Jin-San Yoo â?? President & CEO, PharmAbcine, South Korea

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Dr Jin San-Yoo, president and CEO of PharmA

bcine, lifts the lid on the companyâ??s combination therapy with MSDâ??s blockbuster oncology treatment Keytruda. Dr Yoo explains the rationale behind his decision to base his clinical trials in Australia and provides his assessment of the future for oncology drug development in the global market.

Can you introduce us to PharmAbcine and the work you conduct?

PharmAbcine is a clinical-stage publicly traded company, focusing on innovative next-generation therapeutics to bring clinical benefit to patientsâ?? lives. We started this business with the construction of a fully human antibody library with high quality and diversity. By using this library and a customized selection system, we have developed several innovative pipelines. Half of them are monospecific antibodies; the remainder sophisticated multiplexities.

The most advanced candidate is Tanibirumab, an anti-KDR neutralizing fully human IgG, which completed its phase IIa recurrent GBM trial in Australia in August 2017. It has displayed a 25 percent disease control rate, a clear safety profile (meaning all adverse effects maintain within grade 2), and over 40 percent of patients received benefits from cerebral oedema management. The average life span of recurrent GBM patients is less than 4 months. Not only do some patients live longer thanks to Tanibirumab, but they incur fewer side effects. No common side effects like hypertension, haemorrhage, gastric/lung perforation or proteinuria were observed. Hence, it improves the quality of life for some recurrent GBM patients.

PharmAbcine is now transitioning to focus on more multispecific antibodies. The eventual launch of our multispecific products will extend lifespans and improve the quality of life for cancer patients. Based on that, our PMC-001, PMC-002R, PMC-201, PMC-122 are moving forward.

Through collaborative efforts, we are generating a multiple ADC and CAR based pipeline and are exploring which pair of combinations are the best in terms of safety and efficacy for patients.

What is the scientific rationale for the combination trial of Tanibirumab and Keytruda?

The combination of Immuno Oncology (IO) drugs and angiogenesis inhibitors is very popular nowadays. Therefore, the combination trial of Keytruda as an IO and Tanibirumab as an angiogenesis inhibitor and beyond is not the first such combination. Cyramza is the other product of this type on the market, produced by Eli Lilly. The main biological aspects of these products were elucidated by Roche and Genentech who are running numerous combination trials of Tecentriq as the IO and Avastin as the angiogenesis inhibitor. There are several other R&D organizations that have consistently demonstrated how the VEGF-VEGFR2 pathway acts like the control tower to maintain the immuno-supressing environment for the TIME (tumour immuno microenvironment). In the TIME, there is usually a low presence of innate immune cells like effector cytotoxic T-cells, which are mostly exhausted and cannot perform their cancer-killing duty. It was discovered that the regulatory T-cells usually manage to repress the immune activity in TIME and somehow the VEGF pathway upregulates these regulatory T-cells. To provide clinical benefit to patients, firstly, abnormal tumour vessel must be normalized and reorganized for better delivery of anti-cancer drugs and innate immune cells to TIME. Secondly, it is also necessary to change the â??immune-suppressiveâ?• environment of TIME to â??immuno-supportiveâ?• TIME. We strongly hope that our Tanibirumab with a competitive safety profile can contribute to both missions and enhance the performance of Keytruda.

How did the partnership with Merck & Co (MSD outside of the US) develop?

Five years ago, I first visited Merckâ??s Research Laboratory in Boston and presented my proposal for the combination of Tanibirumab and Keytruda as a research collaboration. Since then, I continued to challenged people at Merck Research Laboratories on both the east coast and west coast with stronger scientific and clinical rationale and evidence. The clinical response rate of Keytruda alone is about 20 percent. In order to improve this, there are several hundred combination trials ongoing. Among them, there are also numerous clinical trials of the Keytruda-Avastin combination and Keytruda-Cyramza combination trials. To differentiate from existing combination trials of IO and Angiogenesis inhibitors, we successfully demonstrated that our phase I and Phase IIa studies of Tanibirumab have superiority to both Avastin and Cyramza in terms of safety and efficacy. Finally, these data packages were appreciated by Merckâ??s team.

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PharmAbcineâ??s ongoing Tanibirumab-Keytruda combination multicentre trials for both rGBM (recurrent Glioblastoma multiforme) and mTNBC (metastatic Triple Negative Breast Cancer) have been ongoing in Australia since December 2018. We are also are exploring this combination for other medical unmet needs.

If we can recruit patients as quickly as planned and if we have the adequate data from our rGBM study, we could present a poster at the SNO (Society for Neuro-Oncology) conference 2019 in Austin, Texas this year. We also are planning to present our mTNBC study at the SABCS (San Antonio Breast Cancer Symposium) 2020.

What was the rationale behind entering into clinical trials in Australia?

We will strategically initiate early-stage trials for our assets in Australia once we have positive data from safety and efficacy. Following this, PharmAbcine will expand globally to recruit a high number of

patients in a short period of time for the efficacy study.

Our decision to base trials in Australia was fourfold. Firstly, I met key opinion leaders in neuro-oncology at the ASCO (American Society of Clinical Oncology) 2015 who wished to conduct clinical trials using Tanibirumab on their rGBM patients. Both Dr Lawrence Cher at Olivia Newton Johnâ??s Cancer Centre and Dr Anna Nowak at The University of Western Australia/Sir Charles Gaidner Hospital are renowned neuro-oncologists with extensive experience conducting clinical trials.

