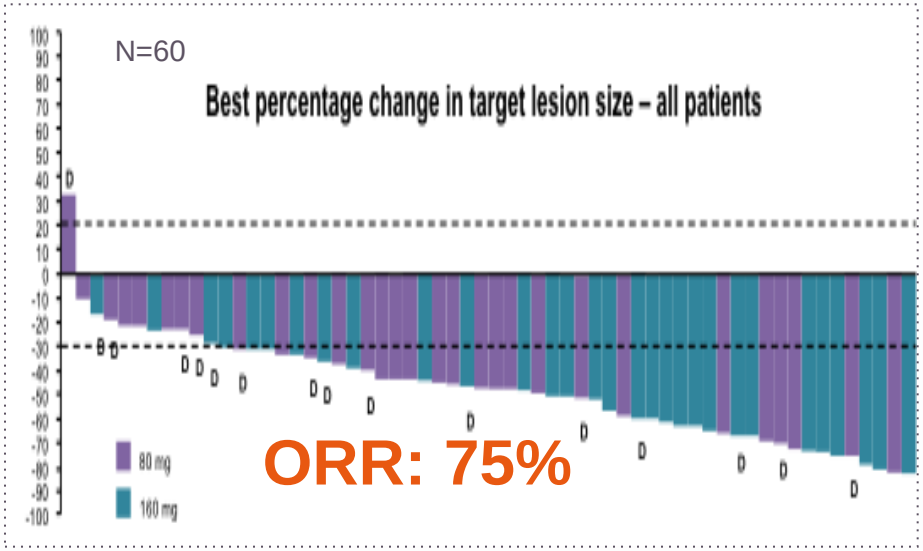
ROCILETINIB

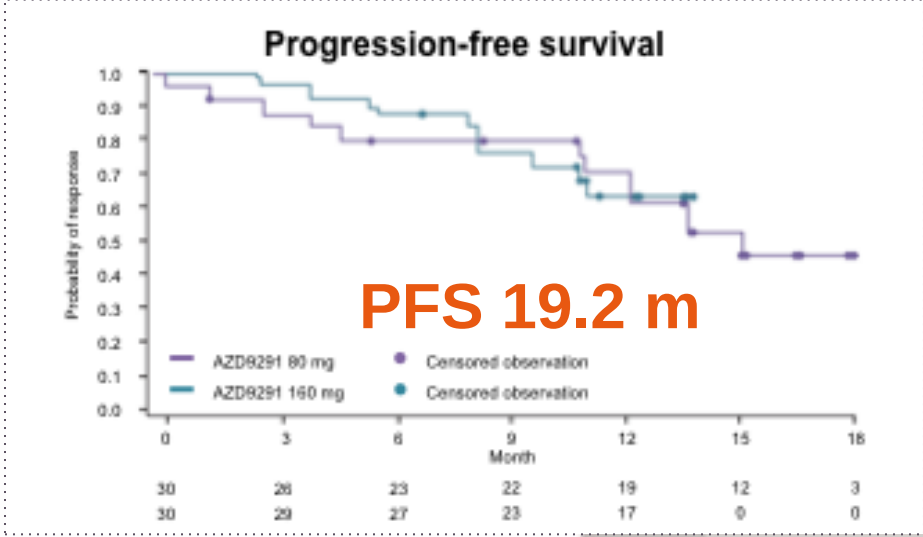


Yu – CCR 2013 * Jänne –NEJM 2015 * Jänne – ELCC 2015 * Sequist – NEJM 2015 * MItsudomi – WCLC 2015

New EGFR TKI at first line?

AURA phase I trial dose escalation / expansion 1st line





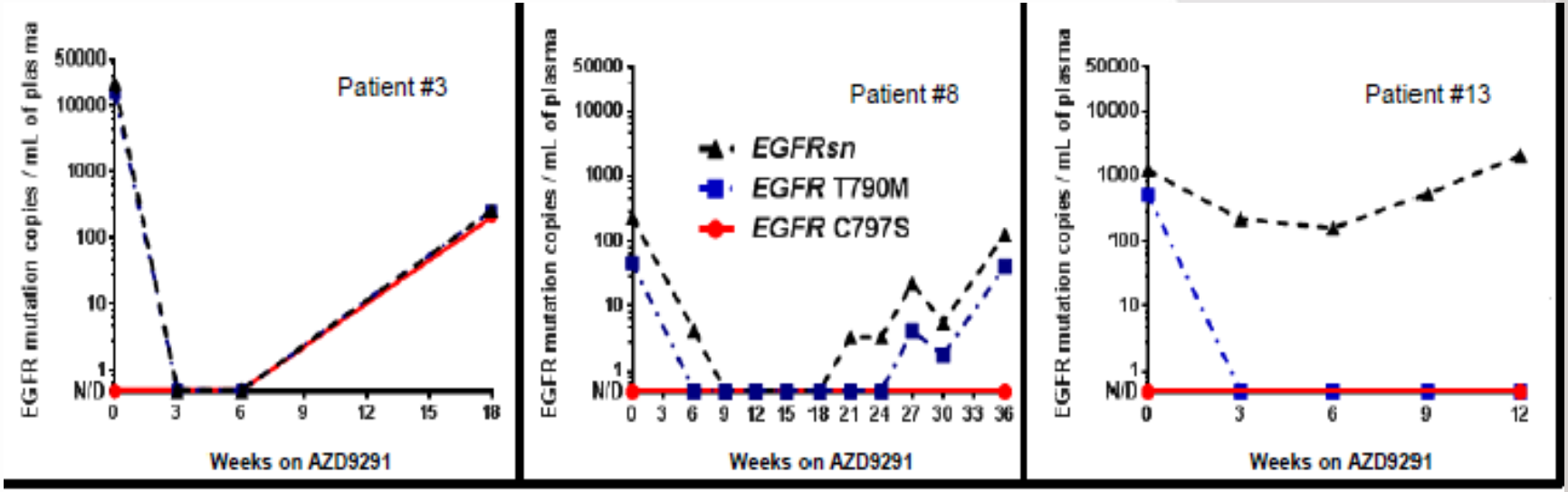
FL-AURA
NCT02296125

Ph III trial of AZD9291 (80 mg/d) compared to Erlotinib or Gefitinib in *EGFR*m NSCLC patients in first-line setting

Primary end-point: PFS
Secondary: ORR, PFS by T790M status, OS

TIGER 1 (NCT02186301): Rociletinib vs. Erlotinib. End Point: PFS

Mechanisms of acquired resistance AZD9291



EGFR Activating Mutation
EGFR T790M
EGFR C797S

22%

More frequent in *Del19*
Resistance to all EGFR TKI

EGFR Activating Mutation
EGFR T790M

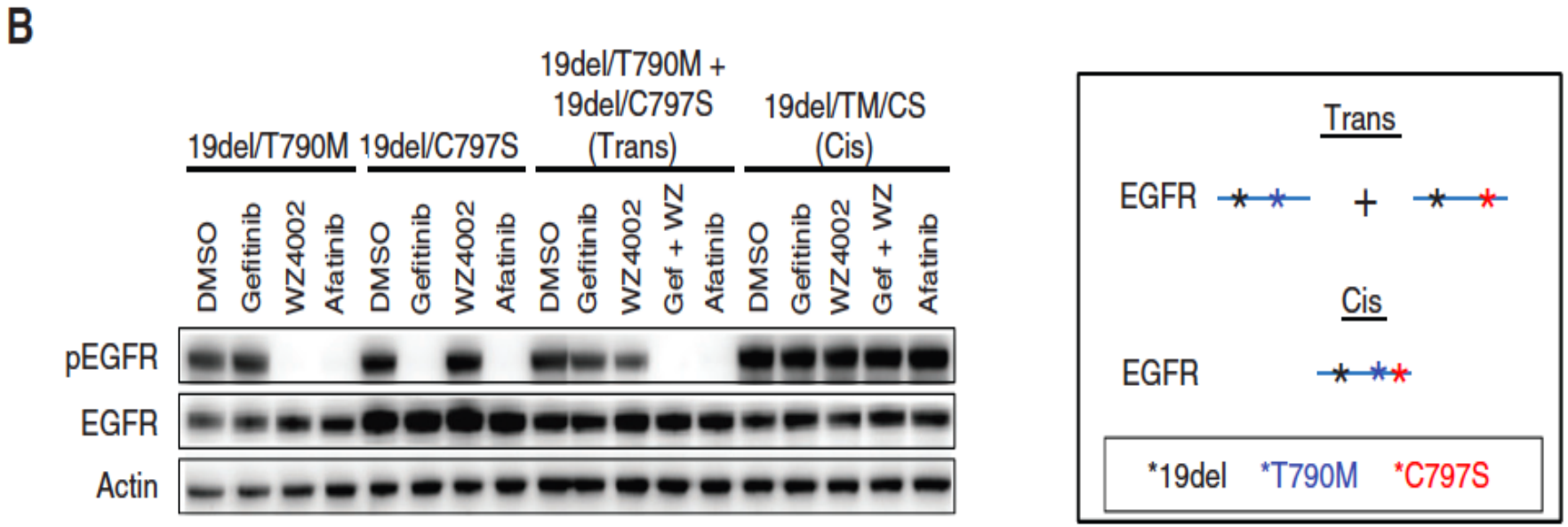
EGFR Activating Mutation
Loss of T790M

48%

HER2 amplification
MET amplification
BRAF V600E mutation

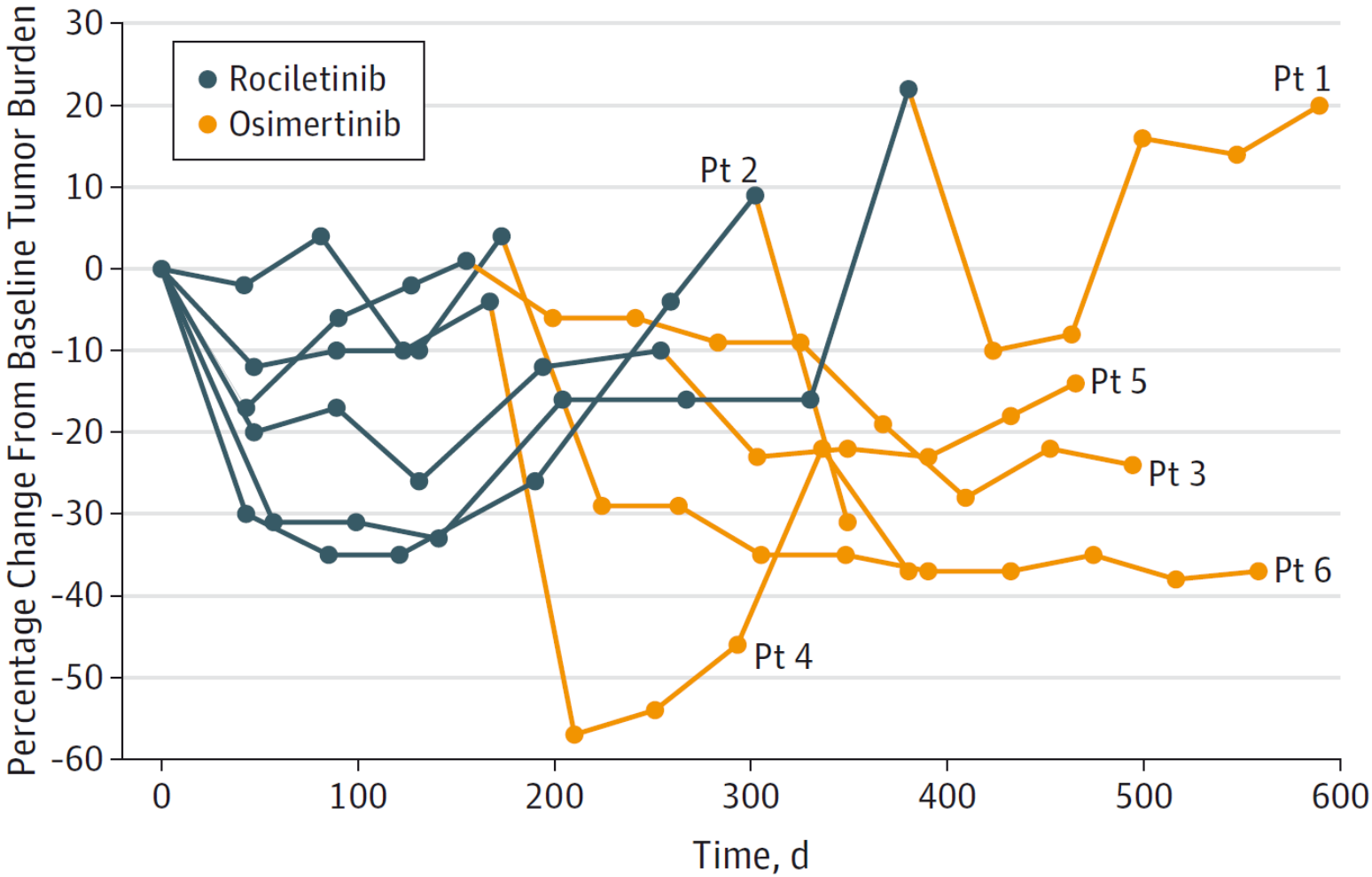
Thress – Nat Med 2015 * Oxnard – WCLC 2015 * Niederst – CCR 2015

C797 cis / trans and EGFR TKI



If the C797S and *T790M* mutations are in *trans* (on a different allele), cells will be resistant to third-generation EGFR TKIs, but will be sensitive to a combination of first- and third-generation TKIs.
If the mutations are in *cis* (on the same allele), no EGFR TKIs alone or in combination can suppress activity

Figure. Longitudinal Response for Each Patient Who Transitioned Directly From Rociletinib to Osimertinib



