The goal of the Highlights of the NCCN Oncology Research Program (ORP) is to provide readers with more information on the ORP, including studies currently accruing patients.

For more information on specific trials, including patient selection criteria, please use the contact information listed with each study.

For more information on the NCCN ORP, including a complete detailing of the clinical studies currently underway at NCCN Member Institutions, please access the NCCN ORP pages at NCCN.org/clinical_trials/clinicians.asp.

Highlights of the NCCN Oncology Research Program

The NCCN Oncology Research Program (ORP) strives to improve the quality of life for patients and reduce cancer-related deaths by advancing cancer therapies through research. Since the program's establishment in 1999, the NCCN ORP has brought millions of dollars in research grants to investigators at NCCN Member Institutions. Research grants are provided to NCCN through collaborations with pharmaceutical and biotechnology companies; these grants are in turn used to support scientifically meritorious cancer research efforts.

NCCN ORP studies typically explore new avenues of clinical investigation and seek answers to important cancer-related questions. All studies are approved and funded through a scientific peer-review process and are overseen by the ORP.

NCCN studies funded through the grant mechanism are highlighted below.

Phase II Combination Trial of Tivozanib and Enzalutamide in Men With Advanced Prostate Cancer

Principal Investigator: M. Dror Michaelson, MD, PhD

Condition: Metastatic castration-resistant prostate cancer

Institution: Massachusetts General Hospital

This single-arm, open-label, phase II clinical trial is testing the safety and effectiveness of tivozanib in combination with enzalutamide for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Enzalutamide has been approved by the FDA for the treatment of prostate cancer, but tivozanib is still investigational, and has not been tested in a combination with enzalutamide before.

All men will receive standard dosing of each drug, with tivozanib administered at 1.5 mg once daily for 3 weeks followed by a 1-week break, and enzalutamide administered continuously at 160 mg once daily. Both will be orally administered. A single dose reduction of tivozanib will be permitted, if necessary, to 1.0 mg daily. Patients will continue on treatment until they experience objective or clinical disease progression or unacceptable toxicity.

Enzalutamide is an androgen receptor antagonist that blocks the activity of the male sex hormones. Prostate cancers are initially dependent on the male hormone testosterone for growth. Hormonal therapies that lower testosterone or block the ability of testosterone to act at the level of the prostate cancer are currently among the most effective treatments for prostate cancers that have metastasized. The effectiveness of hormonal treatments, however, is not permanent, and over time many prostate cancers progress despite these treatments. Enzalutamide is a drug that has been proven to help delay the progression of advanced prostate cancer on average for approximately 8 months.

Tivozanib is an antiangiogenesis medicine that fights different types of cancer by blocking the blood supply to the tumor, so that the tumor does not receive the nutrients it needs to grow. The main goal of this study is to determine whether the combination of tivozanib and enzalutamide is more effective in delaying the progression of disease than when enzalutamide is given alone. This study will also determine whether combined treatment with tivozanib and enzalutamide will have more side effects than treatment with enzalutamide alone.

Because this combination has not been previously tested, a safety run-in will be conducted at the outset of the trial. While waiting for the first 3 patients to complete 1 month of treatment, no more than 10 total patients may be enrolled. These patients will be analyzed for safety and toxicity. If any treatment-related

expected or unexpected grade 3 or higher adverse events occur during the first month of treatment in the first 3 patients, or if the rate of adverse events is greater than 30% among the first 10 patients during the first month of treatment, further accrual will be halted for reconsideration of the appropriateness of the dosing schedules.

Primary Objective:

- Demonstrate an improvement in progression-free survival in men with mCRPC treated with tivozanib and enzalutamide

Secondary Objectives:

- Demonstrate an acceptable tolerability profile of tivozanib and enzalutamide
- Estimate overall survival and time to prostate-specific antigen (PSA) progression
- Evaluate PSA and objective response
- Explore an angiogenesis signature that may predict benefit from vascular endothelial growth factor receptor–targeted therapy in advanced prostate cancer

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