eligible. Direct sequencing using DNA extracted from paraffin-embedded tumor specimens to detect mutations in EGFR (exons 18, 19 and 21) was performed in a central laboratory, and the median time for the analysis required 12 days (range 7-28). The primary objective was the objective response rate of gefitinib in NSCLC patients with EGFR mutations. With the target activity level of 50% and the lowest response rate of interest set at 25%, 23 eligible patients were required to accept the hypothesis.

Results: Between March 2005 and January 2006, EGFR mutations were detected in 32 patients (27%) in 118 screened NSCLC patients. EGFR mutations were significantly frequent in females, in adenocarcinoma histology and never smoker. Twenty-eight of the 32 patients have been enrolled onto this study; 14 patients had deletional mutations in exon 19 and 14 patients had missense mutations in exon 21. Of the 28 patients with EGFR mutations: adenocarcinoma (27), female (18) and never smoker (19). Overall response rate was 77.8 % and disease control rate was 100% (1 CR, 20 PR, 6 SD, 1 NE and no PD ). The median PFS time was 10.8 months (95% CI. 7.3 months to -). The median OS has not yet been reached, and 1Y-S was 80%. In the subset analysis of PFS, there was no significant difference between sex (male vs. female), PS (PS0/1 vs. PS2), number of prior regimens (0 vs. 1/2) and the site of EGFR mutations (exon 19 vs. exon 21). 1Y-S of exon 19 was 92.9% and exon 21 was 68.8%. There was no significant difference. The most common toxicities (grade 2-4) were rash observed in 13 (46%) patients, dry skin in 10(36%) patients and elevated AST/ALT in 6(21%) patients. Interstitial lung disease was occurred in 3(11%) patients. No toxicities were found in the all efficacy endpoints evaluated, including overall survival, 1 year survival, overall response. Regarding toxicity there was a significant increase in rash and diarrhea. No significant difference were observed neither in the incidence of lung interstitial disease nor in other safety parameters.

Conclusions: The combination of standard chemotherapy with EGFR inhibitors did not neither improve survival, progression free survival, nor response rate compared with chemotherapy given alone. These results confirm the lack of benefit of this strategy in unselected patient population. Further investigations are required to identify potential subgroup of patients who could benefit with the addition of these agents including sequential strategies.

P3-153 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6
Uptaded analysis of a randomized phase II trial of early change of a chemotherapeutic doublet versus four cycles of chemotherapy in advanced non small cell lung cancer (NSCLC): the 03-01 Groupe Français de Pneumo-Cancérologie (GFPC) study
Vergnenègre, Alain1 Chouaïd, Christos2 Corre, Romain1 Barlési, Fabrice3 Bérand, Henri1 Vernejoux, Jean-Marc Le Caer, Hervé4 Fournel, Pierre5 Marin, Benoit6 Tillon, Julie7
1 CHU Limoges, Limoges, France 2 CHU St Antoine, Paris, France 3 CHU, Rennes, France 4 CHU, Marseille, France 5 HIA, Toulon, France 6 CHU, Bordeaux, France 7 CH, Draguignan, France 8 CHU, St Etienne, France 9 CHU, Limoges, France 10 CHU, Rouen, France

Background: The optimal strategy in advanced NSCLC with stable disease is not well known. The sequence and the drugs are not defined.

Purpose: To evaluate the efficacy and safety of early modification of chemotherapy doublets in patients with advanced non small cell lung cancer with stable disease (SD).

Methods: Patients with stage IV NSCLC and measurable disease were included in a randomized phase II trial comparing for patients with stable disease after 2 cycles of a platin (P)-gemcitabine doublet (P d1: 75 mg/m2, gemcitabine 1 250 mg/m2 d1, d8 every three weeks) two subsequent cycles of this doublet (arm A) to a switch to another doublet (arm B): paclitaxel 100 mg/m2 d1, d8, d15, gemcitabine 1 250 mg/m2 d1, d8, every four weeks.

Results: Between October 2003 and august 2006, 228 patients (pts) were enrolled (187 males, 41 females), median age 57 y (30-70).

No differences were found in all the efficacy endpoints evaluated, including overall survival, 1 year survival, overall response. Regarding toxicity there was a significant increase in rash and diarrhea. No significant difference were observed neither in the incidence of lung interstitial disease nor in other safety parameters.

Conclusions: The combination of standard chemotherapy with EGFR inhibitors did not neither improve survival, progression free survival, nor response rate compared with chemotherapy given alone. These results confirm the lack of benefit of this strategy in unselected patient population. Further investigations are required to identify potential subgroup of patients who could benefit with the addition of these agents including sequential strategies.

