Two studies show CDK4/6 inhibitors improve overall survival in advanced breast cancer

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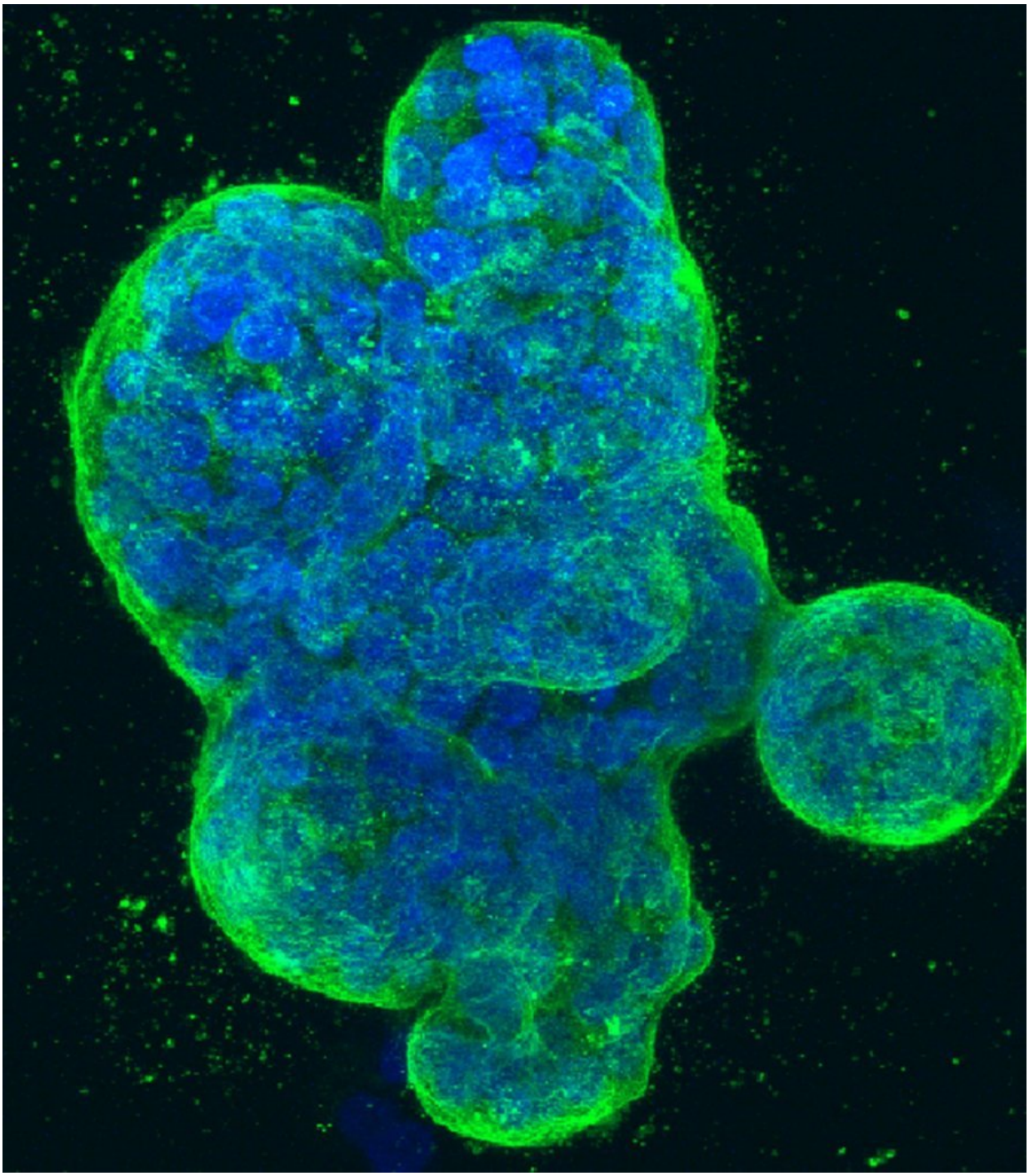

Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. Image created in 2014 by Tom Misteli, Ph.D., and Karen Meaburn, Ph.D. at the NIH IRP.

New data from two studies reported at the ESMO Congress 2019 have shown that treatment with a CDK4/6 inhibitor plus fulvestrant improves overall survival in women with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) advanced breast cancer.

The two studies included different patient populations as well as different CDK4/6 inhibitors used as different lines of therapy: Monarch 2 evaluated abemaciclib plus fulvestrant in patients with advanced breast cancer after failure of endocrine therapy and regardless the menopausal status; the Monaleesa-3 study investigated ribociclib plus fulvestrant as first- or second-line only in postmenopausal patients.

The results give the treating physician the full spectrum of choice of CDK4/6 inhibitor for each individual patient, although the two CDK4/6 inhibitors have slightly different management requirements and toxicity profiles.