Sequist JAMA oncology 2015

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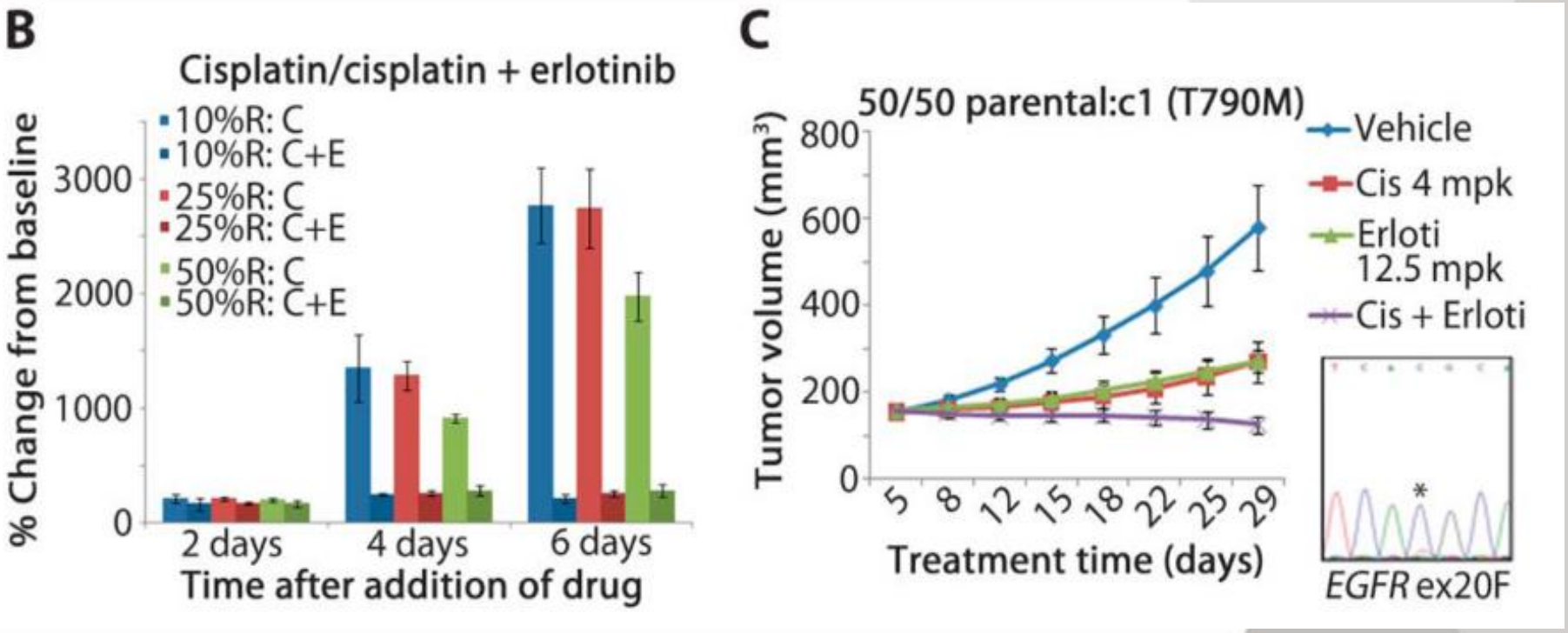
Maintained dependence on EGFR pathway even after AR



Patients may benefit from continued treatment with an EGFR TKI, even after developing T790M-mediated progression of disease

Chmielecky – Sci Transl Med 2011

Acquired resistance to EGFR TKI. IMPRESS

- PD on Gefitinib by RECIST criteria
- Measurable stage IIIB / IV disease
- ECOG 0-1
- activating *EGFR* mutations

N=265

Gefitinib +

Cisplatin / Pem

Max 6 cycles

→ Gefitinib until PD

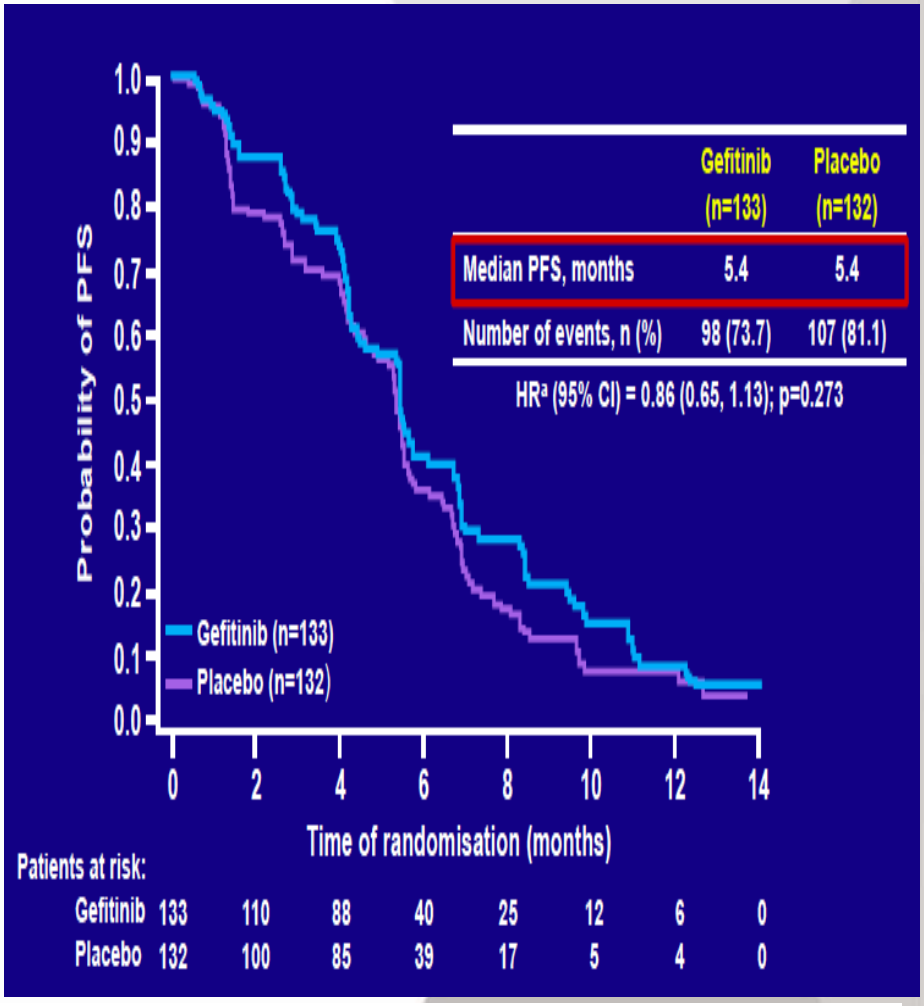
1:1 randomisation

Placebo +

Cisplatin / Pem

Max 6 cycles

→ Placebo until PD



Continuation of gefitinib at PD NOT improve PFS if CT is prescribed as 2nd Line
Subanalysis in *T790M* negative, PFS: 6.7 vs. 5.4, HR 0.67 (0.43-1.03), p=0.07

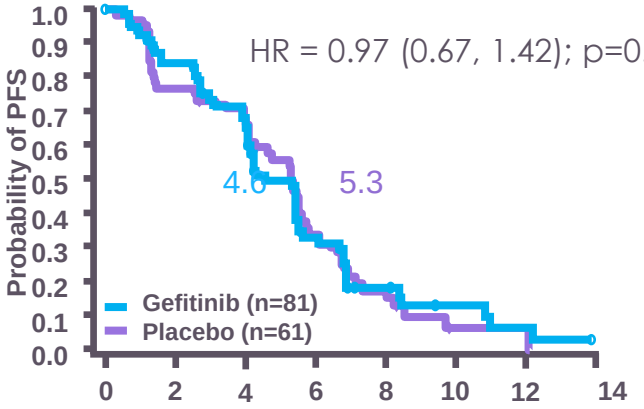
Soria –Lancet Oncol 2015 * Mok – WCLC 2015

IMPRESS : PFS and OS vs T790M

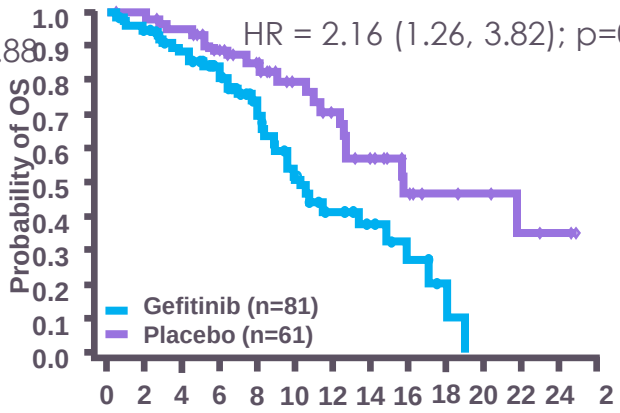
plasmaT790M+ (N=142)

57%

PFS



OS



NO BENEFIT

Mok et al. WCLC 2015

Platinum + TKI do not match

NExUS NSCLC	Gemcitabine + Cisplatin	Sorafenib	904	0.98 [0.83-1.16] p=0.40	0.83 [0.71-0.97] p=0.008
ESCAPE NSCLC	Paclitaxel + carboplatin	Sorafenib	926	1.16 [0.95-1.43] p=0.93	1.0 [0.85-1.18] p=0.51
INTACT-1 NSCLC	Gemcitabine + Cisplatin	Gefitinib 250/500 mg	1093	NC p=0.45	NC p=0.76
INTACT-2 NSCLC	Paclitaxel + carboplatin	Gefitinib 250/500 mg	1037	NC p=0.64	NC p=0.056
TALENT NSCLC	Gemcitabine + Cisplatin	Erlotinib	1172	1.06 [0.90-1.23] p=.49	0.98 [0.86-1.1] p=.74
TRIBUTE NSCLC	Paclitaxel + carboplatin	Erlotinib	1079	0.995 [0.86-1.16] p=.95	0.93 p=.36
CONFIRM-1 CCR	5FU+LV+ oxaliplatin	Vatalanib (PTK/ZK)	1168	NC	0.88 p=0.118
CONFIRM-2 CCR	5FU+LV+ oxaliplatin	Vatalanib (PTK/ZK)	855	0.94 p=0.51	0.83 p=0.026
Hauschild *et al.* Melanoma	Paclitaxel + carboplatin	Sorafenib	270	1.01 [0.76-1.36] p=0.92	0.91 [0.63-1.31] p= 0.49
E2603 Melanoma	Paclitaxel + carboplatin	Sorafenib	823	1.0 [9.7-12.3] p= 0.878	NC

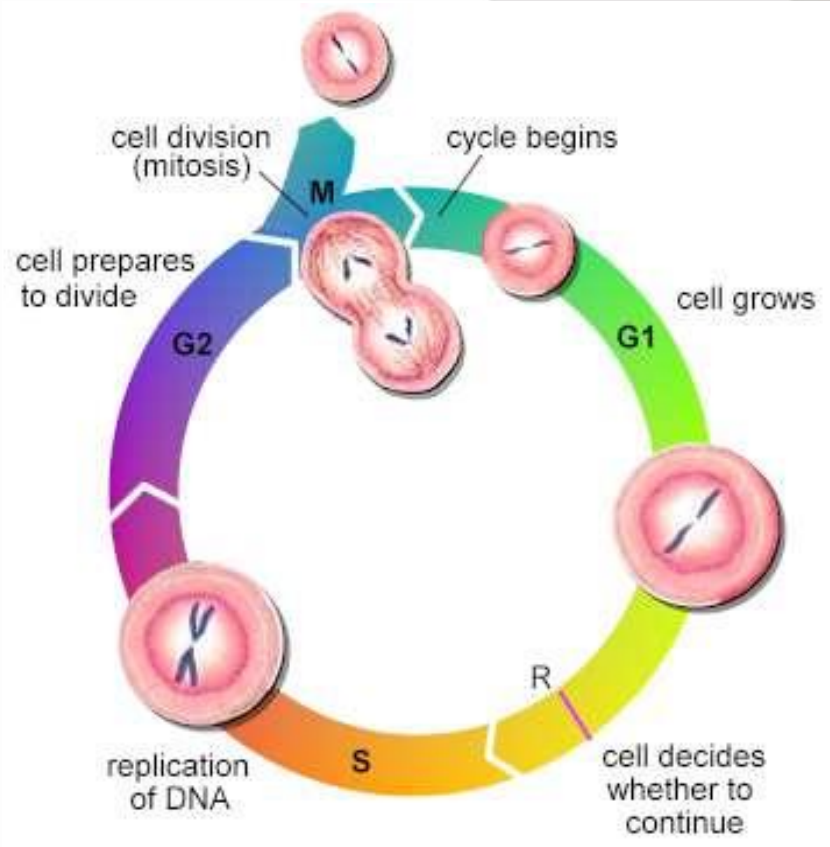
Gatzemeier ESMO 2010, Scagliotti JCO 10, Herbst JCO 05, Gatzemeier JCO 07, Giaccone JCO 04, Herbst JCO 04, Oldenburg ASCO 07, Hecht ASCO 05, Flaherty ASCO 10, Hauschild JCO 09

Integration of EGFR inhibitors and chemotherapy in NSCLC: Concurrent

TKI arrests cancer cells in the G1 checkpoint

Chemo usually work at the mitotic phase (M)

Pulsatile vs. Continuous administration ?



