Xu Ting – Founder, Chairman & CEO, Alphamab Oncology, China

The core business – our research-driven, data-driven approach to innovation – has not changed [post-IPO]. We are committed to developing our portfolio and generating value for our stakeholders

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PharmaBoardroom caught up with Alphamab Oncology's founder, chairman and CEO Dr Xu Ting again 16 months after our last interview to hear about their successful HKEX IPO in December 2019, his commercial expectations for their flagship PD-1/PD-L1 product, and the impact of COVID-19 on their operations.

Dr Xu, since we last interviewed you in December 2018, you have taken Alphamab Oncology to an extremely successful IPO on the Hong Kong Stock Exchange (HKEX) in December 2019. Did the IPO meet your expectations?

Our last interview in December 2018 took place after our Series A fundraising round, which had wrapped up in end-November. We then began our pre-IPO fundraising round, which concluded in end-May 2019, while beginning the whole IPO preparation progress. We listed on the Hong Kong Stock Exchange (HKEX) on 12 December 2019, raising about USD 270 million, which ended up being on the high-end of our price range. We had mixed expectations: based on the previous IPOs of other Chinese biotechs, we thought our valuation could have been better, but the few companies that did IPO right before us were not as well-received as before therefore we decided to price the IPO with a reasonable valuation. The investment climate was rather tough during that period as well, so there was some pressure on the price.

However, we are happy with the outcome with significant support from long-only funds, including prominent names from the US and Europe, with the retail part seeing nearly 200-times oversubscription. Furthermore, on the first day of trading, our share price rose nearly 35 percent so that is a good sign. What is also positive is that it reversed the negative IPO performance trend. This helped paved the way for the IPOs that came after, for instance, with InnoCare and now Akeso Biopharma. I believe our IPO had a positive impact on the market, which is good for the whole China biotech sector.

What made HKEX a better platform for Alphamab Oncology compared to NASDAQ or the Shanghai STAR Board?

We saw some relevant advantages for us in Hong Kong. In terms of overall valuation, the STAR board is the best, followed by Hong Kong and then NASDAQ. The STAR board also has the best liquidity, with NASDAQ being the second-best but we had previously structured the company according to HKEX listing requirements. Now, under the current regulatory requirements, we cannot be dual-listed in Shanghai yet. We may consider going through NASDAQ for liquidity reasons, but it is too early to discuss that.

Four months into running a publicly listed company, what has changed for you as CEO?

The core business – our research-driven, data-driven approach to innovation – has not changed. We are committed to developing our portfolio and generating value for our stakeholders.

However, in terms of governance, as a publicly-listed company, there is a lot more work to do, certainly. We have had to add or improve functions like compliance, corporate social responsibility, financial reporting and budgeting, public and investor relations and so on. We are now in the process of implementing SAP systems to streamline the company’s operations from research to commercialization. There is a lot more to think about beyond research. With R&D, you need to be creative and focused in your approach. With running a publicly-listed company, you need to be disciplined.

2019 was also a prolific year for Alphamab Oncology in terms of clinical development. Could you outline the most exciting milestones for your portfolio?

2019 was really critical for our pipeline development, particularly our three flagship candidates.

KN035, our subcutaneous injectable PD-L1 antibody codeveloped with 3D Medicines, has just finished the first pivotal Phase II trial for high microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR) advanced solid tumours. Its Phase III pivotal trial in biliary tract cancer is also progressing. We also have very good results generated from Japan, which indicated longer dosing interval, dosing up to once every 3-4 weeks. The next step is to evaluate how aggressive we want to position this product on the market and to what extent based on factors like level of competition, etc.

KN026 is our anti-HER2 bispecific antibody. In 2019, we demonstrated that KN026 worked well even in heavily pre-treated, trastuzumab-refractory HER2-Overexpressing metastatic breast cancer, with over 35 percent objective response rate, which exceeded my wildest expectations. We formulated quite a few Phase II trials and we will start a pivotal Phase III in China soon.

