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

Chapters

Dr Paul Mitchell

Dr Santiago Ponce-Aix

Dr Amit Jain

49:50 to 51:47	Chemotherapy in 1st and 2nd Line
51:48 to 52:33	Use of Immunotherapy in 1st Line
52:35 to 53:05	Use of Immunotherapy as Maintenance and in 2nd Line
53:07 to 54:01	NCCN Guidelines
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Panel discussion

59:59 to 1:00:57	Q1: Does the 3-year OS data from CASPIAN influence the long-term efficacy perception of IO + chemo in 1L ES-SCLC patients?
1:00:58 to 1:06:53	Q2 (Dr Tanujaa): Why is it that unlike the non-small cell lung cancer patients our small cell lung cancer patients don't seem to respond as well to immune checkpoint inhibitors? Any idea?
1:06:56 to 1:08:16	Q3: Why do you think Atlantis trial failed?
1:08:17 to 1:10:05	Q4: In your practice what do you use as second line treatment for the platinum refractory patients? Do you use a single agent lurbinectedin or do you do the combination of lurbinectedin plus Irinotecan?
1:10:06 to 1:11:06	Q5: Is lurbinectedin approved in Singapore?
1:11.07 to 1:12:17	Q6. Is the current trial with lurbinectedin plus atezolizumab (first line maintenance) enough for USA full approval of lurbinectedin in second line of SCLC? Or will it be necessary to launch a new phase 3 trial with lurbinectedin to get the full approval?
1:12:18 to 1:15:06	Q7: Thanks, Dr Santiago it's wonderful hearing your insights as you are in the thick of it and you're planning new trials? What are you going to put your money on if you want your phase III, 2nd line trial? What's your combination of choice there's so many ways to do this now? So, if you had to pick one, which one would it be?
1:15:07 to 1:15:56	Q8: You mentioned about PD-L1 in small cell lung cancer, do you routinely test for that in your patients?
1:15:58 to 1:16:39	Q9: Do you routinely re-biopsy your patients who progress on first line or second line therapy?
1:16:40 to 01:18:45	Q10: How important is maintenance immunotherapy in first line SCLC?
01:18:46 to 1:20:53	Q11 (Dr Tanujaa): For example, if you have an extensive stage small cell lung cancer patient and had just had etoposide plus carboplatin

as first-line therapy and they progress without any immune checkpoint inhibitor or a similar situation where limited stage lung cancer had concurrent chemo RT and progress within three months and haven't seen immune checkpoint inhibitors and they are platinum refractory. So, what will be your choice for second line therapy? Would you consider using immune checkpoint inhibitors in the second line or would you still go back to your standard second line chemotherapy options?

1:20:55 to 1:22:25 **Q12: Why temozolomide for your case study? And why not other chemotherapy agents?**

1:22:26 to 1:24:55 **Q13: What do you think of drugs to treat CNS metastasis in the future? What will be the brain penetration of the newer drugs?**

01:24:58 to 01:25:30 **Q14: Do you have any data on the CNS activity of lurbinectedin?**

01:25:31 to 1:27:10 **Q15: Do you often offer local therapy after response to etoposide platinum plus immune checkpoint inhibitors? What do you think about the role of local radiotherapy in this case?**

01:27:14 to 01:28:33 **Q16: What is the most promising biomarker in SCLC according to you?**

1:28:33 to 1:31:07 **Q17: Let's say if we were having this webinar five years down the road, do you think we will be still talking about overall survival being about what slightly more than a year or do you see things changing tremendously? What are your views?**

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.

Introduction for Dr Santiago Ponce-Aix

***Dr Tanujaa*:** Dr. Ponce is a medical oncologist in charge of the Thoracic Tumor Unit of Hospital 12 of Octubre, under the supervision of Dr. Paz-Ares, for the last 10 years. He has been involved in
clinical research, especially dedicated to small cell lung cancer and targeted therapies development. Similarly, He developed the molecular profile program of lung cancer and the molecular tumor board at Hospital 12 de Octubre.

He has contributed to numerous peer-reviewed publications, and he is also the scientific coordinator of the Oncosur Foundation dedicated to the promotion of medical education and independent clinical research. Currently He is working at Institut Gustave Roussy (France) in the Department of Therapeutic Innovation and Early Trials.

New Standard of Care for ES-SCLC

***Dr Ponce*:** We already know that small cell lung cancer has a very high response rate to chemotherapy. For the last 30 years, the standard of care has been platinum etoposide chemotherapy plus or minus prophylactic cranial irradiation. We know that their response rate is around 50% or 70% of the patients that we treat, and the overall survival is around 8 to 10 months.
Right now, this is already changing because we now have the newer standard of care for extensive disease small cell lung cancer with chemoimmunotherapy with the CASPIAN trial and the IMpower133 trial. With atezolizumab and durvalumab improving the overall survival first time ever for those patients. However, we are unable to cure any patients, so we need second line and further treatment for these patients.