Solit – Clin Cancer Res 2005

Integration of EGFR inhibitors and chemotherapy in NSCLC: Intercalated

FASTACT-2 Trial

- **Untreated stage IIIB / IV NSCLC**
- **ECOG PS 0-1**

42% Female, 50% Never-S, 8% Cisplatin, **22% *EGFR* mut**

R

N=451

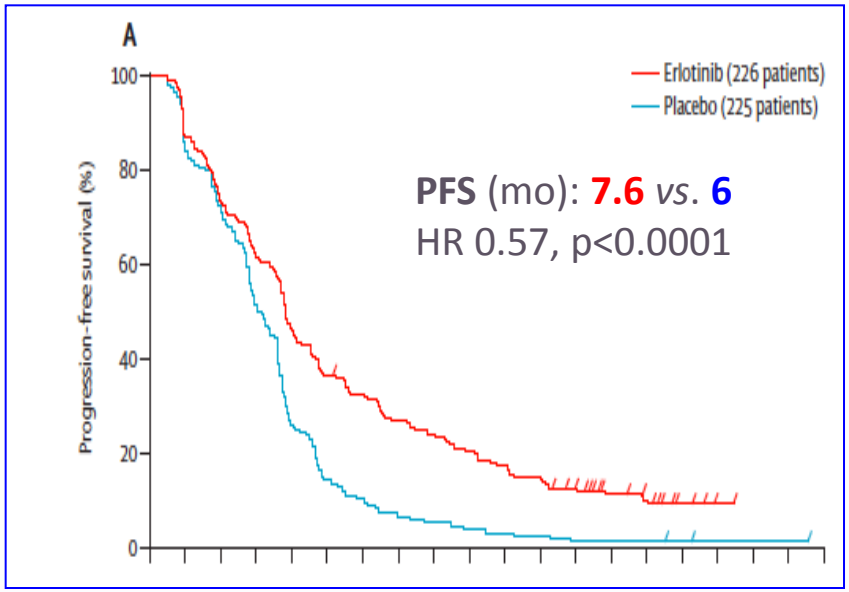
Cis/CBDCA-Gem / 4w + Erlotinib 150 d15-28

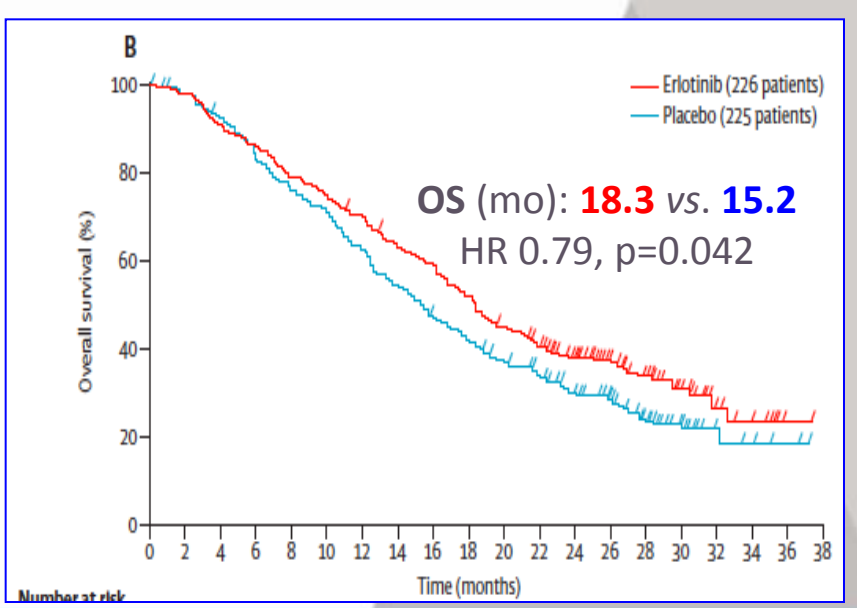
6 CYCLES

Erlotinib

Cis/CBDCA-Gem + Pl / 4w

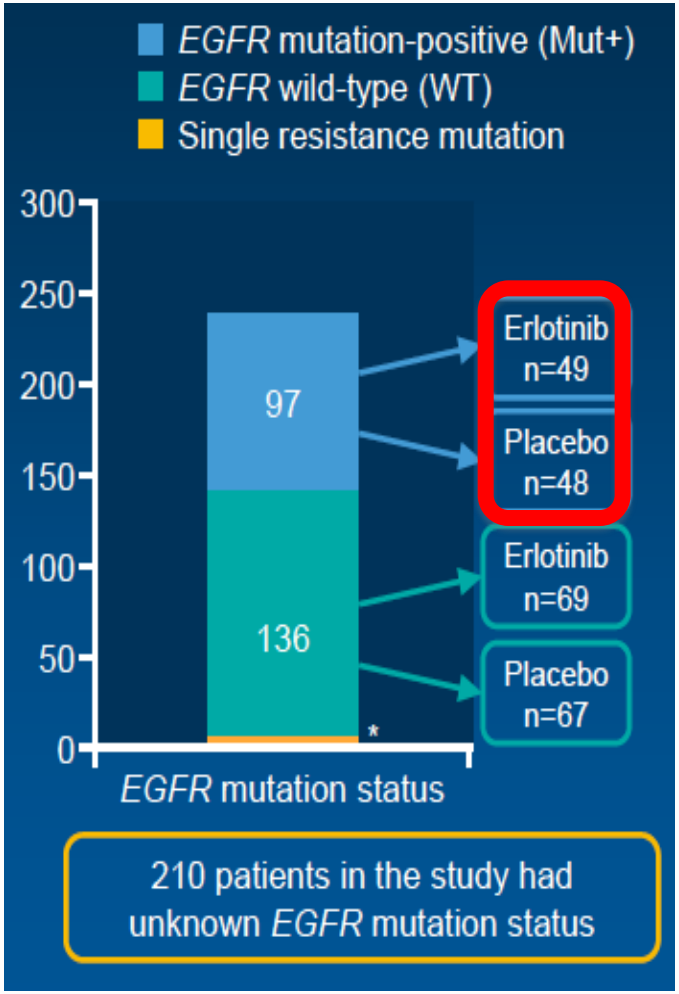
Placebo

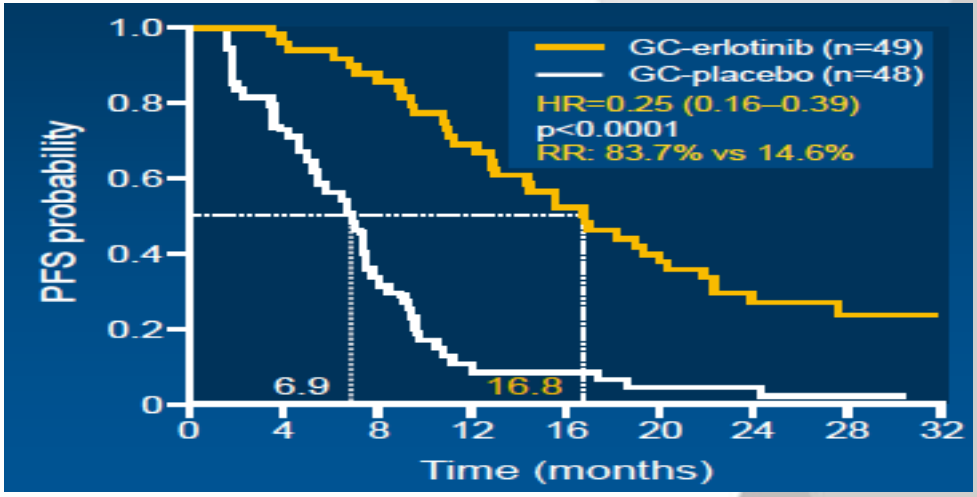


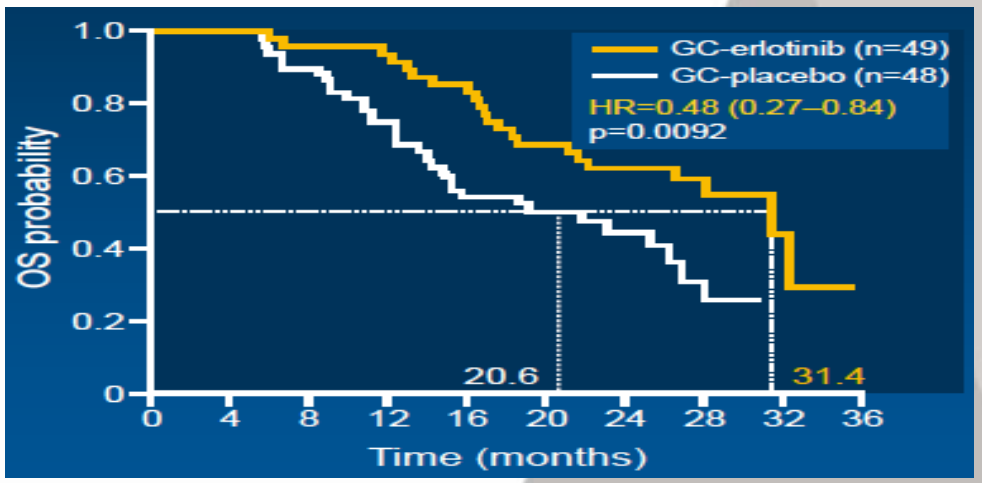


Wu – Lancet Oncol 2013

Integration of EGFR inhibitors and chemotherapy in NSCLC: Intercalated







Wu – Lancet Oncol 2013

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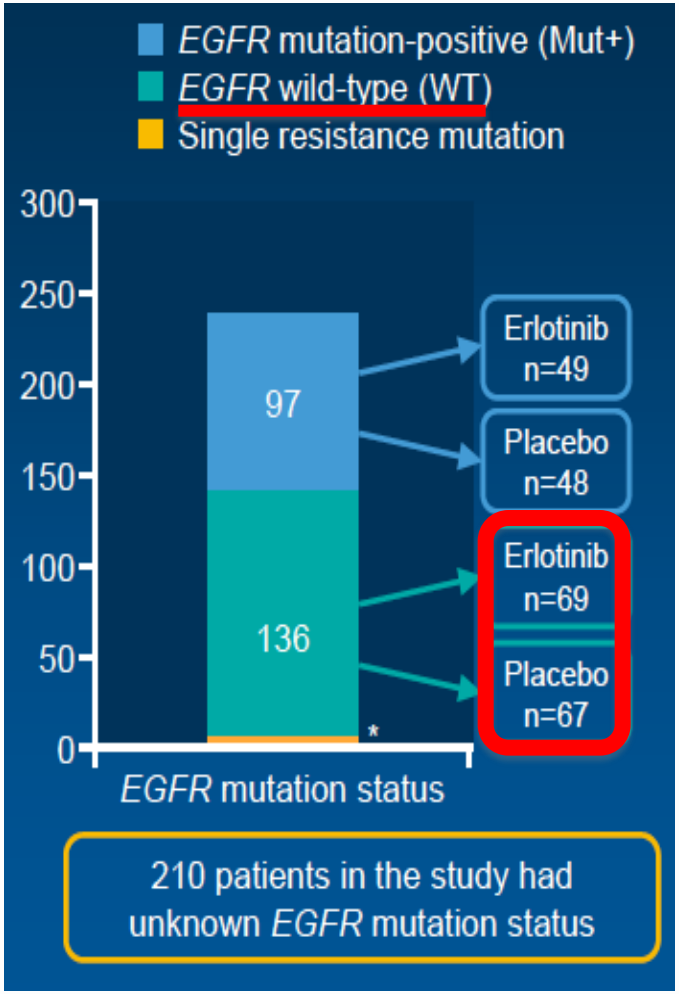
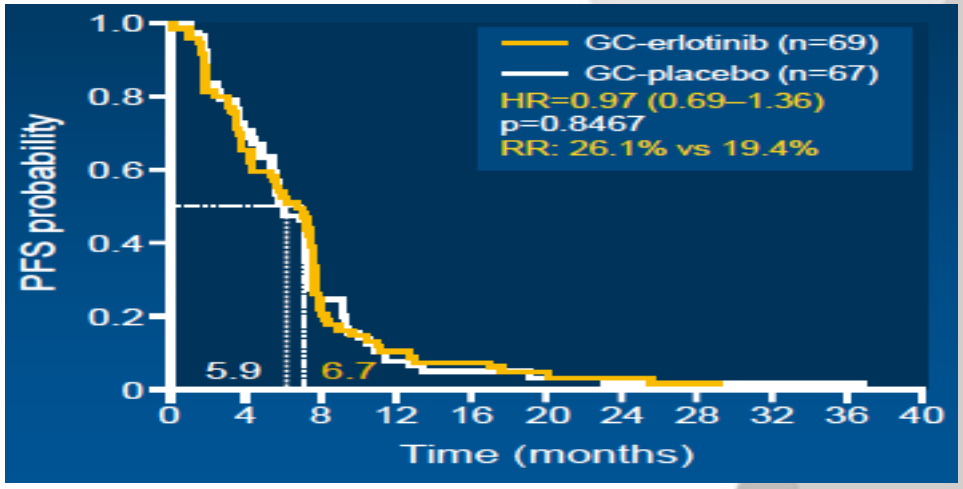
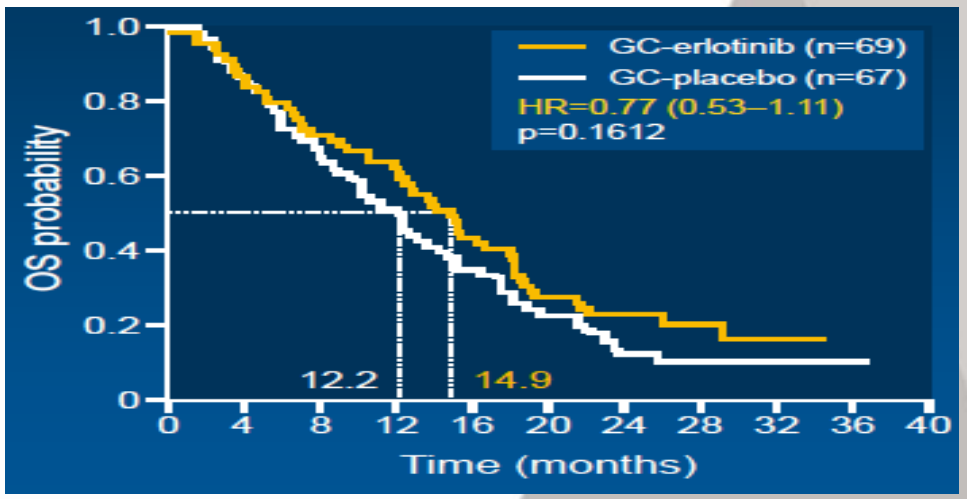
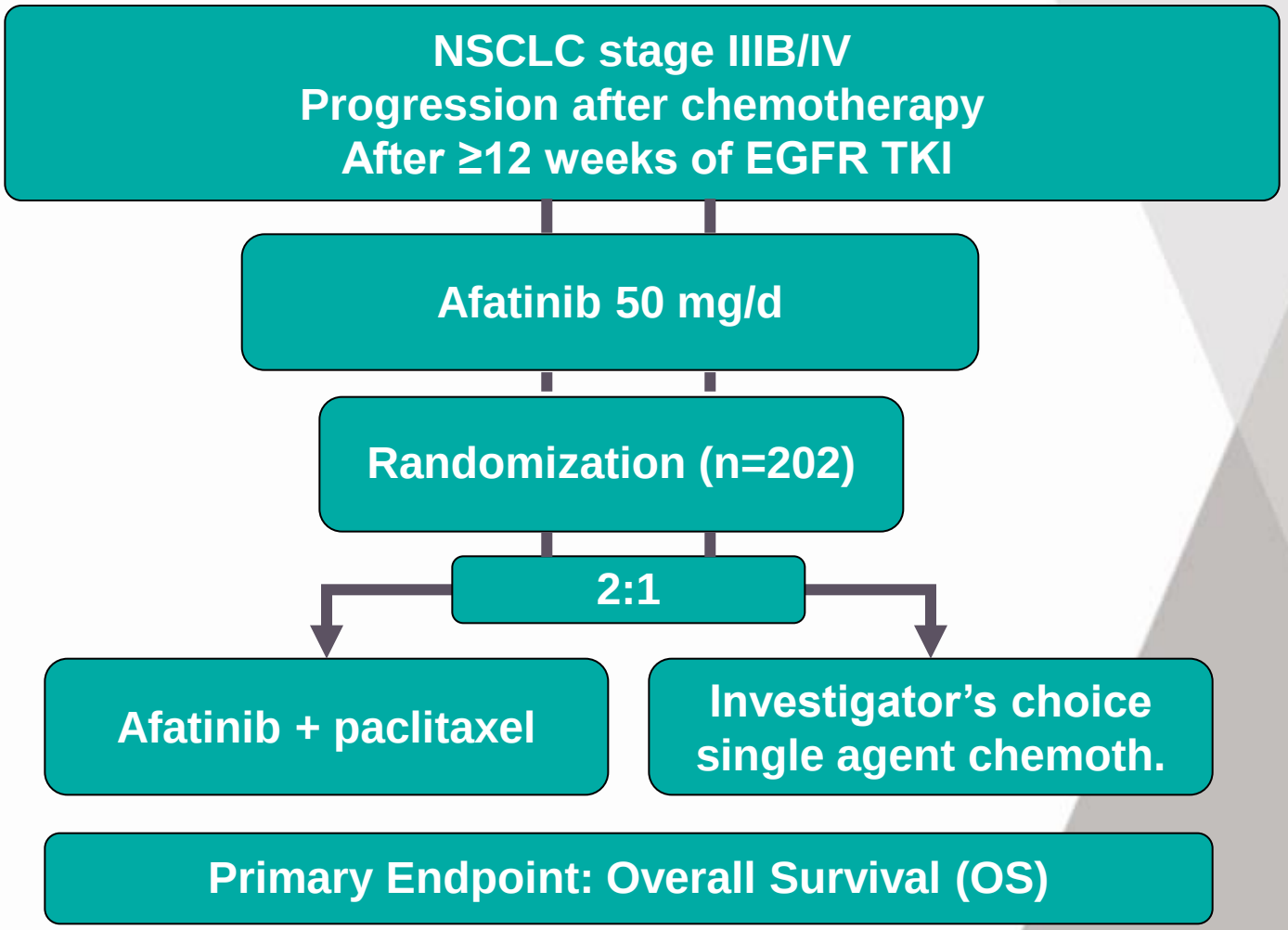