<table>
<thead>
<tr>
<th>EGFR inhibitor+CT</th>
<th>Chemotherapy</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>584/1814 pts</td>
<td>546/1820 pts</td>
<td>1.11 (0.92-1.23)</td>
</tr>
<tr>
<td>1-year OS</td>
<td>764/1771 pts</td>
<td>754/1777 pts</td>
<td>1.03 (0.90-1.18)</td>
</tr>
<tr>
<td>Overall Surv.</td>
<td>1292/1812 pts</td>
<td>1293/1820 pts</td>
<td>1.01 (0.87-1.17)</td>
</tr>
<tr>
<td>Rash Gr 3/4</td>
<td>354/1406 pts</td>
<td>283/1416 pts</td>
<td>1.44 (1.19-1.75)</td>
</tr>
<tr>
<td>Diarrhea Gr 3/4</td>
<td>110/1236 pts</td>
<td>24/1241 pts</td>
<td>3.93 (2.09-5.22)</td>
</tr>
</tbody>
</table>

P3-152 NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6
Role of EGFR inhibitors in combination with chemotherapy (CT) in first line metastatic non small cell lung cancer (NSCLC): a meta-analysis based in published data
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Introduction: CT is the standard of care for patients with metastatic NSCLC. The use of EGFR inhibitors has an emerging role in this disease but it is not clear the potential benefit of adding these drugs in the first line setting. This meta-analysis aims to quantify the treatment effect of EGFR inhibitors plus standard CT in the treatment of advanced NSCLC and compare the combination to standard CT.

Purpose: analyze the efficacy and safety of the addition of EGFR-TKIs, Gefitinib or Erlotinib and Cetuximab to the standard chemotherapy in chemo-naive patients with advanced NSCLC.

Patients and methods: We have made an extensive search in the PubMed, looking for randomized trials (RT) in untreated patients with locally advanced or metastatic NSCLC, that compare standard platinum based chemotherapy with or without anti -EGFR agents. We found five RT that matched with our search criteria: four RT compare EGFR-TKIs with chemotherapy versus standard chemotherapy, and one Phase II RT that explored the addition of Cetuximab in the first line setting. We used the Mantel-Haenszel method to calculate the weighted summary Odds ratio (OR) under the fixed and random effects model.

Results: Data from a total of 3632 patients from 5 randomized trials were included.
95% CI ORR; Arm A: 15.6 [6.49 - 29.45]; Arm B: 21.4 [10.3 - 36.81].

**Conclusion:** The switch between the two regimens is feasible without any major toxicities. Despite higher response rate in favour of the switch strategy, OS and TTP are similar between the two arms. A new censor date is fixed at 1st June 2007. Overall survival and TTP will be updated for a final analysis.

### Table 1

<table>
<thead>
<tr>
<th>Arm</th>
<th>PD (%)</th>
<th>SD (%)</th>
<th>OR (%)</th>
<th>NA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>24.4</td>
<td>53.3</td>
<td>15.6</td>
<td>6.6</td>
</tr>
<tr>
<td>B</td>
<td>11.9</td>
<td>59.5</td>
<td>21.4</td>
<td>7.1</td>
</tr>
</tbody>
</table>

95% CI ORR; Arm A: 15.6 [6.49 - 29.45]; Arm B: 21.4 [10.3 - 36.81]

**P3-154**

NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

**Dynamic contrast-enhanced (DCE) MRI imaging biomarker in Phase I study with imatinib (I) and cisplatin (C) plus docetaxel (D) in patients with advanced non-small cell lung cancer (NSCLC)**

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**Background:** Imatinib inhibits activated PDGF-Rβ and down-regulates VEGF resulting in decreased angiogenesis and improved blood flow favoring enhanced tumor drug delivery.

**Objectives:** 1) determine the MTD for the combination of imatinib and cisplatin plus docetaxel in NSCLC pts; 2) describe non-dose limiting toxicities (non-DLT); 3) evaluate for feasibility and changes tumor angiogenesis measurement by DCE-MRI after treatment with imatinib. DCE-MRI detects specific properties of vascular beds by virtue of the differential distribution of contrast media in normal and pathological regions.

**Methods:** Eligibility: NSCLC with tumor expression of p-PDGF-Rβ. DCE-MRI was performed before and after 7 daily doses of imatinib alone (lead-in) followed by cisplatin plus docetaxel on day 1, every 3 weeks. Once daily imatinib was given with each cisplatin plus docetaxel cycle, on days -5 to +2. Standardized hemodynamic parameters (Ktrans, Ve, Kep) were acquired from DCE-MRI.

