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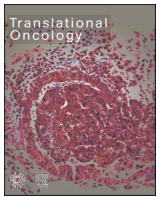

# Nuclear protein in testis carcinoma of the lung

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ABSTRACT

Nuclear protein in testis (NUT) carcinoma is a kind of highly aggressive and fatal solid tumor characterized by a rearrangement of the NUT carcinoma family member 1 (NUTM1) gene located on chromosome 15 q l4, where the most common form of fusion is BRD4-NUT. NUT carcinoma occurred in different organs and was most commonly found in the midline organs and the lungs. NUT carcinoma can occur in patients of almost all ages, having a roughly consistent incidence in both sexes. Most of the patients were diagnosed in advanced stages with an extremely poor prognosis due to the lack of effective treatment. After years of research, the mechanism of NUT carcinoma is still not fully clear, and its therapeutic approaches need to be further studied and explored. In order to gain a more comprehensive understanding of NUT carcinoma and explore the effective treatments, this review aimed to summarize the clinical features, pathological characteristics, differential diagnosis, and treatment strategies for this disease.

## Introduction

Nuclear protein in testis (NUT) carcinoma is a kind of rare cancer characterized by chromosomal rearrangements involving the NUT gene located on chromosome 15 [1]. NUT gene commonly fuses with BRD4 to form the BRD4-NUT oncogene [2]. The tumor was first described in two separate case reports in 1991, both characterized by the t (15;19) translocation [3,4]. As it was once considered inseparable from the midline structure, it was called "NUT midline carcinoma". However, due to successive case reports describing the detection of "NUT midline carcinoma" in structures or organs other than the midline (e.g., Mertens et al. [5] reported a case of NUT carcinoma occurring in the iliac bone in 2007; Ziai et al. [6] reported a case of a NUT-associated salivary gland carcinoma in 2010; Shehata et al. [7] reported a case of NUT carcinoma occurring in the pancreas/liver in 2010), the World Health Organization (WHO) changed its name from "NUT midline carcinoma" to "NUT carcinoma" [8] listing it as a new disease in 2015, while retaining the term "NUT midline carcinoma". More cases have been reported since 1991, and tumors carrying the NUT carcinoma family member 1 (NUTM1) gene translocations have become increasingly recognized. There are not many cases of pulmonary NUT carcinoma till now. The clinical presentation of pulmonary NUT carcinoma is not specific with little relation to smoking, although the average age of patients is younger than patients with other lung tumors. Referring to a large number of literatures, we reviewed the clinicopathological features, diagnostic methods and related treatments of patients with NUT carcinoma of the lung.

## Pathogenesis and genetics

NUT carcinoma is defined by NUTM1 rearrangements, and approximately 75%cases harbored BRD4-NUTM1 fusion resulting from t (15;19) (q14; p13.1) [2]. The remaining cases presented with BRD3-NUTM1 fusion [9], NSD3-NUTM1 fusion [10], ZNF532-NUTM1 fusion [11–13], ZNF592-NUTM1 fusion [14], CIC-NUTM1 fusion [15], MGA-NUTM1 fusion [16,17], or NUTM1 fusion with unknown partner genes. In normal cells, the expression of NUTM1 was restricted to post-meiotic spermatogenic cells, where the histone acetyltransferase p300 was attracted and activated [18,19]. And BET proteins combine

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with transcriptionally active chromatin through associations of one of their bromodomains to acetylated lysine residues of histones, affecting cell cycle progression and cellular proliferation [20]. In tumor cells, the BRD4-NUTM1 fusion protein is still bound to chromatin and attracts p300/creb-binding protein (CBP) histone acetyltransferases to form BRD4-NUT/acetyl-histone/p300-enriched regions. MYC, TP63, and SOX2 all encode transcription factors associated with cancer pathogenesis [21]. The large regions (> 1.5 Mb) correspond to large mega domains of highly acetylated chromatin and act as massive super-enhancers to drive the expression of these several genes, leading to cell proliferation and blockade of cell differentiation [22–24].

