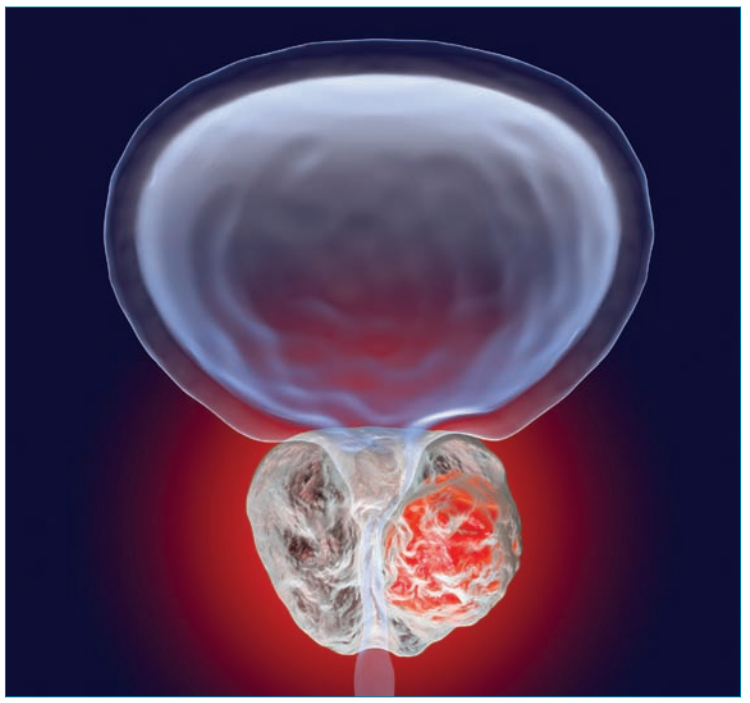
Non-Hormonal Therapy for Recurrent Non-Metastatic Prostate Cancer

BY AVI RETTER, MD

Prostate cancer is the second most commonly diagnosed cancer in American men, with an estimated 160,000 new cases and nearly 27,000 deaths related to the disease reported in the U.S. in 2017. More than one in 12 American men will be diagnosed with prostate cancer in their lifetime, and approximately 3 million are currently living with the disease, according to 2017 NIH SEER projections.

Current treatment includes radiotherapy or prostatectomy, followed by androgen deprivation therapy (ADT) through the use of gonadotropin-releasing hormone agonists or antagonists, or to a lesser extent surgically via bilateral orchiectomy (*ESMO Open* 2016;1(2):e000040). ADT may also be used in patients with a recurrence of elevated prostate-specific androgen (PSA) levels and in metastatic disease.



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Given the prevalence of ADT, the benefits must be weighed carefully against the multiple and significant side effects, and overall impact on the quality of life. A recent study surveyed 441 treating physicians from 19 countries, representing more than 99,000 patients with prostate cancer and found that of those with non-metastatic prostate cancer, 38 percent (or 28,840) received some form of ADT (*ESMO Open* 2016;1(2):e000040).

The most common side effects of continuous ADT include anemia, hot flashes, sexual dysfunction, cognitive dysfunction, bone loss, bone complications, metabolic and cardiovascular consequences, fatigue, depression, and anxiety (*ESMO Open* 2016;1(2):e000040). Changes in body composition (gynecomastia, weight gain, reduced muscle mass and muscle tone, and increase in abdominal fat) are also well-documented (*ISRN Urology* 2013; http://dx.doi.org/10.1155/2013/240108). A recent publication suggested that ADT may also be associated with an increased risk of dementia and called for further evaluation (*JAMA Oncol* 2017;3(1):49-55).

While ADT is effective for certain types of prostate cancer, it is not without risk, leaving a significant need for improved and non-toxic treatment options.

