INTERVIEW

Jean-Charles Soria, MD, PhD

Prof Soria is Full Professor at Paris University XI and Head of the Drug Development Department at Institut Gustave Roussy in Villejuif, France.

Tracks 1-15

Track 1 **Case discussion:** A 60-year-old man and former smoker with metastatic SCC of the lung whose disease progresses after 2 cycles of cisplatin/gemcitabine receives second-line nivolumab therapy

Track 2 Perspective on the use of corticosteroids in patients receiving immune checkpoint inhibitors

Track 3 Contraindications to the use of immune checkpoint inhibitors

Track 4 Clinical experience with anti-PD-1 antibody-associated colitis

Track 5 Evaluation of radiographic scans and monitoring of liver transaminase levels in the determination of "pseudo-progression" versus true disease progression in patients receiving immune checkpoint inhibitors

Track 6 Third-line therapeutic options for patients with progressive SCC of the lung

Track 7 Perspective on the use of the VeriStrat® assay for patients with SCC of the lung

Track 8 Results of the Phase III LUX-Lung 8 trial of second-line afatinib versus erlotinib for patients with advanced SCC of the lung

Track 9 Use of the VeriStrat assay to evaluate tissue samples from the LUX-Lung 8 study

Track 10 Selection of EGFR TKI therapy (afatinib versus erlotinib) in patients with pan-wild-type NSCLC

Track 11 Prophylactic use of antidiarrheal agents in patients receiving afatinib

Track 12 Palliative use of laser ablation for patients with stomatitis

Track 13 **Case discussion:** A 75-year-old woman with advanced T790M-mutant adenocarcinoma of the lung receives osimertinib on an expanded access program

Track 14 Diverse molecular mechanisms of acquired resistance to osimertinib and rociletinib in EGFR-mutant lung cancer

Track 15 Management of rociletinib-associated hyperglycemia

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss your approach to first-line therapy for patients with metastatic SCC of the lung?

PROF SORIA: Cisplatin/gemcitabine is probably the most popular regimen used in Europe for SCC. Carboplatin/paclitaxel is an alternative, and nanoparticle albumin-bound (*nab*) paclitaxel is an agent that is popular in the United States. It is especially appealing because it does not necessitate the administration of steroids.

DR LOVE: These days when confronted with a patient with metastatic SCC, many clinicians would likely be thinking about a checkpoint inhibitor at the time of progres-

sion. Do you believe it is advantageous to use an agent prior to that that does not require corticosteroids, such as *nab* paclitaxel?

PROF SORIA: In "real-life" settings, administering corticosteroids before a checkpoint inhibitor won't change anything. But, of course, when you want to combine an immune checkpoint inhibitor with chemotherapy, being able to use an agent that does not mandate corticosteroids is extremely important. This is one reason why the ongoing Phase III trial evaluating different chemotherapy options, one of which is carboplatin/*nab* paclitaxel, with or without the anti-PD-L1 antibody atezolizumab for chemotherapy-naïve patients with advanced SCC is so intriguing (3.1).

DR LOVE: What are some of the absolute contraindications to using immune checkpoint inhibitors, and do you believe any conditions that are thought to be contraindications actually don't preclude a patient from receiving these agents?

PROF SORIA: We must realize that the data presented to date regarding the tolerability of immune checkpoint inhibitors are based solely on patients who have been enrolled in clinical trials and, therefore, strict inclusion criteria have been applied to them. Now that these agents are out there in the real world, I don't believe that most of my colleagues are thoroughly questioning patients as to whether they have a history of autoimmune disorders such as thyroiditis or psoriasis.

I have personal experience from a recent case at our institution when a patient forgot to tell us that he had psoriasis 5 years ago, and it ended up being a nightmare. After the first infusion of nivolumab, he developed extremely severe psoriasis over 50% of the surface of his body that led to him being admitted to the ICU. Extensive psoriasis is a major concern. If it expands, it is not easy to treat. We were unable to continue the immune checkpoint blockade therapy.

Preexisting Crohn's disease is another contraindication because checkpoint inhibitors can aggravate that condition. With regard to a patient having a history of thyroiditis, I would not consider that to be a contraindication because its treatment is obvious. For hyperthyroiditis, you simply administer beta blockers, and the patient's thyroid function should decrease. I have heard debate over vitiligo being a contraindication to using these agents, but that is not the case. On the contrary, we've seen suggestions

3.1

IMpower 131: A Phase III Trial Evaluating the Efficacy and Safety of the Anti-PD-L1 Antibody Atezolizumab (MPDL3280A) in Combination with Carboplatin/Paclitaxel or with Carboplatin/*Nab* Paclitaxel in Chemotherapy-Naïve Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

Protocol IDs: NCT02367794, GO29437 **Target Accrual:** 1,200 (Open)

Eligibility

- Histologically or cytologically confirmed, treatment-naïve Stage IV squamous NSCLC
- ECOG PS 0-1
- No history of autoimmune disease

R

- Atezolizumab + *nab* paclitaxel + carboplatin
- Atezolizumab + paclitaxel + carboplatin
- *Nab* paclitaxel + carboplatin

www.clinicaltrials.gov. Accessed January 2016.

that patients who have baseline vitiligo tend to experience better responses to immune checkpoint inhibitors.

On a related note, one piece of advice I like to give to my colleagues who are using immune checkpoint inhibitors is not to underestimate the risk of diarrhea. Also, make sure patients understand that if they experience diarrhea, the worst thing they can do is to start taking loperamide because it will exacerbate the condition.

