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Monoclonal Antibody-Based Regimens for Early Relapse Multiple Myeloma

Announcer:
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Dr. Biran:
Hi, this is Noa Biran. Today, I will be discussing the use of Monoclonal Antibody-Based Regimens for Early Relapse Multiple Myeloma.

So monoclonal antibodies are very important in patients with myeloma as well as in other malignancies. They have a variety of myeloma-directed and immunomodulatory effects. So daratumumab and isatuximab both bind to CD38 both have on-tumor effects such as CDC, ADCC, and ADCP, as well as apoptotic effects on the therapy, but they do have significant - somewhat different effects on the immune milieu. Dara may deplete CD38-positive immunosuppressive regulatory cells and isatuximab may have some immunomodulation affects and inhibition of the ectoenzyme activity. Elotuzumab is an antibody with a different target, it binds to SLAMF7 or CS1, and it may have somewhat more direct NK cell activation compared to the CD38 monoclonal antibodies.

Daratumumab with an IMiD and dex has been evaluated in early relapsed myeloma through the POLLUX study as well as the APOLLO study. The POLLUX study has very long follow-up, more than 6.5 years to date. It looked at the combination of dara/len/dex, versus len/dex, and showed significant improvement in median PFS, 38.8 versus 18.6 months.

The APOLLO study was done in patients with slightly later relapsed disease. It was a phase 3, and it showed that the median PFS was superior with the combination of dara/pom/dex, compared to pom/dex alone, with a hazard ratio of 0.63. Of note, almost 80% of patients in this study were lenalidomide-refractory.

The combination of daratumumab has been used with proteasome inhibitors and dex in early relapsed myeloma. The CANDOR study was a phase 3 looking at dara/car/dex, versus car/dex. The median follow-up was 50 months, and we can see that the triplet combination had a median PFS of 28.4 versus 15.2 months, which is statistically significant. And the CASTOR phase 3 study looked at dara/bortezomib/dex, versus bortezomib/dex, and also showed superiority in the triplet versus the doublet.

Isatuximab looked at combination of isa/pom/dex versus pom/dex and the ICARIA-MM phase 3 study, and in patients who had more than 2 prior lines, including lenalidomide and a PI, and in the majority were lenalidomide-refractory, we see a significant improvement in time-to-next-treatment with the triplet compared to the doublet with the hazard ratio 0.55. And as we continue to see longer follow-up, we see a continued improvement in progression-free survival, with a median PFS of 11.1 months versus 5.8 months with pom/dex alone. The IKEMA study evaluated the combination of isa/carfilzomib/dex, versus car/dex in patients who had 1 to 3 lines, median 2 prior lines, and you can see that in this very heavily pretreated patient population, 93% who had prior PI and 20% were refractory to both IMiD and PI, we see a median PFS of not reached versus 19.5 months, which is one of the longest follow-up median PFS we see in this prior lines of therapy. Even though we cannot compare across trials, this is certainly impressive data.

The ELOQUENT trial evaluated elo, lenalidomide, and dex compared to len/dex alone. And you can see that with very long follow-up, the median PFS benefit is maintained as well as the overall survival benefit at a median at 5-year OS, you see that the triplet

combination had 40% alive versus 33% in the doublet combination, and this was statistically significant. The ELOQUENT-3 study evaluated the combination of elo/pom/dex compared to pom/dex alone in very heavily LEN-refractory population, and had a significantly improved median PFS with the triplet compared to the doublet. Also, this one showed an improvement in overall survival.

To summarize, we have several monoclonal antibodies that are used in early relapse myeloma isa or daratumumab, in combination with carfilzomib and dex have demonstrated impressive median progression-free survival to date. The

POLLUX study, which evaluated the combination of dara/len/dex, versus len/dex, has one of the longest median follow-ups and showed a significantly improved median PFS with the triplet compared to the doublet. And elotuzumab should also be considered in this setting, as it showed patients who were heavily LEN-refractory and demonstrated a 2-year PFS a 41% versus 27% with the triplet combination versus the doublet.

Thank you very much.

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