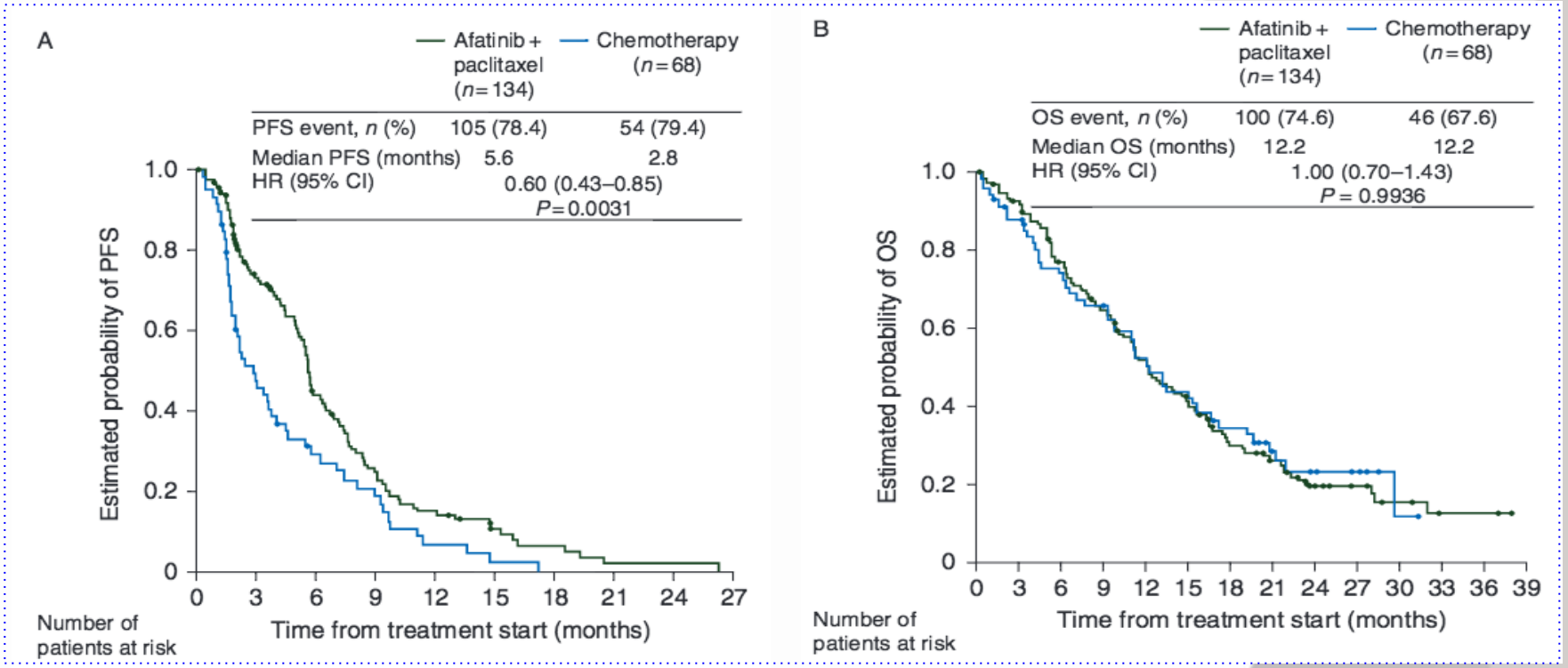
Wu – Lancet Oncol 2013

Lux-Lung 5



Schuler- Ann Oncol 2016

LUX-Lung 5

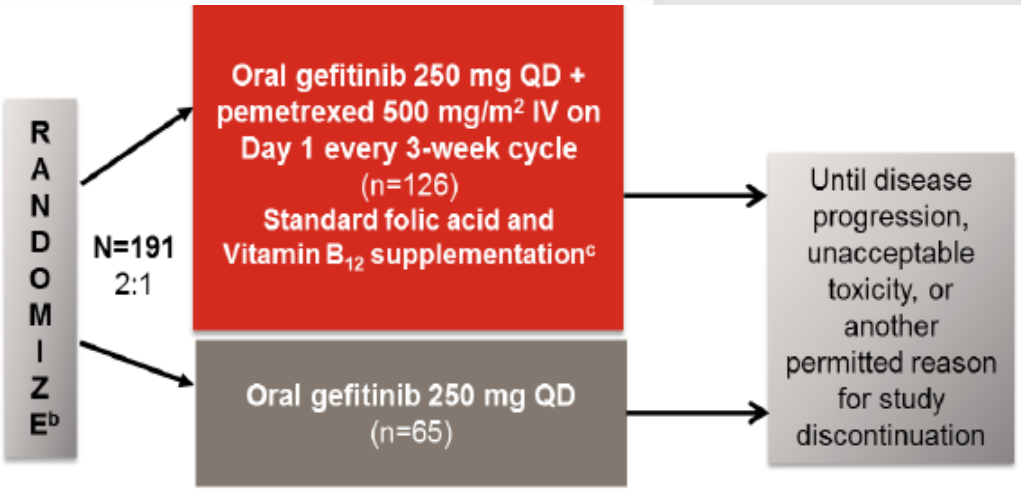


Afatinib plus paclitaxel improved PFS and OR
But not OS

Gefitinib +/- Pemetrexed *EGFR*m

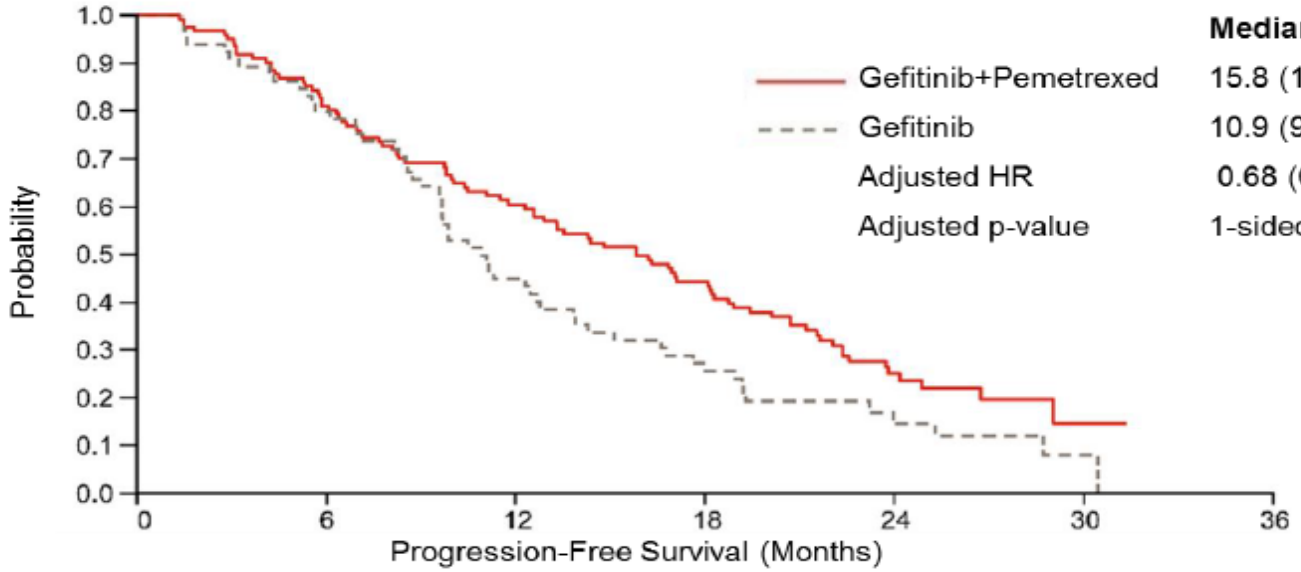
Inclusion Criteria:

- Adult patients ≥18 years (≥20 years in Japan and Taiwan)
- Confirmed advanced (Stage IV) or recurrent NS NSCLC[a]
- Activating EGFR mutations
- ECOG PS ≤1
- No prior systemic chemotherapy, immunotherapy, or biological therapy



- **Enrollment period:** February 2012 – August 2013
- **Data cut-off date:** 22 April 2015

Primary Endpoint: PFS
Key Secondary Endpoints[d]: Overall survival (OS), Overall response, Disease control rate (DCR), Duration of response (DoR), Quality of life (QoL), Safety



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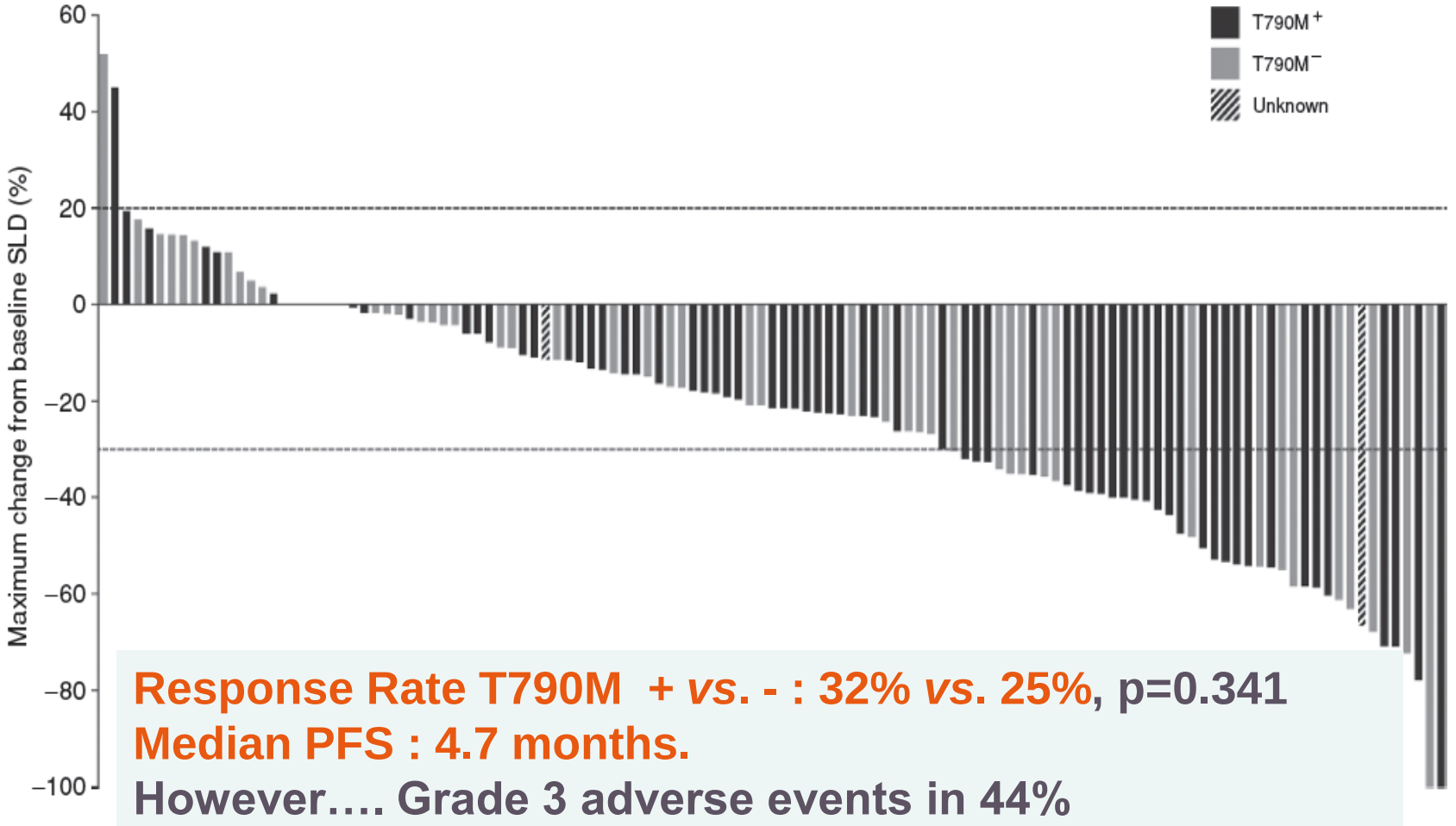
  1) Chemotherapy
  2) Other EGFR inhibitors
  3) Immunotherapy
- One patient, one disease:
  Personalised Medecine is not dead

