THE PLACE OF EGFR *TKI* IN ADVANCED NSCLC

Nick Thatcher, Christie Hospital, Manchester, England

3rd TOPIC
EGFR TESTING

A) IHC testing only in non-squamous only?

B) Mutation testing in non-squamous only?

1st TOPIC
BRAIN METASTASES (BM)

A) Is there a place for EGFR-TKI in the treatment of BM ?

B) Should we treat 1st with RT (to break BBB) or just with RT?

C) What to do if only progression in the brain but not elsewhere?

D) is it safe to give RT and tki together?

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Recommendation 3: patients with symptomatic brain metastases may be considered for treatment with an EGFR TKI.
Strength of recommendation: B
Level of evidence: V

Felip et al 1st ESMO consensus Ann Oncol 2011

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ?

Mitsudomi et al Lancet Oncology 2011

B) Any difference between the tkis ?

Hata et al Lung Cancer 2011

Maintenance or wait and then 2nd line?

Is there a role for TKI in EGFR wt?

Garassino et al J Clin Oncol 2011

C) Which pathways are responsible for TKI resistance ?

What to do if PD during TKI continue or stop?

Oxnard et al Clin Cancer Res 2011

BRAIN METASTASES (BM)

- BBB does not prevent metastatic cells entering brain

If BM < 0,25 mm – BBB is intact

If BM > 0,25 mm – BBB becomes leaky *Fidler, Lancet Oncol 2002*

Incidence about 30% but increasing –better imaging and longer survival with systemic treatment . DCR ≥90 days with TKI - 26% CNS failure rate vs 4% if no DCR

EGFR mut +ve may predispose to BM ; Mut +ve 64% vs 31% in patients with and without BM *Lee Cancer 2010 ;Lee et al ASCO 2011 Abs 18065*

Med Surv 4-11 weeks untreated or 4-6 months treated
Mehta et al JNeuro Onco 2011; Jamal-Hanjani Clin. Cancer Res. 2011

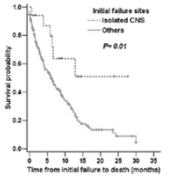
- **Oligometastatic BM** surgery or SRS+WBRT ↑local control ? ↑ OS vs. WBRT alone *ESMO Clinical practice guidelines D`Addario et al Ann Oncol 2010 Jamal-Hanjani Clin. Cancer Res. 2011*

CNS MET FREQUENT SITE OF FAILURE AFTER EGFR TKI THERAPY

Table 2. Pattern of Failure

Progression Site	Clinical Benefit* (n=127) No. (%)	Nonclinical Benefit (n=105) No. (%)	Total (n=232) No. (%)
Any CNS	33 (26)	4 (4)	37 (16)
CNS only	16 (13)	1 (1)	17 (7)
CNS plus other sites	17 (13)	3 (3)	20 (9)
Others	19 (15)	30 (28)	49 (21)

CNS indicates central nervous system.
*Patients with a clinical benefit to epidermal growth factor receptor tyrosine kinase inhibitor.



- Higher incidence of CNS failure as an initial progression in patients who had a clinical benefit from EGFR TKI
- Isolated CNS failure was also more frequent in the clinical benefit group
- However, patients with isolated CNS failure had longer OS from initial failure to death, compared with those with other site failures (12.9 months vs 6.0 months; p=0.01)

Lee, et al. Cancer 2010

BRAIN METASTASES TKIS RCTS

- SAKK 70/03 phase II WBRT 30 Gy + gefitinib or temozolamide trial closed; MS Gef 6.3 months Tmz 4.9 months

Pesce et al Eur J Cancer 2012

- TACTIC (WBRT +/- erlotinib). Closed endpoint not reached (after 2 months, ≥ 20 patients are alive and neurological progression-free on the Tarceva arm)
- But 1st line Mut +ve trials included patients with controlled brain metastases

Zhou et al Lancet Oncol 2011
Rosell et al. ASCO 2011abstr 7503

EGFR TKI CNS PENETRATION

TABLE 3. Cerebrospinal Fluid Concentrations of Erlotinib and OSI-420 on Day 8, Tumor Response, and Change of PS

Case	Erlotinib C_{ss} (ng/ml)	Erlotinib C_{plasma} (%)	OSI-420 C_{ss} (ng/ml)	OSI-420 C_{plasma} (%)	Tumor Response	Change of PS
1	42	4.7	4.7	8.1	Partial response	3 → 2
2	87	5.0	22.3	9.3	Stable disease	4 → 3
3	67	3.2	11.1	1.5	Partial response	3 → 2
4	18	7.7	3	4.4	Stable disease	3 → 3
Mean ± SD	54 ± 30	5.1 ± 1.9	10.8 ± 8.2	5.8 ± 3.6		

administration of erlotinib; PS, performance status.

- At standard dosing (150mg/daily), erlotinib levels in CSF high enough to inhibit WT disease
  - erlotinib penetration rate to CSF was approximately 5% and erlotinib concentration exceeded the IC_{50} of erlotinib in intact tumour cells with WT *EGFR* gene (20 nmol/l; 7.9 ng/ml)[1]
- In contrast, the gefitinib penetration rate to CSF was reported to be less than 1%, and gefitinib CSF concentration did not exceed the IC_{50} of gefitinib when 250 mg gefitinib was administered daily[2,3]

1. Togashi, et al. JTO 2010; 2. Fukuhara, et al. Tohoku J Exp Med 2008
3. Wu, et al. Lung Cancer 2007

ACTIVITY of EGFR TKI in BM

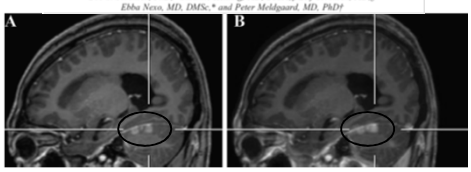
Jamal-Hanjani Clin. Cancer Res. 2011

Study	Treat	Selection	Pat No.	RR%	Survival months
Ceresoli	G	Europe	41	27	PFS 3
Wu	G	EA Adeno	40	32	PFS 9
Porta	E	M +ve	17	82	PFS 11.7 OS 12.9
Kim	G/E	M +ve	23	70	PFS 6.6 OS 19.8
Wu	G	M +ve	110	89	
Wu	E	M +ve or Adeno	48	56 intra + extracranial	PFS +ve 2 3.2 wt 8.2
Kim	G/E	EA Non Smoker	23	74	PFS 7.1 OS 18.8

EGFR TKI CNS PENETRATION

Erlotinib Accumulation in Brain Metastases from Non-small Cell Lung Cancer: Visualization by Positron Emission Tomography in a Patient Harboring a Mutation in the Epidermal Growth Factor Receptor

Britta Weber, MD,† Michael Winterdahl, MMSc,‡ Ashfaque Memon, MD, PhD,* Boe S. Sorensen, PhD,* Susanne Kosding, MD, DMSc,‡ Leif Sorensen, MD,§ Ebba Nexo, MD, DMSc,* and Peter Meldgaard, MD, PhD†*



- Erlotinib accumulates in *EGFR* mut+ CNS met lesions, but absent from normal brain tissue

Weber et al. J Thor Oncol 2011

IS ERLOTINIB EFFECTIVE FOR BM?