## Clinical characteristics

NUT carcinoma is a rare, poorly differentiated, highly aggressive malignant epithelial cell tumor with low overall survival (OS). Giridhar et al. [25] systematically reviewed 119 patients who were reported between 1950 and July 1, 2017, showing that the most common lesion was the lung (42 cases/35.3%), followed by the head and neck (40 cases/33.6%). Other rare primary lesions located in the bladder, eyeball, breast, brain, kidneys, stomach, soft tissues, bones, salivary glands, and pancreas/liver [5-7,26,27]. Initially, NUT carcinoma was thought to occur more commonly in children and young adults, but recent studies revealed that the tumor could occur at almost any age [28], with nearly the same incidence in both men and women [25]. And pulmonary NUT carcinoma mainly occurred in young and middle-aged men with no history of smoking (2:1), and the male-to-female ratio was about 1.89 to 1 [29]. He et al. [30] summarized 20 pulmonary NUT carcinoma patients aged 12 - 68 years old at the time of the diagnosis (the average age and the median age were 33 and 29.5 years old, respectively), 11 of whom were males and 9 were females. Out of the 20 patients with pulmonary NUT carcinoma, 17 were with a detailed clinical history, where the main clinical manifestations included cough (76%), while other symptoms include wheezing (35%), chest tightness (35%), dyspnea (35%), chest pain (35%), shoulder pain (35%), low back pain (35%), hemoptysis or sputum with blood (29%), fever (18%). Table 1 [31–39] shows 23 pulmonary NUT carcinoma cases, 15 men and 8 women whose age at diagnosis was 7 - 74 years, the average age was 37 years, and the median age was 30 years. The clinical manifestations of pulmonary NC in these 23 patients were similar to those reported by HE *et al.*, and the most important clinical manifestation was cough. Some patients were even asymptomatic and were detected solely on routine physical examination [40]. He et al. [30] argued that the onset of the disease is insidious and pulmonary NUT carcinoma has no specific symptoms, while the systemic symptoms are atypical, with no obvious relationship with the history of smoking, while the condition develops rapidly and progresses dangerously. Among the 23 patients with pulmonary NUT carcinoma, 2 were unknown to smoke or not, 7 had smoked for a long time, and 14 had smoked occasionally or never. The result showed that OS could be long or short no matter whether the patient smoked or not, and it is consistent with the previous premise [30] that the disease has no significant relationship with smoking history. In conclusion, the non-specific clinical manifestations of pulmonary NUT carcinoma are difficult to distinguish from other lung diseases in the early stage and are easy to misdiagnose.

## Pathology and molecular characteristics

The origin of tissues in NUT carcinoma is still in controversial till now. French [26] initially argued that NUT carcinoma originated from the early epithelial precursor cell nest, after which it was believed that NUT carcinoma might come from primitive neural crest-derived cells [41]. Den et al. [42] speculated that pluripotent stem cells are the origin of NUT carcinoma cells. Focal squamous differentiation is often observed in the histological morphology of pulmonary NUT carcinoma and immunomarkers P63 and P40 are sometimes positive, which are associated with lung squamous cell carcinoma. Maybe so, primary pulmonary NUT carcinoma was once considered as a subtype of squamous cell carcinoma [43], but was classified as "other epithelial tumors" in lung cancer in 2015 and 2021 by WHO.