Cetuximab + Afatinib

N=126 pre-treated Gefinib / Erlotinib advanced *EGFR*-mutant NSCLC patients



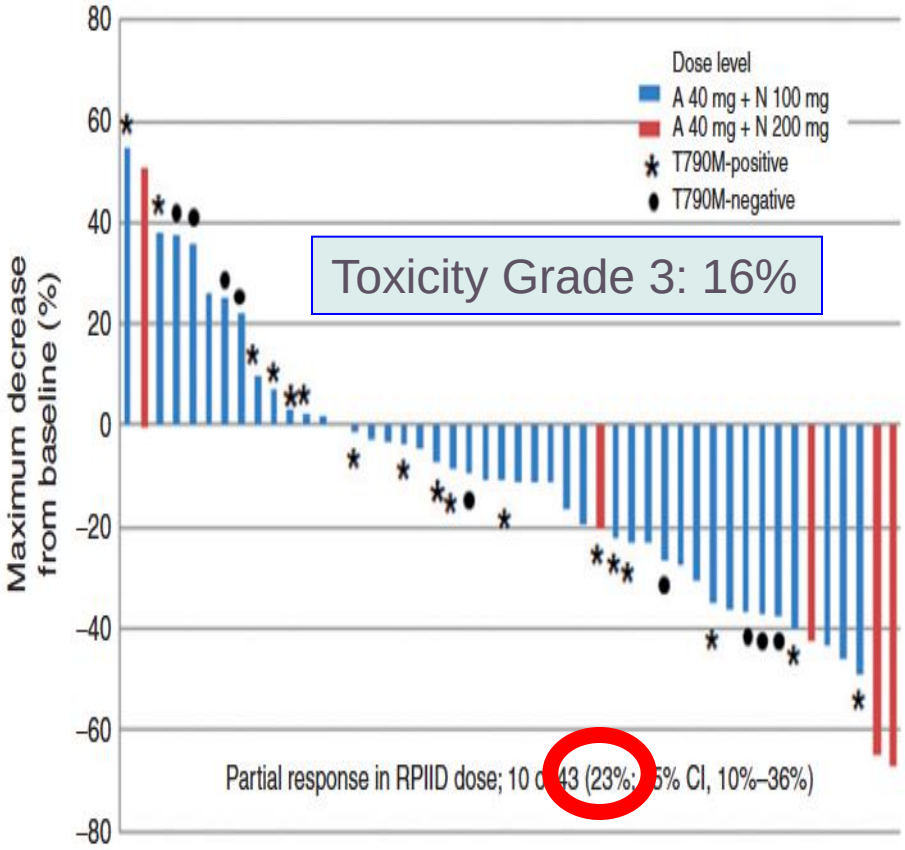
Response Rate T790M + *vs*. - : 32% *vs*. 25%, p=0.341

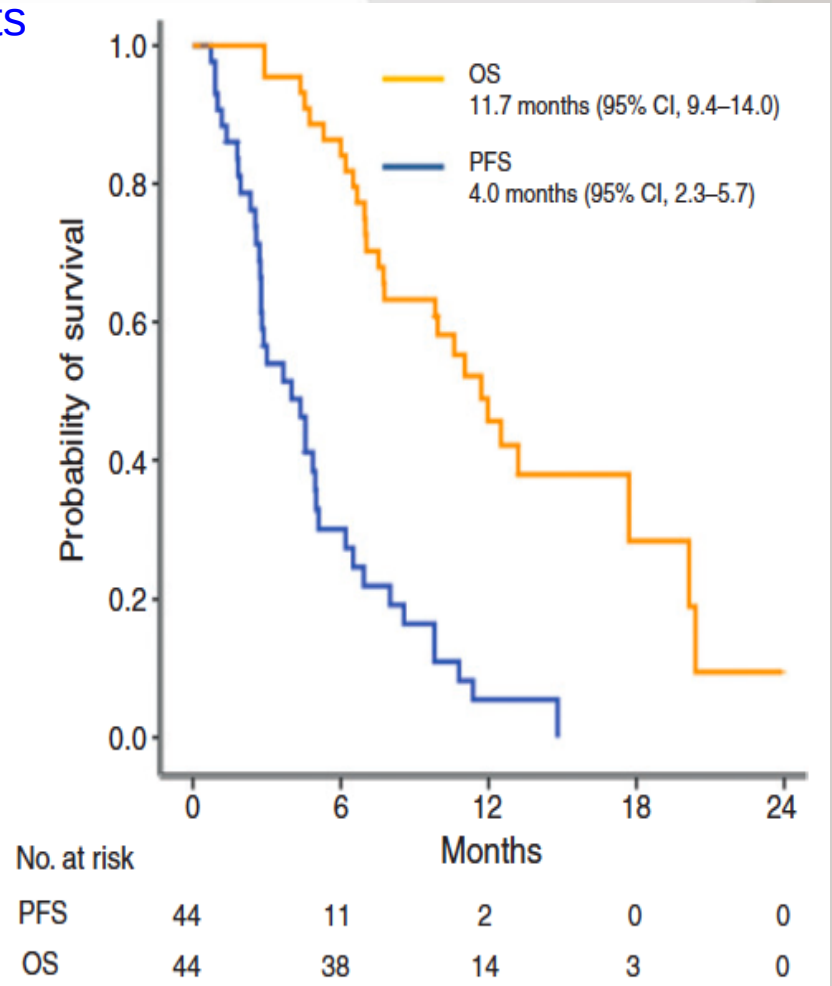
Median PFS : 4.7 months.

However…. Grade 3 adverse events in 44%

Nimotuzumab + Afatinib

50 pretreated *EGFR* mutant NSCLC patients





no differences in RR (p=0.628) or PFS (p=0.720) according the T790M status

Lee CCR 2015

Outline

- **Why should we maintain EGFR inhibition?**
- **‘NGI’ Next Generation EGFR Inhibitors**
- **Keep EGFR inhibition, and…Add…**
  - **1) Chemotherapy**
  - **2) Other EGFR inhibitors**
  - **3) Immunotherapy ?**
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  Personalised Medecine is not dead

Pembrolizumab

	TPS ≥50%		TPS 1-49%		TPS <1%		Total[a]	
	n	ORR, % (95% CI)	n	ORR, % (95% CI)	n	ORR, % (95% CI)	N	ORR, % (95% CI)
Overall	144	38.2 (30.2-46.7)	185	11.9 (7.6-17.4)	80	10.0 (4.4-18.8)	550	20.2 (16.9-23.8)
EGFR wild type	113	39.8 (30.7-49.5)	156	12.2 (7.5-18.4)	63	12.7 (5.6-23.5)	450	21.6 (17.8-25.6)
EGFR mutant	20	20.0 (5.7-43.7)	23	8.7 (1.1-28.0)	14	0.0 (0.0-23.2)	77	7.8 (2.9-16.2)
KRAS wild type	51	29.4 (17.5-43.8)	85	12.9 (6.6-22.0)	40	7.5 (1.6-20.4)	238	16.4 (11.9-21.7)
KRAS mutant	26	30.8 (14.3-51.8)	24	0.0 (0.0-14.2)	11	18.2 (2.3-51.8)	87	17.2 (10.0-26.8)

[a]Includes patients for whom a PD-L1 TPS could not be assigned (n = 141). Data are not shown for patients with unknown *EGFR* (n = 23) or *KRAS* (n = 225) status.
Data cutoff date: January 23, 2015.

M.D. Hellmann
Presented at WCLC 2015

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Conclusion

- Mechanisms of resistance to TKI are heterogenic and dynamic
- ctDNA has to be used as a ‘liquid biopsy’

Conclusion

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- Keep the pressure…
  …. As much as you can
- ctDNA and ‘liquid biopsy’
- NexGen TKIs…
  Which sequence?

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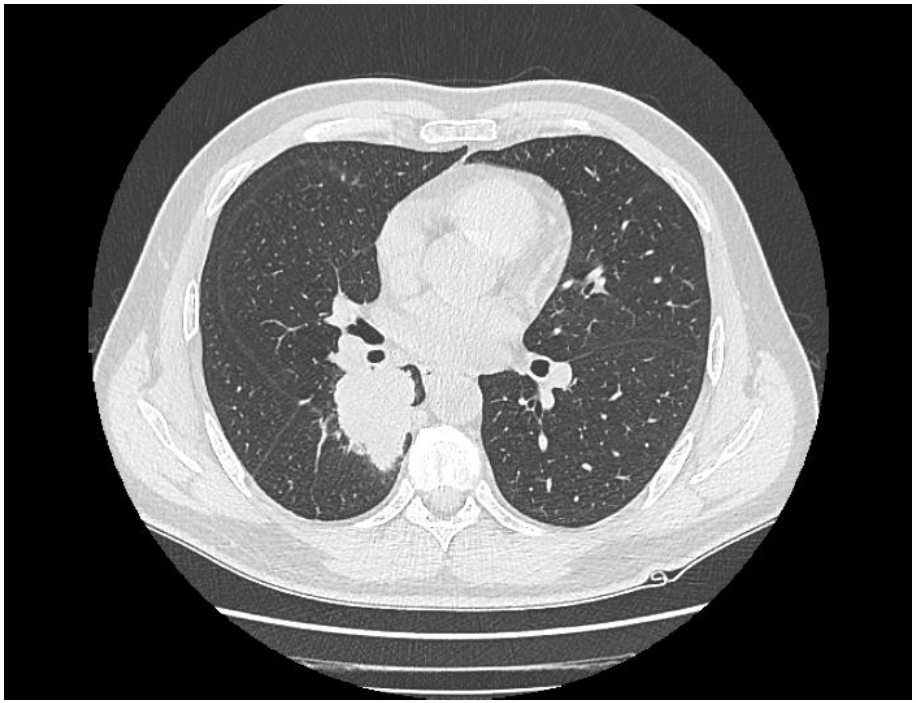
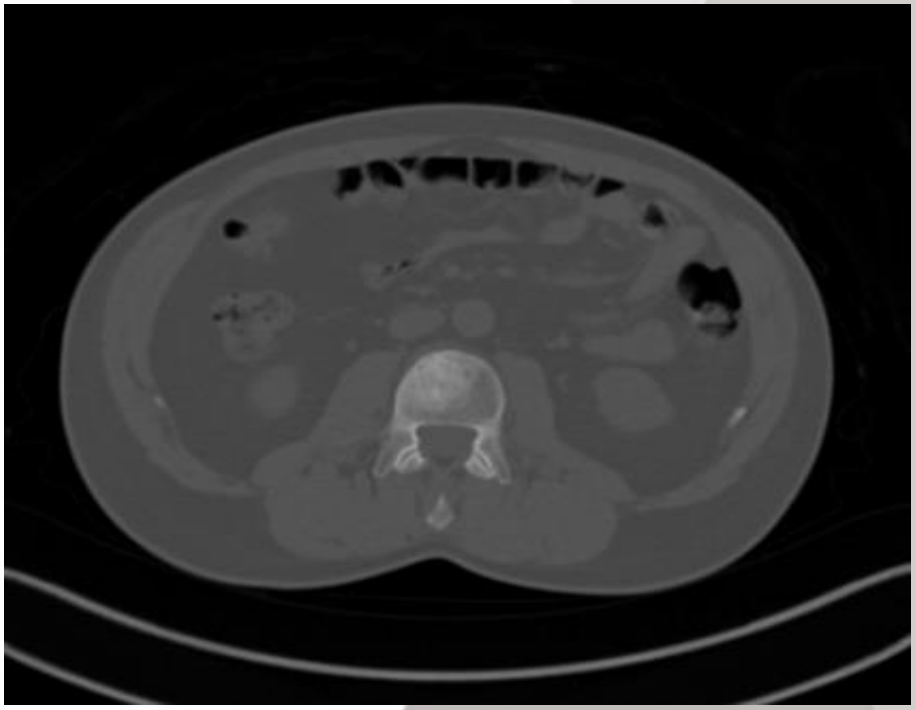
Conclusion

- Mechanisms of resistance to TKI are heterogenic and dynamic
- Keep the pressure…
  …. As much as you can
- Chemotherapy works
- Immunotherapy is there
- “PD” is heteregeneous
- ctDNA and ‘liquid biopsy’
- NexGen TKIs…
  Which sequence?
- Mostly alone
- Combos are tricky
- Local and systemic treatment must be used and sequenced

Clinical Case

- Male. 51 years old. Never-smoker.
- No comorbidities
- 05/2013: Adenocarcinoma right lower lobe (TTF1+)