- Erlotinib has shown to be effective in case reports, case series and phase II trial .Higher RR in BM in Mut +ve, but also effective in wt EGFR

Erlotinib can be effective for BM even after gefitinib failure (penetration rate in CSF higher) *Togashi, J Thor Oncol 2010,5*
Jamal-Hanjani Clin. Cancer Res. 2011

- T790M mutation is associated with multiple metastatic sites but not always with BM . Isolated CNS failure may not have acquired resistance T790 , may respond to reinduction of erlotinib

Jackman et al J Clin Oncol 2006;2010; Balak et al Clin Cancer Res 2006 ; Ruppert et al, Eur Resp J 2009

- Patients with BM without pre-treatment T790M outcome similar to other Mut+ve lung cancers with extra cranial metastases

Moran et al. J Clin Oncol ASCO 2011 abstr 7590

WHAT IF PROGRESSION OF BM?

Sensitivity may remain but need ↑ dose or switch to erlotinib

- •TKI dose escalation: erlotinib 300mg alt die

  CNS response despite prior gefitinib ,CT,WBRTand 150mg erlotinib *Hata et al J Thor Oncol 2011*

- •EGFR mut +ve: erlotinib pulsed weekly 1500 mg despite previous 150 mg dose 9 patients: CNS RR 67% MS 12 months *Grommes et al Neuro Oncol 2011*

- •Patients with PD in BM but not extra cranially may not have acquired resistance. Continuing erlotinib after PD in BM post RT; RR 41% DCR 76% MS 403 days *Shukuya et al Lung Cancer 2011*

- •Or switch after gefitinib failure to erlotinib 125 patients OR 9% MS11.8 months ; 62 pts BM RR 34%(without RT) *Hata et al Lung Cancer 2011*

2ND TOPIC

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Mitsudomi et al Lancet Oncology 2011

B) Any difference between the tkis ?

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Maintenance or wait and then 2nd line?

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Garassino et al J Clin Oncol 2011

C) Which pathways are responsible for TKI resistance ?

What to do if PD during TKI continue or stop?

Oxnard et al Clin Cancer Res 2011

SUMMARY

- •TKI is valid option for BM especially if mut+ve but surgery or SRS for oligometastic disease

  Jamal-Hanjani Clin. Cancer Res. 2011 ;Ceresoli et al Curr Cancer Drug Targets 2012

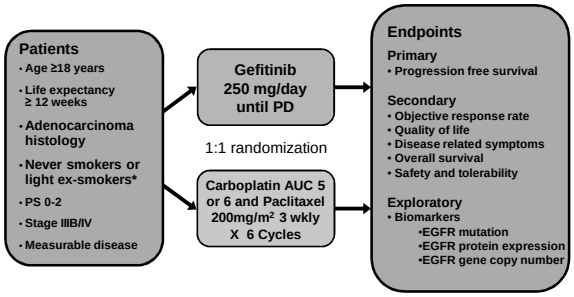
- •Concurrent Erlotinib +WBRT safe *Lind et al IJROBT 2009*

- •TKI may potentiate effectiveness of WBRT

  Gow et al Clin Cancer Res 2008

- •TACTIC trial WBRT +Erlotinib vs WBRT result awaited

IPASS STUDY DESIGN



***Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ≥15 years ago and smoked ≤10 pack yrs**

Carboplatin/paclitaxel was offered to gefitinib patients upon progression

Mok et al N Eng J Med 2009

BRAIN METASTASES

- Is there a place for EGFR-TKI in the treatment of BM ?

  Yes

- Should we treat 1st with RT (to break BBB) or just with TKI ?

  Symptomatic EGFR wt RT +/- tki

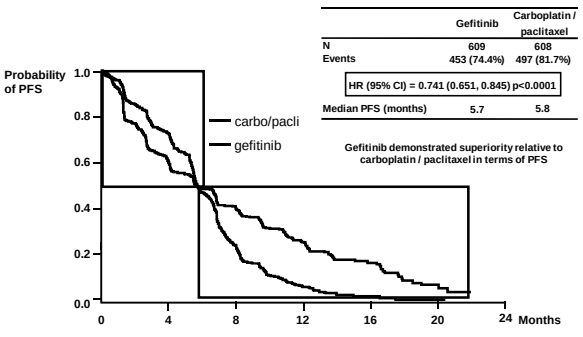
  Mut +ve TKI +/- RT

- What to do if only progressive in the brain but not elsewhere?

  Continue TKI (switch to erlotinib, ↑dose) and brain RT

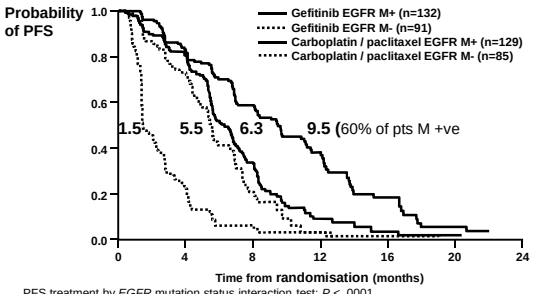
- Is it safe to give RT and tki together? Yes

OVERALL POPULATION: PROGRESSION-FREE SURVIVAL



Mok et al N Eng J Med 2009

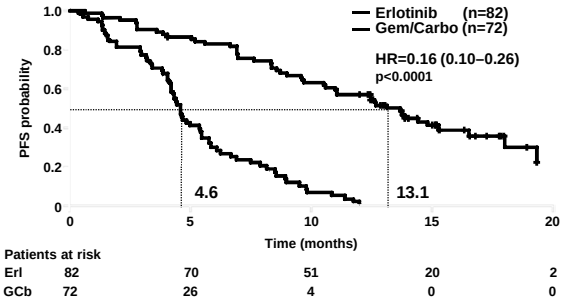
COMPARISON OF PFS BY MUTATION STATUS (60% of selected patients Mut +ve)



PFS treatment by *EGFR* mutation status interaction test: *P* < .0001
Exon 19 deletion advantages > L858R mutation

Mok et al N Eng J Med 2009
Fukuoka et al ASCO 2009 abst 8006
Mok et al WCLC 2009 abst B9.5

OPTIMAL PFS: updated analysis



*Sanger DNA sequencing

Zhou, et al. Lancet Oncol 2011

SURVIVAL TIME of EGFR mut +ve NSCLC

Study	First line	Median OS	Ref
IPASS	Gefitinib	21.6M	Yang CH et. al. Ann Oncol 2010:21;LBA2
	Pac/Car	21.9M	
NEJ002	Gefitinib	27.7M	Inoue A. et al. JCO 2011
	Pac/Car	26.6M	
WJOG3405	Gefitinib	30.9M	Lancet Oncology; 2010:11;121-8
	Doc/cis	Not reached	
First-SIGNAL	Gefitinib	30.6M	Lee JS. et.al. JTO;2009;4: PRS 4
	Gem/cis	26.5M	
I-CAMP	Gefitinib	27.7M	Morita S. et. al. CCR 2009;15:4493-98
	Chemotherapy	25.7M	
SLCG	Erlotinib	27.0M	Rosell R. et al. NEJM 2009;361;958-67

