Lung Cancer Leaps Expected at Scientific Meeting

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The American Society of Clinical Oncology’s (ASCO) Annual Meeting brings together 30,000 oncology professionals from around the world. Educational sessions feature world-renowned faculty discussing state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field. The meeting will take place May 29 – June 2, 2015.

ASCO 2015 promises to advance our knowledge of lung cancer. There are some positive studies that will impact treatments. In particular, it has been a big year for treatment advances for non-small cell lung cancer (NSCLC) which will provide insight into future diagnostic and therapeutic directions.

Immunotherapy

In lung cancer, as expected, several immunotherapy trials will be reported. The Checkmate 017 study, which investigated Opdivo (nivolumab) compared to Taxotere (docetaxel) in patients with squamous cell lung cancer in the second line setting, has already been reported as a press release. Nivolumab was associated with a three month improvement in overall survival compared to chemotherapy, with less toxicity. PD-L1 expression was not prognostic or predictive. These data are from a Phase III study and clearly indicate that immunotherapy is superior to Taxotere from both an efficacy and toxicity perspective.

Similarly the POPLAR study, which investigated Roche’s PD-L1 inhibitor MPDL3280A, was designed to investigate superiority against Taxotere. This study included both adeno- and squamous cell carcinomas, and the interim analysis showed a survival and response benefit restricted to tumours with high PD-L1 expression. For MPDL3280A, the rates of PD-L1 positivity appear to be lower than other assays. The assay measures PD-L1 expression in “tumour infiltrating lymphocytes” (immune cells invading the tumour) rather than tumour cells directly. The correlation between PD-L1 expression and response from this study appears striking, with no response in PD-L1 negative tumours.

There are many other abstracts pertaining to the immune checkpoint inhibitors being presented at ASCO this year. The Checkmate 017 study is practice-changing and suggests that Opdivo should be given to all squamous cell patients, regardless of PD-L1 status. Combinations of CTLA4 blockade (another means of activating the immune system by removing the brakes)/PD-L1 and pathological assessment of PD-L1 in molecularly subtyped tumours will also be reported.

It appears that PD-L1 expression certainly enriches for a group likely to derive maximum benefit, however depending on the assay, up to 20% of PD-L1 negative patients also respond, and indeed compared to chemotherapy these negative patients who respond also derive clinically meaningful survival benefits. There are further issues with tumour heterogeneity.
(differences in molecular characteristics of cancer cells even within the same tumour), and sampling making the companion biomarker a topic we will be talking about for many years to come.

Immune checkpoint inhibitors will be one of the most talked about treatments at this ASCO, as there are emerging data in small cell lung cancer, mesothelioma and in various permutations and combinations in molecularly driven NSCLC.

**Targeted Therapies in Lung Cancer**

Recently, AZD9291 was reported to result in significant response and survival benefit in patients with an acquired resistance mutation (T790M) that had developed after using an EGFR TKI for their EGFR mutant NSCLC. In a subset of patients from the Phase I study, a first line cohort was recruited. AZD9291 appears to be a highly effective drug in the first line setting, with an objective response rate of 70%, a disease control rate of 97% and a toxicity profile that is a lot better than Iressa (gefitinib) or Tarceva (erlotinib). The main question, however, is whether AZD9291 prolong progression free survival. These data are not mature enough, and median progression free survival has not been reached to date. Subsequent studies have already begun recruiting patients that compare AZD9291 to both chemotherapy and an oral TKI.

Other interesting studies show that the combination of BRAF and MEK inhibition (Tafinlar (dabrafenib)) plus Mekinist (trametinib) in BRAF mutant NSCLC is more effective than Tafinlar alone. It will be interesting to see how many patients were screened to discover this subset of patients. It is notable to see similar response data to that seen in melanoma. We still need to determine whether using immune checkpoint inhibitors in this subset is also as effective as it is in melanoma.

Gilotrif compared to Tarceva in squamous cell cancers (Lux Lung 8) will be reported as showing a survival benefit. However, the clinical utility of the one month improvement is likely to be questioned especially given the toxicity of this agent, the widely recognized minimal to modest efficacy of Tarceva in this setting, and the other agents becoming available.

**Brain Mets**

Finally, the plenary session will include a study where patients with 1-3 brain metastases were randomised to either receive stereotactic body radiation therapy (SBRT) plus whole brain radiation therapy (WBRT) or SBRT alone. Over 60% of patients in this study had lung cancer. The addition of WBRT controlled the disease but was associated with significantly greater cognitive decline and no survival advantage. This study suggests that WBRT should not be added to SBRT. By extrapolation, should we be using WBRT at all for 1-3 brain mets? We do not know the details here, so the question of surgery also comes to mind, but that would be contingent on having disease control extracranially.

**Mesothelioma**
For mesothelioma, data from the Keynote 028 study, which investigated Keytruda (pembrolizumab) after failure of initial chemotherapy has already been reported at the AACR Annual Meeting in April. It showed that for around one quarter of patients, the disease actually shrank, and the disease remained stable in about 50%. These data are encouraging and are launching several larger Phase II/III studies.

ASCO will showcase several abstracts pertaining to mesothelioma, including one that is practice changing. The MAPS trial was initially a Phase II French study whose interim analysis was recently reported, and a decision to continue the trial was made. Here the Phase III part of this study is reported. Patients were randomised to receive standard cisplatin/pemetrexed chemotherapy +/- Avastin (bevacizumab/bev) 15mg/kg. This was a large trial with 448 patients. The addition of Avastin prolonged progression-free and overall survival by two months with minimal increase in toxicity. This is the first time an addition to overall survival has been reported in a Phase III trial in mesothelioma since the paper that established the value of cisplatin and Alimta for mesothelioma, 12 years ago!

In mesothelioma, it is good to see some positive results with Avastin, although there will likely be some debate about whether the cost is justified for a survival advantage of only 2 months.

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