Retreatment with Platinum as 2nd Line (>90 days)

***Dr Ponce*:** The first option that we have for these patients is rechallenge of platinum chemotherapy. The definition of sensitivity to platinum is more than 90 days or less and right

now that is the standard approach to say that a patient is platinum sensitive or resistant. One of the options that we have was topotecan as established 2nd line versus rechallenge with platinum for those patients with a relapse for more than 90 days.
We have this trial comparing topotecan versus carboplatin plus etoposide. We have like 80 patients treated in each arm, these are the clinical characteristic of the patients, and we have the result for median progression free survival, which was better for the combination of chemotherapy, 4.7 months versus 2.7 months with a hazard ratio of 0.57 however the median overall survival for both was 7.5 months with a hazard ratio of 1.03. So, for many patients who don't have any other alternative, platinum rechallenge in platinum sensitive patients may be an option. From the point of view of toxicity, it's feasible to do carboplatin plus etoposide again, we already know that one of the major issues with topotecan is the toxicity profile.

Immunotherapy in 2nd line

***Dr Ponce*:** For immunotherapy in second line, we have some data, though it is not very encouraging. We have this trial for pembrolizumab in second line small cell lung cancer after standard of care. And for PD-L1 positive patient we have a response rate of 35%, with a few of them with complete and partial response and a high disease control rate of 43%, those data are less good with PD-L1 negative patient and also, we have a gain in progression free survival and overall survival with PD-L1 positive patients treated with pembrolizumab after standard of care.

We also have this French trial with atezolizumab to investigate the role of immunotherapy as monotherapy in second line. We have an advantage of progression free survival but mainly an overall survival advantage when we treat a patient with atezolizumab versus chemotherapy if those patients are again PD-L1 positive (IC1,2 or 3) versus PD-L1 negative patients in the same way as the pembrolizumab trial.

For second line, we also have some data with those patients harboring high TMB. We have experience with Checkmate-032, investigating Nivolumab + Ipilimumab in patients with small cell lung cancer and those patients with high TMB have a better response rate both with Nivolumab and Nivolumab plus Ipilimumab. Regarding overall survival, those patients receiving Nivolumab plus Ipilimumab with a high mutational burden have an advantage. We don't have this access to this combination in Europe, but Nivolumab plus Ipilimumab may be an option to treat patients with high TMB in SCLC.

We also have the PASSION trial that investigated immunotherapy plus anti-angiogenic therapy. The patients who received Camrelizumab plus apatinib gained an overall survival and so this is another proof that immunotherapy can be continued in second line after chemoimmunotherapy first line as an option for some of the patients.

Biomarker Selection

***Dr Ponce*:** Regarding some biomarker selection, we have NOTCH. The DLL3 expression is quite high in small cell lung cancer. We know that many patients will have overexpression of NOTCH. My thesis was on this, and it's quite frequently expressed in SCLC.

We also have the drug Rovalpituzumab Tesirine (Rova-T), if you remember about five years ago, we had very good response rate with this drug. With almost 30% of the DLL3 positive patients having an objective response and the overall survival was encouraging in patients expressing DLL3 compared to those without DLL3 expression. But unfortunately, the toxicity profile and the median overall survival for this trial was negative with a median overall survival of 6 months and very high toxicity rate, with the discontinuation rate of 5% due to adverse events (AEs) and the Grade 3+ AEs was more than 40%. The main toxicity was thrombocytopenia, photosensitivity, anemia, fatigue and pleural effusion therefore right now this drug is no longer in development.

But regarding NOTCH, as it is a pretty good target for small cell lung cancer, new alternative treatment options are available, we have Tarlatamab, a bispecific monoclonal antibody targeting DLL3 and CD3 in the T cell of SCLC. There are 2 main actions of Tarlatamab, serial lysis of the SCLC cells itself and the T-cell activation. Not only T cell activation, but also the antibodies track the T cells that are active to the core of the disease.

We have the AMG757 Phase 1 trial, where Tarlatamab is really well tolerated only with some cytokine release syndrome at the beginning of the infusion. We are learning about how to infuse this monoclonal antibody and we do inpatient treatment here for 24 hours. We had only one Grade 3 patient, and no related death to cytokine release syndrome and some other toxicities that make the drug feasible. And mainly for patients with a lot of prior lines of treatment and many of them received chemo-immunotherapy as 1st line, lurbinectedin monotherapy, combination therapy with lurbinectedin, treated thereafter with Tarlatamab have had partial response. We have a stable disease and disease control rate ranging about 30% of the patients so with a very heavily pre-treated population we have a very good activity for this drug. For patients with confirmed partial response, the median duration of response was around 9 months, the median time to response was around 2 months. The trial data hasn't matured yet, but maybe this drug can be a new option in the future for this group of patients.

Regarding more biomarker selection, we have many small cohorts in trials, but I think that one of the emerging and important targets in SCLC is going to be the DDR. The genes related to the reparation of the DNA. We have several trials testing PARP inhibitors plus immunotherapy plus chemotherapy. I have some experience with trials that is investigating immunotherapy plus PARP inhibitor for those patients, we still don't have data on the activity but is important maybe to do personalized medicine for those patients by testing the status of DDR.

Lurbinectedin Basket Trial Data

***Dr Ponce*:** Lurbinectedin is an inhibitor of the transcription factors and it has some immune activity with induction of cell proliferation inducing interleukin-6 and interleukin-8. We have an inhibition of the immune response activation checkpoints and, we have induction of angiogenesis that we are currently investigating in the Chinese trials that has shown that angiogenesis may play a role in SCLC.