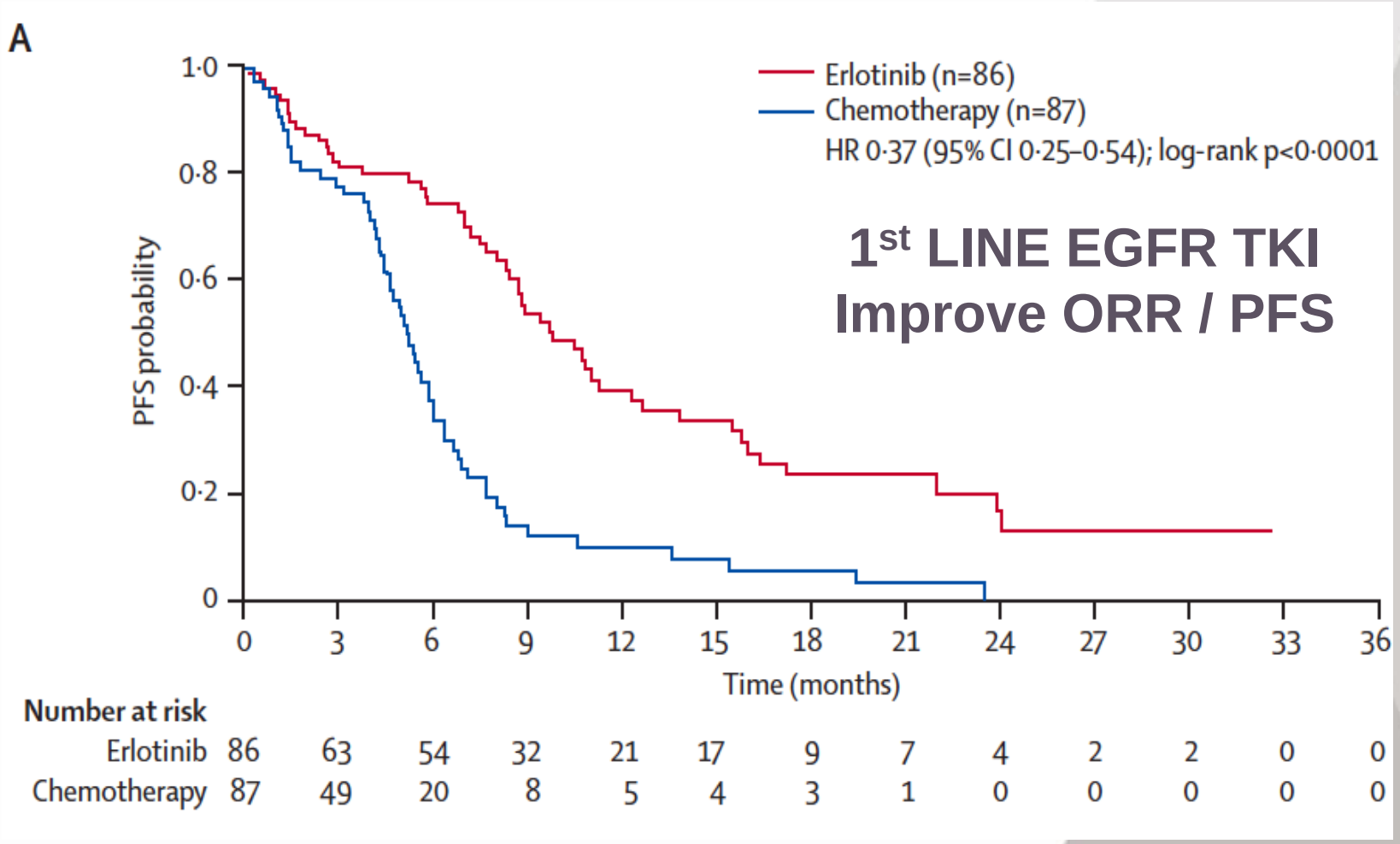




Clinical Case

- **Brain RMI normal. PETscan: oligometastatic in L3.**
- **cT2a N0 M1b (single L3, proven)**
- **Molecular status: Del exon 19 *EGFR* (activating mutation)**
- **21.06.2013: Erlotinib (TARCEVA) 150 mg/d orally**
- **RT L3 (30 Gy. in 10 fractions: 1 to 12.07.2013)**

Clinical Case

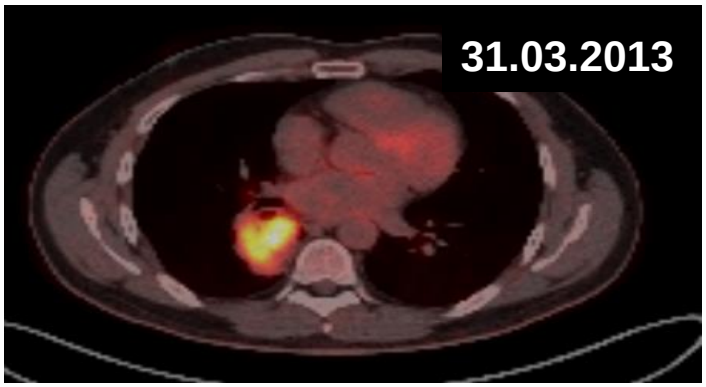


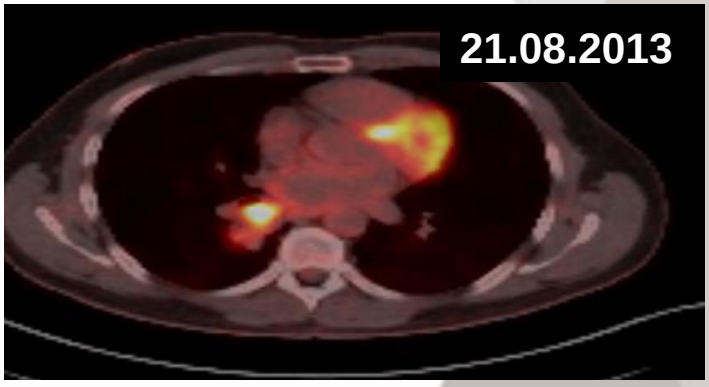
1st LINE EGFR TKI
Improve ORR / PFS

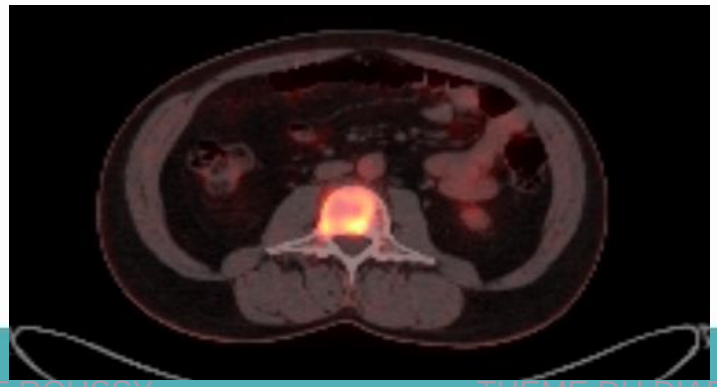
Rosell – Lancet Oncol 2012

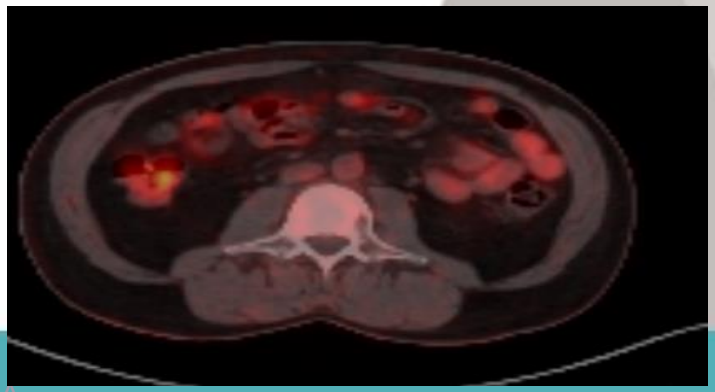
Clinical case

- **PET scan 21.08.2013 (2 months on erlotinib)**
  - L3 negative
  - Metabolic and radiologic PR on lung
- **Local treatment on lung ?? (Surgery, RT…)**



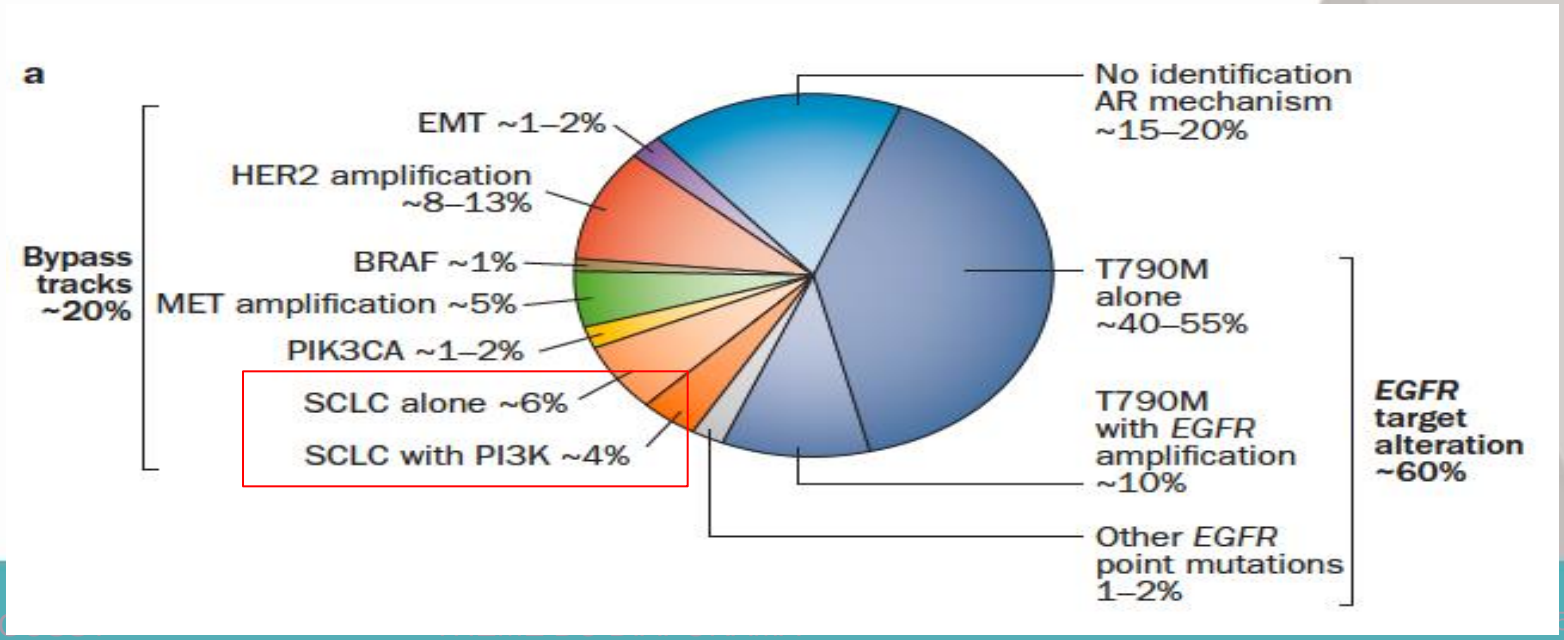






Clinical Case

- **Pre operative work-up**
- **EBUS 17.09.2013:** complete obstruction in right lower lobe.
  - Biopsy: **SMALL-CELL CARCINOMA (SCLC)**
  - Molecular profile: ***Del19 EGFR* mutation**. *KRAS*, *PIK3CA*, *BRAF*, *HER2* mutation negative. MET / HER2 amplification negatives. Mutation TP53 and mutation APC.



Clinical Case

- **Stop Erlotinib (Tarceva) 19.09.2013**
- **Curative treatment of localized SCLC**
- **RT-CT: PAVEP x 5 (last 2 cycles: Platin / VP16) + RT** (Hematologic toxicity grade 4). CT: 21.09.13 to 14.02.2014

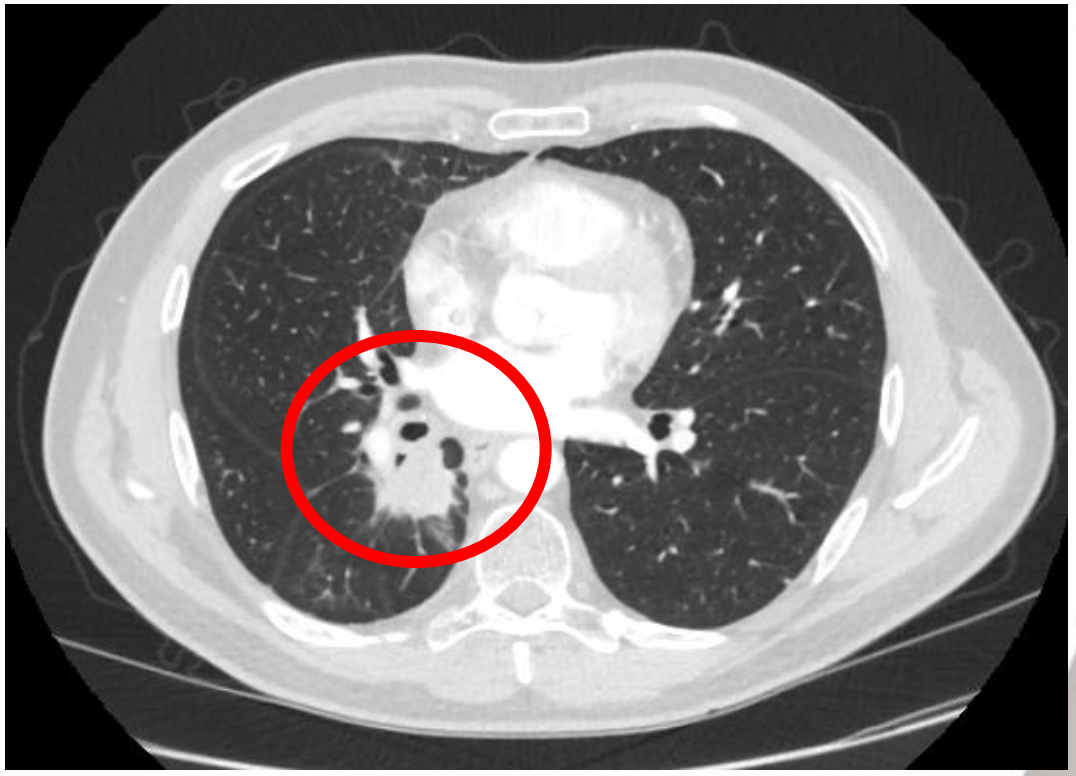
CT1---CT2-RT-CT2-RT-CT2-RT-CT2---CT2

	Higher Initial Dose	Lower Initial Dose
Cyclophosphamide	300 mg/m^2, days 2–5	225 mg/m^2, days 2–5
Cisplatin	100 mg/m^2, day 2	80 mg/m^2, day 2
Doxorubicin	40 mg/m^2, day 1	40 mg/m^2, day 2
Etoposide	75 mg/m^2, days 1–3	75 mg/m^2, days 1–3

Figure 1. Design of a Trial of Higher and Lower Initial Doses of Chemotherapeutic Drugs in Patients with Small-Cell Lung Cancer.

