

REPORT ASCO 2009 ORLANDO : RESPIRATORY ONCOLOGY

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10 MESSAGE HIGHLIGHTS

Early stage non-small cell lung cancer

1. Surgery plus chemotherapy remains the standard approach for most patients. There is a persistent benefit without late toxicities at long-term follow-up in several studies.
2. There is increasing evidence for adjuvant chemotherapy for stage IB with a larger sized primary tumour (>4-5 cm).
3. Timing of chemotherapy does not seem to be critical. The evidence for adjuvant chemotherapy is more solid, the compliance with induction chemotherapy is significantly better.

Locally advanced non-small cell lung cancer

4. For inoperable stage III NSCLC, concurrent administration of full dose platinum and Pemetrexed with 70 Gy was feasible & promising in a phase II randomised trial. Integration of targeted molecules (Cetuximab, Thalidomide) in this setting is studied as well. None of both approaches is ready for clinical practice.
5. A trial on the role of prophylactic PCI in this setting was terminated prematurely due to slow accrual. No benefits emerged, but follow-up is at present too short to draw conclusions.

Advanced non-small cell lung cancer

6. 1st line therapy: biomarker data of a phase III study in Asian never- or few-smokers with adenocarcinoma, comparing Gefitinib 250 mg/d until progression versus max. 6 cycles of Carboplatin-Paclitaxel, were presented. EGFR activating mutation was a crucial biomarker, as patients with a mutation had significantly more benefit from Gefitinib treatment, while the opposite was true in those without mutation.
7. 1st line therapy: biomarker data of the phase III study that showed an overall survival benefit when the EGFR antibody Cetuximab was added Cisplatin-Vinorelbine were shown. No molecular marker could identify patients with increased benefit. Patients in the Cetuximab arm who developed skin rash had a median overall survival of 15 months.
8. 'Maintenance' therapy: overall survival data of a phase III trial of 'maintenance' Pemetrexed in patients achieving disease control after 4 cycles of platinum-based doublet chemotherapy were available. Overall survival was significantly improved from 10 to 13 months in the overall study, and even to 15 months in patients with non-squamous tumours.
9. 'Maintenance' therapy: a phase III study looked at the role of Erlotinib in the same setting. There was a significant effect on progression-free survival, which was chosen as primary study endpoint. Whether this will result in true patient benefits depends on the effects on overall survival and/or quality-of-life. These data are not available yet.
10. Relapsed NSCLC: a large phase III study looked at the role of Vandetanib (a combined EGFR and VEGF tyrosine kinase inhibitor) when added to standard chemotherapy with Docetaxel. There was delay of disease progression, but, clinically more relevant, a well documented significant delay of symptom worsening. This was confirmed in a smaller phase III study with Vandetanib and Pemetrexed.

At the ASCO 2009 meeting, a total of 314 abstracts in the field of respiratory oncology were accepted, less than previous years, perhaps because nearly 1800 abstracts were submitted to the IASLC meeting in San Francisco. A total of 108 were accepted for electronic poster, while 206 were presented, either as poster display (n=140), at poster discussion sessions (n=48), or in oral sessions (n=18).

For this report, we classified studies as *RCT* (large randomised controlled trial, i.e. at least 100 patients per arm), *RCT-small* (small RCT, usually phase 2 RCTs), *RCT-sec* (secondary analyses of previously presented RCTs), or *non-RCT* (non-randomised data, usually phase 2 or other studies). We concentrated on randomised data relevant for the practicing clinician, with sometimes addition of some other abstracts selected because of their innovative or breaking news aspect.

As this report is only the 'extract of the abstracts', the reader is referred with the # sign to the respective abstract in J Clin Oncol 27, Suppl 15, pages 382-431 for more detailed information.

NSCLC – EARLY STAGES (STAGES I, II, SELECTED IIIA)

A systematic review presented at ASCO 2008 (abstract #7546 of ASCO 2008) showed a similar benefit on overall survival for adjuvant compared to neo-adjuvant chemotherapy (HR=0.80 and HR=0.81, respectively), but the statistical power was clearly in favour of adjuvant chemotherapy. More data on (neo-)adjuvant and peri-operative chemotherapy were presented at ASCO 2009.