We have this phase 2 basket trials with lurbinectedin in SCLC that was published in Lancet Oncology last year, with a dose of lurbinectedin at 3.2 mg/m^2, we have a median progression free survival of 4.1 month and for overall survival around 1 year for those patients. Their response rate is quite encouraging for monotherapy, with a huge 67% of the patient having partial response and stable disease. And clinical benefit ranging for more than half of the patients, the disease control rate is around 73% in patients treated with lurbinectedin monotherapy. The PFS was around 4 months, and the overall survival was around 1 year for second line treatment for those patients.

The adverse event profile of lurbinectedin is well known and it is mainly hematological, anemia, thrombocytopenia and neutropenia that is easy to manage with monotherapy. Probably we must make an effort to maintain the doses of lurbinectedin maybe by using growth factors because we know that the exposure to lurbinectedin is directly related to the response rate so it would be better to maintain a good dose of lurbinectedin in this case.

ATLANTIS Trial

***Dr Ponce*:** We have the ATLANTIS trial comparing Lurbinectedin plus doxorubicin vs CAV (cyclophosphamide, doxorubicin vincristine) or Topotecan. The trial was not positive for overall survival, we are going to publish the data soon. We don't have any advantage except probably for the toxicity and we are planning new Phase 3 trial to investigate the effect of lurbinectedin alone in SCLC.

RESILIENT Trial

***Dr Ponce*:** This is the RESILIENT trial, a phase one trial investigating pegylated irinotecan at two doses of 85 and 70 milligrams per meter square. We have some preliminary data that I am going to publish in a few weeks. The response rate is also very encouraging, partial response is around 43% of the patients, stable disease is 26% and objective response rate in total is quite engaging at 43% and more important benefit for this treatment is 72% (BOR: Best overall response) of the patients harboring some kind of activity for pegylated irinotecan. This is an example from our center, a patient with a liver disease who had good response to this drug.

Regarding toxicity, it is similar to lurbinectedin, the main toxicity is hematological, mainly neutropenia in the liposomal irinotecan arm but based on my experience it has a very good toxicity profile and may represent a new option for those patients in the future. The median PFS was at 3.9 months and median overall survival in this phase one is 8 months. This is unpublished data so please don't post this result.

Lurbinectedin plus Irinotecan

***Dr Ponce*:** We also have another combination of irinotecan plus lurbienctedin, and for sure is a good option and we have published this phase one multi-cohort trial with 21 patients in the SCLC cohort, investigating the efficacy of Lurbinectedin at 2 mg/m^2 (it was the researched dose) plus irinotecan at 75 mg/m^2 plus G-CSF. As I said it's important to maintain the dose of lurbinectedin, for all the patients the overall response rate is 72%, clinical benefit that is partial response plus stable disease is 81%, disease control rate is 90% of the patients. Median

duration of the response is 6 months and the median PFS is around 6 months. It is a very encouraging data for patients with refractory disease, in this difficult population we have only 8 patients but with an overall response rate of 50% it's quite good from my point of view and probably one of the best options for those patients with refractory platinum disease. In terms of toxicity, hematological toxicity is the one of the reasons why we need primary prophylaxis of growth factors (G-CSF) and there are a few liver enzyme laboratory abnormalities but really no deaths related to the treatment and feasible to do this combination.

This is the waterfall plot to shown response in patients receiving the combination therapy, with partial response and stable disease at 86% of patient. Importantly, if we look at those patients, irrespective of a good response or no response at the start of the trial, there is activity in both groups with the combination of lurbinectedin plus irinotecan.

Lurbinectedin plus Atezolizumab

***Dr Ponce*:** We have completed the Phase 1 trials that we published last week, it is combining Lurbinectedin with atezolizumab. Lurbinectedin in an escalation manner 2.5 mg/m^2 plus atezolizumab at fixed dose and then the monotherapy dose of lurbinectedin at 3.2 mg/m2 plus atezolizumab at the fixed dose.

The primary objective of this phase one trial is to identify a dose for combining lurbinectedin plus atezolizumab and the final dose of lurbinectedin that we have is 3.2 mg/m^2 and secondary objective is response rate and progression free survival. The following is the characteristics of the patient, we only have second line patients in this study. We only have immune naïve patients, but the trial will have 2 parts, with more than 150 patients including immune pre-treated patients.

Just like any other lurbinectedin trial, the main adverse event is hematological toxicity. The recommended dose is lurbinectedin is 3.2 mg/m^2 plus primary prophylaxis of growth factors due to this toxicity and to avoid decreasing the doses of lurbinectedin. Regarding the activity we have had 7.7% of the patients with complete response, partial response in 50% of the patients, stable disease in 26.9% of the patients and a disease control rate in 84% of the patients. This is really encouraging results, the PFS is not mature yet, the PFS for dose level 1 (lurbinectedin at 2 mg/m^2) is 7 months and with dose level 2 (lurbinectedin at 3.2 mg/m^2) the PFS is 4.4 months.

