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Review

Promising therapy for neuroendocrine prostate cancer: current status and future directions

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Xin Fei, Jia-Wei Xue, Ji-zhongrong Wu, Chong-Yi Yang, Ke-Jie Wang and Qi Ma

Correspondence to:
Qi Ma
Department of Urology, the First Affiliated Hospital of Ningbo University, 52, Liuting Street, Haishu District,Ningbo, Zhejiang 315010, China

Comprehensive Genitourinary Cancer Center, The First Affiliated Hospital of Ningbo University, 52, Liuting Street, Haishu District, Ningbo, Zhejiang 315010, China

Yi-Huan Genitourinary Cancer Group, 52, Liuting Street, Haishu District, Ningbo,Zhejiang 315010, China
fyymaqi@nbu.edu.cn

Ke-Jie Wang
Comprehensive Genitourinary Cancer Center, The First Affiliated Hospital of Ningbo University, 52, Liuting Street, Haishu District, Ningbo, Zhejiang 315010, China
fyywangkejie@nbu.edu.cn

Chong-Yi Yang
Department of Urology, The First Hospital of Ninghai, 142 Taoyuan Middle Road, Yuelong Street, Ninghai county, Ningbo, Zhejiang 315699, China
yang_chongyi@163.com

Xin Fei
Health Science Center, Ningbo University, Ningbo, Zhejiang, China

Jia-Wei Xue
Health Science Center, Ningbo University, Ningbo, Zhejiang, China

Department of Urology, The First Hospital of Ninghai, Ningbo, China

Ji-Zhongrong Wu
Health Science Center, Ningbo University, Ningbo, Zhejiang, China

Department of Urology, Shengzhou People's Hospital, Shaoxing, China

***Abstract*:** Neuroendocrine prostate cancer (NEPC) is a highly aggressive variant of castration-resistant prostate cancer. It is characterized by low or no expression of the androgen receptor (AR), activation of AR-independent signaling, and increased neuroendocrine phenotype. Most of NEPC is induced by treatment of androgen deprivation therapy and androgen receptor pathway inhibitors (ARPIs). Currently, the treatment of NEPC follows the treatment strategy for small-cell lung cancer, lacking effective drugs and specific treatment options. This review summarizes potential novel targets and therapies for NEPC treatment, including epigenetic regulators (zeste homolog 2 inhibitors, lysine-specific demethylase 1 inhibitors), aurora kinase A inhibitors, poly-ADP-ribose polymerase inhibitors, delta-like ligand 3 targeted therapies, a combination of immunotherapies, etc. Other promising targets and future directions are also discussed in this review. These novel targets and therapies may provide new opportunities for the treatment of NEPC.

Plain language summary

This review summarizes potential novel targets and therapies for NEPC treatment, including epigenetic regulators (EZH2 inhibitors, LSD-1 inhibitors), AURKA inhibitors, PARP inhibitors, and DLL3 targeted therapies, and combination of immunotherapies, etc. These novel targets and therapies may provide new opportunities in the treatment of NEPC.

Keywords: uroendocrine prostate cancer, targeted therapy, immunotherapy, clinical trials, delta-like ligand 3

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Introduction

Prostate cancer is typically characterized by a strong overexpression of androgen receptors (AR) and prostate-specific antigen (PSA)[1] and its progression depends on the AR signaling axis. Androgen deprivation therapy (ADT) is currently the first-line treatment for metastatic prostate cancer.[2] However, within 2–3 years of ADT treatment, as resistance to ADT occurs, the tumor often progresses to metastatic castration-resistant prostate cancer (mCRPC).[3] In recent years, with the widespread use of second-generation androgen receptor pathway inhibitors (ARPIs), the treatment pressure on tumor cells has increased abruptly. However, due to the heterogeneity and lineage plasticity of prostate cancer, it may develop new treatment resistance to ARPIs. The prostate cancer cells may maintain or even accelerate growth[4,5] if resistance to ADT and ARPI treatment occurs.

