ILCA 名家访谈丨“双免联合”STRIDE 方案在不可切除肝细胞癌中的疗效及安全性

Dr Sangro: These two checkpoint molecules occur at different stages in the immune response against cancer. While PD-1 acts preferentially in the late stages when the T-lymphocytes have breached the tumor site, CTLA-4 acts both to prime the immune system to start an immune response, but also counteracting the effects of the immune response at the local site through regulatory T-cells. The important point is that some tumors, HCC among them, have proven to be sensitive to CTLA-4 inhibition. We know this from our earliest trial with tremelimumab monotherapy, and from other studies that have included tremelimumab alone, which has a response rate of around 15%, similar to PD-1. The important thing is that, now, with the combination of ipilimumab plus nivolumab, and tremelimumab plus durvalumab, we know that the action of these two checkpoint inhibitors add on to one other, and are even synergistic, and the combinations work better than monotherapies. That is what we need for clinical use.

Dr Sangro: Today, what we know is that the two clinical trials that have tested targeted therapies (tyrosine kinase inhibitors) with PD-1/PD-L1 inhibitors have failed to show positive results. For both COSMIC-312 and LEAP-002, we don’t know the details of the latest results, just a press release, but they failed to show an advantage in the primary endpoint, progression-free survival. This rivals these two compounds having an additive, if not synergistic, effect. So, as of today, combinations should be considered with the purely VEGF inhibitor, bevacizumab, or with the CTLA-4 inhibitor, tremelimumab. We are waiting for the results of the combination of ipilimumab plus nivolumab.

Dr Sangro: When you release the brakes of the immune system using checkpoint inhibitors, you may have adverse events in the form of inflammation in any organ in the human body. When you do dual blockade with two checkpoint inhibitors, then the chances of having this kind of immune-mediated adverse events are higher, but the types of events are similar. Basically, it is inflammatory toxicity to the skin, to the endocrine organs (thyroid, sometimes the adrenal gland) to the liver (hepatitis), and the gastrointestinal system (colitis) and, more rarely, pneumonitis and other really dreadful complications, such as myocarditis and others. Altogether, if you are aware of the possibility of these immune adverse events and you closely monitor the patient, you can avoid them being high-grade, can treat them correctly, and the patient may benefit from their treatment.

The information we have today comes form the HIMALAYA trial, where patients received either sorafenib as a control, durvalumab (an anti-PD-L1 agent) monotherapy, or a combination of durvalumab plus one single priming early dose of tremelimumab. There was an advantage of this regimen called STRIDE (combination of CTLA-4 and PD-L1 inhibition) versus sorafenib. Durvalumab was only non-inferior. This means that the combination is more active. It seems the toxicity side effects are easily managed and not of high frequency. I rarely see a patient who would benefit more from monotherapy than from combination

Dr Sangro: There are two things that we are desperately searching for. One is biomarkers that would allow us to identify those patients who will not benefit from immunotherapy, more than those who will benefit. For those patients, we do have active drugs, the TKIs, and it would be better to start these patients on those drugs as early as possible. So, biomarkers is one thing. The other thing is expanding the possibility of exploiting an immune response by other technologies. We think about adoptive T-cell therapy. We can think about CAR T-cell therapy, called TCR-engineered T-cell therapy. But also, combinations with drugs that provide epigenetic changes that may make the tumors more antigenic and more prone to developing an immune response.