Review Article on Management of Advanced Genitourinary Malignancies

Narrative review of challenges in the management of advanced neuroendocrine prostate cancer

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Abstract: With wide availability of potent androgen receptor targeted agents (ARTAs), the incidence of treatment-related neuroendocrine prostate cancer (t-NEPC) has been dramatically increasing. However, there is no standard effective treatment for this disease state. Recent advances in genomic and molecular medicine have identified some critical features of NEPC that would help in understanding the biology of the disease. Furthermore, invaluable pre-clinical in vivo and in vitro research models that represent NEPC have been developed. These advances in research have revealed a large heterogeneity of t-NEPC with varying degree of androgen receptor (AR), neuroendocrine (NE) marker, and cell cycle associated gene expressions, which may have clinical implication in terms of prognosis and treatment selection. Based on these studies, some potential drug targets have been identified, and early clinical trials are ongoing. In the future, more precise disease classification and biomarker-driven selection of patients will be critical for optimization of treatment for patients with NEPC. In the present review, we describe up-to-date findings of recent research on this topic and introduce ongoing therapeutic developments that are expected to lead to novel treatment strategies for NEPC in the future.

Keywords: Prostate cancer; neuroendocrine (NE); biology; treatment; neuroendocrine prostate cancer (NEPC)

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Introduction

Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of prostate cancer that has features common to small cell carcinoma (SCC) of the lungs and shows resistance to standard androgen deprivation therapy (ADT). Clinically, NEPC is grossly classified based on the presence or absence of pre-treatment as de novo NEPC or treatment-related NEPC (t-NEPC). The former is conventionally thought to arise from neuroendocrine (NE) cells in the prostate gland, and its reported incidence has constantly been less than 2% of prostate cancer cases. By contrast, multiple studies suggest that t-NEPC arises from adenocarcinomas as a consequence of an adaptive response to therapy, and the incidence of t-NEPC has been increasing due to the wide use of potent androgen receptor targeted agents (ARTAs), such as enzalutamide, abiraterone acetate, apalutamide, and darolutamide. Although much information related to the biology of NEPC remains to be elucidated, recent basic research, particularly genomic studies, has identified some important aspects of the disease that may lead to the development of potent therapy for this disease state. In this review, we describe recent findings on NEPC research and introduce ongoing therapeutic developments to improve its management. Of note, most of the content in the review is based on reports published after 2010 that are indexed in PubMed and are written in English. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1131).

Definition and classification of NEPC

Various terminology has been used to describe clinical features of NEPC, such as "anaplastic", "small cell", and "aggressive variant", with each term encompassing a slightly different spectrum of disease. Although the histologic classification of NEPC by the World Health Organization (WHO) used to be analogous to NE tumors of other organs, it did not account for the unique aspects of NEPC. Consequently, there had been contradictory reports regarding its clinical significance (1,2). In 2013, a working committee assembled by the Prostate Cancer Foundation proposed a pathologic classification and definition of NEPC (3). In the proposal, NEPC was classified as follows: (I) usual prostate adenocarcinoma with NE differentiation, (II) adenocarcinoma with Paneth cell NE differentiation, (III) carcinoid tumor, (IV) small cell carcinoma (SCC), (V) large cell NE carcinoma (LCNEC), (VI) mixed NE carcinoma—acinar adenocarcinoma. Notably, t-NEPC was described as an independent category, "Castration-resistant prostate cancer (CRPC) with small cell carcinoma- like clinical presentation".

Histologically, immunohistochemistry (IHC) with synaptophysin (SYP), chromogranin A (CgA), and CD56 may be useful for confirmation of NE differentiation, and ERG FISH assay may be useful to confirm prostatic lineage. In the case of mixed adenocarcinoma and NEPC, prostate- specific markers such as prostate specific antigen (PSA) and NKX3.1 could also be used to confirm the origin of cancer. Other potentially useful IHC markers for the diagnosis of NEPC are positive staining for CD56, p53, thyroid transcription factor-1 (TTF-1), CD44, and forkhead box A2 (FOXA2), and negative staining for Rb and cyclin D1 (4). Because a spectrum of diseases is observed between adenocarcinoma and t-NEPC, including a state called androgen indifferent stage, either pure or mixed histologic features can be seen along with different degrees of expression of the AR pathway and NE markers (5). Clinically, morphology is most important for the diagnosis of SCC or mixed NE carcinoma, and routine IHC of prostate cancer for NE markers is not recommended.

