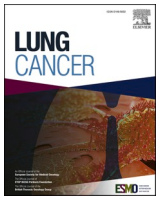
Lung Cancer 201 (2025) 108449

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



NUT carcinoma in children and adolescents: An analysis of the European Cooperative Study Group on pediatric rare tumors (EXPeRT)

Tim Flaadt [a,*], Lauriane Lemelle [b], Michael Abele [a], Calogero Virgone [c,d], Tal Ben-Ami [e], Denis Kachanov [f], Apostolos Pourtsidis [g], Andrea Ferrari [h], Gianni Bisogno [i], Ewa Bien [j], Nuno Jorge Dos Reis Farinha [k], Jan Godzinski [l,m], Yves Reguerre [n], Jelena Roganovic [o,p], Linus D. Kloker [q], Ulrich M. Lauer [q], Dominik T. Schneider [r], Ines B. Brecht [a], Daniel Orbach [b]

[a] *Pediatric Hematology/Oncology, Department of Pediatrics, University Hospital Tuebingen, Germany*
[b] *SIREDO Oncology Center (Care, Innovation, and Research for Children and AYA with Cancer), PSL Research University, Institut Curie, Paris, Fran*
[c] *Pediatric Surgery Division, University of Padua, University Hospital of Padua, Padua, Italy*
[d] *Department of Women's and Children's Health, University of Padua, Padua, Italy*
[e] *Pediatric Hematology Unit, Kaplan Medical Center, Rehovot, Israel*
[f] *Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia*
[g] *Pediatric and Adolescent Oncology Clinic, Children's Hospital MITERA, Athens, Greece*
[h] *Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*
[i] *Department of Women's and Children's Health, University of Padua and Pediatric Hematology Oncology Division, University Hospital of Padua, Padua, Italy*
[j] *Department of Pediatrics, Hematology and Oncology, Medical University, Gdansk, Poland*
[k] *Hospital Center of São João (CHSJ), Porto, Portugal*
[l] *Dept. of Paed. Surgery, Marciniak Hospital, Wroclaw, Poland*
[m] *Dept. of Paediatric Traumatology and Emergency Medicine, Wroclaw Medical University, Poland*
[n] *CHU de Saint Denis, Service d'oncologie et d'hématologie pédiatrique, 97400 Saint-Denis, Reunion, France*
[o] *Department of Hematology and Oncology, Children's Hospital Zagreb, Zagreb, Croatia*
[p] *Faculty of Biotechnology and Drug Development, University of Rijeka, Rijeka, Croatia*
[q] *Department of Internal Medicine VIII, Medical Oncology and Pneumology, University of Tuebingen, Tuebingen, Germany. German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Partner Site Tuebingen, Tuebingen, Germany*
[r] *Clinic of Pediatrics, Dortmund Municipal Hospital, University Witten/Herdecke, Germany*

ARTICLE INFO

Keywords:
NUT carcinoma
Rare tumors
Targeted therapy
Children
EXPeRT group

ABSTRACT

Background and Aims: NUT carcinoma (NC) is a sporadic, highly aggressive tumor that primarily affects children, adolescents, and young adults and is characterized by the presence of somatic *NUTM1* rearrangements. This analysis by the European Cooperative Study Group for Pediatric Rare Tumors (*EXPeRT*) aims to fill the knowledge gap regarding the clinical characteristics of children with NC.

Methods: A retrospective case series of NC-patients aged 0–18 years treated between 2011 and 2023 was conducted using the *EXPeRT* database. Relevant clinical characteristics, including treatment and outcome were recorded.

Results: Twenty-seven patients with a median age of 13 years (range 7–18) were analyzed. Thirteen patients were initially misdiagnosed. Sixteen patients had thoracic and 11 extra-thoracic tumors, including three in the nasal/sinus region and two in the submandibular glands. Despite intense multimodal treatment, median event-free and overall survivals were 1.5 and 6.5 months, respectively.

Abbreviations: AURK, aurora kinase; AYA, adolescents and young adults; BETis, bromodomain and extraterminal (BET) domain inhibitors; CDK, cyclin-dependent kinase; EFS, event-free survival; PE, Cisplatin, etoposide; ESCP, European Standard Clinical Practice Protocol; EXPeRT, European Cooperative Study Group for Paediatric Rare Tumors; FISH, fluorescence in situ hybridization; FRACTURE, French very rare tumors group; GCSF, granulocyte colony-stimulating factor; Gy, Gray; HDAC, histone deacetylase; IHC, immunohistochemical; LDH, lactate dehydrogenase; NC, NUT carcinoma; NGS, next-generation sequencing; NUT, nuclear protein of the testis; OS, overall survival; PFS, progression-free survival; SSG, Scandinavian Sarcoma Group; STEP, German Pediatric Rare Tumor Group; T-VEC, talimogene laherparepvec; VIDE, vincristine, ifosfamide, doxorubicine and etoposide; VDCy/IE, vincristine, doxorubicine, cyclophosphamide/ifosfamide, etoposide.

* Corresponding author at: Department of Hematology and Oncology, University Children's Hospital Tuebingen, Hoppe-Seyler-Str. 1, 72070 Tuebingen, Germany.
E-mail address: tim.flaadt@med.uni-tuebingen.de (T. Flaadt).

https://doi.org/10.1016/j.lungcan.2025.108449
Received 11 February 2025; Accepted 14 February 2025
Available online 19 February 2025

Conclusions: Early diagnosis of NC by examination of the NUTM1 rearrangement in undifferentiated or poorly differentiated carcinomas is crucial in order to initiate specific and intensive therapy as quickly as possible. Similar to adult patients, only a minority of pediatric patients achieved prolonged survival. Therefore, the development of novel therapeutic strategies in future joint clinical trials is essential.

1. Introduction

Amongst very rare childhood tumors, defined as neoplasms with an incidence of < 2/ 1,000,000 per year, are nuclear proteins of the testis (NUT) carcinomas (NC). NC can occur at any age, ranging from infants and neonates to elderly individuals, but most cases are typically observed in adolescents and young adults (AYA). [1,2] These tumors are poorly differentiated squamous cell tumors, defined by specific somatic translocations involving the *NUTM1* gene located on chromosome 15q14, resulting in the pathogenic fusion of the *NUTM1* gene with other genes.[1–3] In the majority of NC cases, the fusion partner gene is *BRD4*, which is located on chromosome 19p13. Several other known translocation partners have been identified, including *BRD3* on chromosome 9q34, and *NSD3* on chromosome 8p12.[4–6].

To date, no strong risk factors for the development of NC or other relevant biomarkers have been identified. Until recently, NC has frequently been misdiagnosed because of its scarcity, the absence of specific clinical, imaging, and histological characteristics, and the fact that it is not confined to a particular organ or body region.[7–9] However, NC can now be efficiently diagnosed by immunohistochemistry, using a highly specific anti-NUTM1 antibody. [10].

