**Highlights ASCO 2011**

- Advanced NSCLC
  - EGFR-TKI in 1st line treatment
  - Maintenance treatment with pemetrexed or EGFR-TKI
- 2nd line treatment options with EGFR-TKIs
- Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed
- SCLC
- Mesothelioma

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**1st line EGFR-TKI vs chemotherapy in EGFR mutation positive NSCLC**

### Inclusion criteria:
- Chemonaive pts with good PS
- EGFR mutation positive

### EGFR-TKI until PD

### Platinum-based chemotherapy up to 4 or 6 cycles

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Ethnicity</th>
<th>EGFR-TKI</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>WJTOG3405</td>
<td>172</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Cis + Doc (Ex)</td>
</tr>
<tr>
<td>NEJ002</td>
<td>228</td>
<td>asian</td>
<td>Gefitinib</td>
<td>Carlo + Pacli (Ex)</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>165</td>
<td>asian</td>
<td>Erlotinib</td>
<td>Carlo + Gemci (4x)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>174</td>
<td>caucasian</td>
<td>Erlotinib</td>
<td>Carlo + Gemci (4x)</td>
</tr>
</tbody>
</table>

**EURTAC: baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Updated analysis</th>
<th>Erlotinib (n=86)</th>
<th>Chemotherapy (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>65 (24–82)</td>
<td>65 (39–81)</td>
<td></td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>82.6</td>
<td>72.3</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>14</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>14</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>EGFR mutation type, %</td>
<td>66.7</td>
<td>73.8</td>
<td></td>
</tr>
<tr>
<td>Exon 19 del</td>
<td>66.7</td>
<td>73.8</td>
<td></td>
</tr>
<tr>
<td>L858R mutation</td>
<td>66.7</td>
<td>73.8</td>
<td></td>
</tr>
</tbody>
</table>

All patients were Caucasian and the majority (~90%) had stage IV disease and adenocarcinoma

**Interim results of the European Erlotinib vs Chemotherapy (EURTAC) trial**

- ORR: 58% vs 15%
- Median PFS (m): 9.7 vs 5.2
- HR for OS: 0.80 [0.47-1.37]

**EURTAC: conclusions**

- EURTAC is the first prospective study of an EGFR tyrosine-kinase inhibitor (TKI) versus chemotherapy for first-line treatment of EGFR mutation-positive NSCLC in Caucasian patients
- The study results confirm significant benefit in PFS of erlotinib over standard chemotherapy
  - 63% reduction in risk of progression (HR=0.37)
- OS data are immature, with high level of known crossover
- No new safety findings (as expected)
- Tolerability of erlotinib consistent with previous studies
NEJ002: 1st line gefitinib vs carbo-pacli in EGFR mutation + NSCLC (updated)

- Progression-free survival
- Overall survival

Influence of EGFR TKI and subsequent therapies on OS

QoL was maintained for a significantly longer duration by gefitinib than carboplatin + paclitaxel.

OPTIMAL: 1st line erlotinib vs carbo+gemci in asian pts with EGFR mutation
**OPTIMAL: 1st line erlotinib vs carbo+gemci in asian pts with EGFR mutation**

![OPTIMAL: 1st line erlotinib vs carbo+gemci in asian pts with EGFR mutation](image)

**Optimal: conclusions**

- This updated analysis of the OPTIMAL study showed that erlotinib is associated with a significant PFS benefit vs standard chemotherapy as first-line treatment for patients with advanced NSCLC whose tumours harbour activating mutations.
- The PFS benefit with erlotinib was regardless of age, gender, PS, disease stage, tumour histology and smoking status.
- Patient QoL was also significantly improved with erlotinib compared with G/C.
- Erlotinib appears to be an important agent in the first-line treatment of EGFR Act Mut+ NSCLC.

