THE PLACE OF EGFR TKI IN ADVANCED NSCLC

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?

2nd TOPIC
A) If Mut +ve is 1st line CT or TKI best?
B) Any difference between the tki's?
C) Which pathways are responsible for TKI resistance?
What to do if PD during TKI continue or stop?

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?

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 Faller, Lancet Oncol 2002
Incidence about 30% but increasing – better imaging and longer survival
  with systemic treatment . DCR ≥90 days with TKI - 20% 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
• Oligometastatic BM surgery or SRS+WBRRT (local control ?) OS vs.
  WBRT alone ESMO Clinical practice guidelines D'Addario et al Ann Oncol 2010
CNS MET FREQUENT SITE OF FAILURE AFTER EGFR TKI THERAPY

- Higher incidence of CNS failure as an initial progression in patients who had a clinical benefit from EGFR TKI therapy
- 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)


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 tumor cells with WT EGFR gene (20 nmol/l; 7.9 ng/ml)
- 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


ACTIVITY of EGFR TKI in BM

<table>
<thead>
<tr>
<th>Study</th>
<th>Treat</th>
<th>Selection</th>
<th>Pat No.</th>
<th>RR%</th>
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<td>EA Adeno</td>
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<td>Porta</td>
<td>E</td>
<td>M+ve</td>
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<tr>
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<td>EA Non Smoker</td>
<td>23</td>
<td>74</td>
<td>PFS 7.1, OS 18.8</td>
</tr>
</tbody>
</table>

ACTIVITY of EGFR TKI in BM


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 ↑ 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 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 J Clin Cancer Res 2009
- 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

OVERALL POPULATION: PROGRESSION-FREE SURVIVAL

IPASS STUDY DESIGN

2ND TOPIC
A) If Mut +ve is 1st line CT or TKI best? Mitsudomi et al Lancet Oncology 2011
B) Any difference between the tiks? Hata et al Lung Cancer Oncol 2011
C) Which pathways are responsible for TKI resistance?
   What to do if PD during TKI continue or stop? Ornard et al Clin Cancer Res 2011

OVERALL POPULATION: PROGRESSION-FREE SURVIVAL


- Gefitinib 250 mg/day until PD
- 1:1 randomization
- Carboplatin AUC 5 or 6 and Paclitaxel 200mg/m² X 6 Cycles
- Patients:
  - Age ≥ 18 years
  - Life expectancy ≥ 12 weeks
  - Adenocarcinoma histology
  - Never smokers or light ex-smokers*
  - PS 0-2
  - Stage IIIB/IV
  - Measurable disease
- Endpoints:
  - Primary: Progression free survival
  - Secondary: Objective response rate, Quality of life, Disease related symptoms, Overall survival, Safety and tolerability
- Exploratory: Biomarker 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


Gefitinib demonstrated superiority relative to carboplatin/paclitaxel in terms of PFS


Overall PFS (months) 5.7 vs 4.5

Gefitinib vs Carboplatin

Probability of PFS

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

![Graph showing comparison of PFS by mutation status](image)

Mok et al. N Eng J Med 2009
Fukuoka et al. ASCO 2009 abst 8588
Mok et al. WCLC 2009 abst B9.5

SURVIVAL TIME of EGFR mut +ve NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>First line</th>
<th>Median OS</th>
<th>Ref</th>
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<tr>
<td>IPASS</td>
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<td>Rosell et al (NEJM 2009)</td>
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<td>NEJ002</td>
<td>Gefitinib</td>
<td>27.7M</td>
<td>Nozato et al (2011)</td>
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<td>WJOG3405</td>
<td>Gefitinib</td>
<td>30.9M</td>
<td>Jänne et al (WCLC 2011)</td>
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<td>First-SIGNAL</td>
<td>Docetaxel</td>
<td>26.9M</td>
<td>Nozato et al (2011)</td>
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<tr>
<td>I-CAMP</td>
<td>Gefitinib</td>
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<td>Nozato et al (2011)</td>
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<tr>
<td>SLCG</td>
<td>Erlotinib</td>
<td>27.0M</td>
<td>Rosell et al (NEJM 2009)</td>
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</table>

EGFR TKIS IN EGFR MUT+ NSCLC:
STUDIES IN CAUCASSIAN PATIENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>n</th>
<th>PFS median months</th>
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<td>NEJ002</td>
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<tr>
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<td>II</td>
<td>33</td>
<td>14.1</td>
<td>Jänne et al. WCLC 2011</td>
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</table>

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

- Phase III study initiated by Tongji University, Shanghai, China
- Primary endpoint: PFS 13.1vs. 4.6 mos HR 0.16 P<0.0001
- Secondary endpoints: ORR, OS, QoL, localisation of PD

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

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

Zhou et al. Lancet Oncol 2011
**PFS in ITT POPULATION**

(UPDATED ANALYSIS 26 Jan 2011)

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

HR=0.37 (0.25–0.54)
Log-rank p<0.0001

![Graph showing PFS in ITT POPULATION](image)