Clinical features of NEPC

The incidence of de novo NEPC has been reported to be less than 2% of prostate cancer cases at the diagnosis (6,7). On the other hand, the incidence of t-NEPC has been increasing recently. It has been reported that t-NEPC may develop in 10–20% of castration resistant prostate cancer (CRPC) patients as a mechanism of treatment resistance (8,9). Clinically, *de novo* NEPC and t-NEPC show similar characteristics. Except for cases with mixed adenocarcinoma, NEPC is unresponsive to hormonal therapy including potent ARTAs, shows rapid progression with low serum PSA relative to tumor burden, and poor prognosis. Some of the scenarios in which clinicians would suspect NEPC rather than adenocarcinoma would be extensive local progression, liver metastasis, and lytic bone metastasis. In such cases, the NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf) recommend metastatic tissue biopsy for histologic confirmation.

For de novo NEPC, the 1- and 5-year survival rates were reported to be 47.9% and 14.3%, respectively (10). A more recent study reported that the overall survival (OS) of 47 cases of de novo NEPC was 16.8 months (11). In the same study, for 40 t-NEPC cases, the median time from adenocarcinoma to t-NEPC diagnosis was 39.7 months with a median of two lines of prior systemic therapy. Median OS of t-NEPC patients was 53.5 months from prostate cancer diagnosis. From the time of NEPC diagnosis, OS did not differ between de novo NEPC and t-NEPC. OS of pure SCC (8.9 months) patients was shorter than that of NEPC with mixed adenocarcinoma (26.1 months). Serum CgA levels were elevated in 48.3% of patients. There were no significant differences in the frequency of AR, RB1, and TP53 aberrations identified between *de novo* NEPC and t-NEPC or between pure SCCs and mixed tumors.

Cellular origin of NEPC

Traditionally, de novo NEPC has been thought to originate from a small population of NE cells present in normal prostate glands. However, differences in the molecular expression of NEPC cells and normal NE cells suggested a correlative relationship between NEPC cells and adenocarcinoma cells (8,12). Furthermore, there are also cases of de novo NEPC harboring rearrangement of the ETS gene that involves androgen-driven promoters, suggesting that de novo NEPC also may be derived from an androgen-driven ancestor (13). Therefore, controversy still remains regarding the origin of de novo NEPC (4).

By contrast, accumulating evidence suggests that t-NEPC arises from adenocarcinomas by trans-differentiation rather than clonal selection of cells originating from NE cells. The TMPRSS2-ERG fusion gene, which is a frequent early

genomic alteration of prostate adenocarcinoma, is found in 50% of t-NEPC cells (14). When tumor samples of metastatic t-NEPC and primary prostate adenocarcinoma obtained from the same patients were compared, there was 100% concordance of ERG rearrangement and Aurora kinase A (AURKA) amplification, and 60% concordance of MYCN amplification between the two. In tumors with mixed features, there was also 100% concordance of ERG rearrangement and 94% concordance of AURKA and MYCN co-amplification between tumor samples obtained from NEPC and adenocarcinoma (15). These data support that t-NEPC arises by trans-differentiation of adenocarcinoma, CRPC cells, or cancer stem cells (16,17). Lineage plasticity is the ability of cells to convert from one cell type to another. In cancer, cells can alter lineages to change their morphology or phenotype and escape treatment stress. In the case of prostate cancer, AR-driven adenocarcinoma can, under certain circumstances (or genomic state as discussed below), alter lineage, or trans-differentiate, to become t-NEPC and escape treatment stress induced by potent AR axis inhibition. In a recent study, single-cell RNA sequencing of 21,292 cells from needle biopsies of 6 CRPC patients, including 3 t-NEPC patients, revealed that NEPC cells displayed a luminal-like epithelial phenotype, also supporting the phenomenon of trans-differentiation of adenocarcinomas (18).

Research models of NEPC

Suitable research models of NEPC are important to understand the biology of the disease and to develop effective therapies. Patient-derived xenografts (PDX), genetically engineered mouse (GEM) models, cell lines, and organoids have been established as experimental models of NEPC. Although the number and variety of NEPC models is still not adequate to represent the diversity of NEPC, the number of available models is increasing in recent times.

