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

**Dr Santiago Ponce-Aix**

## 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 2$^{nd}$ 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 2$^{nd}$ 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 1$^{st}$ 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.