Clinical Trials

**Major finding:** Combined treatment with axitinib and pembrolizumab achieved partial responses in patients with ASPS.

**Concept:** Axitinib blocks VEGFR signaling and restores an immune-responsive tumor microenvironment.

**Impact:** Dual inhibition of VEGFR and PD-L1 signaling is feasible in patients with advanced sarcomas.

**BLOCKADE OF VEGFR AND PD-L1 INHIBITS ALVEOLAR SOFT-PART SARCOMA**

Alveolar soft-part sarcoma (ASPS) typically arises from aberrant upregulation of HIF1α and VEGF and is inherently resistant to chemotherapy. VEGF has been shown to promote tumor angiogenesis and suppress immune responses within the tumor microenvironment, limiting the efficacy of immune checkpoint inhibitors. Previous studies in melanoma and renal cell carcinoma have demonstrated the efficacy of combined inhibition of VEGF signaling and immune checkpoint inhibitors. To evaluate such an approach in sarcoma, Wilky and colleagues conducted a phase II clinical trial in 33 patients with advanced or metastatic sarcomas in which patients received the VEGF receptor tyrosine kinase inhibitor axitinib in combination with the anti–PD-1 inhibitor pembrolizumab. The primary endpoint was 3-month progression-free survival (PFS), and secondary endpoints were incidence of treatment-related adverse events, objective response, clinical benefit, time to progression, and overall survival. For all patients, 3-month progression-free survival was 65.6% (95% CI 46.6–79.3), with a median overall survival of 18.7 months; specifically, 3-month PFS was 72.7% (95% CI 37.1–90.3) in patients with ASPS (n = 12) and 61.9% (95% CI 38.1–78.8) in patients with non-ASPS sarcoma (n = 21).

Grade 3 or 4 treatment-related adverse events included hypotension, autoimmune toxicities, and seizures. Serious adverse events included autoimmune colitis, pneumothorax, seizures, and hypertriglyceridemia. The median duration of response and time to achieve a partial response was 29 weeks and 19.4 weeks, respectively. Clinical benefit was observed in 53.1% (n = 17; 95% CI 35–70.5) of patients, with eight patients achieving partial response and nine patients achieving stable disease; the majority of partial responses occurred in patients with ASPS. Further, PD-L1 positivity was observed in all 9 ASPS biopsies and 6 of 20 (30%) non-ASPS sarcoma biopsies, and most ASPS exhibited high levels of tumor-infiltrating lymphocytes. Taken together, these results show that, in patients with sarcoma, axitinib plus pembrolizumab is most effective in patients with ASPS, thus warranting additional evaluation of this treatment regimen.


**Prostate Cancer**

**Major Finding:** Expression of MFF regulates prostate cancer stem-cell self-renewal and tumorigenicity.

**Mechanism:** BRD4 regulates transcription of mitochondrial factors specifically in prostate cancer stem cells.

**Impact:** BRD4 inhibition blocks prostate cancer stem-cell self-renewal independent of androgen receptor signaling.

**MITOCHONDRIAL FISSION PROMOTES PROSTATE CANCER STEM-CELL SELF-RENEWAL**

Bromodomain and extraterminal domain (BET) proteins, such as BRD4, are chromatin reader proteins that enable cell type-specific transcriptional programs. Due to their context-dependent roles, BRD4 and other BETs have emerged as promising therapeutic targets, especially in prostate cancer, where many patients eventually progress to metastatic hormone-refractory disease. A small population of stem-like tumor cells, called cancer stem cells (CSCs), display self-renewal properties and are hypothesized to drive disease progression. To ascertain the role of BET proteins in prostate CSC biology, Civenni and colleagues assessed the effect of OTX015, a clinically available BRD4 inhibitor, against both androgen-dependent and androgen-independent prostate cancer cell lines. OTX015 treatment reduced prostate cancer cell growth as well as the tumor-sphere formation and self-renewal potential of prostate cells grown in CSC conditions and cells from OTX015-treated xenografts grown ex vivo. OTX015 induced senescence responses in tumor-sphere-forming cells, but not bulk tumor cells. Although BRD4 inhibition induced global transcriptional changes in both CSCs and bulk tumor cells, the transcriptional networks controlled by BRD4 varied between the two populations. Specifically, genes involved in mitochondrial biogenesis and integrity were among the most significantly upregulated in tumor sphere-forming cells relative to bulk and were also downregulated upon OTX015 treatment. Similarly, OTX015 treatment resulted in impaired mitochondrial fission and segregation to drive mitochondrial dysfunction. Mitochondrial fission factor (MFF) was one of the most significantly altered genes upon BRD4 inhibition and was confirmed as a direct BRD4 target by ChIP qPCR. BRD4 occupancy at the MFF promoter was higher in CSCs than in bulk tumor cells. MFF depletion in both androgen receptor (AR)–positive and AR-negative prostate cancer cells significantly reduced tumor-sphere formation, self-renewal, and tumorigenicity in xenografts, thus replicating the effect of BRD4 inhibition. This study identifies an AR-independent role of BRD4 in regulating prostate CSC self-renewal and suggests a potential therapeutic strategy for patients with prostate cancer.

Mitochondrial Fission Promotes Prostate Cancer Stem-Cell Self-Renewal

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