As compliance with adjuvant chemotherapy is known to be far from optimal, the survival results of the Spanish NATCH trial and the French IFCT II trial in early stages NSCLC were eagerly awaited. Both the NATCH and IFCT II trial showed a significantly higher compliance rate to chemotherapy if given preoperatively (**Figures 1 and 2**), however this didn't result in a survival benefit compared to adjuvant or peri-operative chemotherapy. In the NATCH trial, adjuvant and neo-adjuvant chemotherapy were compared to surgery only and no progression free or overall survival difference was observed at 5 year follow-up (**Figure 1**). The potential reasons for the 'negative' results in NATCH could be (1) the use of Carboplatin based chemotherapy; (2) the fact that mainly stage I NSCLC patients were included (clinical stage I 77% and pathological stage I 50%); and (3) a substantial amount of patients were understaged (20-30% finally had stage IIIA-N2 NSCLC as no FDG-PET scan was used for baseline staging).

Figure 1 : Abstract #7500 : phase III NATCH trial.

Patient setting

Operable stage IA – selected IIIA

Randomisation

Induction chemotherapy -> surgery (n=201)

versus

Surgery alone (n=211)

versus

Surgery -> adjuvant chemotherapy (n=212)

Outcome

Primary: progression-free survival at 5 years: 47% vs. 44% vs. 46% (*P*=NS).

Other: better compliance with preoperative chemotherapy. Similar postoperative morbidity & mortality.

Conclusion

Timing of chemotherapy (pre- or postoperatively) probably not a critical issue.

The IFCT II trial was a 'negative' study as well, looking at similar 3 year overall survival rates for neo-adjuvant and peri-operative chemotherapy (**Figure 2**). Potential reasons could be (1) the inclusion of 64% stage I NSCLC (17% stage IA and 47% stage IB); (2) the use of Carboplatin-Paclitaxel chemotherapy. Striking however was that a similar pathological complete response rate was obtained after 2 (peri-operative arm) compared to 4 (neo-adjuvant arm) cycles of chemotherapy.

Figure 2 : Abstract #7530 : phase III IFCT2 trial.

Patient setting

Operable stage IA-II NSCLC.

Randomisation

2 cycles preoperative chemotherapy (plus 2 more if response) -> surgery (n=254)

versus

2 cycles pre-operative chemotherapy -> surgery -> 2 adjuvant cycles (if response preoperatively) (n=253)

Outcome

Primary: intent-to-treat overall survival at 3 years: 68% vs. 69% ($P=0.96$).

Other: better compliance with preoperative chemotherapy. No difference in pathological response rate with two versus four preoperative cycles.

Conclusion

Timing of chemotherapy (pre- or peri-operatively) probably not a critical issue.

In 2008, the IALT data did arise some concern about late chemotherapy related toxicities. At this ASCO, long-term follow-up data of the JBR.10 trial for completely resected stage IB-II NSCLC were presented that showed a durable 11% overall survival benefit for the adjuvant chemotherapy arm at a median follow-up of 9 year (HR=0.78), which was meanly attributed to stage II NSCLC (HR=0.68) (**Figure 3**). This survival benefit became clear from 18 months follow-up onwards and is explained by a significant decrease in lung cancer deaths for the chemotherapy arm (36% vs 43%; $p=0.027$), without a difference in late chemotherapy related cardiovascular deaths or second primary cancer related deaths compared to the observation arm.

Figure 3 : Abstract #7501 : long-term outcome in phase III JBR.10 trial (adjuvant NCI-C trial).

Patient setting

Completely resected stage IB-II NSCLC.

Randomisation

Adjuvant four cycles Cisplatin-Vinorelbine (n=242)

versus

Observation alone (n=240)

Outcome

Primary updated: overall survival after 9 years: 67% vs. 56% (HR 0.78, $P=0.04$).

Other: effect in stage IB dependent on tumour size: if T >4 cm 79% vs. 59% ($P=0.13$).

Conclusion

Persistent benefit of adjuvant chemotherapy after 9 years.

An additional retrospective analysis on the IALT-BIO database demonstrated that only patients who lacked the MSH2 protein (also responsible for the repair of Cisplatin-induced DNA damage, just as ERCC1) benefit from Cisplatin based adjuvant chemotherapy (**Figure 4**). However, the race for clinically applicable predictive markers to better select those patients who benefit from adjuvant chemotherapy is still on as prospective data are awaited.

Figure 4 : Abstract #7502 : predictive value of MSH2 marker in adjuvant chemotherapy (IALT-BIO).