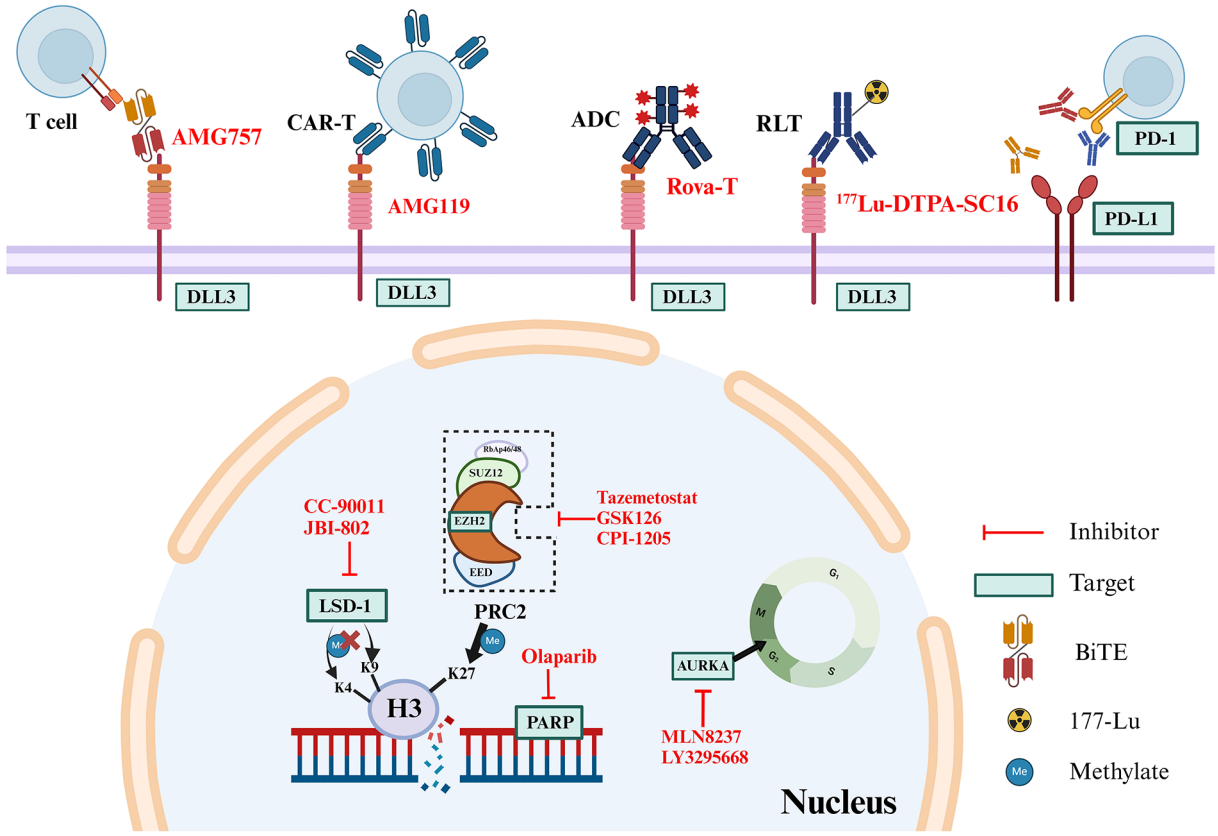

Figure 1. The main potential targets and drugs of NEPC.
Currently, the most studied targets in NEPC include DLL3, EZH2, LSD-1, AURKA, and PARP. Targeted these molecules may bring new treatment benefits to NEPC patients. PD1/PD-L1 may also have potential value in combination with this targeted therapy. Clinical trials are undergoing to prove these targets' value in NEPC patients. In the future, these new targeted therapies and their combinations with PD1/PD-L1 inhibitors may provide a promising strategy for treatment with NEPC.
AURKA, aurora kinase A; DLL3, delta-like ligand 3; EZH2, enhancer of zeste homolog 2; LSD-1, lysine-specific demethylase 1; NEPC, neuroendocrine prostate cancer; PARP, poly-ADP-ribose polymerase.

Neuroendocrine prostate cancer (NEPC) is one of the important reasons for mCRPC resistance to ADT and ARPIs treatment,[4] characterized by low or no expression of the AR and increased neuroendocrine phenotype. Clinically, NEPC can be classified into two types: de novo neuroendocrine prostate cancer (dn-NEPC) and treatment-induced neuroendocrine prostate cancer (t-NEPC). Dn-NEPC is relatively rare and accounts for less than 2% of newly diagnosed prostate cancer; and t-NEPC, which accounts for up to 17% of mCRPC, is an important mechanism for mCRPC to develop resistance to ADT and ARPIs.[5]

Due to the pathological characteristics of small cell/NEPC similar to those of small-cell lung cancer (SCLC), NEPC often follows the treatment strategy of SCLC, including etoposide combined with platinum-based chemotherapy and Programmed cell death 1 ligand 1 (PD-L1) antibody immunotherapy.[6]

In recent years, with further investigation into the pathogenesis of NEPC, some potential important targets involved in the NEPC progression have been identified.[7] These targets mainly focus on the following molecules which include (1) enhancer of zeste homolog 2 (EZH2), (2) lysine-specific demethylase 1 (LSD1), (3) aurora kinase A (AURKA), (4) poly-ADP-ribose polymerase (PARP), (5) delta-like ligand 3 (DLL3), etc. These targets may bring new opportunities in the treatment of NEPC. This article aims to review

these main potential targets (Figure 1) for targeted therapy of NEPC.

EZH2 inhibitors

Therapeutic mechanism of EZH2

EZH2 is the catalytic subunit of the Polycomb Repressive Complex 2, which has histone methyltransferase activity and can catalyze the methylation of the lysine residue at position 27 of histone H3 (H3K27) to regulate the expression of tumor-suppressor genes, playing an important role in epigenetic modifications.[8] Epigenetic modifications can promote the histopathological transformation of prostate adenocarcinoma to NEPC (or dedifferentiation).[9] Long et al.[10] have shown that the use of EZH2 inhibitors can reduce the invasiveness of CRPC cells, impede the progression of t-NEPC, and enhance the response of CRPC cells to enzalutamide. In addition, a close relationship between androgens and EZH2 in t-NEPC has been reported. Several studies revealed that ADT can activate the cAMP response element-binding protein (CREB)/EZH2 axis and promotes the neuroendocrine differentiation of prostate cancer.[11,12] Furthermore, EZH2 can collaborate with N-Myc to drive the transformation of prostate cancer to a neuroendocrine phenotype, providing the basis for targeted therapy against the aggressive subpopulation of mCRPC and NEPC driven by N-Myc in advanced prostate cancer.[13] EZH2 is one of the highest expressed genes in NEPC and may be a promising target for NEPC treatment.[14] Although clinical trials for NEPC have not been conducted, multiple EZH2 inhibitors have entered clinical trials for mCRPC treatment.