Long-term survival or cure is rare and is generally associated with the possibility of tumor resection in localized stages when complete resection can be achieved.[1,11,12].

A retrospective analysis of 63 patients with NC showed no significant differences in progression-free survival (PFS) or overall survival (OS) between patients above and below the age of 18 years, even though younger patients seemed to have a slightly better outcome. [13,14] Indeed, among 29 pediatric patients, PFS was 14 % whereas OS was 30 % at two years. For the 34 adult patients, PFS at one year was 4 % and OS was 5 % at two years, respectively.[13,14] A recently published pediatric German series (11 cases) demonstrated a worse outcome than that reported in cohorts of US pediatric and adult NC patients, probably because of the large number of patients with advanced disease in this limited cohort. [15].

Currently, the primary treatment approach for all patients consists of complete surgical resection either before or after chemotherapy and radiation. [16,17] Due to the highly aggressive nature of this tumor, novel treatment options such as inhibitors of BET proteins (BETis), histone deacetylase (HDAC), EZH2 (Enhancer of Zeste Homolog 2 (Drosophila), and CBP/p300 have been tested in several clinical trials, without yet a clear efficacy. In addition, immunotherapy with PD1/PD-L1 inhibition and oncolytic virotherapy are currently being explored. [19–22].

Due to the rarity of the disease, it seems crucial to disseminate knowledge and establish a straightforward diagnosis of NC to improve its early management and counseling. Recently, the European Standard Clinical Practice (ESCP) Protocol for NC in children and adolescents was published to aid in achieving these goals. [17] This collaborative analysis of the European Cooperative Study Group for Pediatric Rare Tumors (*EXPeRT*) aimed to characterize a contemporary large cohort of children and adolescents with NC across Europe, documenting their clinical characteristics, management, and outcomes to define prognostic risk factors and to help determine whether survival in pediatric patients may be better than that in adults, as suggested by published data.

2. Methods

2.1. Patients

This European retrospective analysis was based on patients registered in the databases of cooperating national rare tumor pediatric working groups and *EXPeRT* members from Germany (n = 12), France (n = 9), Italy (n = 4), Israel (n = 1), and Greece (n = 1). [18] Other European rare tumor working groups had no recorded cases of NC in their databases. The inclusion criteria were pathological diagnosis of NC between 2011 and 2021 and age at diagnosis of ≤ 18 years. According to current guidelines, NC were confirmed by positive NUTM1 antibody staining, fluorescence in situ hybridization (FISH) with split-apart probes, or next-generation sequencing (NGS)-based assays. [17,19–21].

Pseudonymized data (including results from genetic investigations) were collected using standardized proformas designed for this analysis. Family history was evaluated for possible cancer predisposition syndromes by using the modified Jongman criteria. All patients and/or their guardians provided informed consent for data collection within country-specific rare tumor groups and for analysis at diagnosis. [22] Statistical analyses were performed using GraphPad Prism 9.4 (Dotmatics, Boston, MA, USA) and SPSS Statistics, version 29 (IBM, Armonk, NY, USA). Descriptive statistical analysis and chi-square or Fisher's exact tests were used for nominal variables to obtain p values. Kaplan-Meier analysis of event-free survival (EFS) and overall survival (OS) and the Gehan-Breslow-Wilcoxon test were used for survival analysis. Statistical significance was set at $p \leq 0.05$.

3. Results

We identified 27 pediatric patients (Table 1) with a median age of 14.5 years (range, 4 – 18 years) and a relatively balanced sex distribution (male-to-female ratio, 1.25:1). Patients frequently presented with general non-specific symptoms, such as fever (n = 6), weight loss (n = 8), night sweats (n = 13), cough (n = 13, almost all cases of thoracic tumors), pain (n = 16), and dyspnea (n = 6), with a median duration of 2 months (range, 20 days to 6 months) before diagnosis (Table 1). Thirteen patients (48 %) initially had an erroneous diagnosis, such as lung infections or incorrect cancer diagnosis as primitive neuroectodermal tumors (PNET, two patients), thymic carcinoma, lymphoma, or bronchial carcinoma (one patient each). One patient had acute myeloid leukemia (AML M5) eight years prior to NC diagnosis. None of the patients had a family history of a suspected cancer predisposition syndrome.

Sixteen patients had primary thoracic tumors, 11 had extra-thoracic sites including four located in the nasal area or nasal sinuses, and two in the submandibular glands. Other locations included the pancreas, pterygopalatine fossa, vocal cords, and parathyroid glands. One patient had multifocal disease of unknown origin (Table 1).

The median maximum tumor diameter was 6.5 cm (range 0.9–18.8 cm). The majority of the patients (n = 18; 67 %) had metastasis at diagnosis, mainly in the distant lymph nodes (n = 11, 41 %), bone marrow (n = 7, 26 %), and bones (n = 5, 19 %). No distant metastasis in central nervous system was present. (Table 1).

Age, sex distribution, and maximum tumor diameter were comparable between the thoracic and non-thoracic tumors (Table 2). The initial lactate dehydrogenase (LDH) levels were significantly higher in thoracic tumors than in non-thoracic tumors (median: 600 U/l vs. 380 U/l in non-thoracic tumors, p = 0.026). Bone marrow infiltration and

Table 1
Patient characteristics; Abbreviations: No: patient number; Age: age at diagnosis (y, years); m months; NUTM1 positive: positive NUTM1 immunohistochemistry; max. size: maximum tumor diameter, BM: bone marrow; LN: regional lymph nodes; OS: overall survival; EFS: event-free survival in months; AML, acute myeloid leukemia; NK, unknown; CNS; central nervous system. SVCS: Superior vena cava syndrome; n.d.: not determined; m, months.

