

# PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

## Update on the Biology and Management of Neuroendocrine Prostate Cancer



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### H&O What is the definition of neuroendocrine prostate cancer (NEPC)?

**HB** NEPC is an aggressive variant of prostate cancer that typically is diagnosed in the later stages of advanced disease. It is thought to arise as a function of treatment resistance.<sup>1</sup> In its pure form, NEPC is histologically similar to other high-grade or small cell neuroendocrine carcinomas, often expressing classical neuroendocrine markers (eg, chromogranins) and lacking expression of typical prostate markers, such as prostate specific antigen (PSA).<sup>2</sup> The prostate cancer–specific *TMPRSS2-ERG* gene fusion is present in approximately half of NEPC cases, which distinguishes NEPC tumors from neuroendocrine tumors that arise from other primary sites. A break-apart fluorescence in situ hybridization (FISH) assay can be used to assess patients for *TMPRSS2-ERG* fusion in cases of small cell carcinoma of unknown primary tumor site to confirm prostate origin, although a negative test does not rule out NEPC. Notably, a spectrum of morphologies are observed in advanced prostate cancer; we frequently see mixed or overlapping tumors with features of both prostate adenocarcinoma and NEPC.

### H&O How common is NEPC?

**HB** The exact frequency is not well defined because until recently, physicians did not routinely perform biopsies for clinical care in the setting of advanced prostate cancer. Two prostate cancer “Dream Teams,” supported by Stand Up To Cancer and the Prostate Cancer Foundation,<sup>3,4</sup> are systematically assessing biopsy specimens from patients at specific clinical disease states during the course of therapy. This approach will help define the true prevalence.

### H&O Why are we seeing more cases of NEPC than we used to?

**HB** Now that awareness of NEPC has increased, more biopsies are being performed clinically in patients with suspected NEPC. The fact that we are now looking for it is a big difference. It may also be that the prevalence of NEPC is rising as patients progress after more lines of systemic therapy. NEPC is believed to arise as a function of treatment resistance; these tumors rarely arise de novo in the absence of prior therapy. Now that we have more effective agents to treat patients with advanced prostate cancer, including potent drugs that inhibit the androgen receptor (AR)—a key driver of the disease—patients are living longer and can eventually develop resistance to these newer agents. In the vast majority of cases, the tumor cells respond by reactivating AR signaling through AR gene amplifications, mutations, bypass mechanisms, or other means. In a smaller subset of cases, prostate cancer cells that encounter therapies used to block the AR may develop an escape mechanism involving epithelial plasticity, dedifferentiation, and loss of AR expression associated with NEPC.

In other words, we may be seeing a combination of more widespread detection and a true increase in prevalence.

### H&O When should physicians suspect the development of NEPC?

**HB** Oncologists should suspect NEPC in patients who have particularly aggressive metastatic castration-resistant disease that has failed to respond to typical prostate cancer therapies, with progression in the setting of a low or nonrising PSA.<sup>1</sup> Neuroendocrine tumors tend to be less

dependent on the AR, and PSA is an androgen-regulated marker. At this time, the diagnosis is typically based on biopsy. Noninvasive biomarkers such as circulating tumor cells and circulating tumor DNA are areas of research development.

### H&O What is the prognosis for patients with NEPC?

**HB** The prognosis varies depending on the pathologic characteristics and clinical features of the patient. Typically, NEPC tumors that look like pure small cell neuroendocrine carcinomas under the microscope and that lack classical prostate cancer markers—including the AR—are clinically aggressive and respond poorly to standard therapies. We treat these patients much like those with small cell lung cancer, with platinum-based chemotherapy rather than AR blockade, because the diseases tend to behave similarly.