This is the waterfall plot for the patient with different doses of lurbinectedin, which is 2.5 mg/m^2, 3.2 mg/m^2 and 3.2+ mg/m^2 with primary prophylaxis. We have a lot of patients with good response and with complete response also and those patients responding had a very long duration of the response. So, we are going to have more data for this combination for this pure second line population. We are also going to start a trial with a strategy of maintenance platinum plus immunotherapy in the first line and then starting maintenance therapy with lurbinectedin and atezolizumab as per this schema.

Summary

***Dr Ponce*:** In conclusion, it is very clear that chemoimmunotherapy is the standard of care for first line and in the second line we have many alternatives. We can re-challenge with platinum but now we are sure that lurbinectedin has a very good activity in the second line, either monotherapy or in combination with irinotecan. From my point of view lurbinectedin is the standard second line treatment right now for our patients. Irinotecan pegylated or in combination with lurbinectedin may emerge as a potential alternative mainly in combination with lurbinectedin for those patients having a platinum refractory disease. The current approaches combining immunotherapy and chemotherapy and different strategies such as targeted therapy for example NOTCH bispecific antibody may improve the outcome of our patients.

Introduction – Dr Amit Jain

***Dr Tanujaa*:** Dr Amit Jain is a senior consultant medical oncologist at National Cancer Centre Singapore he's just completed his PhD and his research interest is in the field of cancer immunology and he is currently exploring the use of cell therapies for cancer.

Paradigms in Treatment of Extensive SCLC

Dr Jain: I would like to just go through a few paradigms in the treatment of extensive small cell lung cancer that we face as medical oncologists in the clinic. The standard of care is based on clinical demonstration of efficacy rather than a mechanistic understanding of the disease. Most of the first line therapies that we use work in a majority of patients but unfortunately the development of resistance is almost universal. This is a cancer which appears to have a lack of actionable biomarkers even though lots of RB and p53 proteins are common, these are actually rather difficult to target. Enthusiasm for ongoing development of clinical strategies is moderated by historical failure in improving the lethality of this disease.

SCLC – A Challenging Disease

Dr Jain: In Singapore approximately 10 to 15% of lung cancers are small cell lung cancer accounting for about 150 to 200 new cases a year. This is a cancer that is largely a man-made epidemic, it can be attributed to smoking related carcinogens. The cancer is an aggressive cancer with a short doubling time of 25 to 30 days, and this means that without treatment typically patients may only survive weeks. With treatment survival is still dismal, overall survival at five years is generally quoted to be less than 7%. The lethality of this cancer unfortunately has not changed in the last four decades despite this being one of the most extensively tested cancers in both the preclinical and clinical settings.

Amongst newly diagnosed SCLC, 60 to 70% of patients are diagnosed with extensive this stage disease that is incurable. As I mentioned earlier, this disease has not been able to be genomically and immune categorized in terms of lending clinical insights into sub-populations that have different susceptibility. Nevertheless, we continue to be enthusiastic with what may come in the future and currently more than 270 active or recruiting clinical trials are listed on clinicaltrials.gov. This represents a rapid trial and error approach to applying allegiance to this disease that continues to be an unmet need or agents that can traverse the brain, and this is particularly important because amongst all the small cell lung cancer patients we see up to

10% of them may present with brain metastases and unfortunately up to 40% them may experience brain metastases in their lifetime.

Chemotherapy in 1st and 2nd Line

Dr Jain: I am going to quickly summarize chemotherapy use in the first- and second-line setting. Four to six cycles of platinum doublet therapy is well established in the first line. Generally, one would choose carboplatin if there's any issues with whether patients can tolerate cisplatin. The platinum agent of choice may be combined with the etoposide or irinotecan depending on which part of the world one practices in.

Majority of patients unfortunately will still experience relapse within the first year of treatment. There are several labels that may be clinically useful if relapse occurs during treatment, we might call this platinum refractory disease and if it happens within 90 days of completing treatment, we call it platinum resistant disease and if it happens after 90 days then we call this platinum sensitive disease. This is relevant for patients who might be eligible for re-challenge with first line in the setting of platinum sensitivity where rechallenge is preferable. In the second line setting, topotecan remains the only formally approved treatment option and this was derived from a clinical trial comparing topotecan against best supportive care which gave a median overall survival of 26 months in the topotecan arm as compared to 14 months in the arm with best supportive care. Nevertheless, the response rates are modest at best between 10 to 20%.

There are multiple agents that have been tested in the first- and second-line setting, and these have been done in earlier phase clinical trials and therefore are included in the NCCN compendium of active agents that can be used against this disease.

Use of Immunotherapy in 1st Line

Dr Jain: Briefly, the use of immune checkpoint inhibition in the first line has been defined now by the use of atezolizumab and durvalumab in combination with platinum doublet therapy as the speakers before me have mentioned. It is important though to understand that this is in the context with other trials that have not given a clear signal of activity and at least one trial (IDEATE Phase 3) that has read out negative for the addition of immune checkpoint inhibition. Beyond the use of immune checkpoint inhibitors along with platinum doublets, atezolizumab and durvalumab also can be used as maintenance.

