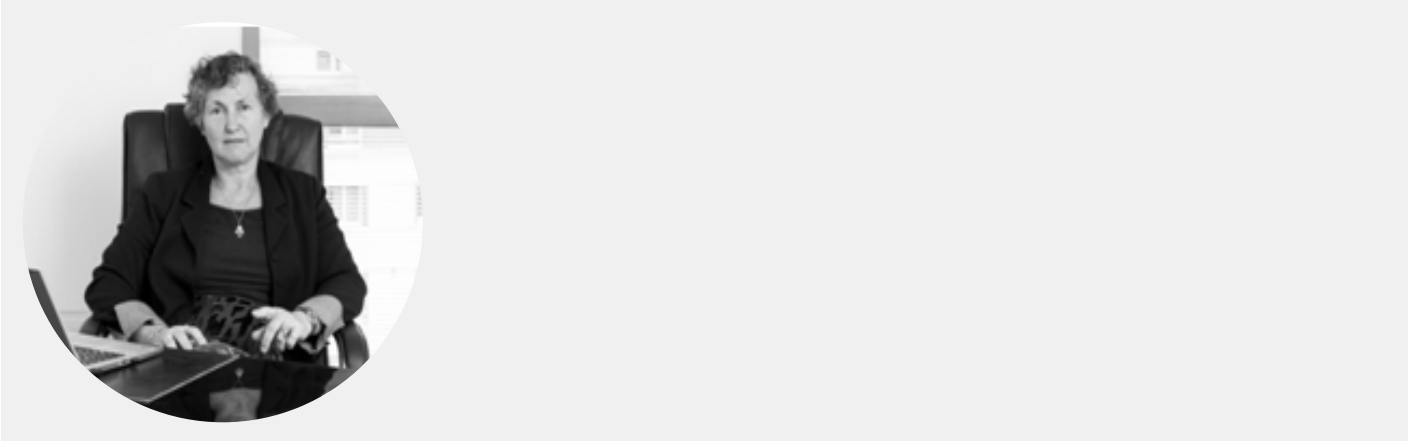
Interview: Dominique Costantini – CEO, OSE Pharma, France



10.12.2015

Tags: Pharma, Pharmaceuticals, France, OSE, Clinical Research, Dominique Costantini, Israel, Cancer, immunotherapy, immuno-oncology, Interview, CEO, Insight, Innovation

Dominique Costantini, the CEO of OSE Pharma, a French biotech company developing immunotherapy products against late-stage (invasive and metastatic) cancer discusses the company's unique targeted approach based on a patented neo-epitopes combination, its plans to break into the immuno-oncology domain and its perspectives on the French regulatory and biotech environments, and emphasizes her team's commitment to innovation.

OSE Pharma succeeded in a spectacular IPO in March this year that was 3.6 times oversubscribed, and ended up raising EUR 21.1 million (USD 22.41), with the mission to "make cancer a chronic disease". Can you briefly introduce OSE Pharma to our audience and tell us what you think has been behind your success?

We are very pleased with our IPO results and we believe it reflects not only the potential in this new domain of immuno-oncology but also the investors' confidence in OSE Pharma's approach. Our vision for the IPO was to explain the science behind our approach, both generally in terms of our involvement in immuno-oncology and specifically in terms of the results of our data.

There is a revolution taking place in the immuno-oncology domain today. In 2012, what convinced us to acquire assets from Takeda was evidence, not a concept – from the results of the phase 2 clinical trial with Tedopi® in non-small cell lung cancer (NSCLC) showing the efficacy of the

treatment and the increase of the survival. The patients included had been previously heavily treated and had a very short survival prognosis. The improvement in the long-term survival rate was significantly correlated with immune response. We have also observed long term survival with 25 percent of patients treated with Tedopi® still alive after 4 years.

