

Prostate Cancer

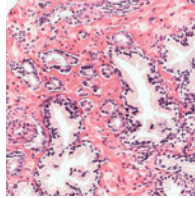
Major Finding: In patients with metastatic castration-resistant prostate cancer, pembrolizumab showed efficacy.

Concept: The phase II trial showed modest objective response rates, but responses attained were durable.

Impact: Some immunotherapies may be effective in this disease; biomarkers for response must be identified.

PEMBROLIZUMAB MONOTHERAPY IS ACTIVE IN METASTATIC PROSTATE CANCER

Metastatic castration-resistant prostate cancer (mCRPC) is characterized by an immunosuppressive tumor microenvironment, implying that immunotherapies may have limited efficacy. However, there is some evidence of antitumor activity for the anti-PD-1 therapy pembrolizumab in patients with mCRPC. Antonarakis and colleagues have reported results from the first three of five cohorts of patients with metastatic or locally confined but inoperable CRPC recruited into an open-label, phase II clinical trial of pembrolizumab monotherapy. All patients had previously received treatment with one or more targeted endocrine therapies and one to two regimens of chemotherapy, one of which was required to have included docetaxel. Across all three cohorts, 258 patients were enrolled, with 133 in cohort 1 (patients with PD-L1-positive disease), 66 in cohort 2 (patients with PD-L1-negative disease), and 59 in cohort 3 (patients with bone-predominant disease, regardless of PD-L1 status). Median overall survival was 9.5 months in cohort 1, 7.9 months in cohort 2, and 14.1 months in cohort 3. The objective response rate (ORR) was 5% (seven of 133 patients) in cohort 1, with two patients experiencing com-



plete radiographic responses, whereas the ORR was 3% (two of 66 patients) in cohort 2. Although the ORR in these cohorts was low, the responses were long lasting, with the median duration of response being 16.8 months. Treatment-related adverse events, the most common of which were fatigue, diarrhea, and decreased appetite, were observed in 60% (155 of 258) of patients, and two deaths were determined to have been treatment related. Exploratory next-generation sequencing studies for predictive biomarkers were not conclusive. Limitations of the study include lack of randomization, lack of a control group, and short follow-up period. Overall, the results of this trial indicate that despite the immunosuppressive tumor microenvironment observed in mCRPC, anti-PD-1 therapy is effective in some patients, and further research should focus on identifying which patients are most likely to respond. ■

Antonarakis ES, Piulats JM, Gross-Goupil M, Goh J, Ojamaa K, Hoimes CJ, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. *J Clin Oncol* 2019 Nov 27 [Epub ahead of print].

Drug Development

Major Finding: A new MYC inhibitor reduced tumor growth in mouse prostate cancer models.

Approach: An *in silico* screen, biochemical assays, and a rapid *in vivo* screen identified candidate drugs.

Impact: MYC may not be “undruggable,” as often thought, and therapies based on the new drug may be in reach.

NOVEL MYC-TARGETING DRUG IS EFFECTIVE IN MOUSE PROSTATE CANCER MODELS

Although MYC proteins are important in cancer development and treatment resistance, efforts to develop drugs targeting them have been largely unsuccessful. Han and colleagues approached this problem by using an *in silico* screen to develop a library of possible MYC-binding small molecules with drug-like properties, then narrowing the list using biochemical assays, such as tests of whether each drug candidate could disrupt MYC-MAX-DNA complex formation. Further shortening the list of options, rapid *in vivo* screening using a mouse model of prostate cancer was incorporated into the strategy, followed by several biochemical assays to test for optimal drug properties. This series of tests identified a chemical dubbed 361 as the top candidate for further testing. Additional experiments suggested that 361 destabilizes MYC by increasing phosphorylation of MYC's T58; also, the drug appears to disrupt MYC-MAX interactions and reduce the expression of some MYC target genes. Treatment with 361 resulted in tumor regression in a mouse model of prostate cancer, and this effect was more pronounced in immunocompetent mice than in immunocompromised mice, suggesting that a functional immune system is required for optimal effects. There was evidence that 361 treatment stimulated an immune response

to tumors, exemplified by increased tumor infiltration of CD3⁺ T cells and upregulation of PD-L1 on tumor cells. Correspondingly, immunocompetent mice exhibited greater suppression of tumor growth when treated with 361 followed by anti-PD-1 than mice treated with either agent alone, indicating that combination treatment with MYC inhibitors and immune-checkpoint blockade may be a promising strategy. Although 361 provided a useful starting point in the search for MYC-inhibiting drugs, it also had unwanted qualities, such as a narrow therapeutic index. Several analogues were thus developed, yielding one, called 975, which had the desirable qualities of 361 with reduced toxicity. The 975 analogue reduced the viability of cancer cells, decreased MYC-target transcription, and exhibited antitumor efficacy that, as with 361, was enhanced by immunocompetence. This study demonstrates that MYC may not be undruggable, as has been suggested, and that therapies targeting MYC—perhaps in conjunction with immune-checkpoint blockade—may be on the horizon. ■

Han H, Jain AD, Truica MI, Izquierdo-Ferrer J, Anker JF, Lysy B, et al. Small-molecule MYC inhibitors suppress tumor growth and enhance immunotherapy. *Cancer Cell* 2019;36:483–97.e15.

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