MSH2 = protein repairing Cisplatin-DNA damage, cooperates with other DNA repair proteins

Acts as a prognostic factor

Untreated arm: MSH2+ : HR 0.66 ; $P=0.01$

Acts as a predictive factor

Adjuvant chemotherapy arm: MSH2+ : HR 1.12 ; $P=NS$ vs. MSH2- : HR 0.76 ; $P=0.03$

Conclusion

MSH2 and ERCC1 have equal predictive power for Cisplatin-based adjuvant chemotherapy.

If MSH2- and ERCC1- status is combined, the HR is 0.65 ($P=0.01$)

NSCLC – LOCALLY ADVANCED STAGES

Concurrent chemoradiotherapy is nowadays considered the standard practice for fit patients with *inoperable* stage III NSCLC aiming for a median survival time of about 20 months. However, the optimal chemotherapy regimen for concurrent use with radiotherapy still has to be defined, and so far induction or consolidation chemotherapy both failed to show benefit in clinical trials when compared to a concurrent chemoradiotherapy approach only. Moreover, clinical data show that 80% of the relapses are distant relapses. Current research focuses on several elements in order to further optimise therapy for inoperable stage III NSCLC: (1) better staging through incorporation FDG-PET; (2) better systemic chemotherapy using full dose chemotherapy and/or molecular targeted therapy; (3) better local control using a higher radiation dose >66Gy, and (4) prophylactic pancreatic irradiation. Some of these elements were addressed during this meeting.

A phase II trial on concurrent chemoradiotherapy with full dose modern chemotherapy (using Carboplatin and Pemetrexed) as well as incorporating FDG-PET met its predefined threshold for median overall survival, which was set at 21 months (**Figure 5**). Although not the primary endpoint, the addition of cetuximab (an EGFR receptor antibody) did not result in any survival benefit. Moreover, a phase III trial adding thalidomide (abstract #7503) to a concurrent schedule was stopped early for futility but also for (thromboembolic) toxicity of thalidomide.

Figure 5 : Abstract #7505 : phase II randomised trial integrating new agents in chemoradiation.

Patient setting

Inoperable stage III NSCLC.

Randomisation

Four cycles full-dose Carboplatin-Pemetrexed + Cetuximab concurrent with 70 Gy radiotherapy (n=51)
versus

Four cycles full-dose Carboplatin-Pemetrexed concurrent with 70 Gy radiotherapy (n=48).

Outcome

Primary: median overall survival 22 months vs. 22 months ($P=0.99$).

Better outcome for non-squamous histology.

Conclusion

Predefined threshold median survival of 21 months met in both arms. Confirmation of safe delivery of Pemetrexed concurrent with high-dose radiotherapy. Role of Cetuximab unclear.

The phase III RTOG 0214 trial randomised non-progressive patients after combined modality treatment for with stage III NSCLC to prophylactic pancreatic irradiation (PCI) or observation (**Figure 6**). Although there was a significant decrease in incidence of brain metastases for the PCI arm, this didn't result in a so survival benefit at 1 year follow-up; however, additional longer follow-up and quality of life data are needed before any firm conclusion can be made.

Figure 6 : Abstract #7506 : phase III trial on role of PCI.

Patient setting

Stage III, non-progressive after surgical or non-surgical combined modality treatment.

Randomisation

Prophylactic cranial irradiation 30 Gy (n=163)

versus

Observation alone (n=177).

Outcome

Primary: overall survival at 1 year: 75.6% vs. 76.9% ($P=0.86$).

Other: underpowered trial, stopped early because of poor accrual.

Conclusion

With the present data, no indication, for PCI in this setting. Longer follow-up and QoL data need to be awaited.

NSCLC – ADVANCED STAGES - FIRST-LINE THERAPY

At the ESMO 2008 meeting, the results of the IPASS (Iressa Pan Asian Study) were presented. This RCT compared Gefitinib 250 mg/d until progression versus 6 cycles of Carboplatin-Paclitaxel in Asian never- or few-smokers with adenocarcinoma. Progression-free survival was in favour of Gefitinib. At this ASCO, biomarker data of this study were presented (**Figure 7**). EGFR activating mutation was a crucial biomarker, as patients with mutations had significantly more benefit from Gefitinib treatment, while the opposite was true in those without mutation.

Figure 7 : #8006 : biomarkers of IPASS, phase III of 1st line Gefitinib in Asian light/never-smokers.