EGFR TKIS IN *EGFR* MUT+ NSCLC: STUDIES IN CAUCASIAN PATIENTS

	Phase	n	PFS median months	Reference
EUROPE				
SLCG	II	217	14.0	Rosell, et al. NEJM 2009
FIELT	II	46	13.0	De Grève et al. ASCO 2011
USA				
CALGB30406	II (randomised)	33	14.1	Jänne, et al. WCLC 2011

OPTIMAL: erlotinib versus gem/carb in *EGFR* mutation+ NSCLC

- **Phase III study initiated by Tongji University, Shanghai, China**

Chemonaïve advanced NSCLC
- ***EGFR* mutation-positive (exon 19 or 21)**
- **ECOG PS 0–2**
- **N=154(549 screened ,29%)**

→ **R** →
- **Erlotinib 150mg/day until PD**
- Gemcitabine (1,000 mg/m², IV, d1 and d8) plus carboplatin (AUC=5, IV d1) repeated every 3 weeks up to 4 cycles

- Primary endpoint: PFS 13.1vs. 4.6 mos HR 0.16P<0.0001
- Secondary endpoints: ORR, OS, QoL and safety

Zhou et al. Lancet 2011

EURTAC Phase III 1st-line study in EGFR Mutation +ve Patients

Advanced NSCLC (stage IIIb/IV), 1st-line, mutations exon 19 or 21, PS 0-2

→ **Erlotinib 150 mg**

→ **Pt-based doublet chemotherapy**

- **Primary endpoint: PFS**
- **Secondary: ORR, 1yOS, OS, safety, QoL, localisation of PD**

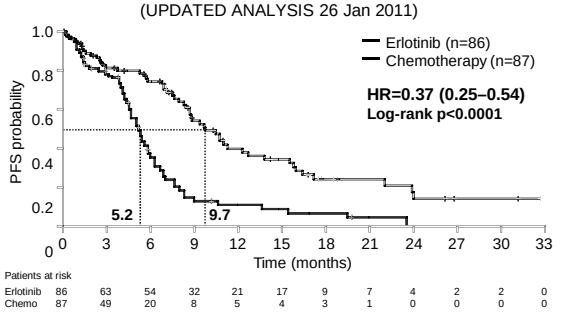
- ***Stratified by:***
  - **Histology (adenocarcinoma *vs.* non-ADC)**
  - **Current/ever smoked *vs.* never smoked**
  - **Chemotherapy (CDDP *vs.* CBDCA)**
  - **Stage (IIIB *vs.* IV)**
  - **ECOG 0 *vs.* 1 *vs.* 2**

CDDP 100 mg/m² iv/Gemcitabine 1,250 mg/m²
CDDP 75 mg/m² iv/Docetaxel 75 mg/m² iv
CBDCA AUC=5/Gemcitabine 1,000 mg/m²
CBDCA AUC=5/Docetaxel 75 mg/m² iv
(up to 4 cycles)

Rosell et al. ASCO 2011abstr 7503

PFS in ITT POPULATION

(UPDATED ANALYSIS 26 Jan 2011)



Rosell et al. ASCO 2011abstr 7503

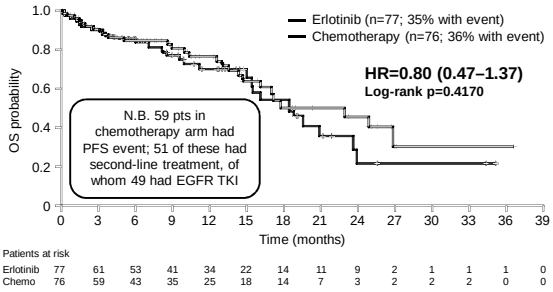
1st line EGFR tki in POOR PS PATIENTS

Parameter	Lilenbaum erlotinib	Hesketh erlotinib	**Inoue gefitinib**
Pat No.	52	81	**30**
PS	2	2	**2-4**
EGFR mut +ve %	0	na	**100**
OR%	4	8	**66**
OS mos	6.6	5	**17.8**

Langer J Clin Oncol 2009
Inoue et al J Clin Oncol 2009

OVERALL SURVIVAL IN ITT POPULATION

(INTERIM ANALYSIS 2 AUG 2010)



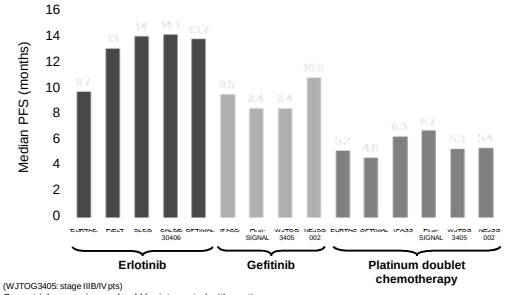
Data cut-off: 2 Aug 2010

Rosell et al. ASCO 2011abstr 7503

FIRST LAW OF ONCOLOGY

Tumour must shrink faster than the patient

SUMMARY OF PFS IN *EGFR* MUT+ STUDIES



(WJTOG3405: stage IIIB/IV pts)
Cross-trial comparisons should be interpreted with caution

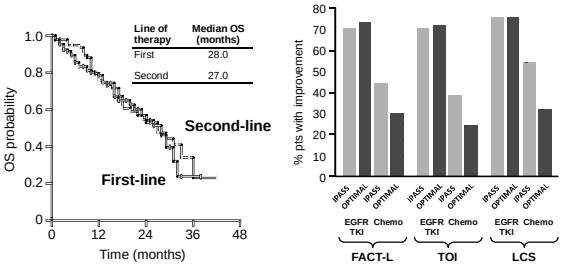
Rosell, et al. ASCO 2011; De Grève, et al. ASCO 2011; Rosell, et al. NEJM 2009; Jänne, et al. WCLC 2011; Zhou, et al. ASCO 2011; Mok, et al. NEJM 2009; Lee, et al. WCLC 2009; Mitsudomi, et al. Lancet Oncol 2010; Maemondo, et al. NEJM 2010

TIME TO USE EGFR TKIs IN *EGFR* MUT+ NSCLC

No difference in OS according to line of treatment

BUT…

First-line EGFR TKI provides QoL benefit over chemotherapy



Rosell, et al. NEJM 2009; Mok, et al. NEJM 2009; Zhou, et al. ASCO 2011

SUMMARY: EGFR TKIS IN *EGFR* MUT+ NSCLC

- **Significant benefits with first-line EGFR TKIs** vs chemotherapy in *EGFR* M +ve
  - significantly longer PFS ;more favourable toxicity profile
  - convenient oral preparation ; QoL benefits

First-line erlotinib has shown superiority over chemotherapy in both Caucasian and Asian patients with *EGFR* Mut+ NSCLC,

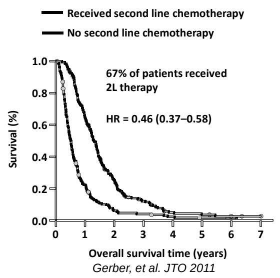
EGFR mutation testing should be performed to guide first-line treatment decisions

Recommendation 12

– An EGFR TKI is the preferred first-line treatment in patients whose tumor harbors an activating EGFR mutation