**Table 1**
Reported cases of pulmonary NUT carcinoma.

| References | Age | Sex | Smoking history (pack year) | Treatment | OS (months) |
|---|---|---|---|---|---|
| [31] | 21 | F | Never | Chemotherapy | 4 |
| | 63 | F | Never | Chemotherapy | 2 |
| | 37 | M | Never | Chemotherapy | 1 |
| | 29 | F | 20 | Chemotherapy, radiation | 3 |
| [32] | 23 | M | 2 | Chemotherapy, Extra pleural pneumonectomy | 2 |
| | 63 | M | UN | UN | 1 |
| | 26 | M | Never | Chemotherapy | 2 |
| | 30 | M | 3 | Chemotherapy | 5 |
| [33] | 23 | M | 180 | Surgery, immunotherapy | 1.5 |
| | 53 | M | 240 | Chemotherapy, targeted therapy | 4.1 |
| | 30 | F | Never | Chemotherapy, immunotherapy | 3 |
| | 25 | M | 90 | Chemotherapy | 1.5 |
| | 74 | M | 360 | Radiation, immunotherapy | 19.5 |
| | 58 | F | Never | Chemotherapy, radiation, immunotherapy | 26.7 |
| [34] | 10 | F | Never | Surgery | 1 |
| [35] | 54 | M | Never | Surgery | 4 |
| | 19 | M | UN | UN | 2 |
| | 62 | F | Never | UN | 5 |
| [36] | 49 | M | Never | Chemotherapy, radiation | 18 |
| [37] | 33 | M | 18 | UN | 4 |
| [38] | 14 | M | Never | Chemotherapy, radiation | 12 |
| | 7 | F | Never | Chemotherapy, radiation | 4 |
| [39] | 48 | M | 60 | Surgery | 6 |

*F* female, *M* male, *UN* unknown, *OS* overall survival.

The characteristic histological morphology of this tumor includes flaky undifferentiated cells with sudden focal squamous differentiation [30]. Tumor cells are small to medium in size and diverse in form, i.e., round, oval, spindle-shaped, or polygonal. Nuclei can be round, oval, or irregular; nucleoli are pronounced, with open chromatin, granular to coarse, with less cytoplasm, and a high nuclear-cytoplasmic ratio. Tumor cells are linear or nest-like in the necrotic background, and in scattered individual cells, the bare nucleus is common. Another characteristic manifestation is the apparently visible neutrophil infiltration under light microscopy [30].

As native NUTM1 protein is usually expressed only in the testes, detecting NUTM1 protein expressed outside the testicles can be

**Table 2**
Immunohistochemical and NUT variant of pulmonary NUT carcinoma.

| | UN/Total number of cases* | +/tested cases |
|---|---|---|
| NUT | 0/23 | 23/23 |
| P63 | 3/23 | 20/20 |
| P40 | 12/23 | 8/11 |
| TTF-1 | 3/23 | 6/20 |
| BRD4-NUT fusion | 6/23 | 10/17 |
| BRD3-NUT fusion | 6/23 | 1/17 |
| variant NUT rearrangement | 6/23 | 1/17 |

*UN* unknown.
* all 23 cases from table 1

diagnosed as NUT carcinoma [44,45]. Positive immunohistochemistry (IHC) NUT is characteristic of this tumor. Table 2 shows 23 pulmonary NUT carcinoma cases with strong diffused nuclear expression of NUT, where most cases of primary pulmonary NUT carcinoma showed positive cytokeratin (CK), P63 (most+), P40 (few+), TTF-1 (few+). Of the 23 cases of pulmonary NUT carcinoma, 17 had FISH analysis. Among these, 10 were tested for BRD4-NUT fusion, and 2 cases were variant NUT rearrangement and BRD3-NUT fusion. The chromosomal translocation characteristics of NUT carcinoma were further confirmed.

## Imaging characteristics

In their study, He et al. [30] reported chest computed tomography (CT) imaging reports in 19 cases of pulmonary NUT carcinoma showing that primary lung masses are mostly located in the center of the lungs, with the right lung (12/19; 63.1%) and lower lobe (8/19; 42.1%) being the most common sites, 36.8% complicated with pleural effusions, and 57.9% accompanied by obstructive atelectasis or obstructive pneumonia. Zhang et al. [46] collected the imaging information of 7 patients with pulmonary NUT carcinoma whose CT mostly revealed an isolated lobular mass, large in size, often accompanied by distant metastases. Five patients with masses were uneven in density, and two patients with uneven masses in moderate intensification in enhanced scans, indicating that the blood supply to the mass was not abundant. However, pulmonary NUT carcinoma tends to grow very fast, aggravates local blood supply insufficiency, and is prone to necrosis, which may be a feature of pulmonary NUT carcinoma. Exiting research [31,38,39,45,47-54] has shown that 96% of pulmonary NUT carcinomas develop distant metastasis, mainly bone metastases (70%) and lymph node metastases (50%), but liver, adrenal glands, skin, pleura, and other metastases are also likely to occur.

