Mechanisms of primary/secondary resistance to EGFR inhibitors

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• How we define PD/resistance in a patient treated with EGFRTki

• Is there a role for chemotherapy?

• Do we accept a different approach for OLIGO and SYSTEMIC PD?

• Primary and Acquired resistance: quick overview

• Target the Resistance
• How we define PD/resistance in a patient treated with EGFRTki

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• Do we accept a different approach for OLIGO and SYSTEMIC PD?

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• Target the Resistance
Some considerations for patients who progress on targeted therapy

- The definition of disease progression in the context of EGFR inhibition may differ from RECIST criteria and “requires” further refinement.
Define Resistance by RECIST

EGFR TKI Resistance by RECIST at 2.6cm

PR at 2cm

Symptomatic PD at 4cm
Cessation of EGFR TKI upon progression

Table 3. Changes in tumor on CT and FDG-PET

<table>
<thead>
<tr>
<th>After stopping gefitinib or erlotinib</th>
<th>After restarting gefitinib or erlotinib</th>
<th>3 wks after adding everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median change in tumor diameter</td>
<td>+9%</td>
<td>-8%</td>
</tr>
<tr>
<td>Mean change in tumor diameter</td>
<td>+9%</td>
<td>-9%</td>
</tr>
<tr>
<td>Range in change in tumor diameter</td>
<td>-13% to +29%</td>
<td>-34% to +15%</td>
</tr>
</tbody>
</table>

Defining resistance by RECIST may lead to premature termination of TKI
ASPIRATION: To optimize treatment duration

Advance stage NSCLC with EGFR Mutation

EGFR TKI

PD By RECIST

PD By doctor Discretion*

PFS 1

PFS 2

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

PI: K Park
Diagnosis (and tests) do not end at the time of diagnosis
BRONCHIAL BIOPSY, NOVEMBER 2010
Adenocarcinoma, acinar

BRONCHIAL ASPIRATE, NOVEMBER 2010
adenocarcinoma
BRONCHIAL BIOPSY, JANUARY 2012
small cell carcinoma

TTF-1

synaptophysin
Emergence of EGFR&ALK Resistance Mechanisms: Rebiopsy of EGFRm&ALK+ tumors at progression

Doebele et al, CCR 2012

Sequist L et al, Sci Transl Med 2011
Zakowski MF et al, NEJM 2006
Morinaga R et al, Lung Cancer 2007
Is there a room for rechallenge?

EGFRm+ pts receiving 1st line treatment with gefitinib with a documented complete (CR) or partial response (PR) or stable disease (SD) >12 weeks as the best response.

Chemotherapy (P-based or docetaxel or pemetrexed monochemo)

RECHALLENGE with gefitinib 250 mg/die

Ph II trial; PI: F De Marinis
EGFR TKI Re-treatment after Acquired Resistance: DFCI/MGH Experience

- Retrospective, 24 pts (over 9.5 yrs) with activating EGFR mutation after AR to gefitinib (30%) or erlotinib (70%)
- RR 4%, SD 63%
- Median interval off EGFR TKI 5 mo (range 2-46 mo)
- Greater benefit w/longer interval of EGFR TKI (PFS 4.4 vs. 1.9 mo for 6 mo interval off EGFR TKI)

Heon, ASCO 2012, Abst#7525
Re-challenge with EGFR TKI after Acquired Resistance

- N = 73 pts with acquired resistance
- OS post-PD better for 56 who had EGFR TKI re-treatment vs. 17 who did not

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-administration (with/without)</td>
<td>0.0003</td>
<td>0.45 (0.30-0.68)</td>
</tr>
<tr>
<td>T790M (with/without)</td>
<td>0.0024</td>
<td>0.57 (0.37-0.82)</td>
</tr>
<tr>
<td>PS (0-1/2-4)</td>
<td>0.0003</td>
<td>3.65 (1.77-8.33)</td>
</tr>
<tr>
<td>Brain metastases (with/without)</td>
<td>0.3266</td>
<td>0.86 (0.63-1.16)</td>
</tr>
<tr>
<td>Leptomeningeal metastases (with/without)</td>
<td>0.2592</td>
<td>1.20 (0.87-1.68)</td>
</tr>
</tbody>
</table>

※Proportional hazards model was used in the analysis.

