Evaluation of a pembrolizumab-8 cycle neoadjuvant regimen without AC for high-risk early-stage HER2-negative breast cancer: Results from the 1-SPY 2 TRIAL


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1-SPY 2 (Figure 1): A multicenter, phase 2 trial platform using response-adaptive randomization with biomarker subtypes to evaluate novel agents and combinations in the neoadjuvant setting for women with high-risk primary breast cancer.

Inclusion criteria: Tumor size ≥2.5 cm; hormone-receptor (HR)+HER2-, MammaPrint (MP) high risk; HR-HER2-; or HER2+.

Primary Endpoint: Pathologic complete response (pCR).

Goal: To identify (graduate) regimens that have ≥85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HER2 status and MP.

Control Arm for HER2 status and MP.

HER2-: weekly paclitaxel x 12 followed by AC.

HER2+: paclitaxel x 4 followed by AC with higher risk early breast cancer patients also considered for neoadjuvant treatment.

Regimens that leave the trial for one of the four reasons: (1) Futility (<10% predictive probability of success); (2) maximum sample size accrual (with a maximum of 85% of success and ≤85%); (3) graduation (30% predictive probability of success); or (d) recommended by the independent DSMB.

To date: 11 experimental arms have been evaluated for efficacy.

Rationale for current regimen: From the findings of the currently ongoing pembrolizumab (Pembro)-8 cycle neoadjuvant trial (Liu et al. JCO 2017) (left), HR-HER2- patients had surgery results at the time the arm was closed. Of the remaining 39 pts, 34 pts have on-therapy MRI assessments.

RESULTS at time of arm closure

Randomized to Pembro-8 vs No AC

Estimated pCR rates in the Pembro-8 vs No AC pts contributing to efficacy analysis at time of arm closure. Pts with surgery results and those with on-therapy MRI results contributed to on-therapy MRI distributions. This was quickly assessed with a small number of patients (shown in Figure 3 below). Although notification of the third reported case prompted the study team to administer AC with pembrolizumab or proceed with definitive surgery (right), 37 pts had surgery results at the time the arm was closed. Of the remaining 39 pts, 34 pts have on-therapy MRI assessments.

CONCLUSIONS

- Although Pembr8-AC performed at least as well as standard paclitaxel followed by AC, the likelihood is very low that the regimen will be superior to paclitaxel-AC in a phase 3 trial.
- Pembrolizumab alone following 12 wks of paclitaxel + pembrolizumab was not sufficient to sustain and/or improve response rate. This was quickly assessed with a small number of patients.
- Nonetheless, several pts with HER2 breast cancer achieved a pCR with pembrolizumab alone q3 wks x 4 after weekly paclitaxel x 12 wks + pembrolizumab q3 wks x 4, suggesting that not all pts require AC.
- De-escalation of treatment may be possible with imaging and biopsy guidance.
- The overall adjuvant Insufficiency (AI) rate was higher likely because we were screening for abnormal cortisol levels.
- However, there were fewer Grade 3 AI toxicities.
- Pembrol8-AC intent-to-treat analysis is ongoing.