## Diagnosis and differential diagnosis

NUT carcinoma has no obvious specificity for clinical manifestations, laboratory tests, and imaging features, while its pathology remains essential for making its diagnosis. A definitive diagnosis of NUT carcinoma requires demonstration of the presence of NUTM1 gene rearrangement, which can be confirmed by IHC with a NUT-specific monoclonal antibody (clone C52). Based on 30 cases with NUT carcinoma, the sensitivity of the C52 IHC and FISH tests was 87% and 93%, respectively, and the specificity was 100%, while the combination of the FISH and C52 IHC tests achieved 100% diagnostic sensitivity [55,56]. Since NUT carcinoma is rare, IHC is not routinely used in every cancer patient, resulting in misdiagnosis or late diagnosis of the disease. IHC staining of anti-NUT monoclonal antibodies should be performed as soon as possible in patients with poorly differentiated or undifferentiated lung tumors, especially younger patients, non-smokers, or those without other risk factors and rapid disease progression, widespread invasion, and poor initial response to treatment. If necessary, it should be performed in combination with FISH to determine whether it is pulmonary NUT carcinoma disease so as to provide appropriate treatment.

It is necessary to distinguish primary pulmonary NUT carcinoma from other pathological types of lung tumors, i.e., (1) low-differentiation squamous cell carcinoma. NUT carcinoma has focal squamous differentiation in morphology and often expresses cell keratin, p63, and P40, which is easily misdiagnosed as squamous cell carcinoma and requires IHC NUT-positive support for diagnosis; (2) small cell lung cancer (SCLC), as both exhibit cytoplasmic scarcity and high Ki-67 proliferation index, but SCLC has no obvious nucleoli and no focal squamous cell differentiation. IHC staining is positive for chromatin protein and synaptoxin and negative for NUT [57,58]. (3) Large cell lung cancer (LCLC), which has no squamous differentiation morphology, and IHC NUT and squamous cell markers are negative; (4) large cell neuroendocrine carcinoma, which are with both neuroendocrine tissue morphology and immune phenotype; (5) lymphoepithelial tumor-like carcinoma, which also expresses markers of squamous cells, but the morphology is not squamous differentiation, accompanied by a large number of lymphocytes and plasma cell infiltration; (6) undifferentiated sarcoma, where IHC NUT, AE1/AE3, and squamous cell markers are negative; (7) high-grade lymphoma (Diffuse Large B-Cell Lymphoma), which is with the immune phenotype of lymphocytes. However, it should be noted that p63 is also expressed in some diffuse large B-cell lymphomas [35]. (8) SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4) deficient Undifferentiated carcinoma, which shows undifferentiated morphology and is composed of sheets of small/epithelioid and/or rhabdoid tumor cells and IHC NUT, p40, Brahma related gene-1(BRG1) are negative [59–61]. In the series of cases collected here, in addition to a relatively non-specific diagnosis (e.g., poorly differentiated carcinoma), other suggested diagnoses include mucinous epithelial carcinoma, germ cell tumors, and adenosquamous carcinoma.

## Therapy strategies

Currently, there is no standard protocol for treating primary pulmonary NUT carcinoma, and currently used treatments include surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, and more.

According to retrospective studies, patients with NUT carcinoma who undergo complete resection of tumors survive significantly longer [43]. Of the 48 patients studied by Chau et al. [2], 22 patients underwent initial surgery, and 50% of those who underwent surgery had 2-year OS, compared with 7% of patients who did not receive 2-year OS ($p=0.003$). Of the 38 patients who received initial treatment, 8 survived at the final follow-up with no evidence of disease (NED); 1 patient underwent surgery alone (NED at 23 months), 1 patient received postoperative assisted radiotherapy (NED at 72 months), and 6 patients underwent postoperative adjuvant chemoradiotherapy (NED at 14, 15, 17, 18, 35, 78 months). Chau et al. [62] collected and analyzed 117 NUT carcinoma patients, confirming the observations associated with surgery (at any point in time) related to improved OS ($P<0.0001$) and event-free survival (EFS, $P<0.0001$). Early radical surgery could significantly improve progression-free survival (PFS) and OS for NUT carcinoma [2,43,62]. Although surgery is an effective method for early primary pulmonary NUT carcinoma, it may not prolong survival in advanced diseases. Due to the aggressive nature of NUT carcinoma, most patients are diagnosed at an advanced stage, thus losing the opportunity for surgical treatment. It also greatly reduces their chance of radical surgery.