Use of Immunotherapy as Maintenance and in 2nd Line

Dr Jain: And this is currently the state of the art for the use of immunotherapy as maintenance in the second line setting. There are some negative trials (Checkmate-451, PIII; Checkmate-331 PIII, Multiples Phase I/II) again that are worth highlighting however in the context of several earlier phase trials that have shown some benefits in the second line setting onwards several immune checkpoints are also included in the NCCN guidelines.

NCCN Guidelines

Dr Jain: As per NCCN guidelines you can see that the first line treatment is defined by a platinum doublet therapy. This can be a platinum drug either in the form of carboplatin or cisplatin combined with either etoposide or irinotecan and given along with immune checkpoint inhibitor which can be either atezolizumab or durvalumab. In the 2nd line setting onwards there are now two preferred regiments either use of topotecan or now lurbinectedin. There are also multiple other agents that have been tested in early phase trials and in phase II setting largely which can be used both as IV and oral agents as well as immune checkpoint inhibitors pembrolizumab and nivolumab.

Lurbinectedin – Key Points

Dr Jain: A few key points to highlights and what we currently understand about how lurbinectedin may play a role in a patient's life. This drug is now approved for use as a single agent based on a Phase II study that showed an overall response rate of 35% amongst 105 patients with a median duration of response of about 5 months. Cytopenia has been the main side effect, and this was given in the setting of patients who had received platinum-based chemotherapy in the first line setting.

In a phase 3 clinical trial called ATLANTIS, lurbinectedin was combined with doxorubicin and compared against CAV or CA + topotecan, while it missed its primary endpoint, it demonstrated tolerability and overall activity in patients. One previous speaker has talked about the combination of Irinotecan and lurbinectedin and this combination will progress into advanced stage clinical trials, and it appears to be promising thus far.

Three early phase ongoing trials that combine immunotherapy with lurbinectedin will be informative for how we can combine checkpoint inhibition with lurbinectedin in the patients who have received first line treatment.

Treatments on the Horizon

Dr Jain: Beyond these drugs that we have mentioned there are other treatments that are in the horizon and there are some challenges with some of what has already been tested. While I mentioned earlier the loss of p53, RB1 proteins and the amplification of *myc* is very common in SCLC and these pathways continue to be extremely challenging to target.

There are multiple novel agents that include PARP inhibitors (Veliparib), alkylating agents (Temozolomide), VEGF inhibitors (Pazopanib) and Aurora kinase inhibitors (Alisertib) that are currently being tested in both phase I and phase II setting. A brief mention is worthwhile for the first targeted therapy that was developed for SCLC which is DLL3 that initially appeared to be a promising target for SCLC and the drug Rovalpituzumab-tesirine is an antibody drug conjugate that was tested with promising results in the Phase I study however in Phase II study with low rates of response and due to toxicity, it appears that the product has now been withdrawn from further testing.

So, looking to the future what we hope additional clinical trials will give us insights into are the optimal sequencing of platinum doublet, immunotherapy, lurbinectedin, single agent

chemotherapy and how we can combine these drugs best. And to do that in the context of patients with varying degrees of platinum sensitivity in order to improve the life spans of our patients with extensive stage SCLC.

Case Study

Dr Jain: I'll briefly go through a case study. Here I describe one of my patients in clinic, a 66-year-old gentleman was diagnosed with extensive stage SCLC in July 2018 with the liver metastasis and was treated with good response with six cycles of platinum doublet therapy. In view of his good response, we considered him for consolidation radiation to the thorax as we hoped it would improve his outcomes. After discussion at a multidisciplinary tumor board, we made the decision to proceed with consolidation radiation and he received 36 Grays in 12 fractions in February 2019. Subsequently and unfortunately, he developed pneumonitis which appeared to have elements of both interstitial pneumonitis as some of the areas that were involved appeared to be outside of the radiation field and there certainly seemed to be an element of radiation pneumonitis as well. We treated this with steroids as well as steroid sparing agents and in consultation with the respiratory doctors. The patient had good disease control for 18 months and had some control over his pneumonitis but thereafter there was a slow progression of his disease. In view of his poor function as well as his preference for an oral form of treatment, I offered him temozolomide. He had an initial partial response that subsequently progressed within two months. Thereafter, the patient was offered best supportive care with home hospice support, and he deteriorated gradually passing away in May 2021.

With the current set of approvals that are now available for small cell lung cancer, there are an increasing number of options that might be available. And for patients like this, where one might be extremely nervous to give any form of immune checkpoint inhibitor, they may be suitable for single agent therapy or new agents such as lurbinectedin.

Panel discussion

Q1: Does the 3-year OS data from CASPIAN influence the long-term efficacy perception of IO + chemo in 1L ES-SCLC patients?

Dr Mitchell: The curves are staying separate so that's looking good, but I think if you look at the data as a package across different immunotherapies, I am not convinced that we're going to see the sort of five-year survival, similar to the effect that we're seeing in non-small cell lung cancer. So, the addition of concurrent and maintenance immunotherapy certainly adds some important component to the small cell treatment. Well, I might be proved wrong, but I think that we're going to have to do better than what we're doing at the moment to really substantially lift those five years survivals.

Q2: Why is it that unlike the non-small cell lung cancer patients our small cell lung cancer patients don't seem to respond as well to immune checkpoint inhibitors? Any idea?

