



## **2007 ASCO Meeting – Lung Cancer**

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## **Lung Cancer**

The Lung Session of the 2007 American Society of Clinical Oncology ASCO Meeting focused on currently approved targeted treatments such as bevacizumab as well as new approaches with other targeted agents such as cetuximab and finally addressing other options of treatment. The single most important study was exploring the use of prophylactic cranial radiation (PCI) for patients with extensive disease small cell lung cancer (ED SCLC). The EORTC 08993 study, in which 286 patients with ED SCLC who had responded to chemotherapy were randomized to PCI or no PCI. The results of this study revealed a significant decrease in the rate of brain metastases at 1 year (14.6% vs 40.4%) for those receiving PCI with a significant improvement in 6 month progression free survival and 1 year survival. The investigators conclude that patients with ED SCLC who respond to chemotherapy should be offered PCI.

The ECOG 4599 study previously reported by Dr. Alan Sandler, demonstrated that the addition of bevacizumab to Taxol/Carboplatin improved progression free survival and overall survival in patients who had previously been untreated with advanced non-small cell lung cancer. Manegold and colleagues reported the results of the AVAIL trial which was meant to be the confirmatory trial to ECOG 4599. This trial randomized patients who were previously untreated with stage IIIB or IV non-squamous cell carcinoma to receive Gemcitabine/Cisplatin chemotherapy plus placebo vs Gemcitabine/Cisplatin with 2 different dose levels of bevacizumab, either 7.5 mg/kg or 15 mg/kg. Manegold



presented the results with respect to progression free survival (PFS) which in fact was the primary end point. This demonstrated a significant improvement in PFS for Gemcitabine/Cisplatin with either dose level of bevacizumab with a HR of .75 for the 7.5 mg/kg dose and .82 for the 15 mg/kg dose. This translated into a median PFS of 6.7 and 6.5 months, respectively compared to 6.1 months for Gemcitabine/Cisplatin alone. In addition, the response rates for both levels of bevacizumab were significantly higher than Gemcitabine/Cisplatin alone with a response rate of 34% at 7.5 mg/kg and 30% at 15 mg/kg compared to 20% for chemotherapy alone. The survival data, however, is not yet available. From a toxicity perspective, there were low rates of severe hemoptysis and pulmonary hemorrhage. The investigators concluded that this trial does confirm a benefit for bevacizumab in advanced non-small cell lung cancer with an improvement in progression free survival as well as response rate. The benefit was seen with both bevacizumab dose levels, suggesting that 7.5 mg/kg may be an appropriate dose. Unfortunately, these results are not as dramatic as those reported in EGOG 4599 and at this point in time it is unlikely that bevacizumab will play an important role in advanced non-small cell lung cancer in Canada. The survival data is eagerly awaited.

The role of the oral tyrosine kinase inhibitors in second line therapy is unclear. Niho and colleagues presented a phase III study of gefitinib vs docetaxel in Japanese patients with advanced non-small lung cancer who had failed one or two prior chemotherapy regimens. They randomized 485 patients to receive either gefitinib 250 mg orally per day vs docetaxel 60 mg/m<sup>2</sup> I.V. every three weeks. The primary objective was to compare the overall survival between gefitinib and docetaxel in this patient population with the aim of demonstrating non-inferiority which would be concluded if the upper limits of the adjusted confidence interval for the hazard ratio was less than 1.25. Although the primary objective of non-inferiority was not met, there was a significant improvement in response rate, time to treatment failure and quality of life for those patients randomized to gefitinib vs those randomized to docetaxel. It is interesting to note that of those patients who were randomized to gefitinib that 36% went on to receive docetaxel, 24% went on to receive other chemotherapy and 40% of patients either received best supportive care or continued



on gefitinib. Of those patients who were randomized to receive docetaxel 53% were crossed to gefitinib, 20% to other chemotherapy and 26% either went on to receive best supportive care alone or continued with docetaxel. From a toxicity point of view, there is a 5.7% incidence of interstitial lung disease compared to only 2.9% in those patients randomized to gefitinib vs those patients receiving docetaxel. In conclusion, although the primary objective, non-inferiority in overall survival was not achieved, there was no statistical evidence of a difference in overall survival between gefitinib and docetaxel. Secondary end points that were largely unaffected by subsequent therapy showed similar or superior efficacy for gefitinib compared to docetaxel. We await with anticipation the results of the much larger INTEREST trial that also compared gefitinib to docetaxel.