Most NUT carcinoma patients not eligible for surgery receive chemoradiotherapy or chemotherapy. Of the 23 patients with pulmonary NUT carcinoma, 6 patients (6/23, 26.1 %) were treated with chemotherapy alone and died of disease progression within 5 months after diagnosis; 5 patients (5/23,21.7%) who were treated with surgery (whether or not preoperative and postoperative adjuvant chemoradiation is performed) died of disease progression within 6 months of diagnosis; among the 5 patients (5/23,21.7%) who were treated with chemotherapy and radiation therapy, the OS of 3 patients (3/23, 13.0%) after diagnosis was 12, 18 and 26.7 months, respectively. In patients with locally advanced stages, concurrent chemoradiotherapy may prolong OS.

In recent years, targeted therapies for NUT carcinoma, including small molecule bromodomain and extra terminal protein inhibitors (BETi) and histone deacetylase inhibitors (HDACi), are being actively studied. The two targeted drugs are promising, either alone or in combination with chemotherapy [63]. Stathis et al. [64] described the results of four NUT carcinoma patients treated with a novel BET inhibitor (Bilabresib) outside the clinical trial, with two patients with symptomatic improvement and another with a stable condition. While all patients eventually died of the disease, two achieved an OS of 18 and 19 months. In the xenograft model of NUT carcinoma, HDACi significantly inhibits

growth, induces differentiation, and improves survival, providing preclinical support for the use of HDACi as a NUT carcinoma-targeted therapeutic agent. CUDC-907 (dual HDAC/PI3K inhibitor) has been found to have effective antitumor activity *in vitro* and *in vivo*, surpassing that of HDACi [63,65,66]. In their study, Munster et al. [67] reported a case of NUT carcinoma patients treated with CUDC-907 after two previous treatments with a long-term stable disease of more than 32 months. The literature suggested that CUDC-907 was most effective against NUT carcinoma cells among MYC-targeted drugs (including BET and HDAC inhibitors), followed by panobinostat (an HDAC inhibitor) and AZD5153 (a divalent BET inhibitor) [65]. In preclinical trials, p300/CBP HAT inhibitors were shown to exert inhibitory effects on NUT carcinoma, while their combination with BETi could synergistically inhibit the growth of NUT carcinoma [68–70]. Zhang et al. [50] tested 9 different concentrations of p300/CBP HAT inhibitor A-485 (ranging from 3.91 nM to 1 μM) combined with 5 different concentrations of BET inhibitor JQ1 (ranging from 6.25 to 100 nM) for NUT carcinoma cell line HCC2429 cells, revealing that the combined treatment of A-485 and JQ1 had strong synergy (ZIP synergy score 13.514). In addition, preclinical studies emphasized that BET inhibitors and immune checkpoint modulators had a synergistic effect [63,71,72]. Hogg et al. and Kagoya et al. [47,48] studies on mouse models as well as *in vitro* models revealed that BETi JQ1 could regulate the expression of the immune checkpoint ligand PD-L1 and is associated with increased anti-tumor cytotoxic T cells. Partial responses [73,74] were observed in 20% - 30% of patients treated with BET inhibitors in phase I trials. However, the response was not long-lasting, which was partly due to dose-limiting toxicity, and all patients eventually died of the disease. In addition, the development of targeted drugs is somewhat hindered by proneness to drug resistance and recurrence problems during treatment; thus, effective combination therapies and alternative treatments need to be urgently developed.