Advances of EZH2 inhibitors in the treatment of NEPC

Tazemetostat is the first FDA-approved oral EZH2 small molecule inhibitor for the treatment of epithelioid sarcoma or relapsed/refractory follicular lymphoma. It has achieved good results in several early clinical trials of mCRPC. The CELLO-1 study is a phase Ib/II trial of tazemetostat combined with enzalutamide or abiraterone/prednisone in treating mCRPC (NCT04179864), and the preliminary results were announced at the 2021 ESMO conference. No dose-limiting toxicity was observed in phase Ib, and the disease control rate (DCR) was 47%.

GSK126, another EZH2 inhibitor entering clinical trials, has been shown to inhibit PSA expression in CRPC and overcome enzalutamide resistance in mCRPC.[15] Compared to CRPC, EZH2 expression is higher in NEPC,[14] suggesting that EZH2 may have higher clinical applicability in NEPC. However, although GSK126 showed promising preclinical data, it has had little effect in clinical trials (NCT02082977).

CPI-1205 is an oral, small-molecule EZH2 inhibitor that selectively binds to EZH2. The ProSTAR study (NCT03480646) was designed to evaluate the efficacy of CPI-1205 in combination with enzalutamide or abiraterone/prednisone in treating mCRPC patients. Preliminary data suggest that patients' PSA decreased (>80%), solid tumors shrank, and circulating tumor cell count decreased. The combination showed good tolerability and safety.[16] In addition, novel EZH2 inhibitors SHR2554 (NCT03741712) and PF-06821497 (NCT03460977) are also under clinical trials.

LSD-1/lysine (K)-specific demethylase 1A inhibitors

Therapeutic mechanism of LSD-1/KDM1A

LSD1, also known as lysine (K)-specific demethylase 1A (KDM1A), is a histone demethylase that specifically removes mono- and dimethylation on lysine 4 (K4) and lysine 9 (K9) of histone H3. It plays a dynamic and reversible role in regulating histone methylation modifications[17] and is closely associated with the occurrence and development of tumors, playing an important role in the regulation of epigenetics. Studies have found that LSD1 is frequently overexpressed in NEPC patients and is associated with tumor proliferation.[18] It can be used as a new anticancer target, and its inhibitors are currently being tested in clinical trials and research. LSD1 is upregulated in many malignant tumors, particularly in invasive and poorly differentiated tumors. Kumaraswamy et al.[18] have found that LSD1 is frequently overexpressed in NEPC patients, and LSD1 promotes the development of NEPC by inhibiting TP53 signaling independently of its demethylase activity. In addition, LSD1 plays recognized roles in normal hematopoietic stem cells and neuronal stem cells.[19] Therefore, LSD1 can serve as a novel antitumor target, and its inhibitors have been tested in clinical trials.

Advances of LSD-1/KDM1A inhibitors in the treatment of NEPC

CC-90011 is the first reversible LSD1 inhibitor to enter clinical trials. In phase I, multicenter study CC-90011-ST-001 (NCT02875223), it was used to treat patients with non-Hodgkin's lymphoma and solid tumors (including two cases of NEPC), and preliminary results showed good tolerability and antitumor activity (clinical benefit rate 37% (95% confidence interval (CI), 16.3%–61.6%)).[20]

JBI-802 is another novel LSD1/HDAC6 dual-target inhibitor that was approved by the FDA in January 2023 for the treatment of SCLC.[21] Existing clinical studies show that compared with LSD1 or HDAC6 targeted inhibitors, JBI-802 has better tolerability and synergistic antitumor activity.[22] A phase I/II multicenter study (NCT05268666) is currently underway to evaluate the maximum tolerated dose, safety, adverse event rate, and overall response rate of JBI-802 in a population of patients with advanced solid tumors with neuroendocrine differentiation.

Bomedemstat, a non-reversible LSD1 inhibitor, is currently under clinical development for the treatment of hematological diseases such as primary thrombocytosis, as well as for malignancies and SCLC (NCT05191797). Bomedemstat also demonstrated significant activity against NEPC, independent of AR expression status in preclinical models,[23] indicating it may be a potential therapy for NEPC.

AURKA inhibitor

Therapeutic mechanism of AURKA

AURKA belongs to the serine/threonine kinase family and plays an important role in controlling the transition from phase G2 to phase M in the cell cycle. It is closely related to cell cycle regulation and tumorigenesis.[24] Second-generation RNA sequencing and oligonucleotide array analysis have revealed that AURKA and MYCN overexpression and gene amplification in 40% of NEPC patients, and their combined action can induce the development of the neuroendocrine phenotype in prostate cells.[25] Preclinical studies have also found that AURKA inhibitors can inhibit the conformational action between AURKA and MYCN, thereby inhibiting the expression of neuroendocrine signaling pathway-related markers and suppressing tumor growth.[26] Therefore, AURKA may become an important target for NEPC treatment.