First ESMO Consensus Felip et al Ann Oncol 2011

WHY MAINTENANCE THERAPY?
MANY PATIENTS DO NOT RECEIVE 2L THERAPY

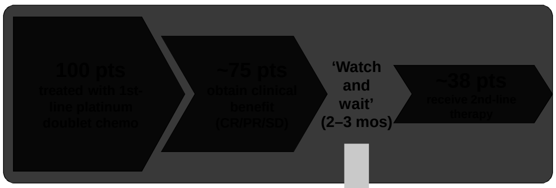


Gerber, et al. JTO 2011

	Control arm	
Trial	% 2L Tx	Median PFS (months)
Brodowicz	57%	2.0
Westeel	NR	3.0
Fidias	63%	2.7
JMEN	67%	2.0
ATLAS	55.5%	3.75
SATURN	72%	2.55
IFCT-GFPC	91%	1.9

Brodowicz, et al. Lung Cancer 2006; Westeel, et al. JNCI 2005; Fidias, et al. JCO 2009; Ciuleanu, et al. Lancet 2009; Cappuzzo, et al. Lancet Oncol 2010; Miller, et al. ASCO 2009; Pérol, et al. ESMO 2010

LIMITATIONS OF THE HISTORICAL 'WATCH AND WAIT' APPROACH



"The treatment paradigm that successfully delivers multiple lines of effective therapy… will be the paradigm that is most likely to improve survival."
Stinchcombe and Socinski, 2009

Many patients receive no further therapy due to rapid deterioration in symptoms and performance status

Stinchcombe and Socinski J Thoracic Oncol 2009

JMEN: MAINTENANCE ALIMTA® (PEMETREXED) AFTER PRIOR PLATINUM IN STAGE IIIB/IV NSCLC

- Stage IIIB/IV NSCLC
- PS 0-1
- 4 prior cycles of gemcitabine, taxane + cisplatin or carboplatin, **with CR, PR, or SD**

2:1 Randomization 28-42 days after cycle 4

Pemetrexed 500 mg/m² (d1,q21d) + BSC (N=441)*

Placebo (d1, q21d) + BSC (N=222)*

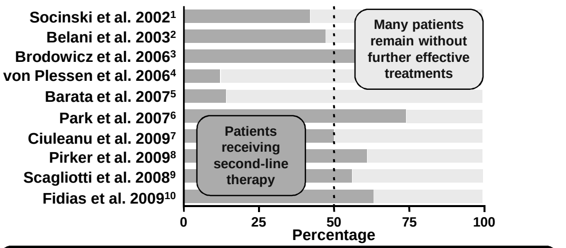
•Primary endpoint from randomisation
PFS in all patients

- Secondary endpoints
OS ; OR ; safety; time to symptom progression; quality of life (PRO)

*B_{12}, folate, dexamethasone given in both arms

Ciuleanu et al Lancet 2009

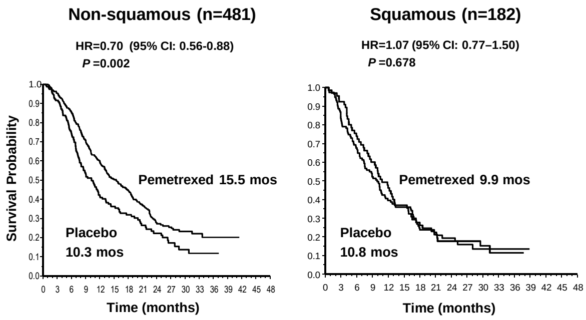
ONLY ~50% OF PATIENTS RECEIVE SECOND-LINE THERAPY



1ST LINE therapy could delay disease progression and provide active treatment for MORE patients

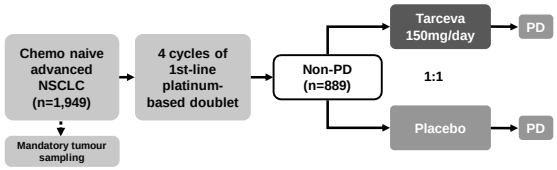
[1]J Clin Oncol 2002; [2]J Clin Oncol 2003; [3]Lung Cancer 2006; [4]Br J Cancer 2006; [5]J Thoracic Oncol 2007; Abs. P2-235; [6]J Clin Oncol 2007;[7] Lancet 2009; [8] Lancet 2009; [9]J Clin Oncol 2008; [10]J Clin Oncol 2009

OVERALL SURVIVAL BY HISTOLOGY



Ciuleanu et al Lancet 2009

SATURN: MAINTENANCE TARCEVA (ERLOTINIB) AND BIOMARKERS

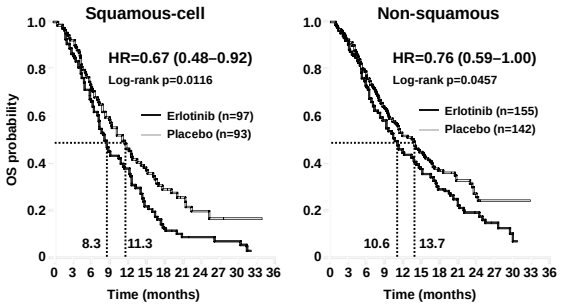


Co-primary endpoints from randomisation
PFS in all patients
PFS in patients with EGFR IHC+ ve

Secondary endpoints
OS in all patients and those with EGFR IHC+ tumours, OS and PFS in EGFR IHC– tumours; biomarker analyses; safety; time to symptom progression; quality of life (QoL)

Cappuzzo et al Lancet Oncol 2010

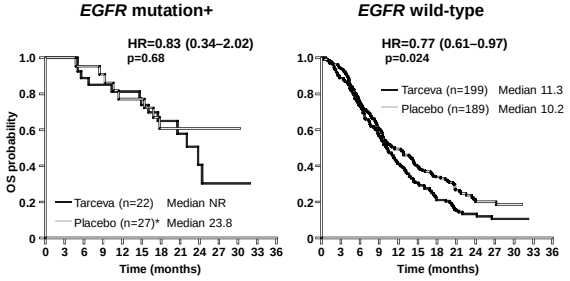
OS IN PATIENTS WITH SD ON FIRST-LINE CHEMOTHERAPY ACCORDING TO HISTOLOGY



Measured from time of randomisation into the maintenance phase

Coudert et al, ELCC 2010 abst 2040

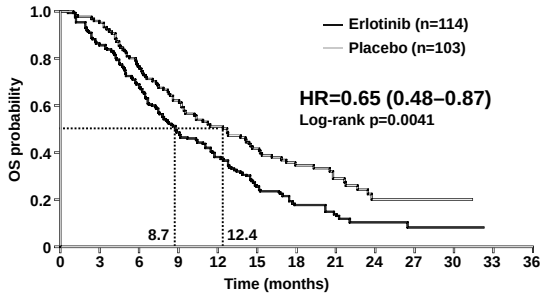
OS WITH MAINTENANCE TARCEVA IN *EGFR* MUTATION+ and WILD-TYPE GROUP



***67% of patients with *EGFR* mutation+ in the placebo arm received a 2nd line EGFR TKI**

Cappuzzo et al Lancet Oncol 2010

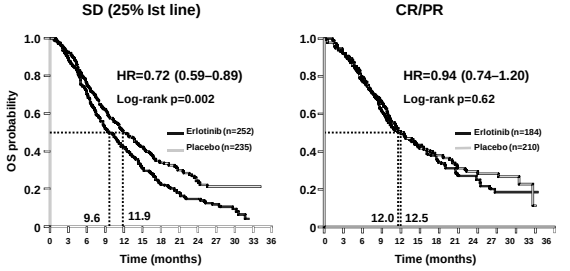
OS in *EGFR* WILD-TYPE GROUP with SD on FIRST-LINE CHEMOTHERAPY