Rosell et al. ASCO 2011abstr 7503

**1st line EGFR tki in POOR PS PATIENTS**

<table>
<thead>
<tr>
<th>Parameter</th>
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<td>EGFR mut +ve %</td>
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<tr>
<td>OR%</td>
<td>4</td>
<td>8</td>
<td>66</td>
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<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

**OVERALL SURVIVAL IN ITT POPULATION**

(INTERIM ANALYSIS 2 AUG 2010)

- Erlotinib (n=77; 35% with event)
- Chemotherapy (n=76; 36% with event)

HR=0.80 (0.47–1.37)
Log-rank p=0.4170

![Graph showing OS survival](image)

N.B. 59 pts in chemotherapy arm had PFS event; 51 of these had second-line treatment, of whom 49 had EGFR TKI

Rosell et al. ASCO 2011abstr 7503

**FIRST LAW OF ONCOLOGY**

Tumour must shrink faster than the patient

**SUMMARY OF PFS IN EGFR MUT+ STUDIES**

![Graph showing summary of PFS in EGFR MUT+ studies](image)

**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

![Graph showing time to use EGFR TKIs](image)


Platinum doublet chemotherapy

First-line EGFR TKI provides QoL benefit over chemotherapy

Rosell, et al. ASCO 2011abstr 7503
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

First ESMO Consensus Felip et al Ann Oncol 2011

LIMITATIONS OF THE HISTORICAL 'WATCH AND WAIT' APPROACH

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

Stinchcombe and Socinski J Thoracic Oncol 2009

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

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

Ciuleanu et al Lancet 2009

ONLY ~50% OF PATIENTS RECEIVE SECOND-LINE THERAPY

Socinski et al. 2002
Brodtowicz et al. 2006
von Plessen et al. 2005
Barata et al. 2007
Park et al. 2007
Ciuleanu et al. 2009
Scagliotti et al. 2008
Fidias et al. 2009

OVERALL SURVIVAL BY HISTOLOGY

Non-squamous (n=481)

Squamous (n=182)

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+ vs

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+ tumours

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)

OS with Maintenance Tarceva in EGFR Mutation+ and Wild-Type Group

OS in EGFR Wild-Type Group with SD on First-Line Chemotherapy

OS in EGFR Wild-Type Group with SD on First-Line Chemotherapy

Mainteinance Therapy ESMO, ASCO Guidelines

Focused Update of Recommendation A6  J Clin Oncol 2011

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.

Cappuzzo et al, Lancet Oncol 2010

[Cappuzzo et al, Lancet Oncol 2010]

[Coudert et al, ELCC 2010 abst 2040]
IS THERE A DIFFERENCE BETWEEN TKIs?

USE OF TKI IN EGFR WILD TYPE NSCLC

• 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

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)


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

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


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%

Thatcher et al. Lancet 2005
Blackhall et al. Lancet Onc 2006

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with EGFR WT disease</th>
<th>HR (95% CI)</th>
<th>Testing method(s)</th>
</tr>
</thead>
</table>
| BR.21 | Erlotinib (n=115) Placebo (n=55) | PFS HR=0.57 p=0.001 | EGFR Scorpion 
  MiFR; direct gene sequencing and fragment analysis |
| SATURN | Erlotinib (n=193) Placebo (n=103) | PFS HR=0.76 p=0.015 | Sanger DNA sequencing |
| SATURN SD | Erlotinib (n=114) Placebo (n=52) | PFS HR=0.72 p=0.031 | |

2. Tsao, et al. NEJM 2005

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

Patients with stage IIIIB/IV, refractory NSCLC; PS 0–3; 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

HAZARD RATIO FOR DEATH BY SUBSETS

<table>
<thead>
<tr>
<th>Subsets</th>
<th>Erlotinib/Placebo</th>
<th>Hazard Ratio</th>
<th>P Values</th>
<th>NEJM 2005</th>
<th>P values</th>
<th>FDA 2005</th>
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<td>EGFR-positive</td>
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</tr>
</tbody>
</table>

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
- ECOG PS (0 or 1 vs 2)
- Smoking history (current vs former vs never)
- Region

Zhu et al J Clin Oncol 2008
Clark et al Clin Lung Cancer 2006

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

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 tiks? 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

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

COMBING OTHER TARGETED THERAPIES WITH ERLOTINIB
COULD IMPROVE OUTCOMES

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

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**

![Image of 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
Chatt 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

- Advanced NSCLC
  Pd after ≥12 weeks
erlotinib with clinical benefit
- Pemetrexed or docetaxel
  X 8 cycles

**ADD CHEMOTHERAPY TO TKI**

**Incorporation of chemotherapy**

- EGFR mutant First-line
  - EGFR TKI + Concurrent Chemotherapy
  - Interception EGFR TKI + Chemotherapy
  - Induction Chemotherapy EGFR TKI