Table 3 [16,44,75-77] summarizes the cases of targeted therapy for NUT carcinoma, and the results show that patients treated with HDACi are more likely to have toxic side effects than patients treated with BETi, and the OS of patients treated with BETi is relatively long, but factors effective chemoradiotherapy are not excluded. Clinical trials of targeted drugs for NUT carcinoma are currently ongoing, and summarized here. A search for "NUT carcinoma" in https://clinicaltrials.gov/ct2/home revealed 13 relevant clinical trials, among which three clinical trials were suspended or withdrawn, and two clinical trials (A Phase I/II clinical trial of the BET inhibitor ZEN003694 in combination with etoposide / platinum therapy in patients with NUT carcinoma; A Phase 1 Study of EP31670 (a dual BET and CBP/p300 inhibitor) in patients with targeted advanced solid tumors) is ongoing. In discontinued clinical trials, more studies on BETi drugs were conducted (9/10, 90%), and only 1 study on CUDC-907. Separately, Dana-Farber Cancer Institute initiated a Phase I clinical trial to evaluate the use of BET inhibitors (BMS-986158 and BMS-986378) in pediatric patients with solid tumors, brain tumors, and lymphomas, as a possible treatment for NUT carcinoma in children. Both drugs are still being studied in adult patients [78].

Immunotherapy drugs in patients with primary pulmonary NUT carcinoma mentioned in the reported literature [79] include PD-1 inhibitors (nivolumab and pembrolizumab) or PD-L1 inhibitors (atezolizumab), and the vast majority of patients receive immunotherapy as second-line or beyond (follow-up) therapy. Two patients with pulmonary NUT carcinoma received combination therapy including pembrolizumab. Their OS were more than 12 months [40]. Xie et al. [33] reported two patients treated with nivolumab and pembrolizumab respectively. One patient treated with pembrolizumab appeared to have a clinical response to PD-1 inhibitors with an OS of 19.5 months, while another patient treated with nivolumab did not seem to benefit from immunotherapy with OS of only 3 months. It is inferred that applying pembrolizumab in combination with chemoradiotherapy may improve OS, but more research data are needed to prove it.

## Prognosis

The prognosis and outcomes of NUT carcinoma are very poor, and the response to conventional chemotherapy drugs or radiotherapy is also poor. Sholl et al. [31] reported eight cases of primary pulmonary NUT carcinoma with a median OS of only 2.2 months. The statistical median OS of cases collected in this review was 4 months (range 1-26.7 months), which is lower than that of 5.5-6.7 months for NUT carcinoma [9,43,62]. Chau et al. [62] studied 124 NUT carcinoma patients and identified three statistically distinct risk groups in patients with available NUT fusion, primary site, and OS data: group A was non-thymic primary, BRD3-NUT, or NSD3-NUT (n = 12, median OS = 36.5 months, 95% CI (confidence interval) = 12.5 to unreported months); group B was non-thymic primary, BRD4-NUT (n = 45, median OS = 10 months, 95% CI = 7 to 14.6 months); regardless of NUT fusion, group C was primary thoracic (n = 67, median OS = 4.4 months, 95% CI = 3.5 to 5.6 months). There were 5 out of 12 (42%) long-term survivors (≥3