Monaleesa-3

Results of the Monaleesa-3 trial have shown that first-line, as well as second-line, treatment with the CDK4/6 inhibitor ribociclib plus fulvestrant significantly improves overall survival in postmenopausal patients with HR+ HER2- advanced breast cancer. The benefits with ribociclib plus fulvestrant were seen in women not previously treated with hormonal therapy as well as in those who had become resistant to endocrine therapy.

"This is a significant, practice-changing report, in that we are now saying that patients with advanced breast cancer will have an overall survival benefit if they get the CDK4/6 inhibitor ribociclib upfront at the time of their recurrence, even if they have not had any prior endocrine therapy at the time of presenting with metastatic disease," said study author Prof Dennis Slamon, University of California Los Angeles, USA.

"The argument has always been by some experts that you should first treat with endocrine therapy alone and then if patients recur, you would add something like a CDK4/6 inhibitor. In other words, you get what you can out of endocrine therapy alone—and save a CDK4/6 inhibitor until the subsequent recurrence. The data from Monaleesa-3 clearly show that if postmenopausal patients receive this right up front there is a very significant benefit—not only in progression free survival, which had already been published—but now with this new report in overall survival—which is the hardest endpoint to reach, and the most important one in terms of making an impact on the disease," Slamon explained.

Commenting on the new data, Dr. Matteo Lambertini, IRCCS Policlinico San Martino Hospital, University of Genoa, Italy, said, "Monaleesa-3 reports remarkable results that further confirm the major improvement in the care of patients with HR+/HER2- advanced disease obtained with the combination of endocrine therapy and CDK4/6 inhibition; this treatment should be made widely available to all our patients in this setting. Uniquely, Monaleesa-3 is the only trial with a CDK4/6 inhibitor to include patients with endocrine sensitive as well as those with endocrine resistant disease. This is the first time we have seen improved overall survival with a combination of a CDK4/6 inhibitor plus fulvestrant in first line."

Monarch 2

A second trial reported at the ESMO Congress 2019, Monarch 2, showed statistically and clinically meaningful improvement in overall survival with the CDK4/6 inhibitor abemaciclib plus fulvestrant in pre-, and peri- as well as in postmenopausal women patients with HR+ HER2- advanced breast cancer resistant to hormonal therapy.

"Results from Monarch 2 study presented two years ago showed significant improvement in progression free survival for patients treated

with the combination of abemaciclib plus fulvestrant compared to fulvestrant alone. Now, with further follow-up we have overall survival data showing a statistically significant and clinically meaningful improvement in overall survival with the combination," said study first author Prof George Sledge, Stanford University School of Medicine, USA.

He suggested, "The main take-home message from this study—and from other similar studies—is that CDK4/6 inhibitors significantly prolong the time patients remain in remission and significantly improve overall survival. Therefore it is very reasonable to think of these as standard of care options for patients with metastatic breast cancer."

Commenting on the relevance of the new studies, Prof Nadia Harbeck, University of Munich, Germany, said, "The results of Monarch 2 nicely complement those reported in Monaleesa-3. Abemaciclib is the third CDK4/6 inhibitor to show an overall survival benefit in advanced HR+ HER2- breast cancer. Together with the data we have seen before with palbociclib and ribociclib, these new data strengthen the argument that we should start treatment in the metastatic setting with a CDK4/6 inhibitor plus endocrine therapy because these drugs substantially improve patient outcomes compared to anti-hormonal treatment alone."

Considering possible limitations of the studies, Harbeck said, "All three of the CDK4/6 inhibitors powered their studies for progression-free survival and not for overall survival. Nevertheless, I think the data are strong enough, taken together, to give us certainty that this is really the way forward in this disease—to go for endocrine-based therapy plus CDK4/6 inhibition and not just endocrine therapy alone." She added that she would like to see detailed quality of life data from Monarch 2 to accompany the survival data and hoped this will be made available in the future. Moreover, she stated that these results make the doctors and patients hopeful for the results of the CDK 4/6 inhibitor studies in early

breast cancer—the first ones of which will be reported in the near future.

More information: (1) LBA7_PR 'Overall survival (OS) results of the phase III MONALEESA-3 trial of postmenopausal patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) advanced breast cancer (ABC) treated with fulvestrant (FUL) + ribociclib (rib)' will be presented by Dennis Slamon during the Presidential Symposium II on Sunday, 29 September 2019, 16:30-18:00 in Barcelona Auditorium (Hall 2). *Annals of Oncology*, Volume 30, Supplement 5, October 2019

(2) LBA6_PR 'Monarch 2: overall survival of abemaciclib plus fulvestrant in patients with HR+, HER2- advanced breast cancer' will be presented by George Sledge during the Presidential Symposium II on Sunday, 29 September 2019, 16:30-18:00 in Barcelona Auditorium (Hall 2). Annals of Oncology, Volume 30, Supplement 5, October 2019

Nicholas C. Turner et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer, *New England Journal of Medicine* (2018). DOI: 10.1056/NEJMoa1810527

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