### H&O What have we learned in recent years about the biology of NEPC?

**HB** Despite distinct tumor pathology and associated clinical features, one key observation, based on genomic studies,<sup>5,6</sup> is that NEPC tumors appear to arise clonally from a prostate adenocarcinoma precursor. As a result, these cells retain many of the common prostate cancer genomic alterations (such as *TMPRSS2-ERG* fusion as described earlier), but they also acquire new molecular alterations. This is an important concept because it provides scientific insights into biologic evolution and may provide an opportunity for early detection or intervention. Certain molecular alterations are enriched in NEPC tumors vs castration-resistant prostate adenocarcinomas, including significant epigenetic changes. A number of disease pathways have been elucidated by our group and others, and preclinical studies are looking at advanced-stage adenocarcinoma and neuroendocrine tumors to see which pathways might be good candidates for treatment. Another area of interest is early identification of patients who are susceptible to NEPC through the use of tissue-based and noninvasive biomarkers. As a field, we are working to better understand the molecular basis of these neuroendocrine prostate tumors and identify novel therapeutic targets.

### H&O Could you talk more about your work on developing these biomarkers?

**HB** In an earlier study, we found that the oncogenic transcription factor N-Myc is highly expressed in NEPC and can drive a neuroendocrine phenotype in preclinical studies.<sup>5</sup> I have since built upon this work through

an ongoing collaboration with Dr David Rickman and Dr Mark Rubin at our institution, and have developed preclinical models that we have used to study N-Myc signaling and treat NEPC. N-Myc is a challenging target to drug. We are therefore developing ways to indirectly target N-Myc signaling, including inhibition of its stabilizing protein, Aurora kinase A. This work has led to an ongoing phase 2 trial of the Aurora kinase A inhibitor alisertib (MLN8237) for patients with NEPC (NCT01799278). This is a multi-institutional trial with 60 patients across 9 centers that recently completed accrual.

Recently, we also published a molecular landscape study in which we further focused on identifying and characterizing the genomic and epigenomic alterations that distinguish NEPC from castration-resistant prostate adenocarcinoma by studying biopsies from a cohort of patients with advanced prostate cancer.<sup>6</sup> This was a collaborative effort between several members of our group at Weill Cornell Medicine plus Dr Francesca Demichelis and her team at the University of Trento in Italy and Dr Levi Garraway at the Broad Institute in Cambridge, Massachusetts. These molecular data have provided new insights into tumor evolution, potential biomarkers, and targets for therapy.

### H&O What other research is being conducted in this area?

**HB** Clinical and translational research efforts have focused on pathologic characterization, including defining intermediate phenotypes,<sup>4</sup> prognostic biomarker development,<sup>7</sup> and treatment science, such as exploring the use of agents being used for other small cell carcinomas (NCT02709889). Improving our understanding of tumor biology and the mechanisms driving NEPC resistance are critical. This includes characterizing the role and potential cooperation of molecular changes observed in NEPC (eg, loss of *RBI* and *TP53*, Aurora kinase A and N-Myc overexpression), and understanding how these changes may suppress androgen signaling and/or influence other emerging NEPC programs such as loss of *REST*,<sup>8</sup> PEG10 de-repression,<sup>9</sup> and activation of stem cell, neuronal, and developmental programs. The use of patient-derived preclinical models, including organoids<sup>10</sup> and patient-derived xenograft models,<sup>10</sup> can help model treatment resistance and accelerate this process.

### H&O What are some of the biggest misconceptions or sources of confusion regarding NEPC?

**HB** Not all patients with clinical features suggestive of AR independence, such as progression despite a low PSA,

have classical neuroendocrine features on biopsy. The choice of what therapy to use should be based on clinical features in combination with pathology. We hope that incorporating molecular biomarkers will help us to better identify those patients who are less likely to respond to hormonally directed therapies so that we can use alternative approaches, such as platinum agents or other drugs in development. We need more clinical trials to focus on the management of this aggressive variant of advanced cancer.

### Disclosures

*Dr Beltran has declared no potential conflicts of interest.*

### Suggested Readings

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