**Table 3**
Reported Cases of NUT carcinoma receiving targeted therapy.

| References | Age | Sex | Initial diagnosis | Final Diagnosis | Therapy (after diagnosis of NUT carcinoma) | Outcome |
|---|---|---|---|---|---|---|
| [33] | 53 | M | pulmonary NUT carcinoma | pulmonary NUT carcinoma | Chemotherapy, gefitinib (PFS=2 weeks), apatinib (PFS=4 weeks) | Death 4.1 months after initial diagnosis |
| [64] | 39 | F | grade 3 invasive ductal carcinoma of the left breast | NUT carcinoma | Palliative radiotherapy (20 Gy), OTX015/MK-8628(8 months,4 cycles of treatment showed partial remission, and disease progression after 13 cycles) | Death 19 months after diagnosis of NUT carcinoma |
| | 22 | M | differentiated carcinoma of the nasopharynx | NUT carcinoma | Chemotherapy, OTX015/MK-8628(2 months,2 cycles of treatment showed partial remission, and disease progression after 3 cycles) | Death 7 months after initial diagnosis |
| | 66 | F | small cell lung carcinoma | pulmonary NUT carcinoma | OTX015/MK-8628(1 months,2 cycles of treatment showed partial remission, and disease progression after 3 cycles), radiotherapy (45 Gy), chemotherapy | Death 18 months after initial diagnosis |
| | 20 | M | NUT carcinoma | NUT carcinoma | Chemotherapy, radiotherapy (60 Gy), OTX015/MK-8628(2 weeks treatment was complicated by grade 4 thrombocytopenia, treatment interruption, rapid disease progression) | Death 5 months after initial diagnosis |
| [75] | 17 | F | UN | NUT carcinoma | Chemotherapy, radiotherapy (30 Gy), vorinostat (5 weeks treatment was complicated by grade 3 thrombocytopenia, treatment interruption, disease was stable 7 weeks following initiation of vorinostat) | Death 10 months after diagnosis and 1 month after targeted therapy interruption. |
| [76] | 10 | M | UN | NUT carcinoma | Vorinostat (5 weeks treatment was complicated by severe nausea and emesis and tumor recurrence), chemotherapy | Death11 months after initial diagnosis |
| [77] | 21 | F | poorly differentiated carcinoma | NUT carcinoma | Chemotherapy, radiotherapy, romidepsin (disease progression after the first course) | Death |

*F* female, *M* male, *UN* unknown, *OTX015/MK-8628* a novel synthetic small molecule targeting BRD2, BRD3 and BRD4, *Vorinostat/Romidepsin* a histone deacetylase (HDAC) inhibitor.

years) in group A and 7 out of 45 (16%) in group B, but no long-term survivors in group C. Therefore, it is inferred that the prognosis of patients with BRD4-NUT fusion is worse than patients with BRD3-NUT or NSD3-NUT fusion, and that regardless of NUT1 fusion, the prognosis of those with primary tumors of the chest tends to be worse than NUT carcinoma at other sites. Molecular techniques can be used to identify specific NUTM1 fusion chaperones, which may have potential prognostic and therapeutic implications [80]. In addition, 5 pulmonary NUT carcinoma patients reported by Xie et al. [33] had higher tumor mutational burden (TMB), but there was a large difference in OS (1.5-16.7 months). Accordingly, it was speculated that TMB, microsatellite instability (MSI), and DNA mismatch repair (MMR) appear to be independent of prognosis [33,81,82]. The survival period of pulmonary NUT carcinoma is shorter than NUT carcinoma at other sites, which may be related to the fact that this form of carcinoma is mostly advanced at the time of diagnosis. Therefore, in diagnosing low-differentiation tumors in the lungs, the possibility of NUT carcinoma should be taken into account, as early diagnosis can enable more aggressive treatment so as to effectively prolong OS.

## Conclusion

This review outlined pulmonary NUT carcinoma, a relatively new concept that still lacks universal understanding and clarity in clinical practice. With pathology and clinician awareness of the tumor and with the use of NUT antibodies, the number of cases of pulmonary NUT carcinoma is expected to increase. The prognosis of pulmonary NUT carcinoma is worse compared with NUT carcinoma at other sites. And the average age of patients with pulmonary NUT carcinoma is younger than that of patients with other types of lung cancer. Distinguishing NUT carcinoma from other low-differentiated tumors and identifying NUTM1 fusion partners are important in assessing prognosis and establishing future targeted therapies. In recent years, many attempts have been made to treat pulmonary NUT carcinoma. However, there is still no standard and consistently effective treatment. Pulmonary NUT carcinoma targeting drugs are in the process of clinical trials, and new drugs will hopefully substantially advance the treatment of patients with pulmonary NUT carcinoma. Future treatments may be biased towards chemoradiotherapy combined with targeted therapy, and BETi drugs have great potential.

## CRediT authorship contribution statement

**Jing Chen:** Writing – original draft, Writing – review & editing, Investigation. **Meihui Li:** Visualization, Formal analysis. **Hongyang Lu:** Conceptualization, Supervision.

## Declaration of Competing Interest

The authors declare no conflicts of interest in this study.

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