We will position KN026 quite aggressively against Roche's Herceptin® because the efficacy and safety are both great. In addition, Herceptin® focuses on HER2+ cancers. The prevalence of HER2+ is 25 percent in breast cancer and around 10-15 percent of gastric cancer, for instance. We started using KN026 against patients with low and intermediate HER2 expression – another market segment that is estimated to account for over 15 percent of solid tumours – and we are getting some great preliminary data showing response. Roche's Herceptin® and Perjeta® combo only works on HER2+ patients so we think there is great potential for our compound to expand to other indications.

Last month we also announced a clinical collaboration agreement with Pfizer to investigate KN026 in combination with their oral CDK4/6 inhibitor, Ibrance®, which is one of Pfizer's most important assets. This is a way for us to attract more attention to our compound as well as help them potentially expand their drug into much wider indications.

Our third pipeline molecule is KN046, which is very exciting because it is a first-in-class PD-L1/CTLA4 bispecific antibody. It is more complicated in anti-cancer mechanism and we are still trying to understand it better. There has been a lot of effort on KN046. We just wrapped up our Australian Phase I dose escalation and expansion trials involving over 50 patients, where we showed activity in certain tumours that do not traditionally respond to PD-1/PD-L1, like pancreatic cancer, stomach cancer and mesothelioma. In China, Phase I/Ib enrollment has proceeded fairly quickly; in 2019, we enrolled almost 100 patients across multiple indications. We now have Phase II trials in esophageal squamous cell carcinoma (ESCC), non-small-cell lung cancer (NSCLC) and

triple-negative breast cancer.

We initiated eight Phase II trials for KN046 in 2019 and as of today, we have almost 400 patients enrolled across these studies. We want to understand better how the molecule works in which indications and with which combinations. In 2020, we will run global pivotal trials, initiate combo studies and collaborate with academic labs and other biotech/pharma companies to perform mechanistic studies on the mode of action to increase our understanding of KN046 further. Already we can see that KN046 has a lot of potential in many indications where PD-1/PD-L1 do not work well.

In addition, in 2019, oncology KOLs in China began an investigator-initiated combination trial of KN026 and KN046. The data set is still too small, but we are starting to see that this combo may have great potential for HER2+ cancers.

Finally, we are also advancing with KN019, which is a lower priority molecule for us as it targets autoimmune diseases, but it is still a good product currently in Phase II stage in China. It could also potentially expand to applications for controlling immune-related adverse events from immune-oncology treatments.

With so many trials across various indications for your pipeline, how will you start to prioritize resources as your candidates advance in the process and start to approach commercialization?

For both KN026 and KN046, both have the potential to work across multiple indications and multiple combos, so our strategy has been to demonstrate proof-of-concept (POC) in as many indications as possible. We will then take a couple of small indications to approve and bring to market as quickly as possible. For instance, we expect to file for BLA for KN046 as well as KN026 in the next one to two years. At the same time, we will start randomized Phase III trials for one or two major indications to position them to compete in more mainstream markets.

Our clinical development strategy is also well-established to leverage the advantage of different markets globally. For instance, our biliary tract cancer indication for KN035 is technically an orphan drug indication but we are looking at nearly 50,000 patients a year in China due to the incidence rate in the Chinese population. Within two years, we have already enrolled 400 patients in China. We can then use our China data to support our US filing because it would be extremely difficult to enrol that many patients in the US. Then when we are ready to file in the US, all we might need

would be a small bridging trial. In this way, we can accelerate our clinical development in the US market. We are also going to look at European countries, particularly in Eastern Europe, where some indications may have higher patient numbers or be less exposed to already approved drugs on the market, to see if we can generate clinical data from there as well.

We remain flexible in terms of our overall strategy and we will continue to seek out win-win collaborations for clinical development and commercialization. For instance, for KN035, we have collaborated with 3D Medicines and TRACON Pharmaceuticals to develop it for the orphan indication of soft tissue sarcoma in the US. It has received Orphan Drug Designation from the US FDA, which gives our product a lot of advantages like priority review and fast-tracked processes. TRACON already has a sales team set up for this indication in the US. This is a good way to preserve our resources for our core priorities like more major indications. For these, we will certainly partner with specialty pharma players in the US as we cannot compete with the giants like MSD or BMS ourselves.