Patient characteristics				Symptoms		Tumor characteristics				Metastases						Outcome		
No.	gender	age (y)	previous malignancy	duration (m) before diagnosis	Symptoms	Primary site	Fusion transcript gene fusion	NUTM1 positive (ICH)	Maximum size (cm)	Presence	liver	BM	lung	LN	bone	Status at the last follow-up	EFS (m)	OS (m)
1	male	3,9	absent	1	swelling	Pterygopalatine fossa	n.d.	yes	4.7	no	no	no	no	no	no	alive	2.7	78
2	male	6,6	absent	3	cough, pain	Lung	n.d.	yes	6	yes	no	no	no	yes	no	dead	0.5	2.8
3	female	7,8	absent	3	cervical lymph-adenopathy	Lymph node	*ZNF532::NUTM1*	yes	4	yes	no	no	no	yes	no	dead	20.6	35
4	male	9,1	absent	4	weight loss, malaise, food intolerance	Lung	n.d.	yes	6	yes	no	no	yes	no	yes	dead	4.9	10.1
5	male	9,3	absent	2	swelling, fever	Salivary gland	n.d.	yes	0.9	no	no	no	no	no	no	alive	132	132
6	male	10,5	absent	2	Pain	Sinus	n.d.	yes	3.5	yes	no	no	no	yes	yes	dead	5.9	9.2
7	male	12,8	absent	2	swelling, dysphagia, facial nerve paralysis	parathyroid gland	*BRD4::NUTM1*	yes	13	yes	no	no	no	yes	yes	dead	4.1	18.3
8	male	13,0	absent	2	dysphonia	Vocal cord	*BRD4::NUTM1*	n.d.	2	no	no	no	no	no	no	dead	17.7	30.2
9	male	13,2	absent	4	weight loss, fever, asthenia, dyspnea	Lung	*BRD4::NUTM1*	yes	10	yes	no	no	no	yes	no	dead	5.3	8.4
10	female	13,2	absent	3	respiratory distress, SVCS, dyspnea	Lung	*BRD4::NUTM1*	yes	7.5	yes	no	yes	yes	yes	yes	dead	4.3	19.0
11	male	13,8	absent	0.5	pain, cough, fever	lung	*BRD4::NUTM1*	yes	11	no	no	no	no	no	no	dead	4.0	5.0
12	female	14,3	absent	6	cough, fever	Lung	*BRD4::NUTM1*	yes	18.8	yes	no	no	no	no	yes	dead	2.1	2.6
13	female	14,5	absent	1	Pain	Multiple	n.d.	yes	6	yes	no	yes	yes	yes	yes	dead	0.5	3.9
14	female	14,5	absent	3	swelling, epistaxis	nasal sinus	n.d.	yes	5	no	no	no	no	no	no	dead	23.3	31.0
15	male	14,8	absent	6	pain, weight loss, fever, dyspnea,	Lung	*BRD4::NUTM1*	yes	6.5	yes	no	yes	no	no	no	dead	1.6	2.4
16	female	15,1	absent	1	weight loss, pain	Pancreas	n.d.	yes	8.4	yes	yes	no	no	no	no	dead	4.6	6.8
17	female	15,2	absent	4	asthma, pain	Lung	n.d.	yes	5	yes	no	yes	no	yes	yes	dead	0.9	16.0
18	female	15,3	AMLM5	1	asthenia, cough	Lung	*BRD4::NUTM1*	yes	9	no	no	no	no	no	no	dead	11.5	18.8
19	male	15,8	absent	2	Pain	Nose	n.d.	yes	3	no	no	no	no	no	no	dead	3.2	9.4
20	female	16,6	absent	1	weight loss, pain, dyspnea, asthenia	Lung	*BRD4::NUTM1*	yes	8.4	yes	no	yes	yes	no	yes	dead	8.1	11.6
21	male	16,8	absent	2	cough, dyspnea, weight loss	Lung	*BRD4::NUTM1*	n.d.	12	yes	no	yes	yes	no	yes	dead	0.7	7.4
22	female	16,8	absent	1	fever, cough, pain	Lung	n.d.	yes	10	yes	yes	yes	no	yes	yes	dead	3.0	6.0
23	male	17,3	absent	1	swelling	Salivary gland	*BRD4::NUTM1*	n.d.	11	yes	no	no	yes	yes	no	dead	0.4	4.0
24	female	17,3	absent	2	cough, dyspnea, weight loss	Lung	*BRD3::NUTM1*	n.d.	7	yes	no	no	yes	yes	no	dead	10.1	109
25	male	17,9	absent	1	cough, pain	Lung	n.d.	yes	3.4	yes	no	no	yes	yes	no	dead	0.4	4.1
26	female	17,9	absent	2	cough, dyspnea	Lung	n.d.	yes	10	yes	no	no	no	yes	no	dead	4.3	5.4
27	male	18,0	absent	1	cough, pain, weight loss, fever	Lung	n.d.	yes	2.4	no	no	no	no	no	no	dead	1.5	4.8

Table 2
Comparison of thoracic and non-thoracic NUT carcinoma characteristics. *Comparison between thoracic and non-thoracic NCs;Abbreviations: LN Lymph node; BM bone marrow; y years; LDH lactate dehydrogenase; n, number of patients.

Characteristics	All patients	Thoracic NC	non-Thoracic NC	p-value*
Patients (%)	27 (100 %)	16 (59 %)	11 (41 %)	
Age at diagnosis (min, max, median; y)	3.9; 18; 13.4	6.5; 18; 15.3	3.9; 17.2; 13	–
Sex				0.147
Male (n; %)	15 (56 %)	7 (26 %)	8 (30 %)	
Female (n; %)	12 (44 %)	9 (33 %)	3 (11 %)	
Median duration of symptoms before tumor diagnosis (months, range)	2 (0.8–6.1)	2 (0.8–6.1)	2 (1.0–4.0)	0.560
Initial LDH level (U/l)	530 (208–1700)	600 (208–1700)	380 (240–390)	**0.026**
Initial misdiagnosis				
Yes (n; %)		9 (33 %)	6 (22 %)	0.930
No (n; %)		7 (26 %)	5 (19 %)	
Maximum median tumor size (cm; range)	6.5 (0.9–18.8)	7.2 (2.4–18.8)	6.5 (0.9–13)	0.184
Metastases at diagnosis				0.300
Yes (n; %)	18 (67 %)	12 (44 %)	6 (22 %)	
No (n; %)	9 (33 %)	4 (15 %)	5 (19 %)	
Location of metastases				
Bone (n; %)	10 (37 %)	8 (30 %)	2 (7 %)	0.086
LN (distant) (n; %)	11 (41 %)	7 (26 %)	4 (15 %)	0.740
BM (n; %)	7 (26 %)	7 (26 %)	0	**0.004**
Lung (n; %)	8 (30 %)	7 (26 %)	1 (4 %)	**0.037**
Liver (n; %)	2 (7 %)	1 (4 %)	1 (4 %)	–

lung metastasis also occurred significantly more often in thoracic tumors: 25.9 % vs. 0 (p = 0.004) and 25.9 % vs. 3.7 % (p = 0.037, Table 2). Since the upper limit of 18 years was selected in the present cohort, analyze of the age as risk factor was not adequate, even if patients with non-thoracic NC tended to be younger.

Four patients underwent R0 resection of their primary tumors, two of them primarily without neoadjuvant therapies, five patients underwent R1/R2 resection after neoadjuvant chemotherapy, and 18 patients underwent exclusive tumor biopsies. Chemotherapy was administered to all patients, with most receiving several lines of chemotherapy, due to relapse or progression.

The best tumor responses were observed in patients receiving intense sarcoma protocols (SSG IX and Ewing sarcoma protocols), including five patients with complete remission (CR). Despite achieving CR, four of these five patients had tumor relapses. The response rate in first-line therapy defined by CR + partial response [PR]) in IRS III/IV patients was 64 % for sarcoma protocols and 25 % for non-sarcoma protocols. (Table 3).