**1st line EGFR-TKI vs chemotherapy in EGFR mutation positive NSCLC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR</th>
<th>PFS</th>
<th>HR PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (subgroup)</td>
<td>71%</td>
<td>6.3 m</td>
<td>0.48</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>62%</td>
<td>6.3 m</td>
<td>0.49</td>
</tr>
<tr>
<td>NEJ002</td>
<td>74%</td>
<td>5.4 m</td>
<td>0.30</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>83%</td>
<td>4.6 m</td>
<td>0.16</td>
</tr>
<tr>
<td>EURTAC</td>
<td>59%</td>
<td>5.2 m</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*P<0.05

**Comparison of overall survival between pts who began 1st-line systemic therapy after gefitinib approval and pts who began treatment before gefitinib approval.**

![Comparison of overall survival between pts who began 1st-line systemic therapy after gefitinib approval and pts who began treatment before gefitinib approval](image)

**Gefitinib as maintenance therapy in pts with advanced NSCLC: INFORM trial**

**Study design**

- **Inclusion criteria:**
  - Stage IIIbIV NSCLC
  - PS 0-2
  - Non-PD following 4 cycles of platinum-based chemotherapy
- **Exploratory biomarkers** (EGFR mutations)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Maintenance arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIb/IV NSCLC</td>
<td>250 mg/d</td>
<td>Placebo</td>
</tr>
<tr>
<td>PS 0-2</td>
<td>until progression</td>
<td>until progression</td>
</tr>
<tr>
<td>Non-PD following 4 cycles of platinum-based chemotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Endpoints:**
- Primary: PFS
- Secondary: OS, ORR, DCR, QoL, and safety
- Exploratory biomarkers (EGFR mutations)
INFORM trial: progression-free survival

The greatest magnitude of effect of pFS was observed in patients with EGFR mutation-positive tumours.

INFORM trial: ORR and OS

SATURN: PFS ~ EGFR mutation status

Hazard ratios for PFS and OS by EGFR mutation status.

Saturn: overall survival

Maintenance EGFR-TKI vs placebo in EGFR mutation positive NSCLC

HR for PFS Mutant EGFR Wild-type EGFR
SATURN 1 0.10 * 0.78 *
INFORM 2 0.17 * 0.86

Paramount: Pemetrexed maintenance following Cisplatin + Pemetrexed

Primary endpoint: PFS

Table 1: Overview of post-study treatments received.
PARAMOUNT: conclusions

- PARAMOUNT met its primary endpoint
- Pemetrexed as maintenance therapy significantly improved PFS versus placebo (HR 0.62)
  - Investigator-assessed PFS was confirmed by the independent assessment
- Pemetrexed was well tolerated, with a safety profile similar to that reported previously in a study of pemetrexed as maintenance therapy in NSCLC
- These data suggest that pemetrexed is effective as maintenance therapy in patients with advanced nonsquamous NSCLC who have received pemetrexed + cisplatin induction therapy

Single agent maintenance therapy for advanced stage NSCLC: a meta-analysis

- Key results
  - OS (HR 0.87, p=0.0003) and PFS (HR 0.84, p<0.0001) were superior with maintenance therapy
  - ‘Switch’ maintenance therapy was associated with significant OS (HR 0.86, p=0.00046) and PFS (HR 0.71, p=0.0001) improvement.
  - ‘Continuation’ maintenance therapy was not associated with survival benefit.
  - Similar improvements in OS and PFS were observed with EGFR-targeted agents (OS HR 0.86, p=0.006; PFS HR 0.76, p<0.0001) and cytotoxic agents (OS HR 0.88, p=0.018; PFS HR 0.87, p<0.0001).

Single agent maintenance therapy for advanced stage NSCLC: a meta-analysis

- Key conclusions
  - Single agent maintenance therapy improves overall survival, though statistical significance was only noted with ‘switch’ maintenance
  - A survival benefit was observed with chemotherapy and EGFR-targeted therapy

NB: Results of PARAMOUNT and the gefitinib maintenance study from ASCO 2011 were not included in this analysis!