- No correlation of benefit w/interval off EGFR TKI seen

Hata, ASCO 2012, A#7528
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Chemo/Erlotinib vs. Chemo Alone at Progression after Acquired Resistance

• N = 78 retrospective review of outcomes
  – chemo alone (N = 44) or
  – chemo/erlotinib (N = 34)

• RR 18% (chemo) vs. 41% with chemo/erlotinib)

• No differences in PFS or OS between these two strategies

Goldberg, ASCO 2012, Abst#7524
IMPRESS: Chemotherapy with or with gefitinib at progression

Advance stage NSCLC with EGFR Mutation

Gefinitinib

PD By RECIST

Primary endpoint: PFS

Gefitinib +
Alimta/Platinum

Alimta/Platinum

Co-PI: Soria J; Mok T
Chemotherapy +/- Ongoing EGFR TKI for Acquired Resistance, with Retreatment

PI: Leora Horn (Vanderbilt)

Advanced NSCLC
Activating EGFR TKI
Resp to EGFR TKI >4 mo
No prior chemotherapy
PS 0/1
N= 120

Cis or Carbo/Pemetrexed + ongoing erlotinib

Cis or Carbo/Pemetrexed

Erlotinib re-treatment

Stratification by:
EGFR mut’n exon 19 vs. exon 21
Time to progression on EGFR TKI <1 yr vs. >1 yr
PS 0 vs. 1

Primary endpoint: progression-free survival
• How we define PD/resistance in a patient treated with EGFR-Tki

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Treatment of TKI Resistance

Oncogenic driven cancer with tumor response to TKI

Oligo-Progression

- Local therapy + continuation of TKI

Systemic Progression

Systemic therapy

Targeting the resistant gene

Chemotherapy

Chemotherapy + TKI
Treatment of TKI Resistance

Oncogenic driven cancer with tumor response to TKI

Oligo-Progression

Local therapy + continuation of TKI

Systemic Progression

Systemic therapy

Targeting the resistant gene

Chemotherapy

Chemotherapy + TKI
Local Therapy in Acquired Resistance: MSKCC

- 18/184 pts/7+ yrs underwent local therapy for extracranial PD
  - CNS PD excluded
- From time of local therapy
  - Median TTP: 10 months
  - Median time to new systemic Rx: 22 months
  - Median OS: 41 months

Yu, ASCO 2012, Abst#7527
**Local treatment** to oligo-progression plus continuation of TKI

- Colorado University collection of 65 patients with oncogenic driven cancer (EGFR mutation or ALK positive)
- All received EGFR TKI or Crizotinib
- PFS 1 defined as <4 sites of progression
  - Local ablative therapy offered to all sites of involvement and continue TKI
- PFS 2 defined as from time of local therapy to second progression

*Weickhardt A et al, Proc ASCO 2012 # 7526*
### PFS of patients treated with local therapy and continuation of TKI therapy

<table>
<thead>
<tr>
<th>Site of first progression</th>
<th>Number of patients</th>
<th>PFS1 (months)(95% CI)</th>
<th>PFS2 (months)(95% CI)</th>
<th>Site of 2nd progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>10</td>
<td>10.9 7.3 – 18.3</td>
<td>7.1 1.7 – 11.3</td>
<td>2 (20%) no prog</td>
</tr>
<tr>
<td>*eCNS†</td>
<td>15</td>
<td>9.0 6.5 – 13.8</td>
<td>4.0 2.7 – 7.4</td>
<td>3 (30%) CNS</td>
</tr>
<tr>
<td>All patients</td>
<td>25</td>
<td>9.8 8.8 – 13.8</td>
<td>6.2 3.7 – 8.0</td>
<td>6 (24%) no prog</td>
</tr>
</tbody>
</table>