Targeted therapy with BETis alone or in combination with chemotherapy was administered to three patients with initial tumor failure, resulting in progressive disease (PD) in all patients. The PD-1 inhibitor pembrolizumab was administered to two patients with initial PR in both patients. Other targeted (HDACi without measurable efficacy) and/or experimental therapies (combination therapy consisting of oncolytic viruses, pembrolizumab, and chemotherapy with PR in one patient) were also administered to two patients after failure of pembrolizumab.

Twenty patients received local radiotherapy with curative intent at a median dose of 52 Gy (range: 21.0–66.6 months), and two received palliative radiotherapy at lower doses.

Only one patient had no progressive disease or relapse after the first-line therapy. The pattern of treatment failure at the first relapse or progression was evaluated for all remaining patients (n = 26): four (15 %) showed isolated locoregional relapse, eight (31 %) had isolated distant tumor disease, and 14 (54 %) had combined locoregional and distant progression or relapse. Only one patient survived after a local relapse with a second line therapy including chemotherapy and radiotherapy.

Overall, 25/27 patients (92.6 %) died: 24 (88.9 %) from tumor progression and one after severe bacterial infection. Median EFS was 0.38 years (4.5 months), 1-year EFS were 15.7 % (95 % CI: 4.9 %–32 %) and the 2-year EFS was 3.9 % (95 % CI: 0.3 %–16.7 %) (Fig. 1A). The median OS of the entire cohort was 0.7 years. One-year OS was 35.1 % (95 % CI: 17.2 % – 52.4 %), and 2-year OS was 23.4 % (95 % CI: 6.0 % – 37.2 %) (Fig. 1F).

Patients with thoracic NCs had significantly worse OS and EFS compared to patients with non-thoracic primary tumors (median OS thoracic vs. non-thoracic 0.5 years and 1.6 years; p = 0.01; median EFS thoracic vs. non-thoracic 0.2 years and 0.8 years, p = 0.008). Metastatic disease was associated with significantly worse OS (median OS 0.6 years vs. 2.5 years; p = 0.05) but not EFS. The extent of surgery (biopsy and R2 resection vs. R0/R1 resection) did not significantly influence the EFS or OS. In addition, the type of fusion transcript (*BRD4::NUTM1* vs. non *BRD4::NUTM1*) could does not appear to significantly impact outcomes.

4. Discussion

NC is an exceptionally rare disease, with only 27 pediatric cases reported over a 10 year-period in five large European countries. As shown in this series, this entity is an emerging diagnosis, often initially misdiagnosed, as broader approaches to tumor genome sequencing and, due to increased attention to NC, specific diagnostic methods such as immunohistochemical staining and FISH analysis are increasingly being applied to unclear cases of pediatric solid tumors.

NCs are exceptionally aggressive, corresponding to a 2-year EFS of 4 % and a 2-year OS of 23 % in the present cohort, with only two long-term survivors. For a cohort of 29 pediatric patients, the international NC registry reported a PFS of 24 % at one year and 14 % at two years and an OS of 41 % at one year and 30 % at two years. Interestingly, pediatric patients had less frequent metastatic disease in the series published by the International USA driven NC Registry than in our series, resulting in better OS and EFS. [13].

Similar to adult patients, the present series of pediatric-only patients demonstrated only a transient response to chemotherapy, which was often followed by rapid tumor progression. [8,19] Nevertheless, further transient responses and some prolonged survival (but no cure) to subsequent lines of therapy could have been observed. Early multimodal and aggressive therapeutic approaches used in clinical practice for pediatric cancers are recommended by the ESCP for NC. [17] The best responses were observed for regimens that employed anthracyclines and cisplatin. Favorable responses to combination chemotherapy consisting of vincristine/cisplatin, doxorubicin, and ifosfamide have been reported [23]. Six patients in our European cohort received this therapy, five of whom showed a significant response. Multimodal protocols, including vincristine, ifosfamide, doxorubicin, and etoposide (VIDE), or vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDCy-IE), or etoposide and cisplatin (PE), were also used in nine patients with transient responses in four patients. Despite the initial response to these regimens, no significant improvement in survival rates could be reached. Early local treatment has been reported to play an essential role in disease control, as tumor progression could be early and the extent of surgical resection with initial radiotherapy have been reported to be predictive of OS and EFS. [13,14,24] In our cohort, complete resection with adjuvant chemoradiotherapy resulted in longer survival without recurrence in the two patients with localized disease. However, widespread local tumor spread was frequent and prevented complete resection with R0 or R1 resections; complete resection could be performed in only five patients. In the present cohort, patients with non-metastatic disease had significantly better OS but not EFS. We assume that this is attributable to the aggressiveness of the disease.

A previous prognostic model within an adult US cohort of patients

Table 3
Details of NC therapies. Abbreviations: Pt. patient number; 1: Scandinavian Sarcoma Group's SSG IX protocol; 2: inhibitors of BET proteins (pat. #24 received 2 BETis, a first generation (Molibresib (GSK525762))and later a second generation BETi (BI 89499) as compassionate use; 3 Octreotide: Octreotide before correct diagnosis; 4: recombinant oncolytic herpes simplex virus talimogene laherparepvec (T-VEC, Imlygic®). CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; MR: mixed response;.

Pt	Line of therapy	Number of cycles	Therapy according to protocol	Chemotherapeutic agents	Targeted therapy	Best response	Outcome at end of treatment line	Radio-therapy	Surgery results
1	First line	2		carboplatin paclitaxel		–	PD	15 Gy	biopsy only
	Second line	1		etoposide, cisplatin		–	PD		
2	First line	9	SSG IX protocol; VAI/PAI	ifosfamide, adriamycin, vincristine, cisplatin		CR	CR	54 Gy	R0
3	First line	4	EWING 2012: VDC-IE	vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide		SD	PD	–	biopsy only
4	First line	1	–	cyclophosphamide, dexamethasone (suspected lymphoma)			PD	21 Gy	biopsy only
	Second line	2	PEI (according to germ cell tumor protocol)	etoposide, ifosfamide, cisplatin			PD		
	Third line	1		docetaxel			PD		
5	First line	4	EWING 2012: VDC-IE	vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide		–	PD	56 Gy	R2
6	First line	4	SSG IX protocol; VAI/PAI	vincristine, cisplatin, adriamycin, ifosfamide		PR (after 2 cycles)	PD	32 Gy	biopsy only
	Second line	2	lung cancer protocol adapted	carboplatin, paclitaxel, etoposide	BETi[2]		PD		
	Third line	3		cisplatin, etoposide and vincristine, doxorubicin and cyclophosphamide, cisplatin, etoposide		–	PD		
7	First line	1	lung cancer protocol adapted	carboplatin, paclitaxel, etoposide			PD	25 Gy	biopsy only
	Second line	2	EWING 2008: VIDE	vincristin, etoposide, doxorubicin, ifosfamide			PD		
8	First line	4		cisplatin, etoposide, doxorubicin		PR (after 2 cycles)	PD	66.6 Gy	R2
9	First line	5		cisplatin etoposide; and carboplatin, doxorubicin and cisplatin		PR (after 3 cycles)	PD	60 Gy	biopsy only
	Second line	5		etoposide	BETi	–	PD		
10	First line	8	PAC	doxorubicin, cisplatin, cyclophosphamide		PR (after 5 cycles)	PD	60 Gy	biopsy only
11	First line	1	lung cancer protocol adapted	Cisplatin, etoposide			PD	–	biopsy only
	Second line	4	EWING 2008: VIDE	vincristine, etoposide, doxorubicin, ifosfamide, cyclophosphamide		PR (after 3 cycles)	PD		
12	First line	1		carboplatin; etoposide cyclophosphamide			PD	30 Gy	R2
	Second line	3	SSG IX protocol; VAI/PAI[1]	ifosfamide, adriamycin, vincristine, cisplatin			PD		
13	First line	2	EWING 2008: VAC	vincristine, actinomycin D, ifosfamide		SD	SD	50 Gy	R0
14	First line	2		gemcitabine, cisplatin		–	PD	–	biopsy only
15	First line	5	Ewing's sarcoma protocol	etoposide, ifosfamide, cisplatin (IEC) and vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide (VDCy-IE)		PR (after 3 cycles)	PD	8 Gy	biopsy only
	Second line	1		cisplatin, gemcitabine			PD		
16	First line	5	TIP	paclitaxel, cisplatin, ifosfamide		CR (after 5 cycles)	PD (after end of therapy)	60 Gy	R0