Measured from time of randomisation into the maintenance phase

Coudert et al, ELCC 2010 abst 2040

OS ACCORDING TO RESPONSE TO FIRST-LINE CHEMOTHERAPY*



***OS is measured from time of randomisation into the maintenance phase**

Cappuzzo et al Lancet Oncol 2010

MAINTENANCE THERAPY ESMO, ASCO GUIDELINES

Recommendation 9

- 'Switch maintenance' treatment with erlotinib or pemetrexed following completion of first-line chemotherapy is an option. Decision factors for the use of 'switch maintenance' include histology, type and response to first-line chemotherapy, residual toxicity, patient's symptoms and preference. Any patient whose tumor harbors an EGFR activating mutation should receive an EGFR TKI as maintenance, if not yet received as first line

For those with **stable disease or response after four cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients , or erlotinib in unselected patients may be considered.**

Focused Update of Recommendation A6 J Clin Oncol 2011

IS THERE A DIFFERENCE BETWEEN TKIs ?

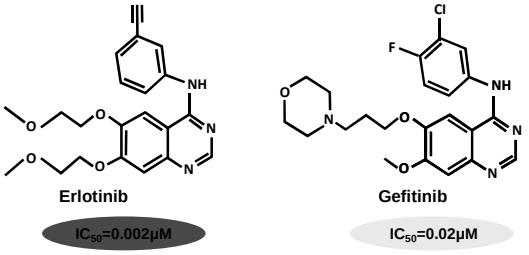
USE OF TKI IN *EGFR* WILD TYPE NSCLC

ERLOTINIB IN 2ND LINE OR MAINTENANCE IS EFFECTIVE IN *EGFR* wt DISEASE

Study	Patients with *EGFR* WT disease		HR (95% CI) Erlotinib vs placebo	Testing method(s)
BR.21[1-2]	Erlotinib (n=115) Placebo (n=55)	PFS	HR=0.57 p=0.001	EGFR Scorpions IM kits; direct gene sequencing and fragment analysis
		OS	HR=0.74 p=0.0924	
SATURN ITT population[4]	Erlotinib (n=199) Placebo (n=189)	PFS	HR=0.78 p=0.0185	Sanger DNA sequencing
		OS	HR=0.77 p=0.0243	
SATURN SD population[3]	Erlotinib (n=114) Placebo (n=103)	PFS	HR=0.72 p=0.0231	
		OS	HR=0.65 p=0.0041	

[1]Zhu, et al. JCO 2008; [2]Tsao, et al. NEJM 2005; [3]Coudert, et al. Ann Oncol 2011; [4]Brugger, et al. JCO 2011

ERLOTINIB AND GEFITINIB: SIMILAR STRUCTURES, DIFFERENT ACTIVITY



Erlotinib IC_{50}=0.002µM

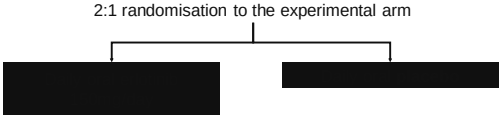
Gefitinib IC_{50}=0.02µM

- Structural differences may affect :plasma, tumour and normal tissue distribution, metabolism ,in-vitro activity, clinical efficacy and toxicity
- Switch after gefitinib failure to erlotinib 125 patients OR 9% DCR 44% MS11.8 months ; 62 pts BM RR 34%(without RT) *Hata et al Lung Cancer 2011*

BR.21: ERLOTINIB PHASE III STUDY IN ADVANCED, REFRACTORY NSCLC

Patients with stage IIIB/IV, refractory NSCLC; PS0–3;
failed one or two prior regimens
EGFR +ve not required

2:1 randomisation to the experimental arm

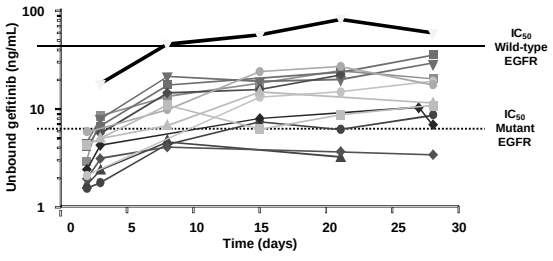


- n=731 patients
- Primary objective: overall survival
- Secondary objectives: response rate, stable-disease rate, duration of response, time to disease progression, and QoL
- 90% power to detect a 33% survival benefit

Shepherd et al N Eng J Med 2005

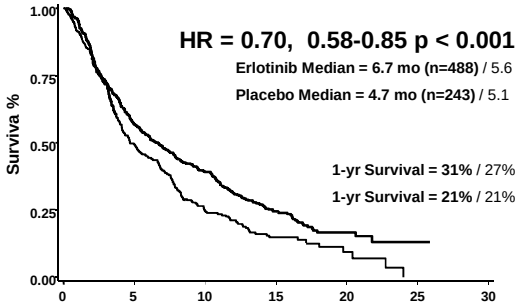
EXPOSURE TO GEFITINIB MAY BE INSUFFICIENT TO INHIBIT WILD-TYPE EGFR

Plasma concentrations versus time in 13 cancer patients, following gefitinib 250mg/day



Li J et al. J Natl Cancer Inst 2006

OVERALL SURVIVAL
ALL PATIENTS



HR = 0.70, 0.58-0.85 p < 0.001

Erlotinib Median = 6.7 mo (n=488) / 5.6

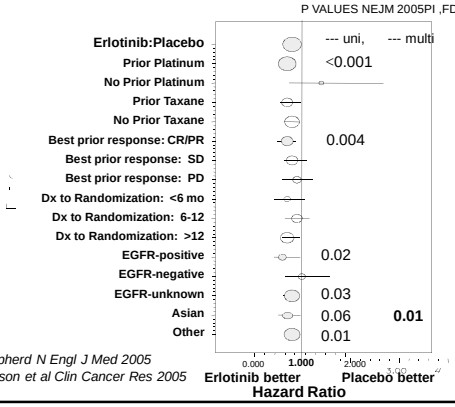
Placebo Median = 4.7 mo (n=243) / 5.1

1-yr Survival = 31% / 27%

1-yr Survival = 21% / 21%

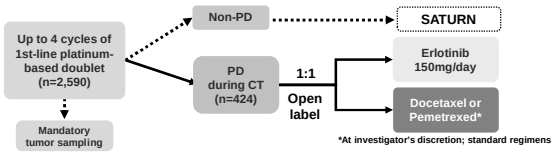
Shepherd et al N Eng J Med 2005
Thatcher et al Lancet 2005
Blackhall et al Lancet Onc 2006

