Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2

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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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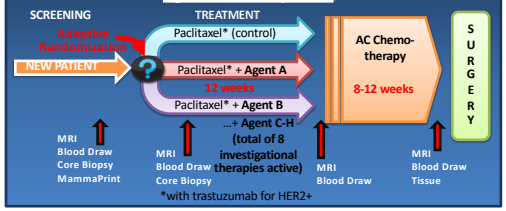
Background and Rationale

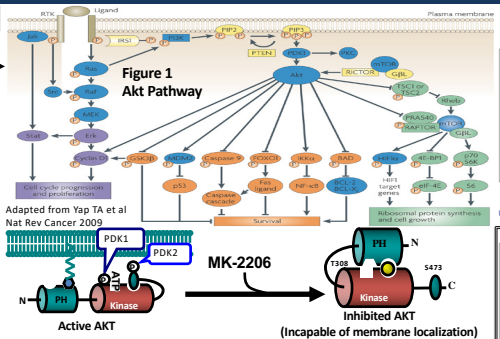
- The Akt serine/threonine kinase is a key node for growth factor receptor-initiated signaling and activates mTOR and downstream effectors. (FIG. 1)
- Complete pathologic response (pCR) to neoadjuvant chemotherapy is a predictor of long-term outcome and can therefore can be used to test the potential benefit of novel targeted therapies when added to standard chemotherapy
- MK-2206 is a selective allosteric inhibitor of Akt1, Akt2, and less so Akt3. MK-2206 does not bind to the active site of Akt, and consequently does not compete with either ATP or peptide substrate for binding to Akt.

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 (AC) x 4, with serial biomarkers (biopsies, blood draw and MRI scans). (FIG. 2)
- Patients were stratified to 8 subsets (Table 1) based on hormone-receptor, HER2, and MammaPrint gene profiling score (hi-1 vs hi-2[MP+]), with combinations of subsets defining 10 agent signatures.
- Primary endpoint was pCR (no residual invasive disease in breast or nodes) and evaluable patients received any taxane +/- investigational therapy.
- Within-patient longitudinal modeling of MRI volume was used during the trial to predict whether the patient would experience a pCR and improve the efficiency of adaptive treatment assignments.
- Patients who progressed, changed to non-protocol therapy or left the treating institution were evaluable and counted as not having pCR. Patients who withdrew consent prior to surgery (without progression or change to non-protocol therapy) were considered nonevaluable for pCR.
- We report results of MK-2206 135 mg daily by mouth evaluated in all 8 subsets. Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superiority over control.
- Graduation by signature is based on Bayesian predictive probability ≥85% for success in a 2-arm, N=300 Phase 3 randomized 1:1 trial with pCR endpoint. Futility stopping occurs when the probability of success is <10% in all 10 signatures.

Fig 2. I-SPY 2 Study Schema





Results

Table 1: Biomarker Subtypes and Overall Prevalence for Entire Trial

All pts enrolled through 4/15/15	MP hi-1		MP hi-2 (MP+)		Totals
	HR+	HR-	HR+	HR-	
HER2+	120 (15%)	41 (5%)	23 (5%)	41 (3%)	225 (28%)
HER2-	217 (27%)	54 (7%)	73 (9%)	237 (29%)	581 (72%)
	337 (42%)	95 (12%)	96 (12%)	278 (34%)	**806 (100%)**