Representative t-NEPC PDX models are LUCAP 49, WISH-PC2, UCRU-PR-2, WM-4A, and MDA PCA 144-13. These models were derived from patients with NEPC that arose after treatment. All of them displayed rapid growth, expression of at least one NE differentiation marker, and lack of AR and PSA (19). LTL331 is an interesting PDX model that alters the phenotype from adenocarcinoma to NEPC (LTL331R) after castration of the host mouse. LTL331 follows the clinical course of trans-differentiation, with initial tumor shrinkage upon castration, and rapid re-growth without a rise in PSA levels. While LTL331 expresses AR and PSA, LTL331R expresses SYP, CgA, and CD56, and loses the expression of AR and PSA (20). This novel PDX model enables comparison of t-NEPC cells with the original adenocarcinoma cells, and genetic and molecular events occurring during the process of trans-differentiation can be studied temporally. One of the molecules conferring aggressiveness to t-NEPC, PEG10, was discovered using this model. PEG10 is a placental gene indispensable for mammalian development that promotes growth and invasion of NEPC through activation of the E2F1 pathway in cells with aberrant p53 and Rb signaling (21). Recently, PEG10 has also been shown to play a role in promoting growth and invasion in NE-like muscle–invasive bladder cancer, and antisense oligonucleotide targeting PEG10 decreased in vivo tumor growth, suggesting its potential as a therapeutic target (22).

Most of older NEPC GEM models express the simian virus 40 (SV40) early genes (the large and/or small T antigens) using the prostate-specific promotor. The transgenic adenocarcinoma of the mouse prostate (TRAMP) model, which is the most widely known model of among the NEPC GEM models, express SV40 large and small T antigens driven by a mouse probasin promotor in the prostate epithelial cells. SV40 large T antigen inhibits the tumor suppressor genes Trp53 and Rb1, and the small T antigen interacts with protein phosphatase 2A (23). The prostatic lesions of the TRAMP model develop with increasing age: low-grade prostatic intraepithelial neoplasia (PIN) by 6 weeks of age, high-grade PIN by 10–16 weeks, well-differentiated adenocarcinomas by 18 weeks, and poorly differentiated carcinomas with NE features by 24 weeks (24,25). Another GEM model is the Trp53 and Rb conditional knockout mouse model. Deficiency of Trp53 and Rb is limited to the prostate by Cre recombinase under the control of Arr2pb promoter, which is a modified rat probasin promoter. PIN occurs in this model by 8 weeks of age, and a poorly differentiated prostatic carcinoma with NE features at 24–50 weeks (26). More recently, a GEM model with conditional knockout of Pten and overexpression of N-myc has also been reported to result in prostate carcinoma with both AR-positive and NEPC tumors (27).

LNCaP cells are originally AR-dependent prostate cancer cells; however, when cultured in androgen-deprived medium, the cells morphologically change to neuron-like appearance with some expression of NE markers. Therefore, conventionally, LNCaP cells have often been used as an in vitro model of NEPC trans-differentiation

(28-30). Some other molecules such as cyclic adenosine monophosphate (31), cytokines (32), and growth factors (33) also induce similar trans-differentiation of LNCaP. Because various stimuli can induce similar NE-like phenotypes, it is possible that the NE phenotype is a default state of LNCaP cells under stressful conditions (4). However, LNCaP cells trans-differentiated to NE-like cell type under these experimental conditions are not representative of clinical NEPC, since these NE-like cells are generally in a quiescent, non-proliferative state, unlike the aggressive t-NEPC observed clinically (4). From recent genomic molecular studies, aberrations in the p53, Rb, and PTEN pathways have been identified to be critical to the development of t-NEPC (34,35). LNCaP cells with either double or triple knockdown of these genes changed lineage and expressed genes common to clinical t-NEPC and showed resistance to enzalutamide. Importantly, these cells showed high expression of SOX2 and EZH2, which are epigenetic programming factors important for lineage plasticity.

Some researchers use PC3 or DU145 cells as alternatives to NEPC cell lines, because they do not express AR. PC3 cells are TP53-null and DU145 cells have TP53 mutations in addition to a loss of RB1. However, because these cell lines are not genuine NEPC models, care should be taken when using these cells as preclinical models of NEPC. NCI-H660 is the only widely used cell line of NEPC which originates from a patient with NEPC. In 1983, this cell line was initially established from a lymph node metastasis from autopsy samples of a patient with extra-pulmonary SCC (36-38). More than 10 years later, the discovery of the TMPRSS2-ERG fusion gene of NCI-H660 proved it to be a valuable NEPC model (39). The cell line is cultured as floating cells with cluster formation similar to many other small cell lung carcinoma cell lines.

