Phosphorylation of AKT kinase substrates predicts response to the AKT inhibitor MK2206 in the I-SPY 2 TRIAL in both HER2- and HER2+ patients

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Abstract

Background: In this phase II trial, the addition of MK2206 to standard chemotherapy has demonstrated meaningful activity in HER2+ breast cancer. Here we examined the phosphorylation of AKT kinase substrates in patients treated with MK2206 in the I-SPY 2 TRIAL. Methods: 150 patients (75% HER2+, 30% TN) were treated with MK2206; 87 controls (54% HER2+ and 11% TN) were treated with standard chemotherapy alone. AKT kinase substrates evaluated included p-AKT (S473), p-S6 (T308), p-mTOR (S2448), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-mTOR (S2448), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458), p-FOXO3a (S253), p-FOXO1 (S249), p-PI3K p85α (Y458). For each substrate, a combination of immunoprecipitation-Western blotting and LCM-based phosphoprotein microarray was used to assess the phosphorylation status. Substrate phosphorylation levels were compared between patients treated with MK2206 and standards. Difference in means analysis was used to identify substrates whose phosphorylation was significantly altered between the two treatment groups. Results: The AKT and FOXO kinase substrates were significantly altered in the MK2206 arm compared to controls. Indeed, the phosphorylation of AKT kinase substrates was significantly increased in the MK2206 arm compared to controls. For example, p-AKT (S473) and p-S6 (T308) were significantly increased in the MK2206 arm compared to controls. Additionally, p-FOXO3a (S253) and p-FOXO1 (S249) were significantly increased in the MK2206 arm compared to controls. For each substrate, the phosphorylation levels were highest in the MK2206 arm and lowest in the control arm. Conclusion: The phosphorylation of AKT kinase substrates was significantly altered between the two treatment groups. The results suggest that the phosphorylation of AKT kinase substrates may be predictive of response to MK2206 treatment.