

**RESPIRATORY ONCOLOGY REPORT OF THE 40<sup>TH</sup> ASCO MEETING, NEW-ORLEANS JUNE 5-8, 2004**  
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**TOP MESSAGES**

- The benefit of adjuvant cisplatin-based chemotherapy in patients with completely resected early stage NSCLC, already convincingly demonstrated in IALT, is now confirmed by two other positive North-American phase III randomised trials. Three to 4 cycles of adjuvant platinum-based chemotherapy are the new standard of care in this setting.
- The positive effect on survival with EGFR blocking agents in the 2<sup>nd</sup> or 3<sup>rd</sup> line treatment of NSCLC, already suggested in previous randomised phase II trials, is confirmed in a large randomised phase III study.

**KEY POINTS**

- FDG-PET at the start of the staging of NSCLC does not reduce the number of tests in the staging process significantly.

- Response to induction chemotherapy on early and post-induction FDG-PET is of prognostic significance in stage IIIA-N2 NSCLC.
- Addition of hyperfractionated carboplatin-sensitised radiotherapy to cisplatin-based preoperative chemotherapy for operable stage III NSCLC did not result in better outcome, but in significantly more toxicity.

- Platinum-based duplet chemotherapy remains the standard for good PS advanced NSCLC.
- Single agent therapy with a modern drug was confirmed to be a good option in poor PS advanced NSCLC. Combinations with biological agents deserve attention.
- Treatment with one agent remains the standard 2<sup>nd</sup> line chemotherapy approach for NSCLC. Combinations of two chemotherapeutic are more toxic, and do not yield better results.

- An increasing number of abstracts deal with biological therapies for NSCLC, especially inhibition of the EGFR axis.
- Two large randomised studies confirm that EGFR-directed therapy should not be given concurrently with platinum-based chemotherapy as 1<sup>st</sup> line treatment of advanced NSCLC, but that they probably should be studied in an other sequence.
- Response to EGFR-blockers is not predicted by immunohistochemical EGFR membrane staining, but many groups report advances in our ability to predict response these agents by other clinical, histological and molecular markers.
- A prospective study in bronchioloalveolar carcinoma confirmed the higher response rate of this type of NSCLC to EGFR blockade.

- No new findings that would change current practice in SCLC are reported.

- The benefit of combination chemotherapy with Cisplatin and an antifolate drug in patients with mesothelioma was already convincingly demonstrated in a previous large phase III trial. In an other smaller study with a similar drug, a same trend is reported.
- Combined modality treatment, including modern chemotherapy, surgery and radiotherapy has a potential value in local stages of mesothelioma.

## **REPORT**

The total number of ASCO abstracts has grown to the incredible number of nearly 9800. There were a total of 371 abstracts in the section 'Lung Cancer' (Proc Am Soc Clin Oncol 23:615A-706A, 2004). Of these, 24 had an oral presentation, 54 were in poster discussion sessions, 153 had a poster display and 140 were published only. This report necessarily is an extract of abstracts, selected based on the ASCO rating, and with further emphasis on either new randomised data or innovative findings, with relevance for colleagues involved with the care of respiratory oncology patients in our country. Findings are mentioned very briefly, and readers are referred to the abstracts for more details.

### **Early stage non-small cell lung cancer**

The results of the Dutch POORT study, examining the role of *upfront FDG-PET* in the staging of newly diagnosed non-small cell lung cancer (NSCLC), were reported (#7000). Patients without obvious signs of dissemination at presentation, i.e. after clinical exam, chest X-ray and bronchoscopy, were randomly assigned to immediate PET or conventional staging. The accuracy of staging was similar in both arms, and upfront FDG-PET did not reduce the number of tests in the staging process significantly.

At the last year's ASCO meeting, the results of the International Adjuvant Lung cancer Trial (IALT) demonstrated a 4 to 5% survival benefit for patients with completely resected stage I to III NSCLC, if postoperative Cisplatin-based chemotherapy was administered.

