[MUSIC PLAYING]

MARTIN EARLE: I'm going to be speaking about three abstracts. The first is the use of pembrolizumab in gastric and GE junction cancers, which have been extensively treated. The second is a new regimen developed by the Germans, adding docetaxel to FOLFOX and looking at its activity in the peri-operative period of potentially resectable gastric and GE junction cancer patients. And the third is the use of a new thymidine kinase inhibitor, lenvatinib, in hepatocellular cancer.

The first is another of the Keynote trials, which the UPCI did participate, looking at the activity of pembrolizumab in advanced gastric and GE junction cancers. As you know, PDL1 and PDL2 is expressed in multiple solid tumors, and there was a previous stage one trial looking at the activity of pembrolizumab in GE junction and gastric cancer, and there was some promising anti-tumor activity.

The Keynote 59 is a huge trial. It's a multicohort trial, and I'm just going to be talking about the first cohort, where they used pembrolizumab in standard doses to treat patients with advanced gastric and GE junction cancers. Now, these patients were extensively treated. They were treated for 24 months until progression.

Eligibility criteria are, as usual, you could be HER2-positive in this trial, and of course, ECOG performance status zero to one, and no CNS metastasis.

Of primary import was overall response rate, and they did look at response as a function of microsatellite instability. Patients were relatively young. I'd like to think that they were relatively young, age 62, mostly male, and worldwide.

On the bottom of the slide, you can see that about 20% of patients had greater than four therapy. So these are pretty advanced end stage patients.

About half of them were PDL1-positive and about a quarter of them were HER2-positive. Bottom line is by RECIST criteria, overall response rate was 11.6%. Looking at this, with respect to PDL1 positivity, in the positive patients, 15.5% response rate versus 6.4%.

Looking at the waterfall plot, about 42% of the patients benefited, and interestingly, at the end, you can see a complete response in a patient who was PDL1 negative, which is always intriguing.

If one looks at treatment as response as a function of MSI status. An MSI-high patient, patients had a 57% response rate versus a 9% response rate, and unfortunately, only 4% of the patients were found to be MSI-high, and this is similar to what you see in colon cancer.

Now, they did a very interesting thing where they looked at expression of 18 genes involved with T cell inflammatory response associated with a tumor. And they looked at gene expression, and they developed a score based upon this expression. And when they did that, they looked at response to the pembrolizumab as a function of the score. And the responders had a higher score versus the nonresponders, and this appeared to be statistically significant. Although, it's really not a home run, as you can see by the error bars, but nonetheless, it's an attempt to look at something other than PDL1 status.

Adverse events were relatively, as one would expect with most thymidine kinase-- with checkpoint inhibitors, and the immune-mediated adverse events occurred in 17.8% of the patients and about 28% of those required steroids.

The progression-free survival is relatively dismal. It's about two months. And as you can see, these were indeed end stage patients, but what's intriguing is that there's a tail at the end of the curve and some patients are out 18, 20 months with progression-free survival, and this is the overall survival curve reflecting that. Again, there's a small tail.

The conclusions were that the pembrolizumab showed some promising antitumor activity. The overall response rate was higher in the PDL1 positive patients than negative, that the treatment was well tolerated, and that it represented a potential treatment option for patients with advanced gastric and GE junction cancer. There are ongoing trials looking at pembrolizumab upfront and with chemotherapy.

The next abstract is an interesting trial done in Germany, looking at a new chemotherapy regimen in the peri-operative period for patients who have gastric and GE junction cancer that is potentially resectable. From the MAGIC trial, published not too long ago, ECF became the standard treatment, which consists of epirubicin, cisplatin, and 5-FU. However, at five years, the survival was only about 36%.

Hence, the Germans decided to develop a new regimen to see if they can improve on that. This new regimen adds docetaxel to what appears to be a modified FOLFOX, where the 5-FU is only administered over 24 hours and the laucovorin dose is a little lower, still a formidable regimen.

The study design looks at gastric cancer patients that are potentially resectable T2 to four, any N. They were randomized to this FLOT regimen, which is cycled every two weeks times four, followed by surgery, followed by adjuvant FLOT versus the standard ECF, which is cycled every three weeks times three, followed by resection, followed by adjuvant therapy. The primary endpoint was overall survival, and they had several secondary endpoints as noted.