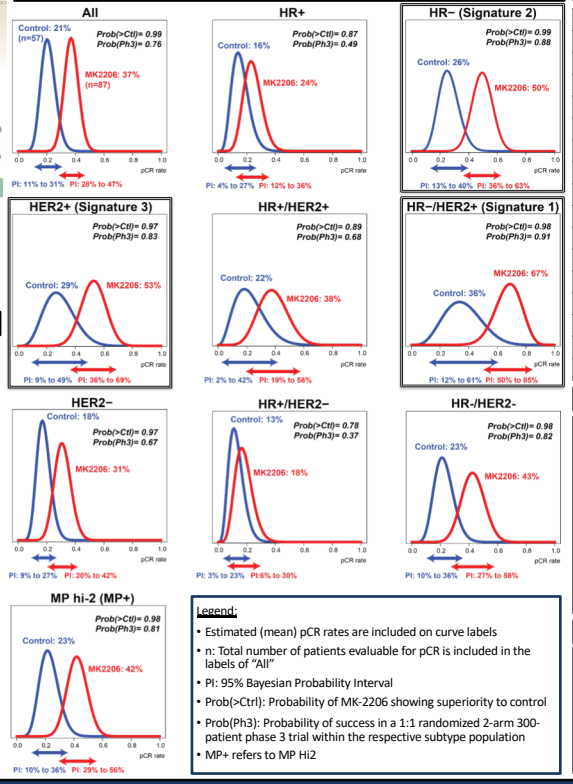
Table 2: Enrollment/Disposition for MK-2206 and Control Arms

- Randomized to MK-2206=94 (34 with trastuzumab) –7 non evaluable for pCR (withdrew consent with no evidence of progression)
- Randomized control=59 (11 with trastuzumab) – 2 non-evaluable for toxicity nor for pCR (received no therapy)

Table 3: Efficacy Results (Graduation Highlighted)

Signature	Estimated pCR Rate (%)			Probability MK-2206 Superior to Control (%)	Predictive Probability Success in Phase 3 (%)
	MK-2206 N=87	Control N=57	Difference		
HR-/HER2+	67.5	36.0	31.5	98.4	90.8
HR-	49.5	26.2	23.3	99.3	87.8
HER2+	52.6	29.0	23.6	96.9	83.2
HR-/HER2-	42.8	22.6	20.2	98.1	81.7
MP+	42.2	22.8	19.4	98.4	80.9
All	37.2	21.1	16.1	99.1	76.1
HR+/HER2+	38.4	22.2	16.2	89.0	68.0
HER2-	31.1	17.9	13.2	97.1	66.5
HR+	24.2	15.7	8.5	86.5	49.3
HR+/HER2-	18.1	12.8	5.3	77.5	36.8

Figure 3: Bayesian pCR Probability Distributions: Results



Legend:

- Estimated (mean) pCR rates are included on curve labels
- n: Total number of patients evaluable for pCR is included in the labels of "All"
- PI: 95% Bayesian Probability Interval
- Prob(>Ctrl): Probability of MK-2206 showing superiority to control
- Prob(Ph3): Probability of success in a 1:1 randomized 2-arm 300-patient phase 3 trial within the respective subtype population
- MP+ refers to MP Hi2

Table 4: Adverse Events

	Control (n=57)	MK-2206 (n=94)
Available for Evaluation, n	**48**	**86**
Missing Data, n	**9**	**8**
Discontinued due to AE	**0**	**4**
Grade 3 / 4, n (%)		
Neutrophil count decreased	6 (13%)	18 (21%)
Rash, maculo-popular	0	13 (15%)
Febrile neutropenia	3 (6%)	12 (14%)
Hypertension	3 (6%)	10 (12%)
White blood cell decreased	4 (8%)	9 (10%)
Rash, acneiform	0	8 (9%)
Anemia	5 (10%)	5 (6%)
Fatigue	0	4 (5%)
Grade 1 / 2, n (%)		
Mucositis, oral	16 (33%)	47 (55%)
Rash, maculo-popular	12 (25%)	43 (50%)
Rash, acneiform	8 (17%)	33 (38%)

Conclusions

- In this adaptively designed trial, the allosteric Akt inhibitor MK-2206 graduated in 3 biomarker signatures on the basis of its predictive probability of statistical success in a 300-patient randomized Phase 3 trial.
- The three signatures for MK-2206 (HER2+/HR-, HR- and HER2+) indicate activity in both HR- and HER2+ disease
- Toxicities seen are those previously described including mucocutaneous toxicities and cytopenias, with the possible exception of more mucositis seen in this trial.
- This adaptive randomized trial provides a platform to rapidly ascertain promising therapies for larger scale studies and to match experimental therapies with responding patient subtypes

References

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