*Includes 3 patients who progressed systemically (eCNS) and simultaneously within the CNS

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* bone, lung, lymph node, adrenal, liver

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*Weickhardt A et al, JTO Dec 2012*
**Future Prospective Study?**

Primary endpoint: PFS
Secondary endpoint: OS, RR, QOL

*Weickhardt A et al, JTO Dec 2012*
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Primary Resistance

- Mutational activation of targets immediately downstream of EGFR can induce resistance to EGFR Tki: one clear example is Ras which can bypass the inhibition of the upstream EGFR signal.

- It is postulated that the loss of PTEN is associated with increased signaling via the PI3K-Akt pathway and thereby enhancing the survival of NSCLC cells, causing resistance to both erlotinib and gefitinib with resultant poor prognosis in NSCLC patients.

- The mechanism of primary resistance includes in-frame insertion mutations in EGFR exon 20, accounting for about 5% of NSCLC patients. De novo resistant T790M mutation on exon 20 has also been reported.

- The presence of c-MET amplification, a transmembrane TK receptor, or its overexpression has also been demonstrated in a subset of patients who had not been treated with EGFR-TKIs and this was also thought to represent a form of primary resistance to EGFR-TKI.

# Incidence of *De Novo* T790M

<table>
<thead>
<tr>
<th>Study</th>
<th>Technique</th>
<th># cases / #EGFRm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inukai, CR 2006</td>
<td>Sequencing, Enriched PCR</td>
<td>1/98 (1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/98 (4%)</td>
</tr>
<tr>
<td>Sequist, JCO 2008</td>
<td>Sequencing</td>
<td>2/34 (6%)</td>
</tr>
<tr>
<td>IPASS, NEJM 2009</td>
<td>SARMS</td>
<td>7/261 (3%)</td>
</tr>
<tr>
<td>Maheswaran, NEJM 2009</td>
<td>SARMS</td>
<td>10/36 (28%)</td>
</tr>
<tr>
<td>Rossell ASCO 2010</td>
<td>Taqman + PNA probe</td>
<td>45/129 (35%)</td>
</tr>
<tr>
<td>Hata, JTO, 2010</td>
<td>PNA-LNA clamp</td>
<td>3/318 (1%)</td>
</tr>
</tbody>
</table>
Acquired Resistance

- IGF seems to be involved in some cases of resistance
- The drug development is hindered by a lack of understanding of the mechanisms involved in the development of resistance.
- EGFR-TKIs (e.g., Erlotinib, Gefitinib) can lead to resistance through mechanisms such as EGFR amplification (5-20%) and overexpression of HGF (10-20%).
- MET amplification (5-20%) and overexpression of HGF (10-20%) can also contribute to resistance.

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MET activates PI3K/Akt signaling in the presence of EGFR-TKI
*Engelman Science 2007, Bean PNAS 2007*

Concomitant inhibition of both EGFR and MET is required to kill resistant cells

Targeting of Both the c-Met and EGFR Pathways Results in Additive Inhibition of Lung Tumorigenesis in Transgenic Mice
*Stabile L et al, Cancer 2010*

MET amplification: 4-22% of NSCLC with acquired EGFR TKI resistance

**Tivantinib: Phase II data**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tivantinib/Erlotinib</th>
<th>Placebo/Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>3.2 (1.9 - 4.2)</td>
<td>2.0 (1.8 - 4.9)</td>
</tr>
<tr>
<td>Non-squamous cell</td>
<td>4.4 (3.5 - 7.3)</td>
<td>2.3 (1.9 - 3.7)</td>
</tr>
<tr>
<td>c-MET FISH &gt; 4</td>
<td>3.6 (1.9 - 5.7)</td>
<td>3.6 (1.7 - 3.8)</td>
</tr>
<tr>
<td>c-MET FISH &gt; 5</td>
<td>5.6 (3.8 - NE)</td>
<td>3.6 (1.8 - 7.3)</td>
</tr>
<tr>
<td>EGFR mutant</td>
<td>5.6 (1.9 - 7.5)</td>
<td>4.9 (1.9 - 8.4)</td>
</tr>
<tr>
<td>EGFR wt</td>
<td>3.2 (1.9 - 4.2)</td>
<td>1.9 (1.8 - 2.3)</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>2.3 (1.8 - NE)</td>
<td>1.0 (0.3 - 1.9)</td>
</tr>
<tr>
<td>KRAS wt</td>
<td>3.6 (1.9 - 4.2)</td>
<td>2.3 (1.9 - 3.7)</td>
</tr>
</tbody>
</table>