SM-88: A Potentially Non-Toxic Treatment

Encouraging preliminary findings from a phase II clinical trial of SM-88 in non-metastatic biochemical recurrent prostate cancer (nmPC) with rising PSA levels suggest that a non-hormonal therapeutic approach may be effective without the unfavorable side effects and decrease in quality of life often reported by prostate cancer patients utilizing hormone therapy.

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SM-88 is a first-in-class combination monotherapy that exploits the aberrant metabolic profile of cancer cells to break down tumor cells' natural defense against the immune system and oxidative stress.

In contrast to normal cells, cancer cells rewire their metabolism to promote growth, survival, proliferation, and maintenance. In a process referred to as the Warburg effect, cancer cells inefficiently convert glucose to adenosine 5′-triphosphate through aerobic glycolysis, which leads to elevated levels of intracellular reactive oxygen species (ROS) (*Cell* 2008;134(5):703-707, *Trends Biochem Sci* 2016;41(3):211-218), and a harsh, acidic microenvironment. To protect itself from these vulnerabilities, cancer cells upregulate transmembrane mucins to safeguard against the ROS-rich milieu. Mucins, in turn, upregulate ROS scavenging enzymes (*J Biol Chem* 2003;278(37):35458-35464, *Nat Rev Cancer* 2009;9(12): 874-885), becoming a key defense against apoptosis (*Biochem Biophys Res Commun* 2013;440(1):179-183).

In addition to altered metabolism, the Warburg effect also facilitates the uptake and incorporation of nutrients into the biomass (e.g., nucleotides, amino acids, and lipids), which is needed to proliferate (*Science* 2009; 324(5930):1029-1033). To meet these demands, cancer cells upregulate amino acid transporters, such as L-amino transferase-1 (LAT1) (*Semin Cancer Biol* 2005;15(4):254-66, *Cancer Res* 2015; 75(15 Supplement) Abstract 5286).

SM-88 eradicates cancer cell defenses against the Warburg-induced acidic, ROS-rich microenvironment. Simultaneously, the drug acts to increase ROS levels, thereby placing increased pressure on the tumor cell and triggering innate apoptotic pathways. Although SM-88 targets multiple pathways to achieve this, broadly, it disrupts cancer cell protein synthesis, effectively suppressing essential nutrients and preventing production of key defense proteins, such as mucins, which protect against ROS.

> Use of SM-88 in non-metastatic biochemical recurrent prostate cancer with rising PSA levels shows that a non-hormonal therapeutic approach may be effective without the unfavorable side effects and decrease in quality of life.

The core component of SM-88 is a dysfunctional tyrosine analog. Tyrosine is an optimal target for cancer therapy because it is a non-essential amino acid, meaning that normal cells can convert phenylalanine to tyrosine instead of having to absorb it (*J Nutr* 2007;137(6 Suppl

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1):1549S-1575S). It is also readily transported into cancer cells by upregulated LAT1. Since mucin has a high tyrosine component, it is thought to be especially vulnerable to the drug, which disrupts protein synthesis and inhibits mucin production, thereby making cancer cells more susceptible to ROS and immune response.

In combination with the tyrosine analog, SM-88 consists of a regimen of repurposed drugs used in microdoses well below the therapeutic range. These molecules help to ensure delivery of the tyrosine analog and sensitize cancer cells to ROS and subsequent apoptosis.

These additional components include rapamycin, phenytoin, and methoxsalen. Rapamycin, a mTOR (mammalian target of rapamycin) inhibitor, works to alter cancer cells' amino acid metabolism (*Science* 2008;320(5882):1496-1501, *Cancer Res* 2015;75(9):1782-1788) by upregulating LAT1 (*Biochem Pharmacol* 2010;80(6):811-818), thereby promoting the uptake of the tyrosine analog into cancer cells.