	<u>IALT (ASCO 2003)</u> (#2)	<u>Canada-US trial</u> (#7018)	<u>US trial (#7019)</u>
N	1867	482	344
Stage	I, II and III	IB and II	IB
Adjuvant therapy	Cisplatin-based/ some RT	Cisplatin-based/ no RT	Carboplatin-based/ no RT
Compliance	76%	65%	85%
5Y relapse-free survival	39.4% vs 34.3%	61% vs 48%	61% vs 50% *
Hazard ratio	0.83 ( $P=0.003$ )	0.70 ( $P=0.012$ )	0.62 ( $P=0.03$ )
5Y survival	44.5% vs 40.4%	69% vs 54%	71% vs 59%*
Hazard ratio	0.86 ( $P=0.03$ )	0.72 ( $P=0.002$ )	0.69 ( $P=0.03$ )

Table 1: Adjuvant chemotherapy studies from ASCO 2003-2004. \*Follow-up until 4 years in the US trial

Two late breaking abstracts this year also dealt with this issue. In the first Canadian-US study, Cisplatin-based *adjuvant chemotherapy* was given to patients with completely resected stage IB or II NSCLC (#7018). In the second North-American trial, the role of adjuvant Carboplatin-Paclitaxel was studied (#7019). Both studies clearly confirmed the benefit of adjuvant chemotherapy (table 1), with even more important absolute differences than in IALT, e.g. in the US study a nearly 50% reduction in risk of lung cancer mortality (34 lung cancer deaths in the observation arm, 19 in the adjuvant arm). The advantage seen in these studies were even larger than those seen in the IALT, maybe because of the more strict cooperative group setting, whereas the global recruitment in IALT may be closer to daily practice. The discussant concluded that 3 to 4 cycles of adjuvant platinum-based chemotherapy are the new standard of care.

### **Locally advanced non-small cell lung cancer**

The prognostic relevance of *early response to induction chemotherapy on FDG-PET* was reported (#7001). In this multi-centre Belgian-Dutch trial, a FDG-PET was performed at baseline, after one, and after three cycles of Cisplatin-based induction chemotherapy. The percent change in FDG-uptake after 1 cycle and after 3 cycles of induction chemotherapy was significantly correlated with survival.

A very important abstract dealt with the comparison of *preoperative chemotherapy versus chemoradiotherapy* in stage III NSCLC (#7004). In this large German phase III randomised study, a preoperative induction regimen based on Cisplatin-Etoposide alone, or the same plus

chemoradiotherapy, were compared. The addition of hyperfractionated chemoradiotherapy to the induction programme did not result in better progression-free or overall survival, but in increased toxicity, mainly oesophagitis and neutropenia. A limitation in the interpretation is the fact that most patients in the chemotherapy induction arm received postoperative irradiation.

A North-American phase III study in unresectable stage III NSCLC compared their standard therapy (concurrent chemoradiotherapy) to the same preceded by 2 cycles of Carboplatin-Paclitaxel (#7005). Survival in both arms was disappointing. There was a 2.6 months difference in median survival in favour of the new approach, but this did not reach significance.

### **Advanced non-small cell lung cancer**

There were no new data to counteract the current practice with a platinum-based duplet as *1<sup>st</sup> line treatment* in patients with good performance status. Two abstracts (#7116, #7117), including one from Belgium, noted that platinum-based chemotherapy also plays an important role in NSCLC patients with brain metastases at diagnosis.

Interesting abstracts focused on the treatment of *patients with poor PS*, for whom single agent treatment with a modern cytotoxic agent may be a good choice. One study (#7058) compared single agent Gemcitabine to Carboplatin-Gemcitabine: median survival or clinical benefit were not significantly different, and there was more toxicity in the combination treatment arm. The discussant pointed at the need for randomised studies comparing single agent with combination chemotherapy in patients with PS=2. An other interesting option may be the addition of a biological agent to a modern cytotoxic agent. One such approach was reported in #7081: in elderly patients Vinorelbine-Gefitinib (Iressa) was active, but with unacceptable toxicity, while Gemcitabine-Gefitinib was both active and safe.

Regarding *2<sup>nd</sup> line treatment*, it was reported at last year's ASCO that Pemetrexed (Alimta) was as effective as Docetaxel (Taxotere), but with a clearly decreased occurrence of neutropenia and neutropenia-related morbidity and mortality. An abstract this year (#7035) reported that symptomatic benefit in that trial was achieved both in patients with response and stable disease, and that this effect was equally present in both arms.

