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[www.reachmd.com](http://www.reachmd.com)

[info@reachmd.com](mailto:info@reachmd.com)

(866) 423-7849

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### Breaking Down the Benchmarks: Pivotal Data on First-Line CDK4/6 Inhibitors

#### Dr. Curigliano:

This is continuous education on ReachMD, and I am Dr. Giuseppe Curigliano from European Institute of Oncology, Milano.

Today I will review the pivotal data on first-line CDK4/6 inhibitors in HR-positive, HER2-negative metastatic breast cancer. We have actually 3 CDK4/6 inhibitors approved—abemaciclib, palbociclib, and ribociclib. Any one of them has been developed in the context of 3 different programs—the MONARCH trials for abemaciclib, the PALOMA trials for palbociclib, and the MONALEESA trials for ribociclib.

If we check the data in endocrine therapy-sensitive disease, we have MONALEESA-2, PALOMA-2, and MONARCH-3. The primary endpoint of these clinical trials was median progression-free survival. All trials demonstrated statistically significant and clinically meaningful improvement in terms of median progression-free survival.

But if you explore the benefit in terms of overall survival, only 2 of them demonstrated an overall survival benefit—the MONARCH trial, with an improvement from 53 months to 66.8 months, and the MONALEESA-2 trial, from 51 months to 63.9 months. Palbociclib did not demonstrate any overall survival benefit.

According to this data, we incorporated the CDK4/6 inhibitors in the treatment algorithm for the guidelines of ESMO, NCCN, and ASCO. So actually, of course, if you have any patient with HR-positive, HER2-negative disease and endocrine therapy-sensitive disease, the best option is an aromatase inhibitor in combination with the CDK4/6 inhibitor.

Anytime you prescribe it, you should consider of course that the magnitude of clinical benefit score is different across CDK4/6 inhibitors, since some of them, namely abemaciclib and ribociclib, demonstrated an overall survival benefit. Some others, like palbo, did not demonstrate an overall survival benefit.

If we move to the first line in endocrine-resistant disease, also here, we have other trials in which the combination eventually is with fulvestrant. And in the context of the treatment algorithm of ESMO, NCCN, and ASCO for endocrine-resistant disease, the frontline treatment in patients without PI3 kinase mutation should be the combination of fulvestrant plus CDK4/6 inhibitors.

Also in this context, abemaciclib demonstrated an overall survival benefit, and that's why here we have a treatment algorithm in which NCCN, ASCO, and ESMO suggested the combination of fulvestrant plus abema, or fulvestrant plus ribociclib, or fulvestrant plus palbociclib.

Well, this is all the time I have today. I hope this brief review is useful for your practice. Thanks for listening.