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

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BACKGROUND

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

Inclusion criteria: Tumor size ≥2.5cm; 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 HR/HER2 status and MP.

Control Arm for HER2- patients: Weekly paclitaxel x 12 wks followed by doxorubicin + cyclophosphamide (AC) q3 wks x 4.

Experimental Arms for HER2- patients: Investigational therapy + weekly paclitaxel x 12 followed by AC.

Regimens may leave the trial for one of four reasons: (1) Futility (<10% probability of success); (2) maximum sample size accrual (with probability of success ≥10% and <85%); (3) graduation (≥85% predictive probability of success); or (4) as recommended by the independent DSMB.

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

Rationale for current regimen: Findings from the graduated, previously reported Pembro4 arm (Nanda et al, ASCO 2017) supported investigation of de-escalating therapy, and determining if pembrolizumab (an anti-PD-1 antibody) alone q3 wks x 4 after weekly paclitaxel x 12 wks + pembrolizumab q3 wks x 4 was sufficient to sustain response without AC.

STUDY SCHEMA

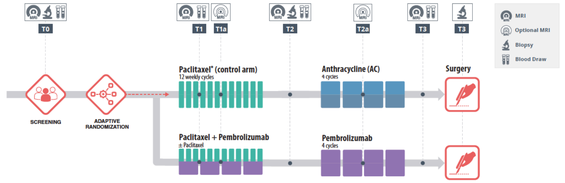

Figure 1: Study schema for Pembro8-noAC and for control.

METHODS

Longitudinal MRI volume reduction from baseline (3 cycles after start of therapy, prior to AC, and prior to surgery) was used to predict pCR for individual participants (pts) until their pCR data became available. A covariate-adjusted Bayesian logistic model adjusting for time trends was used to estimate pCR probabilities and assess graduation. Analysis is modified intent to treat. Pts who received non-protocol therapy (e.g., carboplatin or AC for the Pembro8-noAC arm) were considered as non-pCR. Pembro8-noAC was open to HER2- patients for evaluation in 3 of 10 pre-defined signatures: HER2-, HR+HER2-, and HR-HER2-.

RESULTS

Efficacy Summary

- Pembro8-noAC was randomized to 73 pts, 3 of whom progressed while receiving pembrolizumab alone on study.
- Randomization to this arm continued after the first report of progression because the rate of progression during AC over the course of the trial was estimated to be 6.5% based on serial MRI studies.
- However, notification of the third reported case prompted the study team to ask the DSMB for the summary response for this arm.
- Although it did not meet formal stopping rules for either graduation or futility, Pembro8-noAC was not close to the target threshold pCR rates of 60% for HR-HER2- and 30% for HR+HER2+.
- As a result of this information, combined with documentation of on-treatment progressions, assignment to Pembro8-noAC was discontinued.
- Treatment with pembrolizumab alone was no longer allowed due to the potential concern for progression, and investigators were given the option to administer AC with pembrolizumab or proceed with definitive surgery following the 12 weeks of paclitaxel + pembrolizumab.

ACKNOWLEDGEMENTS

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RESULTS at time of arm closure

Randomized to Pembro8-noAC (n=73)

No on-therapy MRI (n=5) | With on-therapy MRI (n=34) | Had surgery results (n=34)

Figure 3: Pembro8-no AC pts contributing to efficacy analysis at time of arm closure. Pts with surgery results and those with on-therapy MRI contributed to the efficacy findings at time of arm closure (shown in Figure 3 below). 34 pts had surgery results at the time the arm was closed. Of the remaining 39 pts, 34 pts have on-therapy MRI assessments.

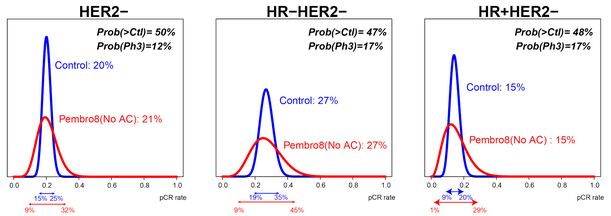

Figure 4: Estimated pCR rates in the Pembro8-noAC and control arms at the time of arm closure. A time-adjusted Bayesian logistic model, based on all pts with information at the time of the closure of the Pembro8-noAC arm, was used to estimate pCR rates. The posterior pCR probability distributions, with its mean and 95% probability interval, along with the probability that Pembro8-noAC is superior to control, denoted as Prob(>Ctl), and the predictive probability of success in a 300-patient 1:1 randomized Phase III trial, denoted as Prob(Ph3), are shown for the HER2- (left), HR-HER2- (middle), and HR+HER2- (right) signatures.

Paclitaxel →AC was EQUAL to Paclitaxel + Pembro x 4 → Pembrox4

RESULTS

Immune-related Adverse Events

	Pembro8-noAC*		Control**	
	All Grade	**Grade 3+**	**All Grade**	**Grade 3+**
Adrenal insufficiency	6 (8.3%)	0 (0%)	0 (0%)	0 (0%)
Hyperthyroidism	2 (2.8%)	0 (0%)	1 (0.3%)	0 (0%)
Hypothyroidism	4 (5.6%)	1 (1.4%)	0 (0%)	0 (0%)
Thyroiditis	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)
Pneumonitis	2 (2.8%)	2 (2.8%)	4 (1.4%)	2 (0.7%)
Colitis	2 (2.8%)	2 (2.8%)	1 (0.3%)	1 (0.3%)
Hepatic enzyme increased	3 (4.2%)	1 (1.4%)	0 (0%)	0 (0%)

* Safety data for 72 Pembro8-noAC patients
** Safety data for 295 Control patients

Immune-related adverse events included grade 3 colitis (n=2), grade 3 pneumonitis (n=1), grade 3 transaminitis (n=1), grade 3 hypothyroidism (n=1), and grade 1-2 adrenal insufficiency (n=6).

CONCLUSIONS

- Although Pembro8-noAC 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 adrenal insufficiency (AI) rate was higher likely because we were screening for abnormal cortisol levels.
  - However, there were fewer Grade 3 AI toxicities
- Pembro8-noAC intent-to-treat analysis is ongoing

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