Clinical Trials

Major finding: Single-agent MEK inhibition is most effective in BRAF inhibitor–naïve melanoma patients.

Approach: Patients with *BRAF*-mutant melanoma were stratified based on previous BRAF inhibitor therapy.

Impact: BRAF inhibitor resistance mechanisms may confer resistance to subsequent MEK inhibitor therapy.

TRAMETINIB HAS MINIMAL ACTIVITY AFTER BRAF INHIBITOR THERAPY

Activating *BRAF* mutations are found in approximately half of cutaneous melanomas and constitutively activate downstream MEK signaling. BRAF inhibitors extend progression-free and overall survival in many patients with metastatic *BRAF*-mutant melanoma, but resistance rapidly develops. First-line MEK inhibitor monotherapy is also effective in patients with metastatic *BRAF*-mutant melanoma, but the effect of sequential use of BRAF and MEK inhibitors is unknown. In an open-label, multicenter, phase II study, Kim and colleagues evaluated the activity of single-agent MEK inhibition with trametinib in patients with metastatic *BRAF*-mutant melanoma enrolled into one of two cohorts: those who had previously been treated with a BRAF inhibitor (either vemurafenib or dabrafenib) and those who had previously received only chemotherapy or immunotherapy. The primary endpoint for both cohorts was to determine the response rate, and a 2-stage design was used such that, if the response rate was lower than 10% at the interim analysis, enrollment would be stopped. Although 20% of patients in the group previously treated with BRAF inhibitors had stable disease, no confirmed responses were observed and enrollment in that cohort was terminated. The median progression-free survival in the BRAF inhibitor-treated group was 1.8 months, and the median overall survival was 5.8 months. However, in the BRAF inhibitor–naïve group, the overall response rate was 25%, with 1 complete response and 13 partial responses, and counting patients with stable disease, the disease control rate was 75%. The median progression-free survival in this group was 4.0 months, and the median overall survival was 14.2 months. These findings indicate that trametinib has minimal activity in patients whose disease has progressed on BRAF inhibitor therapy and suggest that mechanisms of acquired resistance to BRAF inhibitors confer resistance to MEK inhibitors. ■

Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol 2012 Dec 17 [Epub ahead of print].

Prostate Cancer

Major finding: The AR regulates distinct genes in human CRPC tumors compared with prostate cancer cell lines.

Mechanism: *In vivo*-restricted AR binding sites in CRPC are enriched for STAT, MYC, and E2F motifs.

Impact: Cellular context and *in vivo* signals are critical determinants of AR-mediated gene regulation.

THE AR CONTROLS A TISSUE-SPECIFIC GENE EXPRESSION PROGRAM IN CRPC

Transcriptional regulation by the androgen receptor (AR) promotes prostate cancer growth and is implicated in the progression to castration-resistant prostate cancer (CRPC), which is responsive to AR-targeted therapeutic strategies. However, AR-dependent gene signatures that have been characterized *in vitro* using cell lines do not accurately reflect the role of AR signaling in CRPC. To assess whether distinct AR-regulated genes exist *in vivo*, Sharma and colleagues comprehensively assessed AR-binding sites in a panel of human prostate cancer tissues. Although they observed some overlap with the AR-binding profile in prostate cancer cell lines, which are derived from metastatic tumors, most of the AR-binding sites detected in CRPC were not present in cell lines and were associated with active histone marks at gene promoters. These CRPC-specific AR target genes were not stimulated by androgen *in vitro* but were downregulated in xenografts and primary prostate tumors following surgical or chemical castration, respectively, defining an *in vivo*-restricted AR-regulated gene set. Intriguingly, CRPC-specific AR-binding sites did not overlap with motifs for common AR cofactors such as forkhead box A1 (FOXA1) but were instead enriched for E2F, MYC, and STAT motifs, suggesting that altered signaling in CRPC tissue modulates AR activity. Consistent with this idea, AR–FOXA1 interaction was diminished, whereas AR–STAT5 binding was enhanced in prostate cancer cell xenografts compared with isogenic cultured cells, and *in vitro* treatment with cytokines that stimulate these alternate pathways redirected AR binding to CRPC-specific sites. Furthermore, a core 16-gene CRPC-specific AR signature was tightly correlated with tumor recurrence after hormone therapy and was a better predictor of survival compared with an existing *in vitro*-derived AR signature. These findings identify potential markers of disease progression and therapeutic response and emphasize the importance of cellular context in the regulation of gene expression programs. ■

Sharma NL, Massie CE, Ramos-Montoya A, Zecchini V, Scott HE, Lamb AD, et al. The androgen receptor induces a distinct transcriptional program in castration-resistant prostate cancer in man. Cancer Cell 2013;23:35–47.

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