Baseline characteristics, the patients were well-stratified, with respect to the usual suspects. I'm not going to go through them all. About 80% of people were node positive, and other thing that's interesting is that about a quarter of them had signet rings histology, which is just a particularly nasty, aggressive type of cancer.

90% of the patients finished the pre-operative chemotherapy. However, there was a big drop off, where about half of them completed the post-chemotherapy. Patients in the FLOT arm did a little better than the ECF arm.

The rate of resection was higher in the FLOT arm at 94% versus 87%, and free margins were higher in the FLOT arm at 84% versus 77%, both of which were statistically significant.

In terms of downstaging, the FLOT arm was downstaged to TI to a greater extent than the ECF, 25% versus 15%, and note negative status was better in the FLOT arm than in the ECF arm, both of which were statistically significant.

Side effects and operative mortality and complications were about the same in both arms. I don't need to go into details. The only difference in chemo-related toxicity is that ECF had a higher nausea and vomiting and the FLOT arm had higher infection rate and neutropenia.

There were more dead in the ECF arm than in the FLOT arm, and this was statistically significant. And if one looks at the progression-free survival, the median progression-free survival was 18 months in the ECF arm and 30 months in the FLOT arm. This was extended out to five years. Likewise, the overall survival is better in the FLOT arm, 35 months versus 50 months median survival, and, of course, this was projected out five years and appeared to be holding up.

The forest plot shows that all groups seem to benefit by the FLOT chemotherapy versus ECF. And their conclusions were that FLOT increased the rates of a curative surgery and prolonged progression and overall survival, that it was effective across multiple subgroups, and did not increase surgical mortality or morbidity, and that it represented a new standard of care for the peri-operative treatment of adenocarcinoma of the stomach and GE junction.

The third and final abstract is looking at the ReFLECT study, which is looking at lenvatinib, which is a new thymidine kinase inhibitor, comparing it to sorafenib, which is the standard of care for unresectable hepatocellular cancer. This is a large, phase three, international trial.

As you know, hepatocellular cancer is very common worldwide. We're actually seeing many more cases than we did previously. And sorafenib has been the standard of care for advanced patients. There have been several trials looking at other thymidine kinase inhibitors to improve survival, and they have failed. Lenvatinib is relatively new. It's a multifunctional inhibitor of VEGF and a number of other receptors.

The study schema is really straightforward. They took advanced hepatocellular cancer patients who were unresectable. None of the patients could have a tumor volume greater than 50% of the tumor, ECOG performance status and Child-Pugh class were favorable. And it was stratified and randomized one-to-one to sorafenib, which is at standard dose is 400 milligrams BID, versus lenvatinib, which was weight-based, based upon whether or not you were over or under 60 kilograms. The primary endpoint was overall survival.

Patients were stratified well with respect to the usual characteristics. We don't need to go through all of this. It is noted that alpha phenyl protein was slightly higher in the lenvatinib group. Bottom line is the overall survival curves are nearly superimposable, reflective of the hazard ratio of near unity.

If one looks at the forest plots, one sees that the primary benefit is in the lenvatinib arm. Note that the Asian patients seem to benefit better than the Western patients did and that might be significant. When looking at progression-free survival, lenvatinib is superior to sorafenib and it is statistically significant. Again, the forest plots show that there is a benefit across all subgroups and even in the Western versus the Asian Pacific patients.

The waterfall plots show that the overall response rate is 24% versus 9.2%, again, statistically significant. And looking at the areas of the curves, you can see that lenvatinib benefits many more patients than sorafenib.

Side effects were the same, with the exception of more hypertension in lenvatinib and more hand-foot syndrome in sorafenib. They looked at quality of life issues and they were equivalent in both arms. Their conclusions were that lenvatinib demonstrated a non-inferiority to sorafenib with respect to overall survival, and that it achieved statistically significant improvement in progression-free survival, et cetera. The two drugs were comparable with respect to safety and toxicity and based upon the results, lenvatinib is potentially a second option for patients with advanced hepatocellular cancer.