(*continued on next page*)

Table 3 (*continued*)

Pt	Line of therapy	Number of cycles	Therapy according to protocol	Chemotherapeutic agents	Targeted therapy	Best response	Outcome at end of treatment line	Radio-therapy	Surgery results
17	First line	5	Rhabdoid registry	doxorubicin, ifosfamide, carboplatin, etoposide and vincristine, cyclophosphamide, actinomycin D		–	PD	30 Gy	biopsy only
	Second line	1		carboplatin, docetaxel		–	PD		
18	First line	1		ifosfamide, vincristine, actinomycin D doxorubicin		PR (after 1 cycle)	PR	30 Gy	biopsy only
	Second line	1		vincristine, doxorubicin, cyclophosphamide		–	PD		
19	First line	1		vincristine, adriamycin, ifosfamide and cyclophosphamide, etoposide		PR (after 2 cycles)	PR	36 Gy	biopsy only
	Second line	1		carboplatin, etoposide		–	PD		
	Third line	1		etoposide		–	PD		
20	First line	6 & 8	EWING 2008: VIDE & VAC	vincristine, etoposide, doxorubicin, ifosfamide/ cyclophosphamide and vincristine, actinomycin D, ifosfamide		CR (after 4 cycles)	CR	59 Gy	biopsy only
	Second line	1		irinotecan temozolomide		–	PD		
	Third line	3		cisplatin, paclitaxel		PR (after 2 cycles)	PD		
21	First line (emergency)	1		vincristine, doxorubicin, cyclophosphamide		–	PD	–	biopsy only
	Second line	2		cisplatin, adriamycin, cyclophosphamide		–	PD		
	Third line	2	EWING 2012: VDC-IE	vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide		–	PD		
22	First line	3		oxaliplatin, irinotecan, 5-fluorouracil		–	PD	45 Gy	biopsy only
	Second line	3		etoposide, ifosfamide, carboplatin		–	PD		
23	First line	12	SSG IX Protocol; VAI/PAI	ifosfamide, adriamycin, vincristine, cisplatin		CR	CR	64 Gy	R0
24	First line	4	EWING 2012: VDC-IE	vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide		–	PD	–	biopsy only
	Second line	6		gemcitabine, carboplatin			PD		
	Third line	10		gemcitabine, capecitabine		PR (after first, fifth and 8th cycle)	PD		
	Fourth, fifth and sixth line	9			octreotide[3]; pembrolizumab; alisertib; vorinostat; navitoclax; BETi[2]	–	PD		
25	First line	12	SSG IX Protocol; VAI/PAI	ifosfamide, adriamycin, vincristine, cisplatin		CR (after 4 cycles)	PD (after end of therapy)	60 Gy	R1
	Second line	3		pembrolizumab		SD (after 1 cycle)	PD		
	Third line	2		pembrolizumab + Imlygic[4] + carboplatin, etoposide		PR (after 1 cycle)	MR		
26	First line	3		cisplatin, etoposide and etoposide, ifosfamide, cisplatin		–	PD	30 Gy	biopsy only
	Second line	1		adriamycin, docetaxel		–	PD		
	Third line	1		etoposide		–	PD		

(*continued on next page*)

Table 3 (*continued*)

Pt	Line of therapy	Number of cycles	Therapy according to protocol	Chemotherapeutic agents	Targeted therapy	Best response	Outcome at end of treatment line	Radio-therapy	Surgery results
27	First line	8	SSG IX protocol; VAI/PAI	vincristine, cisplatin, adriamycin, ifosfamide		CR (after 3 cycles)	Relapse (5 months after last cycle)	54 Gy	R2

A: Event-free survival (EFS) of the whole cohort (median EFS: 0.4 years); B: Event-free survival of patients with distant metastasis (median EFS 0.3 years) and without (median EFS 0.8 years); C: Event-free survival of patients with thoracic primary tumor (median EFS 0.2 years) and with non-thoracic primary tumor (median EFS 0.8 years); D: Event-free survival of patients with *BRD4::NUTM1* fusion (median EFS 0.4 years) and patients without *BRD4::NUTM1* fusion (median EFS 1.9 years) E: Event-free survival of patients with R0/R1 surgery (median EFS 0.3 years) and patients with R2 surgery / biopsy (median EFS 0.4 years).
F: Overall survival (OS) of the whole cohort (median OS: 0.7 years); G: Overall survival of patients with distant metastasis at diagnosis (median OS 0.6 years) and patients without distant metastasis at diagnosis (median OS 2.5 years); H: Overall survival of patients with thoracic primary tumor (median OS 0.5 years) and overall survival of patients with non-thoracic primary tumor (median OS 1.6 years); I: Overall survival of patients with *BRD4::NUTM1* fusion (median OS 0.6 years) and overall survival of patients with non-*BRD4::NUTM1* fusion (median OS 6 years); J: Overall survival of patients with R0/R1 surgery (median OS 1.5 years) and patients with R2 surgery / biopsy (median OS 0.76 years).

with NC categorized the patients into three groups based on their outcomes. Based on this categorization, patients with non-thoracic NC and non-BRD4 fusion genes had the best outcomes with a median OS of 36.5 months. Patients with non-thoracic NC and *BRD4::NUTM1* fusion genes had an intermediate prognosis with a median OS of 10 months. Finally, patients with thoracic NCs had the worst prognosis, with a median OS of only 4.4 months. [14] Also within the current patients' series, patients with non-thoracic primary tumors had significantly better EFS and OS than those with primary thoracic tumors did. However, because the fusion partner of NUT was determined in only approximately half of the patients with NC, we could not apply this prognostic model entirely to the current cohort. Adults with NC and non-BRD4 fusions generally demonstrated better outcomes; yet, significance was not attained. We expect that this prognostic model will also be applicable to pediatric patients.

