Precision medicine: PI3K targeting in advanced breast cancer

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The remarkable results obtained by adding alpelisib to fulvestrant in patients with hormone receptor-positive, HER2-negative, PIK3CA-mutant advanced breast cancer represent an important step forward in precision cancer medicine [1]. Nonetheless, they raise further issues on what is the appropriate tumor molecular characterization to improve drug response prediction.

Not all patients with PIK3CA-mutant breast cancer benefit from alpelisib, and perhaps some patients with PIK3CA wild-type cancer might benefit, although results in the cohort without PIK3CA mutation are far from being statistically significant. Different PIK3CA mutations have different biological impacts, but other molecular alterations are also likely responsible for these facts. As the authors point out, loss of PTEN is a known mechanism behind resistance to PI3Kα inhibitors [2], mediated by PI3Kβ activation. PTEN loss can coexist with PIK3CA mutations in treatment-naïve patients [3], potentially affecting their responsiveness to PI3K inhibitors. Coexisting alterations in other nodes of PI3K-AKT-mTOR pathway, and in other pathways like the Cyclin D-CDK4/6-Rb pathway, are also involved. Furthering precision medicine will likely require dealing more deeply with the molecular complexity of each single cancer.

Author contributions Andrea Rocca, Elisabetta Melegari and Palleschi Michela conceived the study and wrote the letter.

Compliance with ethical standards

Conflict of interest Andrea Rocca declares to have received two fees from two advisory boards: one for a total of 400 € and the other of 800 € (respectively, Novartis and Pfizer). Elisabetta Melegari and Michela Palleschi declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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