Negative TTF-1 status predicts for negative EGFR-mutation in lungadenocarcinoma

- Prevalence EGFR mutation in study population: 15-19%
- Retrospective study on 301 parafin-embedded tumors

<table>
<thead>
<tr>
<th>EGFR-mutation</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>222</td>
<td>49</td>
</tr>
<tr>
<td>Y</td>
<td>2</td>
<td>28</td>
</tr>
</tbody>
</table>

- Sensitivity: 99% ; Negative predictive value: 93%
  - Patients with lungadenoCA (~30%) that are that are TTF-1 negative have a high (99%) probability of being EGFR WT. These patients could be initiated on chemotherapy while awaiting their results of EGFR mutation testing.

single agent maintenance therapy for advanced stage NSCLC: a meta-analysis

- Study objective
  - To evaluate the effect of single agent maintenance therapy on survival in NSCLC
- Study type/design
  - Meta-analysis of randomized studies that evaluated the effect of single agent maintenance therapy on survival in NSCLC
  - Primary outcome: OS (secondary outcome: PFS)
  - 10 reports (3 abstracts, 7 publications) eligible for inclusion with a total of 3451 patients
  - were not included in this analysis
Highlights ASCO 2011

- The presence of an **EGFR** mutation is the driving factor that determines outcome rather than the clinical characteristics (such as ethnicity, gender, smoking status or histology).
- The detection of **EGFR** mutations in patients with NSCLC is the first molecular predictive factor that offers patients a more effective and convenient targeted therapy than conventional chemotherapy regimens.

Highlights ASCO 2011

- The efficacy of the **EGFR-TKI** in **EGFR** mutation-positive NSCLC patients is independent from the line of therapy: all patients with a known **EGFR** mutation should be treated with an **EGFR-TKI**.
- In the absence of an **EGFR** mutation (or of **EGFR** mutation results), chemotherapy remains the 1st-line treatment of choice.

Highlights ASCO 2011

- **EGFR-TKI** as 1st-line treatment for NSCLC with activating **EGFR** mutations?

<table>
<thead>
<tr>
<th>Pro</th>
<th>Contra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved progression free survival</td>
<td>Logistics of <strong>EGFR</strong> mutation analysis</td>
</tr>
<tr>
<td>Improved response rate</td>
<td>No improved overall survival</td>
</tr>
<tr>
<td>Improved QoL and symptom control</td>
<td></td>
</tr>
<tr>
<td>Favours toxicity profile</td>
<td></td>
</tr>
</tbody>
</table>

**EGFR-TKIs are the new standard of care for the 1st-line treatment for NSCLC with known activating **EGFR** mutations!**

Highlights ASCO 2011

- Advanced NSCLC
  - **EGFR-TKI** in 1st line treatment
  - Maintenance treatment with pemetrexed or **EGFR-TKI**
  - 2nd line treatment options with **EGFR-TKIs**
  - Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed
  - SCLC
  - Mesothelioma

Highlights ASCO 2011

- **Phase III trial of gefitinib vs pemetrexed as second-line treatment in NSCLC**
  - Study performed in Korea (N 141)
  - Primary endpoint: PFS
  - The study closed early due to licensed indication changes for both pemetrexed (non-squamous) and gefitinib (**EGFR** mutation positive tumours) in South Korea
**Phase III trial of gefitinib vs pemetrexed as second-line treatment in NSCLC**

- Conclusion:
  - Gefitinib was associated with superior efficacy to pemetrexed as second-line therapy in clinically selected Korean patients with NSCLC
  - Gefitinib may be preferable to pemetrexed as second-line therapy in enriched NSCLC patients

**Molecular predictors of outcome of gefitinib and docetaxel in previously treated NSCLC: INTEREST trial**

- EGFR mutation-positive patients had longer progression-free survival and higher objective response rate (42.1% vs 21.1%) with gefitinib versus docetaxel.