There are a few other cell lines established from de novo NEPC. The PSK-1 (40) cell line was established from de novo NEPC arising in a patient with Kleinfelter syndrome. However, its detailed genomic status has not yet been studied. The SO-MI (41) cell line was similarly established from de novo NEPC in a young patient. However, because there are only single reports on these two cell lines, it is not clear whether these cell lines could be used as preclinical models to elucidate the biology of this disease. For further in vitro research on NEPC, the establishment of new NEPC cell lines is urgently required.

Recently, a series of NEPC patient-derived tumor organoids has been developed from needle biopsies of metastatic tumors (42). These organoids express clinical NEPC signature genes, including overexpression of MYCN, PEG10, SRRM4, EZH2, SOX2, BRN2, and FOXA2. Moreover, treatment of an organoid with an EZH2 inhibitor resulted in a reduction of H3K27me3 expression and a preferential decrease in the viability. However, additional combination treatment with enzalutamide did not show additive effects or synergy. In the study, the authors also investigated whether cells from NEPC-derived organoids could be re-differentiated to express AR by the inhibition of EZH2; however, unlike what has been reported with other cell models that exhibit plasticity, suppression of EZH2 alone was not sufficient to reverse the phenotype in these terminally differentiated cells. Organoid models are expected to be valuable for investigating the molecular biology of NEPC and for drug screening to discover new treatments for NEPC.

Genomic and molecular characteristics of NEPC

It has been known that aberrant Rb and p53 pathways play important roles in NEPC trans-differentiation, since TRAMP model with deficient Rb and Trp53 due to SV40 large T antigen expression leads to the formation of aggressive tumors with NE features (23). Aberrations in the Rb and p53 pathways are also observed in small cell lung cancer (43,44). The first comprehensive evaluation of the status of Rb, p53, and PTEN in human prostatic SCC showed that loss of Rb protein is a common event (90%) as revealed by a validated IHC assay. In contrast, only 7% of primary high-grade acinar carcinomas showed Rb protein loss. Moreover, loss of PTEN and accumulation of p53 were observed in 63% and 56% of SCC cases, respectively. Of the SCC cases for which copy number analysis or sequencing were available, 85% showed RB1 allelic loss and 60% had TP53 mutation (45). Another study reported that compared to CRPC adenocarcinoma, NEPC displayed a lower frequency of AR somatic alterations (12.8% versus 61.2%, $P<0.001$) and lower AR signaling (mean 0.21 versus 0.42, $P<0.001$), and a higher frequency of RB1 loss (76.6% versus 48.5%, $P=0.002$) and TP53 alterations (68.1% versus 50.5%, $P=0.066$). After adjustment for the presence of liver metastasis, co-occurrence of RB1 loss and TP53 alterations was significantly associated with worsening of OS from the time of NEPC diagnosis (11).

Recently, whole genome and transcriptome analyses of t-NEPC have been performed. The study demonstrated biallelic loss of RB1, elevated expression of CDKN2A and

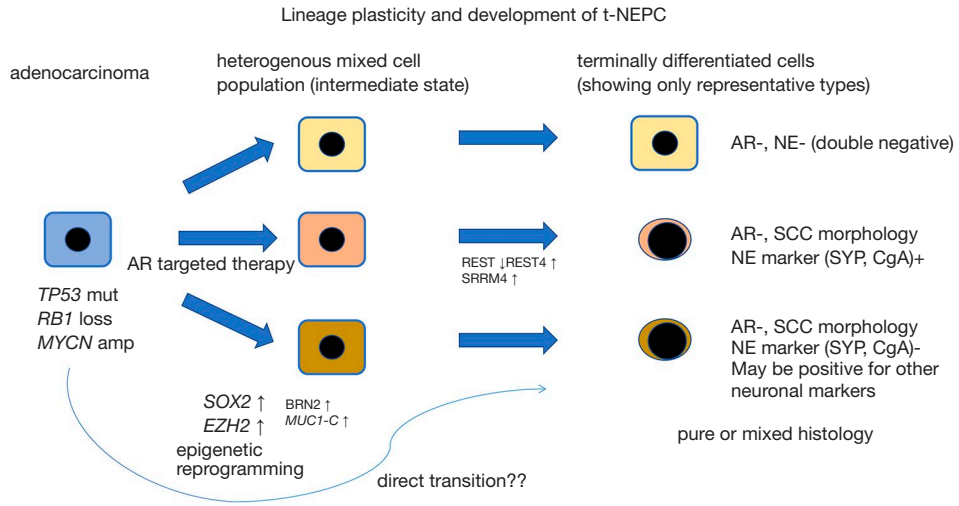

Figure 1 Lineage plasticity and development of t-NEPC.

