ASCP Call to Action Commentary on Ki67 in HR-Positive/HER2-Negative Early Breast Cancer

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"What I Want My Colleagues to Know About Ki67 in HR-Positive/HER2-Negative Early Breast Cancer"

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The “Call to Action” commentary will provide a pathologist’s point of view on addressing the challenges with standardizing Ki67 techniques and inform pathology HCPs about the prognostic as well as potential predictive implications of Ki67 testing including the most recent information from the San Antonio Breast Cancer Symposium.

Breast cancer is the most commonly occurring cancer in women worldwide, with over 2 million new cases in 2018. In the Western world, approximately 75% of breast cancers are hormone receptor positive (HR+). The standard therapy for ER+ breast cancers is endocrine therapy in addition to chemotherapy. In spite of this therapy, it is estimated that 1 in 5 patients with breast cancer still develop metastatic disease, which although treatable, is generally not curable. Furthermore, recent data from randomized clinical trials (TAILORX and RxPONDER) has documented that a large number of patients do not benefit from the addition of chemotherapy. In view of this, there is a great need for additional therapies that can be used to prevent and treat metastases, and CDK4/6 inhibitors appear to fit in this gap.

DNA synthesis and cell division, collectively referred to as the “cell cycle”, are tightly controlled in normal cells. The different phases of the cell are controlled with checkpoints to ensure completion of each stage. Cyclin dependent kinases 4 and 6 (CDKs 4/6) specifically regulate cellular transition from the G1 phase of the cell cycle to the S phase. CDK4/6 inhibitors effectively block the proliferation of sensitive cancer cells by arresting the G1 cell cycle. Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (palbociclib, ribociclib, and abemaciclib) have revolutionized the treatment for patients with HR+/HER2-negative (HER2-) advanced/metastatic breast cancer and have doubled median progression-free survival (PFS) as compared to estrogen modulation therapy alone in clinical trials. Furthermore, recent results from the phase 3 clinical trials in chemotherapy naïve patients have shown improved overall survival (OS) with multiple CDK4/6 inhibitors.

Recent results of the phase 3 monarchE clinical trial in early stage breast cancer have led to the Food and Drug Administration’s (FDA) approval of abemaciclib in combination with endocrine therapy for adjuvant treatment of HR+/HER2-, node-positive early breast cancer at high risk of recurrence with a Ki-67 score ≥20%. This is the first CDK4/6 inhibitor approved for adjuvant treatment of HR+/HER2- breast cancer. The monarchE trial was a randomized clinical trial that enrolled high-risk HR+/HER2- patients, as defined by clinicopathological features (cohort 1), or as defined by high Ki67 (>20) based on the centralized analysis of Ki67 (cohort 2). In the intent to treat population, high Ki67 was associated with prolonged invasive disease-free survival (IDFS) with a hazard ratio of 0.696. Furthermore, in the patients enrolled in cohort 1, high Ki67 was prognostic, being associated with bad outcomes, however, it was not predictive of abemaciclib benefit. This clearly establishes the role of Ki67 as a companion diagnostic.

The nuclear protein Ki67 (pKi67) has long been established as a prognostic biomarker in breast cancer. It is expressed throughout the cell cycle and is widely used as a measure of proliferation marker *a marker of proliferation*. However, ki67 assessment remains controversial. Data from the International Ki67 working group (IKWG) has documented dramatic heterogeneity in its assessment and expressed serious concerns regarding its routine use in an unregulated manner. Over the last decade, these investigators have systematically analyzed the causes of variability and have come up with guidelines regarding the assessment of this marker by immune-histochemistry. In view of this, the

FDA approval of Ki-67 as a companion diagnostic has come as somewhat of a surprise for many in the field and necessitates a detailed look at the issues at hand.

One of the main problems in the analysis of Ki67 is the lack of a negative control. Almost all tissues will have some proliferating cells that are highlighted by this antibody. This has resulted in the antibodies being used at variable dilutions, resulting in different intensities of staining of the nuclei. One of the advantages of the new Ki67 PharmDx assay is that it comes in a ready-to-use format. Several other important features of the assay have also been standardized, such as the definition of what constitutes a positive nucleus and how the slides should be examined. According to the FDA-approved criteria used in the clinical trial, a nucleus is considered positive for Ki67 if it meets the following criteria: 1) The signal must be unequivocally brown; 2) The staining must correspond to a nucleus; 3) The staining must cover the whole chromatin distribution within the nucleus; and 4) The staining must correspond to viable, non-apoptotic cells. Of note, there is a distinction between this definition and that formulated by the IKWG, which defines a nucleus as positive if it is NOT blue; focal nuclear positive would be considered sufficient by the IKWG criteria but not by the clinical trial criteria. Grey nuclei are excluded in the FDA approved criteria.

Another controversial area in the Ki67 analysis is the selection of the area to be evaluated. The FDA-approved criteria does not recommend the “hotspot” method for analysis. The whole slide is evaluated for the area of invasive tumor. Necrotic tumor areas, foci of carcinoma in situ, edge effects, and fixation and processing related artifacts should not be scored. At least 200 viable cells within the invasive component are assessed for expression of Ki67, and the results are expressed as the percentage of positive cells.

There are still several questions that remain to be answered regarding Ki67. These include whether the pathology community can apply the criteria uniformly and get consistent data. The work from IKWG has shown that this is not impossible. The exact number of cells and the areas to be assessed will remain controversial. The congruence of the results from the Agilent assay, as compared with other assays on the market, has not yet been determined. However, in spite of these remaining issues, the Ki67 data from the monarchE trial clearly document certain aspects of Ki67 assay. In cohort 1, selected on the basis of clinical high risk, ki67 has only a prognostic value, i.e. high levels were associated with poor outcomes. However, it must be noted that even patients with low Ki67 obtained benefit from

abemaciclib (HR 0.704). The predictive association of Ki67 for abemaciclib is clearly documented in cohort 2, where there was a dramatic reduction (relative benefit 30.4%; absolute benefit 5.4%) in the risk of developing an invasive recurrence.

A major take home message is that pathologists need to strictly adhere to the scoring guidelines when evaluating companion diagnostic (CDx) assays. Furthermore, we have an important role to play in assisting our clinical colleagues in the management of patients with HR+/ HER2- breast cancers, particularly since more and more of these patients can safely avoid toxic chemotherapies.

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