Based on the NC-specific translocation mechanism, potential molecular targets have been identified, which has led to the generation of target-specific inhibitors, such as BETi (molibresib (GSK525762), amredobresib (BI 89499)), and the PD-1 inhibitor pembrolizumab. Clinical trials have evaluated various generations of BETi compounds in NC, but their efficacy as monotherapies has not yet been proven [25,26]. Recently, several reports of NCs treated with PD-1/PD-L1 inhibitors have demonstrated clinically relevant responses. [27 28] Reports suggest that adult patients with unresectable NCs might benefit more from pembrolizumab than from nivolumab, especially when prior chemoradiotherapy or radiotherapy is involved, which aligns with the treatment strategies in lung cancer patients. [29] In two of our patients, pembrolizumab was administered after chemotherapy and radiotherapy for unresectable PD or relapse, resulting in transient response in both patients.

In the present cohort, patients with longer survival had either localized, non-thoracic disease with sufficient local tumor control. Notably, in all instances of long-term survival, subsequent multimodal treatment approaches lead to disease stabilization and extended survival after disease progression or relapse. In one case, the patient was accurately diagnosed with NC five years after the initial presentation. In addition to the prognostically more favorable *BRD3::NUTM1* fusion, an overall indolent course of the disease can be discussed here; therefore, the therapeutic response should be interpreted cautiously.

5. Conclusion

In conclusion, the long-term survival rate of pediatric patients with NC is low despite transient responses to chemotherapy in some cases and multidisciplinary strategy. Early diagnostic workup of undifferentiated or poorly differentiated carcinomas seems crucial for rapid identification of NC through specific gene rearrangements and initiation of the most effective therapeutic approaches. All pediatric patients diagnosed with NC should be registered in rare tumor registries, ideally with adults' patients to enhance the understanding of this rare tumor entity and establish more efficient treatment recommendations. In parallel, molecular profiling should be conducted systematically to understand the pathogenesis and outcomes of molecular subgroups and to identify potential therapeutic targets. International collaborations such as EXPeRT as well as cooperation between pediatric and adult oncologists should play a vital role in improving knowledge and optimizing treatment and outcomes for children with NC. To ensure the success of future clinical trials, it is essential to conduct evidence-based trials to investigate novel therapeutic strategies.

CRediT authorship contribution statement

Tim Flaadt: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Lauriane Lemelle:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Michael Abele:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Calogero Virgone:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Tal Ben-Ami:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Denis Kachanov:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Apostolos Pourtsidis:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Andrea Ferrari:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Gianni Bisogno:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Ewa Bien:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Nuno Jorge Dos Reis Farinha:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Jan Godzinski:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Yves Reguerre:** Data curation, Writing – original draft. **Jelena Roganovic:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Linus D. Kloker:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Ulrich M. Lauer:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Dominik T. Schneider:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing. **Ines B. Brecht:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Writing – original draft, Writing – review & editing. **Daniel Orbach:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project

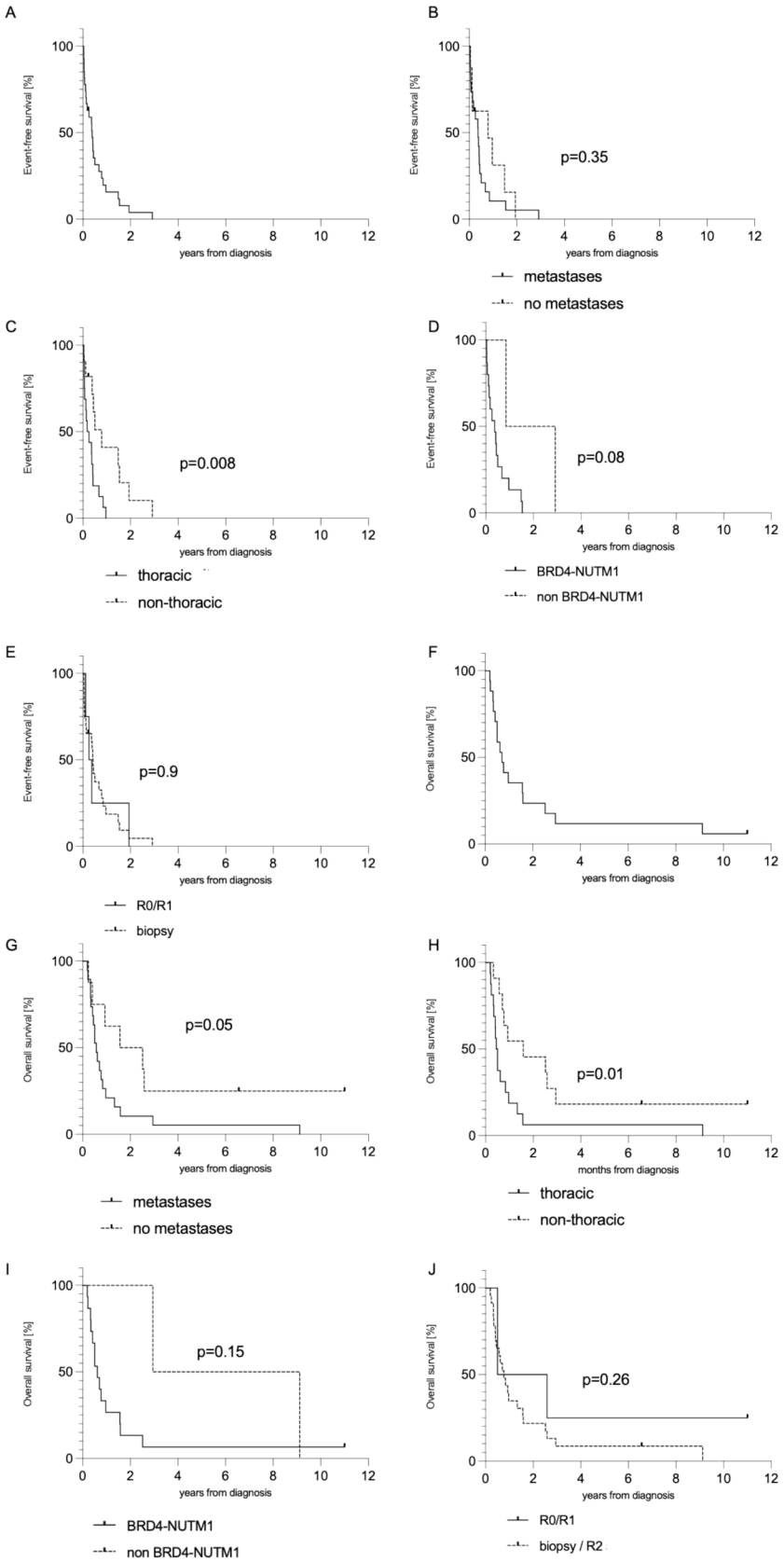


Fig. 1. Outcomes of pediatric patients with NC according to various risk factors: Event-free and Overall survival.

administration, Validation, Writing – original draft, Writing – review & editing.