- A PFS benefit associated with tivantinib plus erlotinib was observed in patients with tumors harboring amplified c-MET, wild-type EGFR, or mutant KRAS.

Cox proportional hazard ratio analysis of median progression-free survival by patient subgroup. Abbreviations: CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazard ratio; PFS, progression-free survival; wt, wild type.

*Sequist L, Shiller J et al, JCO 2011*
Onartuzumab: Phase II data

<table>
<thead>
<tr>
<th>Baseline Risk Factor</th>
<th>Erlotinib +Placebo Median (wk)</th>
<th>Erlotinib +MetMAb Median (wk)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
<th>Erlotinib +MetMAb Better</th>
<th>Erlotinib +Placebo Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects (n=128)</td>
<td>11.1</td>
<td>9.6</td>
<td>1.09 (0.71–1.67)</td>
<td>0.699</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met IHC Scheme II Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n=18)</td>
<td>8.8</td>
<td>5.9</td>
<td>2.94 (0.92–9.40)</td>
<td>0.058</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=38)</td>
<td>11.4</td>
<td>6.1</td>
<td>1.82 (0.79–4.18)</td>
<td>0.151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (n=51)</td>
<td>6.4</td>
<td>12.9</td>
<td>0.57 (0.28–1.14)</td>
<td>0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (n=14)</td>
<td>6.3</td>
<td>11.6</td>
<td>0.36 (0.09–1.33)</td>
<td>0.108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Squamous Cell (n=97)</td>
<td>9.4</td>
<td>9.6</td>
<td>1.05 (0.64–1.74)</td>
<td>0.836</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell (n=31)</td>
<td>11.4</td>
<td>6.3</td>
<td>1.27 (0.55–2.95)</td>
<td>0.579</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 Cigarettes (n=18)</td>
<td>11.7</td>
<td>5.9</td>
<td>2.30 (0.44–11.87)</td>
<td>0.308</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 Cigarettes (n=110)</td>
<td>10.9</td>
<td>9.6</td>
<td>0.99 (0.63–1.55)</td>
<td>0.967</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1 (n=122)</td>
<td>11.3</td>
<td>9.7</td>
<td>1.08 (0.70–1.68)</td>
<td>0.727</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ (n=6)</td>
<td>6.0</td>
<td>5.9</td>
<td>0.85 (0.14–5.24)</td>
<td>0.863</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR Mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildtype (n=99)</td>
<td>10.9</td>
<td>6.1</td>
<td>1.28 (0.80–2.05)</td>
<td>0.308</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant (n=13)</td>
<td>na</td>
<td>na</td>
<td>1.63 (0.10–26.5)</td>
<td>0.728</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS Mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildtype (n=86)</td>
<td>11.3</td>
<td>6.3</td>
<td>1.19 (0.71–2.00)</td>
<td>0.517</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant (n=26)</td>
<td>11.4</td>
<td>6.0</td>
<td>1.04 (0.38–2.79)</td>
<td>0.945</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adequate tissue for central IHC assay of Met receptor, and EGFR testing if EGFR status is unknown

**Patient Selection**
Stage IIIb / IV NSCLC
Measurable no prior chemotherapy
Adenocarcinoma non- or light ex-smoker
Must have tumor tissue available prior to enrollment