Tracks 7-9, 11

DR LOVE: What is your view on the utility of the VeriStrat proteomic assay?

PROF SORIA: The data on VeriStrat are interesting. VeriStrat is a blood-based test that aims at providing a score that tells you whether the patient is more likely to benefit from erlotinib versus chemotherapy (Gregorc 2014; [3.2]). To my surprise, the uptake in the use of this assay has been low, at least in Europe. I only know of a few clinicians in Italy who are using this assay in daily practice. I believe that the community has a sense, especially for patients with nonsquamous NSCLC, that EGFR mutation is the true molecular predictor. On the other hand, maybe using this assay for patients with SCC is a reasonable approach.

We are currently using the VeriStrat assay to analyze hundreds of samples from the LUX-Lung 8 trial, and we hope to be able to share the data with the community this year. We previously reported the primary analysis of this trial, which evaluated afatinib versus erlotinib as second-line therapy for patients with advanced SCC after platinum-based chemotherapy.

The advantage was clear in favor of afatinib compared to erlotinib in terms of response rate, disease control rate, PFS and OS, although some might argue that the latter was marginal because it was a 1.1-month advantage. However, it was statistically significant (Soria 2015a; [3.3]). The quality-of-life results convinced me that afatinib was the better alternative.

A lot of people argue that afatinib is a difficult drug to tolerate — that it causes a lot of diarrhea and stomatitis. Although this may be true, the patient-reported outcomes from the study favored afatinib, probably because it provided better tumor control than erlotinib in this setting, so the overall balance is that the patients have a better quality of life with afatinib than with erlotinib.

With regard to afatinib-associated diarrhea, I always prescribe concomitant loperamide. I have quite a bit of experience with afatinib because we have been using it for many

3.2

Phase III PROSE Trial: Predictive Value of the VeriStrat Proteomic Signature in Non-Small Cell Lung Cancer Treated with Second-Line Erlotinib or Chemotherapy

Median overall survival	Erlotinib	Chemotherapy	Hazard ratio	*p*-value
All patients (n = 134, 129)	7.7 mo	9.0 mo	1.22	0.148
VeriStrat good (n = 96, 88)	11.0 mo	10.9 mo	1.06	0.714
VeriStrat poor (n = 38, 41)	3.0 mo	6.4 mo	1.72	0.022

Gregorc V et al. *Lancet Oncol* 2014;15(7):713-21.

years in various clinical trials, and I never wait for diarrhea to occur. I instruct patients to take 1 loperamide pill a day and then I tell them, "If you experience loose stools, take another."

We also reported at the recent World Lung Cancer Conference a comprehensive genomic analysis of more than 200 patients on the LUX-Lung 8 trial (Soria 2015b). That analysis was unable to identify any subgroup of patients who experienced a greater advantage compared to the overall patient population. Afatinib was better than erlotinib in all of the molecular subgroups that we analyzed. We demonstrated that EGFR mutations do not explain why afatinib is better in this setting. ■

3.3

LUX-Lung 8: Results of a Phase III Trial of Afatinib versus Erlotinib as Second-Line Therapy for Patients with Advanced Squamous Cell Carcinoma of the Lung

Efficacy	Afatinib (n = 398)	Erlotinib (n = 397)	Hazard ratio	*p*-value
Median progression-free survival	2.6 mo	1.9 mo	0.81	0.0103
Median overall survival	7.9 mo	6.8 mo	0.81	0.0077
Disease control rate	51%	40%	—	0.0020
Objective response rate	6%	3%	—	0.0551
	Afatinib (n = 392)		Erlotinib (n = 395)	
Select adverse events	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4***
Diarrhea	59.4%	10.5%	30.9%	2.5%
Rash or acne	61.2%	5.9%	57.0%	10.4%
Stomatitis	24.7%	4.1%	8.6%	0%
Fatigue	13.5%	1.5%	10.4%	1.8%
Nausea	12.2%	1.0%	6.3%	0.8%
Decreased appetite	12.0%	0.8%	9.9%	0.5%
Paronychia	9.9%	0.5%	4.1%	0.3%

* Incidence of Grade 4 diarrhea with afatinib (n = 2) and erlotinib (n = 1); Grade 4 dehydration with afatinib (n = 4) and erlotinib (n = 0)

Soria JC et al; LUX-Lung 8 Investigators. *Lancet Oncol* 2015a;16(8):897-907.

SELECT PUBLICATIONS

Gregorc V et al. **Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): A biomarker-stratified, randomised phase 3 trial.** *Lancet Oncol* 2014;15(7):713-21.

Kuiper JL et al. **VeriStrat® has prognostic value in advanced stage NSCLC patients treated with erlotinib and sorafenib.** *Br J Cancer* 2012;107(11):1820-5.

Soria JC et al; LUX-Lung 8 Investigators. **Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): An open-label randomized controlled phase 3 trial.** *Lancet Oncol* 2015a;16(8):897-907.

Soria JC et al. **Tumor genomic analysis from LUX-Lung 8: A Phase III trial of afatinib versus erlotinib in squamous cell carcinoma of the lung.** *Proc IASLC* 2015b;**Abstract ORAL32.01**.

Stinchcombe TE et al. **A retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in elderly patients (age 70 years or older) with stage IIIB/IV non-small-cell lung cancer.** *J Thorac Oncol* 2013;8(4):443-51.