Advances of AURKA inhibitors in the treatment of NEPC

Alisertib (MLN8237) is a reversible inhibitor of AURKA that can inhibit N-myc signaling and tumor growth by suppressing the interaction between N-myc and its stabilizing factor Aurora-A.[27] It was granted orphan drug certification by the US FDA for the treatment of SCLC in September 2023. NCT01799278 is a phase II open-label clinical trial designed to evaluate the efficacy and safety of Alisertib in NEPC patients. Although the study did not meet its primary endpoint, results showed significant clinical benefits from Alisertib treatment in some advanced prostate cancer patients and patients with molecular features supporting activation of Aurora-A and N-myc.[27]

AK1 (LY3295668) is another highly selective AURKA inhibitor with higher specificity and fewer side effects. AK1 has "synthetic lethality" effects on RB1-deficient tumors.[28] In a phase I/II open-label multicenter study for RB1-deficient cancer patients (NCT03092934), AK1 showed good antitumor activity and safety.[29] Highly selective AURKA inhibitors have become a hot topic in new drug development and clinical research, with the potential to play a role in treating NEPC.

PARP inhibitors

Therapeutic mechanism of PARP

PARP is a DNA repair enzyme that is involved in the process of single-strand DNA repair.[30] Studies have found that PARP is significantly upregulated in prostate cancer compared to normal tissue and is positively correlated with the Gleason score of tumors.[31] PARP inhibitors can inhibit DNA damage response pathways and induce tumor cell apoptosis.[32] A novel MYCN-PARP-DNA damage response pathway has been identified, which is closely associated with the differentiation of NEPC.[33] By inhibiting PARP, the expression of genes in this pathway and neuroendocrine markers can be significantly reduced.[33] Liu et al.[34]

found that PARP inhibitors can block the development of NEPC by inhibiting the GR-MYCN-CDK5-RB1-E2F1 signaling pathway.

Advances of PARP inhibitors in the treatment of NEPC

The "synthetic lethal" effect of PARP inhibitors has been a hot research topic in cancer treatment. Inhibition of PARP can lead to the accumulation of DNA damage, especially in cancer cells that already have homologous recombination repair (HRR) defects (including *BRCA1* or *BRCA2* gene mutations).[35] In NEPC, mutations or dysfunction of HRR genes are more common than in common prostate cancer.[27] Recently, multiple phase III studies have investigated the use of PARP inhibitors in combination with ARPIs for treating mCRPC patients with HRR-related gene changes,[36,37] and have shown significant benefits. Galahad (NCT02854436) is a phase II study evaluating the efficacy and safety of niraparib in mCRPC patients with DNA repair abnormalities. The study included 289 patients, of whom 142 had BRCA mutations. It demonstrated good antitumor activity and manageable safety in patients with treatment-refractory mCRPC and BRCA mutations. Unfortunately, this trial did not include pure small-cell phenotype prostate cancer. Alshalalfa et al.[38] found that NEPC patients had a higher response to PARP inhibitors through in vitro drug sensitivity analysis. This research may provide a new option for the treatment of NEPC. A randomized phase II study (NCT03263650) is also currently underway to assess the efficacy of Olaparib (a PARP inhibitor) maintenance therapy after carboplatin/cabazitaxel induction chemotherapy in patients with aggressive variant prostate cancer (including NEPC). However, there are currently few clinical trials targeting PARP therapy for NEPC patients, and the above data still require further research and clinical validation.

Targeted DLL3 therapy

Therapeutic mechanism of DLL3

DLL3 is a non-typical Notch inhibitory ligand attached to the cell surface, which is closely related to the occurrence and differentiation of NEPC[39] and is a very attractive therapeutic target for NEPC. Studies have found that DLL3 is overexpressed in NEPC cells, while it is expressed at a low level in low-grade prostate cancer.[40] DLL3 is a promising therapeutic target for NEPC with a broad therapeutic prospect.

DLL3 targeted bispecific/tri-specific antibody therapy

Tarlatamab (AMG 757) is a bispecific antibody prepared based on the next generation of bispecific T-cell engager (HLE BiTE®) technology. Its mechanism of action is to target DLL3 and the CD3 molecule on the surface of T cells.[41] By recognizing and connecting CD3 (expressed on T-cell membranes) and DLL3 (expressed on neuroendocrine tumor (NET) cell membranes), it promotes T-cell recognition of NET cells and activates T-cell-mediated tumor lysis. AMG 757 has shown excellent antitumor activity in the treatment of SCLC, and the results of the DeLLphi-301 study (NCT05060016) were first presented at ESMO 2023, with objective response rates (ORRs) of 40% and 32% for the 10 and 100 mg groups, respectively, showing good antitumor activity.[42] On May 16, 2024, FDA-approved Tarlatamab for the treatment of extensive-stage small-cell lung cancer (ES-SCLC) who have disease progression during or after platinum-based chemotherapy. AMG 757 has also demonstrated antitumor activity in NEPC patient-derived xenograft models.[43] A phase I clinical trial of AMG757 (NCT04702737) for NEPC is currently underway, and preliminary results have shown its antitumor activity against metastatic NEPC with a dose-dependent trend. This trial provides further support for the use of Tarlatamab in NEPC.

BI-76453, another DLL3/CD3 IgG-like T-cell engager (TcE), was granted accelerated approval by the FDA on October 3, 2023, due to its potent efficacy and manageable toxic side effects. It is indicated for the treatment of advanced SCLC patients and advanced or metastatic extrapulmonary neuroendocrine carcinoma (NEC) patients. BI-76453 holds great potential in the treatment of NEC. NCT04429087 is an ongoing phase I clinical trial aimed at treating patients with locally advanced/metastatic DLL3-positive SCLC, NEC, or large-cell neuroendocrine carcinoma (LCNEC). Preliminary efficacy data for extrapulmonary neuroendocrine cancer were first reported at the ESMO Congress 2023, demonstrating

encouraging treatment effects. The trial reported an ORR of 36% and a DCR of 57%[44] among patients with urogenital tumors, which may offer a new direction for targeted therapy in NEPC.

