Overall survival and immunologic responses in mPDAC on PEGylated human IL-10 (AM0010) with 5-FU/LV

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Welcome to Partners in Pancreatic Cancer. My name is Joel Randolph Hecht. Today I will be providing highlights from the 2017 ESMO Congress held in Madrid, Spain.

Unfortunately, pancreatic cancer has now become the third most common cause of cancer death in the United States. It is one of the few cancers where mortality is actually increasing. Despite decades of research, how patients do with metastatic disease (which is the vast majority of patients when they present) remains poor. Only about 10% of patients have operable disease at the time of diagnosis, and even most of those end up recurring. Some patients have inoperable locally advanced disease, but eventually almost all patients with pancreatic cancer end up dying from their disease. There have been improvements, particularly in first-line therapy, where combination chemotherapy, either with gemcitabine and nab-paclitaxel or the combination of 5-FU, irinotecan, and oxaliplatin has improved survival; but most people die in a relatively short time. Only recently have people looked at second-line therapy, initially with fluoropyrimidine alone then adding oxaliplatin so that 5-FU and oxaliplatin is a reasonable standard. Even more recently with the addition of nanoliposomal irinotecan or nal-IRI to 5-FU, both of those have somewhat increased life expectancy in second-line, but most people die relatively soon. Only a minority of people seem to have advantages from this. While immunotherapy has revolutionized how we treat other cancers such as melanoma, lung cancer and more recently urothelial cancers and, what I do, gastric cancer, unfortunately standard immunotherapies (particularly checkpoint inhibitors) have not been successful in treating metastatic pancreatic cancer. Therefore, there is clearly an unmet need.

What I am going to discuss today is a trial that I presented using a new immunotherapy called PEGylated IL-10 or AM0010, or more recently pegilodecakin, in an expansion cohort of a phase I trial. This trial was actually part of a multi-cohort trial in multiple different malignancies, but all I am going to talk about today and all that was presented are patients who had pancreatic ductal adenocarcinoma. These patients have been multiply pretreated with multiple lines of therapy and were treated either with AM0010 alone or in combination with 5-FU and oxaliplatin, the combination known as FOLFOX.
What we were able to show was that patients did surprisingly well, and that is all you can say in a nonrandomized trial. Patients who had monotherapy had no responses. A reasonable number of those patients, about over 50%, had disease control at the first scan. The combination with FOLFOX actually seems to be even more potent, with almost 80% of people having disease control. Perhaps even more importantly, median overall survival was 10 months, which is much more than what you would normally expect which is usually in the range of four months. In addition, there also appears to be a tail of the curve where in this updated data that was presented at ESMO, 43% of the patients are still alive at one year. On the other hand, the vast majority of patients who were treated with standard therapies are expected to have died by one year.

PEGylated IL-10 is unusual. It is not a standard checkpoint inhibitor. In fact, IL-10 actually may have multiple effects of both increasing inflammation and decreasing inflammation, depending on which parts of the immune system you are looking at. Some of the things that have been important in basic science for IL-10 have been increases in CD8-positive effector cells. These are the T-cells that seem to be most important in having an immune response. In fact, in this trial and in other trials that have been recently published, there appears to be increasing novel T-cell clones that you can detect after a patient has been treated with PEGylated IL-10. Why the combination with chemotherapy? Chemotherapy, particularly oxaliplatin, can lead to immunogenic cell death which can expose the T-cells to new tumor neoantigens, and the combination both preclinically and in the study, appears to be much more potent.

The next steps for this are a large randomized phase III trial in second-line pancreatic cancer. These are patients who have not been pretreated with a platin. Patients are randomized to receive either FOLFOX or FOLFOX plus PEGylated IL-10. As far as I am aware, there are not any other large trials in second-line pancreatic cancer. There are a number of trials, however, that are underway, both with signal transduction inhibitors as well as antistromal agents such as PEGylated hyaluronidase in the first-line setting. After a long time of really no interesting trials in pancreatic cancer, particularly from an immunotherapy standpoint, we are now at a point where this is going to be one of the largest trials. There are also several smaller trials with other novel agents in this arena. Pancreatic cancer patients have been waiting too long to join in on the immunotherapy revolution.

Thank you very much.