HAZARD RATIO FOR DEATH BY SUBSETS



Shepherd N Engl J Med 2005
Johnson et al Clin Cancer Res 2005

TITAN STUDY DESIGN



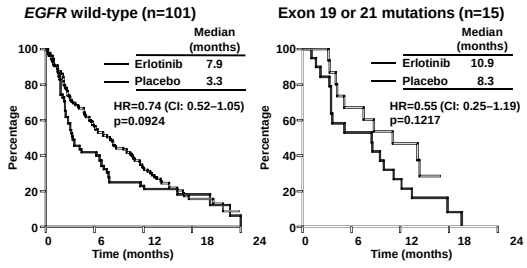
Primary endpoint
- Overall survival (OS)

Secondary endpoints
- PFS, RR, QoL (FACT-L), correlation of biomarkers with clinical outcome

Stratification factors
- Stage of disease at start of chemotherapy (IIIB vs IV)
- ECOG PS (0 or 1 vs 2)
- Smoking history (current vs former vs never)
- Region

Ciuleanu et al IASLC Chicago 2010 abstr 6 /LBOA5

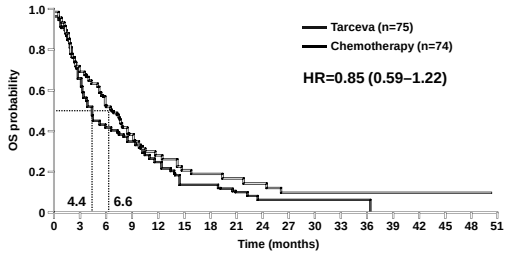
BR.21 RETRO ANALYSIS: SURVIVAL ACCORDING TO *EGFR* MUTATION STATUS



Interaction p=0.47 (not significant)

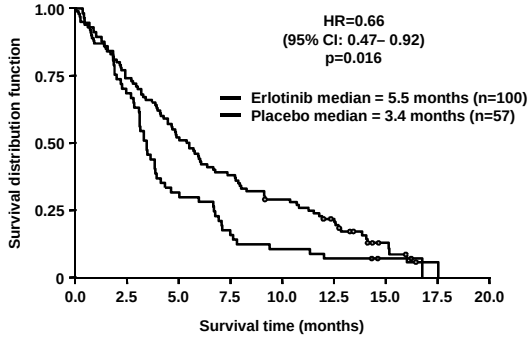
Zhu et al J Clin Oncol 2008

TITAN:OS with erlotinib vs chemotherapy in *EGFR* wild type NSCLC



Ciuleanu et al IASCLC Chicago 2010 abstr 6 /LBOA5

IS THERE A CLINICAL BENEFIT WITH TARCEVA FOR MALE SMOKERS WITH SQUAMOUS-CELL CARCINOMA?



Clark et al Clin Lung Cancer 2006

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ? TKI best but if CT first make sure to give TKI afterwards

B) Any difference between the tkis ? Yes

Maintenance or wait and then 2nd line? Maintenance in some

Is there a role for TKI in EGFR wt? Yes ,erlotinib in maintenance and 2nd line (Saturn; BR21: Titan)

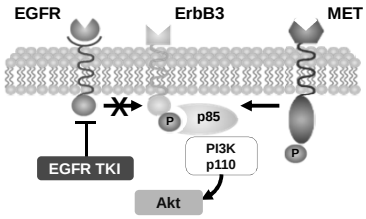
C) Which pathways are responsible for TKI resistance ?

What to do if PD during TKI continue or stop?

Oxnard et al Clin Cancer Res 2011

ASPECTS of RESISTANCE to EGFR TKIs

COMBINING OTHER TARGETED THERAPIES WITH ERLOTINIB COULD IMPROVE OUTCOMES



- The MET receptor signals through the PI3K/AKT pathway and can therefore bypass EGFR inhibition[1–4]
- A dual-targeting strategy may improve anti-tumour activity

Bean, et al. PNAS 2007
Karamouzis, et al. Lancet Oncol 2009

REVERSIBLE EGFR TKI RESISTANCE ?

- Non mutational reversible EGFR tki drug resistance mechanism in PC 9 NSCLC cell lines regained sensitivity *Sharma Cell 2010*
- Case reports of retreatment response *Kurata et al Ann Oncol 2004* *Yano et al Oncol Res 2005*
- 14 pts treated with erlotinib(11 mut +ve) median PFS 12.5 months →CT on PD → retreat with erlotinib
  Interval between 1st and 2nd erlotinib median 9.5 (3-36) months,
  T790 5pts (PR 2; SD 1; PD 2)
  PFS 6.5 (1-16+) mos

Becker et al Eur J Cancer 2011

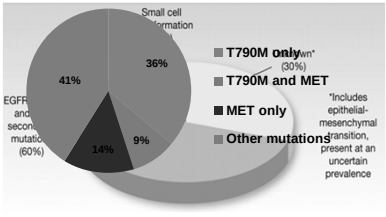
WHAT CAN WE DO AFTER TKI FAILURE ?

- Switch to chemotherapy or add CT to TKI
- Continue EGFR-TKI
- Switch to another EGFR-TKI
  gefitinib to erlotinib
  Irreversible EGFR-TKI?
- Is it better to treat resistance or try to prevent it from emerging ?

COMBINATION OF TARGETED AGENTS

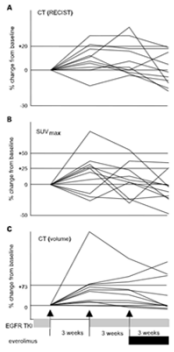
Primary Resistance	Acquired Resistance
De novo T790M mutation	T790M mutation
PIK3CA mutation	c-MET amplification
PTEN loss	EMT
IGF1R	Others
Others	

Kobayashi et al, NEJM 2005
Inukai M et al Cncer Res 2006;;
Engeglman JCI 2006
Bean et al. Proc Natl Acad Sci. 2007;
Engelman et al. Science 2007
Frederick et al Mol Cancer Ther 2007
Sos et al Cancer Res 2009
Gong et al, PLoS ONE 2009



Oxnard et al Clin Cancer Res 2011

RE-CHALLENGE OF EGFR TKI IN RESISTANCE TO EGFR TKI ?

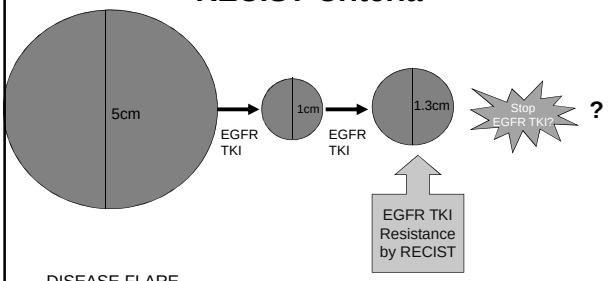


10 patients, resistance to EGFR TKIs
Stop EGFR TKIs for 3 weeks, then restart EGFR TKIs, 3 weeks later add everolimus
After stop : 18% SUVmax and 9% tumor size
Symptomatic progression
Restart EGFR TKI: 4% decreased SUV max
1% decreased in tumor
Symptom improvement

Suggesting that some tumor cells remain sensitive to EGFR TKIs

Riely et al Clin Cancer Res 2007

RECIST Criteria

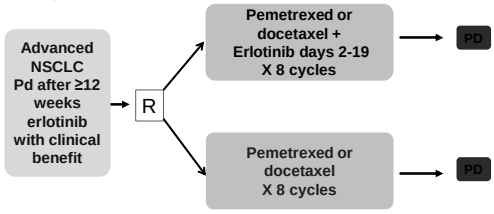


DISEASE FLARE
61 patients with acquired resistance (RECIST PD after benefit)
23% disease flare (hospitalization/death due to PD during wash out)
Shorter TTP, pleural/CNS mets. Not mut stus including T790M
Chaft et al Clin Cancer Res 2011