Phenytoin, a CYP3A4 inducer, acts to increase reactive lipids in the cancer cells (*Trends Cell Biol* 2014;24(8):472-478), which could further offset the ROS balance inside the cell, while methoxsalen works to increase melanin production, which can act as an electron donor to promote a catalytic state and oxidative reactions in tumor cells (*Biochim Biophys Acta* 2009;1794(7):1017-1029, *J Invest Dermatol* 2014;134(6):1512-1518). These drugs serve to drive cancer cells toward ROS-mediated apoptosis.

Trial Design & Interim Results

In an ongoing phase II clinical trial in non-metastatic biochemical recurrent prostate cancer, SM-88 was administered to nine patients (of 15 enrolled) with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1, no radiographically detectable lesions and rising PSA levels, according to Prostate Cancer Working Group 3 criteria.

Of the patient population receiving SM-88, the median age was 78 (range, 62-80) with 50 percent having undergone previous surgery and 50 percent having undergone previous radiotherapy. The large majority of patients had prior ADT, but no patient was currently on ADT. The mean testosterone level was 310.2 ng/dL, median PSA at baseline was 6.4 ng/mL, and the median Gleason score was 7.

Patients were treated orally with SM-88. The tyrosine derivative was administered at 230 mg twice daily along with phenytoin 50 mg, methoxsalen 10 mg, and rapamycin 0.5 mg once daily for 28 days with no break between treatment cycles.

This open-label, multi-center, single-arm study is slated for completion in the first half of 2018, and the preliminary data thus far are promising: SM-88 delays or reduces recurrent nmPC compared to a contemporaneous control group.

During treatment, testosterone increased over baseline while PSA improved (78% demonstrated a decrease in PSA doubling time). Other biomarkers such as radiographic progression-free survival, lactate dehydrogenase, urinary N-teleopeptide, and bone-specific alkaline phosphatase were generally unchanged. Neutrophil-to-lymphocyte ratio, however, showed a significant decrease.

All nine patients taking SM-88 also exhibited an improvement in circulating tumor cell (CTC) levels, with 67 percent demonstrating a 50 percent or greater decline. In subjects with more than one cycle (n=5), CTCs fell to undetectable levels (n=1) or by >30 percent (n=4). The median time to undetectable CTCs was 16 weeks (range, 3-28 weeks).

CTCs are tumor cells released into the blood from the primary tumor or metastasis. CTC levels are a valuable prognostic marker that should be considered along with clinicopathological features, serum PSA, and radiological evaluation levels when assessing patients. By monitoring CTCs and biomarkers, clinicians have a more complete picture of a disease that is known to be dynamic, with different tumor clones arising over

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time in response to different therapies (*Oncotarget* 2017;8(33):54708-54721).

Several studies have established the value of baseline CTC count and CTC changes for overall survival in prostate cancer patients. Furthermore, changes in CTC levels often precede PSA level fluctuation. As such, CTC counts have been included in several phase I/II trials to monitor the efficacy of new treatments (*Oncotarget* 2017;8(33):54708-54721).

SM-88 therapy was also well-tolerated. Overall, 62.5 percent of patients had grade 1/2 adverse events, but no serious adverse events were reported. No patient had to reduce or delay a dose, or discontinue treatment with SM-88. In addition, patient-reported outcomes on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-PR25 questionnaire showed that measures related to intimacy were positive throughout the trial.

Ongoing Research

The results of the phase II study will be used to design a pivotal, phase III randomized control trial evaluating SM-88 against observation or ADT in recurrent nmPC.

While the benefits of ADT are well-established when used as palliative care of symptomatic metastatic disease or as an adjuvant to radiation therapy for high-risk disease, clear evidence of efficacy of ADT is lacking when used for primary therapy of nmPC or for biochemical recurrence following initial local therapy (*N Engl J Med* 2010; 363(19):1822-1832; *J Urol* 2004;172(1):141-145).

Preliminary results from the phase II trial of SM-88 are encouraging and suggest that SM-88 could potentially help delay ADT or provide an alternative to the "wait and see" approach often taken in patients with early-stage prostate cancer, and those who are of advanced age or have other serious health problems. OT