Dr Mitchell: I mean this is not entirely clear, the relationship with PD-L1 and TMB for that matter. There are some data now coming through about different subtypes of small cell and there is a particular inflamed subtype associated with immune related gene upregulation that may be part of the story. I mean it is a very difficult area to investigate in a small cell with the nature of the genetic landscape being mostly loss of gene effect and so it's difficult to interrogate but I think we probably are on the cusp now of getting some really useful information. Over the next few years particularly coming from the immunotherapy trials.

Dr Jain: I think it's been very challenging to find any treatments that have dramatically altered the treatment landscape of small cell lung cancer. We have always made modest improvements; it might well be that this is a highly mutated cancer with some level of immunogenicity but manages to preserve itself as an immune desert. There's a fair amount of work that's ongoing to try and understand how small cell lung cancer makes itself an immune privileged cancer. This might be one avenue of work in the future to try and understand how to alter the tumor microenvironment and that might be one way to hope for immunotherapy in SCLC.

Dr Ponce: About the CASPIAN trial, it is the only one that we have with 3 years follow up probably from IMPower we are not going to have any longer follow up. I agree with Dr Mitchell that we are not going to get the same amount of benefit as non-small cell lung cancer. But I truly believe that having some experience in a long term from the nivolumab and ipilimumab trial especially the Checkmate 032, I had a lot of patients like more than 50 patients treated in this schema and at the end of the day we have like 5% of the patients with long term survivals.
Probably this is linked to a different biological subgroup that we don't still know and if you look to the curves at 3 years probably, we may have around 5% of patients with long term survival at five years. The question is though it can be an immunogenically “hot tumors” (with smoking and a lot of high mutational burden) however it is true that we don't have a lot of PD-L1 expression. It is quite less than non-small cell lung cancer, so it's a different cohort with around 15-20% of the expression and moreover there is a lot of infiltration of T-regulatory cells (T-regs). This infiltration of T-regs is according to the clinician point of view, changing the landscape in a small cell lung cancer. That’s why PD-L1 inhibition only is not enough to keep this benefit.
If we look to the PFS curves and the duration of response in the 1st line CASPIAN and Impower133 trial, comparing even with 1st line squamous cell carcinoma, we are only doing maintenance with immunotherapy. Both the curves are similar, we don't have the same amount of benefit that we see in the Keynote non-squamous where we are giving pembrolizumab plus pemetrexed. Somehow, we are changing the landscape and I think it's going to be very important for the future to do just a maintenance strategy with PD-1 or PD-L1 inhibition plus something else. The trial on the combination of lurbinectedin plus atezolizumab is going to start within the next month as switch maintenance and maybe this is the way to do something else better.

Q3: Why do you think Atlantis trial failed?

Dr Ponce: I think that one of the main issues is the dose of lurbinectedin. We are pretty sure, and we have phase I data right now from the lurbinectedin plus atezolizumab trial, if we decrease the dose of lurbinectedin, it is affecting the efficacy of lurbinectedin. So, it's very different for using one dose or the other and keeping the dose intensity of lurbinectedin is crucial to get the benefit of that drug. So, I think this is the reason why when combining with doxorubicin the dose intensity of lurbinectedin was not optimal as in monotherapy. That is the real reason for not having a benefit from that trial. I truly believe that lurbinectedin is still a very good option in monotherapy at 3.2 mg/m^2. Keeping that dose in the monotherapy which we have already published, and we will be publishing the lurbinectedin plus atezolizumab trials and if we keep that dose, it is quite good. This is probably this is the reason why ATLANTIS trial failed.

Q4: In your practice what do you use as second line treatment for the platinum refractory patients? Do you use a single agent lurbinectedin or do you do the combination of lurbinectedin plus Irinotecan?

***Dr Ponce*:** For those patients, from my experience though we don't have a lot of patients, but based on the data from the phase I trial, lurbinectedin plus Irinotecan seems the best for this challenging patient population. It is quite good enough to go for this. I would do the combination of Irinotecan plus lurbinectedin.

Dr Tanujaa: But you earlier mentioned you were concerned about the dose reduction with lurbinectedin? Is that a problem when combining Irinotecan with lurbinectedin?

Dr Ponce: We have a synergy in between irinotecan and lurbinectedin. It is not the same issue with doxorubicin. Also, with atezolizumab there is a synergy with lurbinectedin, that's the reason why we have some good data. One thing that I did once in my clinical practice was combining liposomal irinotecan that is available in Europe for pancreatic cancer plus lurbinectedin because I think hematological toxicity is decreasing with liposomal irinotecan. Also, data of irinotecan liposome is super good, and I have this experience also.

Q5: Is lurbinectedin approved in Singapore?

Dr Tanujaa: Yes, for Singapore audience lurbinectedin is approved in Singapore. It was approved in September this year. In fact, if anyone wants to know the Singapore experience for lurbinectedin, we had about 13 patients and they were very heavily pretreated patients, so they were not really the typical 2nd line patients. Some of the patients were third line and some were after fourth line. Out of the 13 patients, 8 patients had the combination of lurbinectedin and irinotecan. Generally, the physicians who used it, found that lurbinectedin was easy to use and progression free survival for these group patients was about four months or so. This information is from the 13 patients that we had as part of our patient access program.

