THE PLACE OF EGFR TKI IN ADVANCED NSCLC

Nick Thatcher, Christie Hospital, Manchester, England
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?
2\textsuperscript{ND} TOPIC

A) If Mut +ve is 1st line CT or TKI best?
\textit{Mitsudomi et al Lancet Oncology 2011}

B) Any difference between the tkis?
\textit{Hata et al Lung Cancer 2011}

Maintenance or wait and then 2\textsuperscript{nd} line?
Is there a role for TKI in EGFR wt?
\textit{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?
\textit{Oxnard et al Clin Cancer Res 2011}
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?

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
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.

EGFR TKI CNS PENETRATION

- 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$^{2,3}$

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

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
### ACTIVITY of EGFR TKI in BM


<table>
<thead>
<tr>
<th>Study</th>
<th>Treat</th>
<th>Selection</th>
<th>Pat No.</th>
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<td>Wu</td>
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<td>Kim</td>
<td>G/E</td>
<td>EA Non Smoker</td>
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<td>74</td>
<td>PFS 7.1</td>
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<td></td>
<td>OS 18.8</td>
</tr>
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</table>
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

• 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


• 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 \( \uparrow \) dose or switch to erlotinib

- **TKI dose escalation:** erlotinib 300mg alt die

  CNS response despite prior gefitinib, CT, WBRT and 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% MS 11.8 months; 62 pts BM RR 34% (without RT) _Hata et al Lung Cancer 2011_
SUMMARY

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

- 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
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
2\textsuperscript{ND} 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 2\textsuperscript{nd} 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
**IPASS STUDY DESIGN**

**Patients**
- Age ≥18 years
- Life expectancy ≥ 12 weeks
- Adenocarcinoma histology
- Never smokers or light ex-smokers*
  - PS 0-2
  - Stage IIIIB/IV
  - Measurable disease

**Gefitinib**
- 250 mg/day until PD

**Carboplatin AUC 5 or 6 and Paclitaxel**
- 200mg/m² 3 wkly X 6 Cycles

**Endpoints**
- **Primary**
  - Progression free survival

- **Secondary**
  - Objective response rate
  - Quality of life
  - Disease related symptoms
  - Overall survival
  - Safety and tolerability

- **Exploratory**
  - Biomarkers
    - EGFR mutation
    - EGFR protein expression
    - EGFR gene copy number

*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*
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

Gefitinib EGFR M+ (n=132)
Gefitinib EGFR M- (n=91)
Carboplatin / paclitaxel EGFR M+ (n=129)
Carboplatin / paclitaxel EGFR M- (n=85)

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**

HR = 0.16 (0.10 – 0.26)
p < 0.0001

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Erlotinib (n=82)</th>
<th>Gem/Carbo (n=72)</th>
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<tbody>
<tr>
<td>13.1</td>
<td>4.6</td>
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</table>

PFS probability

Patients at risk

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<th>Patients at risk</th>
<th>Erl</th>
<th>GCb</th>
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<tbody>
<tr>
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</table>

* Sanger DNA sequencing

PFS in ITT POPULATION

(UPDATED ANALYSIS 26 Jan 2011)

PFS probability

Erlotinib (n=86)
Chemotherapy (n=87)

HR=0.37 (0.25–0.54)
Log-rank p<0.0001

Rosell et al. ASCO 2011abstr 7503
# 1st line EGFR tki in POOR PS PATIENTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lilenbaum erlotinib</th>
<th>Hesketh erlotinib</th>
<th>Inoue gefitinib</th>
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<tbody>
<tr>
<td>Pat No. PS</td>
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<td>81</td>
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</tr>
<tr>
<td>EGFR mut +ve %</td>
<td>0</td>
<td>na</td>
<td>100</td>
</tr>
<tr>
<td>OR%</td>
<td>4</td>
<td>8</td>
<td>66</td>
</tr>
<tr>
<td>OS mos</td>
<td>6.6</td>
<td>5</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Langer J Clin Oncol 2009
Inoue et al J Clin Oncol 2009
FIRST LAW OF ONCOLOGY

Tumour must shrink faster than the patient
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

<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>28.0</td>
</tr>
<tr>
<td>Second</td>
<td>27.0</td>
</tr>
</tbody>
</table>

OS probability

Time (months)

0 12 24 36 48

First-line

Second-line

FACT-L

TOI

LCS

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
LIMITATIONS OF THE HISTORICAL ‘WATCH AND WAIT’ APPROACH

100 pts treated with 1st-line platinum doublet chemo

~75 pts obtain clinical benefit (CR/PR/SD)

‘Watch and wait’ (2–3 mos)

~38 pts receive 2nd-line therapy

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

“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

Stinchcombe and Socinski  J Thoracic Oncol 2009
ONLY ~50% OF PATIENTS RECEIVE SECOND-LINE THERAPY

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

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

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

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

2:1 Randomization 28-42 days after cycle 4

- Primary endpoint from randomisation
  PFS in all patients
- Secondary endpoints
  OS; OR; safety; time to symptom progression; quality of life (PRO)

