

REPORT ASCO 2011 CHICAGO : RESPIRATORY ONCOLOGY

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10 MESSAGE HIGHLIGHTS

Early stage non-small cell lung cancer

1. *Adjuvant chemo.* In a phase II randomized trial, adjuvant Cisplatin-Pemetrexed – in comparison with Cisplatin-Vinorelbine – showed a better “feasibility rate” with less toxicity and better dose delivery. Efficacy follow-up is ongoing.

Locally advanced non-small cell lung cancer

2. *PET-CT for stage III.* The first RCT on use of PET-CT led to better staging and RT planning, and this translated in a 4 month better median overall survival (OS), compared to a group with CT alone. SUV predicted outcome.

Advanced non-small cell lung cancer

3. *EGFR mutant positive tumours.* In a phase III randomized trial, a significant benefit in progression-free survival (PFS) of Erlotinib over standard chemotherapy was observed in Caucasians with EGFR mutation positive (EGFR mut+) tumour.
4. *Unselected patients.* A phase II randomized trial compared Erlotinib+Bevacizumab to Cisplatin-Gemcitabine+Bevacizumab in unselected non-squamous NSCLC patients. OS was worse with 1st line Erlotinib-Bevacizumab.
5. *Continuation-maintenance.* In a randomized phase III trial on good PS patients with advanced non-squamous NSCLC without disease progression after 4 cycles of 1st line Cisplatin-Pemetrexed, a significant improvement in PFS (HR 0.62) was seen with Pemetrexed continuation maintenance. The OS data are still immature, but eagerly awaited as the trial is also statistically powered (HR=0.70 and $\alpha=0.05$) to detect a significant OS benefit.
6. *Switch-maintenance.* In a randomized phase III trial in Asian patients without disease progression after 1st line platinum doublet chemotherapy, switch maintenance with Gefitinib led to a significant improvement in PFS (HR=0.42). The magnitude of this benefit is however most likely driven by patients with an EGFR mut+ tumour.
7. *Relapse therapy by Met targeting.* The final efficacy data of a phase II randomized trial confirmed that MetMab+Erlotinib might lead to improved outcome compared to Erlotinib alone, but only in MetDx positive (by IHC) patients. This now needs confirmation in a phase III trial stratifying for EGFR mutation status.
8. In a randomized phase II trial in unselected non-squamous NSCLC comparing 2nd line Pemetrexed+Erlotinib to Erlotinib alone, the combination therapy significantly improved OS.

Other tumours

9. *Small cell lung cancer relapse therapy.* A phase III study compared Amrubicin (a 3rd generation anthracycline) with i.v. Topotecan as 2nd line SCLC treatment. Response rate was 31% vs. 17%, and this translated in a trend for better survival (HR 0.88, $P=0.17$), mostly driven by patients with refractory relapse (HR 0.77, $P=0.047$). Both arms had substantial haematological toxicity.
10. *Mesothelioma maintenance.* A phase III trial targeted the highly angiogenic aspect of mesothelioma by adding maintenance thalidomide after Platinum-Pemetrexed chemotherapy. Although conceptually interesting, the study was totally negative.

At the ASCO 2011 meeting, a total of 203 abstracts in the field of respiratory oncology were presented (233 in 2009), 138 posters, 47 poster discussion items, and 18 oral presentations.

For our report, we classified studies as *RCT* (large randomized controlled trial, i.e. >100 patients per arm), *RCT-small* (often phase 2 RCTs), *RCT-sec* (secondary analyses of previously presented RCTs), or *others* (phase 2 studies, molecular biology analyses, retrospective analyses or surveys, ...). We concentrated on randomized data relevant for the practicing clinician, along with some innovative findings.

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 29 Suppl, 2011, or http://abstract.asco.org/ConfCatView_102.html.

NSCLC – EARLY STAGES (stage I, II, resectable IIIA)

In terms of adjuvant studies, there was only one new randomised study reported this year. Its rationale was that – based on the Canadian BR.10 trial (Winton et al, N Engl J Med 352:2589, 2005) – Cisplatin-Vinorelbine has become a common adjuvant regimen, despite its toxicity and difficult delivery (only half of the patients could have full treatment), and the fact that evidence in the advanced NSCLC setting clearly points at better efficacy/tolerability of more recent doublets.

This randomised adjuvant study with a more recent doublet (TREAT: Trial on Refinement of Early stage Adjuvant Therapy) was presented (**Figure 1**). It concentrated on “feasibility rate” of adjuvant treatment, i.e. absence of severe toxicity or premature treatment withdrawal.

Figure 1: #7002 : phase II randomised adjuvant chemotherapy trial (TREAT).

