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

Panel discussion

Q&A - 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.