PT217 is a bispecific antibody targeting DLL3 and CD47, which has been granted orphan drug status by the FDA in 2022 for the treatment of SCLC. NCT05652686 is an ongoing phase I multicenter clinical trial that aims to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of PT217 in patients with advanced or refractory cancers (including NEPC), which provides a new potential option for NEPC patients.

HPN328 is a trispecific T-cell-activating construct targeting DLL3, CD3, and ALB (albumin) with a long half-life in circulation. In an ongoing phase I/IIa study (NCT04471727) in patients with NEPC and other NETs, the treatment with this drug has shown preliminary efficacy,[45] and demonstrated good tolerability and clinical activity at the ASCO GU 2024.[46] In addition, the NCT04429087 study is testing different doses of BI 764532 in patients with SCLC and other DLL3-positive NETs. Preliminary data presented at the ASCO Meeting 2023 showed an ORR of 33% and 22% in evaluable SCLC and NET patients, respectively.[47] These studies have provided a good foundation for the treatment of DLL3-positive NETs, including NEPC, in the future.

DLL3 targeted antibody–drug conjugate therapy

Rova-T is the first targeted DLL3 targeted antibody–drug conjugate (ADC). In phase I clinical trial, researchers administered Rova-T at a dose of 3 mg/kg intravenously to a DLL3-positive mNEPC patient every 6 weeks until disease progression was observed. The results showed that the maximum diameter of the patient's metastatic lymph nodes decreased from 42 to 24 mm, other metastatic lesions showed complete or partial responses (PRs) after the treatment cycle, and there was no new progression of the disease after two cycles of medication.[40] This provides a new approach for the treatment of NEPC with DLL3-targeted ADC therapy. Unfortunately, the phase III clinical trial of Rova-T in recurrent SCLC (NCT01901653) failed and has been suspended.

YL212 is a new generation of DLL3-targeted ADC, which differs from Rova-T in that it has both extracellular and intracellular cleavage mechanisms and has made improvements in overcoming drug toxicity. Encouraging data has been shown in preclinical experiments, and the clinical application is currently underway, to enter the clinical research stage in the first quarter of 2024.[48]

DLL3-targeted CAR-T therapy

CAR-T-cell therapy, a novel precision-targeted treatment for tumors, is still in the research stage and may be a promising strategy for NEPC.[49] In a phase I trial targeting prostate-specific membrane antigen (PSMA)-directed CAR-T cells for mCRPC (NCT03089203), one patient had a reduction in PSA levels of over 98%, and three patients had PSA reductions of over 30%.[50] Another ongoing trial aims to combine PSMA-directed CAR-T-cell therapy with a PD-1 inhibitor for treating mCRPC (NCT04768608), opening a new treatment paradigm for CAR-T-cell therapy as an alternative treatment option for prostate cancer. These studies prompted the attempt for the application of CAR-T-cell therapy targeting DLL3 in NEPC. Jaspers et al.[51] have developed a CAR-T cell targeting DLL3, which has shown promising antitumor activity in xenograft models and mouse SCLC models, and exhibits significant synergy when combined with PD-1 inhibitors.

AMG119 is the first targeted DLL3 CAR-T-cell therapy for the treatment of relapsed/refractory SCLC patients and is currently ongoing (NCT03392064). Another DLL3-targeting CAR-T, LB2102, is being evaluated in a phase I trial (NCT05680922) for the treatment of ES-SCLC and has also received FDA approval.[52] Preclinical in vivo studies of this therapy have shown that it can effectively shrink tumors compared to traditional CAR-T therapies.

DLL3-targeted radio-ligand therapy

^{177}Lu-DTPA-SC16 is a DLL3-targeting antibody SC16 labeled with Lutetium-177 (^{177}Lu), which can be used for radio-ligand therapy (RLT) and has shown therapeutic activity in NEPC. In a xenograft model of NEPC in mice, ^{177}Lu-DTPA-SC16 demonstrated antitumor efficacy in H660 (NEPC, DLL3 positive) mice, even curing five out of eight mice (63%) at the lowest dose.[53] Another study also pointed out that ^{177}Lu-DTPA-SC16 has low-toxicity antitumor effects.[54] Although ^{177}Lu-DTPA-SC16 has not

yet been tested in humans, it may become a new treatment option for NEPC.

Combination targeted and PD1/PD-L1 inhibitors in NEPC

Immunotherapy is a novel approach that aims to activate the patient's immune system to attack and eliminate tumor cells, thereby achieving the goal of tumor treatment. Unlike targeted therapies that often exhibit drug resistance, immunotherapy, although slower to take effect, can provide long-term benefits to patients, and even a small subset of patients may achieve long-term survival or even be cured. Currently, tumor immunotherapy is mainly divided into cellular immunotherapy and immune checkpoint inhibitor therapy. Advanced prostate cancer was the first solid tumor to achieve a breakthrough in immunotherapy, with the approval of the Sipuleucel-T vaccine for the treatment of advanced CRPC in 2005. However, in recent years, with the development of immunotherapy, immune checkpoint inhibitors such as PD-1/PD-L1 monoclonal antibodies have made breakthroughs in multiple types of cancers but have shown limited success in advanced prostate cancer. Therefore, combination targeted and PD-1/PD-L1 inhibitors have been the focus of clinical studies in the field of advanced prostate cancer immunotherapy. As potential cellular immunotherapy strategies in the treatment of NEPC have been discussed in the part of targeted DLL3 therapy in this manuscript, here we just introduce the application of PD-1/PD-L1 inhibitors in the treatment of NEPC.