*B₁₂, folate, dexamethasone given in both arms

Ciuleanu et al Lancet 2009
OVERALL SURVIVAL BY HISTOLOGY

Non-squamous (n=481)

HR=0.70 (95% CI: 0.56-0.88)

$P = 0.002$

Squamous (n=182)

HR=1.07 (95% CI: 0.77–1.50)

$P = 0.678$

Ciuleanu et al Lancet 2009
SATURN: MAINTENANCE TARCEVA (ERLOTINIB) AND BIOMARKERS

Chemo naive advanced NSCLC (n=1,949)

4 cycles of 1st-line platinum-based doublet

Non-PD (n=889)

1:1

Tarceva 150mg/day

Placebo

Mandatory tumour sampling

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)

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

Cappuzzo et al Lancet Oncol 2010
OS ACCORDING TO RESPONSE TO FIRST-LINE CHEMOTHERAPY*

SD (25% 1st line)
HR=0.72 (0.59–0.89)
Log-rank p=0.002

CR/PR
HR=0.94 (0.74–1.20)
Log-rank p=0.62

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

Cappuzzo et al  Lancet Oncol 2010
OS IN PATIENTS WITH SD ON FIRST-LINE CHEMOTHERAPY ACCORDING TO HISTOLOGY

**Squamous-cell**

- HR = 0.67 (0.48–0.92)
- Log-rank p = 0.0116
- Erlotinib (n=97)
- Placebo (n=93)

**Non-squamous**

- HR = 0.76 (0.59–1.00)
- Log-rank p = 0.0457
- Erlotinib (n=155)
- Placebo (n=142)

Measured from time of randomisation into the maintenance phase

Coudert et al, ELCC 2010 abst 2040
OS in *EGFR* WILD-TYPE GROUP with SD on FIRST-LINE CHEMOTHERAPY

HR=0.65 (0.48–0.87)
Log-rank p=0.0041

Measured from time of randomisation into the maintenance phase
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 AND GEFITINIB:
SIMILAR STRUCTURES, DIFFERENT ACTIVITY

- 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% MS 11.8 months; 62 pts BM RR 34% (without RT) *Hata et al Lung Cancer 2011*
EXPOSURE TO GEFITINIB MAY BE INSUFFICIENT TO INHIBIT WILD-TYPE EGFR

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

ERLOTINIB IN 2\textsuperscript{ND} LINE OR MAINTENANCE IS EFFECTIVE IN *EGFR* wt DISEASE

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with <em>EGFR WT</em> disease</th>
<th>HR (95% CI)</th>
<th>Testing method(s)</th>
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<tr>
<td></td>
<td></td>
<td>PFS</td>
<td>ERLOTINIB vs placebo</td>
</tr>
<tr>
<td>BR.21\textsuperscript{1–2}</td>
<td>Erlotinib (n=115) Placebo (n=55)</td>
<td>HR=0.57 p=0.001</td>
<td>EGFR Scorpions IM kits; direct gene sequencing and fragment analysis</td>
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<td>SATURN ITT population\textsuperscript{4}</td>
<td>Erlotinib (n=199) Placebo (n=189)</td>
<td>PFS HR=0.78 p=0.0185</td>
<td>Sanger DNA sequencing</td>
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<td>SATURN SD population\textsuperscript{3}</td>
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<td>PFS HR=0.72 p=0.0231</td>
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<td>OS HR=0.74 p=0.0924</td>
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<td>OS HR=0.65 p=0.0041</td>
<td>Sanger DNA sequencing</td>
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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

- Daily oral erlotinib
  150mg/day
- Daily oral placebo

- 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
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

P VALUES NEJM 2005 PI, FDA 2005

- Erlotinib:Placebo
  - Prior Platinum
  - No Prior Platinum
  - Prior Taxane
  - No Prior Taxane
- Best prior response: CR/PR
- Best prior response: SD
- Best prior response: PD
- Dx to Randomization: <6 mo
- Dx to Randomization: 6-12
- Dx to Randomization: >12
- EGFR-positive
- EGFR-negative
- EGFR-unknown
- Asian
- Other

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

Erlotinib better
Hazard Ratio

PI, FDA 2005

0.000 1.000 2.000

Erlotinib better
Placebo better
BR.21 RETRO ANALYSIS: SURVIVAL ACCORDING TO EGFR MUTATION STATUS

*EGFR wild-type (n=101)*

- Erlotinib: Median (months) 7.9
- Placebo: Median (months) 3.3
- HR = 0.74 (CI: 0.52–1.05) p = 0.0924

*Exon 19 or 21 mutations (n=15)*

- Erlotinib: Median (months) 10.9
- Placebo: Median (months) 8.3
- HR = 0.55 (CI: 0.25–1.19) p = 0.1217

Interaction p = 0.47 (not significant)

Zhu et al J Clin Oncol 2008
IS THERE A CLINICAL BENEFIT WITH TARCEVA FOR MALE SMOKERS WITH SQUAMOUS-CELL CARCINOMA?