Moreover, the advanced clinical stage of our program also inspired confidence. In June 2014,we had received a favorable opinion on the pivotal phase 3 protocol with Tedopi® in NSCLC from both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). In November this year, we received positive opinion from seven European countries; the study should be initiated by the end of 2015 and will include 500 patients in Europe and in the US.

Can you elaborate more on OSE Pharma's innovative portfolio of immunotherapies for late-stage (invasive and metastatic) cancers and your proprietary Memopi® technology?

Our communication for the IPO was "to develop a personalized weapon against advanced cancers". Our lead product, Tedopi®, is a patented combination of ten neo-epitopes, which are small peptides that generate a specific cytotoxic T-cell response by binding with cellular receptors on the tumor, selected and optimized from five tumor antigens. It is a very targeted approach but not fully personalized, as our epitopes do not come from each patient.

We have identified ten epitopes, largely expressed in late-stage cancer. We have also defined a core responder patient population, which are patients expressing the HLA-A2 antigen, a key receptor for the cytotoxic T-immune response. In its application NSCLC for HLA-A2+ patients, Tedopi® was granted orphan drug status in the US and is considered as personalised medicine for HLA-A2+ patients in Europe.

The science behind epitopes is still very new. During our R&D, we had a pool of over 11,000 epitopes to choose from and our job then was to define ten that could be used productively. Much of the work has been done by Alessandro Sette, who was the CSO of Epimmune – now he is working on epitopes for the treatment of Ebola, which shows the diverse potential in this technology.

Immunotherapy was called the breakthrough of the year in 2013 by *Science* magazine, which explains why it has seen a surge of interest, particularly from Big Pharma but also biotechs. When we spoke to Mr. Jean-Christophe Barland, he outlined BMS' restructuring and new focus on immuno-oncology. How does OSE Pharma differentiate itself from and compete with others?

Currently, the enthusiasm and expertise are primarily based on the science of checkpoint inhibitors, which is non T-specific immunotherapy: research focuses on receptors able to remove the inhibitors preventing T-cells from attacking the tumors. These checkpoint inhibitors are mainly coming from four Big Pharma companies. However, only around 20 percent of patients respond optimally to this therapy, so there is a lot of room for improvement.

We wanted to reconsider conventional cancer therapies and use the specific, acquired adaptive immune system. Our targeted T-cell therapeutic approach uses another mechanism for treatment: we re-educate the body's immunological memory so that the immune system (and particularly T cytotoxic cells) can attack tumor cells by increasing the patients' specific cytotoxic T response against their cancer, which has proven to be very promising so far. In terms of differentiating ourselves in the playing field, our best weapon is our phase 3 trial and its expected results. These results will speak for themselves.

In addition, immuno-oncology is a very diverse field and there are many development opportunities. For instance, we are also considering potential therapy combinations. The selection process for therapy combinations is based on synergy, efficacy and safety requirements. There is strong potential for product expansion and it can also be developed in phase 2 for other cancer indications, or in combination with other immunotherapeutic products or targeted therapies.

OSE Pharma has already signed its first licensing deal with RAFA Laboratories in Israel for long-term licensing and distribution. What is your international partnership strategy at this point in time?

We have an extremely open approach to partnerships. We would like to work with partners because we have a good technology and very strong ambitions but we cannot go into all cancers on our own. We need support to fully explore and develop our potential.

We selected RAFA Laboratories in Israel because they have a long history in the oncology sector and they work with key opinion leaders in this field. Israel may be a country with limited cancer market size but they are very strong in the fields of immunology and immuno-oncology, which is represented by the Weizmann Institute and their strong relationship with Institut Pasteur. Another important advantage for us is that Israel's regulatory system is very closely linked to Europe's, which will facilitate pricing and reimbursement processes in the future.

As I mentioned, our phase 3 trial will be our best spokesperson. In terms of commercialization, we know that Big Pharma has the resources, expertise and time to develop products on a large scale and we are in long-term discussions with many players, who are interested in this domain. For a

biotech, a critical stage is precisely the scale up from phase 2 to phase 3 trials, in terms of manufacturing, distribution and monitoring. It is not easy but it is necessary to demonstrate the potential for industrial production, which is crucial for commercialization.