Patient setting

Resected stage IB-II-T3N1 NSCLC.

Randomisation

Surgery -> adjuvant 4 cycles Cisplatin-Pemetrexed (n=67)

versus

Surgery -> adjuvant 4 cycles Cisplatin-Vinorelbine (n=65)

Outcome

Primary: “feasibility rate”: 96% vs. 75% ($P=0.001$).

Other: grade 3-4 haematological toxicity 10% Cis-Pem vs. 74% Cis-Vino ($P<0.001$).

Dose delivery Cis 90% Pem 90% vs. Cis 66% Vino 64%.

Conclusion

Adjuvant Cisplatin-Pemetrexed is safe, with less toxicity and better dose delivery. For efficacy, longer follow-up is needed.

In the ongoing ECOG 1505 trial (adjuvant chemotherapy ± Bevacizumab, several modern Cisplatin-based doublets are allowed. An interim analysis (**#7013**) reported use of Vinorelbine in 28%, Gemcitabine in 26%, Docetaxel in 34%, and Pemetrexed for non-squamous histology tumours in 12% of the patients. The interim analysis revealed no unexpected toxicities. Enrolment remains hampered by inadequate lymph node sampling in otherwise eligible patients, and end of recruitment is projected in 2013.

Cisplatin-based doublet chemotherapy is a post-operative standard for most fit patients with completely resected stage II and IIIA NSCLC, while the indication remains less clear for stage IB. Abstract **#7015** reported long-term follow-up of the only trial specifically in stage IB (Strauss et al, J Clin Oncol 26:5043, 2008). In this underpowered study, 344 patients with completely resected stage IB NSCLC were randomly assigned to an adjuvant platinum doublet (carboplatin-paclitaxel) or observation. With a median follow-up of 9 years, a trend for better OS remains in place (overall HR 0.80, $P=0.06$). For patients with larger primary tumours (>4 cm), the HR is 0.77 ($P=0.07$), which is a 10% improvement in 5-year survival from 43% to 53%. This long-term analysis confirms the potential benefit of adjuvant chemotherapy for patients with stage IB larger primary tumours. Whether larger means >4 cm as in this trial, or >5 cm as suggested by the most recent TNM, is difficult say, probably tumour size acts as a gradual continuous variable.

Abstract #7004 was an important exploratory analysis of endpoints for adjuvant trials. The standard endpoint is OS. Disease-free survival (DFS) may be an attractive surrogate endpoint, as it is more rapidly available, and not blurred by the effect of increasingly effective therapies at the time of post-operative relapse. Based on individual patient data of 7626 patients in 25 randomised trials, correlation between DFS and OS was very strong, thus good evidence that DFS is a valid endpoint in adjuvant NSCLC trials. Moreover, DFS indeed gave earlier outcome findings.

NSCLC – LOCALLY ADVANCED (unresectable IIIA, IIIB)

The most interesting abstract here was an update on the first RCT comparing PET-CT with PET alone in this setting (**Figure 2**).

Figure 2: #7018 : PET-CT for staging & RT planning in unresectable stage III NSCLC.

Patient setting

Unresectable stage III NSCLC scheduled for chemoradiotherapy.

Randomisation

Staging & RT planning with PET-CT (n=152)

versus

Staging & RT planning with CT alone (n=158)

Outcome

Primary: reported at ASCO 2009: more upstaging with PET-CT, only 118/152 (78%) PET-CT patients received radical RT compared with 146/158 (92%) of CT patients.

Reported now: survival outcomes: 4 month difference in median survival (20 vs. 16 months), 8% in 2-year OS (47% vs. 39% for the CT arm, HR 0.80, 95%CI 0.60-1.00). SUV predicted OS.

Conclusion

PET-CT is the preferred tool in stage III patients, as it is associated with better survival. This is mostly due to stage migration, although an effect of better RT planning cannot be excluded.

A point I would add here is that the 4 month survival difference with PET makes any historical comparison to advocate “therapeutic progress” with new treatments hazardous.

The standard therapy for these patients consists of combined chemoradiotherapy, and there is little to add from this ASCO. Several abstracts (#7016, 7020) reported attempts to improve on standard chemoradiotherapy by adding targeted agents, such as Erlotinib and/or Bevacizumab. Most were negative, added complexity, substantial toxicity (inability to deliver consolidation part of the treatment, squamous cell cohorts closed due to pulmonary bleeding, severe oesophagitis or fistula), and no added benefit. In contrast with metastatic stage, there is still a long road to go with targeted agents in stage III !

One more promising abstract (#7040) described data with Cetuximab added to radiotherapy alone in poor performance status patients unsuitable for combined chemoradiotherapy.

