

Adaptively randomized trial of neoadjuvant chemotherapy with or without the Akt inhibitor MK-2206: Graduation results from the I-SPY 2 Trial.

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Abstract

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Background: A key node of growth and survival signaling pathways is the Akt serine/threonine kinase that activates mTOR and downstream effectors. I-SPY 2 is a randomized neoadjuvant trial to test agents and combinations added to standard chemotherapy. Pathological complete response (pCR) defined as absence of invasive cancer in breast and nodes is the primary endpoint. We report efficacy results for allosteric Akt inhibitor MK-2206.

Methods: Women with invasive breast cancer ≥ 2.5 cm on exam or ≥ 2 cm on imaging were adaptively randomized to 12 weekly paclitaxel (and trastuzumab if HER2+) cycles (control) or in combination with one of several experimental agents followed by doxorubicin/cyclophosphamide x 4. Patients (pts) are stratified to 8 subsets based on hormone-receptor (HR), HER2, and MammaPrint statuses, with combinations of subsets defining agent signatures. MK-2206 135 mg daily by mouth was evaluated in all 8 subsets. Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superiority over control. Graduation by signature and futility stopping was based on Bayesian predictive probability of success in a 2-arm, N=300 Phase 3 randomized 1:1 trial with pCR endpoint.

Results: MK-2206 graduated in the first 3 signatures in the table. Accrual ended with 93 patients assigned to that arm and when 56 pts had been concurrently randomized to control. Final posterior and predictive probabilities are shown for all 10 signatures.

Conclusions: MK-2206 improves pCR rates compared to standard chemotherapy in several breast cancer signatures, defined mostly by HR- and HER2+, sufficiently for evaluation in a Phase 3 neoadjuvant trial powered for event-free survival. Safety data will be presented.

Clinical trial information: [NCT01042379](https://clinicaltrials.gov/ct2/show/study/NCT01042379).

Signature	Estimated pCR Rate			Probability MK2206 Superior to Control	Predictive Probability Success Phase 3
	MK-2206 N=93	Control N=56	Difference		
HR-/HER2+	64.1	35.7	28.4	97.3	87.0
HR-	46.7	26.1	20.6	98.6	82.7
HER2+	49.6	28.9	20.7	95.1	77.7
HR-/HER2-	40.2	22.4	17.8	96.8	75.9
MP+	39.3	22.5	16.8	97.0	74.1
All	35.2	21.1	14.1	97.9	68.6
HR+/HER2+	35.8	22.4	13.4	85.4	61.3
HER2-	29.3	18.0	11.3	95.0	59.0
HR+	22.8	15.9	6.9	81.8	42.5
HR+/HER2-	17.1	13.0	4.1	72.7	31.7