Another study of interest was a late-breaking abstract by Fidias and colleagues that randomized patients with advanced Stage IIIB or IV non-small cell lung cancer who received Gemcitabine/Carboplatin for four cycles following either response or stable disease to receive either immediate docetaxel at 75 mg/m<sup>2</sup> every three weeks until progression to a maximum of 6 cycles or delayed docetaxel in the same doses at the time of progressive disease following first line chemotherapy. The primary end point was overall survival with a hazard ratio of 1.43. Five hundred and fifty-two patients received Gemcitabine/Carboplatin with an overall response rate of 29%. 307 patients were subsequently randomized to receive either immediate docetaxel or delayed docetaxel. Of the 153 patients randomized to immediate treatment, 142 received docetaxel, and of the 154 patients randomized to delayed docetaxel, 91 patients subsequently received this treatment. The results indicated a significant improvement in PFS for immediate chemotherapy with a P-value of < 0.001 and a one year PFS of 20% compared to 9% for the delayed treatment. As well, there was a trend to an improvement in overall survival for immediate chemotherapy with a median survival of 11.9 months compared to 9.1 and a one year survival of 48.5% compared to 38.3% with a P-value of .071. In addition, there was no difference in quality of life between the two treatment arms. This trial suggests that there may be a benefit to consolidation docetaxel following response or stable disease after four cycles of chemotherapy. However, these results



trended but did not show a significant improvement in overall survival and thus, it is unlikely this will result in a change in what is the usual standard of care, ie., delayed second line docetaxel following initial first line therapy.

Gronberg and colleagues presented their phase III trial of Carboplatin with either pemetrexed or gemcitabine as first line treatment. No difference in the primary outcome of this study (quality of life) was demonstrated with no significant differences in outcome for the EORTC QLQ C-30 or LC-13. As well there was no difference in overall survival observed. However, patients receiving pemetrexed/carboplatin experienced significantly less toxicity with respect to leucopenia, granulocytopenia and thrombocytopenia and patients receiving gemcitabine/carboplatin received more blood and platelet transfusions. There was no report of response rate and progression free survival is pending. Thus this trial suggests that pemetrexed and carboplatin has comparable efficacy and less hematological toxicity compared to gemcitabine/carboplatin and this regimen may ultimately be a preferred regimen for older patients and for standard risk patients. However, with the present cost of pemetrexed in Canada, it is unlikely that a change in practice will occur.

There were a number of trials addressing the role of cetuximab in patients with advanced non-small cell lung cancer. Dr. Butts presented a randomized Phase II trial of gemcitabine/cisplatin or carboplatin with or without cetuximab as first line treatment of advanced NSCLC. This demonstrated that the addition of cetuximab to chemotherapy produced a slight prolongation of progression free survival as well as overall survival in this population of patients. There was an increase in non-hematological toxicity in those patients receiving cetuximab with a 14.1% incidence of rash and 4.7% incidence of infection. He concluded that the addition of cetuximab to Gemcitabine/platinum-based chemotherapy is feasible and the safety profile is manageable. Dr. Herbst presented the results of SWOG 0342 that was initially presented last year by Dr. Kelly showing that paclitaxel/carboplatin resulted in an improved response rate of 37% vs 25% for chemotherapy alone. However, survival data presented this year demonstrated no



difference in PFS or median survival, although there was a slight increase in one year survival of 49% vs 43%. There were no major differences in toxicity except for an increase in neuropathy in the concurrent arm. The ongoing SWOG 0536 study will address the use of cetuximab and bevacizumab with paclitaxel/carboplatin

Finally, a very important trial was reported by Dr. Hanna that assessed the role of consolidation docetaxel for patients with Stage III non-small cell lung cancer following induction etoposide/cisplatin with concurrent radiation therapy. Dr. Gandara had previously reported the five year results of SWOG 9504, a Phase II study of etoposide/cisplatin concurrent with radiation followed by consolidation docetaxel which demonstrated a median survival of 26 months and a 5 year survival of 29% suggesting that consolidation docetaxel may improve the outcome of patients with Stage III disease. Dr. Hanna presented the results of the HOG LUN 101 trial that randomized patients following induction etoposide/cisplatin and concurrent radiation therapy to either observation alone or three cycles of docetaxel at 75 mg/m<sup>2</sup> every three weeks. Seventy three patients were randomized to the docetaxel arm and 74 to the observation arm. Forty percent of patients in each arm had Stage IIIA disease and the remainder had Stage IIIB disease. This trial demonstrated no significant improvement in progression free survival with the addition of consolidation docetaxel and no difference in overall three year survival. In addition, consolidation docetaxel was associated with a 10.9% incidence of febrile neutropenia, 11% incidence of infection, a 9.6% incidence of pneumonitis and 5.5% incidence in treatment related deaths with a hospitalization rate of 28.8% compared to only 8.1% in the observation arm. Thus, it is clear that docetaxel consolidation does not improve overall survival when compared to observation following induction chemotherapy and radiation therapy and is associated with significantly greater toxicity. Why this study failed to show a survival advantage with consolidation docetaxel is unknown. The issue of whether any consolidation chemotherapy is necessary following induction therapy is now in question although I suspect that the standard in Canada will continue to be etoposide/cisplatin for two cycles following the induction therapy.



Finally, it should be mentioned that there were a number of abstracts that addressed the role of EGFR biomarkers. The take home message from these trials is that EGFR mutation is neither an independent prognostic marker for early stage adenocarcinoma nor a predictor of survival in advanced non-small cell lung cancer receiving EGFR tyrosine kinase inhibitors as second line therapy. EGFR gene expression by FISH predicts survival in BR-21 but not in TRIBUTE and EGFR protein expression has limited value in prediction of survival and methodology and cut off level must be further validated.