Funding

The German STEP registry (led by D.S. and I.B.) is supported by the GermanChildhood Cancer Foundation, grant numbers DKS 2013.18 A/B, DKS 2018.18 A/B, and DKS 2021.05 A/B. The French Facture database is supported by a grant from the SFCE-Imagine For Margo.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Ines B. Brecht reports financial support was provided by German Childhood Cancer Foundation. Daniel Orbach reports financial support was provided by SFCE-Imagine For Margo. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

Acknowledgments

The authors are thankful to their colleagues in the EXPeRT group, their colleagues from the reporting hospitals, and all patients and their guardians who agreed to share their data.

Ethical Compliance: All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

[1] C.A. French, N.U.T. Carcinoma, Clinicopathologic features, pathogenesis, and treatment, Pathol Int 68 (11) (2018) 583–595.
[2] B.M. Shehata, C.K. Steelman, C.R. Abramowsky, T.A. Olson, C.A. French, D.F. Saxe, R.R. Ricketts, H.M. Katzenstein, NUT midline carcinoma in a newborn with multiorgan disseminated tumor and a 2-year-old with a pancreatic/hepatic primary, Pediatr Dev Pathol 13 (6) (2010) 481–485.
[3] K. Thompson-Wicking, R.W. Francis, A. Stirnweiss, E. Ferrari, M.D. Welch, E. Baker, A.R. Murch, A.M. Gout, K.W. Carter, A.K. Charles, M.B. Phillips, U. R. Kees, A.H. Beesley, Novel BRD4-NUT fusion isoforms increase the pathogenic complexity in NUT midline carcinoma, Oncogene 32 (39) (2013) 4664–4674.
[4] T.M. Stevens, D. Morlote, J. Xiu, J. Swensen, M. Brandwein-Weber, M. M. Miettinen, Z. Gatalica, J.A. Bridge, NUTM1-rearranged neoplasia: a multi-institution experience yields novel fusion partners and expands the histologic spectrum, Mod Pathol 32 (6) (2019) 764–773.
[5] C.A. French, C.L. Ramirez, J. Kolmakova, T.T. Hickman, M.J. Cameron, M. E. Thyne, J.L. Kutok, J.A. Toretsky, A.K. Tadavarthy, U.R. Kees, J.A. Fletcher, J. C. Aster, BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells, Oncogene 27 (15) (2008) 2237–2242.
[6] C.A. French, S. Rahman, E.M. Walsh, S. Kuhnle, A.R. Grayson, M.E. Lemieux, N. Grunfeld, B.P. Rubin, C.R. Antonescu, S. Zhang, R. Venkatramani, P. Dal Cin, P. M. Howley, NSD3-NUT fusion oncoprotein in NUT midline carcinoma: implications for a novel oncogenic mechanism, Cancer Discov 4 (8) (2014) 928–941.
[7] Q.W. Huang, L.J. He, S. Zheng, T. Liu, B.N. Peng, An overview of molecular mechanism clinicopathological factors, and treatment in NUT carcinoma, Biomed Res Int 2019 (2019) 1018439.
[8] L. Lemelle, G. Pierron, P. Freneaux, S. Huybrechts, A. Spiegel, D. Plantaz, M. Julieron, S. Dumoucel, A. Italiano, F. Millot, C. Le Tourneau, G. Leverger, P. Chastagner, M. Carton, D. Orbach, NUT carcinoma in children and adults: a multicenter retrospective study, Pediatr Blood Cancer 64 (12) (2017).
[9] K. Baumgartner, U. Lauer, M. Horger, L. Zender, C. Kloth, Nuclear protein in testis (NUT) midline carcinoma, Rofo 192 (4) (2020) 303–306.
[10] U.M. Lauer, M. Hinterleitner, M. Horger, P.V. Ohnesorge, L. Zender, NUT carcinoma-an underdiagnosed malignancy, Front Oncol 12 (2022).
[11] C.A. French, Pathogenesis of NUT midline carcinoma, Annu Rev Pathol 7 (2012) 247–265.
[12] S. Storck, A.L. Kennedy, K.J. Marcus, L. Teot, J. Vaughn, A.K. Gnekow, B. Markl, I. Leuschner, S.G. DuBois, C.A. French, M.C. Fruhwald, Pediatric NUT-midline carcinoma: therapeutic success employing a sarcoma based multimodal approach, Pediatr Hematol Oncol 34 (4) (2017) 231–237.
[13] D.E. Bauer, C.M. Mitchell, K.M. Strait, C.S. Lathan, E.B. Stelow, S.C. Luer, S. Muhammed, A.G. Evans, L.M. Sholl, J. Rosai, E. Giraldi, R.P. Oakley, C. Rodriguez-Galindo, W.B. London, S.E. Sallan, J.E. Bradner, C.A. French, Clinicopathologic features and long-term outcomes of NUT midline carcinoma, Clin Cancer Res 18 (20) (2012) 5773–5779.
[14] N.G. Chau, C. Ma, K. Danga, H. Al-Sayegh, V. Nardi, R. Barrette, C.S. Lathan, S. G. DuBois, R.I. Haddad, G.I. Shapiro, S.E. Sallan, A. Dhar, J.J. Nelson, C.A. French, An anatomical site and genetic-based prognostic model for patients with nuclear protein in testis (NUT) midline carcinoma: analysis of 124 patients, JNCI Cancer Spectr 4 (2) (2020) pkz094.
[15] T. Flaadt, H. Wild, M. Abele, M. Fruhwald, U. Dirksen, C.F. Classen, C. Seitz, A. Redlich, U.M. Lauer, L. Kloker, C. Kratz, D.T. Schneider, I.B. Brecht, NUT carcinoma in pediatric patients: characteristics, therapeutic regimens, and outcomes of 11 cases registered with the German Registry for Rare Pediatric Tumors (STEP), Pediatr Blood Cancer 71 (3) (2024).
[16] P. Giridhar, S. Mallick, L. Kashyap, G.K. Rath, Patterns of care and impact of prognostic factors in the outcome of NUT midline carcinoma: a systematic review and individual patient data analysis of 119 cases, Eur Arch Otorhinolaryngol 275 (3) (2018) 815–821.