NSCLC – ADVANCED STAGE: FIRST-LINE THERAPY

The final analysis of the OS data from the Japanese NEJ002 trial (#7519) comparing 1st line Gefitinib to platinum doublet chemotherapy in EGFR mut+ NSCLC showed an identical median OS of 27 months for both arms mainly driven by the >98% cross-over to EGFR-TKI in the chemotherapy arm.

A pre-planned QoL analysis in the Chinese OPTIMAL trial (#7520) comparing Erlotinib to platinum-doublet chemotherapy in EGFR mut+ NSCLC found that the odds ratio for a clinically relevant improvement in FACT-L or LCSS on EGFR-TKI was 7 (95%CI 3-15), implying more likely QoL improvement with EGFR-TKI.

Based on the PFS data obtained from the IPASS study, comparing Gefitinib to standard chemotherapy in Asian patients clinically selected for high chance of EGFR mutation, Gefitinib has been registered in >70 countries as first line therapy for NSCLC patients harbouring an activating EGFR mutation (EGFR mut+

NSCLC). A phase III RCT comparing Erlotinib to standard chemotherapy in European Caucasians was presented at this ASCO (**Figure 3**).

Figure 3: #7503: EURTAC: Phase III of Erlotinib vs. chemotherapy in EGFR mut + NSCLC.

Patient setting

European patients with advanced NSCLC with activating EGFR mutation in exon 19 or exon 21, PS 0-2.

Randomization

Erlotinib 150 mg daily until progression (n=86)

versus

Platinum-doublet chemotherapy, every 3 weeks, 4 cycles (n=88).

Outcome

Primary: PFS: HR 0.37 [0.25-0.54], $P=0.0001$, median 9.7 vs. 5.2 months.

Other: OS: immature follow-up. Objective RR 58 vs. 15%, disease progression 7% vs. 13%.

Conclusion

The study confirms significantly better PFS of EGFR-TKIs over standard chemotherapy in EGFR mut+ NSCLC.

First line Erlotinib should however not be used in unselected NSCLC patients. The “Innovations” trial (**Figure 4**) was based on the synergistic effect of Erlotinib and Bevacizumab. This trial, just as TORCH at ASCO 2010, showed a potential detrimental OS outcome associated with 1st Erlotinib+Bevacizumab in unselected patients.

Figure 4 : #7504: Innovations: Phase II of Erlotinib+Bev vs. chemotherapy+Bev in unselected NSCLC.

Patient setting

European patients with advanced NSCLC, PS 0-2.

Randomization

Erlotinib 150 mg daily + Bev 15mg/kg q3w until progression (EB, n=111)

versus

Cisplatin-Gemcitabine for 4 cycles + Bev 15mg/kg q3w until progression (PGB, n=113).

Outcome

Primary: OS: HR 1.39 [0.97-1.99], $P=0.069$, median 12.6 vs. 16.3 months.

Other: PFS: 3.3 vs. 7.7 months (HR 1.77), and more treatment related toxicity.

Conclusion

PGB is superior to EB in unselected NSCLC patients.

Several phase II-III trials in unselected patients (e.g. #7501, #7502, #7512) compared standard chemotherapy to standard chemotherapy plus a targeted agent, and failed to demonstrate an OS benefit, most likely driven by the absence of a biomarker predicting that the new drug is targeting the target:

- **#7501:** Cis-Paclitaxel ± Cadi05 (toll-like agonist, mycobacterium w, an immunomodulator and pure Th-1 response enhancer)
- **#7502:** Carbo-Paclitaxel ± Vadimesan (ASA404, a vascular disrupting agent acting directly on the endothelial cell of tumour blood vessels)
- **#7512:** Carboplatin-Paclitaxel ± Motesanib (a selective oral inhibitor of VEGFR 1, 2, 3; PDGFR; and Kit).

NSCLC – ADVANCED STAGE: MAINTENANCE THERAPY

The classical approach to patients achieving disease control after 4 to 6 cycles of 1st line platinum doublet based chemotherapy is close follow-up with 2nd line therapy at the time of progression. A “maintenance” approach either “continuation” (same agent) or “switch” (other agent), aims at “continued suppression” of malignancy in order to prolong disease control or “early second line” in order to expose more patients to the new single agent, respectively, both with the goal to improve the OS. Two phase III “maintenance”

presentations were presented at ASCO 2011: one with “continuation maintenance” Pemetrexed in Caucasians (**Figure 5**), and one with “switch maintenance” Gefitinib in Asian patients (**Figure 6**).