**HORG: phase III study of erlotinib vs pemetrexed as 2nd or 3rd line treatment**

- Primary endpoint = time to progression (TTP)
- Secondary endpoints = RR, OS, safety

**Similar TTP and OS with erlotinib and pemetrexed in 2nd or 3rd line setting**

**TTP with erlotinib and pemetrexed according to histology**

- Squamous cell carcinoma (TP)
  - TTP: 3.6 months
  - PD: 3.6 months
  - Elixir: 2.3 months
  - Pemetrexed: 4 months

- Non-Squamous cell carcinoma (TP)
  - TTP: 3.6 months
  - PD: 6.9 months
  - Elixir: 2.3 months
  - Pemetrexed: 4 months

**Phase II: Erlotinib +/- MetMAb in 2nd/3rd-line NSCLC**

- Key eligibility:
  - Stage IIIB/IV NSCLC
  - 1–2 prior chemotherapy regimens
  - ECOG PS 0–2

- Stratification factors:
  - Tobacco history
  - PS
  - Histology

- Co-primary objectives:
  - PFS in ‘Met Diagnostic Positive’ patients (est. 50%)
  - PFS in overall ITT population

**Study design**

- Arm A: MetMAb (15 mg/kg IV Q3W) erlotinib (150 mg daily)
- Arm B: Placebo (IV Q3W) erlotinib (150 mg daily)

- PD: Must be eligible to be treated with MetMAb

- Placebo (IV Q3W)
- Elixir (150 mg daily)
- MetMAb (15 mg/kg IV Q3W)
- Add MetMAb (n=27)
- n=137
- n=9
- n=68
**Met IHC as a companion diagnostic**

- Met Diagnostic Positive was defined as majority (≥50%) of tumor cells with moderate or strong staining intensity.
- Met diagnostic status was assessed after randomization and prior to unblinding.
- 93% of patients had adequate tissue for evaluation of Met by IHC.
- 52% of patients with evaluable tissue were “Met Diagnostic Positive.”

**MetMAb plus erlotinib in Met Dx+ pts**

**MetMAb plus erlotinib in Met Dx- pts**

- MetMAb is a potent and selective inhibitor of the Met pathway.
- MetMAb + erlotinib improves PFS and OS in Met Dx+ patients.
  - Not driven by key subpopulations or imbalances in prognostic characteristics.
  - Differences in outcomes between different subpopulations highlight the importance of diagnostic development.
  - A Phase III study evaluating MetMAb + erlotinib in Met Dx+ patients is expected to start accruing patients later this year.

**MetMAb + erlotinib: conclusions**

- MetMAb is a potent and selective inhibitor of the Met pathway.
- MetMAb + erlotinib improves PFS and OS in Met Dx+ patients.
  - Not driven by key subpopulations or imbalances in prognostic characteristics.
  - Differences in outcomes between different subpopulations highlight the importance of diagnostic development.
  - A Phase III study evaluating MetMAb + erlotinib in Met Dx+ patients is expected to start accruing patients later this year.

**Afatinib and cetuximab in NSCLC pts with acquired resistance to erlotinib or gefitinib**

- Double disease (2 diseases) in 1 month: Arm A (Afatinib) vs. Arm B (Cetuximab/Erbitux).
- Patient or investigator response to erlotinib/egitnib.
- Discontinue erlotinib/egitnib for 772 hours.
- Double disease (2 diseases) in 1 month: Arm A (Afatinib) vs. Arm B (Cetuximab/Erbitux).
- Patient or investigator response to erlotinib/egitnib.

- Expansion cohort pts with NSCLC pts with acquired resistance to erlotinib or gefitinib.

- MET cohort expanded with MET-positive patients.
  - Stage IV: 1000 mg orally bid.
  - MET-positive: 1000 mg orally bid.
Afatinib and cetuximab in NSCLC pts with acquired resistance to erlotinib or gefitinib

In this ongoing study, objective responses were observed in T790M-positive and T790M-negative tumours with:
- a confirmed objective response rate of 40%
- a disease control rate of 93%

These data support that EGFR mutation-positive NSCLC, with acquired resistance to erlotinib and gefitinib, continues to depend on EGFR signaling.

