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for patients with HPV16-positive OPC is currently intensive and results in substantial morbidity, albeit with a high survival rate, ongoing trials are evaluating radiation deintensification among patients with HPV-positive OPC. Thus, there may be less intensive treatment options in the future, especially for HPV-driven cancers diagnosed at an earlier stage.

On the basis of available data, we estimate that, in regions like the United States where rates of HPV-driven OPC are rare but increasing, the number of individuals in the population needed to be screened to detect one case of OPC is approximately 5,000 (assuming 70% of tumors are HPV16 positive and 90% assay sensitivity), and the number of individuals who screened positive that would yield one case is approximately 50 (assuming 99.0% specificity); this value decreases to approximately 11 if specificity increases to 99.8% (Table 1). To put this into context, in comparison with cervical cancer screening,[7,8] the number of individuals needed to screen to detect one cancer would be higher for OPC because of differences in incidence, whereas the number of individuals who screen positive needed to detect one case would be lower for OPC because of the high specificity of the HPV16 E6 assay, especially if test characteristics can be further improved.

It is too early to judge the suitability of HPV16 E6 antibody as a screening tool for OPC, and we will continue to evaluate this potentially important cancer prevention opportunity. However, because OPC is only a subset of head and neck cancers, even if this marker is proven successful as a screening test, efforts to evaluate markers for non-HPV–related head and neck cancer are also important if we are to have a global and meaningful impact.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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US Food and Drug Administration Approval of Drugs for the Treatment of Prostate Cancer: A New Era Has Begun

To the Editor: Before 2002, only three drugs were approved by the US Food and Drug Administration (FDA) for the treatment of prostate cancer (PC),[1-3] as shown in Table 1, and only one of these approvals[3] was based on a prolongation of survival from a randomized clinical trial (RCT). Since then, that number has risen to 12,[4] with nearly all new drug approvals (NDAs) a result of a survival benefit that was documented in an RCT. What changed?

In 1993, under the umbrella of the newly formed organization called the Prostate Cancer Foundation (PCF),[5] formerly the Association for the Cure of Cancer of the Prostate (CaP CURE), leading scientific and clinical experts in the treatment of PC were assembled on a board whose mission was to use the resources of PCF to find a way

diagnosis of advanced PC. Significant resources were initially provided by the founder and chairman of this group, Michael Milken, who had been diagnosed with PC in 1993. This was followed by a large fundraising effort by PCF to perpetuate the revenue stream that was needed to support ongoing research initiatives. To date, $510 million have been raised for PC research, making this organization the largest private sponsor of PC research in the world, funding more than 1,600 proposals at nearly 200 research centers in 16 countries.

The NDA for zoledronic acid[4] was issued by the FDA in 2002. This was the first agent shown to decrease skeletal-related events (eg, compression fractures) in an RCT of men with PC whose primary site of metastasis is the skeleton. The impetus for this RCT was a PCF-funded survivorship study that elucidated the relationship between declining bone mineral density and hormonal therapy use in PC. Next, work by clinical leaders in the PCF Clinical Consortium contributed to our understanding that PC was sensitive to taxane-based chemotherapy regimens (ie, docetaxel; sanofi-aventis, Bridgewater, NJ)[4]; docetaxel was FDA approved in 2004 after the publication of two RCTs, one of which was led by a PCF clinical investigator and showed an improvement in survival in men with castration-resistant and

Table 1. Chronological Summary of New Drug Approvals Granted by the FDA for Treatment of Prostate Cancer, Including Contribution by PCF That Led to Approval