Clinical case

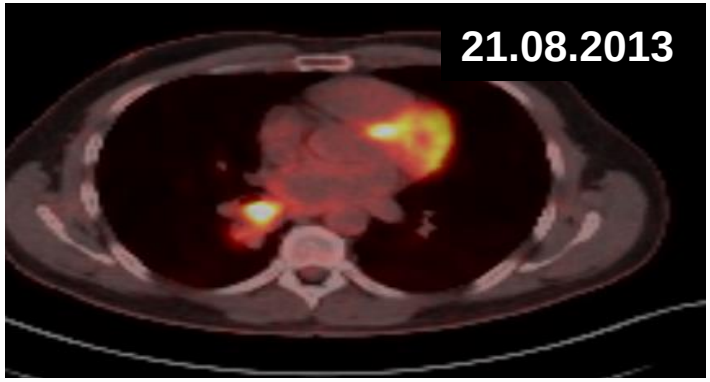
- **TAC 25.02.14:** Stable disease.
- **Brain MRI:** normal

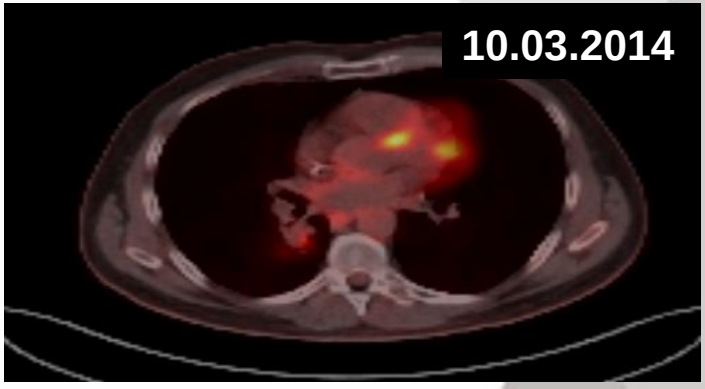


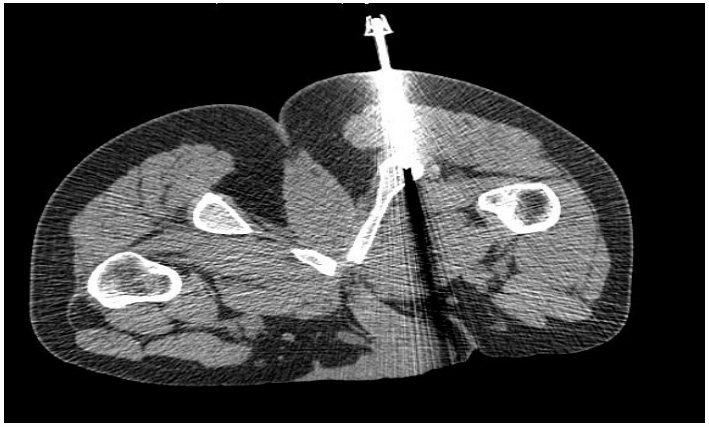
- Local therapy in residual mass? What should we perform?

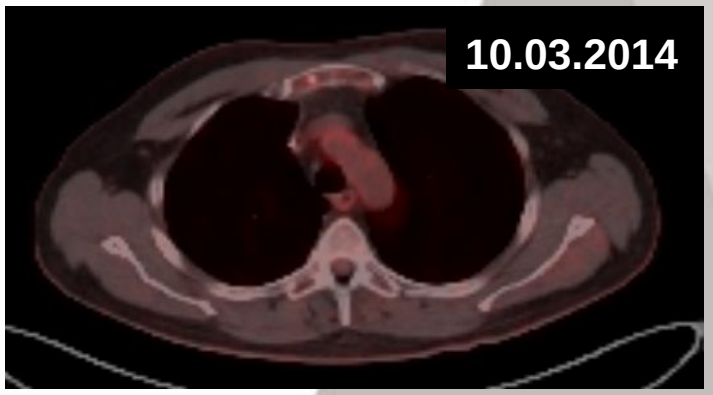
Clinical Case

- **PET scan 10.03.2014:** residual uptake in the lung (RT? NSCLC? SCLC?). New pelvic bone lesion (5 mm, blastic lesion) and sternal lesion.









Clinical Case

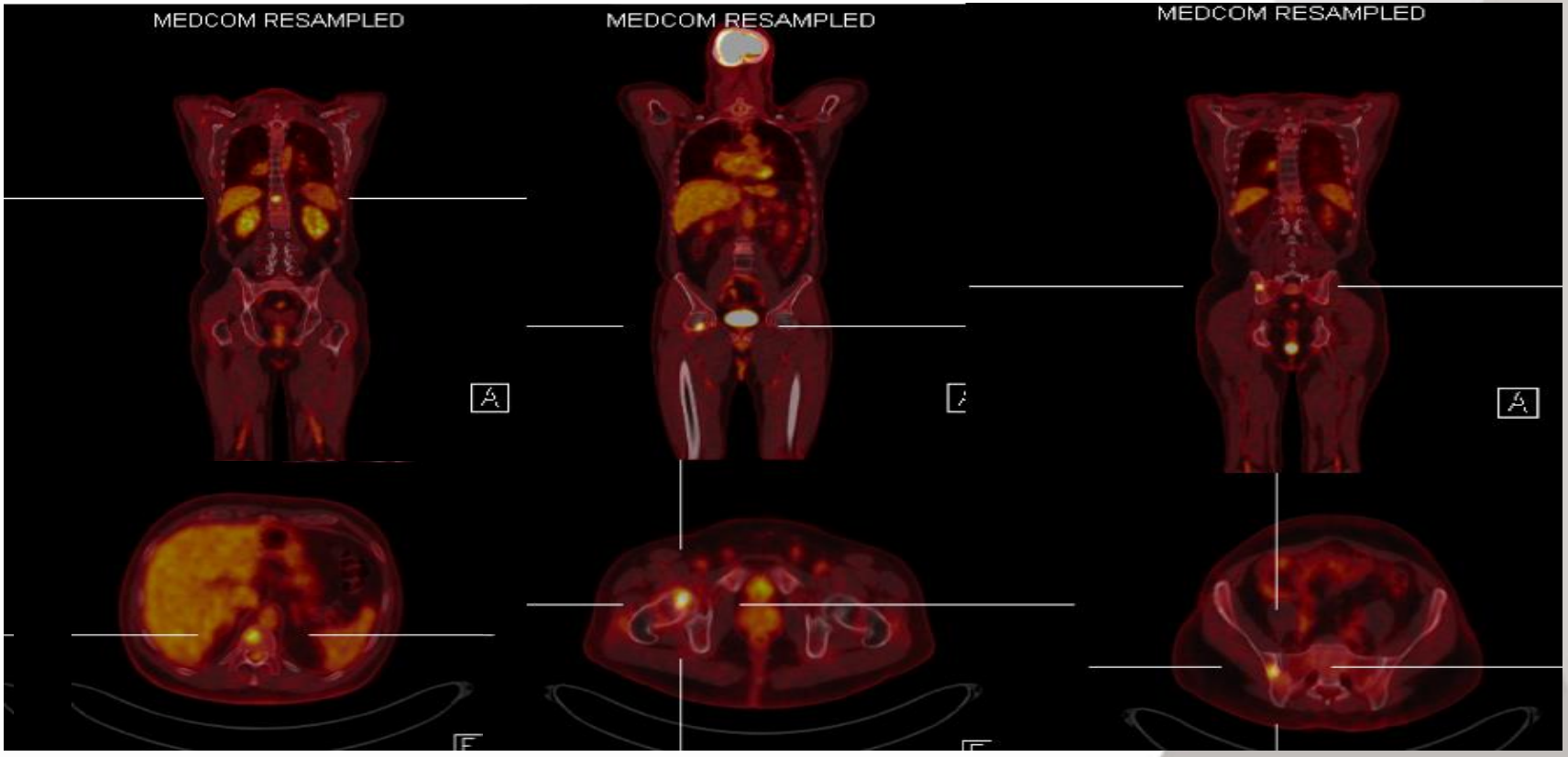
- **Pelvic Bone biopsy 03.04.2014:** necrosis.

- PET scan 22.04.2014:
  - New and diffuse bone blastic lesions (>10)
  - No PD in the lung

- **Erlotinib (Tarceva) 22.04.2014**
- **PET 28.11.2014: Metabolic complete response**

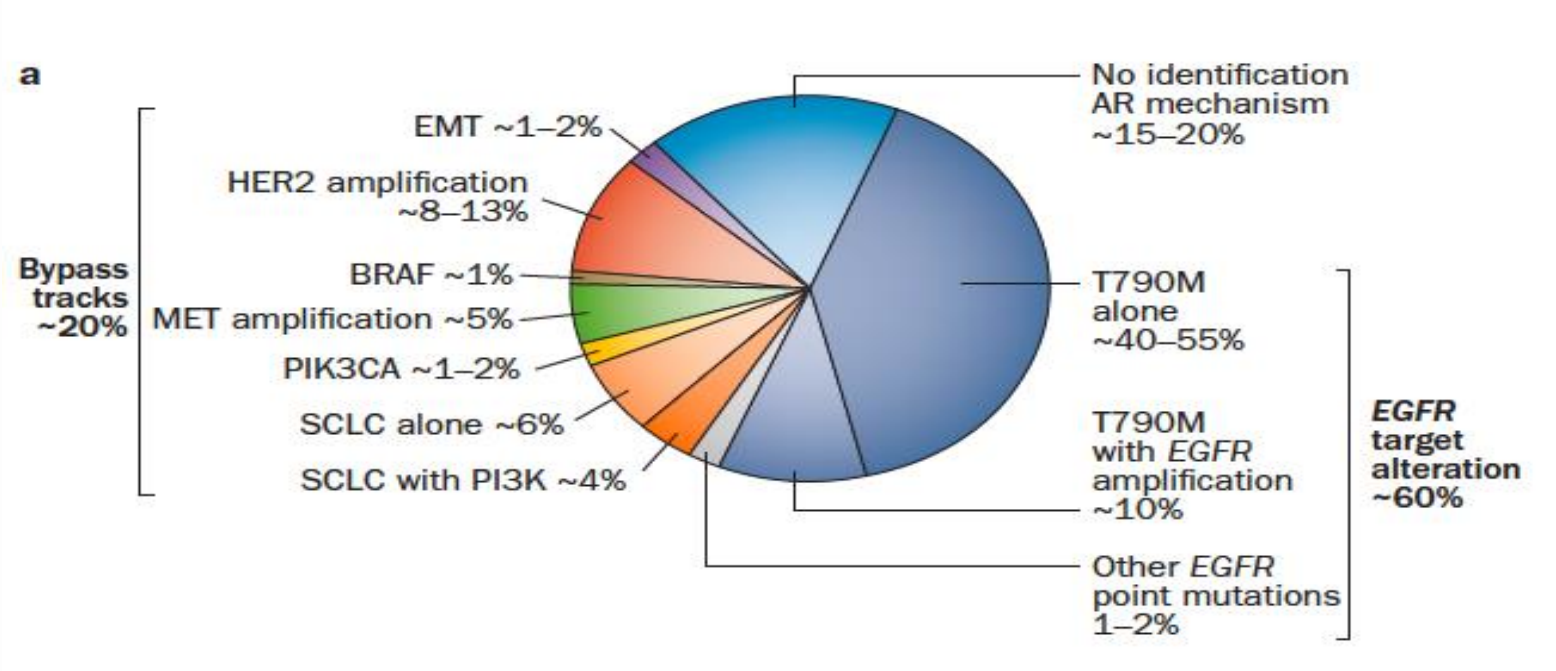
Clinical case

- **After 11 months on erlotinib…….**
- **PET 31.03.2015: New bone lesions** (pelvis, femur, T11)



Clinical Case

- Progression disease after 11 months on EGFT TKI
- Which is the mechanism of acquired resistance?



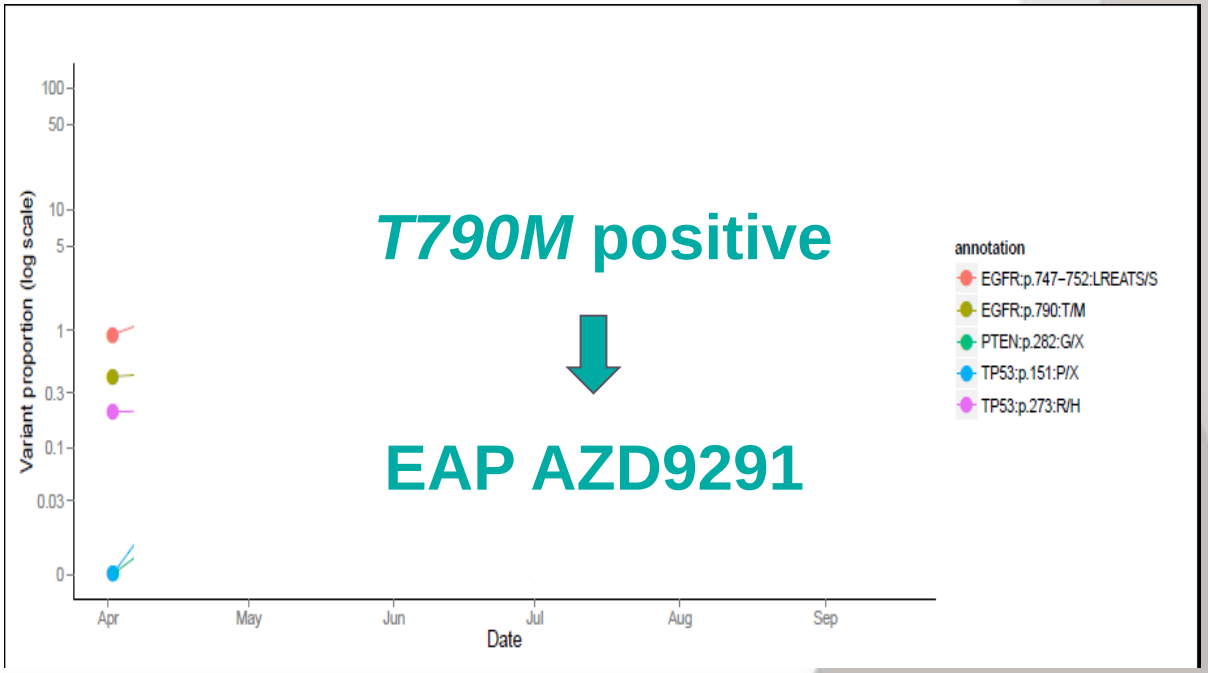
- Not possible to perform a new biopsy…..