**Results:** 14 enrolled pts (9 M, 5 F) were evaluable for toxicity and 13 for response. Six pts were treated at dose level 1 (C+D 60/60 mg/m², and 1 300 mg); one DLT (febrile neutropenia) was seen; there were no DLTs in cohort 2 (60/60 mg/m² and I 400mg; n=3), and two DLTs were observed in cohort 3 (70/70 mg/m² and I 400mg; n=5) - febrile neutropenia and grade 4 diarrhea. For all cohorts, grade 3 and 4 toxicities were: fatigue (7%), nausea (14%), neutropenia (14%), elevated creatinine (7%), and dispnea (7%). Two pts (15%) had partial response, and 6/13 pts had stable disease as their best response. DCE-MRI demonstrated trend in decrease of Ve after 7-day treatment with imatinib (p=0.088).

**Conclusion:** MTD for imatinib and cisplatin plus docetaxel in chemonaive NSCLC pts is 400 mg and 60/60 mg/m², respectively. More, DCE-MRI is feasible in NSCLC pts. DCE-MRI measured reduction in tumor extracellular extravascular space (Ve) suggests decrease in intra-tumoral pressure after PDGF-Rβ inhibition, which could mean improvement in tumor drug delivery. Further studies exploring DCE-MRI as an imaging biomarker-predictor to antiangiogenic therapy in patients with NSCLC are ongoing.

**P3-155**

NSCLC: Molecular Targeted Therapy Posters, Wed, Sept 5 – Thurs, Sept 6

**De-novo induction of lasting cranial remission in previously irradiated and pretreated patients with metastatic non-small cell lung cancer**

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1 Asklepios-Fachkliniken Muenchen-Gauting, Gauting, Germany 2 Klinik für Strahlentherapie und Radioonkologie, LMU, Munich, Germany

**Background:** Brain metastases are a common feature of non-small-cell lung cancer (NSCLC) and are gaining more and more attention, as combined modality treatment and efficient new drug therapies have improved local control and overall survival rates. The clinical management of brain metastases is of critical importance to prevent rapid disease deterioration and symptom-driven worsening of quality of life. Therapeutic options for cranial progression after previous whole brain irradiation and chemotherapy-induced tumor remission are very limited. No established therapeutic approaches exist for cranial relapse after response to previous radiotherapy and systemic chemotherapy. Casuistry reporting of experiences with new agents in such patients may help to build up a rationale for new therapy sequences in this hard-to-treat patient population.

**Methods:** Presented are two case reports arising from our hospitals’ two-years lasting clinical experience with erlotinib, a TK-EGFR-inhibitor approved to treat patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Erlotinib was used in accordance with prescribing information as third-line therapy in two non-smoking women, one with adenocarcinoma and the other one with bronchioloalveolar carcinoma histology. Both patients were initially staged M+ due to distant lymph node and contra-lateral pulmonary tumor manifestation.

**Results:** After occurrence of brain metastases in autumn 2004, both patients underwent standard whole brain irradiation with 40 Gy. The well-tolerated radiotherapy was followed by second-line chemotherapy which resulted in both cases into a consolidation of the thoracic and cranial tumor manifestation for around six months. Pulmonary and cerebral progression requested in both cases for a therapeutic alternative. Tyrosine kinase (TK) inhibition began in July respectively October 2005. In the first patient, therapy was stopped despite ongoing cranial and pulmonary remission after 9 months due to the appearance of hepatic metastasis. In the second patient, erlotinib therapy was continued for 15 months with a lasting cranial (CR) and thoracic (PR) remission. Surgery (partial laminectomy of axis and atlas) plus post-operative cranial-cervical irradiation (40 Gy) were adequate measures to control beginning osseous metastasis in September 2006. After signs of pulmonary recurrence, therapy was stopped in December 2006. In both patients, the therapy was well tolerated with minimal side effects and improved quality of life scores. With view to the generally poor prognosis of metastatic brain cancer with its median survival of 3-4 months, the sustained objective remission and control of cranial metastases for about 9 respectively more than 15 months is noteworthy.

**Conclusions:** The ability of TK-inhibitors as erlotinib to induce objective remissions in brain metastases which occurred after initial whole brain irradiation and which relapsed after previous chemotherapy, requires attention. The observed total survival times of above 18...