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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Spotlight on Europe: Adapting the Evidence

Dr. Curigliano:
This is a Continuous Education on ReachMD, and I am Dr. Giuseppe Curigliano, working at the European Institute of Oncology in Milano.

Today I will provide my perspective on managing HR-positive, HER2-negative metastatic breast cancer in Europe.

And let's start from the clinical practice guidelines of ESMO. If you have an HR-positive, HER2-negative de novo metastatic breast cancer, or with a recurrence after 12 months after the end of adjuvant endocrine therapy, the treatment algorithm, of course, suggests a combination of aromatase inhibitors plus CDK4/6 inhibitors. We know exactly that in this setting, all the clinical trials met the primary endpoint; that was median progression-free survival.

But we know perfectly that some CDK4/6 inhibitors demonstrated overall survival benefit, some others no. The only 2 to demonstrate an overall survival benefit were ribociclib and abemaciclib. In this setting, palbociclib failed to demonstrate an overall survival benefit.

In terms of HR-positive, HER2-negative disease with an endocrine-resistant disease, so a recurrence while on adjuvant endocrine therapy, or in less than 12 months after the end of adjuvant endocrine therapy, once you have progressive disease, it is mandatory to perform the PI3 kinase mutational status. You can do this on tissue biopsy, preferred one, or a liquid biopsy. If PI3 kinase mutant, the best of care is fulvestrant, palbociclib, inavolisib. This is the optimal care, since according to the INAVO120 trial, there is an improvement in median progression-free survival and overall survival.

When you don't have PI3 kinase mutation, the best of care should be fulvestrant plus a CDK4/6 inhibitor.

Of course, what to do if progression to a first-line endocrine therapy in combination with CDK4/6 inhibitors? In this case, you have to consider if the patient has an imminent organ failure or a visceral crisis. In this scenario, a chemotherapy or an ADC like trastuzumab deruxtecan should be the first option. But if you don't have an imminent organ failure, the second-line setting should be a biomarker-driven approach.

So if PI3 kinase mutant or with alteration of AKT1 and PTEN, the optimal combination should be fulvestrant and capivasertib. If PI3 kinase mutant alone, you can use fulvestrant and alpelisib.

When you have ESR1 mutation, in Europe, we have elacestrant actually approved and there is no problem with access. But we know that a few weeks ago, also imlunestrant was approved in the United States by FDA.

If germline mutation of BRCA1 and BRCA2, or PALB2 mutation, which suggests a PARP inhibitor like olaparib or talazoparib, and in case of non-biomarker alteration, exemestane and everolimus, fulvestrant and everolimus, or eventually fulvestrant alone can be an option.

Of course, we have several unmet medical needs in the context of HR-positive, HER2-negative disease. First, I believe that in the biomarker-driven approach, still what we actually have is actually that is a combination of fulvestrant plus a PI3 kinase inhibitor or an AKT inhibitor or an oral SERD alone. The benefit in terms of median PFS in the post-CDK4/6 inhibitors is a benefit between 5 and 7

months. So I really believe we should give more to our patients.

EMBER-3, in the combination arm of imlunestrant plus abemaciclib, achieved an 11-months median progression-free survival benefit. But unfortunately, this combination was not approved by FDA.

Another unmet medical need is for patients with rapid progression to CDK4/6 inhibitors—those patients progressing within the first 6 months of treatment of an AI or fulvestrant plus CDK4/6 inhibitors. This is a special patient population that is a high unmet medical need, and over here, we need more trials, or with a triplet combination or with ADCs.

Well, this is all the time I have today. I hope this brief overview is useful to you, and thanks for listening.