TRIAL DESIGN : Continuation of EGFR TKIs

On relapse only some clones carry resistance mutations,
Others remain dormant while the EGFR pathway remains inhibited
Tumour rebound/ flare when EGFR *tki* stopped on progression

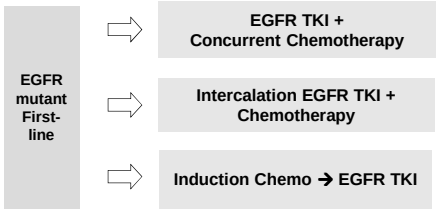
Randomised Phase II
Primary endpoint increase PFS by 50% (3to 4.5 months)
23/78 patients enrolled



Halmos et al ASCO 2011abst TPS211

ADD CHEMOTHERAPY TO *TKI*

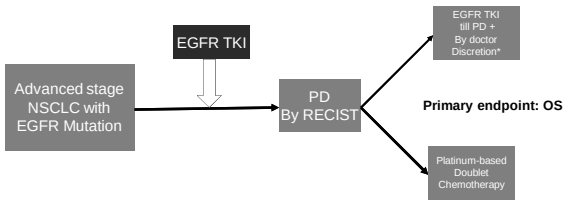
Incorporation of chemotherapy



TREATMENT-BEYOND-PROGRESSION

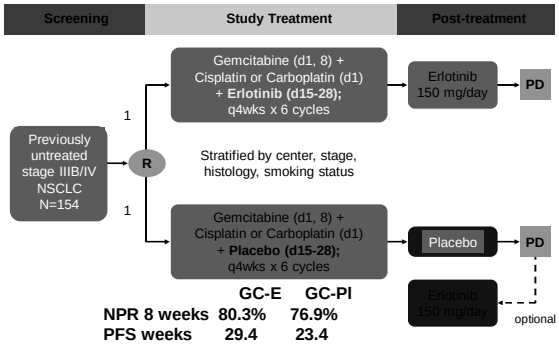
ASPIRATION

(ASIA PACIFIC TRIAL OF TARCEVA AS FIRST LINE IN EGFR MUTATION+ NSCLC)



*Doctor Discretion: Symptomatic progression, multiple progression
Threat to major organ…etc

FIRST-LINE ASIAN SEQUENTIAL TARCEVA PLUS CHEMOTHERAPY TRIAL (FASTACT)



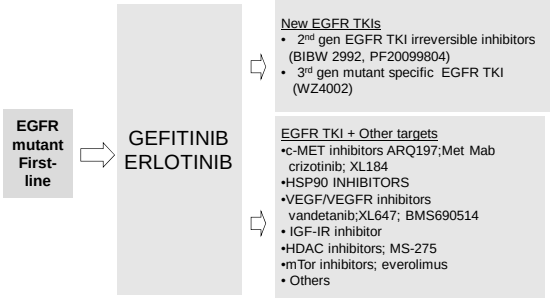
	GC-E	GC-PI
NPR 8 weeks	80.3%	76.9%
PFS weeks	29.4	23.4

p=0.0002

Mok et al J Clin Oncol 2009

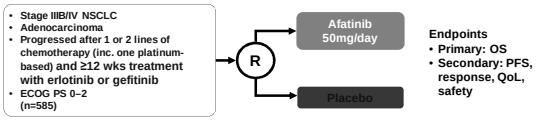
DELAY OR PREVENT THE APPEARANCE OF RESISTANCE TO EGFR TKIS

New EGFR TKIs or combination with new targets



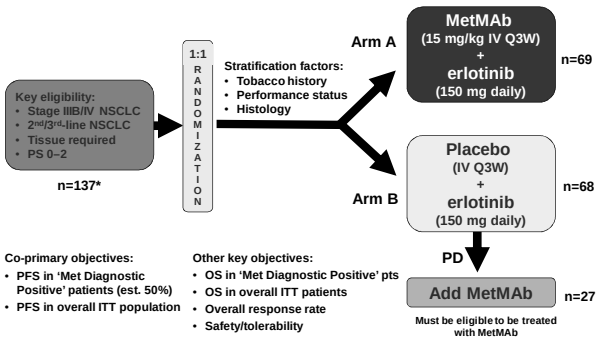
BIBW 2992
LUX-LUNG 1: RATIONALE

- Patients sensitive to gefitinib (G) or erlotinib (E) eventually progress
  - T790M mutation most common cause of resistance
  - Detected in ~50% of such patients
- Afatinib (BIBW 2992)
  - Irreversible EGFR and HER2 inhibitor
  - Preclinical activity against NSCLC with T790M mutations



Miller et al ESMO 2010 abst LBA1

PHASE II: ERLOTINIB +/- METMAB IN 2ND/3RD-LINE NSCLC

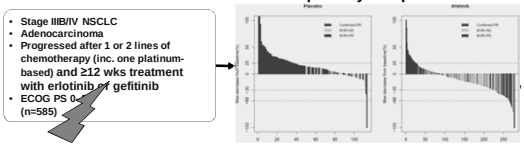


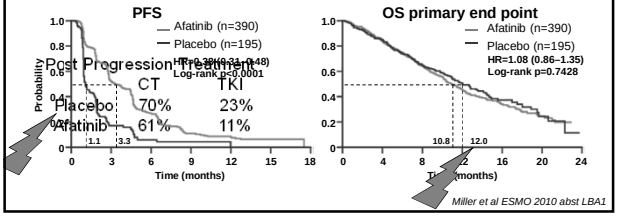
Spigel et al. ASCO 2011 (abstr 7505)

LUNG 1

- Preclinical activity against NSCLC with T790M mutations

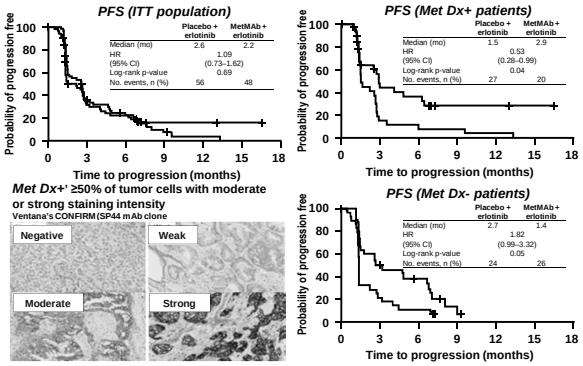
Waterfall plots by independent review





Miller et al ESMO 2010 abst LBA1

EFFICACY



ACTIVITY AND TOLERABILITY OF AFATINIB (BIBW 2992) AND CETUXIMAB IN NSCLC PATIENTS WITH ACQUIRED RESISTANCE TO TKI

–Of 26 patients treated, 22 received the predetermined maximum dose (afatinib 40 mg/day plus cetuximab 500 mg/m^2)
–Median time on prior erlotinib/gefitinib therapy was 2.4 years