When considering chemotherapy for *2<sup>nd</sup> line treatment*, single agent chemotherapy remains the standard. Two presentations confirmed this attitude: Docetaxel-Irinotecan was not more effective than Docetaxel alone (#7033), nor was Docetaxel-Gemcitabine more active than Docetaxel alone (#7034); both studies reported increased toxicity for the duplet.

### **Biological agents in non-small cell lung cancer**

The positive effect on survival with *Epithelial Growth Factor Receptor (EGFR)* blocking agents in the *2<sup>nd</sup> or 3<sup>rd</sup> line treatment* of NSCLC, already suggested in two large randomised phase II trials with Gefitinib (Iressa), was further explored in a large phase III randomised study comparing Erlotinib (Tarceva) with placebo in this setting (#7022). In this study with 731 patients, there was a significant improvement in median survival (6.7 versus 4.7 months) and 1-year survival (31 versus 22%, hazard ratio 0.71, P<0.0001). Perhaps even more important in this population, the improvement of symptoms previously documented in the IDEAL studies is confirmed as well (for cough, chest pain and dyspnea).

Two very large randomised studies compared treatment with platinum-based chemotherapy (Cisplatin-Gemcitabine in Europe, Carboplatin-Paclitaxel in the US) to the same plus the EGFR-blocker Erlotinib (#7010, #7011). There was no sign of improvement in survival or any other treatment outcome endpoint.

Abstract #7028 explored the hypothesis that concurrent use of platinum-based chemotherapy and Epithelial Growth Factor Receptor (EGFR) blocking agents may not have brought what we expected, because concurrent use of EGFR blockers brings cells into G1 cycle arrest, thereby decreasing the effectiveness of chemotherapy, since most chemotherapeutic agents act in the S- or G2-M phase.

Retrospective analysis of a large number of pathology samples confirmed that EGFR expression measured by immunohistochemistry is not a *predictor of response to Gefitinib* (#7013). Recently however, a genetic basis for sensitivity to Gefitinib treatment was described (Lynch et al., N Engl J Med 350:2129-2139, 2004). Several presentations at ASCO also focused on how we could

better predict responsiveness of patients to EGFR blocking agents. Besides the known clinical/histological factors (female gender, never-smoker (#7061, #7062), adenocarcinoma, especially bronchiolo-alveolar), the role of co-expression of EGFR and Her2 was addressed (#7025), the role of downstream markers (#7026), and the role of genetic biomarker panels (#7027).

A prospective trial on Gefitinib treatment for bronchioloalveolar lung cancer was reported (#7014). The disease control rate with Gefitinib 500 mg/day was 49% in 1<sup>st</sup> line and 45% in 2<sup>nd</sup> line. Median survival was 12 to 13 months. Nearly 40% of the patients had a dose reduction to 250 mg/day, which was recommended for future study and maybe for 2<sup>nd</sup> line treatment of this disease in clinical practice.

### **Small cell lung cancer**

SCLC is very sensitive to initial treatment, but most patients experience an early and incurable relapse. Therefore, strategies to eliminate residual disease after 'successful' chemoradiotherapy in limited disease are appealing. Several years ago, 'very promising' findings with adjuvant vaccination with the BEC2-BCG vaccine were reported by a US centre. Today the results of a large (n=515) randomised phase III study are reported (#7020). They are easily summarised: totally negative.

### **Mesothelioma**

At the ASCO meeting of 2 years ago, the superiority of Cisplatin-Pemetrexed (Alimta) over Cisplatin alone was reported in the largest prospective study ever done in mesothelioma. This year, the results of a smaller phase III trial with a similar antifolate drug Raltitrexed (Tomudex) are reported (#7021). There is a trend towards better survival for the combination over Cisplatin alone (P=0.06).

Since the advent of more active chemotherapy and surgical experience, the experience with combined modality treatment approaches for this poor prognosis disease is increasing. In the Swiss experience (#7052), including patients up to stages T2N2, treatment consists of 3 cycles of chemotherapy followed by attempted complete resection, followed by radiotherapy to areas of incomplete resection.