In 2019, the NCCN guidelines for SCLC first included atezolizumab/durvalumab (PD-1/PD-L1 inhibitors) in the EP (carboplatin + etoposide) regimen as a category 1 recommendation and preferred first-line treatment option for ES-SCLC, showing potential application of PD-1/PD-L1 inhibitors in the treatment of NEPC. Bhinder et al.[55] evaluated the tumor immune landscape of NEPC in comparison to other types of prostate cancer and SCLC and found that NEPC had the weakest immune response, with higher expression of PD-L1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). This study may provide a clue for future immunotherapy strategies in NEPC.

Currently, there are relatively limited studies in combination of targeted and PD-1/PD-L1 inhibitors for the treatment of NEPC, and this article provides future prospects for this combination.

EZH2 and LSD1 have emerged as promising targets in the field of epigenetic anticancer research. Chen et al.[56] proposed that the combination of epigenetic modifications with PD-L1/PD-1 inhibitors could produce a synergistic effect. This combination therapy can repair damage to the immune cycle through epigenetic modifications, including reprogramming the tumor-immune environment, triggering immune responses by enhancing tumor antigen presentation and regulating T-cell migration and reactivation.[56] EZH2 is a major driver of immune editing in cancer cells and an immune escape regulator.[57]

Morel et al.[58] found that simultaneous use of EZH2 and PD-1 inhibitors yielded significant therapeutic efficacy in a transgenic tissue transplantation mouse model, suggesting that inhibition of EZH2 can enhance the response of prostate cancer to PD-1 checkpoint blockade. Therefore, future clinical trials of EZH2 inhibitors in combination with anti-PD-1 antibodies for NEPC treatment may be considered. In addition to combination therapy with anti-PD-1 treatment, Goswami et al.[59] found that inhibiting EZH2 expression can improve the efficacy of anti-CTLA-4 therapy, providing strong evidence for the combination trial of CPI-1205 and ipilimumab.

Moreover, Sheng et al.[60] found that targeted knockdown of LSD1 in a melanoma mouse model could promote T-cell immunity and increase the sensitivity of tumors to PD-1 inhibitors. TCGA data analysis showed a negative correlation between LSD1 expression and CD8+ T-cell infiltration in different human cancers.[60] Liu et al.[61] also found that LSD1 inhibition can sustain T-cell vitality, leading to a more durable response to PD-1 inhibitors. Qiu et al.[62] found that both LSD1 inhibitors used alone or in combination with PD-1 blockade exhibited enhanced antitumor effects in mouse models, further supporting this concept. Thus, targeting LSD1 in combination with anti-PD-1/PD-L1 antibodies might also be a new therapeutic strategy for NEPC.

In terms of the combined use of AURKA inhibitors and PD-1/PD-L1 inhibitors, studies have shown that the combination can significantly improve the antitumor effect of alisertib. Wang

et al.[63] found that inhibiting AURKA can promote better infiltration of effective T cells into the tumor microenvironment, thereby enhancing the efficacy of anti-PD-1 therapy in preclinical models. However, Wang et al.[64] found that Alisertib might increase the expression of PD-L1 in tumor cells and promote immune evasion and resistance, which could weaken the antitumor effect of Alisertib. These findings provide new clinical insights for the future use of Alisertib in NEPC treatment.

Regarding the combination of PARP inhibitors and PD1/PD-L1 inhibitors, preclinical studies have shown a synergistic effect when used in combination, but the clinical benefits seem limited, as reported by Yap et al.[65] NCT0459237 is an ongoing phase II clinical trial that aims to assess the efficacy and safety of combining Niraparib with or without Cetrelimab for the treatment of aggressive variant metastatic prostate cancer. We are looking forward to the results of this study to know its therapeutic efficacy and safety in aggressive variant metastatic prostate cancer, including NEPC.

In terms of the combination of DLL3-targeted therapy and PD1/PD-L1 inhibitors, Shirasawa et al.[66] observed that patients with high DLL3 expression showed poorer progression-free survival (PFS) when treated with a PD-L1 inhibitor, which may be related to immune resistance caused by tumor immune suppression. However, Chen et al.[67] found in a preclinical mouse model that the combination of a bispecific antibody to DLL3 and a PD-1 inhibitor significantly improved the efficacy of DLL3-targeted therapy. Thus, combining DLL3-targeted therapy and PD1/PD-L1 inhibitors may provide a new treatment strategy for NEPC. 2028TiP is an ongoing phase I trial designed to evaluate the efficacy of BI 764532 in combination with ezabenlimab (a PD-1 inhibitor) in patients with SCLC and other NECs expressing DLL3, and we are currently recruiting participants.

Radionuclide therapy

NEPC lacks expression of PSMA.[26] However, many studies have found that NEPC shows high radioactive uptake in SSTR (Somatostatin Receptor)-targeted PET.[68] High-affinity SSTR ligands, including TOC, NOC, and TATE, can be used for targeted treatment of NETs. Furthermore, peptide receptor radioisotope therapy with 90Y-DOTA-TOC and 177Lu-DOTA-TATE has been shown to improve the therapeutic efficacy of NETs.[69]

Zhao et al.[70] found that in prostate adenocarcinomas and small-cell neuroendocrine cancers with low levels of PSMA expression, the expression of CDCP1 is increased. They used 4A06 to quantify the number of CDCP1 receptors in each cell. The study showed that radioactive ligand therapy with 177Lu-4A06 can inhibit the tumor growth of NEPC. Therefore, combining CDCP1-targeted RLT with the standard treatment for mCRPC may be a more effective clinical treatment strategy.