Patient setting

First-line therapy in clinically selected SE Asian patients (never- or light-smokers, adenocarcinoma).

Randomisation

Gefitinib 250 mg/day until progression (n=609)

versus

Carboplatin-Paclitaxel 6 cycles maximum (n=606).

Outcome

Primary: progression-free survival: HR 0.74 [0.65-0.85], $P<0.0001$.

Other: EGFR mutation very strong predictor of benefit with Gefitinib (HR 0.48, $P<0.0001$), absence of EGFR mutation strong predictor of benefit with chemotherapy (HR 2.85, $P<0.0001$).

Conclusion

Landmark study of how EGFR-TKIs should be used in 1st line, and of the major predictive role of EGFR activating mutation in that setting.

At the ASCO 2008 meeting, the phase III study comparing Cisplatin-Vinorelbine plus Cetuximab versus the same chemo alone was presented in the plenary session (abstract #3). Overall survival was superior for the investigational arm (HR 0.87, $P=0.04$). Biomarkers of this study were available now (**Figure 8**). None of the molecular markers was predictive for Cetuximab efficacy, in contrast with colorectal cancer where absence of K-ras mutation convincingly predicts benefit. Development of the typical acne-like rash was associated with a much better survival in the patients receiving chemotherapy and Cetuximab.

Figure 8 : Abstract #8007 : biomarkers of FLEX, phase III of adding Cetuximab to 1st line therapy.

Patient setting

Advanced NSCLC with EGFR expression on immunohistochemistry.

Randomisation

Cisplatin-Vinorelbine + Cetuximab -> Cetuximab maintenance (n=557)

versus

Cisplatin-Vinorelbine(n=568).

Outcome

Primary: overall survival: 11.3 versus 10.1 months (P=0.04).

Other: none of the molecular markers (K-ras mutation, EGFR mutation, EGFR FISH) predicted efficacy of Cetuximab. Skin rash after one cycle was associated with a significantly better survival in the Cisplatin-Vinorelbine-Cetuximab arm (HR 0.63 [0.52-0.77] $P < 0.001$; median 15 vs. 8.8 months).

Conclusion

In contrast with colorectal cancer, K-ras mutation did not show predictive value for Cetuximab therapy in NSCLC. Skin rash is associated with better survival.

So, at the ASCO, there were no new large scale data on new compounds in 1st line treatment of advanced NSCLC, but we learned more about how to use the existing ones. EGFR activating mutations are a very strong predictor of benefit from Gefitinib. From previous experience it is known that non-squamous histology predicts better outcome with Pemetrexed based chemotherapy. Typical acne-like skin rash is associated with better survival in Cetuximab treated patients.

NSCLC – ADVANCED STAGES – MAINTENANCE THERAPY

The standard approach to patients achieving disease control after 1st line platinum doublet based chemotherapy is close follow-up with indication of relapse therapy at the time of progression. Results of two important “maintenance” studies were presented.

Mature overall survival results of the phase III trial comparing consolidation Pemetrexed with placebo were available (**Figure 9**). At the ASCO 2008, promising data on progression-free survival had been presented.

Figure 9 : Abstract #8000 : overall survival in phase III JMEN trial (Pemetrexed ‘maintenance’ therapy).

Patient setting

Advanced NSCLC in disease control (response, stable) after 4 cy of platinum doublet (no Pemetrexed).

Randomisation

‘Maintenance’ Pemetrexed q3w until progression (n=441)

versus

‘Maintenance’ placebo q3w until progression (n=222).

Outcome

Primary: progression-free survival: HR=0.60 [0.49–0.73], $P < 0.00001$, median 4.0 vs. 2.0 months (2008).

Other: significant benefit in overall survival: HR 0.79 [0.65-0.95], $P = 0.012$, median 13.4 vs. 10.6 months, even more pronounced in the non-squamous group: HR 0.70, median 15.3 vs. 10.3 months.

Conclusion

Primary endpoint (PFS) significantly improved, but also overall survival benefit. Confirmation of predictive value of non-squamous histology for Pemetrexed activity. Pemetrexed maintenance well tolerated, no cumulative toxicity.

The other phase III trial looked at consolidation with Erlotinib versus placebo in the same setting. The trial was powered for progression-free survival, both in the overall group, as well as in patients with EGFR

immunohistochemistry positive patients (**Figure 10**). The primary endpoint was positive, but overall survival data need to be awaited.

