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I respectfully request the NCCN breast cancer panel to review the enclosed manuscript entitled " Final 10-year results of the Breast International Group 2-98 phase III trial and the role of Ki67 in predicting benefit of adjuvant docetaxel in patients with oestrogen receptor positive breast cancer" (Eur J Cancer. 2015 PMID 26074397) for inclusion in the adjuvant taxane chemotherapy recommendation of breast cancer.

BIG 2-98 is a randomised phase III trial that tested the effect of adding docetaxel, either in sequence to or in combination with anthracycline-based adjuvant chemotherapy, in women with node-positive breast cancer . In this paper we present the 10-year final trial safety and efficacy analyses. We also report an exploratory analysis on the predictive value of Ki67 for docetaxel efficacy, in the BIG 2-98 and using a pooled analysis of 3 other randomised trials. Our results show that after a median follow-up of 10.1 years, the addition of docetaxel did not significantly improve DFS or OS (HR=0.91, 95%CI=0.81-1.04; P=0.16 and HR=0.88, 95%CI=0.76-1.03; P=0.11 respectively). Sequential docetaxel did not improve DFS compared to the sequential control arm (HR=0.86, 95% CI=0.72-1.03; P=0.10).

A pooled analysis of 4 randomised trials showed a benefit of taxanes in highly proliferative (based on ki67%) ER-positive disease but not in low proliferating tumors (interaction test P=0.01).

In conclusion in this paper we report that the previously observed benefit for the addition of sequential docetaxel following doxorubicin in the A-CMF regimen for patients with lymph node positive breast cancer in the BIG 2-98 trial is no longer significant at ten years of follow-up (supporting P Ellis paper ref 405 in NCCN guidelines Version 2.2017). In this mature report, there is no significant difference in disease-free or overall survival.

Decisions about adjuvant chemotherapy for ER positive breast cancers are complex and sometimes an "all or none" approach is used, which means that if a physician decides to administer chemotherapy, an anthracycline-taxane regimen is considered. The data provided in this study suggests that Ki67 identifies a high proliferative subset of patients with ER-positive breast cancer who derive greater benefit from adjuvant taxanes. International groups should be commended for continuing to follow up patients from for up to 10 years and updating the results.

In summary, this is one of the largest of the few adjuvant trials reporting on the 10-year outcome of adjuvant docetaxel in patients with node positive breast cancer. Incorporating docetaxel into adjuvant therapy showed long term safety profile but did not result in an overall improvement in DFS or OS on considering all patients (level one evidence). Pooled analysis of 4 prospective randomised studies in ER positive tumors suggested benefit from taxanes only in patients with ER-positive/ high Ki67 breast cancers (level two evidence).

Sincerely

Amir Sonnenblick