NEPC Study (NCT06379217) is a phase I, open-label, multicenter exploratory safety and efficacy study for NEPC patients, that uses PSMA, Somatostatin Receptor 2 (SSTR2), and gonadotropin-releasing hormone receptor-targeted radiological ligand therapy. This is the first clinical trial to explore the efficacy of radioactive nuclides in NEPC and is expected to start enrolling patients in June 2024.

Other potential targets and future directions

Currently, research on potential targets for NEPC is still ongoing. More potential targets include CXCR2, Glypican-3 (GPC3), KIT, etc., which aim to overcome treatment resistance in NEPC. In addition, B7-H3 ADC, DNA/RNA synthesis inhibitors, and other potential drugs are also under investigation.

CXCR2 is a G protein-coupled receptor that binds to IL-8, regulating the autocrine mechanism of differentiation or function of neuroendocrine cells.[71] Studies have shown that CXCR2 is a driving factor in neuroendocrine phenotype, associated with loss of AR expression, lineage plasticity, and resistance to hormone therapy.[72] Inhibiting CXCR2 can suppress neuroendocrine differentiation in CRPC. However, targeting CXCR2 may pose a risk of neutropenia as CXCR2 is highly expressed in circulating neutrophils.[73]

GPC3 is a heparan sulfate proteoglycan that binds to the cell membrane through glycosylphosphatidylinositol. It is expressed only during embryonic development and is almost absent in adult tissues. GPC3 is an emerging target in liver cancer therapy, showing minimal toxicity in clinical trials. Butler et al.[74] have found that GPC3 is

specifically expressed in neuroendocrine cells, crucial for the vitality of NET cells and tumors displaying neuroendocrine differentiation. Due to its tumor specificity, GPC3 may become a new potential therapeutic target for treating NEPC. Currently, GPC3 targeting is in phase II clinical trials globally, and there are expectations for its application in prostate cancer.

KIT is a transmembrane type III receptor tyrosine kinase involved in multiple signaling pathways, and its dysregulation can lead to tumor formation. Several KIT inhibitors have been approved by the FDA, including imatinib, sorafenib, and sunitinib, etc. Although imatinib had not shown ideal results in the clinical trial for treating prostate cancer (NCT00500110),[75] these trials had not specifically evaluated its effects in patients with high KIT expression and NEPC features. Han et al.[76] found that imatinib showed significant therapeutic effects on NEPC tumors, and through in vitro and in vivo experiments, they found that inhibiting KIT signaling effectively suppressed the growth of both mouse and human NECs. In addition, FOXA2 has been found to play a crucial role in the progression of NECs, with downregulation of FOXA2 reversing the transition from adenocarcinoma to neuroendocrine lineage.[76] In conclusion, FOXA2 drives the lineage plasticity of NEPC and activates the KIT pathway. These findings suggest that inhibiting KIT signaling could be a potential therapeutic target for NEPC and offer possibilities for treatment and insights into the development of NEPC.

DNA/RNA synthesis inhibitors such as lurbinectedin were approved by the FDA in June 2020 for second-line treatment of SCLC patients. Apart from SCLC, lurbinectedin has also been included in clinical trials for NETs. Although only 2 out of 31 evaluable patients showed PRs (ORR = 6.5%; 95% CI, 0.8%–21.4%),[77] lurbinectedin still demonstrated acceptable, predictable, and controllable safety.[77] The EMERGE-201 trial (NCT05126433) is a phase II, multicenter, open-label study evaluating the efficacy and safety of lurbinectedin in patients with advanced or metastatic solid tumors, including a group of NEC patients, to determine whether this subgroup of NETs shows a response rate and disease control more similar to SCLC. The trial was preliminarily completed in December 2023, and the results are eagerly awaited.

B7-H3 (also known as CD276) is a member of the B7 family of immune regulatory proteins and is a major target in SCLC. Ifinatamab deruxtecan (I-DXd; DS-7300) is a novel ADC that consists of an anti-B7-H3 antibody linked with DNA topoisomerase I inhibiting antitumor agent, DXd. In an I/II phase study presented at the 2023 WCLC (OA05.05), the data of I-DXd treatment for solid tumors, including SCLC, were discussed. In the dose escalation portion of this phase I/II study, among 21 advanced SCLC patients, a confirmed ORR of 52.4% (95% CI: 29.8–74.3) was reported. One patient achieved complete response (CR) and 10 patients achieved PR. The observed median duration of response was 5.9 months (95% CI: 2.8–7.5). As of January 31, 2023, the median PFS was 5.6 months (95% CI: 3.9–8.1) and the median overall survival was 12.2 months (95% CI: 6.4–NA). These data indicate high response rates of I-DXd in SCLC patients. Several B7-H3 targeted therapies are currently in early clinical stages, such as the EGFR/B7H3 bispecific ADC IBI3001 (NCT06349408). Although there are currently no approved drugs targeting B7-H3 globally, B7-H3 ADC treatment has shown promising potential in SCLC. In mCRPC and NEPC, B7-H3 ADC is also being explored. Yamada et al.[78] have demonstrated potent single-agent antitumor activity of I-DXd in mCRPC and NEPC, suggesting that B7-H3 may be a potential target in NEPC. Currently, there are relatively few clinical trials of B7-H3 inhibitors in NEPC, but studies have been conducted in mCRPC. NCT05293496 is an ongoing phase I/Ib dose escalation and cohort expansion study evaluating the combination of MGC018 (an Anti-B7-H3 ADC) and checkpoint inhibitors in advanced solid tumors. This clinical trial is expected to have preliminary results released by early 2026.