**Endpoints**
- 1° ORR
- 2° Safety, duration of response, PFS, OS
- Biomarker analysis

**Stratification**
ECOG PS
Smoking Hx
Gender

**Randomization**
1:1

**Cross-over Treatment**
(unti PD, unacceptable toxicity or other discontinuation reasons)

n= 85
gefitinib + ficlatuzumab

n= approx. 60%
gefitinib + ficlatuzumab PD after initial response

n= approx. 60%
gefitinib monotherapy

**End of Treatment**
(all subjects within 30 +/- 3 days after last dose of study treatment will complete an end of treatment visit)

**Endpoints**
- 1° ORR
- 2° Safety, duration of response, PFS, OS
- Biomarker analysis

**Early discontinuations, non-responders, or subjects that do not want to participate in x-over**

*Mok ASCO 2011, NCT01039948*
T790M

Sequist L et al, Sci Transl Med 2011

Ohashi K et al, JCO 2013

~60% second-site EGFR mutations (mostly T790M)
# Second- and Third-generation EGFR TKIs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Generic Name</th>
<th>Target</th>
<th>Recommended dose</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKB-569</td>
<td>Pelitinib</td>
<td>EGFR</td>
<td>50 mg once per day</td>
<td>Phase I*</td>
</tr>
<tr>
<td>CI-1033</td>
<td>Canertinib</td>
<td>EGFR/ERBB2/ERBB4</td>
<td>150 mg once per day</td>
<td>Phase II*</td>
</tr>
<tr>
<td>HKI-272</td>
<td>Neratinib</td>
<td>EGFR/ERBB2</td>
<td>320 mg once per day (than 240 within trial)</td>
<td>Phase II*</td>
</tr>
<tr>
<td>BIBW2992</td>
<td>Afatinib</td>
<td>EGFR/ERBB2/ERBB4</td>
<td>50 mg once per day</td>
<td>Phase III</td>
</tr>
<tr>
<td>PF-00299804</td>
<td>Dacomitinib</td>
<td>EGFR/ERBB2/ERBB4</td>
<td>45 mg once per day</td>
<td>Phase III</td>
</tr>
<tr>
<td>CO-1686</td>
<td>NA</td>
<td>EGFR T790M</td>
<td>NA</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>WZ4002</td>
<td>NA</td>
<td>EGFR T790M</td>
<td>NA</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

*no additional trials planned in lung cancer

Ohashi K et al, JCO 2013
# Irreversible EGFR TKIs

<table>
<thead>
<tr>
<th>Mutation:</th>
<th>WT</th>
<th>Activated</th>
<th>Resistance</th>
<th>Target</th>
<th>Binding mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>wild type H1666</td>
<td>L858R H3255</td>
<td>L858R+T790M NCI1975</td>
<td>EGFR/HER2</td>
<td>Irreversible</td>
</tr>
<tr>
<td>BIBW 2992¹</td>
<td>60</td>
<td>0.7</td>
<td>99</td>
<td>EGFR/HER2</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Gefitinib¹</td>
<td>157</td>
<td>5</td>
<td>&gt;4000</td>
<td>EGFR</td>
<td>Reversible</td>
</tr>
<tr>
<td>Erlotinib¹</td>
<td>110</td>
<td>40</td>
<td>&gt;4000</td>
<td>EGFR</td>
<td>Reversible</td>
</tr>
<tr>
<td>Lapatinib¹</td>
<td>534</td>
<td>63</td>
<td>&gt;4000</td>
<td>EGFR/HER2</td>
<td>Reversible</td>
</tr>
<tr>
<td>CP 724,714²</td>
<td>&gt;4000</td>
<td>561</td>
<td>&gt;4000</td>
<td>HER2</td>
<td>Reversible</td>
</tr>
</tbody>
</table>

IC50 values (nM) for the inhibitory activities of different compounds on the proliferation of NSCLC cells with EGFR mutations

