New Therapy Options in Small Cell Lung Cancer (SCLC) Webinar Transcript

Dr Paul Mitchell

Introduction: Dr Paul Mitchell

***Dr Tanujaa*:** Dr Paul Mitchell holds the positions of medical oncologist at the Olivia Newton-John Cancer Wellness and Research Centre at Austin Health in Melbourne, Australia, Director of the North-Eastern Melbourne Integrated Cancer Service (Cancer Network), and is Associate Professor at the University of Melbourne and at the University of Sydney.

Dr Mitchell was President of the Australasian Lung Cancer Trials Group (ALTG) 2012–16 and has been involved in clinical and laboratory research for over 20 years, focused on lung cancer. He guided the recent establishment, and is Chairman, of the Thoracic Alliance for Cancer Trials (TACT) which brings together national and trans-national lung cancer trials groups. He is immediate past Chair of the Lung Cancer Advisory Committee of Cancer Australia and sits on the Program Assessing Committee of the Health Research Council of New Zealand.

Dr Mitchell trained in Medical Oncology in Auckland, New Zealand before further training and a post-graduate degree at the Royal Marsden Hospital in London, UK. He currently lives in Melbourne.

Background: Small Cell Lung Cancer

***Dr Mitchell*:** We are focusing on the treatment of small cell lung cancer (SCLC). Small cell as you know is a very nasty disease and the 5-year survival for patients around the world is less than 5%. It varies a bit from country to country but is more in the developed world, comprising between 10 and 15% of lung cancer cases. In general, it has been associated with heavy tobacco smoking. One of the problems with small cell is that around 2/3rd of the patients present with extensive stage disease where there are already widespread metastases and also brain metastases are very common in this disease. The treatment up unto this point for the last 20 years at least has been based on platinum etoposide chemotherapy.

For limited stage disease, for potentially curable platinum-based chemotherapy, etoposide for 4 cycles with concurrent thoracic radiotherapy has been shown to improve survival and also prophylactic cranial radiation improves survival in that group of patients.

In extensive stage, platinum etoposide chemotherapy for 4 cycles has really been the standard of care. The role of prophylactic cranial irradiation in extensive stage remains somewhat unclear. We have some trials for and against, but it is possible to treat prophylactic cranial radiation, but we would generally just monitor the patients. Thoracic radiotherapy trials have been generally sequential, and it has also shown some modest benefit. Now the big change is being the advent of immunotherapy.

IMpower133: Atezolizumab + Carboplatin + Etoposide in 1L ES-SCLC

***Dr Mitchell*:** The first important Phase III trial in the extensive stage setting is the IMpower133 trial. Reported a few years ago, this trial is basically a standard of care platinum-based chemotherapy with atezolizumab vs placebo. And atezolizumab was continued until progression of disease or loss of clinical benefits. The usual sort of criteria that you might expect including patients with treated asymptomatic brain metastases. These are the patient characteristics, there were around 200 patients in each arm. Around half of the patients were aged 65 or above much the same in the two arms. For performance status, about 2/3rd where performance status 1 and 1/3rd were performance status 0, much the same in the two arms. A proportion of the patients, less than 10% had brain metastases and around 30 to 40% had liver metastases which is generally seen as a poor prognostic factor.

These are the results of the study at the bottom there is the progression free survival and overall survival at the top. With progression free survival the atezolizumab group is running at the top on the blue curve there with a very modest change in median progression free survival. The hazard ratio was 0.77 and if we turn to the overall survival, we can see that overall survival benefit for the atezolizumab treated group had an improvement in 12 months survival from 38% up to about 52% with a hazard ratio of 0.7. This is the forest plot for these subgroups here, we see in the brain metastases patients it was not entirely clear whether there was a benefit there or not. But relatively small proportion of younger patients having brain metastases for some reason didn't have a clear benefit compared to the older patients. But it is possibly just some scattering anomaly in the data. In terms of the adverse events, with atezolizumab plus platinum-based chemotherapy, the overall profile there are adverse events was much the same as placebo plus chemotherapy. The immune related adverse events were low, but it was clearly higher in the immunotherapy treated group. Particularly rash was more common with both grade 1/2 and 3/4 as compared to chemotherapy alone. Also, there was a small but probably definite increase in incidence of grade 3 and 4 hepatitis, infusion-related reaction and colitis but generally it was well tolerated.