Q6. Is the current trial with lurbinectedin plus atezolizumab (first line maintenance) enough for USA full approval of lurbinectedin in second line of SCLC? Or will it be necessary to launch a new phase 3 trial with lurbinectedin to get the full approval?

Dr Ponce: No, the advice from FDA was to do this maintenance trial with immunotherapy and not to stop the indication in second line because of the basket trial data and the issue with the doses because ATLANTIS did not work, which we really believe is a matter of the dose and it was not a well-designed trial. It is going to be enough with the maintenance trial and the 2SMALL trial, the trial that was presented in second line in combination of atezolizumab with immunotherapy. Based on the landscape, they will keep the approval by the FDA right now in 2nd line and for a future for this combination therapy.

Q7: Thanks, Dr Santiago it's wonderful hearing your insights as you are in the thick of it and you're planning new trials? What are you going to put your money on if you want your phase III, 2nd line trial? What's your combination of choice there's so many ways to do this now? So, if you had to pick one, which one would it be?

Dr Ponce: Actually, I think that for second line I have a bias probably. But with the experience that we have from the phase I trial with atezolizumab plus lurbinectedin. Having a very small number of patients but having this control of the disease and it's quite important that these patients are purely second line. Because many times for small cell lung cancer we enroll second or further line patients, however for all those patients beyond 2nd line or further lines it is a different kind of small cell lung cancer. So those data from lurbinectedin and atezolizumab is coming only from pure second line patients. They have had only one line of platinum based on the schema. No matter what platinum plus therapy they had in the first line.
In the Phase II study, we have two different cohorts, those patients previously exposed to immunotherapy and those patients not exposed to immunotherapy. Each cohort with 80 patients. Therefore, I will bet on Immunotherapy plus chemotherapy.

If we want to go further, I don't know maybe another idea would be to combine AMG757 (Tarlatamab) that is a pretty good drug and is changing the inflammation landscape of immune cell because it is bispecific and probably combining bispecific molecule with lurbinectedin can be a nice idea.

Q8: You mentioned about PD-L1 in small cell lung cancer, do you routinely test for that in your patients?

Dr Ponce: We are now testing because it is a procedure in our hospital. But I did the testing in a big cohort in Spanish cohort, that had more than 500 small cell lung cancer patients. We did the testing in our population because of the results in some other studies in China and a few other studies that showed very high expression of PD-L1. But that was not the case in our trials, less than 15% of patient being had high PD-L1 expression in this Caucasian population of small cell lung cancer.

Q9: Do you routinely re-biopsy your patients who progress on first line or second line therapy?

Dr Ponce: Normally yes, looking at the genes of the reparation of the DNA alteration to enroll those patients in trials. Not just a standard way for patient to be treated with any drug in

second, third or fourth line, but searching those kinds of alterations to have a chance to enroll patients in PARP inhibitor plus immunotherapy trials.

Q10: How important is maintenance immunotherapy in first line SCLC?

Dr Mitchell: I will just add to the previous conversation there, we looked at TMI in small cells in about 160 or 170 cases and by and large we were seeing a lot of PD-L1 expression and immune infiltration. It was very little in the tumor cells and seems to be being this sort of usual pattern We couldn't specifically relate that to the outcomes for those patients as the outcome data was not good enough. But I think there's a common observation.

The question about maintenance IO just if you put around the other way I think generally if you are using maintenance only that's not a proven approach in small cell lung cancer. Trials have been negative including the STIMULI trial. I certainly wouldn't be doing trials where I will be looking at it only in maintenance or only concurrent it just doesn't make any sense. We got the data from the extensive stage patients where there is a clear benefit and so somebody might want to test that sometime in terms of just giving three or four months of immunotherapy without the maintenance, but I think that's probably likely to be ineffective. The other thing is that the curve separates after about 5-6 months or around there. So, it's hard to see where you're getting a substantial effect early on that I think probably the concurrent sort of sets up the environment for later benefit.

Q11 (Dr Tanujaa): For example, if you have an extensive stage small cell lung cancer patient and had just had etoposide plus carboplatin as first-line therapy and they progress without any immune checkpoint inhibitor or a similar situation where limited stage lung cancer had concurrent chemo RT and progress within three months and haven't seen immune checkpoint inhibitors and they are platinum refractory. So, what will be your choice for second line therapy? Would you consider using immune checkpoint inhibitors in the second line or would you still go back to your standard second line chemotherapy options?

Dr Mitchell: It is attractive to try but in reality, the trials have been negative and so if you're going to try that it maybe it's in the context of something novel or a novel combination. It is a difficult population to really get good results and you know often they are only surviving for a few months. So very difficult area I think we are probably going to make more inroads into perhaps dual immunotherapy type of approaches or some of the newer approaches that are starting to look a bit interesting in non-small cell lung cancer.

In limited stage small cell lung cancer, in Australia the proportion of limited stage is normally about a third and I think now for us it is probably less than 10% due to the late presentation. But anyway, I think there are 2 out of the 3 of the existing ongoing limited stage trials, 2 in concurrent and maintenance and one on just maintenance only. So, my money would be on the concurrent plus maintenance as being the way to go.