A core factor in our partnership strategy is the need to select partners who will make our technology a priority for them. We are not looking for partners simply for their name or reputation, we want companies who will be committed to our product.

In addition, to increase our visibility, we are also looking for opportunities to acquire new assets and increase our portfolio. We are constantly looking to the future, assessing our next steps and the best way to get there.

A common complaint of French biotech companies is that France is not as good for biotech development as the US or the UK. For instance, DBV Technologies had to go to the US to obtain sufficient funding. As someone who has founded two biotech companies, BioAlliance Pharma in 1997 and OSE Pharma in 2012, what is your perspective on this?

The US undeniably differs from Europe in terms of financial resources and funding for biotech companies. France does have funds available, but in limited quantity and on a completely different level to the US. The key question is how to substantially improve the environment. It is not simply about increasing the number of VCs and private capital, but there needs to be a comprehensive approach, for instance, to ensure that biotechs at each stage of development, from start-up to commercialization and market launch, have access to adequate funding. Currently, it may be relatively easy to set up a biotech company, but when it comes to the scale-up I mentioned between phase 2 and 3, or even earlier, it is much more difficult due to the expenses involved in setting up clinical trials.

However, without a doubt, the environment has improved in the past decade. More sources of funding are now available. The number of IPOs has increased and the valuations of biotech companies have improved as well. It is still not comparable to the US, but the improvements are welcomed.

The underlying question is, why are biotech valuations so different between the US and Europe? I think it has to do with an underlying mentality. In the US, the biotech industry is more established and the investors believe in its fundamental potential. In France, this is still lacking and there may be more scepticism towards biotechs.

Pharma and biotech companies share the same inherent risk: the risk of R&D. The main difference between pharma and biotech is how they organise and manage that risk. Pharma companies take a pyramid approach, where they start from hundreds or thousands of molecules and then eliminate them through the clinical research process to arrive at a few commercial successes. For biotechs, it may be the opposite – they choose the most promising technology and then they invest their time and expertise in exploiting its benefits to multiple indications and therapies. Ultimately, success boils down to the people behind the research. If your team has conviction and believes in its technology, it will find ways to make it viable.

France is notorious for the complexity and length of its market authorization process. Given your expertise in commercialising products and your experience in pharma and biotech companies, both in Europe and the US, what is your perspective on this?

Fundamentally, it is our choice to work in innovation. With that choice comes various challenges and hurdles, some of which come from the regulatory environment. But given that I believe in the value of innovation, it is up to me to do my best to navigate France's regulatory system.

With OSE Pharma, we have tried to maximize our success rates by maintaining excellent clinical data and selecting an optimal and targeted patient population. These are two main elements for success: judicious patient selection with clean and meaningful data.

We are also conscious of the need to demonstrate increased innovation and efficacy over existing therapies, and our trial's aim is also to prove our efficiency over chemotherapy. We aim to replace, not supplement the existing treatments. As a result, we are also looking at quality of life in addition to survival rates. Compared to chemotherapy, we have limited and very manageable side effects.

We also have an excellent team, whose efforts are indispensable. We exerted great effort in building a team of people we both know and can trust. They are international, they have good networks and they have diverse experience in biotech and pharma. We have an interesting and well-rounded board composition as well.

Finally, I am also using my experience and expertise in both R&D and commercialization to guide OSE Pharma in this regard. Innovation is my motto, and we will do our best to realize it.

What is OSE Pharma's five-year plan?

Most immediately, we would like to see positive results in our upcoming phase 3. We would also like to further develop R&D based on existing technology, and to explore new aspects, for instance, in terms of managing the side effects of immunotherapy.

Our vision is to be fully and actively involved in the field of immuno-oncology.

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