<table>
<thead>
<tr>
<th>EGFR mutation</th>
<th>Gefitinib IC50</th>
<th>PF299 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del E746_A750</td>
<td>4.8 nM</td>
<td>&lt;1 nM</td>
</tr>
<tr>
<td>Del S752_I759</td>
<td>35 nM</td>
<td>2.0 nM</td>
</tr>
<tr>
<td>Del L747_A750InsP</td>
<td>7.4 nM</td>
<td>1.6 nM</td>
</tr>
<tr>
<td>L858R</td>
<td>26 nM</td>
<td>2.6 nM</td>
</tr>
<tr>
<td>L858R/T790M</td>
<td>&gt;10000</td>
<td>300 nM</td>
</tr>
</tbody>
</table>
LUX-Lung 1 – Trial Design

LUX-Lung 1
A multicentre, randomized, double-blind Phase IIb/III trial of BIBW 2992* plus best supportive care (BSC) versus BSC in patients with non-small cell lung cancer (NSCLC) who have progressed after chemotherapy and erlotinib or gefitinib

Patients with:
• Adenocarcinoma of the lung
• Stage IIIB/IV
• Progressed after 1 or 2 lines chemotherapy (incl. 1 platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib
• ECOG 0–2
N=585

Randomization

2:1

Oral BIBW 2992 50 mg once-daily plus best supportive care

Oral placebo once-daily plus best supportive care

Primary endpoint: Overall survival (OS)
Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

PFS (independent review)

PF299 (dacomitinib)- Phase II Trial

- PF299804 was self-administered at a dose of 45 mg once daily, continuously

- Pts with advanced NSCLC previously treated with one or two chemotherapy regimens and erlotinib
### PF299 Patients Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adenocarcinoma</th>
<th>Nonadenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=50</td>
<td>n=16</td>
</tr>
<tr>
<td>Mean (range) age, years</td>
<td>60.7 (37–79)</td>
<td>65.0 (50–84)</td>
</tr>
<tr>
<td>Gender (male/female), n</td>
<td>15/35</td>
<td>14/2</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>27 (54)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (2)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>22 (44)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Mutational status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS wt</td>
<td>50 (100)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>EGFR wt</td>
<td>11 (22)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>EGFR exon 19</td>
<td>13 (26)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>EGFR exon 20</td>
<td>3 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>EGFR exon 21</td>
<td>7 (14)</td>
<td>0</td>
</tr>
<tr>
<td>EGFR sensitizing mutation and T790M</td>
<td>7 (14)</td>
<td>0</td>
</tr>
<tr>
<td>EGFR mutation not specified</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>EGFR unknown</td>
<td>8 (16)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Prior chemotherapy treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 regimen</td>
<td>4 (8)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>2 regimens</td>
<td>18 (36)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>≥3 regimens</td>
<td>28 (56)</td>
<td>7 (44)</td>
</tr>
</tbody>
</table>
Progression-free Survival According to EGFR Mutation Status

- **EGFR mutant (n=26)**
  - Median 19.3 weeks
  - (95% CI: 17.3–31.0)

- **EGFR wild type (n=20)**
  - Median 11.1 weeks
  - (95% CI: 5.0–NA)

Janne P et al, ASCO 2010 abst 7596
Dual Targeting of EGFR

Regales L et al, J Clin Invest 2009
Phase IB Afatinib and Cetuximab

Horn L et al, IASLC 2011
Other targets
FGFR Autocrine/Paracrine Loop

EGFR

EGF
TGFα

FGFR2/3

FGF2
FGF9

Growth and Transformation

TME (fibroblasts)

Gefitinib
Erlotinib

EGF
TGFα

FGF2
FGF9

Courtesy P. Bunn
Three of nine EGFR mutant NSCLC cell lines acquire EGFR TKI-resistance through induction of FGF2 and FGFR1