CASPIAN Trial. Durvalumab + Tremilimumab + Etoposide in ES-SCLC

***Dr Mitchell*:** Following on, fairly short time afterwards similarly designed trial looked at durvalumab in the same setting. This is the CASPIAN trial, similar eligibility criteria, again asymptomatic treated stable brain metastases and here we had platinum-based chemotherapy in addition to that we had durvalumab and there was also an arm including tremilimumab as well as durvalumab. The primary endpoints were overall survival and secondary endpoint was progression free survival, objective response rate etc. I might mention that in both the IMPower133 trial and the CASPIAN trial, it was optional to give prophylactic cranial radiation but thoracic radiotherapy was not allowed. This is the updated overall survival curve for durvalumab plus chemotherapy vs chemotherapy, we can see that the hazard ratio is fairly similar to what we have seen in the IMpower133 with a similar range of hazard ratio of 0.75 and we can see also as in IMPower133, the two curves are sort of separating after 6 to 9 month mark. Addition of tremilimumab to durvalumab plus chemotherapy was possibly doing a little bit better over here but overall, not significantly different from durvalumab plus chemotherapy.

ECOG-ACRIN EA5161 – Cisplatin/Carboplatin + Etoposide + Nivolumab in ES-SCLC

***Dr Mitchell*:** There were two other trials that were reported around the same time. This is a phase II randomized trial for ECOG using Nivolumab that looked at chemotherapy versus chemotherapy plus nivolumab. Generally, we saw much the same as we had with durvalumab and atezolizumab with a hazard ratio of 0.67.

Keynote-606. Pembrolizumab + Etoposide + Cisplatin/Carboplatin in Stage IV SCLC

***Dr Mitchell*:** In keynote 604 study, it was essentially the same design again in terms of looking at pembrolizumab in a similar setting. Stable brain metastases were allowed. The progression free survival, with a hazard ratio of 0.75 was fairly similar to other studies. The overall survival at 0.8 ($p = 0.0164$) wasn't quite as good as the other studies. In fact, the study had been designed with multiple data analysis points and required to have a significance of 0.0128 but it did not reach that significance level. So essentially it had borderline or under borderline significance.

Summary – ES-SCLC: Key First-line Immunotherapy Trials

***Dr Mitchell*:** And here's a quick summary of the 4 trials that have been done in extensive stage SCLC and that have been reported. IMpower133 and CASPIAN trials clearly are positive studies, certainly in Australia we have IMpower133 funded however to date durvalumab hasn't been funded but I think there are other issues other than the efficacy which is really very similar. And Keynote was just not quite so good and didn't actually reach significance.

Checkmate 451 – Maintenance Strategy of Immunotherapy

***Dr Mitchell*:** Also, some earlier data, Checkmate 451 that looked at a maintenance strategy of immunotherapy. We looked at nivolumab plus ipilimumab versus placebo and nivolumab versus placebo. And neither of these studies were positive, there was perhaps a small slope as benefit for the addition of the immunotherapy but with very modest effect.

Biomarkers (PD-L1 and TMB)

***Dr Mitchell*:** One of the problems too in small cell lung cancer is that we do not have clear predictive factors for these patients. It is not clear around the role of PD-L1 expression or TMB and we need better ability to identify which patients are going to do well and which ones aren't.

ES-SCLC: Adding Thoracic Radiotherapy and TROG Phase 2 Study

***Dr Mitchell*:** Just as an aside in the extensive stage small cell lung cancer, from a systematic review, we are looking at the addition of thoracic radiotherapy in extensive stage SCLC. The main study reported is the trial from Slotman 2014, the hazard ratio of 0.84 and overall effect was fairly modest in terms of improvement in survival. If we look at thoracic progression as

a first sign of progression though, it's very clear that radiotherapy will have some impact there.
And this has led to a trial which has just opened, this is the Tasman Radiation Oncology Group (TROG) in conjunction with the Thoracic TOGA, the newly named Thoracic Oncology Group of Australasia, covering Australia and New Zealand. This is a Phase II trial looking at the addition of thoracic radiotherapy concurrently and essentially with the CASPIAN regimen of durvalumab plus chemotherapy and the endpoints here are feasibility and toxicity. We are just using a modest dose of radiotherapy of 30 Gray and 10 fractions with the idea of the number of similar studies happening around the globe and that potentially feeding into a Phase III internationally.