Clinical Case

- **Liquid biopsy (tumor circulating DNA) 04.04.15**
- **Patient asymptomatic, then erlotinib was not stopped**

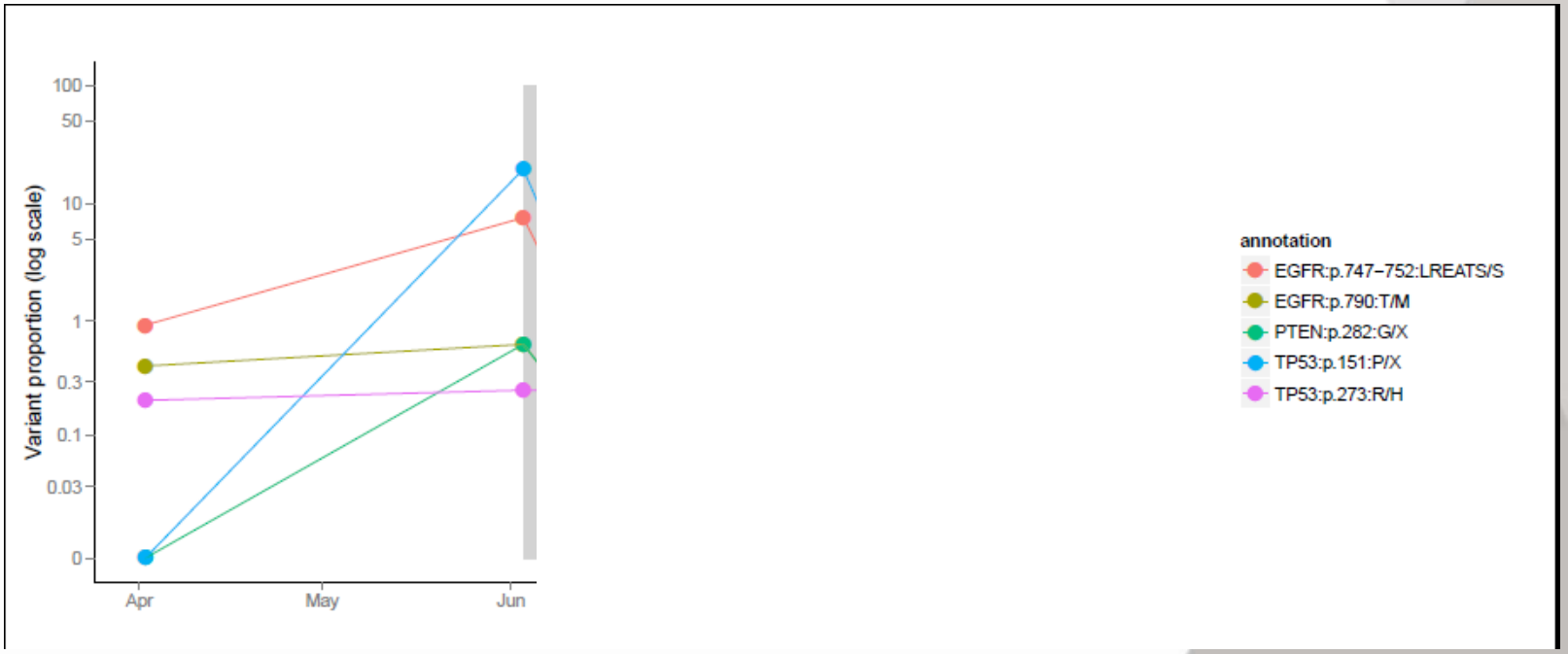
Clinical Case

- **Liquid biopsy (Tumor DNA circulating) 04.04.15**
- **…..Results obtained one month later**
  - *EGFR* mutation in exon 19 (sensitive mutation)
  - *EGFR mutation T790M* mutation (resistance mutation)
  - *PTEN* mutation



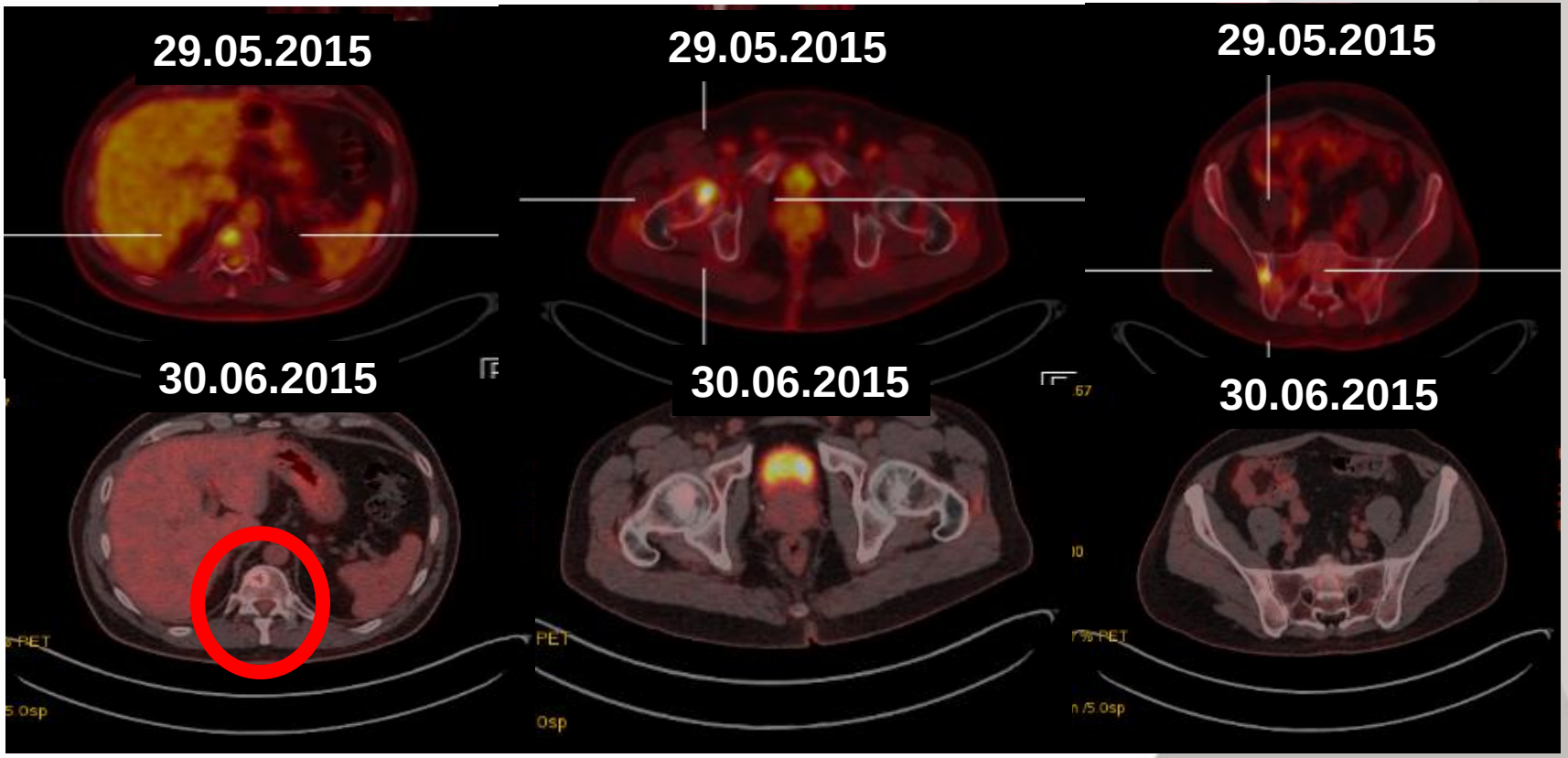
Clinical Case

- **EAP AZD9291 80 mg/d, started on 03.06.2015**
- **New “basal” liquid biopsy performed before AZD9291**
  - *Del19 EGFR* mutation, *T790M* mutation, *PTEN* mutation, 2 mutations de TP53



Clinical Case

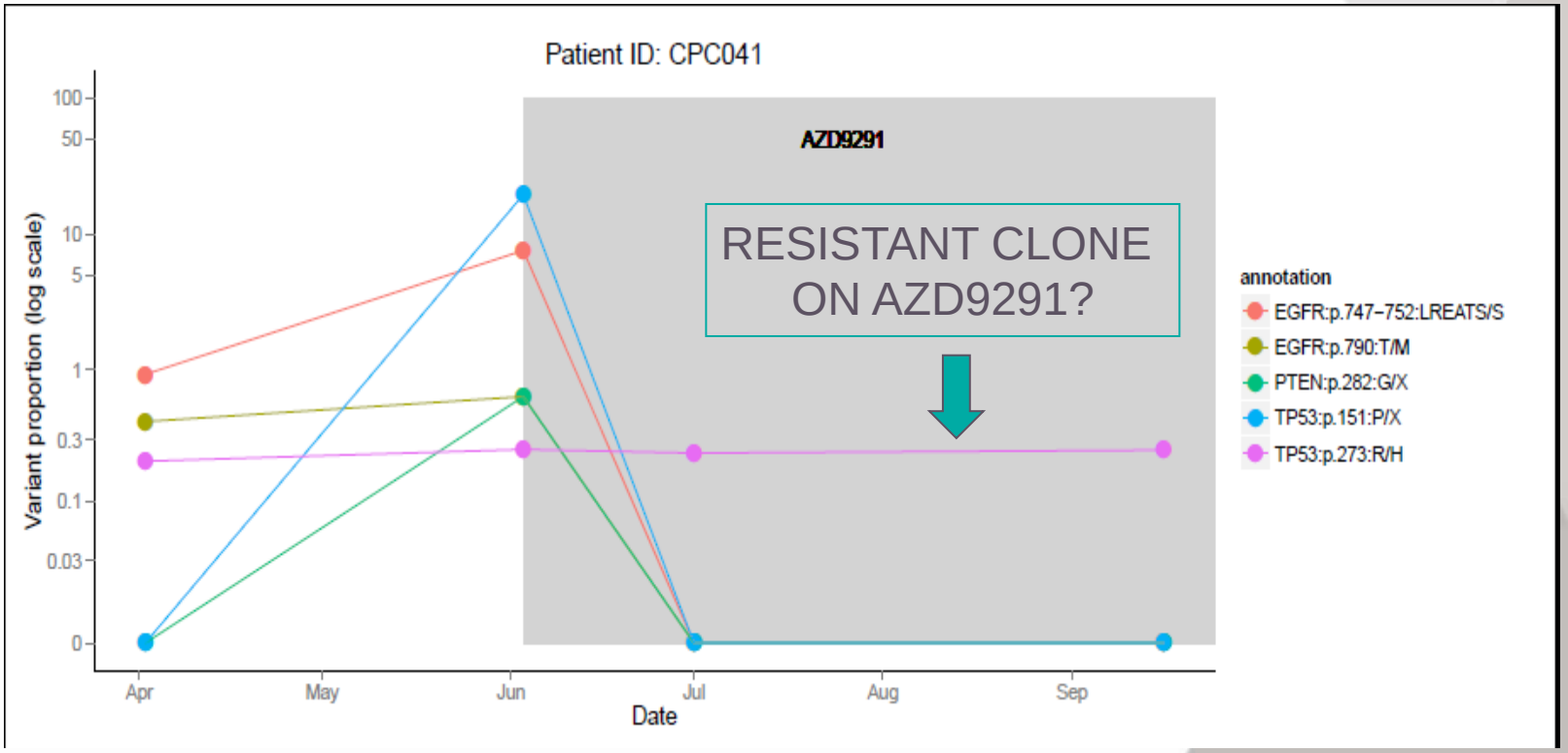
- 1 month on AZD9291, PET 30.06.2015
- CR in all lesions but T11



Clinical Case

- **Liquid biopsy 1 month after AZD9291 on 01.07.2015**

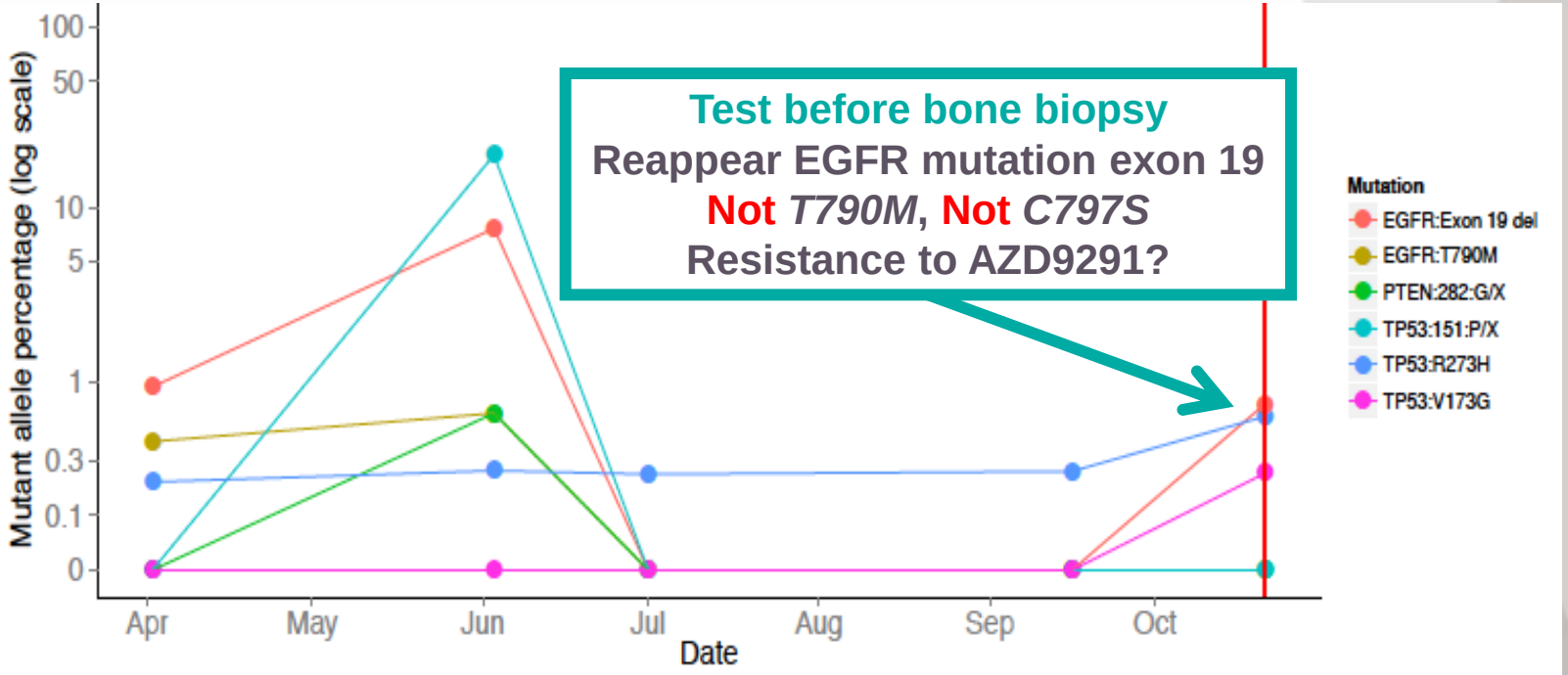
→ Surrogate marker of response



Clinical Case

After 3 months on AZD9291

- **PET 15.09.15: increase uptake in T11**
- **03.11.2015: Biopsy + cryotherapy + cymentoplasty**
  - Biopsy: Poorly differentiated adenocarcinoma. CK7+, TTF1+



- **Best treatment at this time: increase AZD9291 dose? Grapefruit? AZD9291+erlotinib? CT? immunotherapy?**