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>EGFR genotype</th>
<th>Resistance</th>
<th>Resistance Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1650</td>
<td>E746-A750 del</td>
<td>Gefitinib resistant</td>
<td>FGF2 and FGFR1 induction</td>
</tr>
<tr>
<td>H1975</td>
<td>L858R, T790M</td>
<td>BIBW2992 resistant</td>
<td>IGF1R?</td>
</tr>
<tr>
<td>H3255</td>
<td>L858R</td>
<td>Gefitinib resistant</td>
<td>Multi-clonal</td>
</tr>
<tr>
<td>HCC827</td>
<td>E746-A750 del</td>
<td>Gefitinib resistant</td>
<td>MET amplification</td>
</tr>
<tr>
<td>HCC2279</td>
<td>E746-A750 del</td>
<td>Gefitinib resistant</td>
<td>FGF2 and FGFR1 induction</td>
</tr>
<tr>
<td>HCC2935</td>
<td>E746-S752 del, I insert</td>
<td>In process</td>
<td></td>
</tr>
<tr>
<td>HCC4006</td>
<td>L747-A750 del, P insert</td>
<td>Gefitinib resistant</td>
<td>FGF2 and FGFR1 induction</td>
</tr>
<tr>
<td>HCC4011</td>
<td>L858R</td>
<td>In process</td>
<td></td>
</tr>
<tr>
<td>PC9</td>
<td>E746-A750 del</td>
<td>Gefitinib resistant</td>
<td>T790M</td>
</tr>
</tbody>
</table>
Phase I Study of FGFR TKI + Erlotinib
Study: Design

Part 1: MTD determination
Patients:
- Clinically selected
  - Advanced solid malignancies
  - Refractory to SoC or no SoC available
PK data collected
Escalating doses of erlotinib (50-150mg/day po) and FGFR TKI up to RP2D
1 cycle = 4 weeks
Scans every 2 cycles

Part 2:
Patients: advanced stage adenocarcinoma
- Molecularly defined
- No limit on prior regimens
Efficacy and single-/multi-dose PK data collected

EGFR activating mutations
EGFR wt (excluding KRAS mut and ALK+)

Study sites are Univ. Colorado, one or more sites in Asia and one or more other SPORE sites.
Rationale for Hsp90 inhibition in NSCLC

• NSCLC with activating mutations in EGFR
  – Mutated EGFR is a sensitive client protein of Hsp90
  – Both T790M and Met amplification are susceptible to Hsp90 inhibition (Park et al, Abstract 2450 AACR Annual Meeting 2008)

• NSCLC containing wild type EGFR
  – Many NSCLC cell lines are sensitive to Hsp90 inhibitors in vitro
  – Multiple proteins important in the progression of NSCLC are client proteins of Hsp90
    • HER2
    • p-AKT
    • EML4-ALK
    • c-RAF
Study Design

NCT01124864

Phase II Study Population
- Previously treated stage IIIb or IV NSCLC
- ≥2 lines of chemotherapy
- Prior EGFR TKI therapy if EGFR is mutated
- WHO PS ≤2

AUY922 70 mg/m²
KRAS-activating mutation
n=28

AUY922 70 mg/m²
EGFR-activating mutation
n=35

AUY922 70 mg/m²
EGFR/KRAS/ALK wild type
n=33

AUY922 70 mg/m²
ALK+
n=22

Bayesian design:
Primary endpoint – efficacy classified as 3 categories (mutually exclusive):
1. Response (CR or PR) or 2. SD at 18 weeks or 3. No clinical benefit (NCB)
Secondary endpoints – efficacy (OS, or PFS) and PK, safety/tolerability

Null hypothesis (no efficacy): response ≤5%, and NCB ≥85%
Alternative hypothesis (efficacious): response ≥10% (≥20% for ALK+ arm), or NCB ≤60% (≤40% for ALK+ arm)

