Reflections on ASCO 2018

The promise of combination therapy in oncology

One of the features of the recent ASCO meeting in the US was the variety of outcomes of studies involving different combinations of checkpoint inhibitors with other drugs, including studies with chemotherapy. Many assumptions were upended including the role of chemotherapy on its own in an adjuvant setting after surgery.

To gain a better insight into some of the changes taking place in the industry, *MedNous* interviewed two executives of ISA Pharmaceuticals BV, a Dutch company developing therapeutic vaccines for cancer and persistent viral infections. In the interview, Gerben Moolhuizen, the recently appointed chief executive, and Kees Melief, the ISA co-founder and chief scientific officer, commented on some of the ASCO findings.

ISA has a partnership with Regeneron Pharmaceuticals Inc to co-develop its lead vaccine candidate for cervical and head-and-neck cancers as a combination therapy. The ISA vaccine, ISA101, has already shown encouraging results in combination with nivolumab, a checkpoint inhibitor, in patients with incurable human papillomavirus type 16 (HPV16) in a study conducted at the MD Anderson Cancer Center, US. Under the partnership with Regeneron, the vaccine will be taken forward in combination with cemiplimab, Regeneron's investigational checkpoint inhibitor. There are also plans to test ISA101 in combination with standard of care chemotherapy and cemiplimab.

Commenting on the ASCO meeting, Mr Moolhuizen drew encouragement from several presentations, in particular Merck & Co Inc's study of pembrolizumab with standard of care chemotherapy in patients with metastatic squamous non-small cell lung cancer (NSCLC). The study, Keynote-407, showed that the combination therapy significantly improved overall survival, reducing the risk of death by 36% compared with chemotherapy alone. It was the first time that a programmed cell death protein 1 (PD-1) checkpoint inhibitor, combined with chemotherapy, had significantly extended overall survival in the first-line treatment of squamous NSCLC.

"I think what you see in late-stage cancers, or in people who have recurrences after initial treatment, or who have already been diagnosed with metastatic disease, is that everyone is looking for combination therapies. Anti-PD-1 by itself has a limited effect in those settings in general. The big question is: what is the best combination?" Mr Moolhuizen said.

For ISA, this opens the door to vaccines. "We've shown that there is an immunomodulatory role of chemotherapy. We have also shown that you can add a vaccine to an anti-PD-1 or to chemotherapy so we believe that in a late-stage setting a combination therapy will be based on synergistic compounds rather than the more general immuno-modulators," the executive said.

One of the jaw-dropping studies at ASCO was a presentation by French and Canadian researchers showing that the chemotherapy regimen Folfirinox significantly improves overall survival in patients with pancreatic cancer, post-surgery, compared with the current standard of care gemcitabine. This finding has already caused one company, Targovax ASA, to drop a candidate vaccine for pancreatic cancer. It is also expected to send many scientists back to the laboratory for a rethink about chemotherapy.

The ISA executives said the Folfirinox trial results might, in fact, provide an opening for vaccines provided there is more information on the mechanism of action of the chemotherapy. "Regarding Folfirinox, I don't think they [the sponsors] have looked in detail at the surprising results, or the reasons for the surprisingly good results, but it wouldn't surprise me if this treatment doesn't really kill more tumour cells but vastly improves the micro-environment in the tumour and then that is favourable for immune cells to kill more tumour cells," Dr Melief commented.

The tumour microenvironment is the cellular environment in which a tumour exists, including surrounding blood vessels and immune cells. Tumours can influence the microenvironment, while immune cells in the microenvironment can affect the growth and evolution of cancer cells. Tumours are described as 'hot' when they are infiltrated by T cells, 'cold' when they are not, or somewhere in between. The level of immune infiltration reflects whether the immune system is equipped to fight the cancer.

This is where vaccines come into the picture. "We believe that vaccines have a great space to fill because they have a proven capacity to turn so-called cold tumours into hot tumours with many T cells. As a result PD-L1 negative tumours become PD-L1 positive and there are enough T cells to start seeing efficacy from checkpoint blocking," Dr Melief said.

"So I think the design of combination therapies in our mind, and this is not only true for the vaccines, but in general, should be much more science driven. Also the inspection of what chemotherapy does in this space, in this area of immunotherapy, should also lead to a novel inspection of what different chemotherapeutics actually do in the microenvironment," he added.

The ISA portfolio has several compounds targeting cancers including ISA101 in HPV16-positive indications. "We know that our vaccine, plus chemotherapy does well in cervical cancer and we know our vaccine with a checkpoint blocker does well in head and neck cancer," Mr Moolhuizen said. The Merck lung cancer trial showed that a checkpoint blocker can also be successfully combined with chemotherapy, he added. That is the missing piece of the puzzle.

This article was prepared by the *MedNous* editor from a literature search and a telephone interview with Gerben Moolhuizen, chief executive, and Kees Melief, chief scientific officer, of ISA Pharmaceuticals BV in the Netherlands.