HR=0.66
(95% CI: 0.47–0.92)
p=0.016

Survival distribution function

- Erlotinib median = 5.5 months (n=100)
- Placebo median = 3.4 months (n=57)

Clark et al Clin Lung Cancer 2006
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
TITAN: OS with erlotinib vs chemotherapy in *EGFR* wild type NSCLC

**Survival Probability**

- **Tarceva (n=75)**
- **Chemotherapy (n=74)**

**HR=0.85 (0.59–1.22)**

**Time (months)** 0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51

**OS probability** 1.0 0.8 0.6 0.4 0.2 0.0

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*Ciuleanu et al IASCLC Chicago 2010 abstr 6 /LBOA5*
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
COMBINATION OF TARGETED AGENTS

Primary Resistance
- De novo T790M mutation
- PIK3CA mutation
- PTEN loss
- IGF1R
- Others

Acquired Resistance
- T790M mutation
- c-MET amplification
- EMT
- Others

Kobayashi et al, NEJM 2005
Inukai M et al Cancer Res 2006;
Engelmann 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
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 ?
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

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
ADD CHEMOTHERAPY TO TKI

Incorporation of chemotherapy

EGFR mutant First-line

EGFR TKI + Concurrent Chemotherapy

Intercalation EGFR TKI + Chemotherapy

Induction Chemo † EGFR TKI
FIRST-LINE ASIAN SEQUENTIAL TARCEVA PLUS CHEMOTHERAPY TRIAL (FASTACT)

Screening

<table>
<thead>
<tr>
<th>Study Treatment</th>
<th>Post-treatment</th>
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</thead>
<tbody>
<tr>
<td>Gemcitabine (d1, 8) + Cisplatin or Carboplatin (d1) + <strong>Erlotinib (d15-28)</strong>; q4wks x 6 cycles</td>
<td>Erlotinib 150 mg/day</td>
</tr>
<tr>
<td>Gemcitabine (d1, 8) + Cisplatin or Carboplatin (d1) + <strong>Placebo (d15-28)</strong>; q4wks x 6 cycles</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Stratified by center, stage, histology, smoking status

Previously untreated stage IIIB/IV NSCLC N=154

NPR 8 weeks

**GC-E** 80.3%  **GC-PI** 76.9%

PFS weeks

29.4  23.4

p=0.0002

Mok et al J Clin Oncol 2009
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% (3 to 4.5 months)
23/78 patients enrolled

Advanced NSCLC
Pd after ≥12 weeks erlotinib with clinical benefit

R

Pemetrexed or
docetaxel +
Erlotinib days 2-19
X 8 cycles

PD

Pemetrexed or
docetaxel
X 8 cycles

PD

Halmos et al ASCO 2011 abst TPS211
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
New EGFR TKIs or combination with new targets

New EGFR TKIs
- 2nd gen EGFR TKI irreversible inhibitors (BIBW 2992, PF20099804)
- 3rd gen mutant specific EGFR TKI (WZ4002)

EGFR TKI + Other targets
- c-MET inhibitors ARQ197; Met Mab crizotinib; XL184
- HSP90 INHIBITORS
- VEGF/VEGFR inhibitors vandetanib; XL647; BMS690514
- IGF-IR inhibitor
- HDAC inhibitors; MS-275
- mTor inhibitors; everolimus
- Others
Patients sensitive to gefitinib (G) or erlotinib (E) eventually progress. The T790M mutation is the most common cause of resistance, detected in ~50% of such patients.

Afatinib (BIBW 2992) is an irreversible EGFR and HER2 inhibitor. It shows preclinical activity against NSCLC with T790M mutations.

**Stage IIIB/IV NSCLC**
- Adenocarcinoma
- Progressed after 1 or 2 lines of chemotherapy (incl. one platinum-based) and ≥12 wks treatment with erlotinib or gefitinib
- ECOG PS 0–2 (n=585)

**Endpoints**
- Primary: OS
- Secondary: PFS, response, QoL, safety

**Trial Design**
- Afatinib 50mg/day
- Placebo

Miller et al ESMO 2010 abst LBA1
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?
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 with nonsquamous 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 should not preclude the use of EGFR TKIs in the first-line setting
ADENOCARCINOMA
EGFR MUTATION BY (A) SMOKING STATUS AND (B) SEX.

40% smokers

D'Angelo et al. JCO 2011
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 2011/230*
  
  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
PLACE OF TKIS IN ADVANCED NSCLC

NSCLC stage IIIB & IV

EGFR mutated (exon 19 or 21)

- TKI # or
- (Platinum-based doublet)

EGFR wild type & EGFR mutation status unknown

Non-squamous

- Platinum- pemetrexed doublet (+/- bevacizumab)

Squamous

- Platinum-based doublet

1 L

M

TKI # (after chemotherapy)

- Erlotinib# (if stable disease)
- Bevacizumab
- Pemetrexed

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