**TREATMENT-BEYOND-PROGRESSION ASPIRATION**

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

- Advanced stage NSCLC with EGFR Mutation
  - PD By RECIST

- Primary endpoint: OS

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

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

<table>
<thead>
<tr>
<th>Screening</th>
<th>Study Treatment</th>
<th>Post-treatment</th>
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<tbody>
<tr>
<td>NPR 8 weeks</td>
<td>Gemcitabine (dt. 8) + Cisplatin or Carboplatin (dt) + Erlotinib (d15-28) q4wks X 6 cycles</td>
<td>Erlotinib 150mg qd</td>
</tr>
</tbody>
</table>

** DELAY OR PREVENT THE APPEARANCE OF RESISTANCE TO EGFR TKIS**

New EGFR TKIs or combination with new targets

- EGFR TKI + Other targets
  - MET + inhibitors AMG208 Met Mab crizotinib, XL121
  - EGFRVEGFR inhibitors vantelisib, XL1647, BA090514
  - IGF-IR inhibitor
  - HDAC inhibitors, MS-275
  - mTOR inhibitors, etofoxim
  - Others

- Gefitinib ERLOTINIB

<table>
<thead>
<tr>
<th>EGFR mutant First-line</th>
<th>Gefitinib ERLOTINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>New EGFR TKIs</td>
<td></td>
</tr>
<tr>
<td>2nd gen EGFR TKI irreversible inhibitors</td>
<td></td>
</tr>
<tr>
<td>3rd gen mutant specific EGFR TKI</td>
<td></td>
</tr>
</tbody>
</table>

Mak et al J Clin Oncol 2009
**ACTIVITY AND TOLERABILITY OF AFATINIB (BIBW 2992) AND CETUXIMAB**

- 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

<table>
<thead>
<tr>
<th>Progression of disease</th>
<th>Any PR</th>
<th>Best response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (8)</td>
<td>13 (50)</td>
<td>24 (92)</td>
</tr>
<tr>
<td>1 (7)</td>
<td>8 (57)</td>
<td>13 (93)</td>
</tr>
<tr>
<td>3 (7)</td>
<td>2 (67)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>23 (51)</td>
<td>42 (93)</td>
</tr>
</tbody>
</table>

**PHASE III STUDY OF AFATINIB (BIBW 2992): LUX-NSCLC**

- Afatinib (BIBW 2992)
- Patients sensitive to gefitinib (G) or erlotinib (E) eventually progress

**LUNG 1**

- Preclinical activity against NSCLC with T790M mutations
- Waterfall plots by independent review

**ENDPOINTS**

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

**FACTORS FOR ENROLMENT**

- Stage IIIB/IV NSCLC
- Progressed after 1 or 2 lines of chemotherapy (including one platinum-based)
- ECOG PS 0–1
- Histology
- Performance status
- Tobacco history
- EGFR mutation (EGFR mutation-positive NSCLC, with AR to erlotinib and gefitinib, continues to depend on EGFR signaling) erlotinib + cetuximab no activity CCR 2011

**MET DIAGNOSTIC POSITIVE PATIENTS BENEFIT FROM ERLOTINIB + METMAb**

- Of 26 patients treated, 22 received the predetermined maximum dose (afatinib 40 mg/day plus cetuximab 500 mg/m²)
- Median time on prior erlotinib/gefitinib therapy was 2.4 years
- Non-homogeneity across strata

**MET DIAGNOSTIC POSITIVE PATIENTS BENEFIT FROM ERLOTINIB + METMAb**

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**Efficacy**

- Probability of progression free survival in 'Met Diagnostic Positive' pts
- OS in 'Met Diagnostic Positive' pts
- OS in overall ITT patients
- Overall response rate
- Safety/tolerability

**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/m²)
- Median time on prior erlotinib/gefitinib therapy was 2.4 years

**Key Eligibility**

- Stage IIIB/IV NSCLC
- Positive to erlotinib or gefitinib
- Progressed after 1 or 2 lines of chemotherapy (including one platinum-based)
- ECOG PS 0–2
- Histology
- Performance status
- Tobacco history
- EGFR mutation (EGFR mutation-positive NSCLC, with AR to erlotinib and gefitinib, continues to depend on EGFR signaling) erlotinib + cetuximab no activity CCR 2011
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?

3rd TOPIC

EGFR TESTING

A) IHC testing only in non-squamous only? No
B) Mutation testing in non-squamous only? Yes

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 drives selection 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%.

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

ADENOCARCINOMA

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

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
• Similar to NICE UK and Royal College pathologists report

D’Angelo et al. JCO 2011 (40% smokers)
### PLACE OF TKIS IN ADVANCED NSCLC

#### NSCLC stage IIIB & IV

<table>
<thead>
<tr>
<th>EGFR mutated (exon 19 or 21)</th>
<th>EGFR wild type &amp; EGFR mutation status unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous</td>
<td>Squamous</td>
</tr>
</tbody>
</table>

#### 1L
- TKI* or
- (Platinum-based doublet)

#### M
- TKI (after chemotherapy)

#### 2L
- Docetaxel or
- Pemetrexed or
- TKI

**Only in non-squamous NSCLC**

- Erlotinib* or
- Bevacizumab
- Pemetrexed

- Erlotinib** or
- Docetaxel
- Pemetrexed

**IHC + needed for reimbursement**

**EGFR mut + test**