[17] L. Lemelle, T. Flaadt, B. Fresneau, A. Moya-Plana, B. Timmermann, J. Roganovic, A. Ferrari, G. Fichera, U.M. Lauer, T. Ben-Ami, D.T. Schneider, C. Vokuhl, S. Bolle, E. Fox, S.G. DuBois, C. Rodriguez-Galindo, G. Bisogno, A. Surun, I.B. Brecht, D. Orbach, NUT carcinoma in children and adolescents: the expert european standard clinical practice harmonized recommendations, J Pediatr Hematol Oncol (2022).
[18] A. Ferrari, D.T. Schneider, G. Bisogno, Y. Reguerre, J. Godzinski, E. Bien, T. Stachowicz-Stencel, G. Cecchetto, B. Brennan, J. Roganovic, T. Ben-Ami, C. Virgone, N.R. Farinha, S. Mancini, D. Orbach, I.B. Brecht, Facing the challenges of very rare tumors of pediatric age: The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) background, goals, and achievements, Pediatr Blood Cancer 68 (Suppl 4) (2021).
[19] C.A. French, J.L. Kutok, W.C. Faquin, J.A. Toretsky, C.R. Antonescu, C.A. Griffin, V. Nose, S.O. Vargas, M. Moschovi, F. Tzortzatou-Stathopoulou, I. Miyoshi, A. R. Perez-Atayde, J.C. Aster, J.A. Fletcher, Midline carcinoma of children and young adults with NUT rearrangement, J Clin Oncol 22 (20) (2004) 4135–4139.
[20] H. Haack, L.A. Johnson, C.J. Fry, K. Crosby, R.D. Polakiewicz, E.B. Stelow, S. M. Hong, B.E. Schwartz, M.J. Cameron, M.A. Rubin, M.C. Chang, J.C. Aster, C. A. French, Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody, Am J Surg Pathol 33 (7) (2009) 984–991.
[21] M.S. Tsao, A.G. Nicholson, J.J. Maleszewski, A. Marx, W.D. Travis, Introduction to 2021 WHO classification of thoracic tumors, J Thorac Oncol 17 (1) (2022) e1–e4.
[22] T. Ripperger, S.S. Bielack, A. Borkhardt, I.B. Brecht, B. Burkhardt, G. Calaminus, K. M. Debatin, H. Deubzer, U. Dirksen, C. Eckert, A. Eggert, M. Erlacher, G. Fleischhack, M.C. Fruhwald, A. Gnekow, G. Goehring, N. Graf, H. Hanenberg, J. Hauer, B. Hero, S. Hettmer, K. von Hoff, M. Horstmann, J. Hoyer, T. Illig, P. Kaatsch, R. Kappler, K. Kerl, T. Klingebiel, U. Kontny, U. Kordes, D. Korholz, E. Koscielniak, C.M. Kramm, M. Kuhlen, A.E. Kulozik, B. Lamottke, I. Leuschner, D. R. Lohmann, A. Meinhardt, M. Metzler, L.H. Meyer, O. Moser, M. Nathrath, C. M. Niemeyer, R. Nustede, K.W. Pajtler, C. Paret, M. Rasche, D. Reinhardt, O. Riess, A. Russo, S. Rutkowski, B. Schlegelberger, D. Schneider, R. Schneppenheim, M. Schrappe, C. Schroeder, D. von Schweinitz, T. Simon, M. Sparber-Sauer, C. Spix, M. Stanulla, D. Steinemann, B. Strahm, P. Temming, K. Thomay, A.O. Von Bueren, P. Vorwerk, O. Witt, M. Wlodarski, W. Wossmann, M. Zenker, S. Zimmermann, S. M. Pfister, C.P. Kratz, Childhood cancer predisposition syndromes-A concise review and recommendations by the cancer predisposition working group of the society for pediatric oncology and hematology, Am J Med Genet A 173 (4) (2017) 1017–1037.
[23] F. Mertens, T. Wiebe, C. Adlercreutz, N. Mandahl, C.A. French, Successful treatment of a child with t(15;19)-positive tumor, Pediatr Blood Cancer 49 (7) (2007) 1015–1017.
[24] N.G. Chau, S. Hurwitz, C.M. Mitchell, A. Aserlind, N. Grunfeld, L. Kaplan, P. Hsi, D. E. Bauer, C.S. Lathan, C. Rodriguez-Galindo, R.B. Tishler, R.I. Haddad, S.E. Sallan, J.E. Bradner, C.A. French, Intensive treatment and survival outcomes in NUT midline carcinoma of the head and neck, Cancer 122 (23) (2016) 3632–3640.
[25] S. Cousin, J.Y. Blay, I.B. Garcia, J.S. de Bono, C. Le Tourneau, V. Moreno, J. Trigo, C.L. Hann, A.A. Azad, S.A. Im, P.A. Cassier, C.A. French, A. Italiano, V.L. Keedy, R. Plummer, M.P. Sablin, M.L. Hemming, G. Ferron-Brady, A. Wyce, A. Khaled, A. Datta, S.W. Foley, M.T. McCabe, Y. Wu, T. Horner, B.E. Kremer, A. Dhar, P. J. O'Dwyer, G.I. Shapiro, S.A. Piha-Paul, Safety, pharmacokinetic, pharmacodynamic and clinical activity of molibresib for the treatment of nuclear protein in testis carcinoma and other cancers: results of a Phase I/II open-label, dose escalation study, Int J Cancer 150 (6) (2022) 993–1006.
[26] G.I. Shapiro, P. LoRusso, A. Dowlati, T.D. K, C.A. Jacobson, U. Vaishampayan, A. Weise, P.F. Caimi, J.P. Eder, C.A. French, E. Labriola-Tompkins, F. Boisserie, W.E. Pierceall, J. Zhi, S. Passe, M. DeMario, M. Kornacker, P. Armand, A Phase 1 study of RO6870810, a novel bromodomain and extra-terminal protein inhibitor, in patients with NUT carcinoma, other solid tumours, or diffuse large B-cell lymphoma, Br J Cancer 124(4) (2021) 744-753.
[27] L. Marcus, L.A. Fashoyin-Aje, M. Donoghue, M. Yuan, L. Rodriguez, P.S. Gallagher, R. Philip, S. Ghosh, M.R. Theoret, J.A. Beaver, R. Pazdur, S.J. Lemery, FDA approval summary: pembrolizumab for the treatment of tumor mutational burden-high solid tumors, Clin Cancer Res 27 (17) (2021) 4685–4689.
[28] L.D. Kloker, M. Sidiras, T. Flaadt, I.B. Brecht, C.K.W. Deinzer, T. Gross, K. Benzler, L. Zender, U.M. Lauer, Clinical management of NUT carcinoma (NC) in Germany: Analysis of survival, therapy response, tumor markers and tumor genome sequencing in 35 adult patients, Lung Cancer 189 (2024).
[29] X. Li, H. Shi, W. Zhang, C. Bai, M. He, N. Ta, H. Huang, Y. Ning, C. Fang, H. Qin, Y. Dong, Immunotherapy and targeting the tumor microenvironment: current place and new insights in primary pulmonary NUT carcinoma, Front Oncol 11 (2021).