E2F1, and loss of AR and AR-responsive gene expression to be hallmarks of t-NEPC. In addition, by serial analysis, the study identified spatial and temporal intra-patient heterogeneity, supporting the fact that the trans-differentiation of adenocarcinoma to NEPC is a disease state in continuum with each other rather than two discrete states. This implies the necessity for dual targeting of adenocarcinoma and NEPC in some cases of t-NEPC (46). Other genetic aberrations frequently seen in t-NEPC are MYCN and AURKA amplification (7); concurrent amplification of these genes was reported to be more frequent in primary tumors of patients who later developed t-NEPC compared to unselected cases, indicating its possible role as a predictive biomarker for the risk of progression to t-NEPC (15).

At the molecular level, there are multiple important research questions that need to be addressed. Fundamentally, it is important to note that there are two distinct aspects related to NEPC. NEPC is clinically characterized by: (I) expression of NE markers and (II) aggressive growth. Researchers need to recognize that these are independent features of NEPC, although there might be a shared starting point along the trans-differentiation process. For example, RE1-silencing transcription factor (REST) is known as a master regulator of NE markers (47), and alternative splicing of REST by serine/arginine-repetitive matrix 4 (SRRM4) to produce a variant that does not possess a transcriptional repressor domain (REST4) has been reported to promote the emergence of NEPC with CHGA and SYP expression (48,49). However, although LNCaP cells with REST knockdown express high levels of multiple NE genes, including CHGA and SYP, the cells do not acquire an aggressive phenotype (Akamatsu S, 2020, unpublished data). Therefore, the SRRM4-REST axis is less likely to be a direct therapeutic target for NEPC. By contrast, aggressive growth of NEPC seems to be a direct consequence of cell cycle progression caused by dysregulation of the p53 and Rb1 pathways. Concurrent aberration of these pathways leads to activation of E2F1 and subsequent upregulation of growth-promoting genes such as PEG10 (21). However, the expression pattern of NE genes varies between cases of NEPC; therefore, NE marker overexpression may not be a direct consequence of p53 and Rb1 pathway aberrations. Taken together, these recent findings indicate that epithelial plasticity driven by the cooperative effect of Rb1, p53, and PTEN, or N-Myc with subsequent overexpression of epigenetic factors EZH2 and SOX2, may result in heterogeneous populations of AR-indifferent intermediate cells, and additional alterations in pathways such as of the SRRM4-REST axis may result in terminal differentiation of these cells into NEPC. BRN2 is reported to affect the expression of both SOX2 and NE marker genes, thereby may coordinate the process of NEPC differentiation (50). Further genomic and molecular analyses of temporal changes that occur during the trans-differentiation process are needed to elucidate the critical targetable steps that lead to the development of t-NEPC (*Figure 1*).

Diagnostic challenge of t-NEPC in the clinical setting

Although t-NEPC is typically diagnosed by metastatic biopsy, the disease is heterogenous and precise characterization of each case to recommend best treatment option is quite challenging. An unbiased hierarchical clustering of RNA sequencing data for 119 metastatic CRPC biopsy, which included 21 t-NEPC, identified a cluster enriched with t-NEPC (8). Quite interestingly, the cluster included six of 14 pure t-NEPC, two of seven tumors with mixed histology, and four of 90 tumors with pure adenocarcinoma. RB1 loss signature score was higher in the cluster compared to the other cluster, and AR transcriptional score was lower. The cluster was enriched with genes transcriptionally regulated by E2F1, ASCL1, FOXA2, and POU3F2, all of which are implicated in NEPC. The data suggests that histology, transcriptional profiling patten, and clinical prognosis do not link one-to-one. The study also showed that when histology and transcriptome data were combined, there was a greater separation of survival curves than either histologic or genomic analysis alone.