What is interesting in the US is that due to the COVID-19 crisis, at least half of the US are discouraging patients from going to hospitals. As a result, for instance, more than half of the patients on intravenous Herceptin has now switched to subcutaneous infusions. I think once this switch has been made, patients will be reluctant to go back on IV drips because of the inconvenience. Our KN035 is still the only subcutaneous PD-1/PD-L1 in late-stage clinical development so we might have an interesting opportunity there in the US market

Coming to China, looking at your peers that have launched PD-1/PD-L1 products on the market, how do you see the pricing environment in the market?

Looking at annual reports from the two Chinese biotechs that have launched PD-1/PD-L1 products on the China market so far, the price ceiling has averaged CNY 180,000 to 200,000 – or around USD 25,000. My feeling is that this could be halved to around CNY 100,000 – or around USD 15,000, which is significantly different from the typical price tag (after rebates and other discount programs) in the US of around USD 150,000.

Based on this precedent, we can expect our product to be priced in a similar range, especially if we want it to be listed on the National Reimbursement Drug List (NRDL).

At these prices, one of the biotech companies reported an 88 percent gross margin. That is sufficient to support company operations. If prices fall another 50 percent, that gross margin could

fall to, say, 70-75 percent, which is still sustainable for drug development in well-explored areas like PD-1/PD-L1s, where the early drug development risks are relatively small. It is a bit like developing biosimilars. However, it is not ideal for truly innovative drug development.

This is why we have trials running in markets like the US, Europe and Japan. The higher prices there will give us more resources to fund more early-stage real innovative R&D.

Over the past decade or so, China has really invested a huge amount of resources in fostering, encouraging and subsidizing innovative drug R&D with the ambition of becoming a global biotech innovation powerhouse. Will such low prices in the China market undermine that objective?

We can take cellphones as an indicative example. The prices in China are very low but because there is a huge user base and a mass-market here, the industry can still thrive. At the same time, the advancement of digital and mobile technology has further increased its penetration, which in turns drives higher interest, and so on. It is a positive feedback loop. We can see a similar dynamic in the Chinese drug development industry. With government support, there is now so many Chinese biotech companies developing new drugs. Many are crowded around ‘low-risk’ targets like PD-1/PD-L1s. This drives the development of drug development infrastructure, processes and know-how that contribute to the maturation of the whole industry ecosystem in China. You can see the rise of massive CROs like WuXi AppTec and Tigermed. As all these companies learn, grow and mature in their operations, they will soon start to have a transformative impact on the global industry.

Based on my own experience with US companies like Biogen and Serono, they needed around 95 percent gross margins to cover all their expenditures. That is how the US system works. In China, the prices may be lower but gross margins of 70-80 percent are still decent compared to other industries. The system is still self-sustainable.

Looking forward and considering the unfolding COVID-19 situation, what are your expectations for 2020?

We have had to adjust our plans and expectations a little. We had previously considered investing more resources outside of China but with the current situation, we will continue to prioritize clinical development in China because many clinical centres in the country are already back on track while

operations overseas are still experiencing disruption. At the same time, we have to explore how to improve the way we run clinical studies by implementing more remote monitoring to limit site visits, and how to maintain high quality at the same time.

Fortunately, we do not anticipate too much delay. We might see around two to three months delay for our first BLA filing but otherwise, we are still on track with our clinical development plans.

The silver lining is that the COVID-19 situation has helped people understand how fragile the global healthcare system is. The general public may be starting to understand better the value of vaccines and therapeutics. As an indicator, our stock price has been slightly hit by the stock market turbulence, but we are still standing at nearly 50 percent above listing price, which is encouraging. Other Chinese biotechs have also continued to close successful fundraising rounds and IPOs so the investor sentiment in this sector seems to remain strong.

Do you have a final message?

With increasing tension between the US and China as well as an almost global state of isolation as a result of the pandemic, potentially it may be easy for people globally to see China as separate from the rest of the world. But no matter what, we must remember that healthcare and drug development are global. We need to think globally. We need to think more collaboratively.

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