Highlights ASCO 2011

• Advanced NSCLC
  - EGFR-TKI in 1st line treatment
  - Maintenance treatment with pemetrexed or EGFR-TKI
• Local and locally advanced NSCLC
  - PET-CT for radiotherapy planning
  - Adjuvant cisplatin + pemetrexed
• SCLC
• Mesothelioma

Randomized trial of PET/CT vs CT for RT treatment planning in stage III NSCLC

PET-CT

CT

N 152 158
Median OS 20m 16m
2-yr OS 47% 39%

Planning of RT with PET-CT results in significant improvement of OS. This is most likely due to more accurate staging resulting in stage-appropriate treatment.

SUV and clinical stage are strong predictors of OS.
Inclusion criteria:
- Completely resected stage IB, IIA, IIB and T3N1M0 NSCLC
- PS 0-1
- No repeat DLT
- Neutropenia or thrombocytopenia grade 4 for > 7d
- Neurotoxicity grade 3/4 with pneumonia
- Thrombocytopenia with bleeding
- Non-haematological toxicity grade 3/4 related to chemotherapy

Primary endpoint: “clinical feasibility” defined as:
- No death AND
- No non-acceptance by patients leading to premature withdrawal
- No observation of DLT

ORR: 31.1% vs 16.9% (p=0.001)

Cis+Pem vs Cis+VRB as adjuvant CT

Cis+Pem vs Cis+VRB as adjuvant CT

In the FLEX trial:
- Vinorelbine 25 mg/m² d1, q3 wks
- Cisplatin 75 mg/m² d1 every 3 weeks for 4 cycles

Median OS was 9.6 m with cisplatin and 9.4 m with carboplatin

Key results:
- Cisplatin + Pemtrexed is safe and feasible
- Has less toxicity compared to Cis+Vrb
- Has superior dose delivery compared to Cis+Vrb
- High dose density

Cis+Pem vs Cis+VRB as adjuvant CT

Cis-Pem vs Cis+VRB as adjuvant CT

Cis+Pem vs Cis+VRB as adjuvant CT

Cis+Pem vs Cis+VRB as adjuvant CT

In the FLEX trial:
- Vinorelbine 25 mg/m² q3 wks
- Cisplatin 75 mg/m² d1 every 4 weeks for 4 cycles
- No evidence of treatment difference according to gender, stage, PS or
- 2nd line treatment options with EGFR-TKIs
- Local and locally advanced NSCLC
- PET-CT for radiotherapy planning
- Adjuvant cisplatin + pemetrexed
- SCLC
- Mesothelioma

COCIS individual patient data meta-analysis: Carbo vs Cis as 1st line treatment of SCLC

- Study objective:
  - To compare the efficacy of cisplatin- vs carboplatin-based CT for the first line treatment of SCLC
- Key results:
  - Four eligible trials were included with a total of 663 patients
  - Median OS was 9.6 m with cisplatin and 9.4 m with carboplatin
  - HR 1.08; p = 0.69
  - No evidence of treatment difference according to gender, stage, PS or age
  - Haematological toxicity was higher with carboplatin, and non-haematological toxicity was higher with cisplatin
- Key conclusions:
  - COCIS is the first IPD meta-analysis in the treatment of poor prognosis and/or extensive stage SCLC
  - There appears to be no survival difference between cisplatin- and carboplatin-based CT in this setting
Phase III of thalidomide vs observation as maintenance in mesothelioma

- Study objective
  - To determine if thalidomide as maintenance therapy improves PFS in patients with MPM who have not progressed following initial therapy with pemetrexed/carboplatin or cisplatin

- Results
  - No difference in efficacy between study arms: TTP HR: 1.0 (0.7-1.2; p=0.71); OS HR 1.2 (0.9-1.6; p=0.30)
  - No obvious difference in post-study treatments between treatment arms

- Conclusions
  - Thalidomide as switch maintenance therapy in MPM is not effective

Highlights ASCO 2011

- It’s beter to have an advanced (non-squamous) NSCLC than an advanced SCLC or a malignant mesothelioma