Even though histology is still the golden standard of t-NEPC diagnosis, there are also studies trying to identify the disease by means of liquid biopsy. Recently, a CRPC-NE score was developed by combining genomic and epigenomic alterations in ctDNA, which was capable of identifying patients with NE-features (51). Since there is a large heterogeneity among t-NEPC, future studies are needed to identify which types of t-NEPC patients can be diagnosed by the technology. Ultimately, development of more detailed classification of t-NEPC, based not only on histology, that would lead to precise treatment stratification is needed.

Novel therapeutic targets and biomarkers for NEPC

Although no standard treatment exists for either de-novo NEPC or t-NEPC, platinum-based chemotherapy is often administered as a first-line treatment, due to its similarity with SCC of the lungs (52). Sometimes, platinum is combined with taxanes, since taxanes such as docetaxel and cabazitaxel are used as gold standard chemotherapy for CRPC (53,54). Although an initial response is observed in some cases, in general, the duration of the response is short (55). In a single center study of the 40 patients who developed t-NEPC, 3 were treated with platinum alone, 17 with platinum doublets (3 with taxane and 14 with etoposide), and 4 with docetaxel (11). Regardless of the combination treatments, the median progression free survival was less than 5 months. Exceptional response to platinum or PARP inhibitors has been reported for NEPC cases with BRCA1/2 defects (56-58). In a small series of de-novo and t-NEPC, although the rate of somatic DNA repair alteration (BRCA1/2, and ATM) was similar between de-novo and t-NEPC (3/47 *vs*. 4/40), there were more patients with germline DNA repair alterations among de-novo NEPC compared to t-NEPC (5/47 *vs*. 1/40) (11). Although larger studies are needed, identification of patients with DNA repair alterations may help in identifying a group of patients that would benefit from platinum-based therapy or PARP inhibitors.

Multiple molecular targets have been identified through recent genomic/molecular studies and warrant further investigation. Alisertib, an Aurora kinase A inhibitor, has been tested in a phase 2 clinical trial, based on data that AURKA and NMYC amplifications are common genomic alterations in NEPC. Although radiographic progression-free survival at 6 months was 13.4% and median OS was 9.5 months, there were exceptional responders in patients suggestive of N-myc and Aurora-A overactivity (59). The study highlights the diversity of NEPC and the importance of patient selection.

EZH2 is another potential target of t-NEPC. In preclinical NEPC models, treatment with EZH2 inhibitors reversed the NEPC phenotype and re-sensitized tumors to enzalutamide (27,34,60). Several early phase studies are ongoing to test the efficacy of EZH2 inhibitors, either as a single agent or in combination with AR-pathway inhibitors (NCT03460977, NCT03480646). Other major molecular targets of the available inhibitors that are shown to inhibit NEPC growth in preclinical models include BCL2 (61), Wee1 (61), LSD1 (62), and RET kinase (63), and future clinical trials are awaited. Other potential therapeutic targets include BRN2, MUC1-C (64), and PEG10, and research is underway to develop strategies for targeting these genes. Considering the heterogeneity of the disease, appropriate patient selection using companion diagnostics may be necessary to identify the vulnerabilities in each case and maximize therapeutic outcome.

Immunotherapy is also emerging as a potent therapeutic option for multiple cancer types. Immune checkpoint inhibitors have shown some efficacy in SCC of the lungs (65,66). However, in the context of immunotherapy, SCC of the lungs may be different from NEPC, since it is significantly associated with smoking; the efficacy of immune

checkpoint inhibitors in this setting might be affected by mutation patterns and mutation burden (67) related to smoking. Treatment with immune checkpoint inhibitors has been largely unsuccessful in prostate cancer (68), and prostate cancer is considered to have "immune-cold" microenvironment with low number of infiltrating T lymphocytes. EZH2 has been reported to synergize with immune checkpoint inhibitors to enhance the infiltration of $CD8^+$ T cells in tumor microenvironment (69). A clinical trial, which is testing a combination of EZH2 inhibitor with ipilimumab in patients with advanced solid tumors, is ongoing (NCT03525795). Thus, a combination of immune checkpoint inhibitors with agents such as EZH2 inhibitors may be an effective strategy to target some cases of NEPC.

Summary

Although a large part of NEPC biology still remains to be elucidated, recent advances in genomic and molecular research have identified some key features of NEPC. Pertinent research models are being developed that would help advance research in this field. Novel promising molecular targets have been identified, and multiple early phase clinical trials are ongoing. Ultimately, biomarker-driven selection of patients, who might benefit by being treated with these agents, will be critical for optimization of treatment strategies for patients with NEPC.

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