Secondly, Avastin was not the standard of care for rGBM and is not covered by insurance in Australia. Consequently, we do not need Avastinâ??s control arm for the study. Thirdly, there is a high possibility to recruit Caucasian patients, significantly limited in Koreaâ??s homogenous society. In general, global pharma prefers to have a clinical study from Caucasian patients.

In addition, there are tax incentives in Australia: about 43 percent of total expenditure is reimbursed by the Australian Government. Finally, the time difference is more suitable for a company located in Korea, given the communication that is required with the clinical CROs based there.

We recently opened a PharmAbcine subsidiary in Brisbane, Australia. This will establish PharmAbcine as a multi-cultural/multi-ethnic organization and will ease our access to the global talent pool PharmAbcine must utilise for its next steps.

How do you see the treatment of cancer evolving into the future?

I consider cancer to be a multi-complex disease: it affects more than 100 different cell types and often has many different sub-types â?? there are five intrinsic sub-types for breast cancer alone. Even amongst the same subtypes, each patient has a different genetic background.

I always say that cancer is very â??smartâ?•, perhaps the â??smartestâ?• in the body, always devising a solution to bypass treatments whatever they may be. Cancer always has its plan B and plan C. Therefore, it is not sufficient just to shut down one key pathway; it will be more effective if we have a way to shut down their plan A and plan B from the beginning.

PharmAbcine will go in the direction of personalized precision medicine. I am not optimistic that one single drug can cure cancer since cancer has complex heterogeneity and is constantly evolving. It will be a never-ending competition between cancer and cancer drugs. However, I am optimistic that we can make cancer a manageable disease through providing the right drugs and combination therapies to the right patients in near future.

How well prepared is the Korean system to adapt to the cancer treatments of the future?

There is an already well-established healthcare system in Korea with high cancer awareness. The eco-system of the Pharma and Biotech industries has improved dramatically in the past ten years. In the private sector, the number of Korean attendees at the Bio International convention or the JP Morgan healthcare conference has risen significantly. The Korean authorities are constantly seeking the right treatment for the right patient at the right price. In the future, the drugs will be more effective, although much more expensive. In the 1970s, when people were diagnosed with cancer, around 250 USD would be the annual expense on their post-diagnosis treatment; they would have limited survival benefit with huge side effects. Nowadays, an IO drug costs around USD 150,000 per year and patients are suffering with both drug toxicity and financial burden. Consequently, the

Korean Government is controlling those drug price to increase affordability and access for patients.

Korea has a cost-effective healthcare system with annual check-ups for those over 30-years old. We also have highly trained medical doctors and surgeons. In the past, many people died from stomach cancer. However, the death rate declined significantly because Koreans benefited from endoscopes and colonoscopies at their regular health check-ups which could detect stomach cancer at an early stage. I believe that the Korean healthcare industry, including PharmAbcine, can contribute to bettering the lives of cancer patients in near future at an affordable expense.

What are Koreaâ??s strengths and weaknesses in terms of its ability to develop drugs in oncology?

Korea is one of the most favourable destinations for global pharma to base their clinical trials, especially when the intention is to enter the Asian market. Clinical trial centres and staff are well-qualified, and their experience continues to accumulate.

Korea has been very competitive in the IT industry for a long time. Even though the healthcare industry is very different from IT industry, our well-established IT infrastructure can be leveraged through Artificial Intelligence (AI) with clinical big data to develop better drugs in a cost-effective manner. Above all, the commitment of Korean scientists in the healthcare sector will be the foundations to bringing the evolution of AI into the development of next generation drugs. This has the capacity to change the paradigm of current therapy: AI in healthcare will navigate the right drug/right combination to right patients in more accurate way.

Koreaâ??s local pharma industry and domestic market size is limited. While we have focused on investing into R&D to make innovative drugs, this cannot be done in Korea alone. I have always asserted that Switzerland is a good model for the Korean healthcare industry to emulate. For example, Novartis or Roche are present at every hot place â?? open to recruit from the global talent pool. Korean Pharma and biotech should be ready to welcome global talent but should also be open to establishing subsidiaries in promising locations like Silicon Valley or Kendall Square.

Nowadays, the competition within the bio healthcare industry is very high as every country is investing and strives to lead. Fortunately, the Korean Government is very supportive in the endeavour to boost the Korean healthcare industry. However, it would be more synergistic if the Korean Government was more open and flexible with their regulations for next-generation industry. The doubling of the workforce for the regulatory authority, for example, would be an effective operation. This will contribute enormously to shortening the entire oncology drug development time period and this will be a huge benefit for patients, who cannot wait for next-generation therapeutics.

What are your main aspirations for PharmAbcine looking into the future?

2018 was a great year for PharmAbcine, but this year will be even greater. We are so excited with our ongoing combination trials in Australia and phase II Avastin relapsed recurrent GBM trials in the US. We will expand the indication of combination trials for gastric cancer, ovarian cancer, and renal cancer with strong scientific and clinical rationale in the future. We will prepare resources for the initiation of global remained phase IIb recurrent GBM trials to access the global market after phase IIb as an orphan drug.

We remain open for opportunities for win-win research collaborations, co-development, and licensing out agreements with our 20 innovative assets. We are pushing to reach the IND enabling stage

within this year for two candidates. In parallel, we will have a significant presence in Australia, the US and Europe and will play a pivotal role in innovative oncology drug development.

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