Drug	Year of FDA Approval	Disease State	End Point Leading to Approval	PCF Contribution
Estramustine	1981	Metastatic PC	Clinical response rate	Pre-PCF
Mitoxantrone + prednisone	1996	Metastatic PC	Quality of life	Pre-PCF
Goserelin acetate LHRH agonist	1998	Locally advanced PC	Survival	Pre-PCF
Zoledronic acid	2002	Metastatic PC	Skeletal-related events	Funded survivorship studies uncovering declining bone mineral density with HT use, leading to the phase III RCT after which zoledronic acid was approved
Docetaxel	2004	CRMPC	Survival	Funded phase II studies run by PCF clinical investigators revealing that PC was sensitive to docetaxel, leading to the phase III RCTs after which docetaxel was approved
Degarelix	2008	Advanced PC	No testosterone flare as with LHRH agonist	None
Cabazitaxel	2010	CRMPC after docetaxel	Survival	None
Sipuleucel-T	2010	Asymptomatic or minimally symptomatic CRMPC	Survival	Funded the phase II study suggesting efficacy of immunotherapy in PC, leading to the phase III RCT led by a PCF clinical investigator after which sipuleucel-T was approved
Denosumab	2013	Nonmetastatic prostate cancer being treated with androgen deprivation therapy	Skeletal-related events	Brought together the company who had patent rights on denosumab with bone biologists and an expert PCF clinical investigator. The company then turned its attention to PC, and the phase III RCT that led to approval was conducted by a PCF clinical investigator
Abiraterone	2012	CRMPC after and before docetaxel	Survival	Funded the study that defined the mechanism of action of abiraterone, which generated enthusiasm for the phase II and III trials led by PCF clinical investigators that led to approval
Enzalutamide	2012	CRMPC after docetaxel	Survival	Funded the basic science research leading to our understanding that androgen receptor overexpression drives CRMPC, leading PCF-funded investigators to discover enzalutamide. The landmark RCT was led by a PCF investigator
Radium-223	2013	CRMPC after docetaxel	Survival	None

Abbreviations: CRMPC, castration-resistant metastatic prostate cancer; FDA, US Food and Drug Administration; LHRH, luteinizing hormone–releasing hormone; PC, prostate cancer; PCF, Prostate Cancer Foundation; RCT, randomized controlled trial.

avoiding a testosterone flare became possible with a single agent in 2008 with the approval of degarelix,[4] a pure luteinizing hormone–releasing hormone antagonist. Then, in 2010 and 2011, three new agents were approved by the FDA for patients with PC: sipuleucel-T (Provenge; Dendreon, Seattle, WA),[4] the first immunotherapy to stimulate the body's immune system and prolong survival, remarkably, in the absence of a prostate-specific antigen response; Jevtana (cabazitaxel; sanofi-aventis),[4] another taxane-based chemotherapy that prolonged survival after disease progression during treatment with docetaxel; and finally, on September 16, 2011, the FDA granted approval for Xgeva (denosumab; Amgen, Thousand Oaks, CA)[4] as a treatment to increase bone mass in patients who are at high risk of fracture from receiving androgen deprivation therapy for nonmetastatic PC. PCF's sentinel contributions leading to FDA approval for two of these three agents are described in Table 1. During the last 2 years, abiraterone acetate[4] and enzalutamide,[4] two novel forms of hormonal therapy that have been shown in the context of multiinstitutional RCTs to prolong survival and improve patient-reported health-related quality of life for men with castration-resistant and metastatic PC, have been approved by the FDA and are now being tested in earlier stages of the disease by cooperative groups around the world. The expectation is that these agents will increase the probability of cure for men with newly diagnosed high-risk and nonmetastatic PC. PCF played the major role in defining the mechanism of action of these drugs, and in one case, supported the research that led to the discovery of the drug. In both cases, PCF clinical investigators led the RCTs that resulted in FDA approval, as detailed in Table 1. Finally, on May 15, 2013, the first radiopharmaceutical, radium-223,[4] was found to prolong survival in men with PC and bone metastasis refractory to conventional hormonal therapy.[3] By selective uptake in bone and the short distance (< 1 mm) over which the charged particle (ie, alpha particle) acts, damage to surrounding hematopoietic tissues was minimal.

Therefore, of the nine NDAs that occurred after 2002, six were driven by research and collaborations that existed because of PCF, as shown in Table 1. Today, with federal funding initiatives for cancer research continuing to decline, the need for novel approaches, such as that used by PCF to fund the research that lead to NDAs, are needed across all cancers.

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