CR, complete response; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

Shaw A et al, ESMO 2012
## Results: Patient Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographic or characteristic</th>
<th>KRAS-mut (n=28)</th>
<th>EGFR-mut (n=35)</th>
<th>EGFR/KRAS/ALK wt (n=33)</th>
<th>ALK+ (n=22)</th>
<th>All* (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median), years</td>
<td>60</td>
<td>63</td>
<td>63</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>Sex (male), %</td>
<td>17 (61)</td>
<td>10 (29)</td>
<td>15 (45)</td>
<td>7 (32)</td>
<td>52 (43)</td>
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<tr>
<td>WHO PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (36)</td>
<td>13 (37)</td>
<td>10 (30)</td>
<td>9 (41)</td>
<td>43 (36)</td>
</tr>
<tr>
<td>1</td>
<td>18 (64)</td>
<td>19 (54)</td>
<td>20 (61)</td>
<td>11 (50)</td>
<td>70 (58)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>3 (9)</td>
<td>3 (9)</td>
<td>2 (9)</td>
<td>8 (7)</td>
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<tr>
<td>Histology</td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>23 (82)</td>
<td>32 (91)</td>
<td>27 (82)</td>
<td>20 (91)</td>
<td>105 (87)</td>
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<td>Squamous cell carcinoma</td>
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<td>0 (0)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (14)</td>
<td>3 (9)</td>
<td>4 (12)</td>
<td>2 (9)</td>
<td>13 (11)</td>
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<tr>
<td>Prior regimens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
<td>3 (9)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>2</td>
<td>8 (29)</td>
<td>13 (37)</td>
<td>16 (48)</td>
<td>5 (23)</td>
<td>42 (35)</td>
</tr>
<tr>
<td>3</td>
<td>14 (50)</td>
<td>11 (31)</td>
<td>4 (12)</td>
<td>7 (32)</td>
<td>38 (31)</td>
</tr>
<tr>
<td>≥4</td>
<td>5 (18)</td>
<td>8 (23)</td>
<td>13 (39)</td>
<td>9 (41)</td>
<td>36 (30)</td>
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<tr>
<td>Prior ALK inhibitor (crizotinib)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>14 (64)</td>
<td>NA</td>
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<tr>
<td>Prior EGFR TKI</td>
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<td></td>
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<tr>
<td>Erlotinib</td>
<td>NA</td>
<td>34 (97)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Gefitinib</td>
<td>NA</td>
<td>30 (86)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>None</td>
<td>NA</td>
<td>4 (11)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Includes unknown genotype patients (n=3; stratum not listed); NA, not applicable; wt, wild type.

*Shaw A et al, ESMO 2012*
Best CT Response:

**EGFR-mutant Patients (n=25\textsuperscript{†}/35)**

<table>
<thead>
<tr>
<th></th>
<th>EGFR-mutant (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (any PR)</td>
<td>7 (20%)\textsuperscript{‡}</td>
</tr>
<tr>
<td>DCR (CR/PR or SD)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>PFS (18 weeks [95% CI]), %</td>
<td>35.2 (18.7, 52.2)</td>
</tr>
</tbody>
</table>

*Confirmed responses; \textsuperscript{†}Patients with at least one post-baseline scan; \textsuperscript{‡}Including one PR not confirmed.

*Shaw A et al, ESMO 2012*
Best CT Response: *EGFR*-mutant Patients with EGFR TKI as Part of Their Last Regimen (n= 16\(^\dagger\)/19)

<table>
<thead>
<tr>
<th></th>
<th>EGFR-mutant with TKI as part of last regimen (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (any PR)</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>DCR (CR/PR or SD)</td>
<td>13 (68%)</td>
</tr>
<tr>
<td>PFS (18 weeks [95% CI]), %</td>
<td>46.6 (21.6, 68.4)</td>
</tr>
</tbody>
</table>

*Confirmed responses; \(\dagger\)Patients with at least one post-baseline scan.

Shaw A et al, ESMO 2012
Conclusion

• More information and details are needed about this issue
• Unfortunately, at the present time, only chemotherapy is approved in this setting
• Whenever is possible, please contribute to implement knowledge increasing re-biopsies at the time of resistance and including pts in dedicated trials
Save the date!

October 27 - 31, 2013

IASLC 15th World Conference on Lung Cancer
October 27 – October 31, 2013
Sydney, Australia