Limited Stage Small Cell Lung Cancer (LS-SCLC)

***Dr Mitchell*:** Now in terms of limited stage small cell lung cancer, we still really are awaiting convincing data with immunotherapy in this space. The STIMULI trial run by ETOP and the French group and also our Australian New Zealand group joined in, towards the end of the study. We looked at a consolidation approach with nivolumab and ipilimumab and that did not achieve its endpoints. We could see that the durvalumab (ADRIATIC Phase III), atezolizumab (NRG LU005 Phase II/III) and pembrolizumab (KEYNOTE Phase III) studies are ongoing. We are doing the pembrolizumab based study currently, but we have found that during COVID we are seeing very few limited stage small cell patients, just about all are extensive stage.

Second Line Options and Beyond

***Dr Mitchell*:** In terms of the second line options and beyond, there is the old cyclophosphamide, adriamycin, vincristine regimen called VAC and the topotecan Phase III trial was done many years ago which was no difference in efficacy but there was some reduction in toxicity. Topotecan has never really been widely used in Australia, so we mostly used to cyclophosphamide, adriamycin, vincristine but we will also use irinotecan in relapsed patients, and we might use paclitaxel probably more in third line treatment. If they're not particularly good performance status we may use weekly regimen. So by and large we see poor efficacy in patients who fail on treatment or just after completion of chemotherapy and we certainly need more effective regimens.

Summary of 1st Line Therapies in SCLC

***Dr Mitchell*:** So, in conclusion we have clear efficacy data now for the additional concurrent and consolidation checkpoint inhibitor therapy in extensive stage small cell particularly with atezolizumab and with durvalumab. To date the consolidation only approaches in extensive stage and for that matter in limited stage as well have not been successful in terms of the addition of checkpoint inhibitors. It is unclear too whether there's going to be long term survivors with this sort of approach in extensive stage small cell and we're hoping that the addition of concurrent thoracic radiotherapy may achieve high proportion of long-term survivors in that group, hence the interest in the TROG study. The limited stage studies really are awaiting results, we need more clear biomarkers for which patients will benefit from small cell and certainly some more effective drugs.

Zepzelca Access Program Analysis (SCLC)

***Dr Mitchell*:** I would like to present some data on the use of lurbinectedin in Australia, the Zepzelca access program and these patients were treated under an access program. These are the baseline characteristics, there were 62 patients as of August this year that were on the program, the age range is up to 83. Around half of the patients were male, if you looked at this 20 years ago just about all of the patients would be male so small cell has become relatively more common in females. Three fourth of the patients had performance status one and relatively small group of patients were with worst performance status. CNS metastases was seen in about 1/3rd of the patients and about half of them had multiple metastases. These were generally extensive stage patients, 60% had one prior therapy only, so they were treated in the second line. A quarter of patients were treated in the third line setting and we can see in this group of patients, 24% of patients relapsing early, half of patients staying on treatment. In the chemotherapy free interval greater than 3 months, there were half of the patients there and again about 1/4th of patients having chemotherapy free interval of 90 days.
Looking in terms of the duration of the patient who stayed on treatment, as we haven't analyzed the response yet. We can see there is a group of patients that have been on lurbinectedin only for a short period of time and then there's other groups of patients who might be benefiting from the treatment by staying on for 6 to 12 months. One thing we had looked at in terms of the patients in the short chemotherapy free interval is more of these patients, about twice as many patients, relapsed early on lurbinectedin and as compared with the patients who are on longer period of chemotherapy treatment. So, the early patients who had been treated shortly after the cessation of chemotherapy didn't do so well.