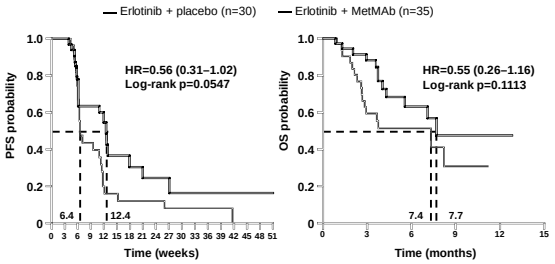
	T790M positive	T790M negative	T790M unknown	No EGFR mutation	Total
Total treated	27	15	3	2	47
Evaluable for efficacy	26	14	3	2	45
Best response	**n (%)**				
Any PR	13 (50)	8 (57)	2 (67)		23 (51)
Confirmed PR	**9 (35)**	**7 (50)**	**2 (67)**		**18 (40)**
SD	11 (42)	5 (36)	1 (33)		19 (42)
Clinical response (any PR + SD)	24 (92)	13 (93)	3 (100)	2 (100)	42 (93)
Progression of disease	2 (8)	1 (7)			3 (7)

• EGFR mutation-positive NSCLC, with AR to erlotinib and gefitinib, continues to depend on EGFR signalling(erlotinib +cetuximab no activity CCR 2011)

Janijgian et al. ASCO 2011 abstr 7525)

MET DIAGNOSTIC POSITIVE PATIENTS BENEFIT FROM ERLOTINIB + METMAB

Analysis of Met diagnostic positive patients*



*12/23 patients from the erlotinib + placebo arm who crossed over to MetMAb were Met diagnostic positive

Spigel, et al. ESMO 2010

2ND TOPIC

A) If Mut +ve is 1st line CT or TKI best ?

TKI best but if CT first make sure to give TKI afterwards

B) Is there a role for TKI in EGFR wt ? Yes in maintenance and 2nd line (Saturn;BR21; Titan)

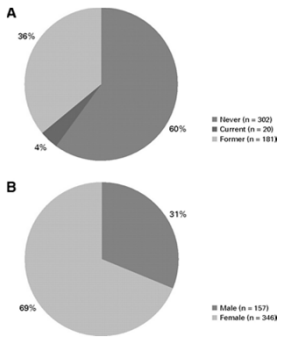
Any difference between the tkis ? Yes Erlotinib efficacy after gefitinib failure *Hata et al Lung Cancer 2011*

C) What to do if PD during TKI continue or stop? Stop and switch to 1st line CT (but emerging data)

Which pathways are responsible for TKI resistance ? T790M, c-MET and others

Is it better to treat resistance or try to prevent it from emerging ?

ADENOCARCINOMA
EGFR MUTATION BY (A) SMOKING STATUS AND (B) SEX.



40% smokers

D'Angelo et al. JCO 2011

3rd TOPIC
EGFR TESTING

A) IHC testing only in non-squamous only? No

B) Mutation testing in non-squamous only? Yes

NSCLC pathology and molecular testing
Recommendation 1

–EGFR somatic mutation testing should be carried out to identify patients eligible for first-line treatment with EGFR TKIs
–Never/former light smokers (<15 packs per year) or patients withnonsquamous histology should be tested for EGFR mutation status regardless of PS
–Patients harboring sensitizing EGFR mutations should be treated with EGFR TKIs regardless of the genotype of the sensitizing mutation (del 19 versus L858R in exon 21)
–IHC and FISH for EGFR are not recommended for routine clinical use
–The concomitant presence of T790M resistance mutation shouldnot preclude the use of EGFR TKIs in the first-line setting

EGFR MUTATION TEST: NONSQUAMOUS ONLY

• US: There were no *EGFR* mutations in 454 squamous carcinomas *Marchetti et al J Clin Oncol 2005*

• Japan: Squamous Ca *EGFR* mutations rate was 3/87 3.4% (possibly adeno squamous) *Miyamae et al Oncology Reports 20111/230*

Phase III gefitinib vs CT 5/228 2.2% *Maemondo et al N Eng J Med 2010*

• The NCCN recommends erlotinib in the United States as first-line therapy for patients who have an ***EGFR*** mutation and who have advanced, recurrent, or metastatic nonsquamous cell NSCLC.

• Similar to NICE UK and Royal College pathologists report

EGFR MUTATION STATUS IS A BETTER PREDICTOR FOR TKI EFFICACY compared to protein expression ,copy number

• Mutant EGFR is biologically linked to ligand independent increased downstream signalling, unlike overexpression of native EGFR.

• When both alterations are present, the mutated EGFR allele is amplified preferentially. This suggests that in cases with both mutation and amplification, the biological advantage is provided by the mutation that drive sselection for copy number gains

• EGFR mutations are more closely linked to known risk factors than is EGFR amplification.

• OR 70% in EGFR mutated cases regardless of EGFR copy number In contrast, EGFR-amplified cases WITHOUT mutations OR 8%.

• In recent, suitably powered phase III trials EGFR mutation status is a better predictor of outcome than EGFR copy no. *Ladanyi and Pao Modern Pathology 2008; Mok et al N Engl J Med 2009; Sholl et al AM J Clin Path 2010;Dahabreh et al Clin Cancer Res 2010*

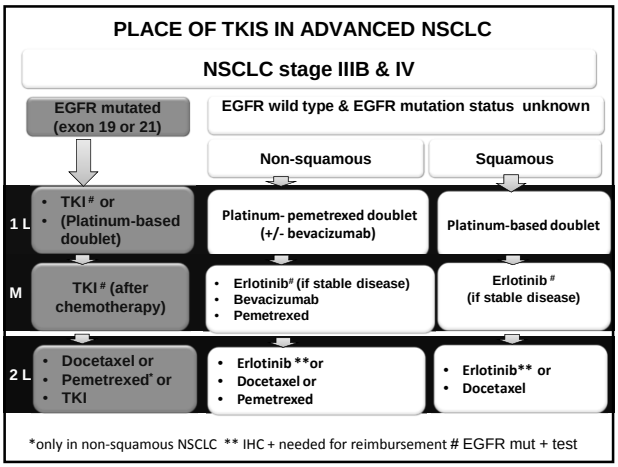
EGFR TESTING

• **IHC**
Total protein *Cetuximab*
Mutant protein *Oral TKIs*

• **FISH and other ISHes**
Gene copy number *Oral TKIs*

• **Mutation analysis**
Particular gene mutations *Oral TKIs*

• Different and get confused


PLACE OF TKIS IN ADVANCED NSCLC
NSCLC stage IIIB & IV
EGFR mutated (exon 19 or 21)
EGFR wild type & EGFR mutation status unknown
Non-squamous
Squamous
1 L
• TKI # or
• (Platinum-based doublet)
Platinum- pemetrexed doublet (+/- bevacizumab)
Platinum-based doublet
M
TKI # (after chemotherapy)
• Erlotinib# (if stable disease)
• Bevacizumab
• Pemetrexed
Erlotinib # (if stable disease)
2 L
• Docetaxel or
• Pemetrexed* or
• TKI
• Erlotinib **or
• Docetaxel or
• Pemetrexed
• Erlotinib** or
• Docetaxel
*only in non-squamous NSCLC ** IHC + needed for reimbursement # EGFR mut + test