Figure 5: #7510: phase III “continuation-maintenance” with Pemetrexed after 1st line Cis-Pemetrexed.

Patient setting

Advanced non-squamous NSCLC with disease control (response/stable) after 4 cy of Cis-Pemetrexed.

Randomization (2:1)

BSC + continuation Pemetrexed 500 mg/m² every 3 weeks (n=359)

versus

BSC + Placebo i.v. every 3 weeks (n=180).

Outcome

Primary: PFS: HR=0.62 [0.49-0.79], *P* =0.0002, median 4.1 (Pem) vs. 2.8 months (BSC alone).

Other: OS immature, but study powered for OS !

Safety: well tolerated, but more toxicity (fatigue, haematological).

Conclusion

Significant improvement in PFS (HR 0.62) with Pemetrexed continuation maintenance in advanced non-squamous (mainly adenocarcinoma) NSCLC with good PS.

Figure 6 : #7511: phase III “switch-maintenance” with Gefitinib after 1st line platinum-based doublet.

Patient setting

Advanced NSCLC with disease control (response/stable) after 4 cy of platinum-based doublet

Randomization

Gefitinib 250 mg daily until progression (n=148)

versus

Placebo daily until progression (n=148)

Outcome

Primary: PFS: HR 0.42 [0.32-0.54], median 3.7 vs. 2.1 months

Other: OS : 18.7 vs. 16.9 months, HR 0.84 (*P*=NS)

Safety: grade 3-4 adverse events in 6.8% of the patients (mainly rash).

Conclusion

Significant increase in PFS with Gefitinib compared to placebo. However, the magnitude of this benefit is most likely attributable to the patients with a EGFR mut+ tumour.

NSCLC – ADVANCED STAGE: RELAPSE THERAPY

Roughly half of the EGFR mut+ NSCLC cases with acquired resistance to reversible EGFR-TKIs have a secondary “gatekeeper” mutation in exon 20 (T790M) that reduces drug binding to the kinase target, while a further 15-20% have amplifications in the MET receptor gene, providing a bypass signalling pathway through kinase switching or via receptor hetero-dimerization. At this ASCO several papers evaluated strategies for overcoming resistance to the first generation EGFR-TKIs.

The next generation EGFR-TKI include irreversible inhibitors (some also target multiple members of the EGFR family), such as Afatinib (BIBW2992). A non-randomised phase II trial in 62 patients enriched for acquired resistance to Erlotinib or Gefitinib evaluated Afatinib 50 mg daily (**#7524**). The primary endpoint objective RR was 13%, disease control rate (DCR) at 8 weeks 72% and the median PFS was 4.4 months. This was comparable to the phase III Afatinib arm (n=390) of LUX-Lung-1, presented at ESMO 2010. As drug resistance appears to be pleomorphic, combinations of drugs or drugs with multiple targets may be more effective in circumventing resistance. An interesting paper addressing this strategy evaluated the combination of Afatinib and Cetuximab in patients with acquired resistance to first generation EGFR-TKI (**#7525**). In 45 evaluable patients, an ORR of 40% and DCR at 8 weeks of 93% was observed. Survival data are immature but eagerly awaited.

Interesting final efficacy data of the MetMab study presented at ESMO 2010 were reported (**Figure 7**).

Figure 7: #7505: Phase II comparing MetMab+Erlotinib to Placebo+Erlotinib.

Patient setting

Unselected advanced NSCLC with progression after one/two chemotherapies.

Randomization

MetMab i.v. q3w + Erlotinib 150 mg daily until progression (n=69)

versus

Placebo i.v. q3w + Erlotinib 150 mg daily until progression (n=68) (cross-over to MetMab in 27)

Outcome

Co-Primary: PFS in all patients: HR 1.09 [0.73-1.62]; in MetMabDx+ patients: HR 0.53 [0.28-0.99].

Other: OS in MetMab+ patients: HR 0.37 [0.19-0.72]

Safety: MetMab+Erlo similar to Erlo alone, except for more mild manageable peripheral oedema.

Conclusion

MetMab+Erlotinib might lead to improved outcome in MetDx positive patients.

The addition of MetMab in a small MetDx+ (c-Met IHC high) population resulted in a 2-fold reduction in the risk of progression and a near 3-fold reduction in the risk of death, with the caveat that the pre-planned biomarker analysis was not statistically designed upfront. Therefore a biomarker based phase 3 design including stratification for EGFR mutation status is now planned.

Based on phase III studies, the classical second line therapy options in unselected patients are Docetaxel or Pemetrexed single agent chemotherapy (the latter only for patients with non-squamous histology), or Erlotinib. A randomized phase II trial looked at combination therapy of Pemetrexed and Erlotinib to improve outcome in non-squamous histology (**#7526**), based on their synergistic activity in preclinical studies (Li et al. Clin Cancer Res 2007).