Q12: Why temozolamide for your case study? And why not other chemotherapy agents?

Dr Jain: This is regarding the case report that I just presented briefly and in the second line setting what I offered my patient temozolomide and the question is why did I choose

temozolomide? It is one of the options that is listed in NCCN. Well, it might have been flavor of the season and it was definitely directed by patient choice, so he didn't want to be tied to hospital visits. At this point in his life, he felt like he'd reached a point where he wanted the simplest possible treatment. He wanted something oral, he didn't want to be tied to chemotherapy suites. So then looking through the oral options and there were some unequivocal spots in his brain and so I was wondering about you know whether I needed something that had some class effect for brain penetration. And those are some of the factors that went into choosing this treatment plus the tolerability which proved to be alright. I didn't expect any response, but he did have a partial response though that was pretty nice to see. Then the other thing at the back of my mind about small cell lung cancer and looking at what happened second line onwards is always concerned about how well we get into the brain because so many patients will end up having CNS failure.

Q13: What do you think of drugs to treat CNS metastasis in the future? What will be the brain penetration of the newer drugs?

Dr Ponce: I have firstly one point for the temozolomide, I don't use it normally. But I will use it sometimes but it's not regularly. But it is quite interesting if you have a few patients who have progressed, and you are giving a few courses of temozolomide and if you test for tumor mutational burden, you can see that the tumor mutational burden might have changed a lot. Therefore, temozolomide can change the immune landscape in every single tumor but also in SCLC. You have some cases of small cell treated with temozolomide and the changes in TMB occurs and then these patients can be enrolled in immunotherapy trials and can have some nice responses because of that it's not a bad idea to give temozolomide and thereafter check the change in the immune landscape.

To address the question of brain metastasis, It is really complicated, when we decided on the design of the CASPIAN trial allowing brain metastasis untreated without radiotherapy because I think brain metastasis is the is one of the issues that we have in small cell lung cancer.
Maybe the strategy of antiangiogenic treatment that we mentioned in second line in the Chinese trial (camrelizumab plus apatinib), maybe anti-angiogenesis can be better explored to improve the penetration into the brain. We have the experience in using anti-angiogenesis in non-small cell lung cancer.

Q14: Do you have any data on the CNS activity of lurbinectedin?
Dr Ponce: No, not yet. We don't have enough data to show that but yes, I have clinical experience of patients having brain mets with good control. But to be honest, I don't have the data right now.

Q15: Do you often offer local therapy after response to etoposide platinum plus immune checkpoint inhibitors? What do you think about the role of local radiotherapy in this case?

Dr Mitchell: That really goes to the trial that we're running at the moment so there is some effect as I indicated in my presentation about radiotherapy in extensive stage small cell. But I'm more interested in the potential benefits of mediastinal radiation in terms of trying to have some effect on the immune response against the cancer. Ultimately yes, there's a local

effect which is fairly modest, but I'll be more interested in whether heading radiotherapy might enhanced immune response.
Dr Tanujaa: In your trial are you giving radiotherapy concurrently with chemotherapy or after the initial therapy?
Dr Mitchell: Theoretically if you are going to use radiotherapy in this way, then it should be given concurrently.
Dr Tanujaa: So far in your trial is it very difficult for your patients to tolerate.
Dr Mitchell: We have only opened just a week ago so I can't tell you as of now.
***Dr Tanujaa*:** Maybe down the road we will hear some data from that study.

Q16: What is the most promising biomarker in SCLC according to you?

Dr Jain: If I was going to take a long view, I think if we look at p53 and RP1 or *myc*, I would pick *myc*, it is a difficult marker but because it's so ubiquitous but that's a dream target.

Dr Mitchell: I think it would be in the inflamed group of tumors. I think we should try to work with in the first instance anyway to try and present therapies. In Impower50 in non-small cell lung cancer strategy like bevacizumab might have an effect there and its possible.

Dr Ponce: Yes, I agree. It is a difficult field.

Q17: Let's say if we were having this webinar five years down the road, do you think we will be still talking about overall survival being about what slightly more than a year or do you see things changing tremendously? What are your views?

Dr Mitchell: I'd be confident we have some effects; we've made some significant progress. I mean the addition of immunotherapy is really the first major benefit for overall survival since chemotherapy was used. So, we shouldn't dismiss that but I think probably it's a 10 year plan rather than a five years.

Dr Taunjaa: So, if it is 10 years do you think you think we would have doubled the overall survival?

Dr Ponce: In last 30 years that we have like more than 40 Phase III trials failing to improve anything in small cell lung cancer. Saying that, I'm still positive and I think that with the immunotherapy and the PD-L1s, and not only different smarter strategies, combinations and so on. I am not sure about doubling the overall survival, but we are in the right path to improve. One of the points that you did mention is that we have to biopsy and re-biopsy patients even with a small cell lung cancer. We are treating all of the small cell lung cancer as the same disease, and we know already that is not the same disease. As SCLC is a difficult disease and patients are not in good condition. To help these patients we have to biopsy, biopsy and biopsy to understand the disease, if not it is going to be very difficult to double the overall survival.