Figure 10 : Abstract #8001 : phase III SATURN trial (Erlotinib maintenance therapy).

Patient setting

Advanced NSCLC in disease control (response, stable) after 4 cy of platinum doublet (no Pemetrexed).

Randomisation

‘Maintenance’ Erlotinib 150 mg/d until progression (n=438)

versus

‘Maintenance’ placebo until progression (n=451).

Outcome

Primary: progression-free survival: HR=0.71 [0.62–0.82], $P < 0.0001$, median 12.3 vs. 11.1 weeks.

Other: clinical characteristics did not predict the PFS benefit. EGFR mutation was a very strong predictor (HR in mutant+ group 0.10 [0.04-0.25], $P < 0.0001$).

Conclusion

Primary endpoint of progression-free survival was met.

Delay of progression with various types of maintenance treatment has been described in the past. But what truly matters for a patient in the non-curative setting of advanced NSCLC is quantity (how long will I live?) and quality (how good will I live?) of survival. In that respect, JMEN is the first approach where a clinically relevant overall survival benefit (median 15.3 versus 10.3 months) was reported. A remaining question for clinical practice is if this approach will have the same result if the initial chemotherapy is Pemetrexed-based (ongoing trial). The question if maintenance should now be standard practice remains a matter of debate. Supporters will say that use of maintenance prevents deterioration of condition leading to inability to tolerate 2nd line therapy when needed. Opponents will say it’s better to give the patient a treatment-free holiday, but with close follow-up so that 2nd line is given when needed. From the existing data, it is not clear which strategy is to be preferred, so discussion with the individual patient is needed.

NSCLC – ADVANCED STAGES – RELAPSE THERAPY

Before ASCO 2009, we had different single agent options: Docetaxel or Pemetrexed as standard chemotherapy, one phase III study showed that Erlotinib was better than placebo as 3rd line therapy for NSCLC (and as 2nd line in patients unfit for chemotherapy), and one global phase III trial showed that Gefitinib was non-inferior to Docetaxel.

In order to improve 2nd line therapy, several trials looked at combination therapy in this setting, until recently without success. At ASCO 2009, two phase III trial with Vandetanib (oral tyrosine kinase inhibitor active in the EGFR and VEGF axis) were reported. One trial compared Docetaxel plus Vandetanib with Docetaxel plus placebo (**Figure 11**), the other (smaller) trial looked at Pemetrexed plus Vandetanib versus Pemetrexed plus placebo.

Figure 11 : Abstract #8010 : Phase III adding Vandetanib to Docetaxel.Patient setting

Advanced NSCLC with progression after one line of chemotherapy.

Randomisation

Docetaxel q3w for 6 cycles + Vandetanib 100 mg/d until progression (n=694)

versus

Docetaxel q3w for 6 cycles + placebo until progression (n=697).

Outcome

Primary: progression-free survival: HR 0.79 [0.70-0.90], $P < 0.001$, median 4.0 vs. 3.2 months.

Other: response rate 17% vs. 10% ($P < 0.001$). Overall survival HR 0.91 [0.78-1.07], $P = 0.20$, median 10.6 vs. 10.0 months. Symptom control (FACT-L scale) HR 0.77 [0.65-0.92], $P < 0.001$.

Safety: more diarrhoea (42% vs. 33%), rash (42% vs. 24%) and neutropenia (32% vs. 27%), less anaemia (10% vs. 15%), nausea/vomiting 23% vs. 32%.

Conclusion

First phase III study to show clinical benefit when chemotherapy and targeted agent are combined in 2nd line setting.

In the companion study with Pemetrexed and Vandetanib, the HR of progression-free survival was similar at 0.86, but this was not significant, probably due to the smaller size of the study. Significant benefits in response rate and symptom control were achieved.

It is likely that the impressive data on the predictive role of EGFR mutation with Gefitinib in 1st line therapy (see above) will impact on the use of EGFR-TKIs in the relapse setting. Patients with EGFR activating mutations will be treated with the EGFR-TKI in 1st line, and no longer in the relapse situation. Therefore, new strategies for better combination treatment for relapsing patients are eagerly awaited, and the use of Vandetanib seems to be a small step in that direction.

For your calendar: ASCO 2010 : June 4-8, 2010, McCormick Place, Chicago.