Conclusion

NEPC, as a highly invasive subtype of CRPC, currently lacks standard treatment options. New targeted therapies such as EZH2 inhibitors, LSD-1 inhibitors, AURKA inhibitors, PARP inhibitors, and especially targeted therapies against DLL3 have shown potential benefits. Clinical trials are currently evaluating their efficacy in NEPC, as shown in Tables 1 and 2. In addition, although the efficacy of PD-1/PD-L1 inhibitors has limited effects in treatment with

Table 1. Clinical trials of EZH2, LSD-1, AURKA, and PARP target hematologic malignancies, solid tumors, and NEPC.

Target	Drug	Trial number	Trial phase	Trial status	Maximum trial phase	Ongoing indications
EZH2	Tazemetostat	NCT04179864	phase I/II	Active, not recruiting	FDA approval	FL, solid tumors, etc.
	GSK126	NCT02082977	phase I	Terminated	Terminated (phase I)	/
	CPI-1205	NCT03480646	phase I/II	Unknown status	Terminated (phase II)	/
	SHR2554	NCT03741712	phase I/II	Terminated	phase III	Lymphoma, mCRPC, etc.
	PF-06821497	NCT03460977	phase I	Recruiting	phase II	mCRPC, SCLC, etc.
LSD-1/KDM1A	CC-90011	NCT02875223	phase I	Active, not recruiting	phase II	AML, HSPC, etc.
	JBI-802	NCT05268666	phase I/II	Recruiting	phase I/II	Solid tumors, SCLC, NET, etc.
AURKA	Alisertib (MLN8237)	NCT01799278	phase II	Completed	phase III	ALCL, solid tumors, etc.
	AK1 (LY3295668)	NCT03092934	phase I/II	Completed	phase I/II	NSCLC, neuroblastoma, SCLC, etc.
PARP	Olaparib	NCT03263650	phase II	Active, not recruiting	FDA approval	mCRPC, BRCA-mutated mCRPC, etc.

ALCL, anaplastic large-cell lymphoma; AML, acute myeloid leukemia; AURKA, aurora kinase A; BRCA, breast cancer susceptibility gene; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; HSPC, hormone-sensitive prostate cancer; LSD1, lysine-specific demethylase 1; mCRPC, metastatic castration-resistant prostate cancer; NET, neuroendocrine tumor; NEPC, neuroendocrine prostate cancer; NSCLC, non-small-cell lung cancer; PARP, poly-ADP-ribose polymerase; SCLC, small-cell lung cancer.

Table 2. DLL3 targeting in neuroendocrine tumors and NEPC-related clinical trials.

Target	Drug	Trial number	Trial phase	Trial status	Maximum trial phase	Ongoing indications
DLL3/CD3	Tarlatamab (AMG 757)	NCT05060016	phase II	Active, not recruiting	FDA approval	SCLC, NEPC, etc.
		NCT04702737	phase I	Active, not recruiting		
	BI-76453	NCT04429087	phase I	Recruiting	phase II	NET, SCLC, etc.
DLL3/CD47	PT217	NCT05652686	phase I	Recruiting	phase I	GEP-NETs, LCNEC, NEPC, etc.
DLL3/CD3/ALB	HPN328	NCT04471727	phase I/II	Recruiting	phase I/II	SCLC
		NCT04429087	phase I	Recruiting		
DLL3 + ADC	Rova-T	NCT01901653	phase I/II	Completed	Terminated (phase III)	GBM, PCa, SCLC, etc.
	YL212	/	/	/	Clinical application	Lung cancer
DLL3 + CAR-T	AMG119	NCT03392064	phase I	Suspended	Terminated (phase I)	/
	LB2102	NCT05680922	phase I	Recruiting	phase I	ES-SCLC, LCNC

ES-SCLC, extensive stage small-cell lung cancer; GBM, glioblastoma; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; LCNC, large-cell non-small lung cancer; LCNEC, large-cell neuroendocrine carcinoma; NEPC, neuroendocrine prostate cancer; NET, neuroendocrine tumor; PCa, prostate cancer; SCLC, small-cell lung cancer.

NEPC,[79] there might be some benefits in combination with targeted therapy.

With the widespread use of second-generation ARPIs in clinical practice in recent years, it is expected that the incidence of NEPC may quickly increase in the next few years. New targeted therapies and their combinations with PD1/PD-L1 inhibitors may provide a promising strategy to overcome this highly aggressive malignant tumor in the future.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agreed on the publication.

Author contributions

Xin Fei: Writing – original draft; Writing – review & editing.

Jia-Wei Xue: Writing – review & editing.

Ji-Zhongrong Wu: Writing – review & editing.

Chong-Yi Yang: Writing – review & editing.

Ke-Jie Wang: Writing – review & editing.

Qi Ma: Writing – original draft; Writing – review & editing.

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ORCID iD

Qi Ma https://orcid.org/0000-0002-5350-0362

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