Figure 8 : #7526: Phase II comparing Pemetrexed+Erlotinib to Pemetrexed+Placebo.

Patient setting

Unselected non-squamous advanced NSCLC with progression after one chemotherapy.

Randomization

Pemetrexed+Erlotinib (n=79)

versus

Pemetrexed (n=86)

Outcome

Primary: PFS : median 3.2 vs. 2.9 months, HR=0.64 [0.44-0.90], $P=0.005$.

Other: OS: 11.8 vs. 7.8 months, HR=0.68 [0.47-0.98], $P=0.019$; ORR 17 vs. 11%.

Safety: combination had greater grade 3-4 haematological toxicity.

Conclusion

Pemetrexed+Erlotinib significantly improved survival in unselected non-squamous NSCLC compared with Pemetrexed.

Both the primary endpoint (PFS) and secondary endpoint (OS) were positive with a HR of 0.64 and 0.68, respectively, but in the absence of the molecular tumour tissue features and with a statistical trial design allowing a 20% chance of a false positive result ($\alpha=0.2$), one should be very prudent with these data.

OTHER TUMOURS (SCLC – MESOTHELIOMA)

There is little discussion about the 1st line choice of Platinum-Etoposide chemotherapy for SCLC. The real treatment challenge is at the time of relapse, which can be either refractory/resistant (i.e. during or less than 3 months after stopping 1st line), or sensitive (i.e. >3 months). For sensitive relapse, both Topotecan as well rechallenging with the initial regimen are options. The others are difficult to treat, but the novel

anthracycline Amrubicin gave promising signals at previous ASCO meetings. An important phase III trial now compared Amrubicin with i.v. Topotecan as second-line treatment for SCLC (**Figure 9**).

Figure 9: #7000: Phase III comparing Amrubicin and i.v. Topotecan.

Patient setting

Relapsing SCLC (both refractory/resistant and sensitive).

Randomization (2:1)

Amrubicin 40 mg/m² i.v. days 1-3 every 3 weeks (n=424)

versus

Topotecan 1.5 mg/m² i.v. days 1-5 every 3 weeks (n=213).

Outcome

Primary: OS: HR 0.88, $P=0.17$, median 7.5 vs. 7.8 months.

Subanalysis refractory patients: HR 0.77, $P=0.047$, median 6.2 vs. 5.7 months.

Other: response rate 31% vs. 17% ($P=0.0002$).

Safety: both treatments had substantial haematological toxicity: grade 3-4 neutropenia (41% vs. 53%), thrombocytopenia (21% vs. 54%), anaemia (16% vs. 30%), infections (16% vs. 10%), febrile neutropenia (10% vs. 4%). Transfusion rates were 32% (A) and 53% (T), all comparisons $P<0.05$. Prophylactic WBC were needed in last 1/3 of the trial.

Conclusion

Amrubicin is active in 2nd line treatment of SCLC, better response rate than Topotecan. Survival trended in favour of Amrubicin, especially in the subgroup of refractory patients.

Likewise, there is little discussion about the 1st line choice of Platinum-Pemetrexed for malignant mesothelioma, but outcome remains limited because of the lack of valid 2nd line choices. As mesothelioma is a highly angiogenic tumour – actually it is the solid tumour with the highest VEGF levels – maintenance therapy with the oral anti-angiogenesis agent thalidomide was studied in a phase III trial (**Figure 10**).

Figure 10: #7006: Phase III maintenance trial with Thalidomide in mesothelioma.

Patient setting

Malignant mesothelioma in disease control after 4 cycles Platinum-Pemetrexed chemotherapy.

Randomization

BSC + Thalidomide 200 mg/d until progression (n=108)

versus

BSC alone (n=108).

Outcome

Primary: PFS: HR 1.00, $P=0.83$, median 16 vs. 15 weeks.

Other: OS: HR 1.28, $P=0.09$, median 11 vs. 13 months.

Safety: very little toxicity.

Conclusion

Thalidomide did not provide any benefit.

A phase II study (#7027) looked at the oral tyrosine kinase inhibitor Cediranib (targets VEGFR 1, 2, 3 and PDGFR) in patients with relapsed mesothelioma. The dose had to be reduced from of 45 mg/d to 30 mg/f for excessive toxicity. This was another anti-angiogenesis failure, as there were only 2 responses in 35 patients who received the tolerable dose.

For your calendar: ASCO 2012 : June 1-5, 2012, McCormick Place, Chicago.